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Enantioselective Total Synthesis of Phomallenic Acid C

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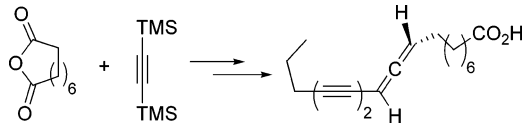
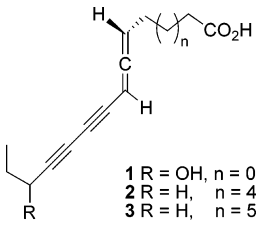


The newly isolated bacterial FAS II inhibitor phomallenic acid C (**3**) was synthesized for the first time as a 16:1 mixture of the (*R*)- and (*S*)-isomer with the diyne-allene motif constructed using a coupling under Negishi conditions. By comparison with the synthetic sample, the natural phomallenic acid C was estimated to be a 3.8:1 mixture of (*R*)-/(*S*)-isomers. This synthesis describes a new synthetic entry to optically active allene diynes.

Introduction

Phomallenic acids A-C (**1**−**3**) were recently isolated by Ondeyka and co-workers[1a] from the fermentation broth of *Phoma* sp. (MF7018, CBS118751). These diyne-allene aliphatic acids have been found[1b] to be new inhibitors of FabF, an essential enzyme in bacterial type II fatty acid synthesis pathway (FAS II).[1c−g] In particular, phomallenic acid C (**3**) showed about 20-fold better activity than that of thiolactomycin and cerulenin against *S. aureus*. It also exhibited a spectrum of antibacterial activity against clinically important pathogens including methicillin-resistant *Staphylococcus aureus*, *Bacillus subtilis*, and *Haemophilus influenzae*. As emergence of resistance to the antibiotics in clinic is a serious problem all over the world, discovery of novel antibiotics, especially those with a mode of action different from all known drugs, is an urgent task. It is already shown that bacterial FAS II (which is essential for bacteria survival) has individual enzymes responsible for each reaction in the pathway, whereas human FAS has all reactions fulfilled by a single multifunctional polypeptide.[2] Therefore, phomallenic acids and related molecules deserve further studies as potential leads for novel antibacterial agents. Herein we wish to describe an enantioselective total synthesis of phomallenic acid C, the most potent component in the family.



Results and Discussion

Our synthesis started from acylation (Scheme 1) of the commercially available bis-trimethylsilylacetylene (**4**) with azelaic anhydride[3] (**5**) under the conditions described by

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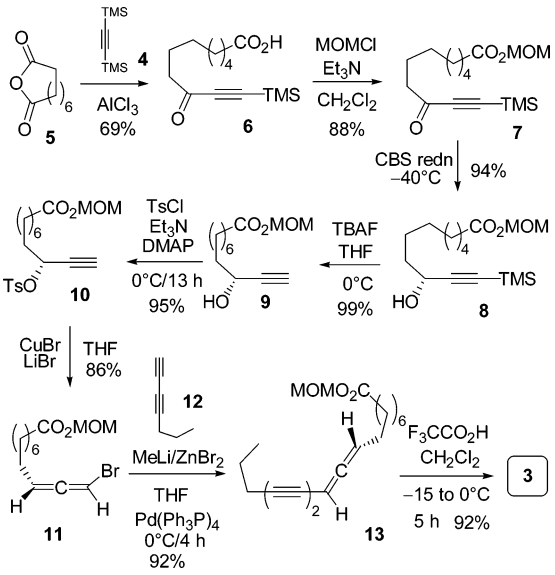
SCHEME 1



Martinelli[4] and co-workers for synthesizing a similar compound from glutaric anhydride. Although the yields were rather high in the original cases, with increase in the ring size of the anhydride the reaction was no longer that clean if equal amounts of anhydride and the acetylene were used. Apart from the desired monoacylated product **6** (ca. 40%), side products containing two acetylene moieties were also formed in substantial yields. To circumvent this problem, excess anhydride must be utilized. In the present case, using 2 equiv of the cyclic anhydride **5**, the yield of **6** was raised to 69%.

