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Technical Note

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A Novel and Practical Synthesis of Ramelteon

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Supporting Information

ABSTRACT: An efficient and practical process for the synthesis of ramelteon **1**, a sedative-hypnotic, is described. Highlights in this synthesis are the usage of acetonitrile as nucleophilic reagent to add to 4,5-dibromo-1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-one **2** and the subsequent hydrogenation which successfully implement four processes (debromination, dehydration, olefin reduction, and cyano reduction) into one step to produce the ethylamine compound **13** where dibenzoyl-L-tartaric acid is selected both as an acid to form the salt in the end of hydrogenation and as the resolution agent. Then, target compound **1** is easily obtained from **13** via propionylation. The overall yield in this novel and concise process is almost twice as much as those in the known routes, calculated on compound **2**.

INTRODUCTION

Ramelteon **1** or (*S*)-*N*-[2-(1,6,7,8- tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)ethyl]propionamide is well-known as a selective melatonin MT1/MT2 receptor agonist which primarily has been used as a treatment of insomnia.[1,2] It was developed by the Japanese company Takeda and approved by the US Food and Drug Administration (FDA) in 2005. With negligible affinity for other neuronal receptors related with gamma-aminobutyric acid and benzodiazepine, ramelteon seldom has the adverse effects, occurring for the traditional sedative hypnotics, such as learning and memory impairment and drug dependence.[3,4] This advantage makes it the first and only prescription sleep medication that is not designated as a controlled substance by the US Drug Enforcement Administration (DEA).[5]

Recently, Zhang et al.[6] and Fu et al.[7] reported new approaches to synthesize ramelteon **1** by asymmetric Michael addition, and both of them required long reaction steps and adopted expensive chiral auxiliaries. However, as the practical synthesis, the key part is the installation of the side chain into the three-fused-ring system at the benzylic position. The Wittig−Horner reaction was the only way to complete the installation so far found in the literature.[8−12] As outlined in Scheme 1, it requires different kinds of phosphorous ylide, which is usually prepared from a trialkyloxyphosphine and chloroacetate or chloracetonitrile.[13] In Addition, more than one step of reduction were employed in both existing routes, and they required either long preparation steps or complicated procedures. Most of all, they all suffer from very low yields.

Our group was interested in exploiting a novel method to install the side chain without involving any Wittig reaction. Since the side chain of key intermediate **8** was composed of two carbons and one nitrogen atom, we attempted to construct the skeleton with acetonitrile as the building block. After the cyanomethyl was added to the ketone **2** with acetonitrile as a nucleophilic reagent, amino-compound **8** could be obtained via a series of reduction by catalytic hydrogenation. Herein, a novel and optimized synthesis of ramelteon was established with short preparation steps and cheap reagents (Scheme 2).

RESULTS AND DISCUSSION

Our studies commenced with the nucleophilic addition of compound **2** (prepared according to the literature[8]) and acetonitrile in tetrahydrofuran with *n*-butyllithium as a base. An exciting result was obtained in the concept-proof test where 2 equiv *n*-butyllithium was employed and the reaction temperature was controlled at −15 °C (Table 1, entry 1). Then, the following experiments showed that the reaction went better with the lower temperature and higher ratio of base and acetonitrile/the substrate. Notably, an excellent yield (77%, Table 1, entry 5) was achieved at −75 °C with the presence of 4 equiv of *n*-butyllithium and acetonitrile. To explore the viability of other base, the reactions were carried out with different alkalis, but the outcome was disappointing with reduced yield or complicated products. For example, when lithium diisopropylamide was used, the yield was declined to 67% (Table 1, entry 7). Even lower yield (33%) was obtained when the reaction was performed at −45 °C (entry 8). Furthermore, in the tests with the nonorganolithium base (e.g., *t*-BuOK, NaH or NaOEt), either the reaction did not go (the starting material **2** was recovered), or it gave too complicated products to purify (Table 1, entries 9−12).

