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Natural Product Synthesis

The Bidirectional Total Synthesis of Sampsonione P and Hyperibone I**

*Katharina Lindermayr and Bernd Plietker**

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a class of acylphloroglucinol-derived natural products that currently consist of more than 120 members.[1–4] The common feature of these natural products is a densely substituted [3.3.1]bicyclononatrione core that possesses only three hydrogen substituents. The lack of hydrogen atoms within this core sets particular challenges in structure elucidation and the assignment of absolute and relative configurations at C7. Within the biosynthesis of these natural products the prenyltransferase-initiated cationic cyclization of acylphloroglucine (**I**) could lead to mixtures of up to four PPAPs (**II**–**V**; Figure 1).[4–6]

While in type A PPAPs the bridgehead carbon atom C5 is substituted by an acyl group, type B PPAPs have a C3 acyl group. Depending on the course of the prenylase-catalyzed cyclization pairs of *trans* (or *endo*) type B PPAPs (**III**)/*cis* (or *exo*) type A PPAPs (**II**) and *exo* type B PPAPs (**V**)/*endo* type A PPAPs (**IV**) are formed. In most cases mixtures of these isomers are obtained from natural sources. While the differentiation between type A and type B PPAPs by spectroscopic methods is unproblematic, the exact assignment of *exo* or *endo* configuration is challenging. The PPAP core possesses only three hydrogen atoms and hence NOE experiments do not give clear information on relative configurations.[7,8] At this point total synthesis aids the structure elucidation.[9]

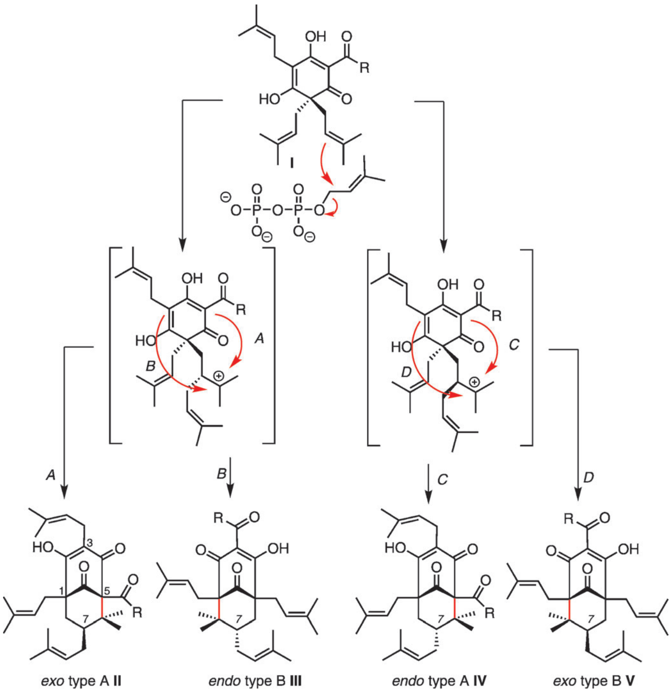

Figure 1. Polyvergent biosynthetic pathway to *exo*- and *endo*-type PPAPs.

The two tetrahydrofuran-annulated type B PPAPs sampsonione P (**1**) and hyperibone I (**2**) are representative examples for the pitfalls of PPAP structure analysis. Sampsonione P was isolated in 2007 from *Hypericum sampsonii*, a genus in the family of Hypericaceae.[10] Hyperibone I, together with eight other PPAPs, was isolated from *Hypericum scabrum* in 2002.[11] In addition to different positions of the tetrahydrofuran ring within the tricyclic core, different C7 configurations were proposed (Figure 2). While for sampsonione P (**1**) an *endo* configuration was suggested, the isomeric hyperibone I was proposed to possess an *exo* configuration (**2a**). The latter stereochemical assignment was mainly based upon comparison with similar compounds and 1D-NMR spectroscopy.

