A Metathesis–Acylation Approach to the Bicyclic Core of Polycyclic Polyprenylated Acylphloroglucinols

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Abstract: An approach to a model compound for polycyclic polyprenylated acylphloroglucinols is developed using a ring-closing metathesis approach to give a substituted cyclooctene. This undergoes cyclization via an intramolecular acylation leading to a substituted bicyclo[3.3.1]nonan-9-one related to hyperforin, nemorosone, clusianone, garsubellin A and other members of the polyprenylated acylphloroglucinol.

Key words: bicyclic compounds, natural products, metathesis, alkene acylation, steric hindrance

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a class of polyketides which contains more than 210 members having interesting bicyclo[3.3.1]nonane, bicyclo[3.2.1]octane or tricyclic core structures, with several prenyl or geranyl substituents and one acyl group at various positions.[1] Prominent members of the PPAPs (Figure 1) are hyperforin (**1**), nemorosone (**2**), clusianone (**3**) and garsubellin A (**4**). Besides their challenging structural features, the PPAPs also show fascinating biological activities,[1,2] which are compelling reasons to develop total syntheses of these natural products.

Synthetic endeavors and total syntheses of PPAPs have been reviewed in several publications,[1,3] whilst some more recent total syntheses of PPAPs have also been described.[4] Furthermore methods to prepare the bicyclo[3.3.1]nonan-9-one core have been reviewed.[5]

Each synthetic approach toward the PPAPs and precursors with a substituted bicyclo[3.3.1] framework published to date starts from a six-membered-ring compound (substituted cyclohexanones, substituted phenols, resorcinols or phloroglucinols), and install a suitable three-carbon unit to complete the bicyclo[3.3.1]nonan-9-one core of the PPAP.

Our idea was to synthesize a suitably substituted cyclooctene derivative and to install the bridging carbonyl group across the cyclooctene ring. Herein, we report our initial results along these lines.

For convenience, and as a proof-of-principle that our strategy was feasible, we first focused our efforts on the simpler model structure **5**, which is structurally related to compounds **1**–**4**.

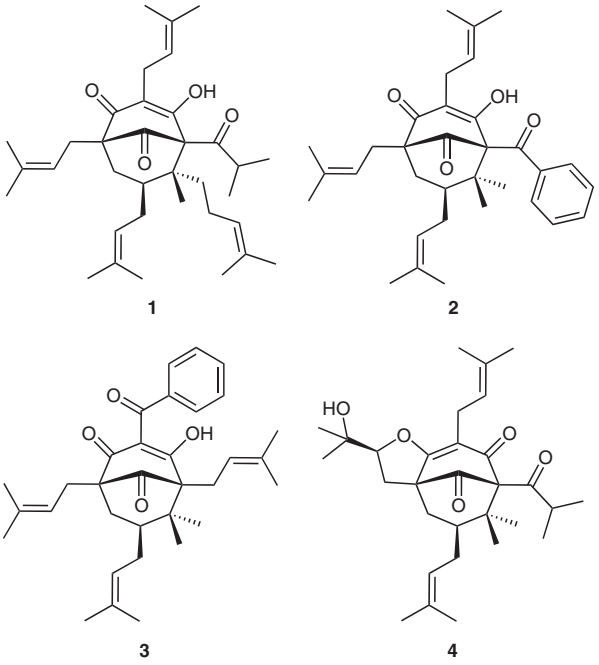
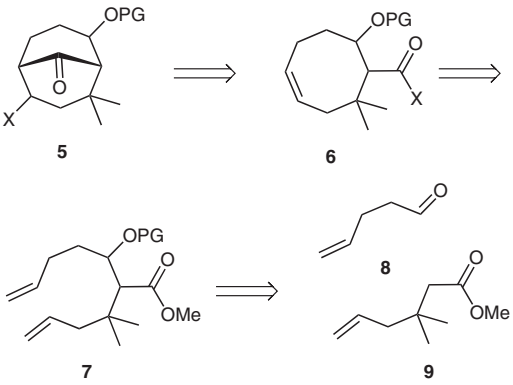


Figure 1 Structures of hyperforin (**1**), nemorosone (**2**), clusianone (**3**) and garsubellin A (**4**)

Retrosynthetic analysis (Scheme 1) of **5** via cyclooctene derivative **6** is straightforward. Compound **5** should be accessible through intramolecular acylation of **6**. The substituted cyclooctene **6** should be formed through ring-closing metathesis (RCM) from **7**, which could be synthe-



Scheme 1 Retrosynthetic analysis of model compound **5**; X = Cl (acid chloride) or OCOR (mixed acid anhydride); PG = protecting group