With the nucleophilic addition product **11** in hand, the next step was the reduction. In order to convert compound **11** into the ethylamine **14**, a series of reactions including debromination, dehydration, olefin reduction, and cyano reduction was involved (Scheme 3). The catalytic hydrogenation was expected to complete all reactions in one-pot procedure. The reduction of the cyano group should be critical and might require high pressure of hydrogen. In order to avoid the additive **17** from the primary amine and the imine in the process, acidic (HOAc/H_2O or HOAc/alcohols) or basic solvent (NH_3/alcohols) should be of the first choice.[14,15]

If the hydrogenation in ambient atmosphere was carried out in the presence of Pd/C as catalyst in CH_3COOH/H_2O (v/v =

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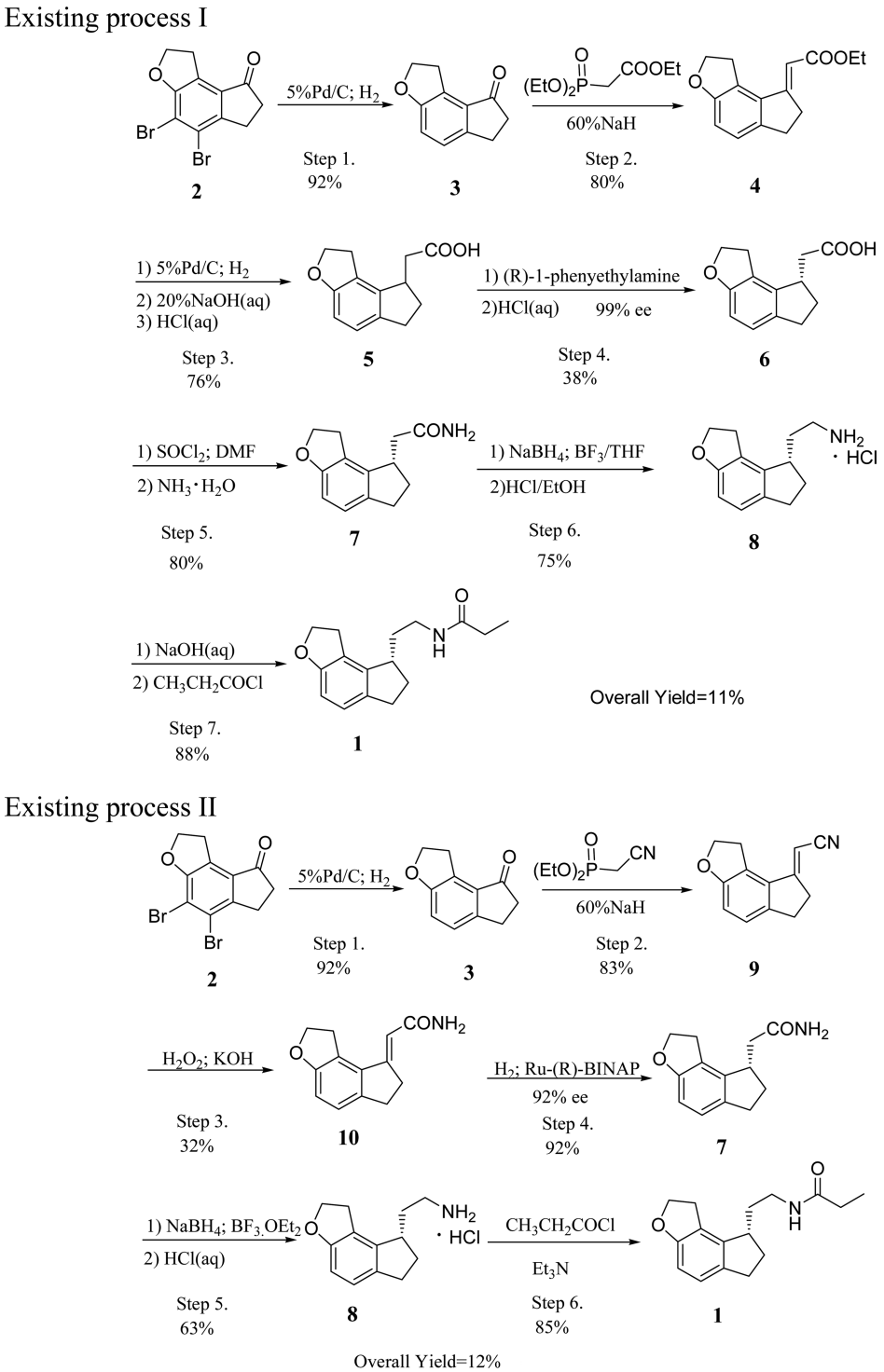
Scheme 1. Existing process I and II[8,10]



