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Enantioselective synthesis of phomallenic acid C, an inhibitor of FAS II pathway

Ken Ishigami [a,*], Tomoko Kato [a], Kazuaki Akasaka [b], Hidenori Watanabe [a]

[a] Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan
[b] Graduate School of Life Science, Tohoku University, Tsutsumidori-Amamiya 1-1, Aoba-ku, Sendai 981-8555, Japan

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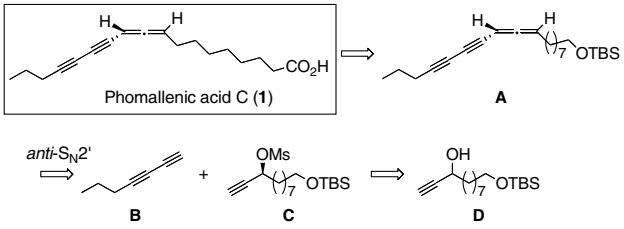
ABSTRACT

Enantioselective synthesis of phomallenic acid C, an inhibitor of bacterial FAS II pathway, was successful. Allenyldiyne structure was constructed by a direct *anti*-S_N2' coupling of propargyl mesylate with diynylindium in the presence of palladium catalyst. Enantiomeric purity was determined by Ohrui–Akasaka method to be 83%ee.

Recently, mechanism-based drugs have been remarkably noticed, since they will potentially provide selective treatments for various diseases such as infections and cancers. In 2006, Ondeyka et al. isolated phomallenic acids A–C from the fermentation broth of *Phoma* sp. as potent inhibitors of the type II fatty acid synthesis (FAS II) pathway.[1] Because fatty acids are essential for bacterial growth and the bacterial FAS II pathway (individual enzymes are responsible for each reaction of the pathway) is different from the human FAS pathway (all reactions are conducted by a single multifunctional polypeptide), these compounds may be potent against infection diseases.[2] Among phomallenic acids A–C, phomallenic acid C shows the most potent activity, which is more potent than cerulenin and thiolactomycin, the known inhibitors of FAS II.[1,3]

Phomallenic acid C has allenyldiyne structure and the absolute configuration was supposed to be *R* according to Lowe's rule.[1,4] Its unique structure as well as the significant biological activity prompted us to undertake the synthesis of phomallenic acid C. Recently, Wu et al. reported the first total synthesis of phomallenic acid C.[5] They succeeded in the enantioselective synthesis of this compound via Negishi coupling of diyne and allenyl bromide, the latter of which was obtained from propargylic tosylate by Vermeer's method.[6]

On the other hand, we selected a direct *anti*-S_N2' coupling of propargylic substrate with diyne as the key step as shown in Scheme 1. We decided to introduce the carboxyl group in the final step of the synthesis after the construction of the allenyldiyne



Scheme 1. Synthetic plan of phomallenic acid C (**1**).

moiety. Intermediate **A** would be obtained from the propargyl mesylate **C** and the known diyne **B**[7] by *anti*-S_N2' coupling. The propargyl mesylate **C** would be prepared via enzymatic acylation of racemic alcohol **D**. Although several coupling reactions of propargylic substrates with acetylenic nucleophiles have been known, those in asymmetric manner have been rarely reported. In order to establish the direct coupling of the propargyl mesylate with the diyne, first of all, we examined racemic synthesis of phomallenic acid C. During our work in progress, Yoshida et al. reported racemic synthesis of phomallenic acids.[8] They used palladium-catalyzed coupling of propargylic tosylates and terminal alkynes, but failed in the enantioselective synthesis.

Racemic synthesis of phomallenic acid C is shown in Scheme 2. The known aldehyde **2**[9] was reacted with acetylide to give alcohol **3**. After removal of TMS group, the alcohol was transformed into the corresponding mesylate **4** in good yield. Then, we tried a direct coupling of mesylate **4** with diyne. The S_N2' reaction of **4** with the acetylide of 1,3-heptadiyne[7] proceeded smoothly in the presence of $CuBr{\cdot}SMe_2$ to give the desired allenyldiyne **5**. Finally, removal

* Corresponding author. Tel.: +81 3 5841 5120; fax: +81 3 5841 8019.
E-mail address: aishig@mail.ecc.u-tokyo.ac.jp (K. Ishigami).

