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Stereocontrolled synthesis of (+)-α-skytanthine by means of an intramolecular Pauson–Khand reaction

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ABSTRACT

Diastereoselective synthesis of (+)-α-skytanthine was established by means of an intramolecular Pauson–Khand reaction of *N*-but-2-yn-1-yl-*N*-[(2*R*)-2-methylbut-3-en-1-yl]-1-(2-nitrobenzene)sulfonamide, in which the newly generated stereogenic center was stereoselectively constructed to be *R* by reflection of the stereochemistry of the methyl group in the starting material.

1. Introduction

(+)-α-Skytanthine has been isolated from *Skytanthus acutus* (Apocynaceae) as a minor monoterpene piperidine alkaloid together with its diastereoisomers, β- γ-, and δ-skytanthines (Fig. 1). Their structures including absolute stereochemistry have been determined on the basis of partial and total syntheses.[1]

Recently, we have succeeded in diastereoselective synthesis of incarvilline **5**, an analgesic monoterpene piperidine alkaloid, by employing an intramolecular Pauson–Khand reaction as a key reaction.[2] Due to the structural similarity between incarvilline and skytanthines, we thought that an intramolecular Pauson–Khand reaction would be applicable to synthesis of skytanthines. Moreover, a similar monoterpene alkaloid, tecomanine **6**, has already been synthesized by Schore[3] using a similar synthetic strategy, although poor stereoselectivity was unfortunately observed during the key reaction. Regarding the synthesis of skytanthines, four chiral syntheses of (+)-α-skytanthine have so far been achieved with magnesium-ene reaction used by Oppolzer,[4a] aza-Claisen rearrangement used by Pombo-Villar,[4b] cyclization under Mitsunobu reaction conditions used by Tsunoda,[4c] and S_N2' anti-reaction used by Helmchen[4d] as key reactions.

Our retrosynthetic route to α-skytanthine **1** involving an intramolecular Pauson–Khand reaction[5] as a key reaction is depicted in Figure 2.

The desired stereochemistry at the 7a-position of α-skytanthine **1** could be constructed stereoselectively by catalytic reduction of an enone **7**, and a methyl group at the 7-position would be epimerized from the β-side to the sterically less hindered α-side of the product by base treatment. The enone **7** could be derived from an optically active enyne **8** by application of an intramolecular Pauson–Khand reaction, in which a newly generated stereogenic center would be constructed

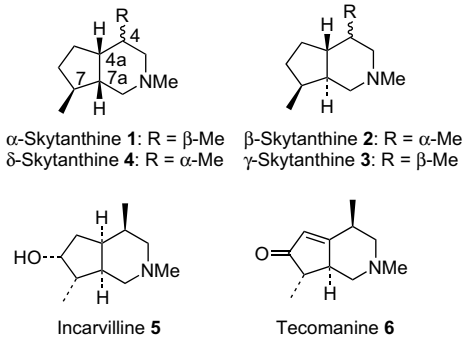

Figure 1. Structures of the skytanthine alkaloids and typical piperidine alkaloids.

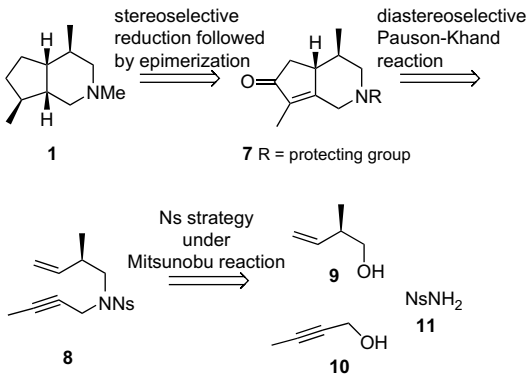

Figure 2. Retrosynthetic route to **1**.