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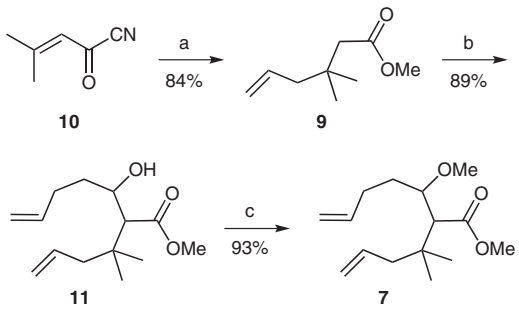
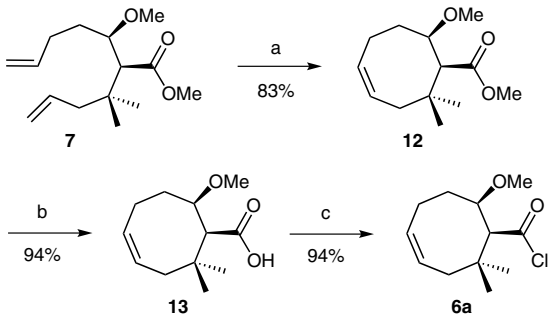
sized through aldol reaction of known compound **9** and commercially available 4-pentenal (**8**).

Methyl hexenoate **9** was synthesized in 84% yield according to the method of Santelli et al.,[6] which involved a titanium tetrachloride ($TiCl_4$) catalyzed Sakurai reaction with 4-methyl-2-oxo-3-pentenenitrile (**10**).[6c] Aldol addition of **9** to aldehyde **8**, following the procedure of Wei et al.,[7] gave diene **11** as a mixture of diastereomers (*syn*/*anti* = 3:1, in agreement with the results of Wei[7]), which were protected as methyl ether **7** using methyl triflate and Proton-sponge® as the base,[8] in 93% yield (Scheme 2). After methylation of the hydroxy group in **11**, the diastereomers were separated and all following reactions were performed with the *syn* diastereomer.



Scheme 2 Preparation of intermediate **7**. *Reagents and conditions*: (a) (i) $TiCl_4$, CH_2Cl_2, allyl trimethylsilane, –78 °C to –30 °C; (ii) MeOH, –30 °C to r.t.; (b) LDA, THF, –78 °C, **8**; (c) Proton-sponge®, MeOTf, CH_2Cl_2, r.t.

The next task was RCM of **7** to give **12**. There are several literature reports on the successful application of the RCM for the synthesis of eight-membered rings.[9] In our case, the use of the Grubbs II catalyst, together with triphenylphosphine oxide as an additive,[10] led to the formation of **12** in a very good yield (Scheme 3). Important for the success of the RCM is the presence of the quaternary carbon with the geminal dimethyl groups (Thorpe–Ingold effect[11]), since RCM reactions with similar compounds[12] under comparable conditions were sluggish and gave low yields.

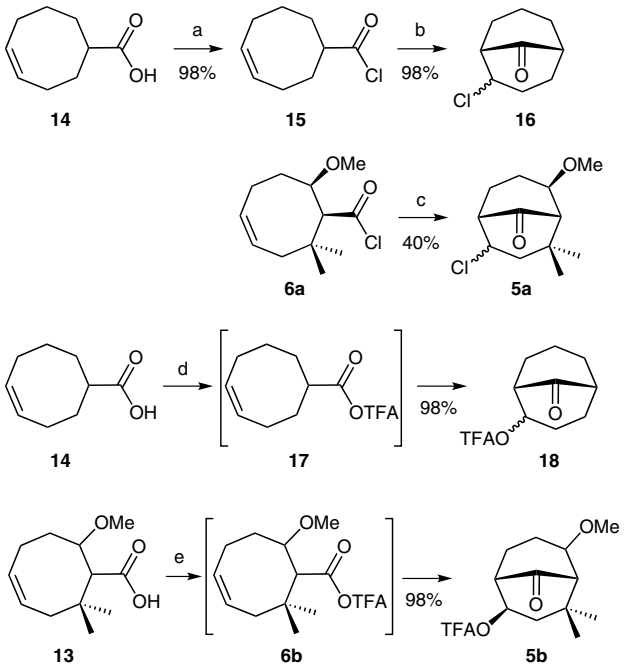


Scheme 3 RCM of **7** (*syn* isomer only) into cyclooctene **12** and conversion into acid chloride **6a**. *Reagents and conditions*: (a) Grubbs II (1.4 mol%), $Ph_3P{=}O$ (5 mol%), Et_2O, reflux; (b) H_2O, DME, LiOH (17 equiv), reflux; (c) $(COCl)_2$, CH_2Cl_2, r.t.

