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The total synthesis of hyperpapuanone, hyperibone L, *epi*-clusianone and oblongifolin A

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Polyprenylated polycyclic acylphloroglucines (PPAPs) are a family of natural products that possess a wide range of different important biological activities because of the relative position and configuration of four substituents that decorate one common central bicyclo[3.3.1]nonane-2,4,9-trione core. The rigid bicyclic framework with its lipophilic side chains and its hydrophilic trione moiety represents a nature-derived lead structure that arranges the substituents (R^1 to R^4) into a defined topographical orientation. As the substituents are responsible for the biological activities, the seven-step synthetic approach presented here sets the stage for an iterative introduction of R^1 to R^4 and thus generates structurally diverse *trans*-type B PPAPs. Four natural and one non-natural *trans*-type B PPAPs were prepared starting from acetylacetone with overall yields that ranged from 6 to 22%. The concept of separating framework construction from decorating transformations plus the minimization of protecting-group operations are the key issues for the realization of our synthetic approach.

Polyprenylated polycyclic acylphloroglucines (PPAPs) are a family of natural products, of which more than 100 members have been discovered to date. Most of these were isolated from plants and trees from *Clusiaceae* (*Guttiferae*). This group of natural products spans a wide range of biological activities, and has antimicrobial, antioxidant, anticancer or antidepressant properties[1–15]. It is surprising to find that this diverse biological activity is probably the consequence of the relative configuration and position of substituents decorated around one common highly oxygenated and densely substituted bicyclo[3.3.1]nonane-2,4,9-trione core[1]. This bicyclic framework can be regarded as a novel type of natural core structure that helps to arrange the corresponding substituents in the correct topographical orientation. The PPAPs are divided into three types (A, B and C) depending on the position of the acyl group on the bicyclic core (Fig. 1)[1]. Apart from the position of the acyl group the configuration of the C7-substituent R^1 relative to the carbonyl bridge is another important issue. The C7 group functions as a molecular anchor unit and thus directs the conformation of the cyclohexanone moiety to be in a chair-like (for *cis*- (or *exo*)-type PPAPs[1]) or in a boat-like conformation (for *trans*- (or *endo*)-type PPAPs[1]) (Fig. 1). This conformational change has a direct influence on the biological activity. In the case of, for example, clusianone[2–4] (a *cis*-type PPAP) the side-chain R^1 is oriented in a *cis* fashion to give the preferred conformation shown in Fig. 1. Inversion of the C7 stereochemistry leads to *epi*-clusianone[4,5] (**2**) (a *trans*-type PPAP) with its boat-like conformation. Although both natural products show a similar bioactivity profile[2–12], *epi*-clusianone (**2**) is significantly less cytotoxic[4].

From a chemical aspect, in particular the densely substituted central core and the remarkable structure–activity relationship have attracted the attention of synthetic chemists within the past five years. As a consequence, elegant and short total syntheses towards *cis*-type PPAPs have been developed[16–26]. However, an efficient approach towards *trans*-type PPAPs is underdeveloped.

Herein, we report a general modular and practical total synthesis of *trans*-type B PPAPs that allows the preparation, starting from acetylacetone (**6**), of a set of natural products in just seven steps with overall yields that range from 6 to 22%. To exemplify the versatility of our approach, we synthesized four natural products, *epi*-clusianone (**2**)[4,5], oblongifolin A (**1**)[13], hyperibone L (**3**)[14] and hyperpapuanone (**4**)[15]. Furthermore, **4** was also prepared as its C1–C5 regioisomer **5**, which was a proposed revised structure for **4** (ref. 1). These natural products possess important biological activities (Fig. 1). To date, detailed studies on the cellular inhibition pathways have been performed only with **2,** which possesses antiproliferative effects on various cancer cell lines through the inhibition of cysteine and serine proteases[12]. Although no in-depth bioactivity studies for **1** and **3** have been published so far, the structural similarity of these compounds to **2** implies a similar bioactivity profile. Obviously, the aryl ketone moiety appears to be essential for the inhibition of tumour cell replication.

