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Total Enantioselective Synthesis of the Endophytic Fungal Polyketide Phomolide H and its Structural Revision**

James McNulty and David McLeod*

***Abstract**: A total synthesis of the proposed structure of the natural polyketide macrolactone phomolide H **2** has been achieved following a bidirectional strategy from L-tartaric acid. The originally assigned structure of phomolide H displayed discordant NMR data in comparison with synthetic **2**. The synthetic strategy developed was extended to prepare diastereomers and epimeric methyl-ethers of the natural product, structural analysis of which allowed for a match of the natural product with diastereomer **27**. The structural revision of phomolide H from **2** to the methanol solvate of compound **27** is presented.*

The naturally occurring nonenolides phomolide G **1** and H **2** (Figure 1) were recently isolated from the endophytic fungus *Phomopsis* sp. collected from a Chinese mangrove (*Kandelia Candel*).[1] The phomolides belong to an expanding class of functionally diverse polyketides that have been isolated over the last few decades[2] mainly from endophytic and entomopathogenic fungi. The nonenolides possess a central ten-member macrolactone core having an aliphatic side chain of varying length appended to C9, as well as a range of polyhydroxyl and olefinic functionalities. As a class, the nonenolides display an impressive range of biological activities including antimalarial,[3a] anticancer,[3b, 3c] and herbicidal activities.[3d, 3e] In addition, specific enzyme inhibitory effects have been reported for nonenolides including calmodulin-dependent cAMP phosphodiesterase activity,[3f] in *vivo* cholesterol lowering[3g] and cytochrome P450-inhibitory activities.[3h] In addition to phomolides G **1** and H **2**, other specific examples include herbarumin II **3**,[3d, 3e] which exhibits phytotoxicity through inhibition of phenylalanine ammonia lyase (PAL), the anticancer (adenocarcinoma) agent Cytospolide A **4**, seimatopolide A **5** of interest against type-2 diabetes and the herbicidal agent pinolidoxin **6**. The nonenolides have increasingly attracted the attention of synthetic organic chemists with the total synthesis of many now being recorded.[5]

The synthesis of nonenolides has served to showcase the development and application of a wide range of synthetic methodologies to access the variously decorated cores in an asymmetric fashion. Biological activities have been shown to be highly dependent on a single stereogenic centre, for example the C2-methyl stereochemistry of cytospolide A is critical for potent activity against human lung cancer (A-549 cell line).[3c] In addition, it is important to note that total syntheses of nonenolides have required a significant number of structural revisions within the class, generally involving the reassignment of a single stereogenic centre.

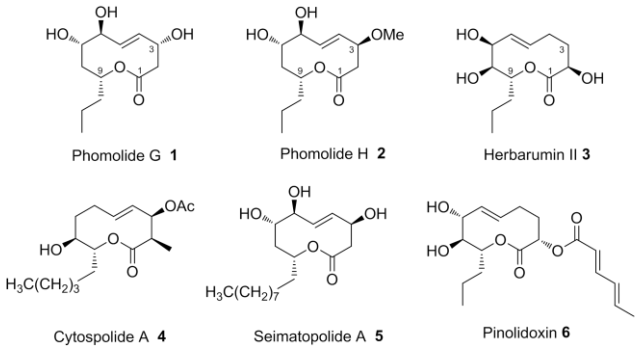
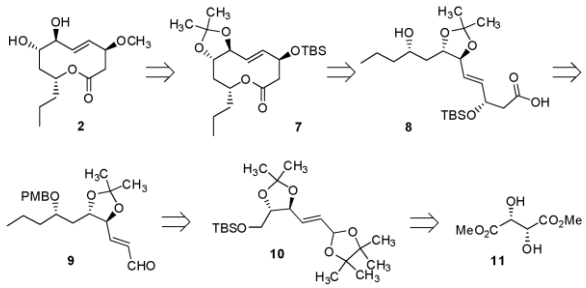


Figure 1. A selection of biologically active nonenolides **1**-**6** isolated from endophytic fungi.

