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Communication

Natural Products Synthesis

Enantioselective Total Synthesis of the Proposed Structure of the Endophytic Fungal Metabolite Phomolide G: Structural Revision and Unambiguous Stereochemical Assignment

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Abstract: A total synthesis of the proposed structure of the natural macrolactone phomolide G (**1**) by a bidirectional strategy from L-tartaric acid is reported. The ω-terminus of the molecule was elaborated by nitrile extension, C3-alkylation and a substrate-controlled 1,3-ketone reduction. The α-terminus was extended by a C_2 aldehyde-to-alkenal homologation followed by an auxiliary controlled aldol reaction. Macrolactonization and deprotection yielded compound **1** (confirmed by X-ray analysis). This putative structure of phomolide G displayed discordant NMR spectroscopic data in comparison with those of the natural product. Detailed inspection of all NMR spectroscopic data available indicated phomolide G to be likely a diastereomer of **1**. The synthetic strategy developed allows control of the absolute stereochemistry at all four chiral secondary alcohol groups. Further manipulation allowed for the preparation of diastereomer **33**, the ^{1}H and ^{13}C NMR spectroscopic data of which are in full accord with that reported for the natural product.

Introduction

An expanding number of functionally diverse polyketide-derived macrolactones, collectively termed "nonenolides", have been isolated over the last few decades.[1] While a few examples are known originating from bacteria (actinomycetes) and marine organisms,[1a] the vast majority of these metabolites have been isolated from endophytic and entomopathogenic fungi. Such fungi live on or within a plant or insect host in either a parasitic or symbiotic relationship.[1] Structurally, the nonenolides consist of a ten-membered macrolactone core having an aliphatic side chain of varying length attached to C9. The ten-membered ring generally contains a range of polyhydroxy and olefinic functionalities and is often further acylated or methylated. A selection of examples **1**–**8** are collected in Figure 1. Given the range of fungi and other organisms that are now known to produce these metabolites in different environments, it is notable to find such functional-group diversity decorating the same, conserved nonenolide core, indicating that the natural products may be derived by selective mutations of a common polyketide synthase pentaketide ancestor with varied initial starter units. These considerations imply that the nonenolides possess a privileged core, and indeed members of this family of compounds are reported to exhibit a wide spectrum of biological activity including antimalarial,[2a] anticancer,[2b,2c] and herbicidal activities,[2d] as well as specific enzyme inhibitory effects, for example against calmodulin-dependent cAMP phosphodiesterase[2e] and in-vivo cholesterol-lowering activity.[2f] Phomolides G (**1**) and H (**2**)[3a] and seimatopolide A (**3**)[3b] (Figure 1) share a common nonenolide core, differing only in the length of alkyl side chain starter unit. Decarestrictine C1 (**4**)[2f] and nonenolide (**5**)[2a] contain only a methyl substituent as the side chain, and other derivatives, such as cytospolide A (**6**),[3c] pinolide (**7**),[3d] and pinolidoxin (**8**),[3e] further exemplify some of the diversity of substitution[1] that has been found within the nonenolide core. The nonenolides have increasingly attracted the attention of synthetic organic chemists with the total synthesis of many now being recorded.[4] In view of the relative positions of the olefin and lactone functionality present, many approaches rely on olefin metathesis/macrolactonization strategies to access the nonenolide core, despite issues of (*E*)/(*Z*) stereocontrol that are often problematic with medium-sized cycloalkenes.[4h]