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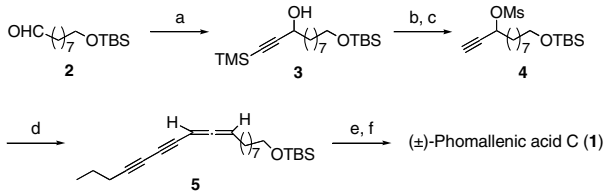
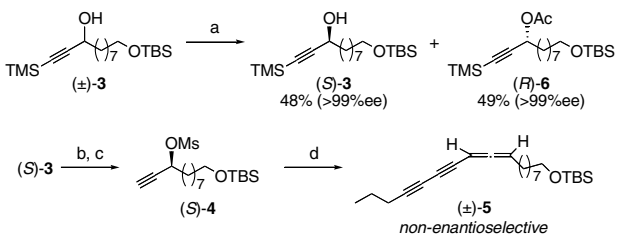


Scheme 2. Synthesis of (±)-phomallenic acid C. Reagents and conditions: (a) Trimethylsilylacetylene, *n*-BuLi, THF, 79%; (b) K_2CO_3, MeOH, 95%; (c) MsCl, Et_3N, CH_2Cl_2, quant.; (d) 1,3-heptadiyne, *n*-BuLi, CuBr·SMe_2, THF, 53%; (e) HF, CH_3CN, 82%; (f) Jones reagent, acetone, quant.

of TBS group of the allenyldiyne **5** and subsequent Jones oxidation afforded (±)-phomallenic acid C (**1**) successfully. Total yield was 33% in six steps from the known aldehyde **2**.

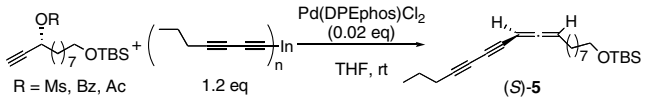
Having succeeded in the construction of allenyldiyne structure as a racemic form, our next interest came to application of this method to the enantioselective synthesis. Synthesis of optically active mesylate (*S*)-**4** is shown in Scheme 3. The racemic alcohol **3** was subjected to enzymatic acetylation using Lipase PS-C (Amano) to give alcohol (*S*)-**3** and acetate (*R*)-**6** both in >99% ee.[10] Absolute configurations and enantiomeric purities were determined by modified Mosher's method and HPLC analysis after the conversion to the corresponding MTPA esters. Alcohol (*S*)-**3** was transformed into mesylate (*S*)-**4** in good yield. Now that propargyl mesylate was obtained enantioselectively, we tried S_N2' coupling in the same manner with the racemic synthesis. But, against our wishes, the reaction did not proceed in stereoselective manner and the coupling product **5** was found to be a racemate by chiral HPLC analysis (Chiralpak AD-H, hex–*i*-PrOH = 100:1, 0 °C) after removal of TBS group. Use of another copper catalyst also gave a racemate.

In 2006, Sarandeses et al. reported stereoselective coupling of triphenylindium with propargylic esters in the presence of palladium catalyst.[11] They reported that the enantiopure propargylic ester gave the chiral allene (84–95% ee) as the *anti*-S_N2' product. According to that, we decided to apply diynylindium to palladium-mediated coupling with propargylic ester. Results are shown in Table 1 and (*R*)-propargyl esters were used for examination. First, In(III) reagent was reacted with the optically active propargyl mesylate **4** under palladium catalysis (entry 1). Allenyldiyne (*S*)-**5** was obtained in 33% yield and it was found to be 70% ee by chiral HPLC analysis after removal of TBS group. The reaction with benzoate or acetate resulted in lower yield and stereoselectivity (entries 2 and 3) and elongation of the reaction time just caused decomposition. And also, In(I) reagent did not afford satisfactory results (entries 4–6). Interestingly, the best result was obtained using In(II) reagent (entries 7–9). The diynylindium was reacted with mesylate (*R*)-**4** to give allenyldiyne (*S*)-**5** in higher enantioselectivity and moderate yield (entry 7). However, changing the equivalent of



