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Total Synthesis of Peniphenones A–D via Biomimetic Reactions of a Common *o*-Quinone Methide Intermediate

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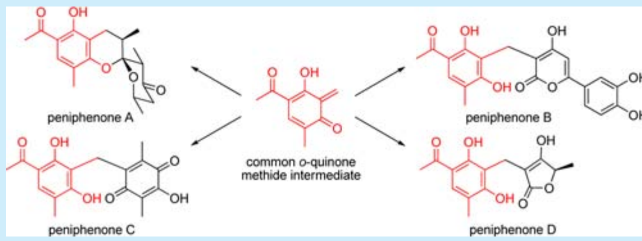
Ⓢ *Supporting Information*

ABSTRACT: The total synthesis of peniphenones A–D has been achieved via Michael reactions between appropriate nucleophiles and a common *o*-quinone methide intermediate. This strategy, which was based on a biosynthetic hypothesis, minimized the use of protecting groups and thus facilitated concise syntheses of the natural products. The most complex target, the benzannulated spiroketal peniphenone A, was synthesized enantioselectively in nine linear steps from commercially available starting materials.



o-Quinone methides are reactive intermediates that have found increasing utility in organic synthesis in recent years.[1] The proposed involvement of *o*-quinone methides in biosynthetic pathways makes their application in biomimetic natural product synthesis particularly attractive.[2] Peniphenones A–D (**1–4**) (Figure 1) are a family of aromatic polyketide natural products isolated from a mangrove fungus, *Penicillium dipodomyicola* HN4-3A, by Lu, She, and co-workers.[3] Peniphenones B and C were found to exhibit potent inhibitory activity against *Mycobacterium tuberculosis*.

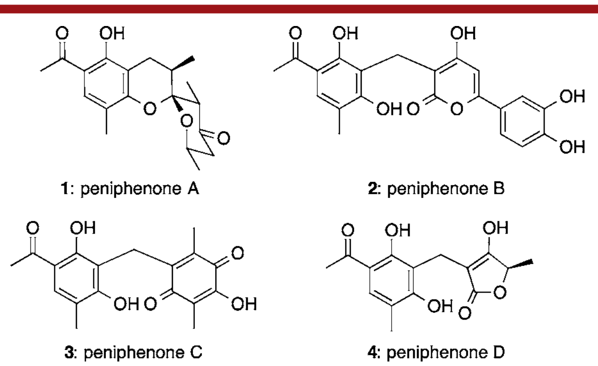
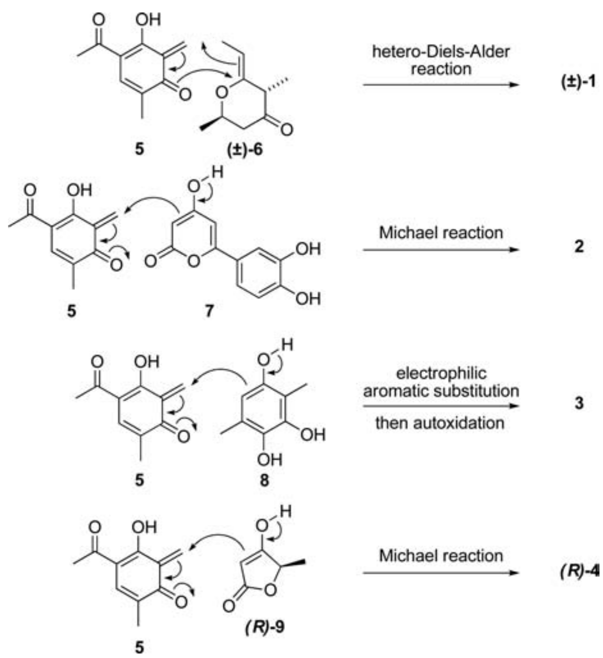


Figure 1. Peniphenones A–D.

The biosynthesis of peniphenones A–D was proposed to involve various reactions of a common *o*-quinone intermediate, **5** (Scheme 1). Peniphenone A (**1**) is the most complex natural product in this family, with a tricyclic benzannulated spiroketal scaffold containing four stereocenters.[4]

Unusually for a stereochemically rich natural product, peniphenone A was isolated as a racemate. We therefore propose that peniphenone A could result from a nonenzymatic hetero-Diels–Alder reaction between *o*-quinone methide **5** and racemic exocyclic enol ether **6**. Peniphenone B

Scheme 1. Proposed Biosynthesis of Peniphenones A–D



(**2**) could be biosynthesized via a Michael reaction between pyrone **7** and *o*-quinone methide **5**. Peniphenone C (**3**) could be formed from an electrophilic aromatic substitution reaction between 3,6-dimethyl-1,2,4-benzenetriol (**8**) and *o*-quinone methide **5** followed by spontaneous aerobic oxidation to give the hydroxyquinone ring of **3**. Finally, peniphenone D ((*R*)-**4**) could arise from a Michael reaction between (*R*)-5-methyltetronic acid (**9**) and *o*-quinone methide **5**. Peniphenone D has previously been proposed as a biosynthetic