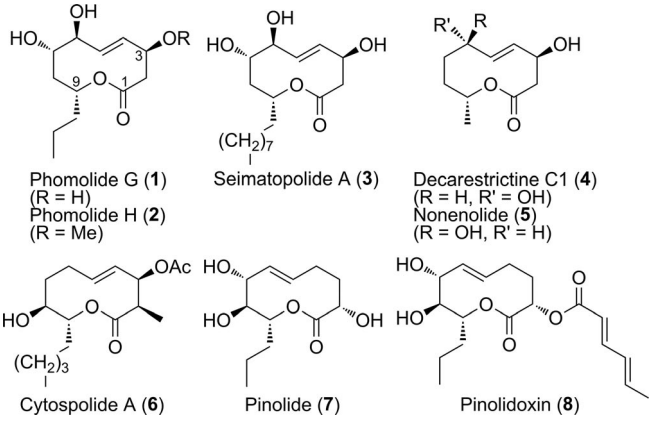

Figure 1. Structures of selected nonenolides **1**–**8** isolated from endophytic and entomopathogenic fungi.

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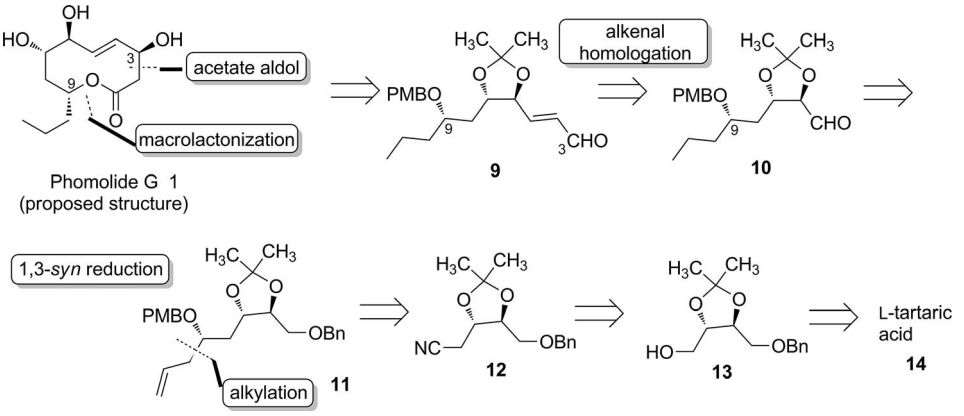
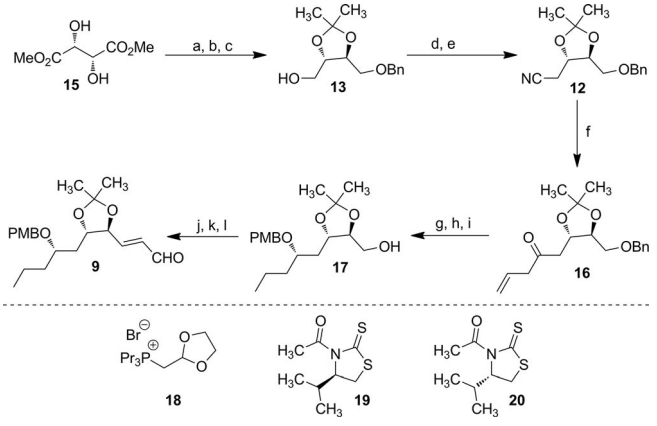


Scheme 1. Retrosynthetic analysis of phomolide G (**1**). The natural product numbering scheme is employed throughout. (Bn = benzyl, PMB = 4-methoxybenzyl)

In view of the important biological activities described within the nonenolide class, we decided to investigate a synthesis of phomolide G (**1**) as an entry to such macrolactones following the retrosynthetic analysis outlined in Scheme 1. We envisioned a Mitsunobu[5] macrolactonization subsequent to a Nagao[6] acetate aldol from intermediate **9**. This alkenal would be accessed by a C_2 aldehyde-to-alkenal homologation[7] from aldehyde **10**. Aldehyde **10** could be obtained from the homoallylic alcohol **11** by a substrate-controlled *syn*-1,3 reduction[8] of the corresponding ketone, and we considered that this ketone could be accessed by allylation[9] of the nitrile **12**, obtained by cyanide-mediated homologation of the iodide derivative of alcohol **13**, which in turn is readily available in 4 steps from L-tartaric acid (**14**). This synthetic strategy allows for the absolute stereocontrol at secondary alcohol groups C3 and C9 through auxiliary control and macrolactonization under Mitsunobu (inversion) or Yamaguchi-type (retention) conditions, respectively. In addition, the ready availability of both D- and L-tartaric acid and chirons analogous to **13** in the 2,3-*anti* series (from D-glucose) would allow, in principal, access to any of the diastereomers of phomolide G (**1**).