In their 2006 review, Grossman and Ciochina proposed that based on characteristic NMR shifts hyperibone I might

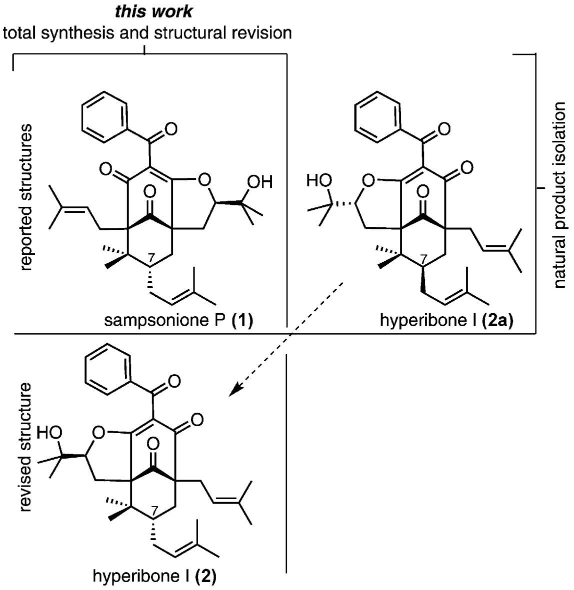

Figure 2. Molecular structures of sampsonione P (**1**) and hyperibone I (**2a**, **2**); confirmation and revision.

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[*] Dipl.-Chem. K. Lindermayr, Prof. Dr. B. Plietker
Institut für Organische Chemie, Universität Stuttgart
Pfaffenwaldring 55, 70569 Stuttgart (Germany)
E-mail: bernd.plietker@oc.uni-stuttgart.de

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better be regarded as an *endo* type B PPAP (**2a**).[4] After careful comparison of NMR data of known PPAP structures, they found that an *exo* configuration leads to a difference in chemical shifts of 0.3–1.2 ppm for the two H6 atoms and the characteristic shift of C7 is within the range of 41–44 ppm. In contrast, *endo* isomers have only a small difference in the chemical shifts of the H6 atoms (0.0–0.2 ppm) and the chemical shift of C7 is 45–49 ppm.

Recently we disclosed a short total synthesis of *endo* type B PPAPs.[12] The strict separation of framework-constructing from framework-decorating steps permitted the selective variation of the substitution pattern without affecting the general synthetic approach. Based on these results and the divergence in the stereochemical assignment of hyperibone I we envisioned a total synthesis to be the only way to fully assign the structure of hyperibone I. Herein we describe a short divergent nine- and ten-step total synthesis of sampsonione P and hyperibone I. The NMR spectra for both PPAPs are in almost perfect agreement with the reported data of the natural products and confirm Grossman's hypothesis that hyperibone I is an *endo* type B PPAP (Figure 2).

With regard to the structural differences between sampsonione P and hyperibone I, we thought the facile electrophilic oxidation of an electron-rich prenyl side chain in the presence of a less electron-rich allyl substituent would be a suitable regioselectivity switch for the formation of the tetrahydrofuran ring at a late stage in the total synthesis (Figure 3).[13] In order to verify this strategy, regio- and diastereoselective allylation or prenylation at different stages of the synthesis was necessary.

Starting from acetylacetone (**6**), (α-allylvinyl) methyl ketone (**7**) was prepared in a two-step/one-pot procedure consisting of an allylation and a deacylating aldol condensation[14] in good overall yield (Scheme 1). The subsequent tandem Michael addition/Dieckmann condensation using dimethyl acetonedicarboxylate and regioselective 1,2-addition[15] gave rise to cyclohexenone **9** in high overall yields. This starting material represents the point of divergence for the two syntheses.

