Nickel-catalyzed dimerization of pyrrolidinoindoline scaffolds: Systematic access to chimonanthines, folicanthines and (+)-WIN 64821

Mitsuhiro Wada, Takahisa Murata, Hideaki Oikawa, and Hiroki Oguri*

Introduction

Despite substantial progress on metal-mediated formation of C(sp$^3$)-C(sp$^3$) bonds, most of the synthetic protocols thus far developed have been aimed at manipulating primary and secondary alkyl halides and their equivalents. Metal-promoted activation of sterically demanding tertiary alkyl halides presents inherent difficulties due to the two major side-reactions of elimination and hydrodehalogenation. Protocols for cross-coupling reactions with tertiary alkyl halides to form quaternary carbon centers have been very limited. Recent synthetic studies on bissesquiterpene lactones reported by Baldwin and dimeric pyrrolidinoindoline alkaloids (1, 3, 5 and 6), as shown in Fig. 1, offered a breakthrough in the formation of highly sterically congested C(sp$^3$)-C(sp$^3$) bonds in elaborated systems (Scheme 1). Movassaghi devised elegant approaches involving Co(I)-mediated reductive dimerization to install vicinal stereogenic quaternary carbon centers. Whilst the efficient applications of the Co(I)-mediated dimerization for total synthesis of bispyrrolidinoindoline diketopiperazine alkaloids by Movassaghi, de Lera, and Sodeoka, have been reported, this protocol requires stoichiometric amounts of CoCl$_2$(PPh$_3$)$_3$. Herein we report an alternative catalytic protocol employing nickel complex for the dimerization of tertiary alkyl bromides (Scheme 2). Although this method requires stoichiometric amounts of manganese as a reductant, applicability of the cost-effective catalytic protocol was illustrated by systematic synthesis of dimeric alkaloids including chimonanthines (1, 2), folicanthines (3, 4), and (+)-WIN 64821 (6) (Fig. 1).
Dimethylacetoamide (DMA) was one of the most suitable solvents (DMA > DMF > NMP > CH₃CN > DMPU > DMSO, THF >> toluene), and dimerization took place efficiently at high concentrations (greater than 1 M solution of 7 in DMA). Control experiments in the absence of either manganese or the phosphine ligand resulted in almost no conversion. The use of anhydrous NiCl₂ substantially retarded the catalytic conversions (entry 10). Treatment of anhydrous NiCl₂ with water (6 equiv. to NiCl₂) in DMA before mixing with DPPE and manganese substantially restored the yield of 8 (52%) (entry 11), suggesting that a hydrated nickel species is necessary to effect dimerization reproducibly. In contrast, the presence of large amounts of water (more than 10 equiv. based on 7) in the reaction mixture with NiCl₂·6H₂O led to a marked decrease in the yield of dimer 8. After optimization of the nickel(II) salt (entries 12–14), catalytic dimerization employing NiCl₂·6H₂O successfully proceeded at room temperature to afford 8 in 74% yield with suppression of the formation of 10 (entry 14). This catalytic protocol is capable of producing gram quantities of 8 (> 3 g, 76% optimum yield) (entry 15). Loading of the catalyst (NiCl₂·6H₂O and DPPE) could be reduced to 2.5 mol% to provide 8 in comparable yield (63%) (entry 16, also see ESI).

The addition of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) to the reaction mixture inhibited catalytic conversion almost completely, with trace amounts of adduct 14 forming instead.