Whereas ring closure is accelerated via the Thorpe–Ingold effect, the subsequent hydrolysis of carboxylic acid ester **12** was retarded by the steric congestion exerted by the geminal dimethyl grouping. After trying different methods for the hydrolysis of sterically hindered esters,[13] the method of Snider et al.[13c] was found to work best, giving acid **13** in 94% yield, although the reaction time was rather long (ca. 4–5 days; Scheme 3). Crystallization from chloroform gave crystals of **13** suitable for X-ray analysis.[14] Transformation of the acid **13** into acid chloride **6a** was straightforward using oxalyl chloride.[15]

The next part of our strategy was the transannular cyclization reaction of the acid chloride **6a** across the eight-membered ring. Such Friedel–Crafts-like acylation reactions of double bonds are well known,[16] but are rarely applied to natural product syntheses due to competing side reactions, for example, polymerization of the olefin. Intramolecular acylations for ring-closing reactions have also been published,[16] and even the transformation of cyclooct-4-ene carboxylic acid **14** into cyclooct-4-ene carboxylic acid chloride **15** and subsequent cyclization to give 2-chlorobicyclo[3.3.1]nonan-9-one (**16**) have been reported.[17] Hence, we began our acylation studies (Scheme 4) by repeating the conversion of acid chloride **15** into bicyclic **16**. Whereas Kretschmar[17a,b] reported a reaction time of 72 hours for the uncatalyzed cyclization in 1,2-dichloroethane at reflux temperature, and Kraus[17d] obtained similar results after reaction for 12 hours, we found that the cyclization was complete after seven to nine days. The product was obtained in quantitative yield as a mixture of diastereomers (*endo*/*exo* = 3:2, in agreement with Kraus[17d]). When we used aluminum chloride ($AlCl_3$) or other Lewis acids as the catalyst under similar conditions, we obtained inferior results.[18] Therefore, the cyclization of acid chloride **6a** was carried out in 1,2-dichloroethane as solvent at reflux temperature. The reaction was complete after only 21 hours to give **5a** as a mixture of diastereomers (*exo*/*endo* = 18:1) in 40% yield after chromatography,[19] together with 9% of the elimination product (structure not shown). Similar to the results obtained in the RCM reactions (Scheme 3), this increase in the rate of cyclization can be interpreted as a result of the Thorpe–Ingold effect of the geminal dimethyl arrangement.

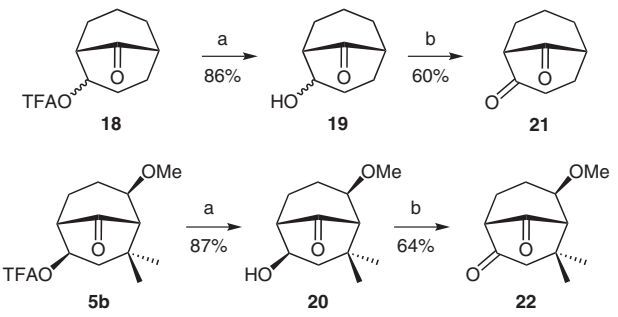
Since increasing the reactivity of the acid chloride **6a** was unsuccessful,[18] we reasoned that mixed anhydride **6b** might also add across the eight-membered ring to the double bond, resulting in the construction of the carbonyl bridge and introduction of an oxygen next to a bridgehead atom (similar to the arrangement in PPAPs). Mixed trifluoroacetic anhydrides[20] have been described in the literature and are easily prepared from carboxylic acids and trifluoroacetic anhydride (TFAA).[20b] Thus, we attempted to synthesize the mixed anhydride **17** according to the literature,[20b] and found that cyclization into 2-trifluoroacetoxybicyclo[3.3.1]nonan-9-one (**18**) occurred almost instantaneously at room temperature (Scheme 4). The product was obtained as a mixture of diastereomers



Scheme 4 Transannular cyclization of cyclooctenecarboxylic acid derivatives. *Reagents and conditions*: (a) $(COCl)_2$, neat, r.t.; (b) DCE, reflux; (c) DCE, reflux; (d) TFAA, $CHCl_3$, r.t.; (e) TFAA, $CHCl_3$ (free of stabilizers), 0 °C.