Changing the substituent R^4 from an aryl to an alkyl group causes a change in the bioactivity. Although **4** shows no activity against cancer cell lines, it possesses a significant antimicrobial activity[15]. Similar studies carried out with *epi*-clusianone (**2**) revealed an even broader antimicrobial activity[10]. From the available bioactivity data, it can be concluded that this natural product family might offer new perspectives for pharmaceutical research. However, as mentioned above, one of the main problems is the lack of efficient access to structurally diverse *trans*-type B PPAPs. This fact hampers their systematic exploration and can, to some extent, be attributed to the small amounts of material available from natural resources.

A variety of natural products show similar core structures and differ only in their substitution pattern. The PPAPs might be regarded as an impressive example of nature's structural diversity.

Results and discussion

Retrosynthesis. At the outset of our synthetic studies, we thought that a clear separation of the framework (that is, the bicyclo[3.3.1]nonatrione core) construction and decoration (the introduction of the corresponding substituents R^1 to R^4) could set the basis for a conceptually unprecedented and general approach towards *trans*-type B PPAPs. A strict realization of this concept would allow for a variety of substitution patterns without changing the entire synthetic strategy and offers the chance of a future bioactivity-directed synthesis of defined PPAP libraries. Furthermore, a special emphasis was placed on the practicability of the synthesis. Using a combination of well-established

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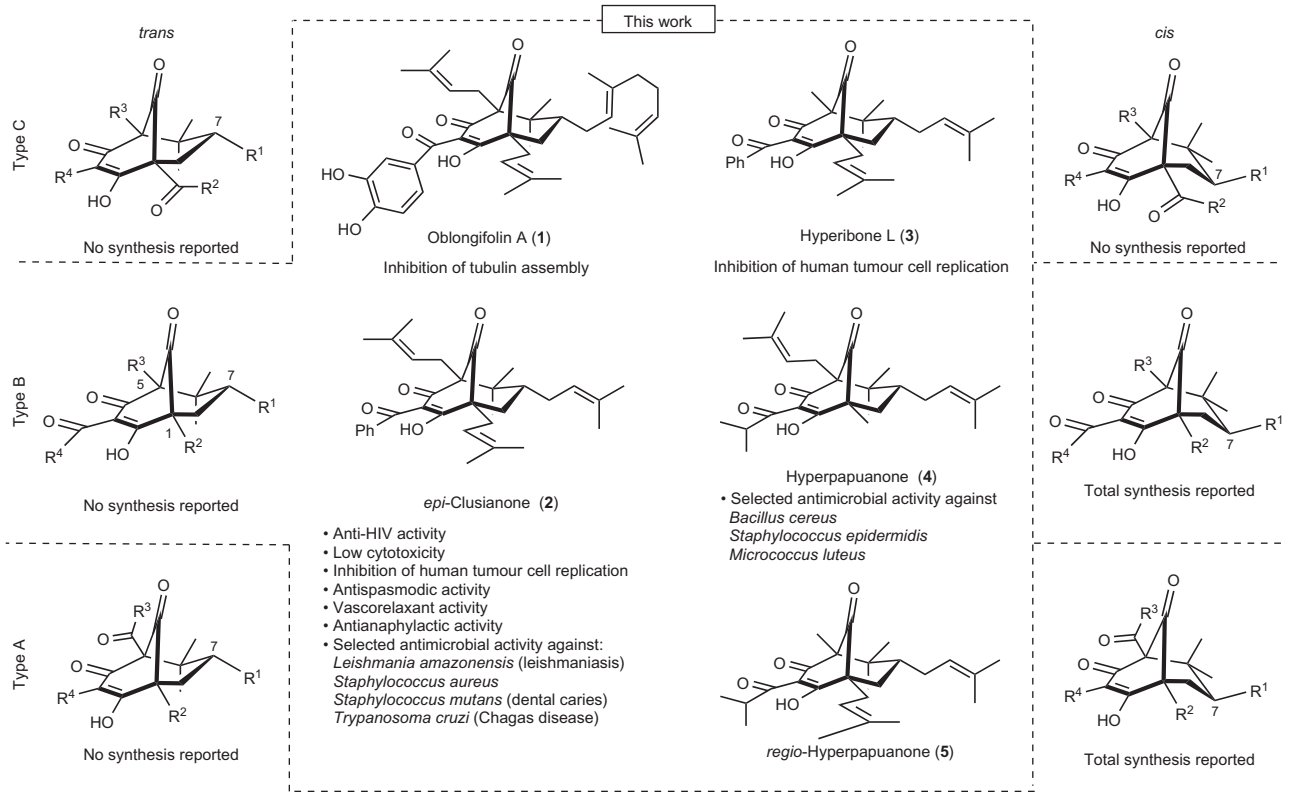