### Table 1. Screening and optimization of catalytic dimerization of 7 (exo).

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (15 mol%)</th>
<th>metal</th>
<th>ligand</th>
<th>8 (dimer)</th>
<th>10</th>
<th>9</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl₂ DPPE</td>
<td>trace</td>
<td>77</td>
<td>9</td>
<td>7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>FeCl₂ DPPE</td>
<td>trace</td>
<td>14</td>
<td>64</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>InCl₃ DPPE</td>
<td>12</td>
<td>&lt;5</td>
<td>74</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CoCl₂ DPPE</td>
<td>46</td>
<td>18</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>NiCl₂·6H₂O DPPE</td>
<td>60</td>
<td>17</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>NiCl₂·6H₂O PPh₃</td>
<td>11</td>
<td>10</td>
<td>19</td>
<td>36</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>NiCl₂·6H₂O DPPF</td>
<td>28</td>
<td>17</td>
<td>20</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>NiCl₂·6H₂O DPPB</td>
<td>46</td>
<td>14</td>
<td>&lt;5</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>NiCl₂·6H₂O DPPP</td>
<td>56</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>NiCl₂ DPPE</td>
<td>trace</td>
<td>7</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>NiCl₂ + 6H₂O DPPE</td>
<td>52</td>
<td>13</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>NiF₂·4H₂O DPPE</td>
<td>trace</td>
<td>&lt;5</td>
<td>83</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>NiBr₂ + 6H₂O DPPE</td>
<td>58</td>
<td>14</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>NiI₂·6H₂O DPPE</td>
<td>74</td>
<td>&lt;5</td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>NiI₂·6H₂O DPPE</td>
<td>76</td>
<td>6</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>NiI₂·6H₂O DPPE</td>
<td>63</td>
<td>17</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Average of two trials.  *

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (2.5 mol%), reaction time (24 h).</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>NiF₂·4H₂O DPPE, trace (15 mol%), 24 h</td>
</tr>
</tbody>
</table>

### Scheme 3. An attempt for nickel-catalyzed dimerization of 7 in the presence of TEMPO.
Although the reaction mechanism remains elusive at this stage, it is likely that the catalytic dimerization reaction involves a radical intermediate. Nickel-catalyzed reductive coupling capable of generating a tertiary radical equivalent as a potent reactive species could provide a novel, cost-effective method for the formation of congested C(sp³)-C(sp³) linkages overcoming the severe steric constraints.

We then explored the substrate scope of the nickel-catalyzed dimerization reaction, focusing on the participation of the methoxycarbonyl group at C1 located in the vicinity of the reaction center (C3a) (Scheme 2). Reductive dimerization of endo-11 furnished the corresponding dimer 12 in 42% yield. Taking into account the moderate yield compared to the exo-isomer [7 → 8 (74%)], it appeared the stereochemical difference had an impact on the assembly of monomers. Meanwhile, the exo-methoxycarbonyl group located on the same face of the bromide atom in 7 was not essential for nickel-catalyzed dimerization. This prompted us to adopt this protocol for the dimerization of pyrrolidinoindoline 16 derived from tryptamine (Scheme 4), which lacks a substitutent at C1. Dimerization of (±)-16 under optimized conditions for monomer 7 (Table 1, entry 14) produced a pair of desired dimers, C₂-18 (13%) and meso-19 (18%). In this system, there was a considerable drop in the combined yield (31%) of the dimers and increased formation of 15 (15%) and 17 (17%). To suppress elimination and formal reduction to give 15 and 17, respectively, we attempted to conduct the dimerization reaction at a lower temperature with modification of the nickel catalyst. The use of NiCl₂·6H₂O and 1,2-bis(diphenylphosphino)benzene (DPPBz) at 4 °C improved the combined yield of the dimers to 55% [C₂-18 (25%) and meso-19 (30%)]. Reduction of C₂-18 with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in refluxing toluene afforded (±)-folicanthine 3 in 81% yield, which allowed confirmation of structural assignments. As an alternative, the removal of Boc groups and subsequent reduction gave (±)-chimonanthine 1¹,²,³ in good yield. Essentially the same conversions of meso-19 provided the corresponding meso-folicanthine 4⁴ and meso-chimonanthine 2.⁵ In pioneering studies to emulate a possible biosynthesis of the simplest tryptamine-based dimers, oxidative homodimerization of two suitable indole or oxindole precursors was applied to achieve concise synthesis of the dimeric pyrrolidinoindoline alkaloids 1–4 in racemic and meso forms.⁶ The development of nickel-catalyzed reductive dimerization offers a different approach for the syntheses of chimonanthes (1, 2) in six steps and folicanthines (3, 4) in five steps from tryptamine, respectively.⁷

