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

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While metal-promoted activation of tertiary alkyl halides often causes elimination and hydrodehalogenation, we have developed a nickel-catalyzed reductive dimerization that allows the generation of a potently reactive tertiary radical equivalent to form a very congested C(sp^3)-C(sp^3) bond even below room temperature. The catalytic protocol is applicable to the dimerization of several pyrrolidinoindoline scaffolds through an appropriate choice of catalyst to accommodate different substrate reactivities with functional group compatibilities. The efficiency of the nickel-catalyzed protocol was successfully demonstrated through systematic total synthesis of chimonanthines, folicanthines and (+)-WIN 64821.

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.[1] 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[2] as well as reductive dimerization[3] with tertiary alkyl halides to form quaternary carbon centers have been very limited.[4] Recent synthetic studies on bissesquiterpene lactones reported by Baldwin[5] and dimeric pyrrolidinoindoline alkaloids (**1**, **3**, **5** and **6**),[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[7] to install vicinal stereogenic quaternary carbon centers.[6,8] Whilst the efficient applications of the Co(I)-mediated dimerization for total synthesis of bispyrrolidinoindoline diketopiperazine alkaloids by Movassaghi,[9] de Lera,[10] and Sodeoka,[11] have been reported, this protocol requires stoichiometric amounts of $CoCl(PPh_3)_3$. 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).[12]

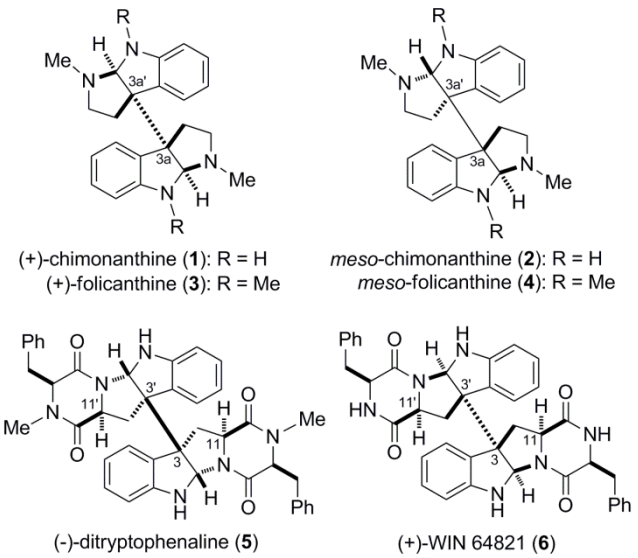

Fig. 1. Dimeric pyrrolidinoindoline alkaloids **1**–**6** with symmetric and stereochemical variations.

Results and Discussion

Conditions for catalytic dimerization were screened employing the tertiary bromide **7** as a monomeric substrate (Table 1). A series of metal sources (15 mol%) were tested using a phosphine ligand in the presence of manganese (1.2 equiv.). While the use of $CuCl_2$, $FeCl_3$ and $InCl_3$ mainly resulted in elimination, yielding **9** as the major product (entries 1–3), the attempt using $CoCl_2$ produced the desired C_2-dimer **8** in 46% yield (entry 4).[13] This catalytic reductive dimerization was improved by the use of $NiCl_2 \cdot 6H_2O$, giving rise to **8** in 60% yield (entry 5).[14] Based on systematic screening of the dimerization conditions (see ESI), we used 1,2-bis(diphenylphosphino)ethane (DPPE) as the optimum ligand for dimerization of **7** to afford **8** (entries 5–9).

