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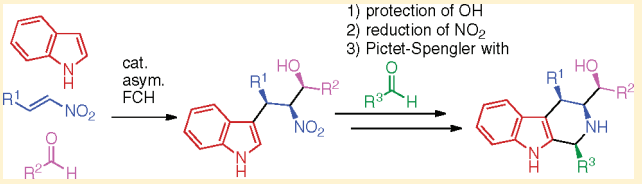
Easy Access to Fully Functionalized Chiral Tetrahydro-β-Carboline Alkaloids

Takayoshi Arai,* Makiko Wasai, and Naota Yokoyama

Department of Chemistry, Graduate School of Science, Chiba University, Inage, Chiba 263-8522, Japan

Supporting Information

ABSTRACT: A four-step synthetic route to fully substituted chiral tetrahydro-β-carbolines (THBCs) is described. Starting from the (*R*,*S*,*S*)-Friedel–Crafts/Henry adduct obtained from three-component coupling of an indole, nitroalkene, and aldehyde catalyzed by imidazoline-aminophenol–CuOTf, the (1*S*,3*S*,4*R*)-THBCs were readily synthesized in a three-step operation including reduction of the nitro-functionality and Pictet–Spengler cyclization.



β-Carboline skeletons are frequently encountered in pharmacology due to their significant biological activity in binding to serotonin receptors in the CNS (central nervous system). As demonstrated by recerpine (**1**), the tetrahydro-β-carbolines (THBCs) show more complex stereochemical diversity, and the complex structures of these molecules has been strictly linked with their specific biological activities (Figure 1).[1] For access to the highly substituted β-carboline framework, tryptophan has been widely utilized as the key precursor. Pictet–Spengler cyclization of tryptophan-derived substrates can incorporate C1 and C3 functionalities into the THBCs.[2] However, obtaining 4-substituted β-carbolines, such as ZK 93423 (**2**),[3] jadiffine (**3**),[4] and neonaucleoside C (**4**),[5] normally requires elaborate multistep syntheses to introduce substituents at the C4-position.

Busacca and co-workers reported a Pd-mediated cross-coupling of arylboronic acids and Grignard reagents for the preparation of 4-aryl-, 4-alkyl-, and 4-acetylcarboline derivatives.[6] Bandini and Umani-Ronchi et al. reported an elegant intramolecular cyclization to give a variety of 4-functionalized THBCs.[7] Roussi et al. recently reported direct functionalization at the 4-position of THBCs.[8] In Roussi's methodology, the substituent at position 4 is introduced by nucleophilic attack to an oxidized intermediate of the THBC. Although these studies represent outstanding contributions toward obtaining functionalized tetrahydro-β-carbolines, a more flexible synthetic approach is still desirable for the development of diverse β-carbolines.

In a research program aimed at exploring new asymmetric catalysts, we have succeeded in developing chiral imidazoline–aminophenol–metal catalysts.[9] A chiral imidazoline–aminophenol–CuOTf complex was able to catalyze the asymmetric Henry reaction, Friedel–Crafts reaction, and tandem Friedel–Crafts/Henry (FCH) reaction. The resulting highly functionalized indoles provide a fascinating precursor for the synthesis of β-carbolines. Herein, we report the successful transformation of FCH adducts to THBCs.

Aiming toward the synthesis of fully functionalized THBCs, we prepared a series of FCH adducts, as listed in Scheme 1.

A chiral imidazoline–aminophenol–CuOTf complex was able to catalyze the asymmetric FCH reaction of an indole, nitroalkene, and aldehyde to give the corresponding (*R*,*S*,*S*)-FCH adducts as the major isomers.[10]

Reduction of the major isomers (having over 99% ee) of the (*R*,*S*,*S*)-FCH adducts (**1a**–**d**) to the corresponding β-amino alcohols (**2a**–**d**) was examined (Table 1). Reduction using nickel boride, which has been widely utilized for the reduction of nitroaldol adducts, resulted in a mixture of amines **2** with hydroxyamines **3**.[11] In contrast, the conventional method using Zn powder under acidic conditions more readily reduced the nitro functionality to give the desired β-amino alcohols **2** predominantly while maintaining the diastereo- and enantiopurities.[12] For substrate **1c** having an alkyl substituent at the R^1 position, in particular, the Zn-nanopowder[13] was quite powerful for the reduction.

