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A Chiral-Pool-Based Approach to the Core Structure of (+)-Hyperforin

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Asymmetric entry to the bicyclic core structure of (+)-hyperforin is presented. The developed synthetic strategy features a carefully orchestrated stereochemical relay from the single chiral center residing within (–)-Wieland–Miescher ketone and an intramolecular aldol reaction to cast the [3.3.1] bicyclic scaffold found in a diverse array of polycyclic polyprenylated acylphloroglucinols.

Introduction

Polycyclic polyprenylated acylphloroglucinols (PPAPs) constitute a fascinating family of natural products that is found to display a broad spectrum of biological properties. Among them, (+)-hyperforin (**1**), nemorosone (**2**), and garsubellin A (**3**) instigated significant interest from the synthetic community mainly because of their challenging molecular architecture in conjunction with their promising antidepressant, antimalarial, antibacterial, antioxidant, and antineurodegenerative activities (Figure 1).[1] Significant progress have been made in the last decade towards the synthesis of a diverse array of PPAP congeners;[2] however, asymmetric entry to the densely functionalized bicyclo[3.3.1]nonane-2,4,9-trione or bicyclo[3.2.1]octane-2,4,8-trione core of the PPAPs remains a formidable synthetic challenge. Evidently, only four asymmetric total syntheses of (+)- and (–)-clusianone,[3] (+)-hyperibone K,[4] and *ent*-hyperforin[5] have been accomplished, together with sporadic reports on asymmetric model studies.[6] In particular, the landmark total synthesis of *ent*-hyperforin reported in 2010 by Kanai, Shibasaki, and co-workers[5] that featured a catalytic asymmetric Diels–Alder reaction to introduce the C8 quaternary center further highlighted the difficulties associated with this unique structural element that is absent in other members of the PPAP family. Indeed, the complications encountered in connection with the introduction of this additional quaternary center, asymmetrically, may explain the relatively few synthetic reports of hyperforin in contrast to those available for its PPAP siblings.

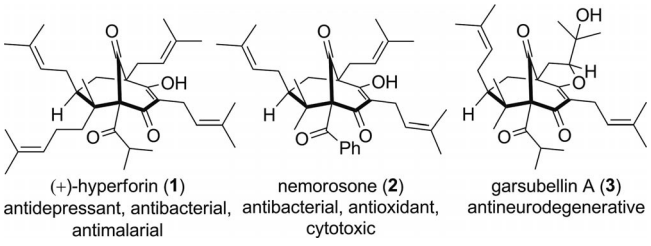

Figure 1. Structures of selected PPAPs along with their biological activities.

Results and Discussion

With an appreciation for historical synthetic studies towards hyperforin and its related PPAPs in mind, here we report our progress towards the synthesis of the core structure of (+)-hyperforin (**1**) by exploiting (–)-Wieland–Miescher ketone (**7**) as a convenient source of asymmetric information.[7] Recent reports from the laboratories of Theodorakis,[8] Bonjoch,[9] and Hanessian[10] have beautifully showcased the utility of optically enriched Wieland–Miescher ketone in the preparation of highly functionalized chiral materials for natural product synthesis. Furthermore, the total synthesis of taxol reported by the Danishefsky group featured ingenious use of (+)-Wieland–Miescher ketone to rapidly access a substituted cyclohexane.[11] Inspired by this latter report, our proposed synthesis of the core structure of (+)-hyperforin (**1**) called for a late-stage construction of the [3.3.1] bicyclic system from highly substituted and suitably functionalized cyclohexanone **4**. A critical element of the synthesis, as alluded to earlier, is the introduction of the two quaternary centers at the C5 and C8 positions. In this context, we envisaged that the former could be controlled through a Claisen-type rearrangement from stereochemically defined allylic alcohol **5**, whereas the latter could originate from (–)-Wieland–Miescher ketone (**7**) derived cyclohexanone **6** (Scheme 1).