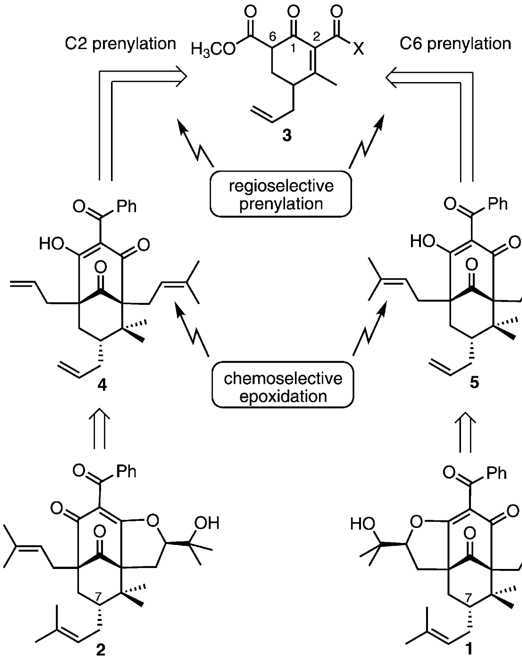
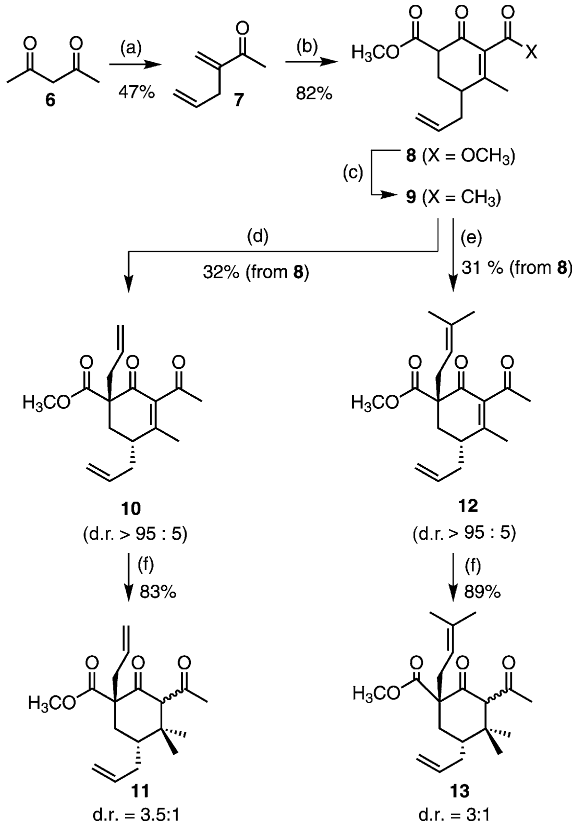


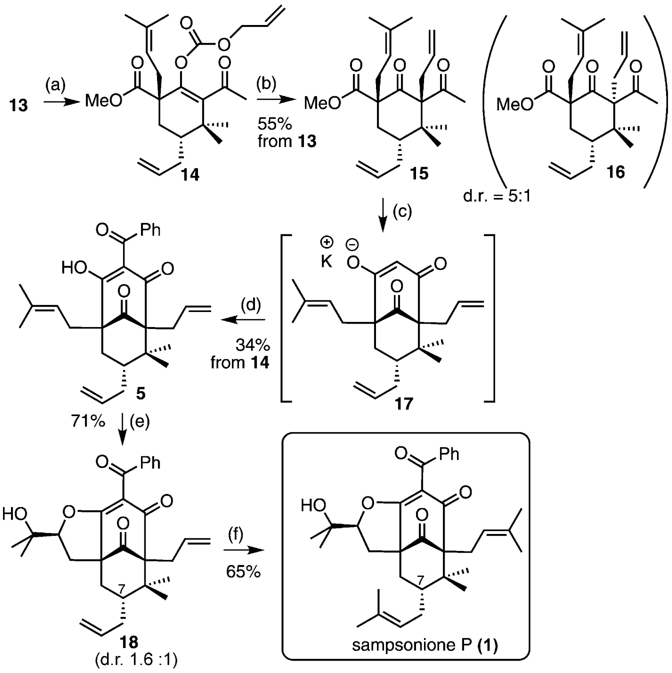
Figure 3. Retrosynthesis.