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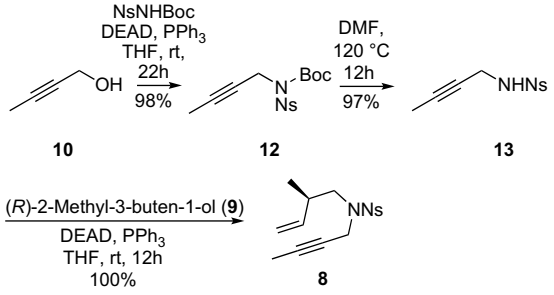
with the desired stereochemistry by reflection of the stereochemistry of the methyl group in the starting enyne.[6] Finally, enyne **8** could be obtained by condensation of three components, alkenyl alcohol **9**, alkynyl alcohol **10**, and 2-nitrobenzenesulfonamide **11**.

2. Results and discussion

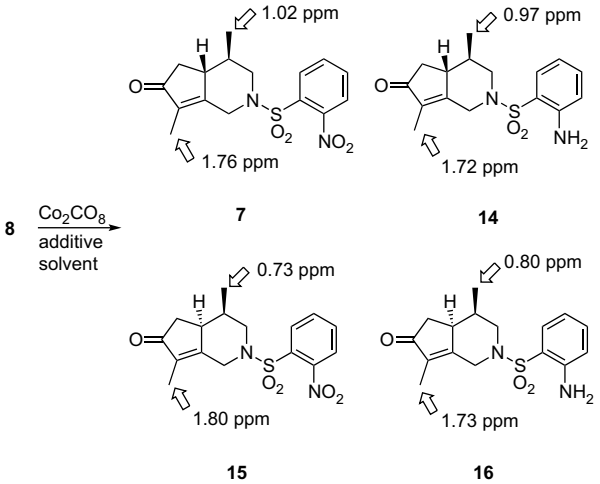
The desired tertiary amide **8** was prepared by adopting Fukuyama's methodology[7] using 2-nitrobenzenesulfonylamine as a nitrogen source. Treatment of 2-butyn-1-ol **10** with *N*-Boc derivative of **11** in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine in THF at room temperature[8] for 22 h gave alkynylamide **12** in 98% yield. After removal of the Boc group of **12** by heating in DMF at 120 °C, the resulting secondary amide **13** was further reacted with (*R*)-2-methylbut-3-en-1-ol **9**[9] under similar Mitsunobu reaction conditions[8] to afford the tertiary amide **8** in 97% yield from **12** (Scheme 1).



Scheme 1. Preparation of enyne **8**.

With the requisite enyne **8** in hand, we explored optimal reaction conditions for intramolecular Pauson–Khand reaction, and the results obtained are summarized in Table 1. First, we attempted Pauson–Khand reaction of **8** with dicobalt octacarbonyl (1.05 equiv) in dichloromethane in the presence of 4-methylmorpholine

Table 1
Pauson–Khand reaction of enyne **8**



Entry	Additive (equiv)	Solvent	Atm	Temp (°C)	Time (h)	Yield (%)			
						7	**14**	**15**	**16**
1	NMO (10), MS 4 Å	CH_2Cl_2	Ar	0 to rt	24	20	19	3	3
2	TMANO·$2H_2O$ (5)	THF/H_2O (3:1)	—	0 to rt	7	6	71	—	8
3	*t*-BuSMe (3.5), MS 4 Å	DCE	CO	83	3	—	49	—	7
4	None	Toluene	CO	60	24	27	32	7	6
5	MS 4 Å	CCl_4	CO	77	24	33	—	10	—
6	MS 4 Å	C_6F_6	CO	80	24	—	42	—	6

N-oxide (NMO)[10a] (10 equiv) and molecular sieves 4 Å under an atmospheric pressure of argon at 0 °C to room temperature for 24 h to give a mixture of diastereoisomeric cyclization products (**7** and **15**) in 20 and 3% yields, respectively (entry 1). In this reaction, poor stereoselectivity was observed with relatively low yields. However, formation of small amounts of reductive products (**14** and **16**) was also observed during this reaction. Pauson–Khand reactions of **8** with dicobalt octacarbonyl under an atmospheric pressure of carbon monoxide in various solvent systems in the presence or absence of an additive were also investigated (see Table 1) to find optimal reaction conditions for the desired cyclization product, since a similar reaction under CO atmosphere afforded good results in the synthesis of incarvilline. The use of *tert*-butyl methyl sulfide[10c,d] in refluxing dichloroethane, the best reaction conditions for the synthesis of incarvilline, afforded the desired product **14** in 49% yield together with the undesired reduction product **16** in 7% yield (entry 3).