Results and Discussion

Dimethyl L-tartrate (**15**) was converted into the reduced monobenzyl ether derivative **13** (Scheme 2) by standard chemistry. This was then converted into the iodide by an Appel reaction and to the nitrile derivative **12** without incident. Reaction with allylzinc bromide[9] and mild aqueous acidic hydrolysis provided the ketone **16**, 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 **16** was achieved by using lithium aluminium hydride in the presence of excess lithium iodide in diethyl ether at low temperatures,[8] furnishing the 1,3-*syn* diastereomer of the homoallylic alcohol with *dr* > 9:1. The alcohol was protected as its *p*-methoxybenzyl (PMB) ether **11** (Scheme 1), and reduction in the presence of W-4 Raney nickel catalyst allowed benzyl ether hydrogenolysis[10] as well as reduction of the terminal olefin to yield the PMB-protected derivative **17**. Parikh–Doering oxidation[11] of **17** gave the corresponding aldehyde, which was homologated to the C_2-extended alkenal **9** by using the functionalized phosphonium salt **18**.[7]

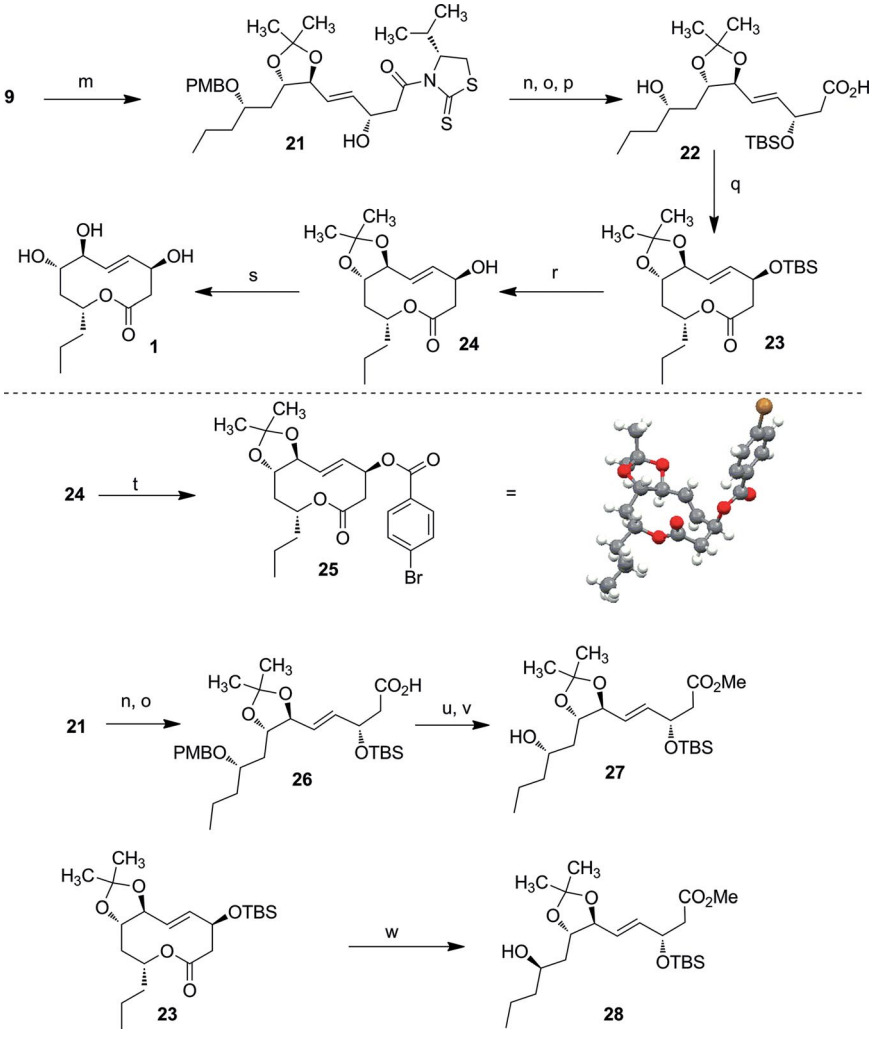


Scheme 2. Reagents and conditions (yields are of isolated products): (a) 2,2-DMP, PTSA, PhMe, reflux, 16 h, 86 %. (b) $LiAlH_4$, THF, reflux, 1 h, 82 %. (c) NaH, BnBr, THF, 0 °C to room temp., 16 h, 92 %. (d) PPh_3, I_2, 1*H*-imidazole, THF, 0 °C to room temp., 2 h, 89 %. (e) KCN, TBAI (10 mol-%), DMSO, room temp., 3 d, 91 %. (f) Allylzinc bromide, THF, room temp., 15 min, 84 %. (g) $LiAlH_4$, LiI, Et_2O, –100 °C, 2 h, 91 % (*dr* ≥ 9:1). (h) NaH, PMBCl, DMF, 0 °C to room temp., 3 h, 78 %. (i) W-4 Raney Ni, H_2 (1 atm), EtOH, room temp., 2 h, 87 %. (j) SO_3•py, DMSO, TEA, CH_2Cl_2, 0 °C, 4 h. (k) **18**, KO*t*Bu, THF/DMF (4:1, v/v), 0 °C to room temp., 6 h, 82 % (two steps). (l) PTSA, acetone, room temp., 1 h, 93 %. (PTSA = *p*-toluenesulfonic acid, Bn = benzyl, TBAI = tetrabutylammonium iodide, DMP = dimethoxypropane, PMB = *p*-methoxybenzyl, TEA = triethylamine)