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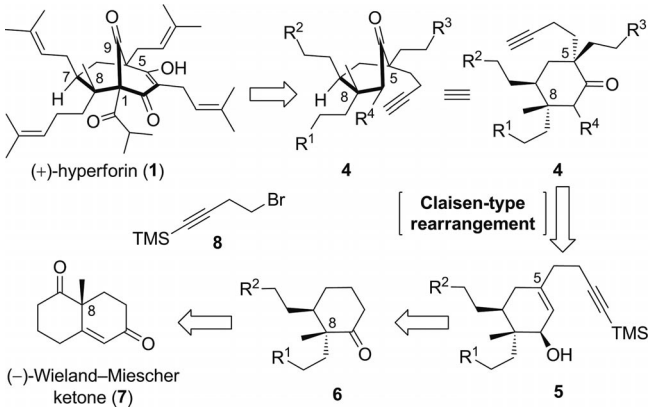
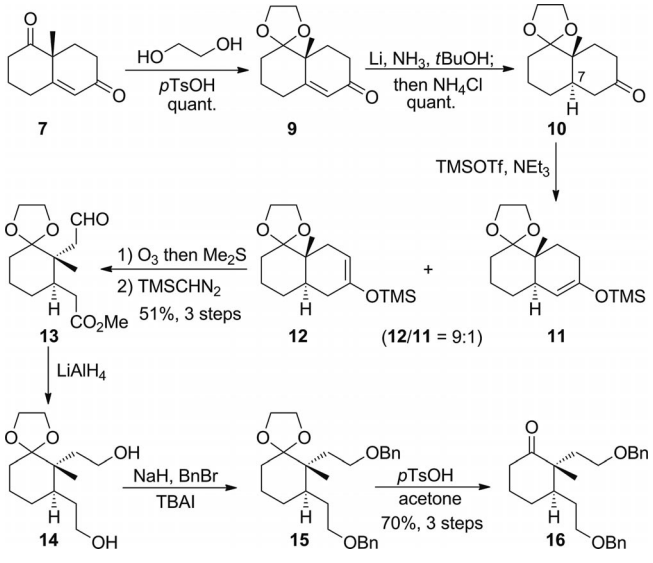


Scheme 1. Retrosynthetic analysis towards the [3.3.1] bicyclic core structure of (+)-hyperforin (**1**).