The carboxylic group in **6** was then masked as a MOM ester to prevent otherwise unavoidable concurrent reduction of the acid functionality. We first tried the conditions reported by Tanabe[5] (MOMCl/Et_3N/DMF) but only obtained an unexpected product without the TMS protecting group at the terminal alkyne. Another protocol for converting a carboxylic acid into the corresponding MOM ester in the literature was described by Nakamura[6] (*i*-Pr_2NEt/MOMCl/THF). Although the original authors reported 100% yield for their product, with **6** as the substrate, the desired ester **7** was formed in only 53% yield. Using CH_2Cl_2 as the reaction solvent proved to be beneficial. Thus, under the MOMCl/Et_3N/CH_2Cl_2 conditions, the yield of **7** could be raised to 88%.

The next step was to establish a stereogenic center by asymmetric reduction of the ketone group at the propargylic position. As the CBS[7a–c] (Corey–Bakshi–Shibata) reduction at such positions has been proved to be highly stereoselective and the absolute configuration of the product is predictable, we opted to use this method to reduce **7** into **8**. The yield of the reduction was very good. The enantiomeric excess value, however, was not easy to measure by chiral HPLC at this stage due to lack of a proper chromophore in the molecule.[7d] Therefore, we left this to a later stage of our synthesis.

The TMS protecting group was removed with *n*-Bu_4NF before activation of the propargylic hydroxyl group to avoid any potential complication at later stages. The resultant **9** was then treated with *p*-TsCl in CH_2Cl_2 in the presence of catalytic amounts of DMAP at 0 °C, yielding tosylate **10** in 95% yield. With a strong UV chromophore in the molecule, the enantiomeric excess (ee) value of **10** was readily determined (>96%) on a CHIRAL OD column by HPLC analysis.[8i]

The chirality of the propargylic position was then transferred to the allene axis via the corresponding tosylate under the LiBr/CuBr[8a–g] conditions. By treatment of **10** with 1.5 equiv of LiBr/CuBr·SMe_2 in THF at ambient temperature, the key intermediate **11** was obtained in 86% yield with a purity of 88% ee (determined[8j] later, *vide infra*). It appears that the conversion from **10** to **11** was not entirely stereospecific because the ee value dropped from 96% to 88%.[8k–l]

It is interesting to note that if the reaction was performed at refluxing temperature in the presence of a larger excess (3.3 equiv) of added LiBr/ CuBr·SMe_2, the transformation proceeded significantly faster but the optical rotation of the product **11** reduced drastically from +146.5 to only +34.8.

Construction of the allene-diyne partial structure is a key issue and a major difficulty in the present work. This is because closely related literature precedents[9] are scant, although synthesis[10] of allen-yne species from coupling of a bromoallene with an alkyne is a commonplace. Besides, no chemical synthesis of optically active allene-diynes or allen-ynes has ever

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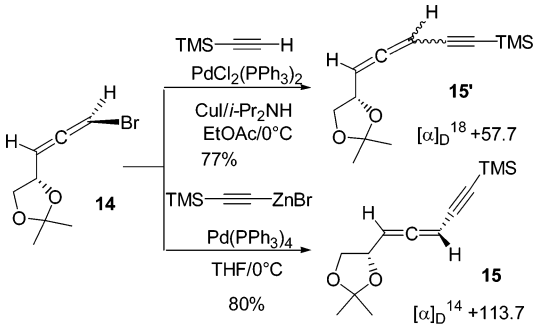
SCHEME 2



been published (to the best of our knowledge). Up to now, the only coupling example involving optically active allenes we can find in the literature is that reported in 1985 by Elsevier and Vermeer[11] (coupling of halloallenes with PhZnCl or Ph_2Zn). In fact even determination of the optical purity of allenes is also an unsolved problem if there is no other stereogenic centers at the positions immediately next to the allene axis. For these reasons, it is desirable to use a coupling protocol that may offer highest stereoselectivity so far known.