A Nagao acetate aldol reaction[6] of aldehyde **9** (Scheme 3), employing the (*R*)-thiazolidinethione **19**, gave the *syn*-aldol **21** as the major adduct. The aldol product was protected as its TBS ether, the auxiliary rapidly cleaved selectively with basic peroxide, and the PMB ether now removed oxidatively by using DDQ, providing the *seco*-acid derivative **22**. This compound was subjected to a standard Mitsunobu reaction[5] employing DIAD to afford the macrolactone **23**. Stepwise removal of the protecting groups was achieved by removal of the TBS group using TBAF to give **24**, the acetonide derivative of **1**, and finally acidic hydrolysis by using TFA in wet-acetonitrile to yield macrolactone **1** with the putative structure assigned to natural phomolide G.[3a] Inspection of the NMR spectroscopic data for natural phomolide G in comparison to our synthetic material **1** revealed the overall data to be similar in many respects, but not identical, in particular the ^{13}C NMR spectroscopic data in

respect to the chemical shift values for the secondary alcohol carbon atoms (δ = 71.6, 72.5, 76.0, 78.1 ppm for the natural product[3a] as compared to δ = 67.6, 73.0, 76.9, 79.7 ppm for **1**). In order to confirm the structure of compound **1** as prepared in Schemes 2 and 3, the late-stage alcohol **24** was converted into its corresponding 4-bromobenzoate derivative **25**, which fortunately proved to be crystalline. A single-crystal X-ray structure determination of compound **25** confirmed the absolute and relative stereochemistry as depicted in **1**. In order to further prove that the Mitsunobu reaction **22** → **23** proceeded with inversion of stereochemistry, the pre-Mitsunobu intermediate **21** was converted into **26** as before (Scheme 3), and intermediate **26** converted into the methyl ester **27**. The Mitsunobu product macrolactone **23** was independently subjected to methanolysis to yield the acyclic methyl ester **28**. Comparison of the NMR spectroscopic data of compounds **27** and **28** revealed them to be epimeric at the secondary alcohol position C9, confirming the inversion of configuration during the Mitsunobu process.[12] Overall, the X-ray structure of **25** and chemical correlations affirm the stereochemical outcome of the 1,3-ketone reduction, the acetate aldol and the Mitsunobu reactions as described. The data[3a] point to the likelihood that natural phomolide G is a diastereomer of the reported structure **1**.

