Natural Products

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Total Synthesis of the Marine Antibiotic Pestalone and its Surprisingly Facile Conversion into Pestalalactone and Pestalachloride A**

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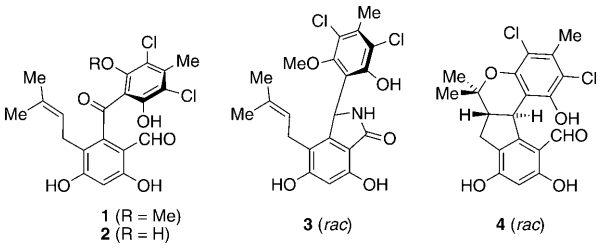
In 2001, Fenical and co-workers reported the isolation and structure elucidation of pestalone (**1**), a chlorinated, highly functionalized benzophenone produced by a marine fungus of the genus *Pestalotia* in response to bacterial challenge.[1] Besides a moderate in vitro cytotoxicity against various tumor cell lines (mean $GI_{50} = 6.0\ \mu M$), pestalone (**1**) was reported to exhibit highly potent antibiotic activity against methicillin-resistant *Staphylococcus aureus* (MIC = 37 ng mL^{-1}) and vancomycin-resistant *Enterococcus faecium* (MIC = 78 ng mL^{-1}). This prompted Fenical to emphasize that "*the potency of this agent toward drug-resistant pathogens suggests that pestalone should be evaluated in more advanced, whole animal models of infectious disease.*"[1] Consequently, pestalone (**1**) is considered a particularly promising molecule with antibiotic properties.[2]

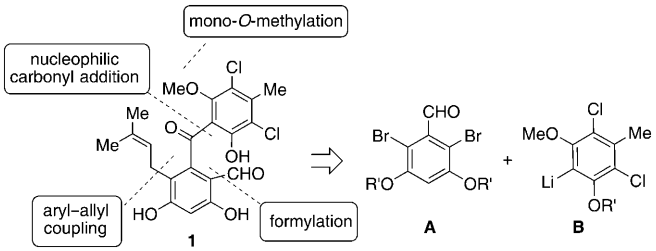
Recently, Che and co-workers identified a few strongly antifungal metabolites (e.g. **3** and **4**) from the plant endophytic fungus *Pestalotiopsis adusta* which they named the pestalachlorides.[3] These compounds are structurally closely related to **1** and, interestingly, were obtained as racemates indicating a non-enzymatic biosynthesis or a particularly facile mode of racemization.[3]

Owing to their obvious biological potential, their limited availability from natural sources, and their challenging chemical structures,[4] pestalone (**1**) and its congeners are interesting target molecules for chemical synthesis. Our first study in 2003 resulted in the synthesis of deformylpestalone,[5] and little later a total synthesis of **1** (and its demethylated derivative **2**)[6] was communicated by Nishiyama et al.[7] Remarkably, no further biological studies have been reported since then.

We describe herein a highly efficient and practicable synthesis of **1** which makes it possible for the first time to prepare substantial amounts of this natural product for further chemical and biological studies. Moreover, we report some surprising transformations (including the one-step transformation of **1** to *rac*-**3**) shedding light on the possible "biosynthetic" relationship of **1** with the pestalachlorides.



The strategy behind our synthesis is summarized in Scheme 1. As a key consideration, we intended to assemble the benzophenone scaffold from a 2,6-dibromobenzaldehyde building block of type **A** by reaction with a lithiated arene of type **B** and subsequent oxidation. The bromo functionalities should then be used for the introduction of the prenyl and the formyl side chains at a later stage in the synthesis. The selective generation of the mono-*O*-methylated structure was considered to be possible by appropriate protecting-group manipulations.[5,7]



Scheme 1. Retrosynthetic analysis for pestalone (**1**).