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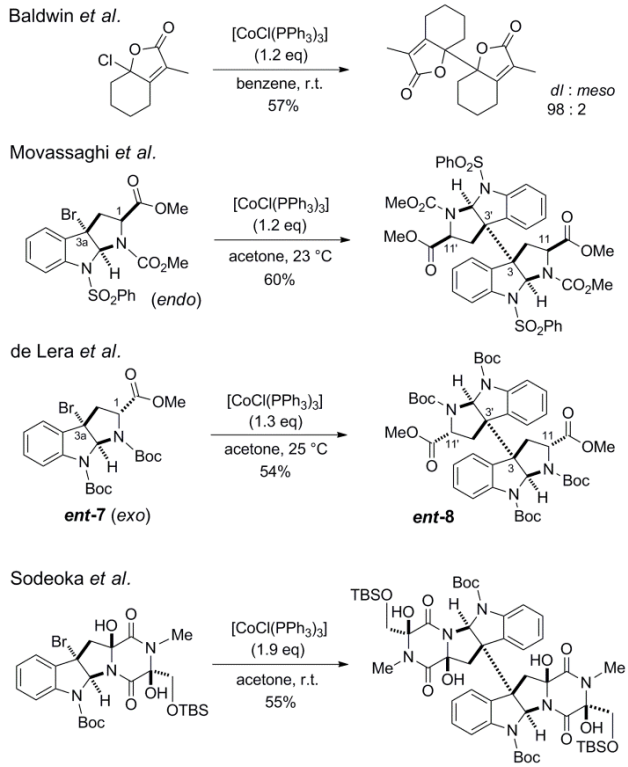
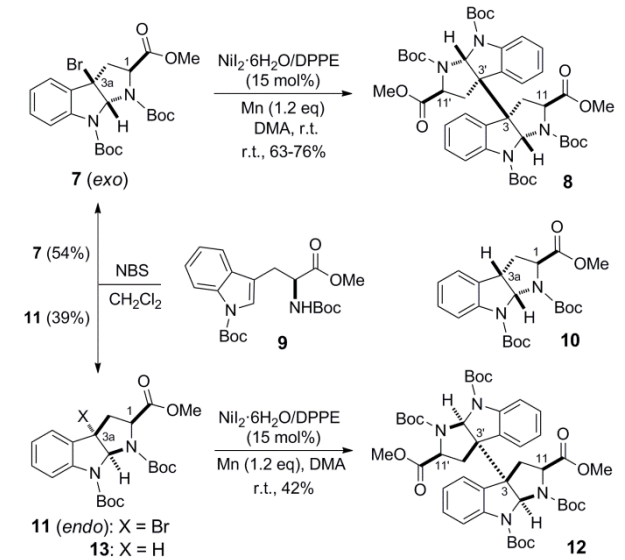


Scheme 1. Cobalt-mediated dimerization of various monomers by Baldwin, Movassaghi, de Lera and Sodeoka.



Scheme 2. Nickel-catalyzed reductive dimerizations.

Dimethylacetoamide (DMA) was one of the most suitable solvents (DMA~DMF > NMP > CH_3CN > 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 $NiCl_2$ substantially retarded the catalytic conversions (entry 10). Treatment of anhydrous $NiCl_2$ with water (6 equiv. to $NiCl_2$) 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.[15] In contrast, the presence of large amounts of water (more than 10 equiv. based on **7**) in the reaction mixture with $NiCl_2{\cdot}6H_2O$ led to a marked decrease in the yield of dimer **8**. After optimization of the nickel(II) salt (entries 12–14), catalytic dimerization employing $NiI_2{\cdot}6H_2O$ 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 ($NiI_2{\cdot}6H_2O$ and DPPE) could be reduced to 2.5 mol% to provide **8** in comparable yield (63%) (entry 16, also see ESI).

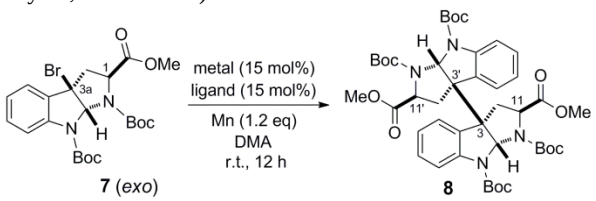
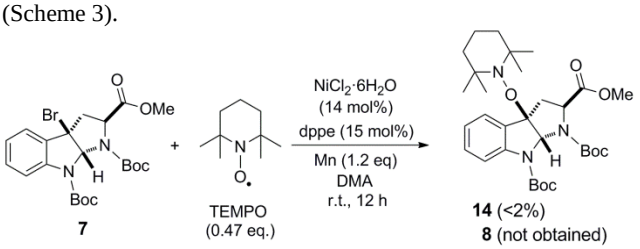