With the β-amino alcohols **2** in hand, the Pictet–Spengler condensation was examined in the reaction of **2a** with benzaldehyde. However, in this case, use of the typical acidic conditions resulted in a inseparable mixture of compounds.[2,14] The mix of products was assumed to result from oxazolidine ring formations mediated by intramolecular cyclization of the hydroxy group to the generated imine intermediate. This consideration led us to perform simple protection of the hydroxy group. After examination of several protecting groups, triethylsilyl (TES) was selected as the most appropriate group for further transformation. The corresponding O-TES derivatives **4a**–**d** were easily obtained using TESCl and imidazole in DMF (see details in the Supporting Information).

The Pictet–Spengler reaction using **4a** and benzaldehyde still proved difficult to promote by the simple addition of Brønsted

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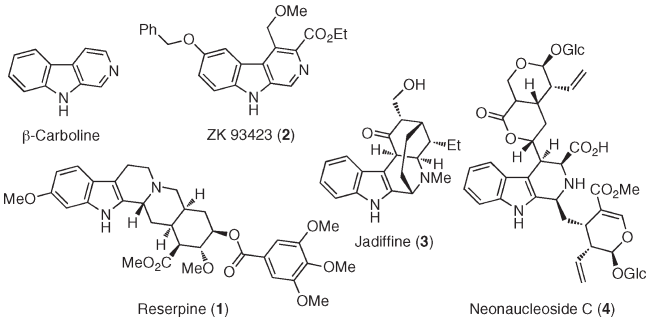
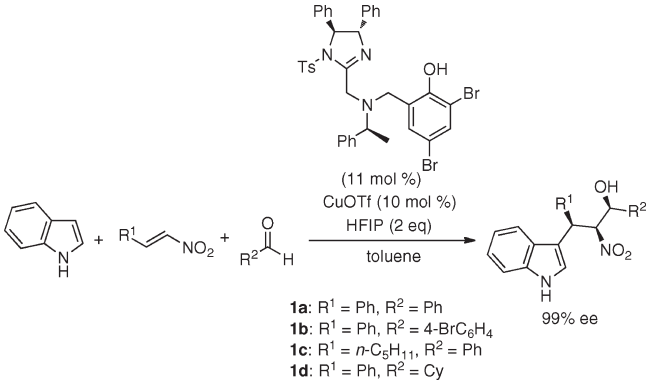


Figure 1. Representative examples of β-carboline alkaloids.

Scheme 1. Tandem Catalytic Asymmetric Friedel–Crafts/Henry Reaction



acid and/or Lewis acids. However, the problem was soon resolved by preformation of the imines before the Pictet–Spengler cyclization. Thus, after formation of the imine in $CHCl_3$, subsequent treatment with TFA gave the desired Pictet–Spengler adduct **5a** in 47% yield (Table 2, entry 5). The use of $MgSO_4$ and 3 equiv of aldehyde for effective formation of the imine improved the yield of **5a** to 67% (entry 6).

Interestingly, the TES group was removed under the cyclization conditions, and the THBCs **5** could be isolated as a single isomer.

Under the optimized conditions, the generality of the stereoselective construction of THBCs was examined (Table 3).

Various aromatic aldehydes can be incorporated in the Pictet–Spengler reaction to give the product in quite high diastereoselectivities. Among the reactions examined, that with an alkyl R^1 group gave a mixture of diastereomers in a ratio of 21:1. When the aliphatic aldehydes were examined, unfortunately, the Pictet–Spengler products were obtained in low yields (ca. 10–20%).

X-ray crystallographic analysis of the Pictet–Spengler adduct obtained in entry 2 of Table 3 revealed a (1*S*,3*S*,4*R*)-configuration for the THBC ring (Figure 2).