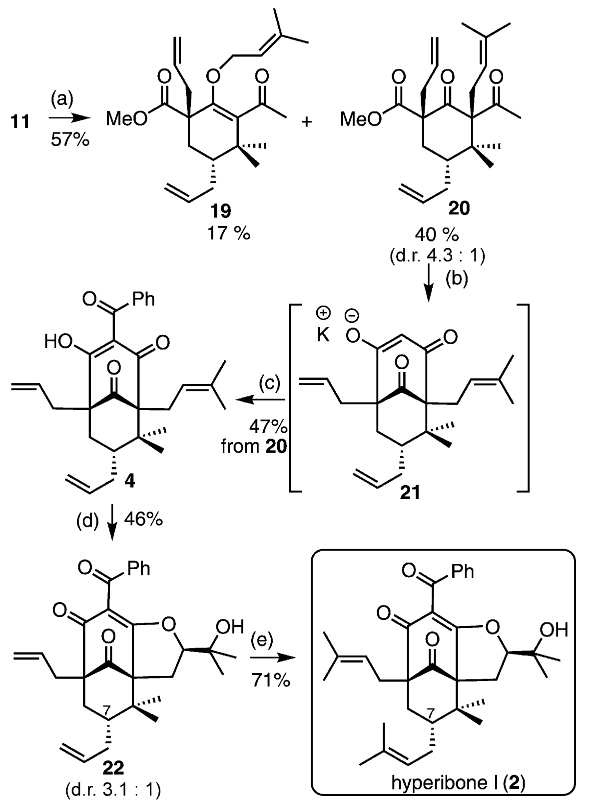
Scheme 1. Bidirectional total synthesis of sampsonione P and hyperibone I: preparation of cyclohexanones **11** and **13**. Reagents and conditions: a) NaH, allyl bromide, ethanol, 0 °C–RT, 15 h, then K_2CO_3, $CH_2O_{(aq)}$, RT, 15 h; b) MeMgCl, dimethyl 1,3-acetonedicarboxylate, methanol, 0–60 °C, 18 h; c) NaH, MeLi, THF, 0 °C; 5 h; d) NaH, prenyl bromide (for **13**) or e) allyl bromide (for **11**), THF, 0 °C–RT, 15 h; f) LiCl, CuI, MeMgBr, Me_3SiCl, THF, −78 °C, 4 h.

Allylation using prenyl bromide under basic conditions gave the corresponding cyclohexenone **12** in excellent diastereoselectivity in favor of the *trans*-bis-allylated stereoisomer. We were pleased to find that the introduction of the sterically less demanding allyl side chain, which is required for the synthesis of hyperibone I, proceeded equally well and with good diastereoselectivity (leading to **10**). The 1,4-addition of MeCu[16] to **10** and **12** furnished the corresponding *gem*-dimethyl moiety that is found in many PPAPs.

With these key intermediates in hand we then turned our attention to the total synthesis of sampsonione P (Scheme 2). Unexpectedly, the introduction of the allyl side chain proved to be problematic. Direct allylation using allyl bromide in the presence of base gave only the undesired allyl vinyl ether. Metal-catalyzed intermolecular Tsuji–Trost allylation provided the C-allylation product **15** as a mixture of stereoisomers along with varying amounts of the allyl vinyl ether. However, transformation of the allyloxycarbonyl derivative **14** in a Pd-catalyzed decarboxylative Tsuji–Trost allylation



Scheme 2. Total synthesis of sampsonione P. Reagents and conditions: a) NaH, allyl chloroformate, DMF, 0 °C–RT, 3 h, then b) [Pd_2dba_3], *p*-Tol_3P, toluene, 60 °C, 16 h; c) KO*t*Bu, THF, then d) PhC(=O)CN, THF, 0 °C–RT, 48 h; (e) *m*CPBA, CH_2Cl_2, 0 °C, 30 min; f) Grubbs II cat. (0.15 equiv), 2-methyl-2-butene, CH_2Cl_2, 40 °C, 20 h. *m*CPBA: *meta*-chloroperbenzoic acid.



Scheme 3. Total synthesis of hyperibone I. Reagents and conditions: a) $KOCMe_2Et$, 1,3-dimesitylimidazolin-2-ylidene hexafluorophosphate (0.2 equiv), $Bu_4N[Fe(CO)_3(NO)]$ (0.2 equiv), methyl(2-methyl-3-butene-2-yl)carbonate, THF/MTBE, RT–80 °C, 20 h;b) KO*t*Bu, then c) PhC(=O)CN, THF, 0 °C–RT, 48 h; d) *m*CPBA, CH_2Cl_2, 0 °C, 2 h; e) Grubbs II cat. (0.15 equiv), 2-methyl-2-butene, CH_2Cl_2, 40 °C, 20 h. MTBE: *tert*-butyl methyl ether.

gave the desired *cis* product **15** in a diastereomeric ratio of 5:1.[17–19] Treatment of **15** with KO*t*Bu in THF at 0 °C gave enolate **17**, which reacted with benzoylcyanide to give the desired C-benzoylated [3.3.1]bicyclononatrione core **5** in good yield. Treatment of **5** with *m*CPBA at 0 °C for one hour led to the chemoselective epoxidation of the prenyl side chain with concomitant cyclization to give the precursor (**18**) to sampsonione P containing the tetrahydrofuran motif.[13] Oxidation of the allyl side chains was not observed. The desired product **18** was obtained in good yields albeit in low diastereoselectivity. The mixture of isomers was subjected to a cross-metathesis[20] using 2-methyl-2-butene and the Grubbs II catalyst to give the corresponding product **1** in good yield (Scheme 2). At this stage separation of the stereoisomers proved to be nonproblematic and was achieved by conventional column chromatography. Sampsonione P (**1**) was unambiguously identified by comparison of the NMR data with the reported data.[10,21]