Figure 1 | Classification of PPAPs and total syntheses accomplished. Total syntheses of *cis*-type A and B PPAPs like, for example, garsubellin A (refs 16,17), nemoroson[20,23], *ent*-hyperforin[22], clusianone[18–21,24], plukentione[25] and hyperibone K (ref. 26) have been achieved. HIV = human immunodeficiency virus.

easy-to-operate methodologies and a minimization of protecting group operations, only a small number of synthetic transformations may be necessary, which thus increases both the practicability and the efficiency of the total synthesis. A brief retrosynthetic analysis is sketched in Fig. 2. With regard to the framework construction, the Dieckmann reaction of a densely substituted cyclohexanone **III** and a tandem Michael addition–Knoevenagel condensation to give a cyclohexenone **IV** are key steps that would allow quick access to the bicyclo[3.3.1]nonatrione core **II**. Neither transformation had been used for the construction of strained bicyclic ring systems, so they needed to be elaborated within this synthetic context. The iterative framework decorations via nucleophilic substitutions using alkylating, allylating or acylating conditions allow for a regioselective generation of the correct substitution pattern in which the C7 stereocentre orchestrates the trajectory of the incoming electrophiles to set up the stereogenic centres with the correct relative configuration (Fig. 2).

Synthesis. Acetylacetone (**6**) serves as a common starting material and was allylated in the first step using sodium hydride (NaH) and the corresponding allylating agent R^1–X (Fig. 3). This early stage of the synthesis represents our first diversification point (Fig. 3) and paves the way for the total synthesis of oblongifolin A (**1**), which possesses a geranyl side chain, and the total synthesis of the C7-prenylated compounds **2**–**5**. We subjected the corresponding allylation products directly to a deacylating aldol-type α-methylenation using potassium carbonate (K_2CO_3) in an aqueous formalin solution[27]. The α,β-unsaturated ketones **7** and **8** were obtained in good yields starting from **6** and were employed in a subsequent tandem Michael addition–Knoevenagel condensation to give the cyclohexenone cores **9** and **10** in 86% and 89% yield, respectively. Both α-methylenation and ring-forming condensation are framework-constructing operations and were performed under identical conditions independent of the structure of the starting material. A regioselective 1,2-addition[28] of methyllithium to the diesters **9** and **10** gave rise to the corresponding methyl ketones,

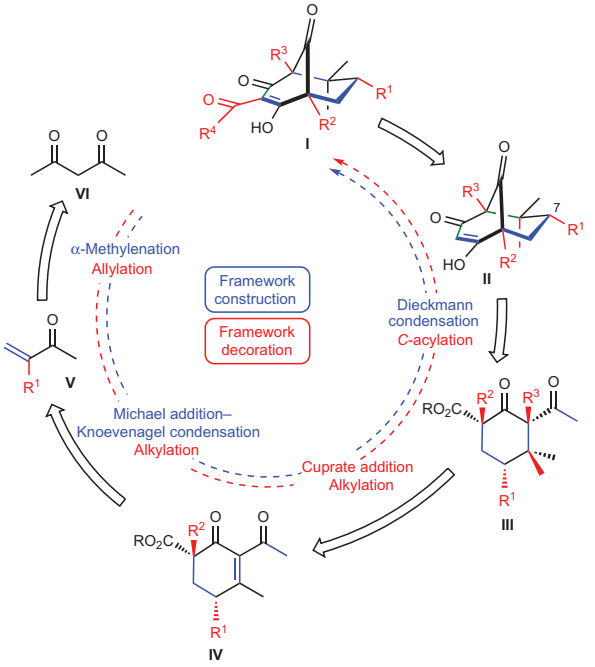

Figure 2 | Retrosynthetic analysis. As the *trans*-type B PPAPs differ mainly in the arrangement of the substituents R^1 to R^4, the retrosynthetic approach was designed to separate the steps that build the core structure (framework construction) from those that introduce the substituents (framework decoration).

