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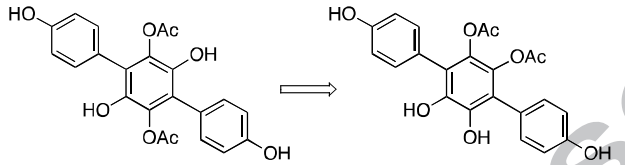

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Structural Revision of Kynapcin-12 by Total Synthesis, and Inhibitory Activities against Prolyl Oligopeptidase and Cancer Cells

Shunya Takahashi[a]*, Ayaka Yoshida[a,b], Shota Uesugi[c], Yayoi Hongo[a], Ken-ichi Kimura[c], Koji Matsuoka[b], and Hiroyuki Koshino*[a]

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ABSTRACT

Kynapcin-12 is a prolyl oligopeptidase (POP) inhibitor isolated from *Polyozellus multiplex*, and its structure was assigned as **1** having a *p*-hydroquinone moiety by spectroscopic analyses and chemical means. This paper describes the total syntheses of the proposed structure **1** for kynapcin-12 and 2',3'-diacetoxy-1,5',6',4"-tetrahydroxy-*p*-terphenyl **2** isolated from *Boletopsis grisea*, revising the structure of kynapcin-12 to the latter. These syntheses involved double Suzuki-Miyaura coupling, CAN oxidation, and LTA oxidation as key steps. The inhibitory activities of synthetic compounds against POP and cancer cells were also evaluated.

Terphenyls are aromatic hydrocarbons consisting of a chain of three benzene rings.[1] Structurally, these compounds can be classified into three types in which the terminal rings are *ortho* (*o*)-, *meta* (*m*)-, or *para* (*p*)-substituents of the central aromatic ring. Most natural terphenyls belong to *p*-terphenyl derivatives, and some of them have been reported to exhibit significant biological activities such as potent immunosuppressants, neuroprotective, and cytotoxic activities. In 2000, Song et al. isolated a new *p*-terphenyl from the methanolic extract of *Polyozellus multiplex* and named it kynapcin-12.[2] The structure was determined to be **1** by spectroscopic and chemical means; the position of two acyl groups was deduced by the experimental results that the natural product did not form the corresponding phenylboronate and that its colourimetric test[3] for detecting a catechol function was negative. This structure seemed to be of interest because natural *p*-terphenyls with diacyl groups at the central ring have been isolated so far as a regioisomeric mixture except the corresponding catechol derivatives.[4,5] The natural product exhibits an inhibitory activity (IC_{50} = 1.25 μM) against prolyl oligopeptidase (POP, EC3.4.21.26).[6] POP is a serine protease and it cleaves the carboxyl side of proline in peptides that are <30 amino acids in length such as oxytocin, vasopressin and neurotensin, etc.[7] Recent studies have revealed that the enzyme participates in several functions of the central nervous system and that it was a target in memory and neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.[8,9] It has also been reported that POP inhibition suppressed the growth of human neuroblastoma cell line, NB-1 and human gastric cancer cell line, KATO III, respectively.[10,11] Therefore, POP inhibitors are expected to be a promising tool for the prevention and treatment of neurodegenerative diseases and cancer. Recently, we have been engaged in synthetic studies on natural *p*-terphenyls, resulting in the total synthesis of vialinins A,[12] B,[13] and telephantin G.[4] As part of our continuing studies in this field, we describe herein total synthesis of kynapcin-12 which dictates revision of the formula to **2**. The inhibitory activities of synthetic compounds against POP and cancer cells were also evaluated.

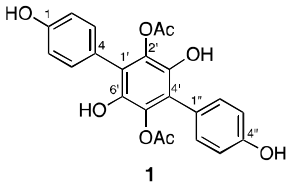

Figure 1. The original structure for kynapcin-12 (**1**) and its revised form **2**.