Before the present project, we already encountered similar coupling problems in another (still ongoing) project. To gain knowledge of the stereoselectivity of the existing coupling protocols in the context of reaction with alkynes, we performed some model studies. For practical concerns, we chose **14** (cf. Supporting Information) as the starting bromoallene species and the commercially available TMSC≡CH as the alkyne. It was hoped that the presence of an additional stereogenic center immediately next to the allene axis would assist detection, and perhaps even separation, of the allene isomers.

We first examined the coupling under the Sonogashira[12] conditions, which was employed by many previous investigators in the synthesis of allen-ynes. The yield of the coupling product was rather good (77%, Scheme 2). However, the ^{1}H NMR spectrum was much more complicated than expected for a single enantiomer, suggesting presence of an extensively racemized allene axis. Next, we tried the Negishi's[13] protocol, where the alkyne was converted to a more reactive zinc salt before the coupling, and the reaction thus could be carried out under milder conditions. To our gratification, this time the product gave a much cleaner ^{1}H NMR spectrum (cf. Supporting Information) and a specific rotation (+113.7) much higher than that (+57.7) obtained under the Sonogashira conditions. The sign of specific rotation is also compatible with what is predicted for (*S*)-allene according to the rules[14,15] of Lowe and Brewster, confirming an inversion of the configuration of the allene axis during the coupling as originally observed by Elsevier and Vermeer[11] in the coupling of bromoallenes with PhZnCl or Ph_2Zn.

On the basis of the results of the model study, in the synthesis of **3** we opted to employ the Negishi protocol to install the diyne moiety onto the allene. Thus, reaction of bromoallene **11** with diyne **12** (which could be prepared from 1,4-dihydroxy-but-2-yne following the literature[16] procedures) led smoothly to the desired product ester **13**. As expected, the configuration of the allene axis was also inverted, with a specific rotation of −198.5. The MOM protecting group was then removed by treatment with F_3CCO_2H in CH_2Cl_2 to afford the end product phomallenic acid C (**3**).

It is noteworthy that while IR,[17] UV, MS, and ^{1}H and ^{13}C NMR data of our synthetic sample are consistent with those reported for the natural one, the specific rotation ($[\alpha]_D^{23}$ −241.4 (*c* 0.40, MeOH) is significantly larger than reported for the natural one (lit.[1a] $[\alpha]_D^{23}$ −160 (*c* 0.40, MeOH), revealing the latter was substantially racemized. Considering that under the Negishi conditions the allene axis might partially racemize as implied by the outcomes of Elsevier and Vermeer[11] as well as our model study, we suspected that even our sample was not enantiopure. To find out the true situation, after completion of the synthetic work we also made much effort in examining enantiomeric purity of our chiral allene species by chiral HPLC.[18]

The end product **3** is a free carboxylic acid, which is often not easy to analyze by chromatography. Therefore, we performed the analysis on the MOM ester **13**. Because of the lack of precedents of successful separation of such chiral diyne-allenes (without any other stereogenic center in the molecule), the work along this line was fruitless in the beginning. Many tries on CHIRAL OD, AD, and OJ columns completely failed. Finally, the newly marketed CHIRALPAK IC column resolved the problem. The results clearly showed that the MOM ester **13** was a 16:1 (88% ee) mixture of allenic isomers. As hydrolysis of the MOM ester is unlikely to affect the allene axis, the end product **3** is also expected to be a 16:1 mixture (88% ee). The specific rotation of pure (*R*)-**3** is thus calculated to be $[\alpha]_D^{23}$ −273.6 (*c* 0.40, MeOH). Consequently, the natural **3** reported by Ondeyka and co-workers[1a] should be a 3.8:1 mixture of the (*R*)- and (*S*)-isomers.

Using the same HPLC conditions, the bromoallene **11** was shown also to be an allenic mixture with a ratio of 20:1 (90% ee). As the isomeric ratio dropped from 20:1 (90% ee) to 16:1 (88% ee) when **11** was transferred into **13**, partial racemization must have occurred to the allene axis. This deduction is in line with the observation of Elsevier and Vermeer[11] in their coupling of bromoallene with phenyl zinc reagents, where the coupling products were estimated to be of 87% ee (ca. 14.4:1).