We became interested in developing a two-directional approach towards the nonenolides in view of the important biological activities described, and recently reported a total synthesis of phomolide G **1** that required a structural revision at the C3 secondary alcohol.[5c] The discrepancies seen in the NMR spectra reported for phomolide G **1**[5c] and the original structural assignment as the C3-epimer of **1**,[1] in conjunction with reports on the total synthesis of phomolide H **2** through *O*-methylation of late-stage intermediates *en-route* to **1**,[5a, 5b] prompted us to undertake the total synthesis of phomolide H **2** in order to confirm the structure. In this work we report the total synthesis of the putative structure of phomolide H **2** (Scheme 1) and its C3 epimer, as well as a revised constitution and the stereochemistry of natural phomolide H.



Scheme 1. Retrosynthetic analysis of the proposed structure of phomolide H **2**. TBS = tertbutyldimethylsilyl, PMB = 4-methoxybenzyl.

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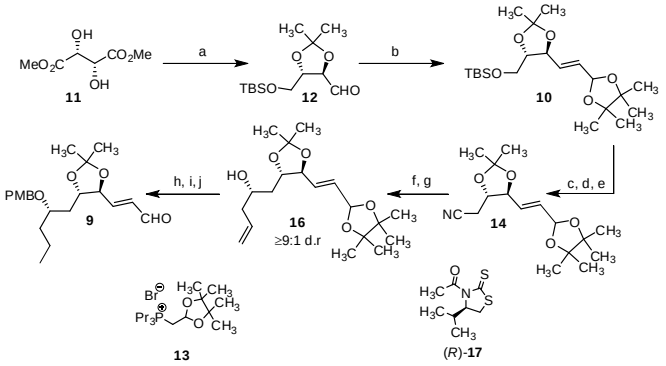
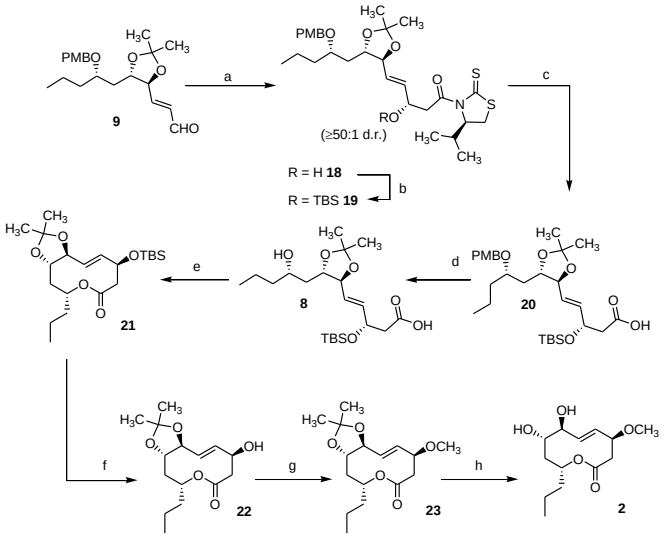
A retrosynthetic analysis of phomolide H is shown in Scheme 1. Briefly, we expected that **2** would be available by selective removal of the TBS-group from **7**, methylation of the C3-alcohol and removal of the acetonide. Intermediate **7** would be obtained from the seco-acid **8** via a Mitsunobu[6] macrolactonization with inversion at C9, and that **8** would be derived via a Nagao[7] acetate aldol on intermediate **9**. This alkenal would be accessed by allylation of the nitrile derived from **10**, and that **10** would be available from a C2 aldehyde to alkenal homologation[8] on the known 4-TBS-protected-2,3-acetonide of L-threose, available in 4-steps from L-tartaric acid dimethyl ester **11**.



Scheme 2. Reagents and conditions: Yields are of isolated products. **a)** ref. 10 51% over four steps. **b)** **13**, KOtBu, THF, 0 °C to 23 °C, 82%. **c)** TBAF, THF, 0 °C, 93%. **d)** PPh_3, I_2, 1*H*-imidazole, THF, 0 °C to 23 °C, 87%. **e)** KCN, TBAI (10 mol%), DMSO, 23 °C, 67%. **f)** Allylzinc bromide, THF, 23 °C, 81%. **g)** $LiAlH_4$, LiI, Et_2O, -100 °C, 92% (≥9:1 d.r.). **h)** $(PPh_3)_3RuCl_2$, H_2 (1 atm), Benzene/EtOH (1:1 v/v), 23 °C, 94%. **i)** NaH, PMBCl, DMF, 0 °C to 23 °C, 84%. **j)** $FeCl_3$•$6H_2O$, acetone, 23 °C, 63%. TBAF = *tetrabutylammonium fluoride*, TBAI = tetrabutylammonium iodide, PMB = *p*-methoxybenzyl.