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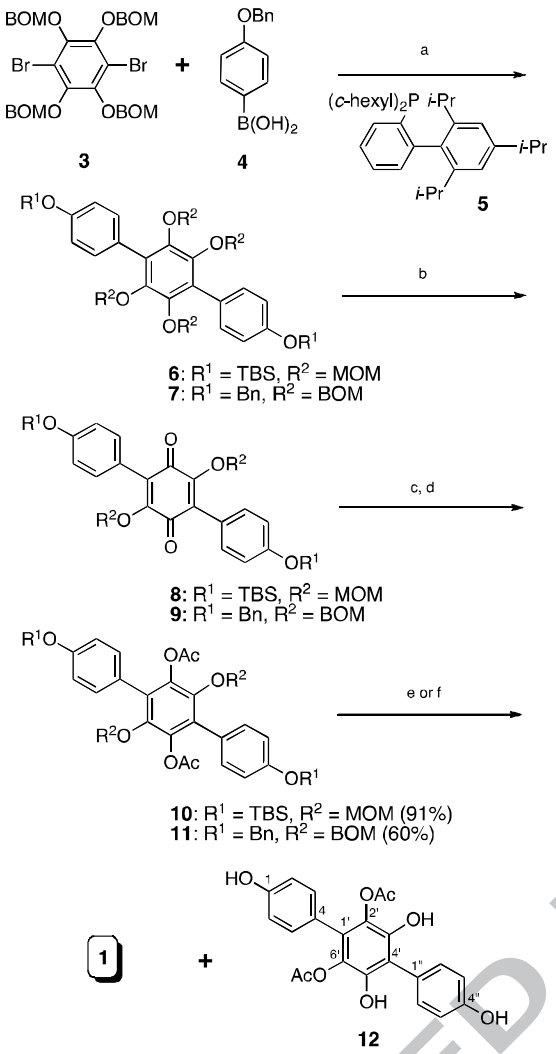


Scheme 1

Synthesis of the proposed structure **1** for kynapcin-12 and its isomer **12**. Reagents and conditions: (a) $Pd(OAc)_2$, **5**, K_3PO_4, aq. THF, 70 °C, 81% for **7**; (b) CAN, aq. THF, rt, 72% for **9**; (c) $Na_2S_2O_4$, aq. THF, rt; (d) LHMDS, THF, -78 °C, and then AcCl, -78 -> 0 °C 91% for **10** from **8**, 60% for **11** from **9**; (e) TFA-H_2O (15:1), rt, 88% for **1**+**12** (**1**/**12** = 7/2) from **10**; (f) H_2, $Pd(OH)_2$/C, THF, MeOH, rt, 35% for **1**+**12** (**1**/**12** = 3/4) from **11**.

Synthesis of **1** started from sodium dithionite reduction of *p*-quinone **8**[14] obtained by ceric ammonium nitrate (CAN) oxidation of **6** (Scheme 1). The resulting hydroquinone was treated with *n*-BuLi in THF at -78 °C and then the addition of acetyl chloride gave diacetate **10**[15] in high yield. Brief treatment of this with degassed TFA-H_2O (15:1) furnished a single product as judged by TLC analysis. However, ^{1}H-NMR (d_4-MeOH) analyses showed it to be an inseparable mixture of **1** and its *m*-isomer **12** (**1**:**12** = ca.3:1) which attained equilibrium (**1**:**12** = ca. 1:3) after 12h. The migration of an acetyl group to adjacent hydroxyls under acidic conditions is well documented.[16] In order to suppress the acyl migration at the final stage, we next implemented a second approach that employed the benzyloxymethyl (BOM) group as a hydroxyl protection. The double Suzuki-Miyaura coupling[17] of **3** and **4** was accomplished by the action of $Pd(OAc)_2$ and K_3PO_4 in the presence of the Buchwald ligand **5**,[18,19] giving **7** in good yield. Different from the case of oxidation of **6**, the BOM group in **9** was found to be

Table 1. ^{1}H-NMR data (δ) for natural kynapcin-12, **1**, **2**, and **12** in MeOH–d_4.

position	Kynapcin-12[a,b]	**1**[b,c]	**12**[b,c]	**2**[b,d]
2 (6)	6.83 d (8.4)	6.82 d (8.7)	6.78 d (8.7)	6.82 d (8.8)
3 (5)	7.16 d (8.4)	7.14 d (8.7)	7.03 d (8.7)	7.15 d (8.8)
2" (6")	7.16 d (8.4)	7.14 d (8.7)	7.25 d (8.3)	7.15 d (8.8)
3" (5")	6.83 d (8.4)	6.82 d (8.7)	6.85 d (8.3)	6.82 d (8.8)
CH_3	1.90 s	1.94 s	1.92 s	1.92 s