Next, the chiral C₂-dimer 12, derived from L-tryptophan, was condensed with an L-phenylalanine component 20 to give (+)-WIN 64821 (6), a potent substance P antagonist isolated from Aspergillus sp. cultures (Scheme 5). Removal of Boc groups with TMSI and site-selective condensation of the resulting tetramine with 20 followed by diketopiperazine formation upon heating afforded (+)-WIN 64821 (6).⁹a,²¹f,²⁴ De Lera and co-workers reported a versatile and stereo-controlled route starting with D-tryptophan, in which Co(I)-mediated dimerization of ent-7 and subsequent epimerization of the resulting ent-8 provided the same intermediate 12.²⁴ This study, through nickel-catalyzed dimerization of 11, provides an alternative and concise method of access to 12 employing an inexpensive L-tryptophan derivative. Thus, synthetic approaches for installing a particular amino acid component at the latest stage of the process could provide divergent access to structural variants of biologically intriguing natural products.

![Scheme 4. Systematic syntheses of chimonanthes and folicanthines.](image)

![Scheme 5. Total synthesis of (+)-WIN 64821 (6) from L/D-tryptophan.](image)
Conclusions
In summary, we developed nickel-catalyzed reductive dimerization reactions of pyrrolidinoindoline units to construct vicinal stereogenic quaternary benzylic carbon centers. This flexible catalytic protocol is applicable to the efficient construction of a series of bispyrrolidinoindoline scaffolds through an appropriate choice of catalyst to accommodate different substrate reactivities. The finding described herein extends the range of application of nickel-catalyzed reductive couplings to enable direct and efficient formation of the highly sterically congested C(sp^3)-C(sp^3) bond. Biosynthetic dimerization often results in improved binding affinity and specificity to biological targets in small molecule ligands through multipoint molecular recognition. Given the profound differences in the physical and functional properties of monomers and dimers, site-selective and stereo-controlled dimerization of an elaborated monomer is a valuable synthetic tool in the development of optimal screening collections of functional small molecules.

Experimental section

All reactions were performed under a nitrogen atmosphere unless otherwise specified. NMR spectra were recorded on JEOL ECA Q600, JNM-ECX 400 (1H/400 MHz, 13C/100 MHz), and Bulk VRSP 500 (1H/500 MHz, 13C/125 MHz) spectrometers. Chemical shifts are reported in δ (ppm) using chloroform as an internal standard of δ 7.26, and 77.16, methanol as an internal standard of δ 3.31, and 49.00, and dimethyl sulfoxide as an internal standard of δ 39.52 for 1H and 13C NMR, respectively. Data for 1H NMR are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), qin (quintet), m (multiplet), br (broad). ESI-spectra were recorded on JEOL the AccuTOF LC-Plus JMS-T100. Optical rotations were recorded on JASCO DIP-360 digital polarimeter. The medium pressure liquid chromatography (MPLC) purifications were performed on a YAMAZEN YFLC-AL580. Where necessary, solvents were distilled from appropriate drying agents prior to use. Reactions were monitored by thin layer chromatography using Merck Millipore TLC Silica gel F254 plates (0.25 mm) which were visualized using UV light, p-anisaldehyde stain, and PMS stain. Flash column chromatography was performed using Kanto Silica Gel 60N or Amino silica-gel [Kanto Silica Gel 60 (spherical) NH2].

Materials

NiCl2 was purchased from Wako Pure Chemical Industries, Ltd. and used after vacuuming for 5 h. NiCl2·6H2O, NiF2·4H2O, NiBr2, CuCl2, FeCl4, and CoCl2 were purchased from Wako Pure Chemical Industries, Ltd. and used as received. NiI2 was purchased from Alfa Aesar and used as received. NiI2·6H2O was purchased from Nacalai Tesque, Inc. and used as received. Manganese and InCl3 were purchased from Aldrich Chemical Co. and used as received. The ligands (SciOPP and TMS-SciOPP) were provided through the generous gift by Prof. Masaharu Nakamura (Kyoto Univ.) and Prof. Takuji Hatakeyama (Kwansei Gakuin Univ.).