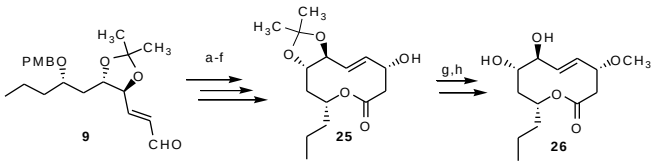
To synthesize the reported structure **2** for phomolide H, L-dimethyltartrate **11** was first protected as the 2,3-acetonide (Scheme 2), both esters were reduced using $LiAlH_4$, and the resulting 1,4-diol monosilylated as its TBS-ether followed by Swern oxidation[9] leading to aldehyde **12**.[10] The protected threose **12** was then subjected to a Wittig reaction employing the pinacol-acetaldehyde phosphonium salt **13**, known as DualPhos, which allowed for stereoselective olefination (*E*/*Z*, >5:1) to the latent alkenal **10**. With the latent enal installed, removal of the silyl-protecting group was carried out with TBAF, the resulting alcohol converted to the iodide via an Appel reaction[11] and, with suitable conditions, to nitrile derivative **14**. Reaction with allylzinc bromide[12] and mild aqueous acidic hydrolysis provided the ketone **15** which was stable enough for full characterization but which slowly isomerized to the α,β-unsaturated ketone if stored at room temperature over several days. Chelation-assisted reduction of the ketone **15** was achieved using lithium aluminium hydride in the presence of excess lithium iodide at low temperature in diethyl ether,[13] furnishing the 1,3-*syn*-diastereomer of the homoallylic alcohol **16** in excellent yield and with good stereoselectivity (*dr* ≥9:1). Chemoselective hydrogenation of the terminal alkene using tris(triphenylphosphino)ruthenium(II) dichloride (5 mol%)[14] was followed by protection of the C9 alcohol as its *p*-methoxybenzyl (PMB) ether. The bis-allylic acetal/alcohol **10** displayed exceptional stability throughout this series of transformations allowing for synthesis of the alkyl (omega) portion of the polyketide, including stereoselective installation of the C9 alcohol. Chemoselective removal of the pinacolacetal group to liberate the sensitive α,β–unsaturated aldehyde was achieved with $FeCl_3$•$6H_2O$ in acetone to give α,β–unsaturated aldehyde **9** .



Scheme 3. Reagents and conditions: Yields are of isolated products. **a)** (*R*)-**17**, $TiCl_4$, DIPEA, CH_2Cl_2 -78 °C, 82% (4:1 d.r.). **b)** TBSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 90%. **c)** LiOH·H_2O, H_2O_2, THF/H_2O (4:1, v/v), r.t., 82%. **d)** DDQ, CH_2Cl_2, 23 °C, 84%. **e)** PPh_3, DIAD, PhMe, 0 °C to 23 °C, 57%. **f)** TBAF, THF, 0 °C, 92%. **g)** MeI, Ag_2O, DMS, 23 °C, 83% **h)** TFA, MeCN/H_2O (4:1, v/v), 23 °C, 82%. DIPEA = *N,N*-diisopropylethylamine, TBS = tert-butyldimethylsilyl, Tf = trifluoromethansulphonyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIAD = diisopropylazodicarboxylate,TBAF = tetrabutylammonium fluoride, DMS = dimethylsulfide, TFA = trifluoroacetic acid.