The present results suggest that although coupling of a bromoallene with a diyne appears to be a straightforward approach to the synthesis of the diyne-allene motif, better coupling conditions are still to be found if higher enantioselectivity is desired. Perhaps even approaches other than the direct coupling should also be considered.

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(17) It is noteworthy that there is a very weak peak at 2142 cm^{-1} in the IR spectrum of **3**, which was not included in the data listing in ref 1a. Inclusion of this weak signal in the IR spectrum of **3** is rationalized by the presence of a much more intense/unambiguous peak at the same wave number in the IR of the MOM ester **13**.
(18) It should be noted that the frequent use of specific rotation data for quick comparison of enantiomeric purity between different samples in the present work is warranted as follows: (1) there is only one chiral element in the molecule, and (2) the specific rotation is rather large. However, in general specific rotation is not a sensitive/reliable indicator for enantiomeric purity, especially when the substrate molecule contains more than one chiral element and/or the absolute value of specific rotation is rather small.

In summary, the recently isolated novel FAS II inhibitor phomallenic acid C (**3**) has been synthesized for the first time through an eight-step route with an overall yield of 39% from acetylene **4**. The synthetic sample was a 16:1 mixture of the (*R*)- and (*S*)-isomer (88% ee). The specific rotation for pure (*R*)-isomer is calculated to be $[\alpha]_D^{23}$ −273.6 (*c* 0.40, MeOH), which indicates that the isolated natural **3** was a 3.8:1 mixture (58% ee) rather than a single enantiomer as one might expect.

Experimental Section

9-Oxo-11-trimethylsilanyl-undec-10-ynoic Acid (6). Powdered anhydrous $AlCl_3$ (450 mg, 3.27 mmol) was added in portions to a solution of bis-trimethylsilylacetylene **4** (170 mg, 1.0 mmol) and anhydride **5** (340 mg, 2.0 mmol) in dry CH_2Cl_2 (15 mL) stirred in an ice−water bath. The stirring was continued at the same temperature for 2 h, and at ambient temperature for 18 h with cooling (ice−water bath) 1 N HCl was carefully added to the viscous dark-brown mixture. The organic layer was separated, washed in turn with 1 N HCl, water, and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent left a dark-brown oil, which was purified by column chromatography (4:1 PE/EtOAc) to give **6** as a yellowish oil (186 mg, 0.69 mmol, 69% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (t, J = 7.4 Hz, 2H), 2.37 (t, J = 7.4 Hz, 2H), 1.66 (q, J = 6.9 Hz, 4H), 1.41−1.26 (m, 6H), 0.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.0, 180.1, 102.0, 97.7, 45.2, 34.0, 28.9, 28.8, 28.7, 24.6, 23.8, −0.75; FT-IR (film) 3500−2400 (a lump), 2932, 2858, 2150, 1710, 1678, 1253, 847, 762 cm^{-1}. EI-MS *m*/*z* (%) 268 (M$^+$, 0.1), 140 (37), 125 (100), 97 (31), 75 (68), 55 (48). Anal. Calcd for $C_{14}H_{24}O_3Si$:C, 62.64, H, 9.01. Found C, 62.61, H, 9.13.

Methoxymethyl 9-Oxo-11-trimethylsilanyl-undec-10-ynoate (7). Et_3N (0.43 mL, 3.12 mmol) was added to a solution of acid **6** (643 mg, 2.40 mmol) in dry CH_2Cl_2 (12 mL) stirred in an ice−water bath, followed by MOMCl (0.22 mL, 2.88 mmol). After completion of the addition, the mixture was stirred at the same temperature for 7 h before being diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Rotary evaporation and column chromatography (12:1 PE/EtOAc) gave the MOM ester **7** as a yellowish oil (659 mg, 2.11 mmol, 88% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (s, 2H), 3.47 (s, 3H), 2.56 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.73−1.59 (m, 4H), 1.40−1.24 (m, 6H), 0.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.8, 173.2, 102.0, 97.6, 90.2, 57.5, 45.2, 34.2, 28.9, 28.8, 28.7, 24.7, 23.8, −0.8; FT-IR (film) 2934, 2858, 2149, 1744, 1678, 1464, 1253, 1147, 1086, 933, 847, 763 cm^{-1}. ESI-MS *m*/*z* 335.2 ([M + Na]$^+$). Anal. Calcd for $C_{16}H_{28}O_4Si$:C, 61.50, H, 9.03. Found C, 61.64, H, 9.07.