**Exo-Bromide (7) and endo-bromide (11).** To a solution of NBS (294 mg, 1.65 mmol, 1.1 eq.) in dichloromethane (150 mL), 9 (626 mg, 1.5 mmol) was added. After being stirred at room temperature for 26 h, the mixture was treated with saturated aqueous solution of Na2SO3 and extracted with chloroform. Organic layer was washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was filtered through a short plug of silica gel to give a mixture of the desired bromides (693 mg, 1.39 mmol, 93%).

**General procedure for nickel-catalyzed dimerization.**

To a mixture of metal catalyst (0.120 mmol, 15 mol%) and DPPE (47.8 mg, 0.120 mmol, 15 mol%) in DMA (650 μL) was added bromide 7 (398 mg, 0.800 mmol), and resulting mixture was purged with nitrogen. After treatment with Mn (50.5 mg, 0.920 mmol, 1.15 eq.), the resulting suspension was immediately purged with nitrogen and stirred at room temperature for 12 h. The mixture was diluted with AcOEt and treated with 1 N HCl. After separation of aqueous phase, organic layer was washed with H2O x2, 1 N HCl, saturated aqueous solution of Na2SO3, and brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to isolate dimer 8,10 byproducts (9 and 10) and recovered substrate 7.
Dimerization of endo-bromide 11. According to general procedure, bromide 11 (398 mg, 0.800 mmol) was treated with NiI2·6H2O (50.5 mg, 0.120 mmol, 15 mol%) and Mn (50.5 mg, 0.919 mmol, 1.15 eq.) in DMA (650 μL) at room temperature for 12 h under nitrogen atmosphere to afford C2-dimer 10 (42%), 13C NMR (100 MHz, CDCl3): δ 173.24, 152.51, 142.48, 132.19, 128.38, 123.52, 117.79, 81.61, 80.82, 59.07, 52.18, 44.90, 33.03, 28.41, 28.33; HR-MS (ESI): calcd. C2H51N2O6 [M+H]+ 419.2177, found 419.2172; [α]28D -100 (c 1.0, CHCl3).

**Dimerization of bromide 16.** According to general procedure, bromide 16 (318 mg, 0.800 mmol) was treated with NiCl2·6H2O (28.5 mg, 0.120 mmol, 15 mol%), DPPBz (53.9 mg, 0.121 mmol, 15 mol%), and Mn (67.2 mg, 1.22 mmol, 1.5 eq.) in DMA (1000 μL) at 4 °C for 20 h under nitrogen atmosphere to afford C2-18 (25%), meso-19 (30%), 15 (9%), 17 (9%).

18. Rf = 0.25 (CH2Cl2:AcOEt = 4:1); 1H NMR (400 MHz, CDCl3, 50 °C): δ 7.45 (2H, d, J = 7.9 Hz), 7.12-0.73 (4H, m), 6.85 (2H, td, J = 7.5, 0.8 Hz), 6.34 (2H, s), 3.83 (2H, dd, J = 11.2, 7.4 Hz), 3.73 (6H, s), 2.82 (2H, td, J = 11.4, 5.5 Hz), 2.24 (2H, td, J = 12.0, 7.6 Hz), 2.14 (2H, dd, J = 12.1, 5.4 Hz), 1.60 (18H, s); 13C NMR (100 MHz, CDCl3, 50 °C): δ 154.99, 152.17, 143.16, 131.44, 129.18, 123.52, 123.06, 116.69, 81.97, 79.13, 60.93, 52.70, 45.46, 33.44, 28.55; HR-MS (ESI): calcd. for C2H51BrN2O6K [M+K]+ 657.2895, found 657.2900.

19. Rf = 0.37 (CH2Cl2:AcOEt = 4:1); 1H NMR (400 MHz, CDCl3, 50 °C): δ 7.63 (2H, d, J = 7.6 Hz), 7.24 (2H, m), 6.95 (2H, t, J = 7.3 Hz), 6.79 (2H, br-s), 6.17 (2H, s), 3.74 (2H, m), 3.71 (6H, s), 2.84 (2H, td, J = 11.5, 5.3 Hz), 2.12 (2H, dd, J = 12.0, 5.2 Hz), 1.98 (2H, m), 1.52 (18H, s); 13C NMR (100 MHz, CDCl3, 50 °C): δ 154.90, 151.94, 143.93, 131.59, 129.53, 123.57, 117.32, 81.78, 78.23, 60.49, 52.60, 45.82, 33.11, 28.38; HR-MS (ESI): calcd. for C42H42N2O6Na [M+Na]+ 675.2895, found 675.2882.