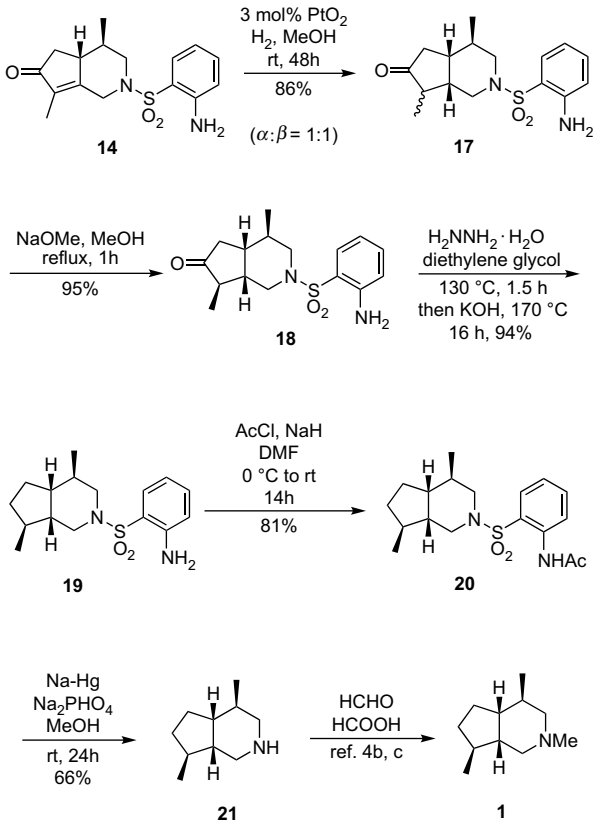
The reaction in toluene at 60 °C without an additive gave four isomers (**7**, **14**, **15**, and **16**) in 27, 32, 7, and 6% yields, respectively (entry 4). It should be noted that the reaction in carbon tetrachloride in the presence of MS 4 Å gave cyclization products (**7** and **15**) in 33 and 10% yields, respectively, without formation of reduction products (entry 5). Surprisingly, by the use of hexafluorobenzene not containing hydrogen as the solvent, the nitro group was completely reduced to furnish amino derivatives (**14** and **16**), in 42 and 6% yields, as isolable products (entry 6). Although the mechanism for the reduction of a nitro group in Pauson–Khand reaction is still not clear at present, the best result was obtained when enyne **8** was treated with dicobalt octacarbonyl (1.05 equiv) in aqueous THF in the presence of trimethylamine *N*-oxide[10b] (5 equiv) as the additive at ambient temperature for 7 h to give the desired product **14** in 71% yield (entry 2).

Catalytic hydrogenation of enone **14** over platinum oxide in MeOH gave ketone **17** in a ratio of ca. 1:1 as an inseparable mixture of diastereoisomers in 86% yield, which upon treatment with sodium methoxide in refluxing MeOH afforded the thermodynamically stable ketone **18** as a single isomer in 95% yield. Conversion of ketone **18** to the corresponding methylene derivative **19** was successfully achieved by Wolff–Kishner reduction[11] in 94% yield. Although difficulties were initially encountered in removal of the (2-amino)benzenesulfonyl group of **19**, e.g., failures in attempted reduction with various dissolving metals, such as lithium and sodium metals, and lithium naphthalenide in appropriate solvents, or catalytic reduction over palladium catalysts, treatment of **19** with sodium-amalgam according to Huang's procedure[12] afforded the desired secondary amine **21** in low yield. To improve the conversion yield to **21**, amine **19** was converted to its acetyl derivative **20** prior to its reduction by treatment with acetyl chloride in the presence of sodium hydride in DMF. Again, treatment of **20** with sodium-amalgam in MeOH in the presence of Na_2HPO_4 provided **21** in 66% yield. Amine **21** was also obtained in 39% yield from **20** by treatment with sodium naphthalenide.

Finally, N-methylation of amine **21** with formaldehyde and formic acid afforded (+)-α-skytanthine **1**, the spectroscopic data of which were identical to those previously reported (Scheme 2).