Methoxymethyl (9*R*)-9-Hydroxy-11-trimethylsilanyl-undec-10-ynoate (8). (*R*)-2-Methyl-CBS-oxazaborolidin (3.12 mL, 1.0 M in toluene, 3.12 mmol) was added to a solution of the ketone **7** (488 mg, 1.56 mmol) in dry THF (15.6 mL) stirred at −42 °C. The stirring was continued for 10 min before $BH_3{\cdot}SMe_2$ (3.9 mL, 2.0 M in THF, 7.8 mmol) was introduced. The mixture was stirred for another 1 h. The reaction was quenched by addition of EtOH (5.9 mL), followed by water. The mixture was diluted with Et_2O, washed with water, and dried over anhydrous Na_2SO_4. Rotary evaporation and column chromatography (10:1 PE/EtOAc) gave alcohol **8** as a colorless oil (460 mg, 1.47 mmol, 94% yield): $[\alpha]_D^{23}$ +0.19 (*c* 1.78, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (s, 2H), 4.34 (t, J = 6.5 Hz, 1H), 3.46 (s, 3H), 2.35 (t, J = 7.4 Hz, 2H), 2.07 (br s, 1H, OH), 1.73−1.58 (m, 4H), 1.52−1.23 (m, 8H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 106.9, 90.1, 89.1, 62.7, 57.5, 37.5, 34.2, 29.0, 28.92, 28.87, 25.0, 24.7, −0.2; FT-IR (film) 3480 (br), 2927, 2858, 2169, 1743, 1463, 1250, 1088, 843, 761 cm^{-1}. ESI-MS *m*/*z* 337.2 ([M + Na]$^+$), 332.3 ([M + NH$_4$]$^+$); ESI-HRMS Calcd for $C_{16}H_{30}O_4SiNa$ ([M + Na]$^+$) 337.1806; found 337.1804.

Methoxymethyl (9*R*)-9-Hydroxy-undec-10-ynoate (9). *n*-Bu_4NF (1.52 mL, 1 M solution in THF, 1.52 mmol) was added to a solution of **8** (460 mg,1.47 mmol) in THF (7 mL) stirred in an ice−water bath. The mixture was stirred for 10 min before being diluted with Et_2O, washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation, and the residue was chromatographed on silica gel (6:1 PE/EtOAc) to give the free alkyne **9** as a colorless oil (352 mg, 1.46 mmol, 99% yield): $[\alpha]_D^{20}$ +2.80 (*c* 1.87, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23 (s, 2H), 4.37 (t, J = 6.1 Hz, 1H), 3.47 (s, 3H), 2.47(d, J = 2.0 Hz, 1H), 2.36 (t, J = 7.7 Hz, 2H), 1.98 (br s, 1H, OH), 1.76−1.59 (m, 4H), 1.53−1.28 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 90.2, 85.1, 72.8, 62.2, 57.6, 37.6, 34.3, 29.1, 29.0, 28.9, 24.9, 24.7; FT-IR (film) 3466 (br), 3290, 2932, 2857, 2107, 1740, 1464, 1158, 1087, 932 cm^{-1}. ESI-MS *m*/*z* 265.2 ([M + Na]$^+$), 260.2 ([M + NH$_4$]$^+$); ESI-HRMS Calcd for $C_{13}H_{22}O_4Na$ ([M + Na]$^+$) 265.1410; found 265.1408.