20. Rf = 0.71 (CH2Cl2:AcOEt = 4:1); 1H NMR (500 MHz, CDCl3): δ 7.64 (1H, d, J = 7.6 Hz), 7.20 (1H, td, J = 7.7 Hz), 7.14 (1H, t, J = 7.4 Hz), 7.01 (1H, td, J = 7.5, 0.8 Hz), 6.38 (1H, d, J = 6.4 Hz), 3.99 (1H, t, J = 7.0 Hz), 3.84 (1H, dd, J = 11.2, 7.5 Hz), 3.73 (3H, s), 2.89 (1H, td, J = 11.6, 5.7 Hz), 2.14 (1H, m), 2.07 (1H, dd, J = 12.3, 5.5 Hz), 1.57 (9H, s); 13C NMR (125 MHz, CDCl3): δ 155.43, 152.63, 143.04, 131.94, 128.27, 123.91, 123.33, 116.34, 81.60, 76.48, 52.63, 45.49, 45.11, 31.37, 28.49; HR-MS (ESI): calcd. C17H23N2O6Na [M+Na]+ 341.1472, found 341.1485.

**C2-Chimonanthine ([α]1)-** Trifluoroacetic acid (TFA, 3.7 ml) was slowly added to a stirred solution of C2-dimer 18 (236 mg, 3.47 g, 13.7 mmol) in dichloromethane (60 mL) to treat a solution of NBS (2.50 g, 14.1 mmol) in acetonitrile (30 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then added saturated aqueous solution of Na2S2O5. The resulting mixture was extracted with chloroform, and combined organic extracts were washed with brine, dried over Na2S2O5, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford bromide 16 (5.04 g, 12.7 mmol, 93%) as a white solid.
0.372 mmol) in dichloromethane (3.7 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C and then warm up to room temperature. After being stirred for 2 h, the resulting mixture was concentrated under reduced pressure. The residue was diluted with chloroform and then treated with saturated aqueous solution of NaHCO₃. The combined chloroform extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford meso-di-aniline (S-3, see ESI) (131 mg, 0.301 mmol, 81%) as a white solid. A solution of C₂-di-aniline (57.3 mg, 0.132 mmol) in toluene (1.9 mL) was treated with a 3.3 M toluene solution of sodium bis(2-methoxyethoxy)alumínium hydride (Red-Al) (420 µL, 1.39 mmol, 10.5 eq.) at room temperature. The mixture was then heated to reflux for 1.5 h.

After being cooled to room temperature, excess reagent was quenched by slow addition of 2 M ammonia dissolved in methanol and dichloromethane (1/9). The resulting mixture was concentrated under reduced pressure and filtered through a pad of amino silica-gel. The filtrate was concentrated under reduced pressure, and the residue was purified by silica-gel column chromatography (dichloromethane/2 M ammonia in methanol) to afford C₂-folicanthine (±)-1 (40.7 mg, 0.117 mmol, 89%) as a white powder. The NMR spectra were identical to the literature data.7,30 (±)-1: R₂ = 0.15 (CHCl₃:MeOH = 7:1);

1H NMR (400 MHz, CDCl₃, 50 °C): δ 7.18 (2H, d, J = 7.4 Hz), 6.98 (2H, t, J = 7.5 Hz), 6.65 (2H, t, J = 7.4 Hz), 6.53 (2H, d, J = 7.7 Hz), 4.39 (2H, br-s), 4.23 (2H, br-s), 2.61-2.45 (6H, m), 2.32 (6H, s), 2.06 (2H, m); 13C NMR (100 MHz, CDCl₃, 50 °C): δ 150.97, 133.61, 128.19, 124.58, 118.73, 109.35, 85.44, 63.70, 52.87, 37.30, 35.91; HR-MS (ESI): calcd. for C₂₂H₂₇N₄ [M+H]+ 347.2230, found 347.2248.