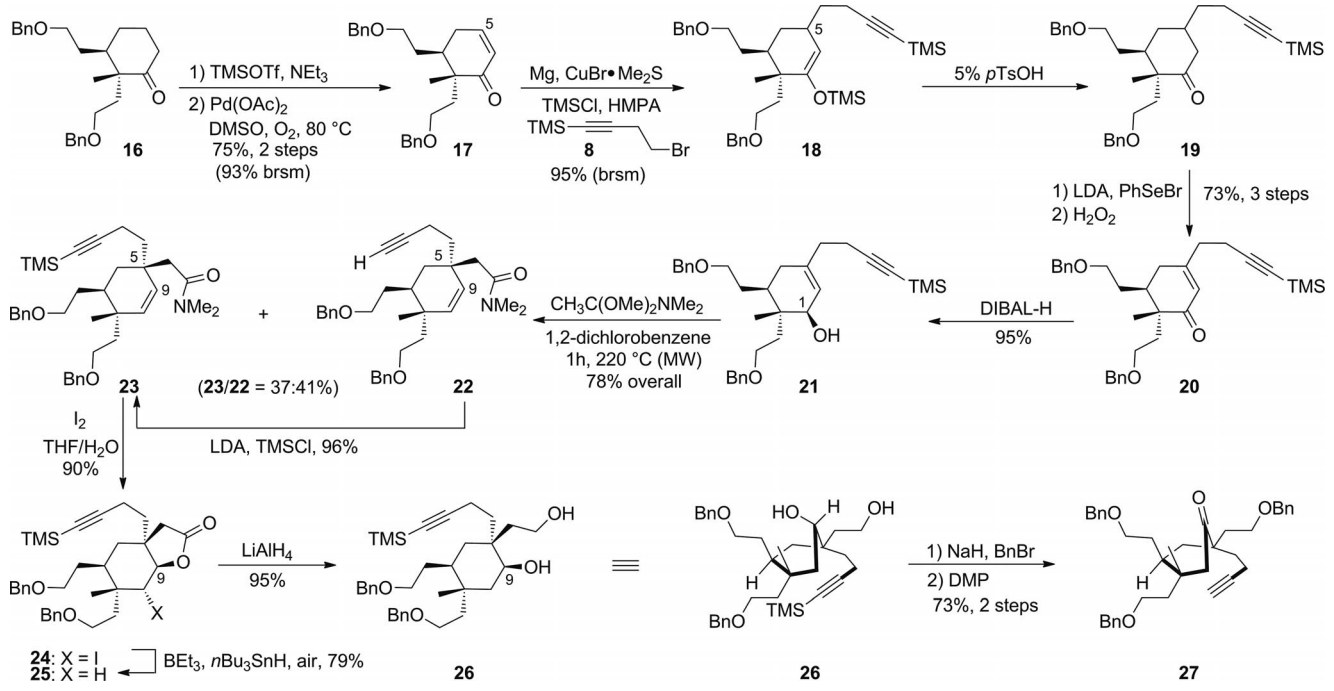
Our synthesis commenced with a chemoselective protection of (–)-Wieland-Miescher ketone (**7**) as dioxolane derivative **9**,[12] and subsequent Birch reduction to provide ketone **10** as a single stereoisomer (quant. yield over the two steps, Scheme 2). In doing so, the C7 stereogenic center of (+)-hyperforin was also conveniently introduced. Silyl enol ether formation of bicyclic ketone **10** (TMSOTf, NEt_3) proceeded smoothly to afford **12** as a 9:1 mixture with its regioisomer **11**. Oxidative rupture of bicyclic silyl enol ether **12** was achieved through ozonolysis, thereby revealing substituted cyclohexane **13** upon esterification ($TMSCHN_2$, 51% over the three steps). It is worth noting that regioisomeric silyl enol ether **11** could also serve as a valuable intermediate to advance our hyperforin campaign forward, where it could be obtained exclusively through Birch reduction of enone **9** followed by quenching with TMSCl.



Scheme 2. Synthesis of functionalized cyclohexanone **16**. TMS = trimethylsilyl, *p*TsOH = *p*-toluenesulfonic acid, Bu = butyl, OTf = trifluoromethanesulfonate, Me = methyl, Bn = benzyl, TBAI = tetrabutylammonium iodide.

However, further elaboration of TMS enol ether **11** proved less satisfactory (25% over the two steps), and often afforded complicated mixtures primarily attributed to the isomerization of **11** into more stable **12**. As a precautionary measure to facilitate our ensuring synthetic studies, aldehyde-ester **13** was exhaustively reduced ($LiAlH_4$), and the resulting hydroxy groups were guarded as benzyl ethers. Liberation of the dioxolane moiety of **15** (*p*TsOH) then afforded ketone **16** in 70% yield over the three steps.