The (1*S*,3*S*,4*R*)-configuration differs in stereochemistry from Roussi's adduct,[8] and thus, our method can provide a new series of fully substituted chiral THBCs. DFT calculation at the B3LYP/6-311G level suggests that the (1*S*,3*S*,4*R*)-Pictet–Spengler cycloadduct obtained in Figure 2 is more stable than the (1*R*,3*S*,4*R*)-epimer by 8.034 kJ/mol, which explains the diastereomeric ratio of 25/1 at 300 K.

Removal of the TES group under the acidic conditions of Pictet–Spengler cyclization would be explained by the close proximity of the nitrogen atom of the THBC adduct to the hydroxy group. Thus, the presence of the TFA acid group near the nitrogen base of the THBC results in spontaneous cleavage of the Si–O bond to give **5**.

In conclusion, we have readily obtained fully substituted (1*S*,3*S*,4*R*)-THBCs in a four-step synthesis starting from the previously developed catalytic asymmetric FCH reaction. This new family of diverse chiral THBCs offers a fascinating source for pharmacological investigations. As such, biological assays on the obtained THBCs are underway in our research group.

EXPERIMENTAL SECTION

Friedel–Crafts/Henry Reaction. Imidazoline–aminophenol ligand (14.9 mg, 19 μmol) in toluene (0.43 mL) was added to $(CuOTf)_2 \cdot C_6H_6$ (4.4 mg, 8.7 μmol) under Ar, and the mixture was stirred for 2 h at room temperature. To the resulting clear green solution were sequentially added 1,1,1,3,3,3-hexafluoroisopropyl alcohol (35 μL, 0.34 mmol), benzaldehyde (34.6 μL, 0.34 mmol), nitrostyrene (25.4 mg, 0.17 mmol), and indole (39.8 mg, 0.34 mmol). After being stirred at the indicated temperature,[8b] the reaction mixture was purified by silica gel column chromatography (hexane/AcOEt = 3:1) to afford the adduct **1a** (47.5 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br, 1H, N*H*), 7.82 (d, 1H, J = 7.7 Hz), 7.12–7.45 (m, 14H), 5.67 (dd, 1H, J = 11.2 Hz, 3.4 Hz), 5.25 (d, 1H, J = 11.2 Hz), 5.03 (br, 1H), 3.25 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 72.1, 96.0, 111.5, 114.0, 119.3, 120.3, 122.4, 122.7, 125.2, 126.3, 127.4, 128.4, 128.7, 128.8, 136.2, 138.9, 139.3; HRMS calcd for $C_{23}H_{20}N_2O_3$ (M) 372.1474, found m/z 372.1477; $[\alpha]^{20}_D$ = +50.2 (c = 0.2, $CHCl_3$); IR (neat) 3419, 3029, 1548, 1369 cm^{-1}. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane/2-propanol, 0.8 mL/min, 254 nm); minor enantiomer t_R = 38.6 min, major enantiomer t_R = 43.8 min.

Reduction of FCH Adducts (Entry 3, Table 1). To a stirred solution of FCH adduct **1a** (103.5 mg, 0.278 mmol) in MeOH (2.5 mL) were added AcOH (0.83 mL), 1 N aq. HCl (1.7 mL), and Zn powder (363.5 mg, 5.56 mmol) at rt. After the mixture was stirred at rt for 15 h, the insoluble residue was filtered, and then MeOH was removed by evaporation under reduced pressure. The remaining aqueous phase was neutralized by addition of aq. $NaHCO_3$ solution and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of Na_2SO_4 by filtration, the solution was concentrated under reduced pressure. The residual crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 30:1) to afford the β-amino alcohol **2a** (94.2 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.45 (m, 2H), 7.15–7.36 (m, 11H), 7.11 (m, 1H), 4.69 (d, J = 1.4 Hz, 1H), 4.43 (d, J = 9.9 Hz, 1H), 3.90 (dd, J = 2.3, 10.0 Hz, 1H), 1.28 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 142.4, 136.3, 128.7, 128.6, 128.3, 127.0, 126.6, 125.6, 122.2, 121.5, 119.6, 119.5, 117.8, 111.1, 71.8, 60.1, 46.0; HRMS calcd for $C_{23}H_{23}N_2O$ (M + H) 343.1805, found m/z 343.1800; $[\alpha]^{25.0}_D$ = +2.0 (c = 0.71, $CHCl_3$); IR (neat) 3416, 3059, 3028, 1453, 908, 737, 701 cm^{-1}.