C₂-Folicanthine ([±]-3). A solution of 18 (127 mg, 0.200 mmol) in toluene (2.85 mL) was treated with a 3.3 M toluene solution of sodium bis(2-methoxyethoxy)alumínium hydride (Red-Al) (950 µL, 3.14 mmol, 15.7 eq.) at room temperature. The mixture was then heated to reflux for 2 h. After being cooled to room temperature, excess reagent was quenched by slow addition of 2 M ammonia dissolved in methanol and dichloromethane (1/9). The resulting mixture was concentrated under reduced pressure and filtered through a pad of amino silica-gel. The filtrate was concentrated under reduced pressure, and the residue was purified by silica-gel column chromatography (dichloromethane/2 M ammonia in methanol) to afford C₂-folicanthine (±)-3 (60.2 mg, 0.161 mmol, 81%) as a white powder. The NMR spectra were identical to the literature data.7,30 (±)-3: R₂ = 0.32 (CHCl₃:MeOH = 7:1);

1H NMR (400 MHz, CDCl₃, 50 °C): δ 6.99 (2H, t, J = 7.7 Hz), 6.95 (2H, d, J = 7.4 Hz), 6.52 (2H, t, J = 7.4 Hz), 6.28 (2H, d, J = 7.8 Hz), 4.41 (2H, br-s), 3.00 (6H, s), 2.67 (2H, br-s), 2.51-2.34 (10H, m), 1.97 (2H, m); 13C NMR (100 MHz, CDCl₃, 50 °C): δ 153.02, 132.72, 128.41, 123.96, 116.98, 106.15, 92.22, 62.90, 52.90, 37.99, 35.43, 35.35; HR-MS (ESI): calcd. for C₂₂H₂₇N₄ [M+H]+ 347.2230, found 347.2256.

meso-Folicanthine (meso-4). A solution of meso-dimer 19 (128 mg, 0.202 mmol) in toluene (2.9 mL) was treated with a 3.3 M toluene solution of sodium bis(2-methoxyethoxy)alumínium hydride (Red-Al) (950 µL, 3.14 mmol, 15.5 eq.) at room temperature. The mixture was then heated to reflux for 2 h. After being cooled to room temperature, excess reagent was quenched by slow addition of 2 M ammonia dissolved in methanol and dichloromethane (1/9). The resulting mixture was concentrated under reduced pressure and filtered through a pad of amino silica-gel. The filtrate was concentrated under reduced pressure, and the residue was purified by silica-gel column chromatography (dichloromethane/2 M ammonia in methanol) to afford meso-folicanthine 2 (42.8 mg, 0.123 mmol, 89%) as a white powder. The NMR spectra were identical to the literature data.7,30 (±)-4: R₂ = 0.13 (CHCl₃:MeOH = 7:1);

1H NMR (400 MHz, DMSO, 100 °C): δ 6.88 (2H, m), 6.63-6.30 (6H, m), 5.66 (2H, br-s), 4.61 (2H, br-s), 2.74 (2H, m), 2.46 (2H, m), 2.38-2.25 (8H, m), 1.92 (2H, dd, J = 10.8, 4.8 Hz); 13C NMR (100 MHz, DMSO, 100 °C): δ 152.03, 132.33 126.88, 123.28, 115.72, 106.77, 82.52, 62.59, 51.17, 36.27, 34.92; HR-MS (ESI): calcd. for C₂₂H₂₇N₄ [M+H]+ 347.2230, found 347.2248.