To probe the general feasibility of the concept, we first elaborated a synthesis of per-*O*-methyl-pestalone **12** (Scheme 2). Starting from commercial 5-methylresorcinol (**5**), we prepared building block **6** through successive halogenation[5] and double *O*-methylation. As the second building block, the aldehyde **8** was prepared by bromination of commercially available **7**. When **6** was treated with *n*BuLi in 2-Me-THF[8] and the resulting lithiated species (of type **B**) was reacted with **8**, the desired coupling product *rac*-**9** was obtained in high yield. Alcohol *rac*-**9** was then oxidized under Dess–Martin conditions[9] to give the pure crystalline benzophenone **10**. The prenyl side chain was introduced by bromine–lithium exchange using phenyllithium,[10] followed by addition of CuCN·2 LiCl and coupling of the resulting cuprate intermediate with prenyl bromide. The formylation of

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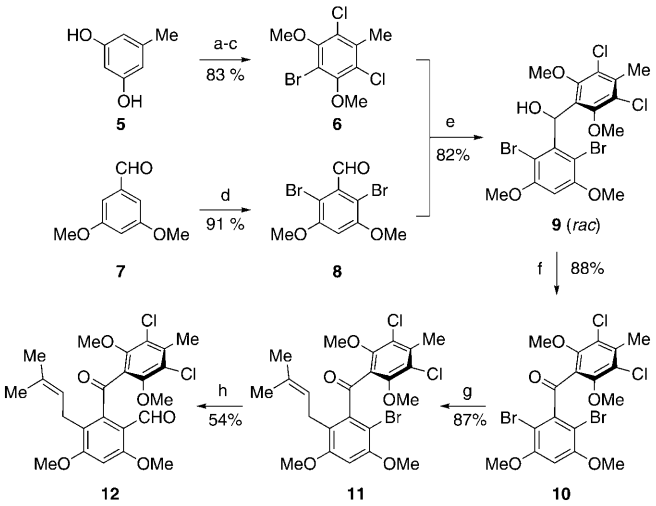
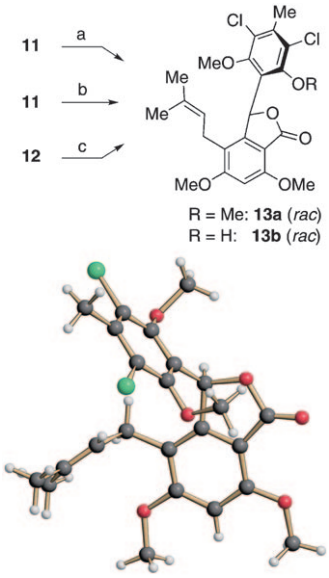


Scheme 2. Synthesis of per-*O*-methyl-pestalone (**12**). Conditions: a) SO_2Cl_2, $CHCl_3/CH_3CN$ (5:1), 3 h, RT; b) Br_2, CH_3CN, RT, 6 h; c) NaH, Me_2SO_4, DMF, RT, 12 h; d) NBS, CH_3CN, RT, 6 h; e) *n*BuLi, 2-Me-THF, −35 °C, 30 min, then addition of **8**, −35 °C→RT, 18 h; f) DMP, CH_2Cl_2, RT, 15 h; g) PhLi, THF, −78 °C, 30 min, then CuCN·2 LiCl, prenyl bromide; h) *n*BuLi, $MgBr_2$·OEt_2, THF, −78 °C, 30 min, then HCO_2Et, −78 °C→RT. 2-Me-THF = 2-methyltetrahydrofuran, DMP = Dess–Martin periodinane, NBS = *N*-bromosuccinimide.

11 proved to be difficult (see below) but was finally achieved in satisfying yield by reaction of an organomagnesium intermediate (obtained from **11** with *n*BuLi and subsequent transmetalation with $MgBr_2$) with ethyl formate. The structure of **12** was confirmed by X-ray crystal structure analysis (Figure 1), which also revealed the strongly twisted conformation of the benzophenone core. This strong twist and the resulting shielding of the keto function by the *ortho*-aryl substituents may also explain its remarkable resistance towards the organolithium reagents used in the transformations of **10** and **11**.