(*exo*/*endo* = 3:4). Due to the observed Thorpe–Ingold effect[11] during cyclization of **6a**, cyclization of acid **13** via mixed anhydride **6b** was expected to be much faster and therefore was performed at 0 °C. Product **5b** formed smoothly in almost quantitative yield as the *exo* diastereomer only. To complete the synthesis of bicyclic model compounds related to PPAPs, we cleaved the trifluoroacetoxy group in compounds **18** and **5b** with saturated aqueous $NaHCO_3$ solution at room temperature in 86% and 87% yields, respectively. Subsequent oxidation of resulting alcohols **19** and **20** with Dess–Martin periodinane (DMP) gave the diketones **21** (60%) and **22** (64%) (Scheme 5). Compared to PPAPs, the last introduced carbonyl group is 'on the wrong side' of the bicyclic framework. Studies toward modification of the described synthesis to establish this carbonyl group 'on the right side' of the molecule, and the use of compound **22** as an intermediate for the synthesis of PPAP analogues, are currently underway in our group. Selected experimental procedures are given in the Supporting Information.

In summary, we have developed a short and efficient synthesis of a substituted bicyclo[3.3.1]nonan-9-one related to the core structure of PPAPs. The method is based on a ring-closing metathesis to give a cyclooctene derivative and a simple transannular cyclization of a mixed trifluoroacetic anhydride. Adjusting this strategy to enable the syntheses of PPAPs in both racemic and enantiomerically pure form is currently underway, and the results will be published in due course.



Scheme 5 Synthesis of bicyclo[3.3.1]nonandiones. *Reagents and conditions*: (a) sat. aq $NaHCO_3$, r.t.; (b) DMP, CH_2Cl_2, r.t.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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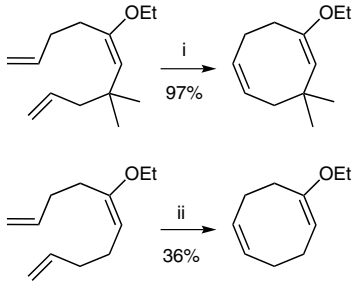
(12) (a) In a related RCM reaction with the Grubbs II catalyst (Scheme 6), we also observed acceleration exerted by a geminal dimethyl arrangement (Feidt, E. unpublished results).



Scheme 6 *Reagents and conditions:* (i) Grubbs II (1.4 mol%), Ph_3P=O (5 mol%), Et_2O, reflux, 30 min. (ii) Grubbs II (1.4 mol%), Ph_3P=O (5 mol%), Et_2O, reflux, 2 d.

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(14) (a) Crystal structure representation of **13** (Figure 2): Crystals suitable for single crystal X-ray analysis were obtained from $CHCl_3$. The data were collected at 133 K on a Bruker AXS X8Apex CCD diffractometer operating with graphite-monochromated MoKα radiation. Frames of 0.5° oscillation were exposed; deriving data in the θ range of 2–37° with a completeness of ~99%. Unit cell: triclinic, *P*-1, a = 7.1553(4) Å, b = 7.4403(4) Å, c = 11.4373(7) Å, α = 83.096(2)°, β = 77.747(2)°, γ = 74.477(3)°, V = 572.02(6) Å^3. Structure solution and full least-squares refinement with anisotropic thermal parameters of all non-hydrogen atoms and free refinement of the hydrogens were performed using SHELX.[14b] The final refinement resulted in: $R1$ = 0.036. Crystallographic data for this structure have

been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Copies of the data can be obtained free of charge on quoting the deposition number CCDC 990861 (www.ccdc.cam.ac.uk/data_request/cif). (b) Sheldrick, G. M. *Acta Crystallogr. A* **2008**, *64*, 112.

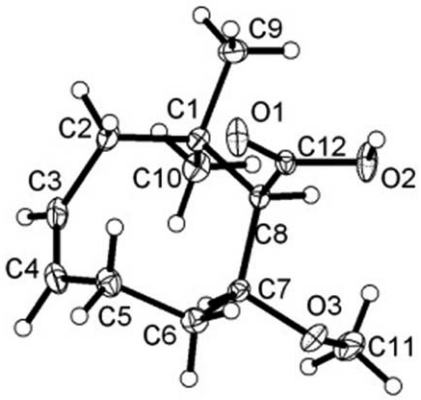

Figure 2 Structure representation for **13** with ellipsoids at 50% probability

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(18) The elimination product, bicyclo[3.3.1]non-2-en-9-one, became the main product and the total yield decreased. Since acid bromides and acid iodides are more reactive than acid chlorides, we also added tetrabutylammonium bromide or tetrabutylammonium iodide to the reaction mixture to form the acid bromides and acid iodides in situ, but this also led to decreased yields of the corresponding cyclization products and larger amounts of elimination products.

(19) Interestingly, the ^{1}H and ^{13}C NMR spectra of **5a** before and after chromatographic purification were identical; it seems that either **5a** decomposes to some extent during chromatography, or is partially absorbed irreversibly.

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