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Synthetic studies toward neovibsanins A and B: construction of the neovibsanin core utilizing palladium(0)-catalyzed carbonylative cyclization with carbon monoxide

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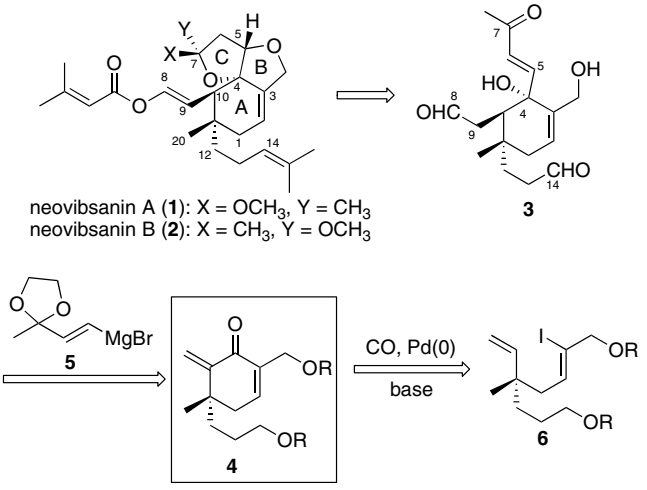
Abstract

The core A-ring of neovibsanins A (**1**) and B (**2**), which are potent neurotrophic agents isolated from the leaves of *Viburnum awabuki*, have been effectively constructed by the intramolecular palladium(0)-catalyzed carbonylative cyclization of alkenyl iodide with carbon monoxide.

Keywords: Neovibsanins A and B; Pd-catalyzed carbonylative cyclization; Neurotrophic activity

Neovibsanins A (**1**) and B (**2**), isolated from the leaves of *Viburnum awabuki* by Fukuyama et al.,[1] are classified into rearranged vibsane-type diterpenes, which consist of more complex and tricyclic structures than the other vibsane-type members.[2] Among a number of vibsane family members, **1** and **2** have unusual structures based on the cyclohexene core (A-ring) fused with two tetrahydrofurans having five chiral carbons, including two quaternary centers and two side chains. In addition, **1** and **2** significantly promote neurite outgrowth of NGF-mediated PC12 cells,[2] and are therefore expected to be lead compounds for developing anti-Alzheimer's disease drugs. Their architectural complexity, outstanding neurotrophic activity, and extreme scarcity have attracted the interest of our synthetic group. In this Letter, we report our studies toward the construction of a core A-ring **4** for neovibsanins A (**1**) and B (**2**), featuring palladium-catalyzed carbonylative cyclization with carbon monoxide.

As seen in our synthetic strategy, outlined in Scheme 1, we conceived that the cyclohexadienone **4** would serve as the key intermediate for elaboration to precursor **3** that



Scheme 1. Synthetic plan targeting neovibsanins A and B, and the key synthetic intermediate **4**.