(+)-WIN 64821 (6). Idodotrimethylsilane (220 µL, 1.62 mmol, 10.6 eq.) was added dropwise to a solution of the C₂-dimer 12 (128 mg, 0.153 mmol) in acetoniitride (3.1 mL) at 0 °C. The resulting solution was stirred at 0 °C for 90 min and then treated with saturated aqueous solution of Na₂SO₄. The resulting mixture was extracted with chloroform 4.5 times. Combined extracts
were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford crude tetra-amine (S-4, see ESI) (81.7 mg) as a yellow amorphous. The crude tetra-amine was subjected to the next reaction without further purification. To a solution of Boc-Ph-C$_8$H$_4$N$_3$O$_7$ (126 mg, 0.475 mmol, 3.1 eq.), HOAc (73 mg, 0.536 mmol, 3.5 eq.), HATU (195 mg, 0.514 mmol, 3.4 eq.), and 2,6-lutidine (260 µL, 2.23 mmol, 14.6 eq.) in DMF (1.3 mL) was added the solution of the crude tetra-amine (81.7 mg) in DMF (2 mL) at 0 °C. After being warmed up to room temperature, the mixture was stirred for 7 h. The solution was diluted with AcOEt and treated with saturated aqueous solution of NaHCO$_3$. After separation of organic layer, the aqueous phase was extracted with AcOEt. Combined organic extracts were washed with saturated aqueous solution of NaHCO$_3$, H$_2$O x3, and brine. The extract was dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford dipeptide S-5 (108 mg, 0.116 mmol, 76% for 2 steps). Dipeptide (79 mg, 0.085 mmol) was dissolved in 4 N HCl/dioxane (2 mL, 0.04 M) at 0 °C. After being stirred at 0 °C for 15 min, the mixture was warmed up to room temperature, stirred for 2 h, and then concentrated under reduced pressure. The residue was diluted with chloroform and treated with saturated aqueous solution of NaHCO$_3$. The resulting mixture was extracted with chloroform, washed with brine. The combined extracts were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to produce crude tetra-amine. The crude tetra-amine was used as neat and heated at 180 °C for 15 min under nitrogen atmosphere. The residue was purified by silica-gel column chromatography to afford (+)-WIN 64821 (6) (33.2 mg, 0.050 mmol, 59%). The NMR spectra were identical to the literature data. 9a (+)-WIN 64821 (C$_{40}$H$_{37}$N$_6$O$_4$ [M+H]$^+$ 665.2871, found 665.2893; [α]$_D$ = 0.60 (AcOEt:EtOH = 9:1); 1H NMR (500 MHz, CD$_3$OD): δ 2.00 (9H, s), 2.34 (2H, t, $J$ = 7.5 Hz), 4.87 (2H, br-s), 4.15 (2H, t, $J$ = 7.17-7.06 (10H, m), 6.73 (2H, t, $J$ = 7.5 Hz), 6.67 (2H, d, $J$ = 7.8 Hz), 6.07 (2H, s), 5.89 (2H, s), 4.87 (2H, br-s), 4.15 (2H, t, $J$ = 5.3 Hz), 4.05 (2H, t, $J$ = 8.6 Hz), 3.08 (2H, dd, $J$ = 14.7, 5.0 Hz), 3.04-2.94 (4H, m), 2.50 (2H, dd, $J$ = 14.0, 8.0 Hz); 13C NMR (125 MHz, CD$_3$OD): δ 169.78, 168.86, 149.94, 137.28, 131.35, 130.27, 130.07, 129.29, 127.57, 126.00, 120.15, 110.36, 80.47, 60.88, 57.68, 56.91, 36.74, 36.02; HR-MS (ESI): calcd. for C$_{40}$H$_{37}$N$_6$O$_4$ [M+H]$^+$ 665.2871, found 665.2893; [α]$_D$ = 214 (c 0.45, MeOH). The optical rotation data for (+)-WIN 64821 (6) reported in the literatures: [α]$_D$ +200.0 (0.15, MeOH). [α]$_D$ +230 (c 0.15, MeOH). [α]$_D$ [2]

Acknowledgements

This work was financially supported by JSPS KAKENHI (Grant No. 24651253) and Science and Technology Research Partnership for Sustainable Development Program (SATREPS) of the Japan Science and Technology Agency (JST). We thank Prof. Masaharu Nakamura (Kyoto Univ.) and Prof. Takuju Hatakeyama (Kwansei Gakuin Univ.) for the generous gift of ligands and insightful discussions.

Notes and references

32 During the evaluation of this manuscript, a related nickel-catalyzed dimerization of pyrrolidinoindoline scaffold has been reported, see: Y. Peng, L. Luo, C.-S. Yan, J.-J. Zhang and Y.-W. Wang, J. Org. Chem., ASAP (DOI: 10.1021/jo401936v).