1:1) at 60 °C for 18 h, the debromination product **15** was obtained in a yield of 77% (Table 2, entry 1). When hydrogen pressure was elevated to 0.5 MPa, the dehydration product **9** was isolated along with **15** (Table 2, entry 2). Fortunately, the desired product 14 was obtained when the pressure was increased to 2.0 MPa, and the best yield (89%) was encountered at 3.0 MPa (Table 2, entries 3 and 4). Surprisingly, if the solvent ($HOAc/H_2O$) was replaced by $HOAc/CH_3OH$, the reaction, carried out in the same time as in entry 4, did not go to the end, giving a mixture of compound **9** and **12**, terribly, together with the additive **17**. Under the same condition, the basic solvent resulted in a lower yield of **12** (Table 2, entries 8 and 9). To assess the alternative catalyst, hydrogenation in CH_3COOH/H_2O or NH_3/CH_3OH at 3.0 MPa with Raney nickel were carried out, and the dehydration compound **9** was the main product (Table 2, entries 10 and 11).

As a base, compound **14** was a slightly yellow oil and unstable in ambient conditions. In general, salt formation is an easy way to get the stable solid. We did obtain the

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Scheme 2. New route

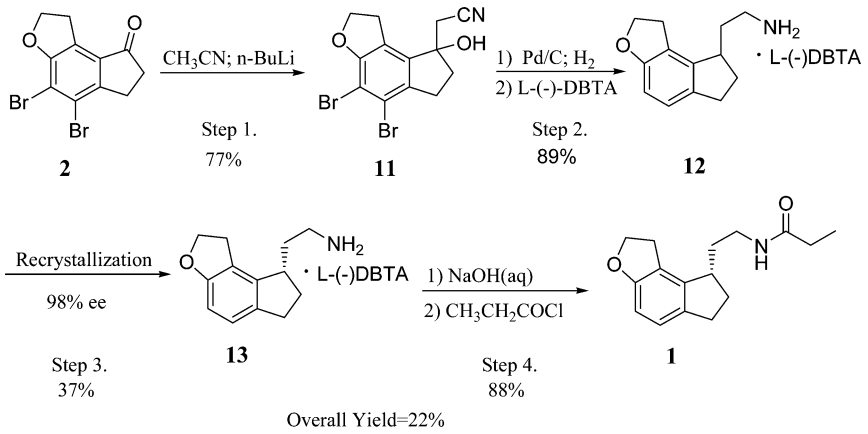
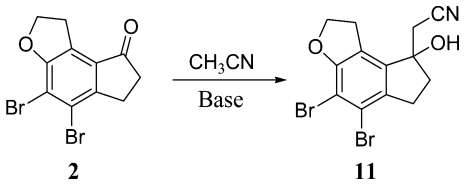


Table 1. Optimization of nucleophilic addition[a]



entry	base (equiv)	CH_3CN (equiv)	temperature (°C)	yield[b] (%)
1	*n*-BuLi (2)	2	−15	12
2	*n*-BuLi (2)	2	−45	28
3	*n*-BuLi (2)	2	−75	43
4	*n*-BuLi (3)	3	−75	59
5	*n*-BuLi (4)	4	−75	77
6	*n*-BuLi (6)	6	−75	56
7	LDA[c] (4)	4	−75	67
8	LDA[c] (4)	4	−45	33
9	*t*-BuOK (4)	4	25[d]	complex mixture
10	NaH (4)	4	25[d]	complex mixture
11	NaOEt (4)	4	25	recovery of starting material 2
12	NaOEt (4)	4	60	complex mixture

[a]The reaction was carried out in tetrahydrofuran for 2 h. [b]Isolated yield. [c]LDA = lithium diisopropylamide. [d]Recovery of starting material **2** below 0 °C.

hydrochloride or hydrobromide of **14** as a stable solid. However, since the next step was the resolution where the racemic amine **14** would react with an acidic resolution agent to deliver the desired (*S*)-isomer product, dibenzoyl-L-tartaric acid was selected both as an acid to form the salt **12** in the end of hydrogenation and as the resolution agent. After recrystallization of **12**, the (*S*)-amino salt **13** was obtained. Eventually, target compound **1** was converted from **13** via propionylation with propionyl chloride.

CONCLUSION

In summary, the novel and practical synthesis of ramelteon offers distinctive advantages over the reported routes. Beginning with the same material, our new synthetic routes only included three reactions, such as nucleophilic addition, hydrogenation, and propionylation with an overall yield of 22%, which was almost twice as much as those existing processes. The conventional Wittig−Horner reaction was abolished, with no phosphorous ylide, but acetonitrile was used as the nucleophilic reagent. Besides, four reduction processes were successfully implemented into one step of hydrogenation.