Scheme 3. Synthesis of optically active propargyl mesylate and S_N2' reaction. Reagents and conditions: (a) Lipase PS-C 'Amano' I, vinyl acetate, *i*-Pr_2O, rt, 12 days; (b) K_2CO_3, MeOH, 95%; (c) MsCl, Et_3N, CH_2Cl_2, quant.; (d) method A: 1,3-heptadiyne, *n*-BuLi, CuBr·SMe_2, THF, −75 °C, 53%, method B: 1,3-heptadiyne, *n*-BuLi, CuI, LiI, THF, −75 °C, 34%.

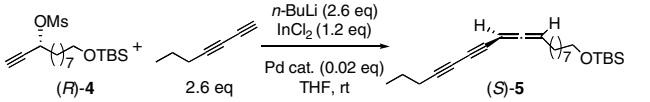
Table 1



Entry	In reagent	R	Time	Yield (%)	ee[a] (%)
1	$InCl_3$	Ms	30 min	33	70
2	(*n* = 3)	Bz	40 min	15	14
3		Ac	40 min	9	13
4	InCl	Ms	2 h	29	49
5	(*n* = 1)	Bz	3 h	18	35
6		Ac	3.7 h	11	15
7	$InCl_2$	Ms	6 h	46	80
8	(*n* = 2)	Bz	Over night	15	42
9		Ac	Over night	20	26

[a] Determined by HPLC after removal of TBS group (Chiralpak AD-H, hex–*i*-PrOH = 100:1, 0 °C).

Table 2



Entry	Pd reagent	Time	Yield[a]	ee[b]
1	$Pd(DPEphos)Cl_2$	6.0 h	46	80
2	$Pd(dppf)Cl_2$	2.5 h	78 (quant.)	70
3	$Pd(dppe)Cl_2$	2.0 h	54	83
4	$Pd(dppp)Cl_2$	2.5 h	63 (quant.)	41
5	$Pd(dppb)Cl_2$	2.5 h	50 (82%)	76
6	$Pd(PPh_3)_4$	1.5 h	10 (31%)	94
7	$Pd(PPh_3)_2Cl_2$	5.5 h	19 (80%)	94

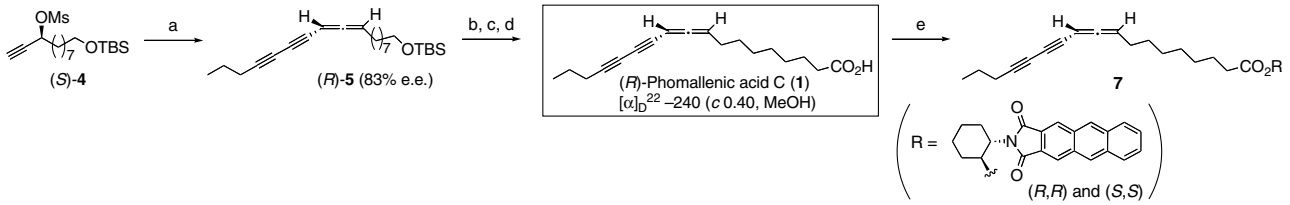
[a] ( ): Based on recovery.
[b] Determined by HPLC after removal of TBS group (Chiralpak AD-H, hex:*i*-PrOH = 100:1, 0 °C).

the In(II) reagent and/or palladium catalyst just resulted in lowering the stereoselectivity (data not shown).

Thus, we tried optimization of palladium catalyst (Table 2). As shown in entry 3, $Pd(dppe)Cl_2$ was found to slightly improve the stereoselectivity and (*S*)-**5** was obtained in good yield. In the case of $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$, the best enantioselectivities were observed, while the yields were poor (entries 6 and 7).