3. Conclusion

In summary, we were able to establish an alternative stereoselective chiral synthesis of (+)-α-skytanthine **1** by employing an intramolecular Pauson–Khand reaction of enyne as a key reaction. In this synthesis, we found that the configuration at the 4a-position of the cyclized product was stereoselectively constructed by reflection of the stereochemistry of the methyl group in the starting enyne. Interestingly, it was found that a nitro group was reduced to an amino group by Pauson–Khand reaction even with the use of a solvent not containing hydrogen. We are investigating further



Scheme 2. Synthesis of (+)-α-skytanthine **1**.

application of this synthetic strategy to the synthesis of other biologically active natural products having an azabicyclo[4.3.0]nonane ring system.

4. Experimental

4.1. General

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on Bruker AV400 (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz) instruments for solutions in $CDCl_3$, and chemical shifts are reported on the scale from internal TMS. MS spectra were measured with a JEOL JMS-600 and JMS-SX 120 spectrometers. Elemental analyses were performed on a Yanaco-MT5.

4.2. *tert*-Butyl but-2-yn-1-yl[(2-nitrophenyl)sulfonyl]-carbamate 12

To a stirred solution of but-2-yn-1-ol **10** (0.29 ml, 3.48 mmol), *N*-Boc-2-nitrobenzenesulfonamide (1.00 g, 3.31 mmol), and triphenylphosphine (1.79 g, 6.62 mmol) in THF (7 ml) was added diethyl azodicarboxylate (DEAD) (2.2 M in toluene, 3.01 ml, 6.22 mmol) at ambient temperature. After being stirred for 22 h at the same temperature, the mixture was concentrated to remove the solvent. The residue was subjected to column chromatography on silica gel. Elution with hexane–EtOAc (3:1, v/v) gave **12** (1.15 g, 98%) as colorless needles. Mp 108–109 °C; IR: ν_{max} 2982, 1738, 1545, 1441, 1369 cm^{-1}; ^{1}H NMR: δ 8.32 (dd, J=6.7, 2.0 Hz, 1H), 7.79–7.74 (m, 3H), 4.49 (d, J=2.3 Hz, 2H), 1.85 (t, J=2.3 Hz, 3H), 1.37 (s, 9H); ^{13}C NMR: δ 149.8, 147.8, 134.3, 133.3, 132.8, 131.9, 124.5, 85.5, 80.1, 73.9, 37.2, 27.8, 3.6; HRMS m/z (CI) calcd for $C_{15}H_{19}N_2O_6S$ (M^++H) 355.0963, found 355.0984. Anal. Calcd for $C_{15}H_{18}N_2O_6S$: C, 50.84; H, 5.12; N, 7.90. Found: C, 50.85; H, 5.09; N, 7.97.

4.3. *N*-But-2-yn-1-yl-2-nitrobenzenesulfonamide 13

A stirred solution of **12** (354 mg, 1 mmol) in DMF (4 ml) was heated to 120 °C for 12 h. After being cooled to room temperature, the mixture was treated with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–EtOAc (5:2, v/v) furnished **13** (247 mg, 97%) as colorless needles. Mp 112–113 °C; IR: ν_{max} 3307, 1538, 1420, 1337, 1164 cm^{-1}; ^{1}H NMR: δ 8.20 (d, J=1.6 Hz, 1H), 7.94–7.91 (m, 1H), 7.80–7.73 (m, 2H), 5.61 (br t, J=5.4 Hz, 1H), 3.96–3.93 (m, 2H), 1.46 (t, J=2.4 Hz, 3H); ^{13}C NMR: δ 147.9, 134.2, 133.7, 132.8, 131.6, 125.4, 81.6, 72.7, 34.0, 3.2; HRMS m/z (CI) calcd for $C_{10}H_{11}N_2O_4S$ (M^++H) 255.0439, found 255.0430. Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96; N, 11.02. Found: C, 47.25; H, 4.02; N, 10.91.