With trisubstituted cyclohexanone **16** efficiently prepared with high stereochemical fidelity, the introduction of the C5 quaternary center was the next task on the agenda (Scheme 3). In this context, functionalization of the C5 methylene carbon of ketone **16** first called for a Saegusa–Ito oxidation [TMSOTf, NEt_3; then $Pd(OAc)_2/O_2$][13] to afford enone **17** in 75% yield over the two steps [93% based on recovered starting material (brsm)]). After extensive optimization of the reaction conditions, conjugate addition of the organocuprate reagent ($CuBr{\cdot}Me_2S$, TMSCl, HMPA) derived from alkynyl halide **8**[14] proceeded smoothly to afford TMS enol ether **18** as a single diastereoisomer (95% brsm), though the stereochemistry of the newly formed stereocenter at C5 could not be determined at this juncture. However, the stereochemical outcome of this alkylation process was inconsequential due to the subsequent conversion of **18** into enone **20** through initial enol ether hydrolysis (*p*TsOH) followed by oxidative selenium chemistry (LDA, PhSeBr; then pyridine/H_2O_2, 73% yield over the three steps). It is worth noting that the direct conversion of TMS enol ether **18** into enone **20** under enolate oxidation conditions proved less satisfactory. Reduction of enone **20** under DIBAL-H conditions afforded allylic alcohol **21** exclusively, where the newly formed hydroxy stereocenter was crucial and indirectly validated by a later intermediate (vide infra). With allylic alcohol **21** secured, the stage was set for the generation of the C5 quaternary center through a Claisen-type stereochemical relay (from C1). However, the fruition of this transformation necessitated intense experimental efforts, where the venerable Ireland–Claisen,[15] Johnson–Claisen,[16] and selenium-mediated[17] Claisen rearrangements all proved unsatisfactory. At last, implementation of the Eschenmoser–Claisen protocol[18] (*N*,*N*′-dimethylacetamide dimethyl acetal) promoted the anticipated sigmatropic rearrangement with concomitant introduction of the C5 quaternary center, as evident in product amides **22** and **23**. The optimized reaction condition required microwave irradiation at 220 °C for 1 h to afford a separable mixture of TMS-protected alkyne **23** and terminal alkyne **22** in 37 and 41% yield, respectively, where silylation of terminal alkyne **22** (LDA, TMSCl, 96%) permitted recycling of this material. Next, oxygenation at the C9 position that later represents the bridged ketone oxygen of hyperforin/PPAPs took advantage of the iodolactonization protocol, which proceeded in the presence of iodine in THF/H_2O (3:1) to provide lactone **24** in 90% yield. Although a stable crystalline derivative of iodide **24** could not be obtained for X-ray crystallographic analysis, extensive NOESY studies of bicyclic lactone **24** offered convincing evidence to support



Scheme 3. Synthesis of alkynyl ketone **27** from ketone **16**. TMS = trimethylsilyl, OTf = trifluoromethanesulfonate, Ph = phenyl, Ac = acetyl, DMSO = dimethyl sulfoxide, Bn = benzyl, LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide, *p*TsOH = *p*-toluenesulfonic acid, DIBAL-H = diisobutylaluminum hydride, Me = methyl, MW = microwave irradiation, Et = ethyl, Bu = butyl, DMP = Dess–Martin periodinane, brsm = based on recovered starting material.

the proposed structure and thus the indirect validation of the stereochemical outcome of the reduction of enone **20** (Figure 2).

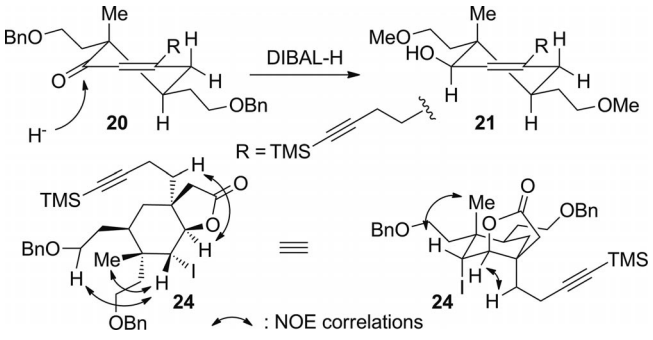
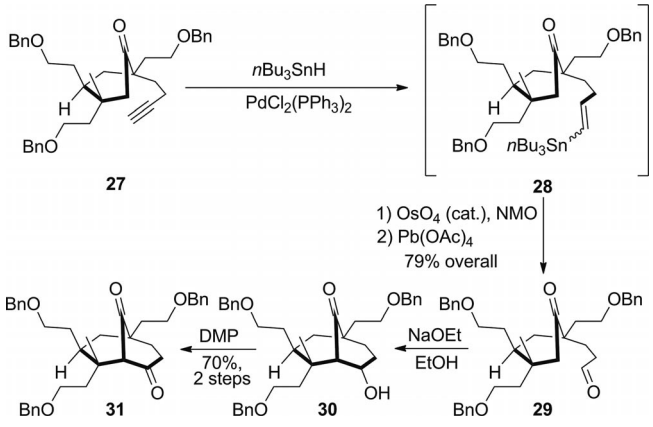


Figure 2. Proposed model for the stereoselective reduction of enone **20** and determination of the stereochemistry through key NOE correlations of **24**.