The synthetic strategy devised for the construction of **1** was designed to allow access to epimeric derivatives at C9 by Yamaguchi-type macrolactonization reactions on an intermediate such as **22**, or to C3-epimeric compounds from acetate aldol reactions of the alkenal **9** with the thiazolidinethione antipode (*S*)-**20**. On the basis of the significant NMR discrepancies seen at C3 (^{1}H and ^{13}C NMR) between the natural product and compound **1** (Table 1), we elected to next pursue the latter strategy as outlined in Scheme 4. The Nagao acetate aldol reaction of **9** with antipode **20** now provided the *syn*-aldol intermediate **29** as essentially a single diastereomer (*dr* > 20:1), indicating this to be the stereochemically *matched-pair*. Intermediate **29** was protected as its TBS ether, the auxiliary rapidly cleaved select-



Scheme 3. Reagents and conditions (yields are of isolated products): (m) **19**, $TiCl_4$, DIPEA, CH_2Cl_2 –78 °C, 15 min, 82 % (*dr* = 4:1). (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temp., 1 h, 90 %. (o) LiOH•H_2O, H_2O_2, THF/H_2O (4:1, v/v), room temp., 1 h, 82 %. (p) DDQ, CH_2Cl_2, room temp., 1 h, 84 %. (q) PPh_3, DIAD, PhMe, 0 °C to room temp., 2 h, 63 %. (r) TBAF, THF, 0 °C, 1 h, 92 %. (s) TFA, MeCN/H_2O (4:1, v/v), room temp., 15 h, 83 %. (t) 4-bromobenzoyl chloride, TEA, DMAP, CH_2Cl_2, room temp., 1 h, 86 %. (u) MeI, K_2CO_3, acetone, room temp., 1 h, 93 %. (v) DDQ, CH_2Cl_2, room temp., 1 h, 87 %. (w) K_2CO_3, MeOH, room temp., 18 h, 61 %. [DIPEA = *N*,*N*-diisopropylethylamine, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethylsulfonyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIAD = diisopropylazodicarboxylate, TBAF = tetrabutylammonium fluoride, DMAP = 4-(dimethylamino)pyridine, TFA = trifluoroacetic acid]