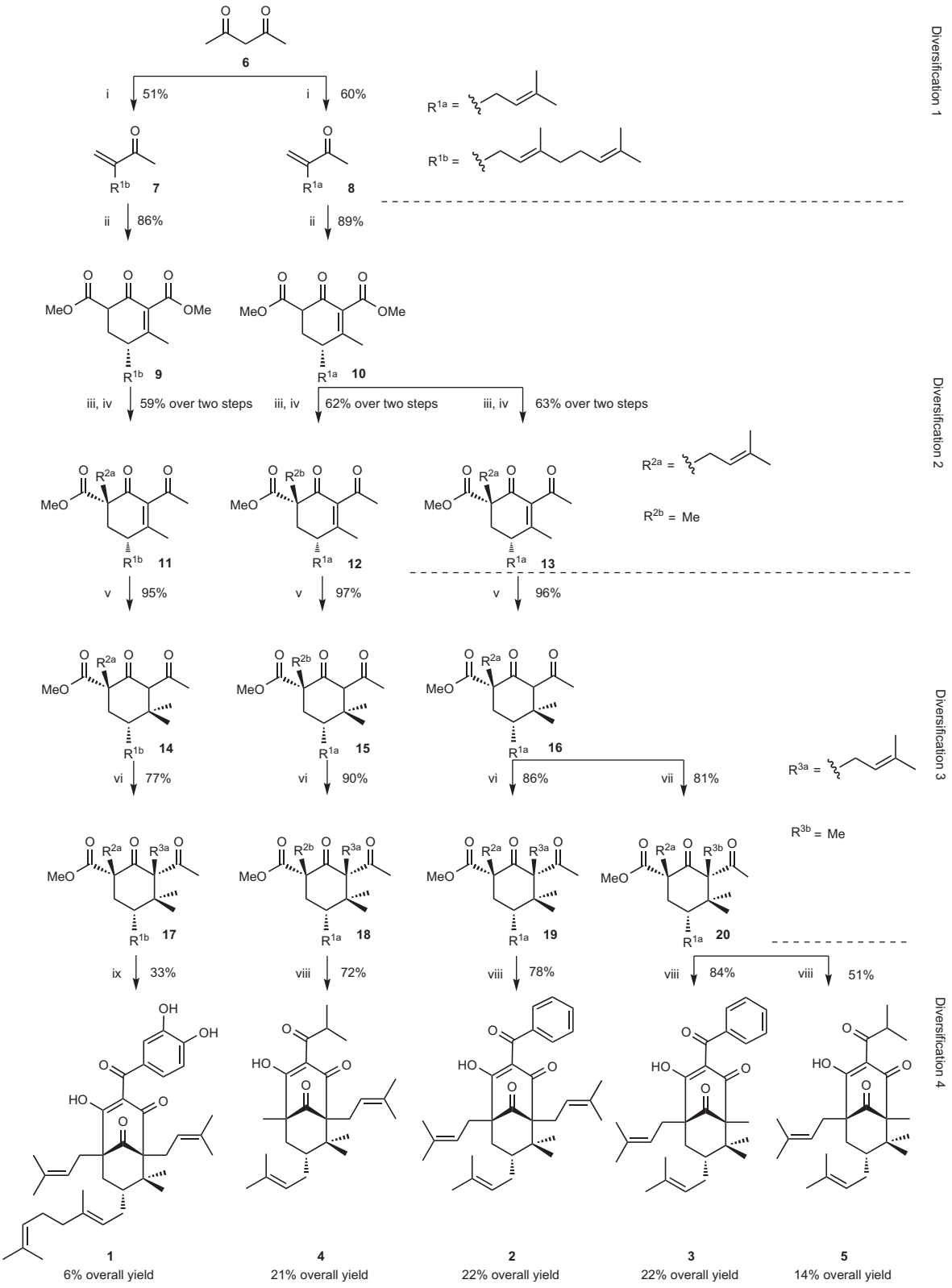

Figure 3 | Total synthesis of oblongifolin A (1), hyperpapuanone (4), *epi*-clusianone (2), hyperibone L (3) and *regio*-hyperpapuanone (5). i, NaH (1.1 equiv.), R^1X (1.5 equiv.), ethanol, 0 °C to room temperature (r.t.), 15 h, then K_2CO_3, formaldehyde, r.t., 5 h; ii, methylmagnesium chloride (2.0 equiv.), dimethyl 1,3-acetonedicarboxylate (1.0 equiv.), methanol, 0 to 60 °C, 15 h; iii, NaH (1.1 equiv.), methyllithium (2.3 equiv.), THF, 0 °C, 5 h; iv, NaH (1.1 equiv.), 18-crown-6 (0.1 equiv.), R^2X (1.5–2.5 equiv.), THF, 0 °C to r.t., 15 h; v, lithium chloride (2.02 equiv.), CuI (2.0 equiv.), methylmagnesium bromide (2.0 equiv.), Me_3SiCl (2.0 equiv.), THF, −78 °C, 5 h; vi, KO-*t*-amylate (2.0 equiv.), 1,3-dimesitylimidazolin-2-ylidene hexafluorophosphate (0.1 equiv.), $Bu_4N[Fe(CO)_3(NO)]$ (0.1 equiv.), 2-methyl-3-butene-2-yl methylcarbonate (2.0 equiv.), THF/methyl-*t*-butyl ether, 0 to 80 °C, 20 h; vii, KH (1.1 equiv.), 18-crown-6 (0.1 equiv.), MeI (2.0 equiv.), dimethoxyethane, 0 °C to r.t., 15 h; viii, KO-*t*-Bu (2.0 equiv.), R^4–C(=O)CN (3.3 equiv.), THF, 0 to 35 °C, 24 h; ix, same as viii, but 0 °C to r.t. and additional basic work-up with K_2CO_3, methanol.