With the successful installation of the three crucial stereogenic centers at C7, C8, and C5 of (+)-hyperforin, in particular the quaternary centers residing at C5 and C8, the formation of the [3.3.1] bicyclic system was pursued in earnest. In preparation for this event, removal of the iodine residue from **24** under standard conditions (AIBN, nBu$_3$SnH at 80 °C) was found to be unsatisfactory, and a solution was ultimately secured by performing the reaction at low temperature (i.e., –78 °C) in the presence of Et$_3$B as a radical initiator (79% yield). Reduction of bicyclic lactone **25** (LiAlH$_4$, 95%) followed by the selective benzylation of resulting diol **26** (NaH, BnBr) took place uneventfully, where the latter transformation proceeded with concomitant removal of the TMS group. Subsequent DMP-mediated oxidation (73% over the two steps) afforded ketone **27**, in readiness for the casting of the bicyclic core structure of (+)-hyperforin (Scheme 3).

In view of the rich repertoire of cyclization strategies documented in the synthetic studies towards PPAPs[2] and the synthetic versatility of alkynyl ketone **27**, as a proof-of-principal study we were first attracted to the efficiency of the intramolecular aldol reaction that had been demonstrated previously (Scheme 4).[5] In this context, partial reduction of the terminal alkyne to the corresponding alkene was found to be capricious under a variety of conditions. However, we soon discovered a streamlined procedure that enabled the conversion of alkyne **27** into aldehyde **29** through initial hydrostannation [PdCl$_2$(PPh$_3$)$_2$, nBu$_3$SnH][19] of alkyne **27**. In situ generated vinyl stannane **28** was not isolated but instead directly treated with OsO$_4$ and NMO to afford the corresponding diol, where the latter compound was used in its crude form and treated with Pb(OAc)$_4$ to furnish desired keto aldehyde **29** in 79% yield over the three steps. Gratifyingly, the proposed intramolecular aldol reaction proceeded smoothly under the influence of NaOEt, where the so-obtained [3.3.1] bicyclic hydroxy ketone was oxidized (DMP) to afford diketone **31** in 70% yield over the two steps. Indeed, diketone **31** possesses the key structural elements required in (+)-hyperforin and represents a plausible intermediate to be further elaborated to both the naturally occurring and designed compounds in view of the related synthetic work.[2]



Scheme 4. Synthesis of the functionalized [3,3,1] bicyclic core of (+)-hyperforin (**1**). Bn = benzyl, Bu = butyl, Ph = phenyl, Ac = acetyl, NMO = *N*-methylmorpholine *N*-oxide, DMP = Dess–Martin periodinane.

Conclusions

In summary, a chiral-pool approach involving the use of (–)-Wieland–Miescher ketone (**7**) as a readily accessible chiral building block rendered a high-yielding preparation of the functionalized [3,3,1] bicyclic core structure of (+)-hyperforin (**1**). Key synthetic maneuvers involved oxidative rupture of decalin **12**, enone reduction/Eschenmoser–Claisen rearrangement to cast the C5 quaternary center, a one-pot alkyne hydrostannation/dihydroxylation to circumvent the troublesome alkyne partial reduction, and an efficient intramolecular aldol cyclization. Further efforts and full account of our journey towards (+)-hyperforin (**1**) will be reported in due course.

Supporting Information (see footnote on the first page of this article): General information for the Experimental Section, experimental procedures and compound characterization, and ^{1}H and ^{13}C NMR spectra for all compounds.

Acknowledgments

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