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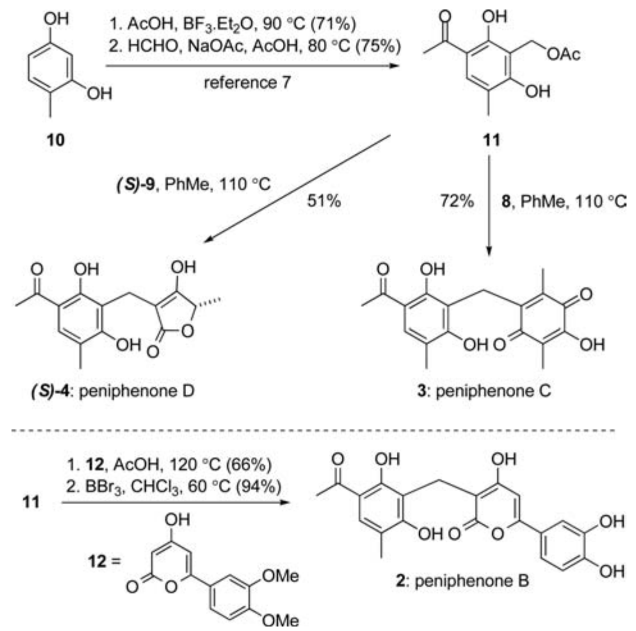
precursor of penilactone A, a related natural product isolated from the Antarctic deep-sea-derived fungus *Penicillium crustosum* PRB-2.[5]

In order to synthesize peniphenones B–D, we intended to thermally generate[6] *o*-quinone methide **5** from **11** (which was synthesized in two steps from 4-methylresorcinol (**10**) according to our previously published procedure[7]) and then react it in situ with suitable nucleophilic partners via biomimetic Michael reactions (Scheme 2). Thus, the synthesis

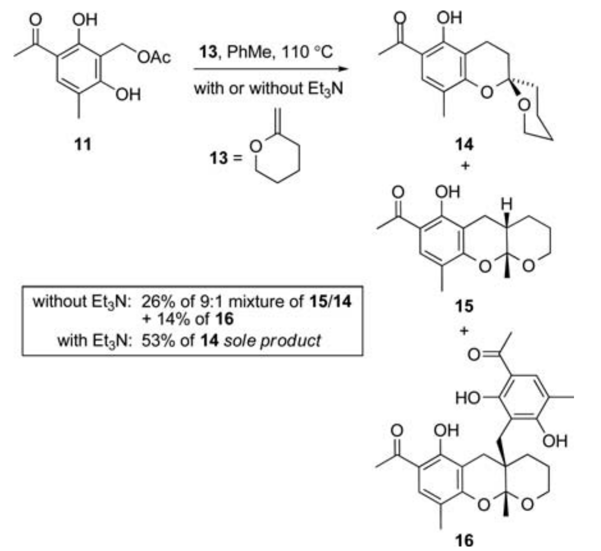
Scheme 2. Total Synthesis of Peniphenones B–D



of peniphenone B (**2**) was achieved by heating **11** in the presence pyrone **12**[8] in AcOH to give peniphenone B dimethyl ether as a solid precipitate, which was filtered and then treated with BBr_3 to give peniphenone B (**2**). The synthesis of peniphenone C (**3**) was accomplished by heating **11** with 3,6-dimethyl-1,2,4-benzenetriol[9] (**8**) in toluene. This gave peniphenone C directly, presumably via an electrophilic aromatic substitution reaction between **8** and *o*-quinone methide **5** followed by spontaneous aerobic oxidation. The synthesis of (*S*)-peniphenone D ((*S*)-**4**) was completed by heating **11** with 1 equiv of (*S*)-5-methyltetronic acid[10] (**9**) in toluene. We recently employed similar reaction conditions, but with an excess of **11**, to synthesize the related *Penicllium* metabolite penilactone A.[7] Indeed, during those earlier studies we synthesized peniphenone D (as a minor and undesired byproduct) before its isolation as a natural product had been reported. Our synthetic (*S*)-peniphenone D had an optical rotation of $[\alpha]_D^{25} = -6.8$ (*c* 1.13, MeOH), which differs significantly from the natural product data of Lu and She, who reported $[\alpha]_D^{25} = -72$ (*c* 0.5, MeOH) for (*R*)-peniphenone D. The absolute configuration of natural (*R*)-peniphenone D was established via single-crystal X-ray diffraction studies using Cu Kα radiation.