4.4. *N*-But-2-yn-1-yl-*N*-[(2*R*)-2-methylbut-3-en-1-yl]-2-nitrobenzenesulfonamide 8

To a stirred solution of **13** (6.12 g, 24.1 mmol), (*R*)-2-methylbut-3-en-1-ol **9** (2.73 ml, 26.5 mmol), and triphenylphosphine (7.82 g, 28.9 mmol) in THF (48 ml) was slowly added diethyl azodicarboxylate (DEAD) (2.2 M in toluene, 13.1 ml, 28.9 mmol) at ambient temperature. After being stirred for 12 h at the same temperature, the mixture was concentrated under reduced pressure to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–EtOAc (3:1, v/v) gave **8** (7.79 g, 100%) as colorless needles. Mp 61–62 °C; $[\alpha]_D^{24}$ +2.57 (c 1.00, $CHCl_3$); IR: ν_{max} 3080, 2974, 2923, 1546, 1373, 1358, 1165 cm^{-1}; ^{1}H NMR: δ 8.03–8.02 (m, 1H), 7.71–7.61 (m, 3H), 5.68 (ddd, J=17.4, 10.3, 7.7 Hz, 1H), 5.07 (dd, J=17.6, 0.9 Hz, 1H), 5.00 (dd, J=10.3, 0.9 Hz, 1H), 4.14 (d, J=2.4 Hz, 2H), 3.31 (d, J=7.6 Hz, 2H), 2.55–2.48 (m, 1H), 1.64 (t, J=2.4 Hz, 3H), 1.02 (d, J=6.7 Hz, 3H); ^{13}C NMR: δ 148.4, 140.6, 133.5, 132.9, 131.3, 130.9, 124.0, 115.3, 82.0, 71.7, 51.9, 37.2, 36.2, 17.4, 3.3; HRMS m/z (EI) calcd for $C_{15}H_{18}N_2O_4S$ (M^+) 322.0987, found 322.0974. Anal. Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.88; H, 5.63; N, 8.69. Found: C, 55.85; H, 5.65; N, 8.61.

4.5. Typical procedure for Pauson–Khand reaction of 8

Entry 2. To a solution of **8** (3.02 g, 9.94 mmol) in THF (75 ml) was added dicobalt octacarbonyl (3.93 g, 10.9 mmol) at ambient temperature under an argon atmosphere. After being stirred for 2 h, the reaction mixture was cooled to 0 °C in ice bath and then a solution of trimethylamine *N*-oxide dihydrate (TMANO·2H_2O) in H_2O (25 ml) was added dropwise to the mixture at the same atmosphere. After being stirred for further 7 h at room temperature, the mixture was quenched with 5% HCl solution (50 ml) at 0 °C and stirred for further 12 h. The resulting solution was extracted with Et_2O, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–EtOAc (1:1, v/v) furnished **7**, **14**, and **16** as amorphous products.

Entry 4. To a solution of **8** (3.08 g, 9.52 mmol) in toluene (100 ml) was added dicobalt octacarbonyl (3.78 g, 10.5 mmol) at ambient temperature under an argon atmosphere. After being stirred for 2 h, the stirred mixture was heated at 60 °C under an atmospheric pressure of CO for 24 h. After being cooled to room temperature, the mixture was filtrated through Celite pad to remove the insoluble materials. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel.

Elution with hexane–EtOAc (1:1, v/v) gave **7**, **14**, **15**, and **16** as amorphous products, respectively.

4.6. (4*R*,4a*R*)-4,7-Dimethyl-2-[(2-nitrophenyl)sulfonyl]-1,2,3,4,4a,5-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one 7

$[\alpha]_D^{25}$ −119.32 (*c* 1.00, $CHCl_3$); IR: ν_{max} 1704, 1544, 1372 cm^{-1}; ^1H NMR: δ 8.06–8.04 (m, 1H), 7.75–7.64 (m, 3H), 4.82 (dd, *J*=14.4, 1.6 Hz, 1H), 3.87 (ddd, *J*=13.2, 4.0, 1.8 Hz, 1H), 3.60 (d, *J*=14.4 Hz, 1H), 2.70 (dd, *J*=13.2, 11.3 Hz, 1H), 2.60 (dd, *J*=18.7, 6.4 Hz, 1H), 2.30–2.27 (m, 1H), 2.03 (dd, *J*=18.7, 2.6 Hz, 1H), 1.77–1.76 (m, 3H), 1.58–1.50 (m, 1H), 1.02 (d, *J*=6.6 Hz, 3H); ^{13}C NMR: δ 207.5, 162.9, 148.1, 135.7, 133.9, 132.0, 131.8, 130.9, 124.3, 51.9, 45.1, 45.0, 39.0, 38.6, 17.3, 8.0; HRMS *m*/*z* (EI) calcd for $C_{16}H_{18}N_2O_5S$ (M^+) 350.0936, found 350.0909.