Table 1. Screening and optimization of catalytic dimerization of **7** (*exo*).

entry	catalyst (15 mol%)		yield (%)[a]			
	metal	**ligand**	**8 (dimer)**	**10**	**9**	**7**
1	$CuCl_2$	DPPE	trace	trace	77	–
2	$FeCl_2$	DPPE	trace	14	64	–
3	$InCl_3$	DPPE	12	<5	74	–
4	$CoCl_2$	DPPE	46	18	<5	–
5	**$NiCl_2{\cdot}6H_2O$**	**DPPE**	**60**	17	8	–
6	$NiCl_2{\cdot}6H_2O$	PPh_3[b]	11	10	19	36
7	$NiCl_2{\cdot}6H_2O$	DPPF	28	17	20	<5
8	$NiCl_2{\cdot}6H_2O$	DPPB	46	14	<5	10
9	$NiCl_2{\cdot}6H_2O$	DPPP	56	<5	<5	<5
10	$NiCl_2$	DPPE	trace	trace	7	75
11	$NiCl_2$ + $6H_2O$	DPPE	52	13	5	–
12	$NiF_2{\cdot}4H_2O$	DPPE	trace	<5	trace	83
13	$NiBr_2$ + $6H_2O$	DPPE	58	14	<5	–
14	**$NiI_2{\cdot}6H_2O$**	**DPPE**	**74**	<5	13	–
15[c]	$NiI_2{\cdot}6H_2O$	DPPE	76	6	9	–
16[d]	$NiI_2{\cdot}6H_2O$	DPPE	63	17	<5	-

[a] Average of two trials. [b] Ligand (30 mol%). [c] **7** (5 g scale). [d] catalyst (2.5 mol%), reaction time (24 h).

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 (Scheme 3).

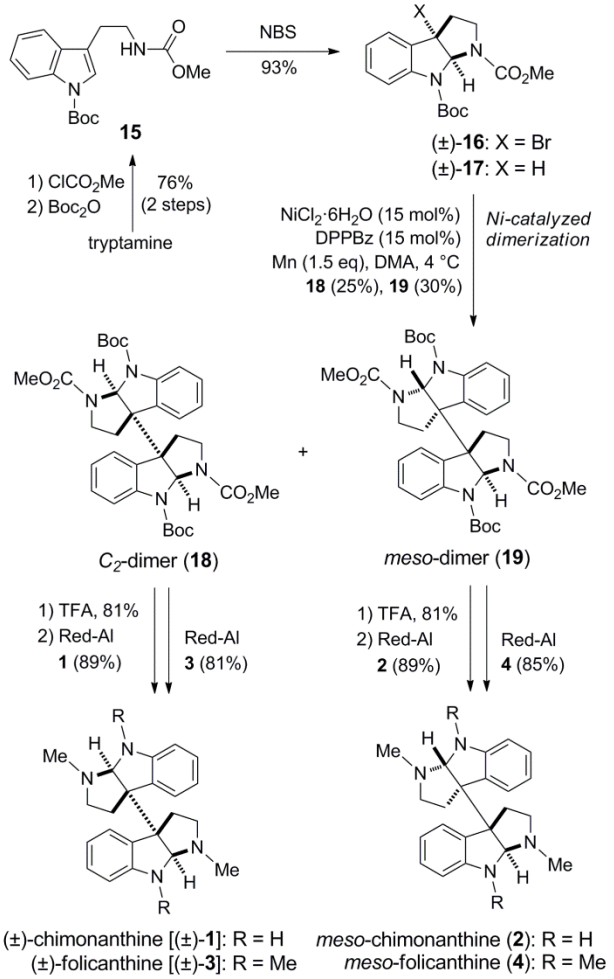


Scheme 3. An attempt for nickel-catalyzed dimerization of **7** in the presence of TEMPO.