A Nagao acetate aldol reaction[7] of aldehyde **9** (Scheme 3) employing $TiCl_4$ and the (*R*)-thiazolidinethione **17**, prepared from D-valine,[15] gave the non-Evans *syn*-aldol **18** as the major adduct in 67% yield (*dr* ≥4:1). The aldol product was protected as its TBS-ether **19** and then the auxiliary was cleaved selectively using basic peroxide (LiOH, H_2O_2) leading to the corresponding carboxylic acid **20**. The protective PMB-ether was then removed oxidatively using DDQ, providing the *seco*-acid derivative **8**. This compound was subjected to a standard Mitsunobu reaction[6] employing DIAD, to afford the fully protected macrolactone **21**. Removal of the silyl-group protecting the C3 alcohol was achieved using TBAF to give **22**. Methylation of the C3 hydroxyl group proceeded smoothly using a modified Kuhn methylation[16] to give methyl ether **23**, which was then subjected to acidic hydrolysis of the acetonide using TFA in wet-acetonitrile to yield macrolactone **2**, the putative structure assigned to natural Phomolide H.[1] Unfortunately, the ^{1}H- and, in particular, ^{13}C-NMR spectrum of synthetic **2** strikingly *mismatched* that reported for the natural product.[1] In particular, significant chemical shift differences were observed for C3 of the synthetic derivaive **2** in comparison to the natural prduct (See Table 1 and *vide infra*).

At this point we suspected a misinterpretation of the ROESY spectra regarding the configuration of C3 for the natural product, which was reported as *S*.[1] This led us to next undertake the synthesis of the C3-epimer of compound **2**, a process that could be readily achieved utilising the antipode auxiliary of **17**. The Nagao acetate aldol reaction of **9** employing (*S*)-thiazolidinethione **17** now provided the C3 epimer of **18** as essentially a single diastereomer (*dr* >20:1). The synthetic route proceeded as described above with



Scheme 4. Reagents and conditions: Yields are of isolated products. Reagents and conditions: Yields are of isolated products. **a)** (*S*)-**17**, $TiCl_4$, DIPEA, CH_2Cl_2 -78 °C, 86% (>20:1 d.r.). **b)** TBSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 89%. **c)** $LiOH{\cdot}H_2O$, H_2O_2, THF/H_2O (4:1, v/v), 23 °C, 89%. **d)** DDQ, CH_2Cl_2, 23 °C, 81%. **e)** PPh_3, DIAD, PhMe, 0 °C to 23 °C, 59%. **f)** TBAF, THF, 0 °C, 87%. **g)** MeI, Ag_2O, DMS, 23 °C, 86% **h)** TFA, MeCN/H_2O (4:1, v/v), 23 °C, 85%.

similar yields to reach the cyclized alcohol **25** (Scheme 4). Methylation of the allylic alcohol (MeI, Ag_2O) and subsequent hydrolysis of the acetonide under acidic conditions (TFA, *wet* CH_3CN) afforded methyl ether **26** (Scheme 4). Unfortunately, once again the spectroscopic data proved to be discordant to the data reported for the natural product (Table 1).

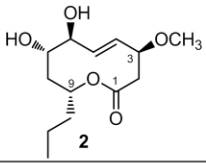
In order to reconcile the similarities and differences seen in the NMR data comparing natural phomolide-H[1] with the two diastereomeric methyl ethers **2** and **26**, we tabulated the ^{13}C-data alongside that of the two C3-diastereomeric alcohols **27** and **1** (Table 1). These alcohols were prepared by acetonide hydrolysis on intermediates **23** and **25** respectively, we note also that compound **1** is synthetic phomolide G.[5c] Careful examination of all of the ^{13}C-NMR data, including Δδ ppm differences in comparison with the natural product, revealed key differences (Table 1, see also Figures S1-3, supporting information). The ^{13}C-NMR signals associated with the C3 carbon of the diastereomeric methyl ethers **2** and **26** were both significantly deshielded (>9.0 ppm) as compared with the natural product. Further, the ^{13}C-NMR signals associated with the methyl ether C13 in **2** and **26** were themselves at an identical shift in each diastereomer but located 7.0 ppm higher than the methyl ether assigned to the natural material.