Reduction of FCH Adducts (Entry 5, Table 1). To a stirred solution of FCH adduct **1c** (40.7 mg, 0.121 mmol) in MeOH (1.1 mL) were added AcOH (0.36 mL), 1 N aq. HCl (0.73 mL), and Zn-nanopowder (158.2 mg, 2.42 mmol) at rt. After the mixture was stirred at rt for 3 h, the insoluble residue was filtered, and then MeOH was removed by evaporation under reduced pressure. The remaining aqueous phase was neutralized by addition of aq. $NaHCO_3$ solution and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were

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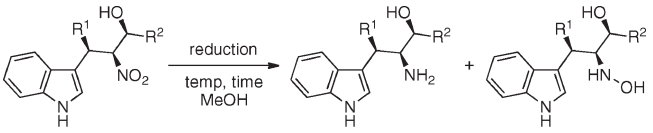
Table 1. Reduction to β-Amino Alcohols

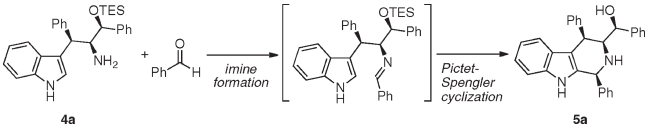


1 2 3

					yield (%)	
entry	substrate	conditions	temp (°C)	time (h)	2	3
1	**1a**	$NiCl_2$ (1 equiv)−$NaBH_4$ (12 equiv)	0	0.5	20	57
2	**1a**	Zn (10 equiv), 1 N HCl/AcOH (2:1)	0	24	59	26
3	**1a**	Zn (20 equiv), 1 N HCl/AcOH (2:1)	rt	15	99	—[b]
4	**1b**	Zn (20 equiv), 1 N HCl/AcOH (2:1)	rt	18	99	—
5	**1c**	Zn[a] (20 equiv), 1 N HCl/AcOH (2:1)	rt	3	98	—
6	**1d**	Zn[a] (20 equiv), 1 N HCl/AcOH (2:1)	rt	3	99	—

[a] Zn-nanopowder[13] was utilized. [b] Not obtained.

Table 2. Optimization of Pictet−Spengler Cyclization Using 4a

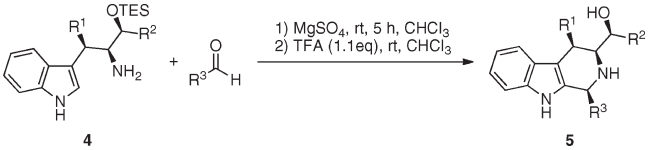


4a 5a

entry	imine formation	Pictet−Spengler cyclization	yield (%)
1		AcOH	—[b]
2		TFA	~30
3		$MgSO_4$	—
4		$Yb(OTf)_3$	—
5	rt, 5 h, $CHCl_3$	TFA (1.1 equiv), rt, 19 h	47
6[a]	$MgSO_4$, rt, 5 h, $CHCl_3$	TFA (1.1 equiv), rt, 19 h	67

[a] 3 equiv of aldehyde was utilized. [b] Not obtained.

Table 3. Stereoselective Synthesis of THBCs



4 5

entry	R^1	R^2	R^3	time (h)	yield (%)
1	Ph	Ph	Ph	19	67[a]
2	Ph	Ph	4-BrC_6H_4	20	58[a]
3	Ph	Ph	4-$NO_2C_6H_4$	19	72[a]
4	Ph	Ph	4-$CH_3C_6H_4$	25	38[a]
5	Ph	Ph	3-ClC_6H_4	19	63[a]
6	Ph	4-BrC_6H_4	Ph	19	68[a]
7	Ph	4-BrC_6H_4	4-ClC_6H_4	19	70[a]
8	*n*-C_5H_{11}	Ph	Ph	21	64[b]
9	Ph	Cy	4-$NO_2C_6H_4$	24	52[a]