To investigate the possibility of a direct biomimetic synthesis of peniphenone A, we conducted a model [4 + 2] cycloaddition between *o*-quinone methide **5** and 2-methylenetetrahydro-2*H*-pyran[11] (**13**), a simplified version of exocyclic enol ether **6** (Scheme 3).[12] Thus, *o*-quinone methide precursor **11** was heated with excess **13** in toluene.

Scheme 3. Model [4 + 2] Cycloaddition between an *o*-Quinone Methide and an Exocyclic Enol Ether



This unselective reaction formed a 9:1 mixture of the undesired benzannulated ketal **15** and the desired benzannulated spiroketal **14** in 26% yield, together with the bisadduct **16** in 14% yield. Thermal generation of *o*-quinone methide **5** from **11** generates AcOH, which we reasoned could catalyze the isomerization of exocyclic enol ether **13** to the corresponding endocyclic enol ether. This endocyclic enol ether could then undergo Michael reactions with the in situ-generated *o*-quinone methide **5** to give **15** or **16**. Similar isomerizations in *o*-quinone methide cycloadditions have been observed previously.[6,12c] Control of the reaction was achieved by the addition of 2 equiv of Et_3N, which neutralized the AcOH byproduct and thus prevented the isomerization of **13**, so that the [4 + 2] cycloaddition with *o*-quinone methide **5** gave **14** as the sole product.

Although we have thus confirmed the viability of a direct *o*-quinone methide cycloaddition approach to peniphenone A, we have so far been unable to synthesize enol ether **6**. We therefore synthesized peniphenone A via a closely related strategy involving Michael addition of an enolate to *o*-quinone methide **5** followed by spiroketalization (Scheme 4). The synthesis began with a stereoselective Evans aldol reaction between acyl oxazolidinone **17** and chiral aldehyde **18** (synthesized in two steps from methyl (*R*)-3-hydroxybutyrate[13]) to give an aldol adduct that was converted into Weinreb amide **19**. Treatment of **19** with EtMgBr then gave ethyl ketone **20**, which was further protected with TBSOTf to give the di-TBS ether **21**. The next step involved the generation of reactive enolate **22** and its Michael reaction with the in situ-generated *o*-quinone methide **5**. This represents a rather challenging transformation, as the strong amide bases required to form unstabilized enolates can also undergo Michael reactions with *o*-quinone methides.[14] We therefore chose LiTMP as a sterically hindered amide base for enolization in an attempt to minimize such undesired additions to the *o*-quinone methide intermediate.[15] Thus, treatment of ketone **21** with an excess of LiTMP in THF/HMPA followed by addition of *o*-quinone methide precursor **11** gave the coupled product **23** (although this compound was not fully characterized because of difficulties in purification). We propose that the Michael reaction proceeds via initial

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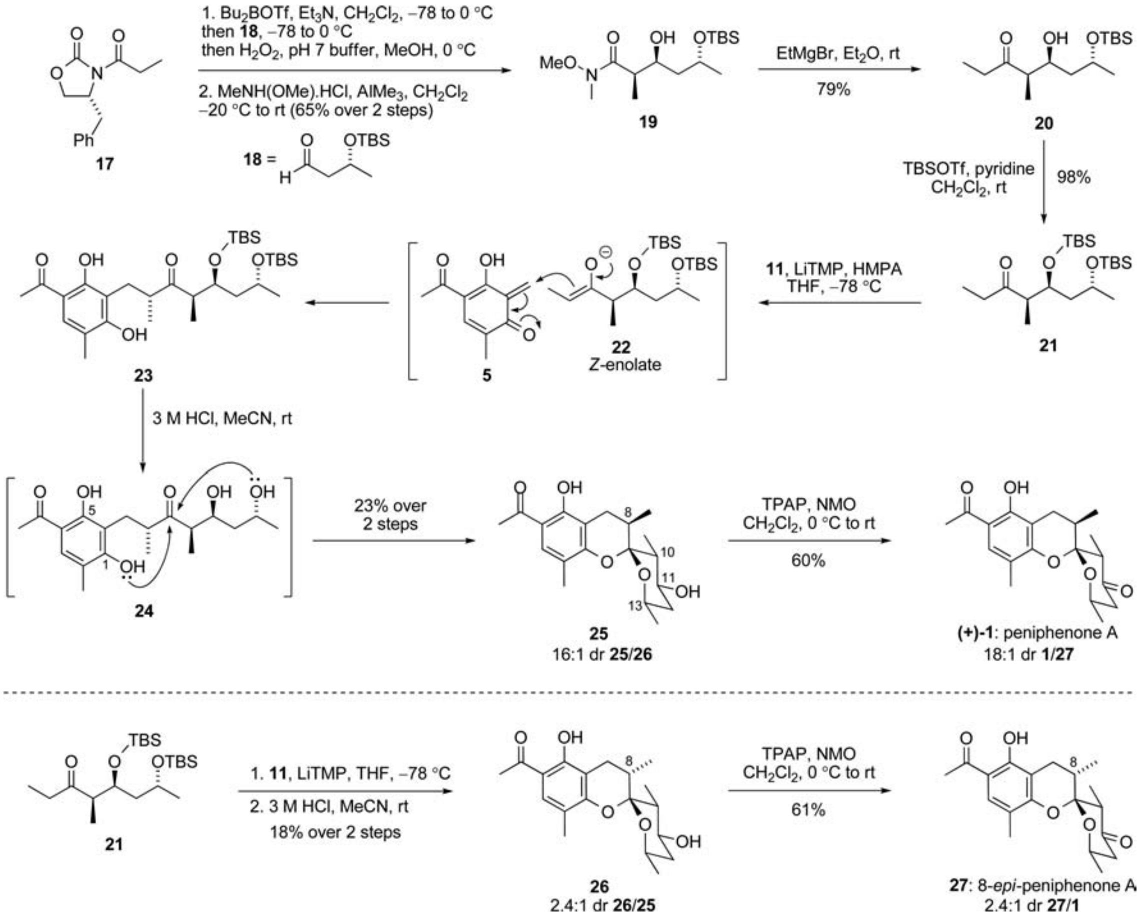
Scheme 4. Total Synthesis of Peniphenone A and 8-*epi*-Peniphenone A