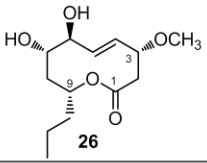
The natural material exhibits a characteristic set of signals in the ^{1}H-NMR, which corresponds to the protons attached to C3 and C9, located immediately beside one another at ~δ 4.7 ppm. Examination of the synthetic compounds **2** and **26** revealed that neither diastereomer exhibited this pattern; in fact, both showed increased shielding of the C3 proton in comparison to the natural product.

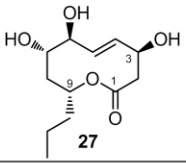
Considering similarities, the conformity of the ^{13}C-NMR data for compound **27** in comparison to natural phomolide H, see Table 1, was startling! The ^{1}H-NMR data (See supporting information) for synthetic **27** also proved identical to that of phomolide H, with the obvious deletion of the signals corresponding the methoxy substituent at C3. These data immediately drew our attention to the data reported for the methoxy group in the natural product. These signals (^{13}C=48.8 ppm and ^{1}H=3.31 ppm) in fact correspond to the solvent methanol in deuterated acetone. Natural phomolide H was isolated over Sephadex LH-20 eluting with methanol followed by column chromatography.[1] This data and process raised the possibility that phomolide H may in fact be compound **27** and methanol contamination. Evidence for this was obtained by spiking the NMR tube containing **27**, in deuterated acetone, with one equivalent of CH_3OH. The full set of NMR data for **27**+MeOH now proved an identical match to that reported for phomolide H. The signals which were assigned to correspond with the methyl ether in the natural product[1] showed no HMBC or NOE correlations connecting the methoxy signal to the polyketide backbone. Further, the HR-Q-TOF-MS data reported form the methyl ether **2** (M+Na = 281.1532) does not match that of the calculated formulae (281.1365).[1] In fact, no definitive data is presented for the assignment of the methyl ether constitution or connectivity as depicted in **2**, it appears that a methanol peak was erroneously assigned as a C3-methyl ether.[1]

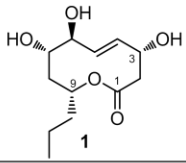
The overall structure and stereochemistry, including absolute stereochemistry, of synthetic **27** is fully supported by X-ray crystallographic analysis (see also supporting information) on the C3 4-bromobenzoate derivative **24** (Scheme 5), thus securing this structure in relation to natural phomolide H. We also note that optical rotation data for **27** $[\alpha]_D$ –20.4° (MeOH, *c* 0.19), was similar to that reported for the natural product, –17.5 (MeOH, *c* = 0.76).

Two previous reports[5a,b] exist in the literature claiming the total synthesis of phomolide H as structure **2**. The paper by Meshram and colleagues concludes that their synthetic data "exhibited identical