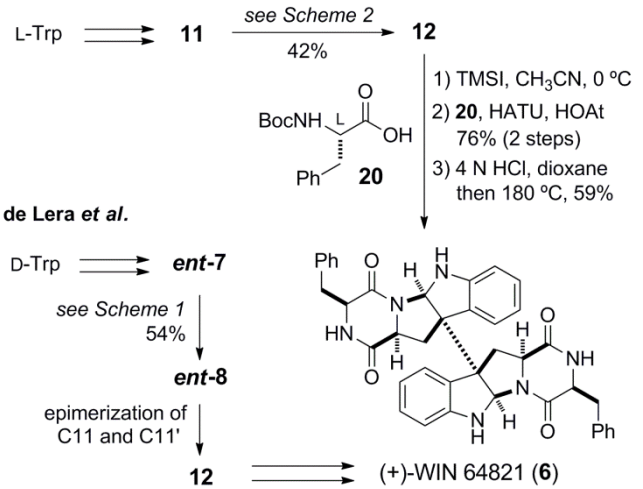
Although the reaction mechanism remains elusive at this stage, it is likely that the catalytic dimerization reaction involves a radical intermediate.[16] Nickel-catalyzed reductive coupling capable of generating a tertiary radical equivalent as a potent reactive species could provide a novel, cost-effective and potentially general protocol for the formation of a congested $C(sp^3)$-$C(sp^3)$ linkages overriding 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 substituent at C1. Dimerization of (±)-**16** under optimized conditions for monomer **7** (Table 1, entry 14) produced a pair of desired dimers, C_2-**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 $NiCl_2{\cdot}6H_2O$ and 1,2-bis(diphenylphosphino)benzene (DPPBz) at 4 °C improved the combined yield of the dimers to 55% [C_2-**18** (25%) and *meso*-**19** (30%)]. Reduction of C_2-**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 **1**[17,18] in good yield. Essentially the same conversions of *meso*-**19** provided the corresponding *meso*-folicanthine **4**[19] and *meso*-chimonanthine **2**.[20] 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 form.[21] The development of nickel-catalyzed reductive dimerization offers a different approach for the syntheses of chimonanthines (**1**, **2**) in six steps and folicanthines (**3**, **4**) in five steps from tryptamine, respectively.[22]

Next, the chiral C_2-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).[23] Removal of Boc groups with TMSI and site-selective condensation of the resulting tetra-amine 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**.[10] 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 chimonanthines and folicanthines.



Scheme 5. Total synthesis of (+)-WIN 64821 (6) from L/D -tryptophan.

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.[25,26] 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 α400, JNM-ECX 400 (^{1}H/400 MHz, ^{13}C/100 MHz), and Bulker VSP 500 (^{1}H/500 MHz, ^{13}C/125 MHz) spectrometers. Chemical shifts are reported in δ (ppm) using chloroform as an internal standard of δ 7.26, and 77.16, acetonitrile as an internal standard of δ 1.94, and 118.26, methanol as an internal standard of δ 3.31, and 49.00, and dimethyl sulfoxide as an internal standard of δ 2.50, and 39.52 for ^{1}H and ^{13}C NMR, respectively. Data for ^{1}H NMR are reported as follows: chemical shift (number of hydrogens, multiplicity, coupling constant). Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad). ESI-Mass 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-AI-580. 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 F_{254} 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) NH_2].

Materials

$NiCl_2$ was purchased from Wako Pure Chemical Industries, Ltd. and used after vacuuming for 5 h. $NiCl_2 \cdot 6H_2O$, $NiF_2 \cdot 4H_2O$, $NiBr_2$, $CuCl_2$, $FeCl_3$, and $CoCl_2$ were purchased from Wako Pure Chemical Industries, Ltd. and used as received. NiI_2 was purchased from Alfa Aesar and used as received. $NiI_2 \cdot 6H_2O$ was purchased from Nacalai Tesque, Inc. and used as received. Manganese and $InCl_3$ were purchased from Aldrich Chemical Co. and used as received. The ligands (SciOPP and TMS-SciOPP)[27] 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**[28] (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 Na_2SO_3 and extracted with chloroform. Organic layer was washed with brine, dried over Na_2SO_4, 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%, **7** (*exo*) : **11** (*endo*) = 100 : 71). These diastereomers were easily separated by silica-gel column chromatography to produce **7** (*exo*)[10] and **11** (*endo*), 54% and 39% yields, respectively.