As a noteworthy fact, we discovered a strong tendency of the formylated product, that is, the pestalone derivative **12**, to undergo isomerization (disproportionation) leading to lactones (arylphthalides) of type *rac*-**13** which are related to pestalachloride A (Scheme 3). Thus, during our initial attempts to achieve the formylation of **11** through reaction



Scheme 3. Top: Unexpected formation of lactones of type *rac*-**1**; bottom: structure of *rac*-**13a** in the crystal (C dark gray, H light gray, Cl green, O red).[19] Conditions: a) *n*BuLi, $MgBr_2$·OEt_2, THF, −78 °C, 30 min, then DMF, −78 °C→RT, formation of *rac*-**13a** detected by NMR; b) CO/H_2 (15 bar), 1.4 mol% $Pd(OAc)_2$, 4 mol% [cataCXium A], TMEDA, 100 °C, 20 h, 51% of *rac*-**13a**; c) LiSEt (4 equiv), DMF, 70 °C, 4 h, 37% *rac*-**13b**, 14% *rac*-**13a**. cataCXium A = di-1-adamantyl-*n*-butylphosphane, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

of the Grignard intermediate with DMF (instead of ethyl formate) or through Pd-catalyzed hydrocarbonylation according to Beller et al.,[11] the lactone *rac*-**13a** appeared as the main product. Also, treatment of **12** with LiSEt in DMF resulted in the formation of *rac*-**13a** and its monodemethylated derivative *rac*-**13b**.

This surprisingly facile lactone formation can be rationalized in terms of a Cannizzaro–Tishchenko-type reaction[12] (Scheme 4). We suppose that an intermediate of type **15** (either formed by nucleophilic addition to an aldehyde precursor of type **14** or as an intermediate during the reaction of a Grignard precursor with a formyl derivative) undergoes intramolecular hydride transfer. The resulting alkoxide (**16**) then readily cyclizes to the lactone **17**.

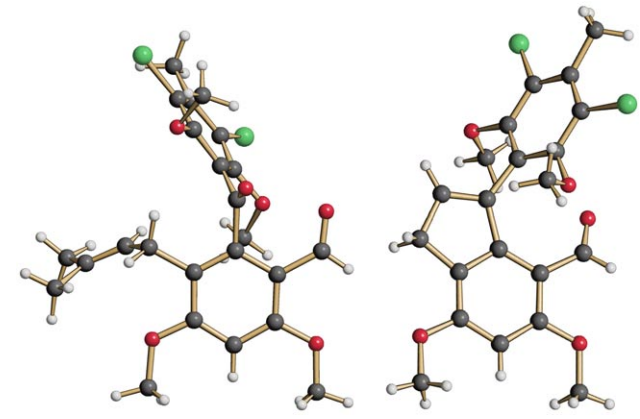
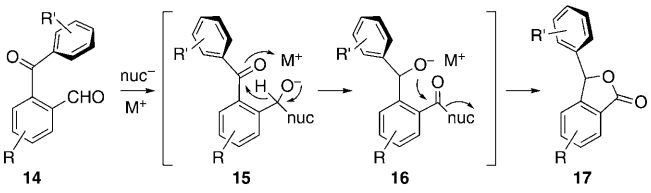
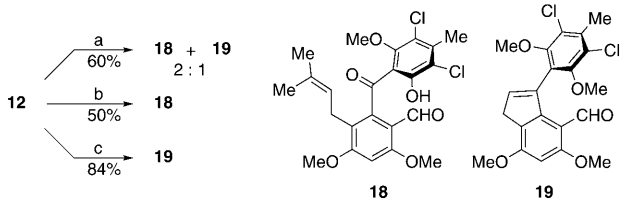


Figure 1. Structure of per-*O*-methyl-pestalone **12** (left) and the arylindene **19** (right) in the crystal. C dark gray, H light gray, Cl green, O red.[19]



Scheme 4. Nucleophile-induced conversion of *ortho*-formylbenzophenones **14** into arylphthalides **17** in a Cannizzaro–Tishchenko-type reaction.