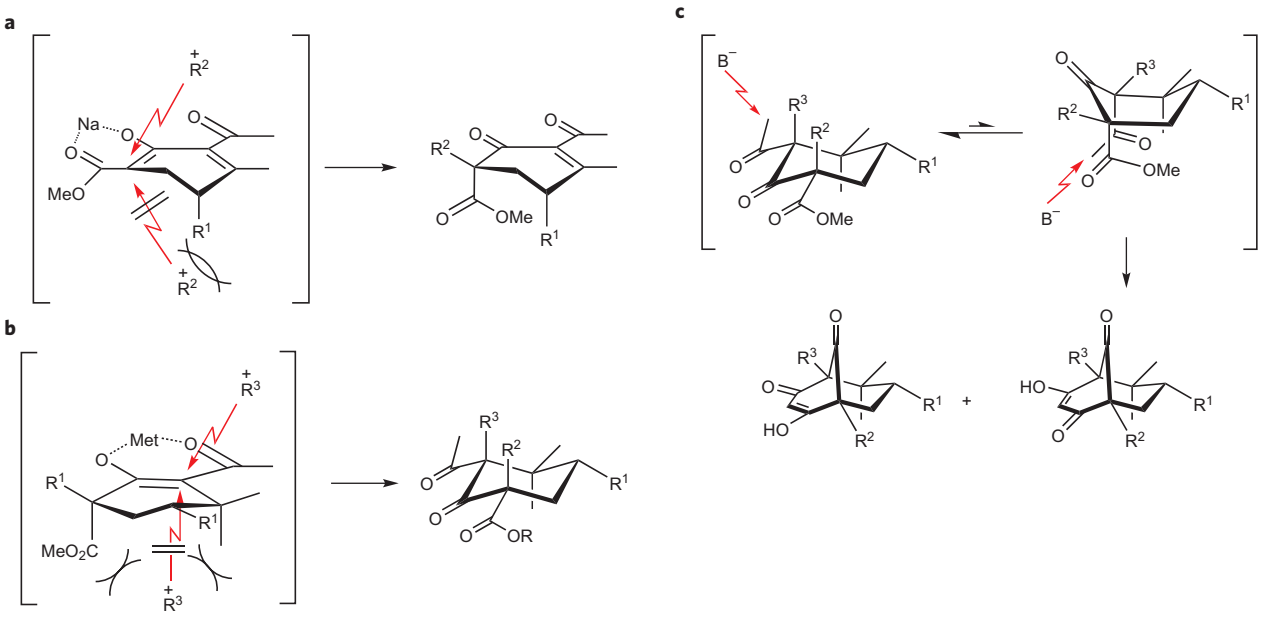

Figure 4 | Stereochemical rationale for the allylations and Dieckmann condensation. a, The stereoselective course of the allylation of cyclohexenones **9** and **10** is directed mainly by the axially oriented substituent R^1, which shields the bottom face of the almost planar enolate. **b**, For the allylation of cyclohexanones **14–16** the trajectory of the incoming electrophile is directed by the axially oriented methyl and carboxylate groups. **c**, The resulting cyclohexenones **17–20** have to flip from a chair-like to a boat-like confirmation for the Dieckmann condensation to take place. Red arrows indicate the potential trajectories for approach of electrophiles or bases rather than electron movement. Where there are two possibilities, curved lines represent steric repulsion that leads to one trajectory being favoured.