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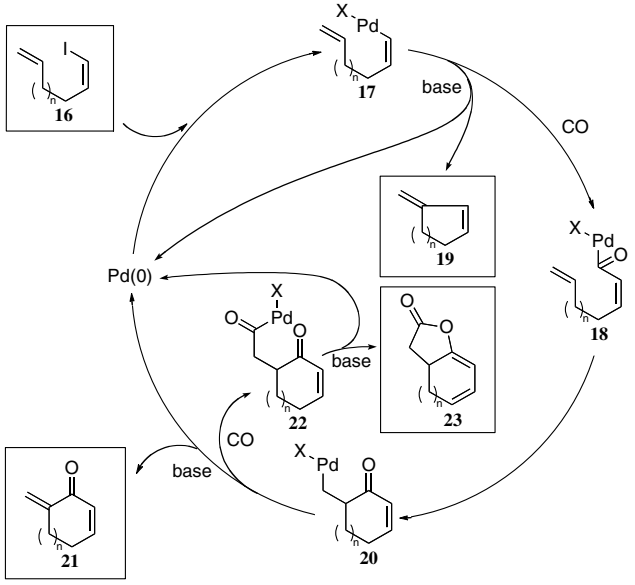
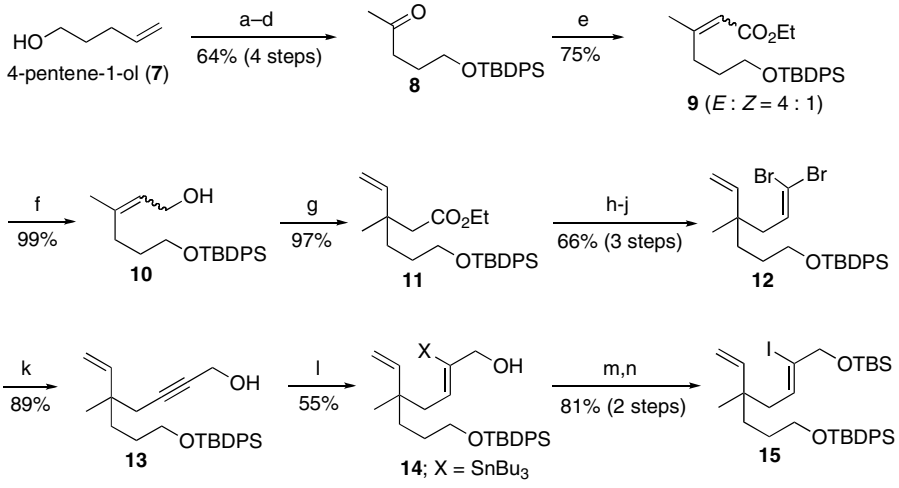
could be readily converted to neovibsanins A (**1**) and B (**2**), because the enone moiety of **4** would be a competent scaffold to introduce a variety of functionalities requisite to the synthesis of **1** and **2**. Namely, **3** would be derived from **4** by a two-step operation involving C1 homologation at the C-9 position and the addition of the C4 unit with alkenylmagnesium reagent **5** to the C-4 ketone. Subsequent intramolecular *oxy*-Michael addition at C-5 of **3**, the formation of acetal at C-7, the Wittig olefination at C-14, and the final esterification with senecioyl chloride at C-8 would allow us to achieve total synthesis of **1** and **2**. Thus, we initially focused on the synthesis of **4** corresponding to the neovibsanin core A-ring. We employed palladium(0)-catalyzed carbonylative cyclization with carbon monoxide to synthesize **4** for which precursor **6** would be suitable.

First, the required precursor **15** for palladium(0)-catalyzed carbonylative cyclization was prepared, starting with 4-penten-1-ol (**7**), as shown in Scheme 2. TBDPS protection of the hydroxy group in **7** followed by ozonolysis of the terminal olefin yielded the aldehyde, which in turn reacted with MeMgI and then the resulting hydroxy group was oxidized with PCC, giving rise to methylketone **8** in 64% yield over four steps. The subsequent Horner–Wadsworth–Emmons–Wittig reaction of **8** with $(EtO)_2P(O)CH_2CO_2Et$ gave **9** as an *E*/*Z* (4:1) isomeric mixture. Reduction of **9** with DIBAL provided the allyl alcohol **10**, which was subjected to the Johnson–Claisen rearrangement[3] with excess triethyl orthoacetate in the presence of a catalytic amount of *n*-propionic acid at 200 °C for 3 days to give the rearranged compound **11** in 97% yield. Successive reduction of the ester moiety of **11** with $LiAlH_4$ yielded the alcohol, which was homologated to α,α-dibromoalkene **12** by PCC oxidation and Corey–Fuchs dibromoolefination.[4] Treatment of **12** with *n*-butyllithium gave lithium acetylide,[5] which was in situ trapped with paraformaldehyde to furnish the propargyl alcohol **13** in 89% yield. The hydrostannation[6] of **13** on heating at 65 °C with *n*-tributyltin hydride in the presence of AIBN (0.05 equiv) proceeded with complete regio and stereoselectivity to give rise to (*Z*)-alkenylstannane **14** in moderate yield. Replacement of butyltin in **14** by iodine afforded the cyclization precursor **15**[7] after TBS protection in 81% yield.