EXPERIMENTAL SECTION

General. Unless otherwise noted, stated reagents were commercially available and used without purification. NMR data were obtained using either Bruker V-400 or Varian

Scheme 3. Processes in hydrogenation

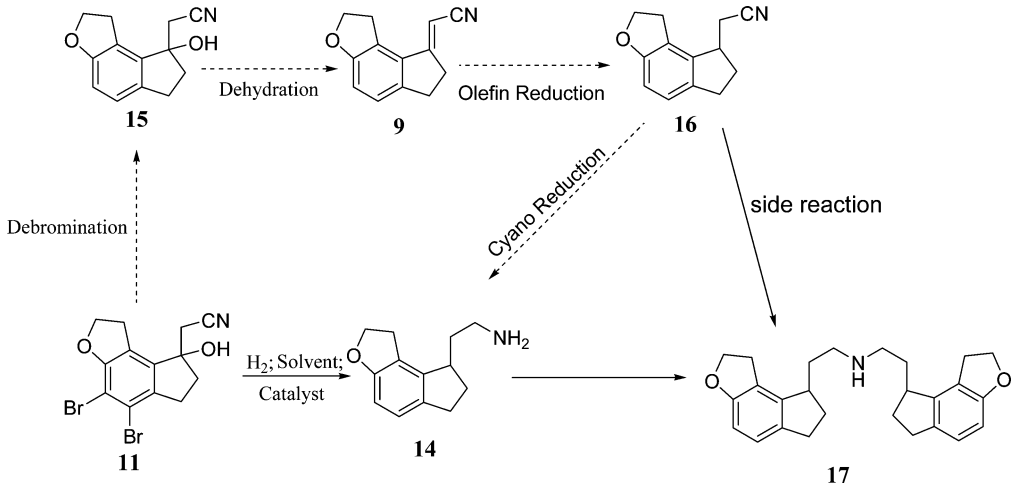


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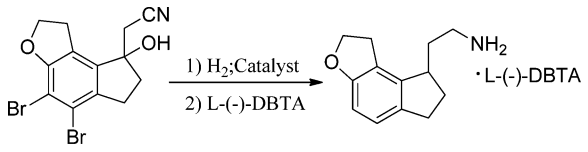
Table 2. Optimization of catalytic hydrogenation[a]



11 **12**

entry	solvent (v/v)	catalyst[b]	pressure (MPa)	product (yield,[c] %)
1	CH_3COOH/H_2O (1:1)	Pd/C	atm	**15** (77)
2	CH_3COOH/H_2O (1:1)	Pd/C	0.5	**15, 9**
3	CH_3COOH/H_2O (1:1)	Pd/C	2.0	**12** (49)
4	CH_3COOH/H_2O (1:1)	Pd/C	3.0	**12** (89)
5	CH_3COOH/H_2O (2:1)	Pd/C	3.0	**12** (87)
6	CH_3COOH/H_2O(1:2)	Pd/C	3.0	**12** (73)
7	CH_3COOH/CH_3OH (1:1)	Pd/C	3.0	**9, 17, 12**
8	NH_3(13%)/CH_3OH	Pd/C	3.0	**12** (52)
9	NH_3(13%)/ CH_3CH_2OH	Pd/C	3.0	**12** (54)
10	NH_3(13%)/CH_3OH	Raney-Ni	3.0	**9, 12**
11	CH_3COOH/H_2O (1:1)	Raney-Ni	3.0	**9, 12**

[a]Reaction run at 60 °C for 18 h. [b]15 wt % Pd/C or 20 wt % Raney-Ni. [c]Isolated yields.

INOVA-400 instrument at 400 mHz for ^{1}H and 100 Hz for ^{13}C in either $CDCl_3$ or DMSO-d_6. The chemical shift were reported in δ ppm relative to TMS. The melting points were determined by Buchi M-565 apparatus. Specific optical rotations were performed using Rudolph Automatic Polarimeter IV, at measurement wavelength: 589 nm. HPLC was used to establish the purity of compound **1** using Dionex U3000; HPLC column: Symmetry Shield RP C18 4.6 mm × 250 mm, particle size 5 μm, 1 mL/min flow, detection at 289 nm. The enantiomeric purity of compound **13** and compound **1** was also monitored by HPLC (HPLC column: Diacel Chiralcel OD-RH 4.6 mm × 150 mm, 5 μm). Further information is also shown in the Supporting Information.