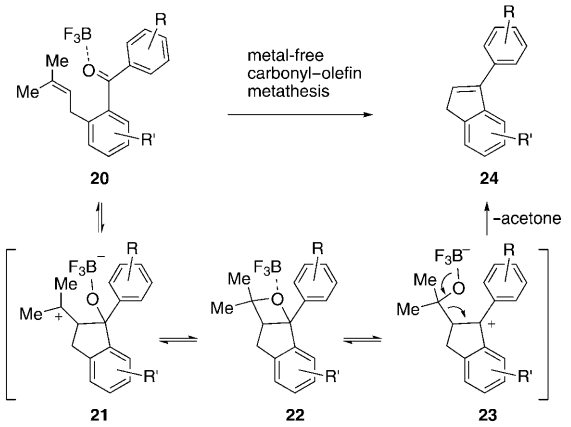
Having succeeded in synthesizing per-*O*-methyl-pestalone **12** (Scheme 2), we tried to remove the protecting groups (→**1**). However, while nucleophilic reagents such as LiSEt[13] could not be employed for the previously mentioned reasons (lactone formation), treatment of **12** with BBr_3 only led to a complex mixture (decomposition). With $BF_3{\cdot}SMe_2$[14] the mono-demethylated product **18** was obtained (Scheme 5),



Scheme 5. Mono-demethylation versus arylindane formation on treatment of per-*O*-methyl-pestalone (**12**) with BF_3. Conditions: a) $BF_3{\cdot}SMe_2$ (1.7 equiv), CH_2Cl_2/SMe_2 (1:2), 0 °C, 2 h, 40% **18**, 20% **19**; b) $BF_3{\cdot}SMe_2$ (6 equiv), CH_2Cl_2/SMe_2 (1:2), −30 °C, 75 min; c) $BF_3{\cdot}SMe_2$ (1.7 equiv), CH_2Cl_2, 0 °C, 45 min.

however, only if the reagent was used in excess at −30 °C in CH_2Cl_2/SMe_2 (1:2). Interestingly, treatment of **12** with a smaller excess of the same reagent at 0 °C in CH_2Cl_2 afforded the arylindene **19** in high yield, the structure of which was again secured by means of X-ray crystallography (Figure 1).

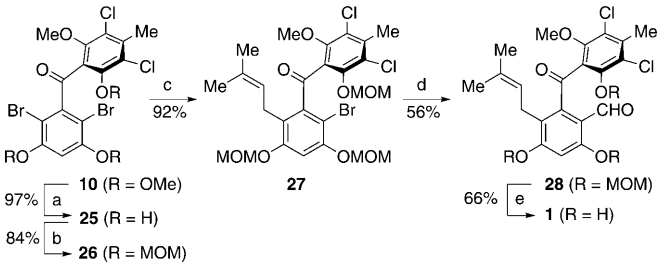
The unexpected and facile formation of the indene derivative **19** from **12** actually represents a rare and (to the best of our knowledge) by far the most efficient example of a metal-free carbonyl–olefin metathesis reaction.[15] A plausible mechanism is given in Scheme 6. It involves the cyclization of



Scheme 6. Possible mechanism for the BF_3-catalyzed, metal-free carbonyl–olefin metathesis of *ortho*-prenyl benzophenones.

20 to form the tertiary carbenium ion **21**, which isomerizes to the benzylic cation **23** via an oxetane intermediate **22**. Finally, the product **24** is liberated together with acetone in an entropically favored fragmentation step.

Considering the pitfalls associated with the use of either nucleophilic or Lewis acidic reagents in the end game, the total synthesis of pestalone was successfully completed after a protecting-group change at the stage of the dibromobenzophenone **10** (Schemes 2 and 7). First, treatment of **10** with a slight excess of BBr_3 gave rise to the triply demethylated derivative **25** in high yield.[16] After reprotection of all three