7: R_f = 0.48 (Hex:AcOEt = 3:1);^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (1H, br-s), 7.42-7.29 (2H, m), 7.13 (1H, t, *J* = 7.5 Hz), 6.40 (1H, s), 3.89 (1H, dd, *J* = 10.4, 6.3 Hz), 3.75 (3H, s), 3.21 (1H, dd, *J* = 12.6, 6.3 Hz), 2.82 (1H, dd, *J* = 12.5, 10.4 Hz), 1.59 (9H, s), 1.41(9H, br-s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.68, 152.37, 141.70, 133.02, 130.77, 124.54, 123.37, 118.79, 83.97, 82.47, 81.67, 59.89, 59.63, 52.55, 42.24, 28.42, 28.36; HR-MS (ESI): calcd. $C_{22}H_{29}BrN_2O_6Na$ $[M+Na]^+$ 519.1101, found 519.1128; $[\alpha]_D^{25}$ -144 (*c* 1.0, $CHCl_3$).

11: R_f = 0.44 (Hex:AcOEt = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (1H, br-s), 7.31-7.24 (2H, m), 7.04 (1H, t, *J* = 7.5 Hz), 6.44 (1H, s), 4.54 (1H, d, *J* = 8.7 Hz), 3.27 (1H, d, *J* = 12.9 Hz), 3.13 (3H, s), 3.08 (1H, dd, *J* = 12.9, 9.3 Hz), 1.60 (9H, s), 1.47 (9H, br-s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.92, 152.29, 142.64, 132.58, 130.79, 124.03, 118.27, 84.49, 82.28, 81.63, 60.51, 59.78, 52.18, 43.56, 28.49, 28.38; HR-MS (ESI): calcd. $C_{22}H_{30}BrN_2O_6$ $[M+H]^+$ 497.1282, found 497.1284; $[\alpha]_D^{25}$ +76 (*c* 1.0, $CHCl_3$).

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 again 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 H_2O x2, 1 N HCl, saturated aqueous solution of Na_2SO_3, and brine, dried over Na_2SO_4, 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**.

8: R_f = 0.39 (Hex:AcOEt = 2:1);^{1}H NMR (400 MHz, DMSO, 95 °C): δ 7.37 (2H, d, *J* = 8.0 Hz), 7.21-7.11 (4H, m), 6.91 (2H, m), 6.09 (2H, s), 3.70 (2H, m), 3.68 (6H, s), 2.64 (2H, dd, *J* = 12.7, 7.0 Hz), 2.25 (2H, dd, *J* = 12.7, 9.5 Hz), 1.57 (18H, s), 1.33 (18H, s); ^{13}C NMR (100 MHz, DMSO, 95 °C): 171.39, 151.26, 150.45, 141.16, 130.28, 128.72, 123.47, 122.23, 115.86, 80.84, 80.04, 78.61, 58.07, 57.75, 51.35, 34.49, 27.43, 27.27; HR-MS (ESI): calcd. for $C_{44}H_{58}N_4O_{12}Na$ $[M+Na]^+$ 857.3943, found 857.3957; $[\alpha]_D^{27}$ -133 (*c* 1.0, $CHCl_3$).

10: R_f = 0.46 (Hex:AcOEt = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (1H, br-s), 7.21 (1H, t, *J* = 7.6 Hz), 7.15 (1H, d, *J* = 7.4

Hz), 7.03 (1H, t, *J* = 7.5 Hz), 6.36 (1H, d, *J* = 5.9 Hz), 4.00-3.90 (2H, m), 3.71 (3H, s), 2.53 (1H, dd, *J* = 12.7, 6.9 Hz), 2.27 (1H, ddd, *J* = 12.7, 10.0, 7.2 Hz), 1.56 (9H, s), 1.39 (9H, br-s); ^{13}C NMR (125 MHz, $CDCl_3$): 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. $C_{22}H_{31}N_2O_6$ $[M+H]^+$ 419.2177, found 419.2172; $[\alpha]_D^{28}$ -100 (*c* 1.0, $CHCl_3$).