4.7. (4*R*,4a*R*)-2-[(2-Aminophenyl)sulfonyl]-4,7-dimethyl-1,2,3,4,4a,5-hexahydro-6*H*-cyclopenta-[*c*]pyridin-6-one 14

$[\alpha]_D^{23}$ −80.48 (*c* 1.00, $CHCl_3$); IR: ν_{max} 3475, 3372, 1703 cm^{-1}; ^1H NMR: δ 7.59 (dd, *J*=8.0, 1.3 Hz, 1H), 7.34–7.30 (m, 1H), 6.79–6.74 (m, 2H), 5.12 (br s, 2H), 4.73 (dd, *J*=13.6, 1.2 Hz, 1H), 3.86 (ddd, *J*=12.3, 3.8, 1.6 Hz, 1H), 3.31 (d, *J*=13.6 Hz, 1H), 2.55 (dd, *J*=18.7, 6.4 Hz, 1H), 2.42 (dd, *J*=12.3, 11.5 Hz, 1H), 2.17 (m, 1H), 1.98 (dd, *J*=18.7, 2.6 Hz, 1H), 1.72 (dd, *J*=1.6, 1.2 Hz, 3H), 1.57–1.45 (m, 1H), 0.97 (d, *J*=6.6 Hz, 3H); ^{13}C NMR: δ 207.7, 163.6, 146.3, 135.4, 134.4, 130.1, 117.83, 117.75, 117.27, 52.0, 45.2, 45.0, 39.0, 37.9, 17.3, 7.9; HRMS *m*/*z* (EI) calcd for $C_{16}H_{20}N_2O_3S$ (M^+) 320.1194, found 320.1201.

4.8. (4*R*,4a*S*)-4,7-Dimethyl-2-[(2-nitrophenyl)sulfonyl]-1,2,3,4,4a,5-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one 15

$[\alpha]_D^{26}$ +47.5 (*c* 1.00, $CHCl_3$); IR: ν_{max} 1704, 1546, 1372 cm^{-1}; ^1H NMR: δ 8.06–8.04 (m, 1H), 7.77–7.70 (m, 2H), 7.68–7.65 (m, 1H), 4.85 (dd, *J*=14.3, 1.5 Hz, 1H), 3.81 (ddd, *J*=12.8, 2.5, 2.0 Hz, 1H), 3.62 (d, *J*=14.3 Hz, 1H), 3.22 (dd, *J*=12.8, 2.3 Hz, 1H), 2.93–2.89 (m, 1H), 2.43 (dd, *J*=19.1, 6.4 Hz, 1H), 2.27–2.19 (m, 1H), 2.18 (dd, *J*=19.1, 2.4 Hz, 1H), 1.81–1.80 (m, 3H), 0.73 (d, *J*=6.8 Hz, 3H); ^{13}C NMR: δ 208.1, 161.0, 148.1, 137.0, 133.9, 131.78, 131.73, 131.03, 124.3, 52.1, 45.5, 41.5, 36.8, 31.6, 10.3, 7.9; HRMS *m*/*z* (EI) calcd for $C_{16}H_{18}N_2O_5S$ (M^+) 350.0936, found 350.0913.