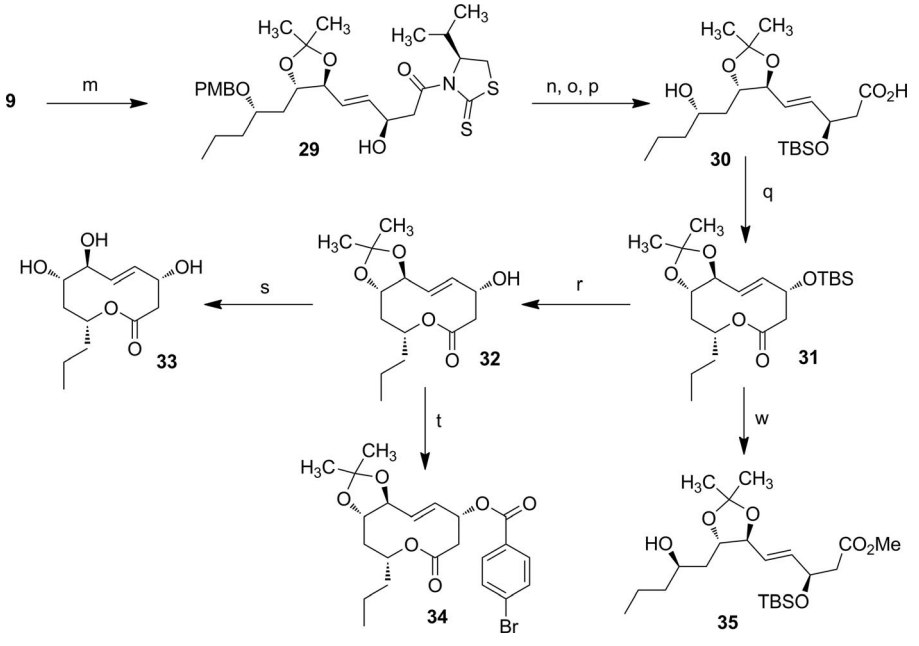
ively with basic peroxide, and the PMB ether then removed oxidatively by using DDQ to provide the *seco*-acid derivative **30**. This compound was subjected to the standard Mitsunobu reaction[5] conditions employing DIAD as before to yield the macrolactone **31**. Stepwise removal of the protecting groups was also achieved in this case by removal of the TBS group using TBAF to give **32**, followed by acidic hydrolysis using TFA in wet acetonitrile to afford macrolactone **33**, the C3-epimer of the structure assigned to natural phomolide G.[3a] As before (Scheme 3) the Mitsunobu reaction was proven to proceed by inversion[12] at C9 through conversion of intermediate **31** into **35**, and comparison of **35** with the product obtained from **29** (steps n, o, u, v), which proved to be the C9-epimer of **35** (see the Supporting Information). The 4-bromobenzoate derivative **34** was also prepared and isolated as an oil, resisting all attempts at crystallization to date. Inspection of the ^{1}H and ^{13}C NMR spectroscopic data (Table 1) for natural phomolide G in comparison to the synthetic material **33** revealed an identical match in the same solvents and under the same conditions as reported for the natural product. Natural phomolide G was reported as levorotatory with a specific rotation of –10.4 in methanol.[3a] Synthetic phomolide G of absolute stereochemistry depicted in **33** also proved to be levorotatory but exhibited a higher magnitude of specific rotation of –65 to –69 at the same concentration in methanol.

There are two previous reports[4a,4b] on the total synthesis of phomolide G as structure **1** in the literature. The first publication[4a] contains no procedural or spectroscopic information. The second report, which follows an overall similar strategy to the first one, contains a supplemental section with select ^{1}H

Table 1. Comparison of the NMR spectroscopic data (δ in ppm; J in Hz) for natural phomolide G[3a] and compounds **1** and **33**.[a]

Atom	Natural product		Compound **1**		Compound **33**	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1		169.8		170.3		169.8
2	2.20 (t, J = 10.1)	45.2	2.44 (dd, J = 11.8, 3.3)	44.5	2.21 (t, J = 10.4)	45.2
	2.50 (dd, J = 10.1, 5.6)		2.55 (dd, J = 11.8, 3.9)		2.51 (dd, J = 10.2, 5.8)	
3	4.21 (q, J = 8.7)	71.6	4.67 (m)	67.6	4.22 (dd, J = 15.6, 9.3)	71.6
4	5.60 (dd, J = 15.8, 8.7)	136.4	5.88 (dd, J = 15.8, 3.1)	136.3	5.61 (dd, J = 15.8, 8.6)	136.4
5	5.05 (dd, J = 15.8, 8.8)	128.1	5.50–5.64 (m)	127.2	5.06 (dd, J = 15.8, 9.4)	128.1
6	3.55 (t, J = 8.8)	78.1	3.74 (dd, J = 12.2, 5.9)	79.7	3.57 (t, J = 9.1 Hz)	78.1
7	3.18–3.21 (m)	76.0	3.35 (d, J = 2.4)	76.9	3.17–3.28 (m)	76.0
8	1.67–1.69 (m)	41.1	1.81–1.85	42.0	1.69–1.72 (m)	41.1
9	4.63–4.66 (m)	72.5	4.74 (dt, J = 12.2, 6.0)	73.0	4.64–4.72 (m)	72.5
10	1.33–1.38 (m)	39.0	1.42–1.56 (m)	39.9	1.33–1.45 (m)	39.0
11	1.17–1.21 (m)	18.1	1.27–1.33 (m)	19.0	1.15–1.23 (m)	18.1
12	0.77 (t, J = 7.3)	13.2	0.89 (t, J = 7.4)	14.2	0.79 (t, J = 7.4)	13.2