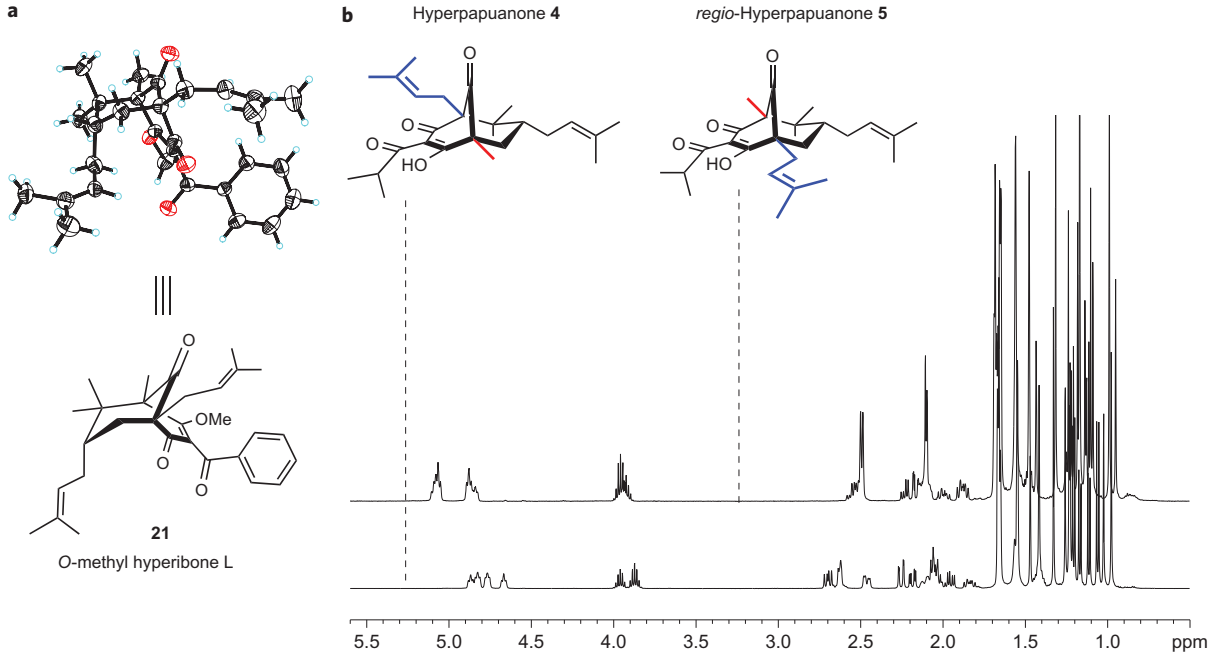

Figure 5 | Structural confirmation of hyperpapuanone (4). a, X-ray structure of *O*-methyl hyperibone L (**21**). **b**, ^{1}H NMR data for hyperpapuanone (**4**) and *regio*-hyperpapuanone (**5**). Hyperibone L (**3**) and *regio*-hyperpapuanone (**5**) differ only in the acyl group. The structural confirmation of hyperibone L (**3**) by X-ray crystallography of its corresponding *O*-methyl ether **21** confirms indirectly the structure of hyperpapuanone (**4**). The correct three-dimensional assembly of three of the four substituents found both in **5** and **3** plus a direct comparison of the ^{1}H NMR spectra of hyperpapuanone **4** and its regioisomer **5** with the reported spectra of the isolated natural products confirm the structure originally proposed[15].