The total synthesis of hyperibone I (**2**) was tackled subsequently (Scheme 3). As already observed in the synthesis of sampsonione P, the introduction of a prenyl group proved to be problematic. In analogy to related transformations in the total syntheses of *epi*-clusianone and oblongifolin A,[12] Fe-catalyzed allylic substitution was the only way to obtain synthetically useful amounts of the desired product **20.** However, only a modest diastereoselectivity of 4.3:1 was achieved in favor of the *cis* product with formation of **18** as a byproduct.[22]

Following the base-promoted intramolecular Claisen cyclization to give **21**, the enolate was trapped using benzoylcyanide to provide bicycle **4** in good overall yield. Gratifyingly, the subsequent *m*CPBA-mediated epoxidation was accompanied by ring opening and cyclization to give the corresponding tetrahydrofuran derivative **22**. Finally cross-metathesis with 2-methyl-2-butene furnished product **2** in good overall yield and a diastereomeric ratio of 3.1:1.0. Product **2** was unequivocally identified as hyperibone I by comparison with the NMR data of the isolated natural product.[21]

Although the *endo* configuration of PPAPs obtained through our synthetic strategy was proven in our previous study,[12] we performed in-depth NMR measurements in order to secure the relative configuration of synthetic **1** and **2** (Figure 4). The use of [D_6]benzene as the solvent proved to be important in order to resolve the relevant proton signals at C6 and C7 in **1** and **2**, respectively. The C7 substituent occupies a pseudo-axial orientation within the cyclohexanone core which can be assumed based on solution experiments and X-ray crystallographic analysis of the related hyperibone L.[12] In case of hyperibone I (**2**) a strong NOE was observable between $H_{(eq.,C7)}$ and $H_{(ax.,C6)}$ and a weak NOE to $H_{(eq.,C6)}$. Furthermore, a strong NOE was visible between $H_{(ax.,C6)}$/$H_{(eq.,C7)}$ and $CH_{3(ax.,C8)}$. $CH_{3(eq.,C8)}$ showed a strong NOE to $H_{(eq.,C10)}$, $H_{(eq.,C11)}$, and $H_{(C27)}$. Based on these data we propose

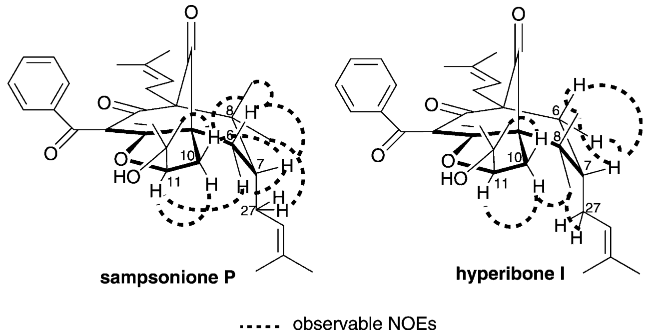


Figure 4. Characteristic NOEs in sampsonione P and hyperibone I (recorded in [D$_6$]benzene).

the revised structure of hyperibone I to possess the relative configuration shown in Figure 3 and to be an *endo* type B PPAP.

In summary, we have presented the first total synthesis of sampsonione P and hyperibone I in ten and nine steps, respectively, starting from acetylacetone. The strict separation of framework-decorating and framework-constructing transformations allowed us to selectively introduce a prenyl group. Owing to the different rates in the epoxidation of prenyl and allyl groups, we could form the tetrahydrofuran motif at a late stage in the synthesis. The final cross-metathesis provided the desired remaining prenyl side chains in good overall yield. The key step of the two syntheses is the introduction of the last allyl or prenyl substituent by either a decarboxylative Tsuji–Trost allylation or a Fe-catalyzed allylation. Both the total syntheses and the in-depth spectroscopic investigations confirmed the reported structure of sampsonione P and the previously proposed revised structure of hyperibone I.

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