Palladium(0)-catalyzed carbonylative cyclization and related reactions have been well investigated by Negishi and co-workers.[8] Three possible cyclic acylpalladium processes in the absence of nucleophiles are summarized in Scheme 3. The first organopalladium intermediate **17** is generated via oxidative addition of ω-alkenyliodide **16**



Scheme 3. Three possible pathways of intramolecular palladium(0)-catalyzed carbonylative cyclization of ω-terminal olefin-containing iododienes in the absence of nucleophiles.



Scheme 2. Reagents and conditions: (a) TBDPSCl, CH_2Cl_2, Et_3N, DMAP; (b) O_3, CH_2Cl_2/MeOH, $NaHCO_3$, −78 °C, then Me_2S; (c) MeMgI, THF, 0 °C; (d) PCC on Celite, CH_2Cl_2; (e) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 °C; (f) DIBAL, CH_2Cl_2; (g) $(EtO)_3CCH_3$, $CH_3CH_2CO_2H$, 200 °C, 3 days; (h) $LiAlH_4$, THF, 0 °C; (i) PCC on Celite, CH_2Cl_2; (j) CBr_4, PPh_3, CH_2Cl_2; (k) *n*-BuLi, THF, −78 °C, then $(CHO)_n$, rt; (l) Bu_3SnH, AIBN, THF, 65 °C; (m) TBSCl, Et_3N, DMAP, CH_2Cl_2; (n) I_2, CH_2Cl_2, 0 °C.

containing a terminal vinyl group. The insertion of CO to **17** leads to acylpalladium(II) intermediate **18**. The generated acylpalladium(II) species **18** then undergoes intramolecular cyclic acylpalladation to produce cyclic palladium(II) intermediate **20**, which is decomposed to **21** by reductive β-elimination of Pd(0). This mechanistic process is necessary for realizing the preparation of **4**. However, this reaction is also accompanied not only by the formation of the cyclic Heck reaction product **19** through **17**, but also by the formation of the enol lactone **23** via the homologated acylpalladium intermediate **22** derived from **20** under carbonylative conditions.

Thus, the reaction conditions[8a–c] must be carefully set up so as not only to produce the desired products but also to suppress competing side reactions. In addition, the scope of this reaction of terminal vinyl-containing iododienes **16** is thought to be essentially limited to the synthesis of five-membered enones, and neither small ring ketones nor larger rings such as six- and seven-membered enones have been observed in useful yields. With the general outcome of this reaction in mind, our attention was focused on applying Pd(0)-catalyzed carbonylative cyclization to specifically produce the neovibsanins core A ring **4**.