Dimerization of *endo*-bromide 11. According to general procedure, bromide **11** (398 mg, 0.800 mmol) was treated with $NiI_2 \cdot 6H_2O$ (50.5 mg, 0.120 mmol, 15 mol%), DPPE (47.6 mg, 0.119 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 C_2-dimer **12**[10] (42%), **13**[29] (17%), and **9** (17%).

12: R_f = 0.30 (Hex:AcOEt = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ 7.38 (2H, d, *J* = 7.1 Hz), 7.09 (2H, m), 6.96 (2H, d, *J* = 7.5 Hz), 6.79 (2H, t, *J* = 7.5 Hz), 6.37 (2H, s), 4.53 (2H, t, *J* = 4.7 Hz), 3.06 (6H, s), 2.53 (4H, d, *J* = 4.9 Hz), 1.61 (18H, s), 1.48 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ 171.33, 152.17, 143.74, 130.52, 129.50, 125.11, 122.51, 117.37, 81.91, 79.47, 77.36, 59.29, 51.84, 35.91, 28.58; HR-MS (ESI): calcd. for $C_{44}H_{58}N_4O_{12}Na$ $[M+Na]^+$ 857.3943, found 857.3957; $[\alpha]_D^{28}$ +97 (*c* 1.0, $CHCl_3$).

13: R_f = 0.47 (Hex:AcOEt = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (1H, br-s), 7.17 (1H, t, *J* = 7.7 Hz), 7.08 (1H, d, *J* = 7.4 Hz), 6.95 (1H, t, *J* = 7.4 Hz), 6.41 (1H, d, *J* = 6.6 Hz), 4.56 (1H, d, *J* = 8.7 Hz), 3.96 (1H, t, *J* = 6.6 Hz), 3.13 (3H, s), 2.58 (1H, d, *J* = 12.9 Hz), 2.52 (1H, m), 1.58 (9H, s), 1.46 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.34, 152.59, 143.38, 131.82, 128.43, 124.03, 123.12, 117.26, 81.51, 80.82, 76.92, 59.49, 51.95, 44.92, 33.87, 28.53, 28.45; HR-MS (ESI): calcd. $C_{22}H_{31}N_2O_6$ $[M+H]^+$ 419.2177, found 419.2171; $[\alpha]_D^{27}$ +5.0 (*c* 1.0, $CHCl_3$).

***tert*-Butyl 3-(2-((methoxycarbonyl)amino)ethyl)-1*H*-indole-1-carboxylate 15.** A solution of tryptamine (4.01 g, 25.1 mmol) and triethyl amine (10.4 mL, 75.0 mmol) in 1:1 mixture of chloroform and acetonitrile (170 mL) was added methyl chloroformate (2.30 mL, 30.0 mmol) at 0 °C and stirred for 15 min. The solution was then heated to 35 °C and stirred for 1.5 h. After being cooled to 0 °C, the resulting reaction mixture was diluted with chloroform and treated with 1 N HCl. The combined chloroform extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford methyl carbamate (**S-1**, see ESI) (4.29 g, 19.6 mmol, 78%) as a light brown amorphous. A solution of methyl carbamate (773 mg, 3.54 mmol) in 2:1 mixture of dichloromethane and THF (24 mL) was treated with Boc_2O (920 mg, 4.22 mmol) and DMAP (40.3 mg, 0.33 mmol, 9 mol%). The solution was stirred at room temperature for 50 min and concentrated under reduced pressure. The resulting residue was purified by silica-gel column chromatography to afford **15** (1.11 g, 3.46 mmol, 98%) as a white amorphous. **15**: R_f = 0.51 (Hex:AcOEt = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (1H, br-s), 7.54 (1H, d, *J* = 7.6 Hz), 7.42 (1H, s), 7.32 (1H, t, *J* = 7.3 Hz), 7.25 (1H, t, *J* = 7.2 Hz), 4.79 (1H, br-s), 3.67 (3H, s), 3.52 (2H, m), 2.91 (2H, t, *J* = 6.8 Hz), 1.67 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.16, 149.85, 135.77, 130.48, 124.67, 123.38, 122.68, 119.02, 117.67, 115.50, 83.76, 52.21, 40.80, 28.38, 25.79; HR-MS (ESI): calcd. $C_{17}H_{22}N_2O_4Na$ $[M+Na]^+$ 341.1472, found 341.1491.