[a]Ref. 2 (400 MHz). [b]Numbers in parentheses are *J* values. [c]600 MHz. [d]500 MHz

Table 2. ^{13}C-NMR data (δ) for natural kynapcin-12, **1**, **2**, and **12** in MeOH–d_4.

position	Kynapcin-12[a,b]	**1**[c]	**12**[c]	**2**[d,e]
1	158.1	158.1	158.2	158.2
2 (6)	116.0	115.9	115.8	116.0
3 (5)	132.6	132.6	132.0	132.6
4	125.0	125.3	125.3	125.0
1'	123.8	125.2	129.7	123.8
2'	134.8	140.9	131.0	134.9
3'	142.5	136.7	146.1	142.5
4'	123.8	125.2	119.5	123.8
5'	134.8	140.9	146.1	134.9
6'	142.5	136.7	131.0	142.5
1"	125.0	125.3	125.3	125.0
2" (6")	132.6	132.6	133.3	132.6
3" (5")	116.0	115.9	116.1	116.0
4"	158.1	158.1	157.9	158.2
C=O	170.6	171.0	171.4	170.6
CH_3	20.1	20.5	20.5	20.1

[a]Ref. 2 (100 MHz). [b]The original data for 2',5' and 3', 6' denoted in ref 2 were opposite. [c]150 MHz. [d]125 MHz. [e]The carbon-numbering system was conveniently according to one shown in Figure 1.

labile toward the CAN oxidation. Prolonged reaction time caused over-oxidation, resulting in a formation of de-BOM quinone. Thus, the CAN oxidation of **7** was carefully performed by monitoring the progress of the reaction by TLC, affording **9** in good yield. Reduction of **9** followed by acetylation led to a *p*-hydroquinone derivative **11**. Hydrogenolysis of **11** with $Pd(OH)_2$ afforded an inseparable mixture of **1** and **12** (**1**/**12** = ca.3:4) again, and the pure *p*-hydroquinone **1** could not be isolated. Extensive NMR analysis, however, revealed the structure of each isomer unambiguously (Table 1 and 2). The NMR data of **1** were inconsistent with those of kynapcin-12 reported, showing that the proposed structure **1** was incorrect. In addition, the reported data also did not match with those of **12**. We also observed that **1** was unstable toward air oxidation and that gradually changed to the corresponding *p*-quinone **13** by ^{1}H-NMR analyses (Fig. 2). When used as a non-degassed solvent, this oxidation was fast in d_6-acetone and slow in d_4-MeOH. In

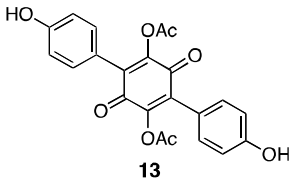
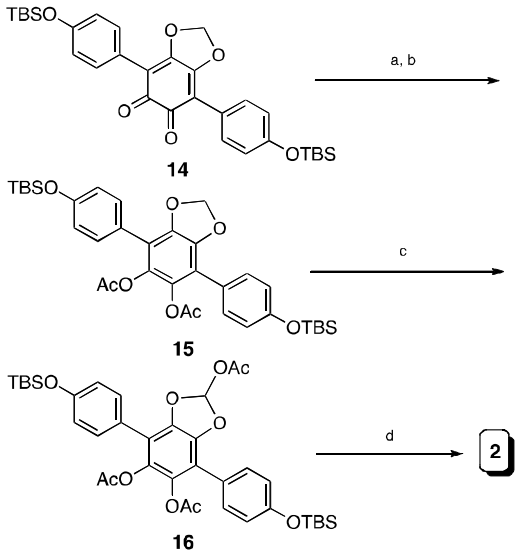


Figure 2. The structure of an oxidised product of **1**.

the literature,[2] kynapcin-12 could be obtained as a single isomer and the comment with regard to the oxidised product was not

denoted. Re-examining the NMR data of the natural product, we found that the data of the carbon signals derived from terminal aromatic rings of natural kynapcin-12 were similar to those of **1** rather than **12**. This finding suggests that the real structure of kynapcin-12 would be a C_2 symmetry compound such as **2**. Such consideration prompted us to prepare **2**. The known *o*-quinone **14**[12] was transformed into diacetate **15** according to the method described above. Lead tetraacetate (LTA) oxidation of **15** proceeded without trouble to give triacetate **16** in a quantitative yield. Final deprotection[20] was performed by brief treatment of **16** with HF·pyridine followed by the action of TBAF, affording **2**. The NMR data of synthetic **2** were consistent with those of the natural product reported (Table 1 and 2).[2]