Having succeeded in the construction of allenyldiyne stereoselectively, optically active phomallenic acid C (**1**) was synthesized. For the total synthesis, $Pd(dppe)Cl_2$ was chosen as a catalyst and (*S*)-**4** was converted to (*R*)-**5** (83% ee), which was subjected to oxidation to afford (*R*)-**1**(Scheme 4). The removal of TBS group and Jones oxidation, in the same manner as the synthesis of the racemate, gave (*R*)-**1** ($[\alpha]_D^{22}$ −201 (*c* 0.40, MeOH)), but partial racemization was observed by HPLC analysis of its (*R,R*)- and (*S,S*)-2-(2,3-antharcenedicarboximido)cyclohexyl derivatives **7**[12] (Ohrui–Akasaka method[13,14]). On the other hand, two-step oxidation under milder conditions gave (*R*)-phomallenic acid C (**1**) without any racemization ($[\alpha]_D^{22}$ −242 (*c* 0.385, MeOH)). Enantiomeric purity was determined by Ohrui–Akasaka method to be 83% ee. The analytical and spectroscopic data of synthesized (*R*)-**1**[15] were identical to the reported data.[1,5]

In conclusion, we have accomplished the enantioselective synthesis of phomallenic acid C. Allenyldiyne structure was constructed by a direct *anti*-S_N2' coupling of propargyl mesylate with indium(II) diacetylide in the presence of palladium catalyst. Enantiomeric purity was determined by Ohrui–Akasaka method and this is a first case which applied Ohrui–Akasaka method to the allene with axial chirality. The total yield was 34% in eight



Scheme 4. Synthesis of (*R*)-phomallenic acid C. Reagents and conditions: (a) 1,3-Heptadiyne (2.6 equiv), *n*-BuLi (2.6 equiv), $InCl_2$ (1.2 equiv), Pd(dppe)Cl_2 (0.02 equiv), THF, rt, 39% (quant. based on recovery); (b) HF, CH_3CN, 96%; (c) Dess–Martin periodinane, CH_2Cl_2, 99%, (d) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, THF, *t*-BuOH, H_2O, 99%, (e) 2-(2,3-antharcenedicarboximido)cyclohexanol, EDC, DMAP, toluene, CH_3CN.

steps. Work is under way to refine enantioselectivity and yields, and the results will be reported in a full account.

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12. The esters were separated on Develosil ODS-HG-3 (4.6 × 150 mm, Nomura Chemical Co., Aichi, Japan). The fluorescence intensities of the derivatives were monitored (emission at 460 nm, excitation at 298 nm). Mixtures of methanol/acetonitrile/THF (4:8:3) were used as mobile-phase solvents (flow rate: 0.2 ml/min), and the column temperature was kept at −50 °C. Retention time: (*S*,*S*)-derivative [102 min (minor), 112 min (major)], (*R*,*R*)-derivative [102 min (major), 112 min (minor)].
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15. Synthesized (*R*)-**1** could be stored stably at −20 °C for several months. Spectral data of synthesized (*R*)-**1**: ^{1}H NMR (500 MHz, CD_3CN) δ (ppm) 8.86 (1H, br), 5.53 (1H, q, *J* = 6.5 Hz), 5.43 (1H, dtt, *J* = 6.5, 3.0, 1.0 Hz), 2.29 (2H, m), 2.25 (2H, t, *J* = 7.5 Hz), 2.04 (2H, dq, *J* = 3.0, 6.5 Hz), 1.54 (2H, br quint, *J* = 7.5 Hz), 1.53 (2H, sext, *J* = 7.5 Hz), 1.40 (2H, m), 1.25–1.34 (6H, m), 0.95 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, CD_3CN) δ (ppm) 215.1, 175.2, 94.8, 85.2, 75.5, 75.0, 69.6, 65.7, 34.2, 29.7, 29.7, 29.5, 29.3, 28.6, 25.6, 22.5, 21.8, 13.7. UV (MeOH) λ_{max} = 210 (33231), 239 (8535), 252 (13111), 266 (19103), 281 (15217) nm. IR (film) ν = 3500–2300 (br), 2236, 2137, 1943, 1701, 1459, 1419 cm^{-1}. ESI-HRMS *m*/*z* calcd for $C_{18}H_{24}NaO_2$ $[M+Na]^+$ 295.1669, found 295.1689.