4.9. (4*R*,4a*S*)-2-[(2-Aminophenyl)sulfonyl]-4,7-dimethyl-1,2,3,4,4a,5-hexahydro-6*H*-cyclopenta-[*c*]pyridin-6-one 16

Compound **16** could not be isolated as a single product and was obtained as a mixture with **14**. Selected data for **16**: ^1H NMR: δ 7.59 (dd, *J*=7.9, 1.4 Hz, 1H), 7.35–7.30 (m, 1H), 6.80–6.74 (m, 2H), 5.13 (br s, 2H), 4.71 (dd, *J*=13.4, 1.4 Hz, 1H), 3.72 (ddd, *J*=12.0, 2.6, 2.0 Hz, 1H), 3.33 (d, *J*=13.4 Hz, 1H), 2.87 (dd, *J*=12.0, 2.4 Hz, 1H), 2.84–2.79 (m, 1H), 2.40–2.35 (m, 1H), 2.22–2.17 (m, 2H), 1.74 (dd, *J*=2.0, 1.3 Hz, 3H), 0.80 (d, *J*=6.9 Hz, 3H); ^{13}C NMR: δ 208.4, 162.1, 146.4, 136.7, 136.7, 134.5, 130.2, 117.8, 117.7, 117.3, 52.0, 45.7, 41.6, 36.8, 31.3, 10.6.

4.10. (4*R*,4a*R*,7*R*,7a*S*)-2-[(2-Aminophenyl)sulfonyl]-4,7-dimethyloctahydro-6*H*-cyclopenta[*c*]pyridin-6-one 18

A solution of **14** (3.90 g, 12.2 mmol) in MeOH (120 ml) in the presence of PtO_2 (84 mg, 0.37 mmol) was stirred at room temperature for 24 h under an atmosphere of hydrogen. The mixture was filtered through Celite pad to remove the insoluble materials and the filtrate was again subjected to catalytic hydrogenation over PtO_2 (84 mg, 0.37 mmol) as described above. After removal of the insoluble materials by filtration, the filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane–EtOAc (3:2, v/v) furnished an inseparable mixture of diastereomers **17** in a ratio of ca. 1:1 (3.37 g, 86%) as a colorless oil.

A stirred solution of **17** (430 mg, 1.34 mmol) and NaOMe (233 mg, 4.01 mmol) in MeOH (13 ml) was heated at 65 °C for 1 h. After being cooled to room temperature, the mixture was treated with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–EtOAc (3:2, v/v) furnished a single diastereomer **18** (410 mg, 95%) as a colorless oil. $[\alpha]_D^{24}$ −24.52 (*c* 1.00, $CHCl_3$); IR: ν_{max} 3479, 3377, 1732 cm^{-1}; ^1H NMR: δ 7.59 (dd, *J*=8.0, 1.5 Hz, 1H), 7.31 (ddd, *J*=8.3, 7.2, 1.5 Hz, 1H), 6.79–6.73 (m, 2H), 5.04 (br s, 2H), 3.79–3.73 (m, 2H), 2.79 (dd, *J*=12.7, 3.5 Hz, 1H), 2.41–2.33 (m, 1H), 2.31 (dd, *J*=18.9, 6.5 Hz, 1H), 2.32–2.22 (m, 1H), 2.19 (t, *J*=11.8 Hz, 1H), 1.91–1.85 (m, 1H), 1.75 (ddd, *J*=12.6, 6.1, 1.8 Hz, 1H), 1.59–1.48 (m, 1H), 0.98 (d, *J*=6.9 Hz, 3H), 0.89 (d, *J*=6.5 Hz, 3H); ^{13}C NMR: δ 219.4, 146.2, 134.3, 130.2, 118.1, 117.7, 117.2, 51.5, 45.6, 43.6, 42.9, 42.7, 39.2, 32.1, 17.0, 12.2; HRMS *m*/*z* (EI) calcd for $C_{16}H_{22}N_2O_3S$ (M^+) 322.1351, found 322.1331.