Methoxymethyl (9*R*)-9-(Toluene-4-sulfonyloxy)-undec-10-ynoate (10). Et_3N (0.27 mL, 1.93 mmol) and DMAP (10 mg) were added in turn to a solution of alcohol **9** (334 mg, 1.38 mmol) in dry CH_2Cl_2 (7 mL) stirred at 0 °C. After completion of the addition, the mixture was stirred at the same temperature for 13 h before being diluted with Et_2O, washed in turn with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation, and the residue was chromatographed (8:1 PE/EtOAc) to give tosylate **10** as a colorless oil (521 mg, 1.32 mmol, 95% yield): $[\alpha]_D^{23}$ +40.9 (*c* 1.42, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 5.23 (s, 2H), 5.05 (t, J = 5.5 Hz, 1H), 3.46 (s, 3H), 2.45 (s, 3H), 2.41 (s, 1H), 2.35 (t, J = 7.6 Hz, 2H), 1.89−1.74 (m, 2H), 1.69−1.56 (m, 2H), 1.49−1.22 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 144.8, 133.7, 129.6, 128.0, 90.1, 78.9, 76.1, 71.0, 57.5, 35.5, 34.2, 28.9, 28.8, 28.5, 24.6, 24.3, 21.6; FT-IR (film) 3276 (sharp), 2928, 2857, 2124, 1743, 1598, 1466, 1371 cm^{-1}. ESI-MS *m*/*z* 419.2 ([M + Na]$^+$); ESI-HRMS Calcd for $C_{20}H_{28}O_6NaS$ ([M + Na]$^+$) 419.1499; found 419.1497.

Methoxymethyl (*S*)-11-Bromo-undeca-9,10-dienoate (11). A solution of tosylate **10** (280 mg, 0.71 mmol) in dry THF (1 mL) was added to a mixture of LiBr (92 mg, 1.07 mmol) and $CuBr{\cdot}SMe_2$ (220 mg, 1.07 mmol) in dry THF (5 mL) stirred at ambient temperature. The resultant light gray-coffee colored mixture was stirred at ambient temperature for 6 h before the reaction was quenched by addition of sat. aq NH_4Cl (2.5 mL). The mixture was diluted with Et_2O, washed in turn with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was chromatographed (50:1 PE/EtOAc) to afford bromoallene **11** as a colorless oil (186 mg, 0.61 mmol, 86% yield): $[\alpha]_D^{23}$ +146.5 (*c* 1.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 1H), 5.39 (q, J = 6.8 Hz, 1H), 5.23 (s, 2H), 3.46 (s, 3H), 2.36 (t, J = 7.5 Hz, 2H), 2.15 (q, J = 7.4 Hz, 2H), 1.72−1.58 (m, 2H), 1.49−1.22 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 173.3, 100.9, 90.2, 72.2, 57.5, 34.3, 28.98, 28.95, 28.9, 28.7, 28.2, 24.7; FT-IR (film) 3061, 2929, 2856, 1954, 1743, 1464, 1197, 1159, 1086, 932, 653 cm^{-1}. ESI-MS *m*/*z* 327.2 ([M + Na]$^+$), 307.2 ([M + H]$^+$), 305.2 ([M + H]$^+$); ESI-HRMS calcd for $C_{13}H_{21}O_3BrNa$ ([M + Na]$^+$) 327.0566; found 327.0569.

Methoxymethyl (*R*)-Octadeca-9,10-diene-12,14-diynoate (13). MeLi·LiBr (0.80 mL, ca. 1.5 M in Et_2O, 1.20 mmol) was added via a syringe to a solution of diyne **12** (110 mg, 1.20 mmol) in dry THF (6 mL) stirred at −78 °C under argon. The mixture was stirred at this temperature for 1.5 h and then at ambient temperature for another 2 h. A THF solution of dried $ZnBr_2$ (1.2 mL, 1.0 M, 1.20 mmol) was introduced. The mixture was stirred at ambient temperature for 10 min (to afford a 0.14 M solution of the zincated diyne), before being transferred to a flask containing $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) stirred at −78 °C under argon. A solution of bromoallene **11** (114 mg, 0.37 mmol) in dry THF (3 mL) was then introduced via a syringe. After completion of the addition, the mixture was stirred at 0 °C until TLC showed disappearance of