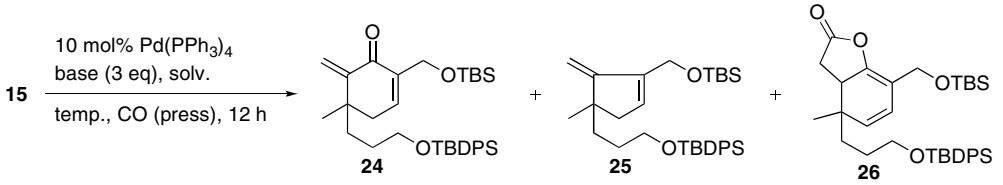
First, we examined the typical Negishi's conditions.[8d,e] Namely, **15** was reacted with 10 mol % $Pd(PPh_3)_4$ in the presence of Et_3N in THF at 100 °C under CO (4 MPa) atmosphere, resulting in the formation of an inseparable complex mixture along with a trace amount of Heck-type compound **25**[9] that could be detected by ^1H NMR of the crude product (Table 1, entry 1), and neither the desired cyclohexadienone **24** nor bicyclic compound **26** were observed as anticipated. To our surprise, however, the same reaction was carried out under reduced CO pressure (0.4 MPa) to yield **24**[10] and **25** in 15% and 36% yield, respectively, in addition to recovered starting material (49%). With 1,4-dioxane as a solvent, the reaction rate was remarkably accelerated, thereby inducing the starting material **15** to disappear in 12 h (entries 3 and 4 in Table 1) to give **24** in 14% yield along with **25** as the main product (86%). These results encouraged us to further explore the potential scope of the Pd(0)-catalyzed carbonylative cyclization with CO to realize specific synthesis of the desired cyclohexadienone **24**.

First, we focused on the effect of catalysts and ligands. All reactions were carried out in the presence of 10 mol % Pd catalysts with K_3PO_4 (3 equiv) in 1,4-dioxane at 70 °C for 12 h (Table 2). When using $Pd_2(dba)_3$, no reaction occurred (entry 1). In contrast, the use of $Pd(dppf)_2$ was found to dramatically enhance reactivity and selectivity in this reaction to provide the desired compound **24** as the major product in moderate yield (entry 2). On the other hand, the steric bulk of the ligand was also preferred for the formation of **24** when $Pd(OAc)_2$ was used as the catalyst (entries 3–7). Although these reaction conditions could substantially suppress the formation of the competing Heck-type product **25**, carboxylic acid **27**[11] that was not observed under other catalytic conditions occurred in significant amounts. This side reaction is most likely to be explained presumably by trapping the acylpalladium intermediate with OH^-.

After a number of trials, we were pleased to find that 10 mol % $PdCl_2(PPh_3)_2$ as a catalyst not only improved the ratio in favor of the formation of **24** over other products but also brought about the highest isolation yield (55%) of **24** (entry 8).[12] If the reaction was employed under the same catalytic conditions at room temperature, **24** was solely obtained in 10% yield along with the recovery starting material **15**, which is recyclable (entry 9). After various bases were examined (entries 10–13), 3 equiv of K_3PO_4 were found to be the most effective base suitable for the 10 mol % $PdCl_2(PPh_3)_2$ catalytic system in the specific Pd(0)-catalyzed carbonylative cyclization.

In conclusion, we constructed the core A-ring **24** of neovibsanins A (**1**) and B (**2**) by applying Pd(0)-catalyzed carbonylative cyclization with carbon monoxide to **15** under the following reaction conditions: 10 mol % $PdCl_2(PPh_3)_2$ with K_3PO_4 (3 equiv) in 1,4-dioxane under ambient CO atmosphere (0.4 MPa) at 70 °C for 12 h. To the best of our knowledge, this is the first example of Pd(0)-catalyzed carbonylative cyclization with carbon monoxide to afford cyclohexadienone derivative in practical yield. Further development of this type of reaction and studies toward

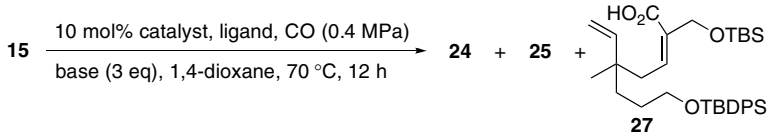
Table 1
Palladium(0)-catalyzed carbonylative cyclization of **15** under Negishi's conditions



Entry	Base	Solv.	Temp. (°C)	Press. (MPa)	Ratio[a] (**15**:**24**:**25**)
1	Et_3N	THF	100	4	(—:—:—)[b]
2	Et_3N	THF	72	0.4	(49:15:36)
3	Et_3N	1,4-Dioxane	100	0.4	(0:14:86)
4	K_3PO_4	1,4-Dioxane	100	0.4	(0:13:87)

[a] The ratio was determined by ^1H NMR (300 MHz).
[b] The condition resulted in complex mixture.