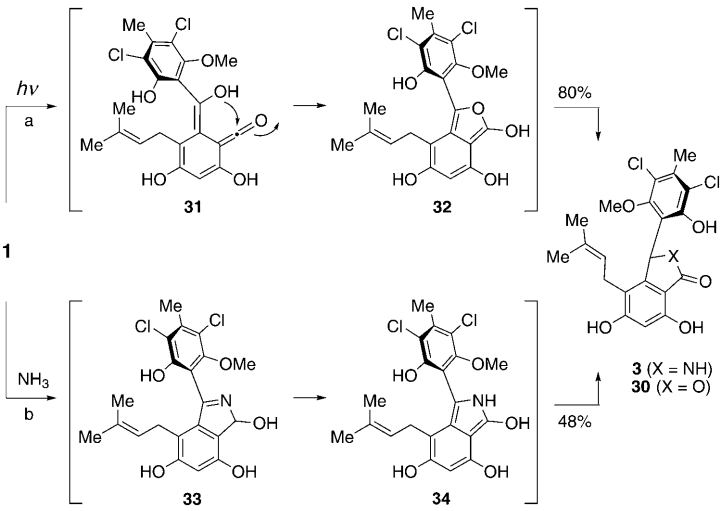
Scheme 7. Completion of the total synthesis of pestalone (**1**). Conditions: a) BBr_3 (5.5 equiv), CH_2Cl_2, RT, 3 h; b) dimethoxymethane, AcCl, cat. $ZnBr_2$, CH_2Cl_2, DIPEA, RT 3 h; c) PhLi, THF, −78 °C, 30 min, then CuCN·2 LiCl, prenyl bromide; d) *n*BuLi, LiCl (3 equiv), THF, −78 °C, 30 min, then HCO_2Et, −78 °C→RT; e) HCl (6 M), 1,4-dioxane, 63 °C, 100 min. DIPEA = diisopropylethylamine, MOM = methoxymethyl.

phenolic functions as MOM ethers,[17] both the prenylation (of **26**) and the subsequent formylation (of **27**) proceeded smoothly under the optimized conditions. Fortunately, the MOM protecting groups were cleaved from **28** in good yield (with 6 M aqueous HCl in dioxane) to give the natural product pestalone (**1**), as unambiguously proven by the analytical data.

This synthesis of **1** requires only 10 steps and proceeds with an overall yield of 16% starting from commercially available orcinol (**5**). Notably, most intermediates are crystalline solids and only the last three steps require chromatographic purification. Thus, the synthesis of **1** could be performed on a multigram scale enabling us to also investigate some aspects of the reactivity of this interesting molecule. When a solution of **1** in $[D_6]$DMSO was irradiated with UV light (350 nm) a new product was formed in a clean (albeit rather slow) process. To our surprise, this photoproduct turned out to be lactone *rac*-**30**, which could be easily assigned by NMR in comparison to the Cannizzaro–Tishchenko product *rac*-**13b**. A plausible mechanism for this remarkable transformation (Scheme 8) involves cyclization of the primary photo-enol **31** to give the isobenzofurane **32**. Finally, tautomerization leads to the isolated product *rac*-**30**, which we named pestalalactone.

Intrigued by the almost voluntary formation of **30** and its close structural relationship to pestalachloride A (**3**), we also probed the possibility of converting pestalone (**1**) directly into **3**. And indeed, when **1** was treated with NH_3 in aqueous NH_4Cl (pH 8.0), pestalachloride A (**3**) was formed as the only major product (Scheme 8). We assume that cyclic iminohemiaminal (**33**) forms initially,[18] which then tautomerizes via the isoindol **34** to the product (*rac*-**3**).

In conclusion, we have elaborated a short and efficient total synthesis of pestalone (**1**), its antifungal relative pestalachloride A (**3**), and some structural analogues, which are now available for detailed biological studies. Moreover,



Scheme 8. Conversion of pestalone (**1**) into pestalalactone (**30**) or pestalachloride A (**3**). Conditions: a) *hν* (350 nm), DMSO, RT, 6 d; b) NH_3/NH_4Cl, H_2O, 1,4-dioxane, RT, 80 min.

our work has revealed some unique reactivities of pestalone-type compounds (such as nucleophile- or photoinduced Cannizzaro–Tishchenko-type reactions and metal-free carbonyl–olefin metathesis), which exploit the intense interaction of functional substituents at the twisted benzophenone core of **1** (or **12**). The surprisingly facile conversion of **1** into *rac*-**3** under almost neutral conditions might explain the formation of the racemic natural product *rac*-**3** in nature (under non-enzymatic conditions) and might also be of relevance for understanding the molecular mechanism of action of **1** as an antibiotic compound.

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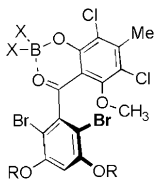

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[19] CCDC 781109 (*rac*-**13a**), CCDC 781110 (**12**), and CCDC 781111 (**19**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