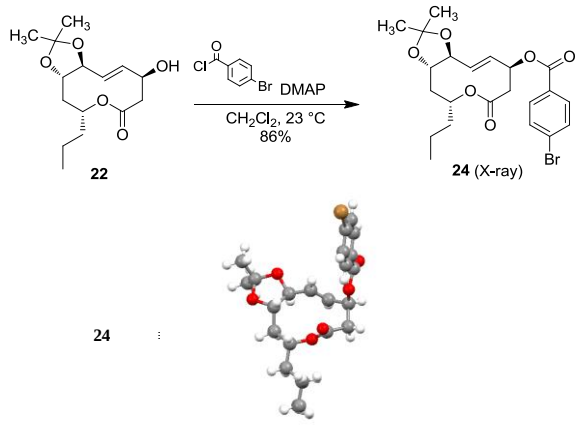






Position	Phomolide-H δ (ppm)[1]	Structure **2**	Δδ (ppm)	Structure **26** (ppm)	Δδ (ppm)	Structure **27** (ppm)	Δδ (ppm)	Structure **1** (ppm)	Δδ (ppm)
1	170.0	168.6	-1.4	169.7	-0.3	169.4	-0.6	169.8	-0.2
2	43.6	40.4	-3.2	42.4	-1.2	43.6	0.0	45.2	1.6
3	66.6	75.8	9.2	80.2	13.6	66.7	0.1	71.6	5.0
4	135.4	132.3	-3.1	134.4	-1.0	135.4	0.0	136.4	1.0
5	126.3	127.5	1.2	131.1	4.8	126.3	0.0	128.1	1.8
6	78.8	78.6	-0.2	78.0	-0.8	78.8	0.0	78.1	-0.7
7	75.9	75.9	0.0	75.8	-0.1	76.0	0.1	76	0.1
8	41.1	40.9	-0.2	41.1	0.0	41.1	0.0	41.1	0.0
9	72.2	72	-0.2	72.7	0.5	72.2	0.0	72.5	0.3
10	38.9	38.9	0.0	38.9	0.0	39.0	0.1	39	0.1
11	18.0	18	0.0	18.1	0.1	18.1	0.1	18.1	0.1
12	13.3	13.3	0.0	13.2	-0.1	13.3	0.0	13.2	-0.1
13	48.8	55.8	7.0	55.8	7.0	NA	NA	NA	NA

Table 1. Comparison of the ^{13}C-NMR (CD_3COCD_3) data for Natural phomolide H[1] and compounds **2, 26**, **27** and **1**



Scheme 5. Synthesis of the C3-(4'-bromobenzoyl)-ester of compound **23** and the X-ray structural determination (CCDC 1439915) of the benzoate **24**, confirming the structure and absolute stereochemistry as shown.

spectral data to that of the natural product", although no supplementary data is presented.[5a] The paper by Reddy and co-workers concludes similarly that their synthetic data was "identical in all respects with the data reported in the literature".[5b] Both groups have also claimed total syntheses of phomolide G,[5a,b] despite the subsequent structural revision that was required for this natural product.[5c] We look forward to further information on the synthesis and full discussion on the structure of these compounds by these authors.

In conclusion, we report a total synthesis of compound **2**, the structure originally assigned to the natural product phomolide H, the spectroscopic data of which do not match. Noting the differences seen at C3 of the natural product and **2**, the C3-epimeric methyl ether **26** was prepared, the data of which also proved a mis-match with the natural product. The two corresponding C3 epimeric alcohols **27** and **1** were also prepared and analysis of all data permitted a match between the natural product and the methanol solvate of the diastereomer **27**. On the basis of the structural mis-match and the experimental information reported herein, a structural revision of phomolide H from the (3*S*)-methyl ether **2**[1] to the (3*S*)-alcohol isomer **27** is warranted.

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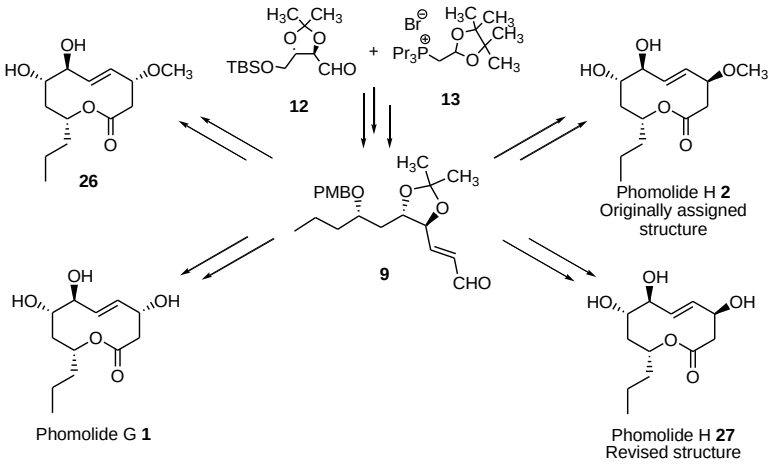
Natural Product Synthesis

J. McNulty,* D. McLeod_____
Page – Page

Enantioselective total synthesis of the reported structure of the nonenolide Phomolide H and structural revision to the methanol-solvate of **27** are demonstrated.



A total synthesis of the proposed structure of the natural polyketide macrolactone phomolide H **2** has been achieved following a bidirectional strategy from L-tartaric acid. The originally assigned structure of phomolide H displayed discordant NMR data in comparison with synthetic **2**. The synthetic strategy developed was extended to prepare diastereomers and epimeric methyl-ethers of the natural product, structural analysis of which allowed for a match of the natural product with diastereomer **27**. The structural revision of phomolide H from **2** to the methanol solvate of compound **27** is presented.