Scheme 2

Synthesis of the revised structure **2** for kynapcin-12. Reagents and conditions: (a) $Na_2S_2O_4$, aq. THF, rt; (b) LHMDS, THF, -78 °C, and then AcCl, -78 -> 0 °C 70% from **14**; (c) LTA, benzene, 80 °C, 99%; (d) HF·Pyr, CH_2Cl_2, rt, and then TBAF, CH_2Cl_2, rt, 69%.

After completion of the total synthesis of **2**, we found that such a compound has already been isolated from *Boletopsis grisea*[21] as a natural product by the CAS database. However, no report of synthetic studies on the natural product has suggested the necessity of structural confirmation by chemical synthesis.[22] Our synthetic work confirms the structure of *p*-terphenyl **2** derived from *Boletopsis grisea* as well as the revision of the structure of kynapcin-12.

We next examined the effect of synthetic compounds on the inhibition activity of POP and the cytotoxicity against human acute promyelocytic leukemia cell line, HL60, according to the modified method of Yoshimoto et al.[7,23] or Kimura et al.[24] Since separation of **1** was impossible, the bioassay could be performed for the mixture **1** and **12** (ca. 2:3). We could not gain reliable data of **9** and **11** due to the low solubility in DMSO and/or in the assay buffer. As shown in Table 3, compounds synthesised in Scheme 2 rather than in Scheme 1 showed relatively strong inhibitory activity. Compounds **1+12** and **16** exhibited a potent POP inhibition activity. The reason why our synthetic sample **2** showed a slightly weak inhibitory activity compared to that in the literature[2] is not clear. For cytotoxicity against HL60 cells, compounds **8**, **14**, **15**, and **16** were observed to be strong. It is interesting that an orthoester **16** showed both potent inhibition activities against POP and HL60 cells. These results are not only useful for designing new anti-amnesic drugs, but also for anti-cancer agents.

Table 3. Inhibitory activity of synthetic samples **1+12, 2, 6-8, 10**, and **13-16**, toward POP and HL60

	IC_{50} (μM)	
Compound	POP	HL60
1+12	2.5	10.5
2	15.2	>20.0
6	>50.0	14.4
7	>50.0	>20.0
8	11.5	6.5
10	>50.0	19.1
13	14.9	>20.0
14	15.1	2.8
15	17.7	2.9
16	3.5	4.2
propeptin[a,b]	1.4	-

[a] Ref. 25. [b]This compound was used as a positive control.

Total synthesis of the proposed structure **1** for kynapcin-12 and its *o*-isomer **2**, and the detailed NMR analyses revealed that the real structure of kynapcin-12 should be revised to be **2**. A fully *O*-protected form of **2** such as **16** was shown to have potent inhibitory activities against POP and HL60 cells.

Acknowledgments

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15. *Spectral data of new compounds*:
Compound **7**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45 (4H, d, *J* = 8.8 Hz), 7.42 (4H, brd, *J* = 7.5 Hz), 7.36-7.25 (18H, m), 7.11 (8H, brd, *J* = 7.5 Hz), 7.00 (4H, d, *J* = 8.8 Hz), 5.04 (4H, s), 4.96 (8H, s), 4.11 (8H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 158.0, 144.4,

137.6, 136.9, 132.6, 130.5, 128.6, 128.2, 127.9, 127.7, 127.5, 127.4, 126.5, 114.2, 96.5, 70.5, 69.9; HRMS (ESI$^+$) calcd for $C_{64}H_{58}O_{10}Na$ $[M+Na]^+$ 1009.3928, found 1009.3932.

Compound **9**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43 (4H, brd, *J* = 7.4 H), 7.40-7.30 (14H, m), 7.07-7.03 (10H, m), 5.24 (4H, s), 5.10 (4H, s), 4.24 (4H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 183.7, 159.2, 152.1, 136.7, 136.6, 132.3, 130.4, 128.6, 128.3, 128.1, 128.0, 127.9, 127.4, 122.0, 114.4, 96.1, 71.0, 70.0; HRMS (ESI$^+$) calcd for $C_{48}H_{40}O_8Na$ $[M+Na]^+$ 767.2621 , found 767.2620.