Bromide 16. A solution of tryptamine derivative **15** (4.37 g, 13.7 mmol) in dichloromethane (60 mL) was treated with 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 Na_2SO_3. The resulting mixture was extracted with chloroform, and combined organic extracts were washed with brine, dried over Na_2SO_4, 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. **16**: R_f = 0.41 (Hex:AcOEt = 3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (1H, d, *J* = 7.6 Hz), 7.37 (1H, dd, *J* = 7.6, 0.9 Hz), 7.30 (1H, m), 7.10 (1H, td, *J* = 7.6, 0.9 Hz), 6.38 (1H, s), 3.78 (1H, m), 3.74 (3H, s), 2.90-2.79 (2H, m), 2.75 (1H, m), 1.59 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.84, 152.24, 142.10, 132.46, 130.62, 124.33, 123.82, 117.49, 84.16, 82.26, 62.22, 52.85, 46.41, 41.21, 28.38; HR-MS (ESI): calcd. $C_{17}H_{21}BrN_2O_4K$ $[M+K]^+$ 435.0316, found 435.0302.

Dimerization of bromide 16. According to general procedure, bromide **16** (318 mg, 0.800 mmol) was treated with $NiCl_2 \cdot 6H_2O$ (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 C_2-**18** (25%), *meso*-**19** (30%), **15** (9%), **17** (9%).

18: R_f = 0.25 (CH_2Cl_2:AcOEt = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ 7.45 (2H, d, *J* = 7.9 Hz), 7.12-7.03 (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); ^{13}C NMR (100 MHz, $CDCl_3$, 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 $C_{34}H_{42}N_4O_8Na$ $[M+Na]^+$ 657.2895, found 657.2920.

19: R_f = 0.37 (CH_2Cl_2:AcOEt = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 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); ^{13}C NMR (100 MHz, $CDCl_3$, 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 $C_{34}H_{42}N_4O_8Na$ $[M+Na]^+$ 657.2895, found 657.2882.

17: R_f = 0.71 (CH_2Cl_2:AcOEt = 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (1H, d, *J* = 7.6 Hz), 7.20 (1H, t, *J* = 7.7 Hz), 7.14 (1H, d, *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); ^{13}C NMR (125 MHz, $CDCl_3$): 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. $C_{17}H_{22}N_2O_4Na$ $[M+Na]^+$ 341.1472, found 341.1485.

***C*$_2$-Chimonanthine [(±)-1].** Trifluoroacetic acid (TFA, 3.7 mL) was slowly added to a stirred solution of C_2-dimer **18** (236 mg,

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 $NaHCO_3$. The combined chloroform extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford C_2-dianiline (**S-2**, see ESI) (131 mg, 0.301 mmol, 81%) as a white solid. A solution of C_2-dianiline (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)aluminum 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 resulting residue was purified by silica-gel column chromatography (dichloromethane/2 M ammonia in methanol) to afford C_2-chimonanthine (±)-**1** (40.7 mg, 0.117 mmol, 89%) as a white powder. The NMR spectra were identical to the literature data.[7,30] (±)-**1**: R_f = 0.15 ($CHCl_3$:MeOH = 7:1); ^{1}H NMR (400 MHz, $CDCl_3$, 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); ^{13}C NMR(100 MHz, $CDCl_3$, 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 $C_{22}H_{27}N_4$ $[M+H]^+$ 347.2230, found 347.2256.

***C*$_2$-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)aluminum 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 resulting residue was purified by silica-gel column chromatography (dichloromethane/2 M ammonia in methanol) to afford C_2-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**: R_f = 0.32 ($CHCl_3$:MeOH = 7:1); ^{1}H NMR (400 MHz, $CDCl_3$, 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); ^{13}C NMR (100 MHz, $CDCl_3$, 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 $C_{24}H_{31}N_4$ $[M+H]^+$ 375.2543, found 375.2556.