Table 2
Palladium(0)-catalyzed carbonylative cyclization of **15**



Entry	Catalyst	Ligand (equiv)	Base	Isolation yield of **24**	Ratio[a] (**15**:**24**:**25**:**27**)
1	$Pd_2(dba)_3$	—	K_3PO_4	—[b]	(—:—:—:—)
2	$Pd(dppf)_2$	—	K_3PO_4	40	(0:60:40:0)
3	$Pd(OAc)_2$	PBu_3 (3)	K_3PO_4	19	(17:23:46:14)
4	$Pd(OAc)_2$	PPh_3 (3)	K_3PO_4	23	(13:30:39:18)
5	$Pd(OAc)_2$	P(*p*-tol)$_3$ (3)	K_3PO_4	14	(35:20:5:40)
6	$Pd(OAc)_2$	PCy_3 (3)[c]	K_3PO_4	38	(0:49:5:46)
7	$Pd(OAc)_2$	PCy_3 (0.3)[c]	K_3PO_4	47	(0:66:8:26)
8	$PdCl_2(PPh_3)_2$	—	K_3PO_4	55	(0:77:23:0)
9[d]	$PdCl_2(PPh_3)_2$	—	K_3PO_4	10	(79:21:0:0)
10	$PdCl_2(PPh_3)_2$	—	*i*-Pr_2NEt	18	(77:19:4:0)
11	$PdCl_2(PPh_3)_2$	—	Na_2CO_3	15	(71:22:7:0)
12	$PdCl_2(PPh_3)_2$	—	*t*-BuOK	16	(0:22:78:0)
13	$PdCl_2(PPh_3)_2$	—	AcOK	—[e]	(—:—:—:—)

[a] The ratio was determined by ^{1}H NMR (300 MHz).
[b] The condition resulted in complex mixture.
[c] Toluene solution (0.48 M) of PCy_3 was used.
[d] The reaction was carried out at room temperature for 24 h.
[e] No reaction was observed.

total synthesis of neovibsanins A (**1**) and B (**2**) from the key intermediate **24** are currently in progress.