[a] Isolatable compounds were only a single diastereoisomer of the Pictet−Spengler reaction and the recovered **4**. [b] Diastereomixture in a ratio of 21/1.

dried over anhydrous Na_2SO_4. After removal of Na_2SO_4 by filtration, the solution was concentrated under reduced pressure. The residual crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to afford the β-amino alcohol **2c** (39.9 mg, 98%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (br, 1H), 7.26−7.39 (m, 7H), 7.18 (m, 1H), 7.01−7.08 (m, 2H), 4.51 (d, *J* = 5.2 Hz, 1H), 3.19 (t, *J* = 5.7 Hz, 1H), 2.95 (m, 1H), 1.05−2.10 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 136.6, 128.3, 127.4, 126.9, 126.3, 122.0, 121.6, 119.2, 119.2, 117.4, 111.2, 73.7, 61.8, 38.9, 32.0, 29.2, 27.5, 22.5, 14.0; HRMS calcd for $C_{22}H_{29}N_2O$ (M + H) 337.2274, found *m*/*z* 337.2263; $[\alpha]^{22.7}_D$ = −6.3 (*c* = 0.65, $CHCl_3$); IR (neat) 3414, 3292, 3059, 2952, 2927, 2857, 1455, 741, 703 cm^{-1}.

TES Protection (for 2a). To a stirred solution of **2a** (94.9 mg, 0.277 mmol) in dry DMF (1.4 mL) were added TESCl (93.0 μL, 0.554 mmol) and imidazole (94.3 mg, 1.39 mmol) at 0 °C. After being stirred for 1 h, the reaction mixture was quenched by addition of H_2O. The mixture was extracted with Et_2O (5 mL × 3), and the combined organic layers were dried over anhydrous Na_2SO_4. After removal of Na_2SO_4 by filtration, the solution was concentrated under reduced pressure. The residual crude product was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to afford the O-TES derivative **4a** (103.7 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.41 (m, 2H), 7.19−7.35 (m, 9H), 7.11−7.18 (m, 2H), 7.05 (m, 1H), 4.84 (d, *J* = 3.6 Hz, 1H), 4.22 (d, *J* = 8.4 Hz, 1H), 3.65 (dd, *J* = 3.8, 8.6 Hz, 1H), 0.76 (t, *J* = 7.9 Hz, 9H), 0.30−0.42 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 142.8, 136.3, 129.1, 128.3, 128.0, 127.2, 126.9, 126.6, 126.2, 122.0, 121.3, 119.4, 119.2, 118.3, 111.0, 75.3, 61.0, 46.6, 6.7, 4.8; HRMS calcd for $C_{29}H_{37}N_2OSi$ (M + H) 457.2670, found *m*/*z* 457.2661; $[\alpha]^{24.6}_D$ = −2.0 (*c* = 0.33, $CHCl_3$); IR (neat) 3421, 3166, 3060, 3027, 2953, 2911, 2875, 1454, 1060, 738, 700 cm^{-1}.

TES Protection (for 2d). To a stirred solution of **2d** (47.7 mg, 0.137 mmol) in dry DMF (0.69 mL) were added TESCl (46.0 μL, 0.274 mmol) and imidazole (46.6 mg, 0.685 mmol) at rt. After being stirred for 1 h, the reaction mixture was quenched by an addition of H_2O. The mixture was extracted with Et_2O (5 mL × 3), and the combined organic layers were dried over anhydrous Na_2SO_4. After removal of Na_2SO_4 by filtration, the solution was concentrated under reduced pressure. The residual crude product was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to afford the O-TES derivative **4d** (50.7 mg, 80%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (br, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.29−7.35 (m, 3H), 7.22−7.27 (m, 2H), 7.10−7.15

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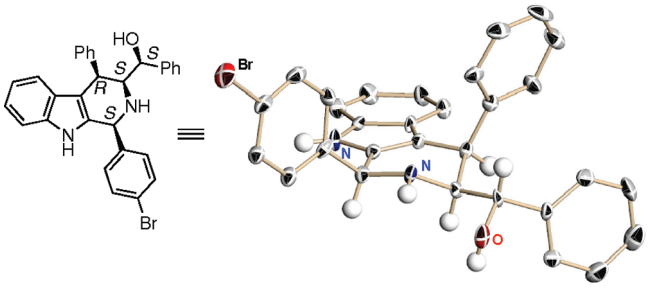

Figure 2. X-ray structure of Pictet−Spengler cycloadduct (entry 2, Table 3).