the starting **11** (ca. 4 h). The mixture was diluted with Et_2O, washed in turn with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (50:1 PE/Et_2O) gave **13** as a colorless oil (107 mg, 0.34 mmol, 92% yield): $[\alpha]_D^{23}$ −198.5 (*c* 1.15, MeOH). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 5.58 (q, J = 6.6 Hz, 1H), 5.56−5.49 (m, 1H), 5.19 (s, 2H), 3.40 (s, 3H), 2.35 (t, J = 7.4 Hz, 2H), 2.33 (t, J = 7.7 Hz, 2H), 2.13−2.02 (m, 2H), 1.68−1.30 (m, 12H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 214.8, 173.1, 94.2, 90.3, 84.2, 75.4, 75.0, 69.1, 65.9, 57.2, 34.4, 29.5 (2 C's), 29.3, 29.1, 28.4, 25.3, 22.3, 21.4, 13.4; FT-IR (film) 2931, 2856, 2238, 2142, 1946, 1743, 1463, 1162, 1086, 933, 864 cm^{-1}. EI-MS *m*/*z* (%) 255 (M −OMOM, 10), 144 (66), 129 (100), 115 (48), 45 (89); EI-HRMS Calcd for $C_{20}H_{28}O_3$ (M^+) 316.2038; found 316.2049.

Phomallenic Acid C (3). With cooling (ice−NaCl−water bath) and stirring, F_3CCO_2H (0.3 mL, 4.03 mmol) was added to a solution of ester **13** (33 mg, 0.105 mmol) in CH_2Cl_2 (2 mL). The stirring was continued at the same temperature for 5 h, when TLC showed completion of the reaction. The mixture was diluted with Et_2O, washed in turn with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (2:1 PE/Et_2O) gave phomallenic acid C **3** as a yellowish oil (26 mg, 0.096 mmol, 92% yield): $[\alpha]_D^{23}$ −241.4 (*c* 0.40, MeOH) (lit.[1a] $[\alpha]_D^{23}$ −160 (*c* 0.40, MeOH)). UV (MeOH)$_{\lambda max}$ 205 (shoulder), 211, 238, 251, 265, 280 nm. ^{1}H NMR (400 MHz, CD_3CN) δ 10.0−7.50 (very broad/flat lump, 1H, COOH), 5.53 (q, J = 6.8 Hz, 1H), 5.46−5.40 (m, 1H), 2.30 (t, J = 7.5 Hz, 2H), 2.26 (t, J = 7.6 Hz, 2H), 2.05 (dq, J = 3.4, 6.9 Hz, 2H), 1.59−1.48 (m, 4H), 1.45−1.27 (m, 8H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 215.1, 175.4, 94.8, 85.2, 75.5, 75.0, 69.6, 65.7, 34.2, 29.74, 29.68, 29.5, 29.3, 28.6, 25.6, 22.5, 21.8, 13.7; FT-IR (film) 3600−2300 (a lump), 2927, 2855, 2238, 2142, 1946, 1737, 1709, 1463, 1277 cm^{-1}. ESI-MS *m*/*z* 295.2 ($[M + Na]^+$), 290.3 ($[M + NH_4]^+$), 273.2 $[M + H]^+$); ESI-HRMS Calcd for $C_{18}H_{24}O_2Na$ ($[M + Na]^+$) 295.1669; found 295.1668. Compound **3** is not very stable; additional spot(s) appeared on TLC after storage in neat form for a couple of months in a −78 °C freezer.

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Supporting Information Available: General remarks for Experimental Section, chiral HPLC analysis of **10**, **11**, and **13**, experimental procedures for the preparation of **14** and **15**, ^{1}H and ^{13}C NMR spectra of **6**, **7**, **8**, **9**, **10**, **11**, **13**, and **3**, ^{1}H NMR spectra of **14**, **15, 15′**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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