[a] [D$_6$]acetone (600 MHz, δ in ppm, J in Hz).



Scheme 4. Reagents and conditions (yields are of isolated products): (m) **20**, $TiCl_4$, DIPEA, CH_2Cl_2 –78 °C, 15 min, 86 % (*dr* ≥ 20:1). (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temp., 1 h, 89 %. (o) LiOH•H_2O, H_2O_2, THF/H_2O (4:1, v/v), room temp., 1 h, 89 %. (p) DDQ, CH_2Cl_2, room temp., 1 h, 81 %. (q) PPh_3, DIAD, PhMe, 0 °C to room temp., 2 h, 59 %. (r) TBAF, THF, 0 °C, 1 h, 87 %. (s) TFA, MeCN/H_2O (4:1, v/v), room temp., 15 h, 84 %. (t) 4-bromobenzoyl chloride, TEA, DMAP, CH_2Cl_2, room temp., 1 h, 90 %. (w) K_2CO_3, MeOH, room temp., 18 h, 72 %.

and ^{13}C NMR spectroscopic data. Inspection of these data reveals that the synthetic data *do not* match that reported for natural phomolide G.[3a] This data[4b] is recorded in a solvent different to that of the natural product.[3a] We have recorded the spectra of both compounds **1** and **33** in the original medium,[3a] as well as in that reported by Reddy and co-workers,[4b] confirming the mismatch. The NMR spectroscopic data of compounds **1** and **33** do not match the data reported by Reddy and co-workers, while that of compound **33** is identical to that of the natural product (Table 1). Additionally, compound **23** reported above (Scheme 3), the structure of which is secured according to the sequence **23** → **24** → **25** (X-ray analysis) is reported as a late-stage intermediate in the synthesis of Reddy and co-workers, the ^{1}H and ^{13}C NMR spectroscopic data of which[4b] do not match with this structure.

Conclusions

We report an asymmetric synthesis of the macrolactone **1**, the putative structure originally assigned to the natural nonenolide (–)-phomolide G,[3a] the ^{1}H and ^{13}C NMR spectroscopic data of which do not match that of the natural product. We also report the asymmetric synthesis of the C3-epimeric nonenolide **33**, the data of which proved to be an identical match to that of natural (–)-phomolide G. The structure of the natural product should thus be revised to compound **33**, and this work therefore represents the first report on the total synthesis and structure of this natural nonenolide. The general synthetic strategy reported permits synthesis of all diastereomers of the phomolide nonenolide core at positions 3 and 9, while use of D-tartrate or other carbohydrate-derived C_4-chirons should allow access to diastereomers equivalent to **13**. The pivotal terminal olefin introduced here as in **11** is designed to allow access to homologous analogs such as seimatopolide (**3**) by cross-metathesis or hydroboration/cross-coupling sequences. The synthesis of a series of diastereomers and homologs based on this general synthetic strategy and detailed investigation of their biological activities is under active investigation in our laboratories.

CCDC 1439915 (for **25**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Acknowledgments

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Keywords: Polyketides · Asymmetric synthesis · Nonenolides · Total synthesis · Macrolactones

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