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.

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Neovibsanins A (1) and B (2), isolated from the leaves of Viburnum awabuki by Fukuyama et al., are classified into rearranged vibsane-type diterpenes, which consist of more complex and tricyclic structures than the other vibsane-type members. 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, 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.
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 1,4-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 carbonative cyclization with carbon monoxide to synthesize 4 for which precursor 6 would be suitable.

First, the required precursor 15 for palladium(0)-catalyzed carbonative 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)CH2-CO2Et 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 rearrangement3 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 LiAlH4 yielded the alcohol, which was homologated to α,α-dibromoalkene 12 by PCC oxidation and Corey–Fuchs dibromoefinilation.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 hydrostannation6 of 13 on heating at 65 °C with n-tri-butyltin 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 after TBS protection in 81% yield.

Palladium(0)-catalyzed carboxylative 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 α-alkenyliodide 16.

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**Scheme 2.** Reagents and conditions: (a) TBDPSCI, CH2Cl2, Et3N, DMAP; (b) O3, CH3Cl2/MeOH, NaHCO3, −78 °C, then Me2S; (c) MeMgl, THF, 0 °C; (d) PCC on Celite, CH2Cl2; (e) (EtO)2P(O)CH2-CO2Et, NaH, THF, −78 °C; (f) DIBAL, CH3Cl2; (g) (EtO)2CCl3, CH3CH2CO2H, 200 °C, 3 days; (h) LiAlH4, THF, 0 °C; (i) PCC on Celite, CH2Cl2; (j) CBr4, PPh3, CH2Cl2; (k) n-BuLi, THF, −78 °C, then (CHO)2; (l) Bu3SnH, AIBN, THF, 65 °C; (m) TBSCI, Et3N, DMAP, CH2Cl2; (n) I2, CH2Cl2, 0 °C.

**Scheme 3.** Three possible pathways of intramolecular palladium(0)-catalyzed carboxylative cyclization of α-terminal olefin-containing iododienes in the absence of nucleophiles.
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 homoligated acylpalladium intermediate 22 derived from 20 under carboxylative conditions.

Thus, the reaction conditions a, b 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 carboxylative cyclization to specifically produce the neovibsanins core A ring 4.

First, we examined the typical Negishi’s conditions. Namely, 15 was reacted with 10 mol % Pd(PPH₃)₄ in the presence of Et₂N 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 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 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 carboxylative 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 K₃PO₄ (3 equiv) in 1,4-dioxane at 70 °C for 12 h (Table 2). When using Pd₂(dba)₃, no reaction occurred (entry 1). In contrast, the use of Pd(dpdpf)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 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 % PdCl₂(PPh₃)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). 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 K₃PO₄ were found to be the most effective base suitable for the 10 mol % PdCl₂(PPh₃)₂ catalytic system in the specific Pd(0)-catalyzed carboxylative cyclization.

In conclusion, we constructed the core A-ring 24 of neovibsanins A (1) and B (2) by applying Pd(0)-catalyzed carboxylative cyclization with carbon monoxide to 15 under the following reaction conditions: 10 mol % PdCl₂(PPh₃)₂ with K₃PO₄ (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 carboxylative cyclization with carbon monoxide to afford cyclohexadienone derivative in practical yield. Further development of this type of reaction and studies toward

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### Table 1

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* The ratio was determined by ¹H NMR (300 MHz).

b The condition resulted in complex mixture.
total synthesis of neovibsanins A (1) and B (2) from the key intermediate 24 are currently in progress.

Acknowledgments

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References and notes

7. Data for 15: Rf = 0.45 (EtOAc/hexane = 1:20); IR ν 3072 cm−1; 1H NMR (300 MHz, CDCl3) 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, 3H), 0.08 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 146.3, 135.6, 134.1, 130.5, 129.5, 127.6, 112.4, 108.3, 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 C33H51O2Si2I, 663.2553; found, 663.2553.
9. Data for 25: Rf = 0.44 (EtOAc/hexane = 1:20); IR ν 3072 cm−1; 1H NMR (300 MHz, CDCl3) 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); 13C NMR (75 MHz, CDCl3) 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 C33H51O3Si2, 563.3377; found, 563.3368.
10. Data for 27: Rf = 0.46 (EtOAc/hexane = 1:5); IR ν 3072, 1664 cm−1; 1H NMR (300 MHz, CDCl3) δ 7.68–7.65 (m, 4H), 7.44–7.35 (m, 6H), 6.89 (t, 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); 13C NMR (75 MHz, CDCl3) δ 188.8, 151.3, 141.7, 128.4, 137.5, 133.9, 133.9, 129.6, 127.6, 118.8, 64.0, 60.4, 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 C33H52O3Si2, 563.3377; found, 563.3368.
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); 13C 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$_4$Si$_2$Na, 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$_3$PO$_4$ (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$_3$N = 100:1) gave 24 (47.9 mg, 0.0850 mmol, 55%) and 25 (11.4 mg, 0.0213 mmol, 14%).