*Preparation of 8-Hydroxy-4,5-dibromo-(1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-yl)acetonitrile (**11**).* A 500 mL flask was charged with anhydrous tetrahydrofuran (200 mL) and *n*-butyllithium in hexane 2.5 M (96.4 mL, 0.24 mol) was added at −75 °C under a nitrogen atmosphere, followed by a solution of acetonitrile (9.881g, 0.24 mol) in tetrahydrofuran (50 mL). After stirring for 30 min, compound **2** (20 g, 0.06 mol) was added to the resulting white suspension and stirred for 2 h at −75 °C. The yellow reaction mixture was poured into 500 mL ice−water. The aqueous mixture was extracted with 2 × 200 mL ethyl acetate, dried over $MgSO_4$, and filtered. The organic layer was evaporated under vacuum to give the crude product of **11** as a light yellow solid. It was recrystallized with toluene to give the desired product as a white solid (17.298 g, 77% yield). Mp: 174−175 °C. ^{1}H NMR(400 MHz, DMSO-d_6): δ 2.16 (m, 1H); 2.32 (m, 1H); 2.84 (m, 2H); 3.08 (dd, J = 1.6, 2H); 3.40 (m, 2H); 4.66 (m, 2H,); 5.94 (br s, 1H). MS (ES+): m/z 396 $(M + Na)^+$.

*Preparation of (S)-2-(1,6,7,8-Tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethylamine Dibenzoyl-L-tartaric Acid(**13**).* A solution of **11** (12g 0.03 mol) in acetic acid (60 mL) and H_2O (60 mL) was subjected to hydrogenation in the presence of palladium 10% on carbon (1.8 g) in a hydrogen pressure (3.0 MPa) at 60 °C for 18 h. After hydrogen absorption ceased, the catalyst was removed by filtration. The filtrate was concentrated to dryness, and the residue was neutralized with 10% NaOH (aq). The mixture was extracted with 4 × 30 mL ethyl acetate, dried over $MgSO_4$, and filtered. Then, dibenzoyl-L-tartaric acid (11.517 g, 0.03 mol) was added to the filtrate and stirred at room temperature for 1 h and filtered to afford a white solid of 2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)ethylamine dibenzoyl-L-tartaric acid (**12**) (16.063 g, 89% yield).

The above **12** (11.220 g, 0.02 mol) was recrystallized with acetonitrile: ethyl alcohol = 5:4 to afford a white solid of (*S*)-2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)-ethylamine dibenzoyl-L-tartaric acid (**13**) (4.151 g, 37% yield, 98.6% ee). Mp: 1.69−171 °C. ^{1}H NMR(400 MHz, DMSO-d_6): δ 1.60 (m, 2H); 2.05 (m, 2H); 2.71 (m, 4H); 3.07 (m, 3H); 4.45 (m, 2H); 5.66 (s, 2H,); 6.54 (d, J = 8, 1H); 6.89 (d, J = 8, 1H); 7.50 (m, 4H); 7.63 (m, 2H); 7.93 (d, J = 4, 4H); 8.00 (br s,2H). MS (ES +): m/z 204 $(M + H)^+$. $[\alpha]_D$ −115.2 (c = 1.0, MeOH).