Acknowledgments

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7. *Data for* **15**: $R_f = 0.45$ (EtOAc/hexane = 1:20); IR ν 3072 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.66 (m, 4H), 7.43–7.35 (m, 6H), 5.89 (t, $J = 6.9$ Hz, 1H), 5.70 (dd, $J = 10.8$, 17.4 Hz, 1H), 5.01 (dd, $J = 0.9$, 10.8 Hz, 1H), 4.91 (dd, $J = 0.9$, 17.4 Hz, 1H), 4.25 (br s, 2H), 3.63 (t, $J = 6.0$ Hz, 2H), 2.20 (d, $J = 6.9$ Hz, 2H), 1.54–1.44 (m, 2H), 1.40–1.34 (m, 2H), 1.06 (s, 9H), 0.98 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 135.6, 134.1, 130.5, 129.5, 127.6, 112.4, 108.8, 71.6, 64.5, 46.3, 39.9, 36.8, 27.4, 26.9, 25.8, 22.8, 19.2, 18.3, −5.2; HRMS *m*/*z* (CI^+): $[M+H]^+$ calcd for $C_{33}H_{52}O_2Si_2I$, 663.2551; found, 663.2553.
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9. *Data for* **25**: $R_f = 0.44$ (EtOAc/hexane = 1:20); IR ν 3072 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.63 (m, 4H), 7.41–7.33, (m, 6H), 5.96 (br s, 1H), 4.71 (s, 1H), 4.53 (br s, 1H), 4.31 (br d, $J = 2.4$ Hz, 2H), 3.60 (t, $J = 4.7$ Hz, 2H), 2.33 (br dd, $J = 2.4$, 17.7 Hz, 1H), 2.12 (br dd, $J = 2.4$, 17.7 Hz, 1H), 1.43–1.37 (m, 4H), 1.06 (s, 3H), 1.02 (s, 9H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 143.2, 135.6, 134.1, 131.2, 129.5, 127.5, 99.1, 64.5, 60.0, 45.0, 44.1, 38.1, 28.9, 28.0, 26.9, 25.9, 19.2, 18.4, −5.3; HRMS *m*/*z* (CI^+): $[M+H]^+$ calcd for $C_{33}H_{51}O_2Si_2$, 535.3427; found, 535.3409.
10. *Data for* **24**: $R_f = 0.48$ (EtOAc/hexane = 1:10); IR ν 3072, 1664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.61, (m, 4H), 7.41–7.34 (m, 6H), 6.89 (tt, $J = 2.1$, 4.2 Hz, 1H), 6.01 (d, $J = 1.2$ Hz, 1H), 5.22 (d, $J = 1.2$ Hz, 1H), 4.39 (br d, $J = 2.1$ Hz, 2H), 3.58 (t, $J = 4.8$ Hz, 2H), 2.35 (br d, $J = 4.2$ Hz, 2H), 1.49–1.34 (m, 4H), 1.15 (s, 3H), 1.02 (s, 9H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 151.3, 141.7, 128.4, 137.9, 135.6, 133.9, 129.6, 127.6, 118.8, 64.0, 60.0, 40.4, 38.9, 35.2, 27.5, 26.9, 25.9, 25.2, 19.2, 18.4, −5.4; HRMS *m*/*z* (CI^+): $[M+H]^+$ calcd for $C_{34}H_{51}O_3Si_2$, 563.3377; found, 563.3368.
11. *Data for* **27**: $R_f = 0.46$ (EtOAc/hexane = 1:5); IR ν 3072, 1689 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4H), 7.44–7.35, (m, 6H),

6.49 (t, $J = 6.9$ Hz, 1H), 5.69 (dd, $J = 10.8$, 17.4 Hz, 1H), 5.05 (d, $J = 10.8$ Hz, 1H), 4.94 (d, $J = 17.4$ Hz, 1H), 4.33 (s, 2H), 3.62 (t, $J = 6.0$ Hz, 2H), 2.71 (dd, $J = 6.9$, 16.2 Hz, 1H), 2.58 (dd, $J = 6.9$, 16.2 Hz, 1H), 1.53–1.33 (m, 4H), 1.06 (s, 9H), 0.98 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 146.0, 142.6, 135.6, 134.0, 130.1, 129.5, 127.6, 112.8, 64.5, 63.3, 39.9, 39.8, 37.0, 27.4, 26.9, 25.9, 22.5, 19.3, 18.3, −5.4; HRMS m/z (FAB$^+$): $[M+Na]^+$ calcd for $C_{34}H_{52}O_4Si_2Na$, 603.3302; found, 603.3313.

12. *Typical procedure for carbonylative cyclization*: The suspension of $PdCl_2(PPh_3)_2$ (11.0 mg, 0.0156 mmol) and anhydrous K_3PO_4 (97.7 mg, 0.460 mmol) in 1,4-dioxane (1.5 mL) was stirred at 70 °C under CO (0.4 MPa) atmosphere. After 10 min, the solution of **15** (101.8 mg, 0.154 mmol) in 1,4-dioxane (2.0 mL) was added to the orange reaction mixture via a cannula, and stirred for 12 h at the same temperature. The resulting black mixture was poured into satd NaCl–water (3:20, 23 mL), and extracted with ether (3 × 20 mL). Ether extracts were dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel column chromatography ($SiO_2 = 6$ g, hexane/$Et_3N = 100:1$) gave **24** (47.9 mg, 0.0850 mmol, 55%) and **25** (11.4 mg, 0.0213 mmol, 14%).