(m, 3H), 7.02 (m, 1H), 4.19 (d, J = 10.0 Hz, 1H), 3.70 (dd, J = 1.4, 7.2 Hz, 1H), 3.58 (dd, J = 1.5, 10.0 Hz, 1H), 1.88 (br, 1H), 1.62−1.84 (m, 5H), 0.90−1.33 (m, 5H), 0.86 (t, J = 8.0 Hz, 9H), 0.51 (q, J = 8.0 Hz, 6H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 136.1, 128.9, 128.4, 127.3, 126.2, 122.0, 120.4, 119.4, 119.2, 118.3, 110.9, 76.7, 54.9, 48.0, 42.3, 30.1, 30.0, 26.6, 26.5, 26.4, 7.0, 5.6; HRMS calcd for $C_{29}H_{43}N_2OSi$ (M+H): 463.3139, found: m/z 463.3127; $[\alpha]^{23.0}_D$ = −63.1(c = 1.0, $CHCl_3$); IR (neat) 3418, 3166, 3060, 2925, 2875, 2852, 1455, 1011, 738, 702 cm^{-1}.

Pictet−Spengler Reaction (Entry 1, Table 3). A suspension of **4a** (38.8 mg, 0.0805 mmol), benzaldehyde (24.5 μL, 0.242 mmol), and $MgSO_4$ (80.5 mg) in dry $CHCl_3$ (0.81 mL) was stirred for 5 h at rt under Ar. After addition of TFA (6.6 μL, 0.089 mmol), the mixture was further stirred for 19 h at rt. The reaction was quenched by an addition of $NaHCO_3$ solution. The remaining insoluble residue was filtered and then extracted with $CHCl_3$ (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4. After removed of Na_2SO_4 by filtration, the solution was concentrated under reduced pressure. The residual crude product was purified by silica gel column chromatography (hexane/AcOEt = 6:1) to afford the tetrahydro-β-carboline **5** (23.2 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.62 (m, 3H), 7.35−7.50 (m, 6H), 7.18−7.30 (m, 7H), 7.06−7.16 (m, 2H), 7.02 (m, 1H), 6.87 (m, 1H), 5.35 (d, J = 1.6 Hz, 1H), 4.02 (d, J = 9.7 Hz, 1H), 3.95 (dd, J = 1.8, 4.1 Hz, 1H), 3.83 (dd, J = 4.1, 9.7 Hz, 1H), 3.40 (br, 1H), 2.37 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 140.4, 140.0, 136.2, 135.2, 129.9, 129.2, 128.7, 128.6, 128.5, 128.5, 127.9, 126.7, 126.5, 121.9, 119.5, 118.5, 114.4, 110.8, 74.5, 64.0, 59.5, 39.9; HRMS calcd for $C_{30}H_{26}N_2O$-Na (M + Na) 453.1937, found m/z 453.1920; $[\alpha]^{25.7}_D$ = −6.4 (c = 1.0, $CHCl_3$); IR (neat) 3412, 3332, 3060, 3030, 2919, 1493, 1454, 909, 737, 701 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical and spectral characterization data for all compounds, and crystallographic information files (CIF) of Pictet−Spengler cycloadduct (entry 2, Table 3). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: tarai@faculty.chiba-u.jp.

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(10) Although the structure of major FCH adduct is reported as the (*R,R,R*)-form in ref 9b, the correct structure is the (*R,S,S*)-form. We apologize for causing confusion. Corrigendum: *Angew. Chem., Int. Ed.* **2010**, *49*, 9555.
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