*Preparation of (S)-N-[2-(1,6,7,8-Tetrahydro-2H-indeno-[5,4-b]furan-8-yl)ethyl]propionamide (**1**).* To a solution of **13** (4 g, 7 mmol) in tetrahydrofuran (40 mL) was added 20% NaOH (aq) (1.120 g, 28 mmol) and stirred at −10 °C. Then propionyl chloride (0.777 g, 8.4 mmol) was added dropwise at −10 °C. After that, the reaction mixture was stirred at room temperature for 2 h, and ethyl acetate (40 mL) and water (40 mL) were added. After separation, the aqueous layer was extracted with 2 × 30 mL ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated to give a solid, which was recrystallized from ethanol and water to afford a white solid of **1** (1.570 g, 85% yield, 99.8% ee). Purity by HPLC 99.6%. Mp: 115−116 °C (113−115 °C in literature[8]). ^{1}H NMR(400 MHz, $CDCl_3$): δ 1.39 (t, 3H); 1.63 (m, 1H); 1.83 (m, 1H); 2.02 (m, 1H); 2.16 (dd, J = 8, 2H); 2.28 (m, 1H); 2.78 (m, 1H); 2.83 (m, 1H); 3.14 (m, 1H); 3.22 (m, 2H); 3.33 (m, 2H); 4.54 (m, 2H); 5.38 (br s, 1H); 6.61 (d, J = 8, 1H); 6.97 (d, J = 8, 1H). ^{13}C NMR(100 MHz, $CDCl_3$): δ 173.85, 159.56, 143.26, 135.92, 123.52, 122.28, 107.56, 71.26, 42.37, 38.17, 33.66, 31.88, 30.82, 29.86, 28.73, 10.01. MS (ES+):m/z 282 $(M + Na)^+$. $[\alpha]_D$ −57.3 (c = 1.0, $CHCl_3$, −57.8 in literature[8]). Anal. ($C_{16}H_{21}NO_2$) Calc: C, 74.10; H, 8.16; N, 5.40; found: 74.09; H, 8.17; N, 5.47.

*Preparation of 8-Hydroxy -(1,2,6,7-tetrahydro-8H-indeno-[5,4-b]furan-8-yl)acetonitrile (**15**).* A solution of **11** (2 g, 0.005 mol) in acetic acid (10 mL) and H_2O (10 mL) was subjected to hydrogenation in the presence of palladium 10% on carbon (1.8 g), while hydrogen was bubbled into the reaction mixture at 60 °C for 18 h. Then, the catalyst was removed by filtration. The filtrate was concentrated into dryness. Water was added into the residue and then extracted with 3 × 10 mL ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. After concentration, the residue was separated by column chromatography with ethyl acetate−hexanes 1:9, and compound **15** was obtained as a white solid (0.813 g, 77% yield). Mp: 122−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (m, 1H); 2.52 (m, 1H); 2.80 (dd, J = 16, 2H); 2.91 (m, 2H), 3.32 (m, 2H); 4.57 (m, 2H); 6.73 (d, J = 8, 1H); 6.97 (d, J = 8, 1H). MS (ES+):m/z 238 $(M + Na)^+$.

*Preparation of 2-(1,2,6,7-Tetrahydro-8H-indeno[5,4-b]-furan-8-ylidene)acetonitrile (**9**).* A solution of **11** (2 g, 0.005 mol) in acetic acid (10 mL) and H_2O (10 mL) was subjected to

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hydrogenation in the presence of palladium 10% on carbon (1.8 g) in a hydrogen pressure of 0.5 MPa at 60 °C for 18 h. Then, the catalyst was removed by filtration. The filtrate was concentrated to dryness. Water was added into the residue and then extracted with 3 × 10 mL ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. After column chromatography with 5% ethyl acetate in hexanes, compound **9** was obtained as a yellow solid (0.354 g, 34% yield). Mp: 149−150 °C (146−151 °C in literature[10]). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (t, 2H); 3.11 (m, 2H); 3.30 (t, 2H); 4.66 (t, 2H); 5.44 (t, 1H); 6.85 (d, J = 8, 1H); 7.10 (d, J = 8, 1H). MS (ES+):m/z 198 $(M + H)^+$.

Preparation of 2,2′-Bis(1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-yl)-diethylamine (17). A solution of **11** (2 g, 0.005 mol) in acetic acid (10 mL) and CH_3OH (10 mL) was subjected to hydrogenation in the presence of palladium 10% on carbon (1.8 g, 15 wt %) in a hydrogen atmosphere (3.0 MPa) at 60 °C for 18 h. Then, the catalyst was removed by filtration. The filtrate was concentrated to dryness. Water was added into the residue. The mixture was neutralized with 10 wt % NaOH (aq), extracted with 4 × 30 mL ethyl acetate, dried over $MgSO_4$, and filtered. After that, compound **17** was separated by column chromatography (5% methanol in dichloromethane) as a white solid (0.259 g). Mp: 225−227 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69 (m, 2H); 1.99 (m, 2H); 2.24 (m, 2H); 2.40 (m, 2H); 2.82 (m, 8H); 3.09 (m, 4H); 3.28 (m, 2H); 4.50 (m, 4H); 6.58 (d, J = 8, 2H); 6.90 (d, J = 8, 2H); 9.68 (br s, 1H). MS (ES+):m/z 390 $(M + H)^+$.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and spectroscopic characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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