stereoselective enolization of ketone **21** to give (*Z*)-enolate **22**, as is generally favored in THF/HMPA.[16] The subsequently added *o*-quinone methide precursor **11** could then react with the excess LiTMP to form *o*-quinone methide **5** in situ, which is rapidly trapped by chiral (*Z*)-enolate **21** to give **23**. Exposure of **23** to 3 M HCl in MeCN induced double desilylation and concomitant spiroketalization of diol **24** to give **25** along with a trace amount of the C-8 epimer **26** (16:1 dr). Spiroketalization of **24** occurred selectively by attack of the C-1 phenol rather than the C-5 phenol, as the latter is deactivated by hydrogen bonding to the adjacent C-15 ketone.[17] Formation of the new C-9 stereocenter at the center of the spiroketal is highly diastereoselective, as **25** can adopt a conformation in which the C-10, C-11, and C-13 substituents are all equatorial. The characterization of **25** and **26** (which was achieved by 2D NMR studies including the observation of NOESY correlations) was the only way we could measure the stereoselectivity of the Michael reaction between **22** and **5** (i.e., the formation of the C-8 stereocenter). The overall yield for the conversion of **21** to **25** is rather modest, but this is compensated for by a significant increase in molecular complexity (including the generation of two stereocenters and two rings) over these two steps. Finally, **25** was oxidized using TPAP and NMO to complete a nine-step synthesis of (+)-peniphenone A (**1**), which was obtained in 18:1 dr (as shown by ^{1}H NMR spectroscopy). The optical rotation of our synthetic (+)-**1** was $[\alpha]_D^{25}$ = +85.6 (*c* 0.88, MeOH). However, in their isolation report, Lu and She reported the chiral HPLC resolution of natural (±)-**1** to give (+)-**1** ($[\alpha]_D^{25}$ = +167 (*c* 0.2, MeOH)) and (−)-**1** ($[\alpha]_D^{25}$ = −172 (*c* 0.2, MeOH)). Furthermore, on the basis of experimental and calculated ECD spectra, Lu and She predicted that the absolute configuration of (+)-**1** is 8*S*,9*S*,10*S*,13*S*, whereas our work conclusively shows that the absolute configuration of (+)-**1** should be reassigned as 8*R*,9*R*,10*R*,13*R*.

We also conducted a Michael reaction between *o*-quinone methide **5** and the presumed (*E*)-enolate generated from ketone **21** in neat THF, i.e., in the absence of HMPA.[16] When the crude product of this reaction was treated with 3 M HCl in MeCN, the major spiroketal product was **26**, formed as the major component of a 2.4:1 mixture with **25**. This suggests that the stereochemical outcome of the key *o*-quinone methide Michael reaction is reversed by the addition of the HMPA cosolvent. Oxidation of **26** with TPAP then gave 8-*epi*-peniphenone A (**27**) as the major component of a 2.4:1 mixture with peniphenone A (**1**).

In conclusion, we have achieved concise total syntheses of peniphenones A–D. Peniphenones B–D were formed by thermal generation of an *o*-quinone methide followed by Michael reactions with appropriate enolic or aromatic nucleophiles. Peniphenone A was synthesized by Michael addition of an unstabilized enolate to an *o*-quinone methide under basic conditions followed by acid-catalyzed spiroketalization as the key steps. We believe that a similar strategy could be applied to the synthesis of natural products structurally related to peniphenone A, such as the virgatolides[18] and chaetoquadrins.[19]

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and full characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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