Compound **10**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.23 (4H, d, *J* = 8.8 Hz), 6.87 (4H, d, *J* = 8.8 Hz), 4.63 (4H, s), 3.04 (6H, s), 2.01 (6H, s), 0.99 (18H, s), 0.20 (12H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.5, 155.3, 143.6, 140.2, 131.4, 130.1, 125.6, 119.9, 98.9, 56.9, 25.7, 20.4, 18.3, -4.4; HRMS (ESI$^+$) calcd for $C_{38}H_{54}O_{10}NaSi_2$ $[M+Na]^+$ 749.3153, found 749.3148.

Compound **11**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43 (4H, d, *J* = 8.0 Hz), 7.39-7.25 (16H, m), 7.13 (4H, brd, *J* = 7.5 Hz), 6.98 (4H, brd, *J* = 7.5 Hz), 5.06 (4H, s), 4.77 (4H, s), 4.24 (4H, s), 1.99 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.6, 158.4, 143.7, 140.3, 137.3, 136.8, 131.5, 129.9, 128.6, 128.3, 128.0, 127.6, 127.6, 127.5, 125.1, 114.6, 96.8, 70.7, 70.0, 20.4; HRMS (ESI$^+$) calcd for $C_{52}H_{46}O_{10}Na$ $[M+Na]^+$ 853.2989, found 853.2971.

Compound **13**: ^{1}H-NMR (500 MHz, d_6-acetone): δ 7.25 (4H, d, *J* = 8.7 Hz), 6.93 (4H, d, *J* = 8.7 Hz), 2.22 (6H, s); ^{13}C-NMR (150 MHz, d_6-acetone): δ 180.7, 168.9, 159.7, 148.0, 134.0, 132.6, 120.3, 115.9, 20.2; HRMS (ESI$^-$) calcd for $C_{22}H_{15}O_8$ $[M-H]^+$ 407.0767, found 407.0769.

Compound **15**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36 (4H, d, *J* = 8.5 Hz), 6.87 (4H, d, *J* = 8.5 Hz), 6.00 (2H, s), 2.05 (6H, s), 1.00 (18H, s), 0.22 (12H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.6, 155.6, 142.9, 134.9, 130.7, 123.8, 119.9, 116.8, 101.6, 25.6, 20.3, 18.2, -4.4; HRMS (ESI$^+$) calcd for $C_{37}H_{48}O_{10}NaSi_2$ $[M+Na]^+$ 731.2684, found 731.2668.

Compound **16**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.75 (1H, s), 7.37 (4H, d, *J* = 8.8 Hz), 6.89 (4H, d, *J* = 8.8 Hz), 2.11 (3H, s), 2.07 (6H, s), 1.00 (18H, s), 0.24 (12H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.7, 168.4, 155.9, 140.3, 135.7, 130.7, 123.2, 120.0, 117.5, 113.0, 25.7, 21.1, 20.3, 18.2, -4.4; HRMS (ESI$^+$) calcd for $C_{35}H_{46}O_8NaSi_2$ $[M+Na]^+$ 673.2629, found 673.2634.

Compound **2**: mp 228-230 °C (lit.[2] 184-185 °C, lit.[21] 229-230 °C); UV λ_{max} (MeOH) nm (logε): 225.5 (4.32), 263.0 (4.27); ^{1}H-NMR (500 MHz, d_4-MeOH): δ 7.15 (4H, d, *J* = 8.8 Hz), 6.82 (4H, d, *J* = 8.8 Hz), 1.92 (6H, s); ^{13}C-NMR (125 MHz, d_4-MeOH): δ 170.6, 158.2, 142.5, 134.9, 132.6, 125.0, 123.8, 116.0, 20.1; HRMS (ESI$^+$) calcd for $C_{22}H_{18}O_8Na$ $[M+Na]^+$ 433.0899, found 433.0901.

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20. Only the use of HF·pyridine or TBAF required a long duration for the global deprotection, resulting in a low yield of the desired final product. In contrast, acid treatment of **16** caused de-acetylation of the catechol moiety although such a condition was successfully employed at the final step in the total synthesis[12] of vialinin A.
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