which represent the starting materials for diversification 2 (Fig. 3). α-Allylation or methylation led to cyclohexenones **11–13** in good overall yields with a high level of control of the relative stereochemistry in favour of the desired *trans*-diastereoisomers. The high level of stereoinduction can be rationalized by assuming a pseudo-axial orientation of the substituent R^1 within the deprotonated cyclohexenone (Fig. 4a). With the functionalized cyclohexenones **11–13** in hand, the addition of methyl copper in the presence of lithium chloride and trimethylsilyl chloride (Me_3SiCl) allowed a 1,4-methylation[29] to yield the corresponding cyclohexanones **14–16** in 95–97% yield, which then were subjected to α-methylation using NaH and methyl iodide (MeI). Fortunately, the new C–C bond was formed with a high preference for the desired diastereoisomer in which both exocyclic carbonyl groups are

oriented in a *cis*-fashion towards each other (Fig. 4b). Unfortunately, using standard allylating agents instead of MeI led to an undesired *O*-allylation. The desired *C*-allylation product was accessible only via an Fe-catalysed allylic substitution developed recently by our group as a methodological spin-off project[30–32]. Fortunately, by employing this methodology the desired products **17**–**19** were obtained in good yields and acceptable diastereoselectivities. With these materials available we approached the Dieckmann condensation to the strained central bicyclo[3.3.1]nonatrione core. To achieve the desired C–C bond formation, the cyclohexanone ring has to flip from the thermodynamically more stable chair-like into the more reactive boat-like conformation, which orientates the reactive centres in close proximity towards each other (Fig. 4c). This transformation was achieved using potassium *tert*-butoxide (KO-*t*-Bu) in tetrahydrofuran (THF) under mild conditions. Trapping of the intermediate enolate using acyl cyanides led to the formation of the *C*-acylated natural products **2**–**5** as a mixture of tautomers in good isolated and overall yields (Fig. 3). Only for the total synthesis of oblongifolin A **1** was an additional deprotection step necessary. Subjecting the crude aryl *bis*-acetate to a basic work-up led to the formation of the desired natural product **1**. Double-bond isomerization or retro-Dieckmann-type ring openings/deacylations were not observed.

Structural confirmation of hyperpapuanone (4). Fortunately, we were able to obtain, by X-ray crystallography, the structure of hyperibone L (**3**) in its *O*-methylated form (Fig. 5), which proved that the C7 stereocentre had the correct relative configuration. As hyperibone L (**3**) and *regio*-hyperpapuanone (**5**) differ only in the acyl group R^4, X-ray crystallography might also serve as proof for the structure of **5**. A ^{1}H NMR spectroscopy comparison (Fig. 5) of **4** and **5** with the reported data[15] supports that the structure proposed originally for **4** is correct.

Summary

Herein we report a short, high-yielding synthetic approach towards *trans*-type B PPAPs. The concept of a strict separation between framework construction and framework decoration proved to be the key for the successful synthesis of four natural and one non-natural product, which differ in their substituents R^1 to R^4. With this synthetic approach in hand, future work will concentrate on the elaboration of an enantioselective version, as well as an extension towards the total synthesis of *trans*-types A and C PPAPs. Hopefully, this work and the creation of a library of *trans*-type PPAP analogues will set the stage for in-depth studies of the structure–activity relationships.

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Author contributions

N.B. prepared the natural products **1**–**5**. K.M. was involved in model studies towards the synthesis of *O*-methyl hyperibone and crystallized this compound (see Supplementary Information). B.P. designed the study, analysed the data and wrote the paper. All the authors discussed the results and commented on the manuscript.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to B.P.