***meso*-Chimonanthine (*meso*-2).** Trifluoroacetic acid (TFA, 7 mL) was slowly added to a stirred solution of *meso*-dimer **19** (442 mg, 0.696 mmol) in dichloromethane (7 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C and then warm up to room temperature. After being stirred for 1.5 h, the resulting mixture was concentrated under reduced pressure. The residue was diluted with chloroform and then treated with saturated aqueous solution of $NaHCO_3$. The combined chloroform extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford *meso*-dianiline (**S-3**, see ESI) (245 mg, 0.563 mmol, 81%) as a pale yellow amorphous. A solution of *meso*-dianiline (60.6 mg, 0.139 mmol) in toluene (2.0 mL) was treated with a 3.3 M toluene solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (450 µL, 1.49 mmol, 10.7 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 resulting residue was purified by silica-gel column chromatography (dichloromethane/2 M ammonia in methanol) to afford *meso*-chimonanthine **2** (42.8 mg, 0.123 mmol, 89%) as a white powder. The NMR spectra were identical to the literature data.[31] *meso*-**2**: R_f = 0.13 ($CHCl_3$:MeOH = 7:1); ^{1}H 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); ^{13}C 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 $C_{22}H_{27}N_4$ $[M+H]^+$ 347.2230, found 347.2248.

***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)aluminum 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 resulting residue was purified by silica-gel column chromatography (dichloromethane/2 M ammonia in methanol) to afford *meso*-folicanthine **4**[19] (64.4 mg, 0.172 mmol, 85%) as a white powder. *meso*-**4**: R_f = 0.27 ($CHCl_3$:MeOH = 7:1); ^{1}H NMR (400 MHz, DMSO, 100 °C): δ 7.00 (2H, t, *J* = 7.9 Hz), 6.50-6.28 (6H, m), 4.09 (2H, br-s), 2.75 (2H, m), 2.59 (6H, s), 2.42-2.26 (10H, m), 1.91 (2H, m); ^{13}C NMR (100 MHz, DMSO, 100 °C): δ 153.65, 132.47, 127.45, 123.00, 116.22, 106.29, 90.73, 62.26, 51.55, 35.65, 35.45, 35.02; HR-MS (ESI): calcd. for $C_{24}H_{31}N_4$ $[M+H]^+$ 375.2543, found 375.2544.

(+)-WIN 64821 (6). Iodotrimethylsilane (220 µL, 1.62 mmol, 10.6 eq.) was added dropwisely to a solution of the C_2-dimer **12** (128 mg, 0.153 mmol) in acetonitrile (3.1 mL) at 0 ºC. The resulting solution was stirred at 0 ºC for 90 min and then treated with saturated aqueous solution of Na_2SO_3. The resulting mixture was extracted with chloroform 4-5 times. Combined extracts

were dried over Na_2SO_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-Phe-OH (126 mg, 0.475 mmol, 3.1 eq.), HOAt (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 NH_4Cl. 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_2O x3, and brine. The extract was dried over Na_2SO_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_2SO_4, filtered, and concentrated under reduced pressure to produce crude tetra-amine. The crude tetra-amine was used as neat and heated at 180 ºC 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 (**6**): R_f = 0.60 (AcOEt:EtOH = 9:1); ^{1}H NMR (500 MHz, CD_3CN): δ 7.34 (2H, d, *J* = 7.5 Hz), 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); ^{13}C NMR (125 MHz, CD_3CN): 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 $C_{40}H_{37}N_6O_4$ $[M+H]^+$ 665.2871, found 665.2893; $[\alpha]_D^{25}$ +214 (*c* 0.45, MeOH). The optical rotation data for (+)-WIN 64821 (**6**) reported in the literatures: $[\alpha]_D$ +200.0 (*c* 0.15, MeOH),[23] $[\alpha]_D^{21}$ +230 (*c* 0.15, MeOH).[9a]

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