4.11. (2-{[(4*R*,4a*R*,7*R*,7a*R*)-4,7-Dimethyloctahydro-2*H*-cyclopenta[*c*]pyridine-2-yl]sulfonyl}phenyl)amine 19

A stirred solution of **18** (460 mg, 1.43 mmol) and hydrazine monohydrate (0.69 ml, 14.3 mmol) in diethylene glycol (14 ml) was heated at 130 °C for 1.5 h. After removal of an excess hydrazine hydrate under reduced pressure, KOH (942 mg, 14.3 mmol) was added to the mixture, and the whole was heated at 170 °C. After being stirred for 16 h at the same temperature, the resulting solution was treated with saturated NH_4Cl solution and extracted with Et_2O. The ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–EtOAc (3:1, v/v) gave **19** (416 mg, 94%) as a colorless oil. $[\alpha]_D^{24}$ +37.12 (*c* 1.00, $CHCl_3$); IR: ν_{max} 3479, 3377, 2952, 2870, 1620 cm^{-1}; ^1H NMR: δ 7.56 (dd, *J*=8.0, 1.5 Hz, 1H), 7.30–7.26 (m, 1H), 6.75–6.71 (m, 2H), 5.07 (br s, 2H), 3.63–3.55 (m, 2H), 2.73 (dd, *J*=12.1, 3.7 Hz, 1H), 2.10 (t, *J*=11.3 Hz, 1H), 2.03–1.86 (m, 2H), 1.75–1.66 (m, 1H), 1.56–1.39 (m, 4H), 1.22–1.12 (m, 1H), 0.92 (d, *J*=6.4 Hz, 3H), 0.83 (d, *J*=6.4 Hz, 3H); ^{13}C NMR: δ 146.2, 133.9, 130.3, 118.3, 117.5, 117.0, 51.9, 47.0, 45.3, 45.0, 33.0, 32.3, 31.8, 27.7, 19.2, 17.4; HRMS *m*/*z* (EI) calcd for $C_{16}H_{24}N_2O_2S$ (M^+) 308.1558, found 308.1580.

4.12. (2-{[(4*R*,4a*R*,7*R*,7a*R*)-4,7-Dimethyloctahydro-2*H*-cyclopenta[*c*]pyridine-2-yl]sulfonyl}phenyl)acetamide 20

A solution of **19** (450 mg, 1.46 mmol) and AcCl (0.22 ml, 2.92 mmol) in the presence of sodium hydride (60% in oil, 88 mg, 2.19 mmol) in DMF (14 ml) was stirred for 14 h at 0 °C to room temperature. The reaction mixture was treated with water and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–EtOAc (4:1, v/v) afforded **20** (412 mg, 81%) as a colorless oil. $[\alpha]_D^{25}$ +26.76 (*c* 1.00, $CHCl_3$); IR: ν_{max} 3355, 2952, 2871, 1708, 1334, 1152 cm^{-1}; ^1H NMR: δ 9.53 (br s, 1H), 8.45 (d, *J*=8.3 Hz, 1H), 7.75 (dd, *J*=8.0, 1.5 Hz, 1H), 7.58–7.54 (m, 1H), 7.23–7.18 (m, 1H), 3.57–3.51 (m, 2H), 2.68 (dd, *J*=12.0, 3.7 Hz, 1H), 2.21 (s, 3H), 2.07 (t, *J*=11.2 Hz, 1H), 1.97–1.87 (m, 2H), 1.79–1.67 (m, 1H), 1.56–1.40 (m, 4H), 1.21–1.16 (m, 1H), 0.94 (d, *J*=6.2 Hz, 3H), 0.83 (d, *J*=6.4 Hz, 3H); ^{13}C NMR: δ 168.3, 136.5, 134.0, 129.6, 124.3, 123.6, 122.8, 51.8, 46.8, 45.2, 44.7, 33.1, 32.2, 31.7, 27.6, 25.1, 19.1, 17.3; HRMS *m*/*z* (CI) calcd for $C_{18}H_{26}N_2O_3S$ (M^+) 350.1664, found 350.1639.

4.13. (4*R*,4a*R*,7*S*,7a*R*)-4,7-Dimethyloctahydro-1*H*-cyclopenta[*c*]pyridine 21

To a stirred suspension of **20** (230 mg, 0.66 mmol) in MeOH (6.6 ml) in the presence of anhydrous disodium hydrogenphosphate (933 mg, 6.57 mmol) was added sodium–mercury amalgam (1.15 g) at ambient temperature. After being stirred for 24 h, the mixture was filtrated through Celite pad to remove the insoluble materials. Concentration of the filtrate gave a residue, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$–MeOH–25%NH_4OH (100:100:1, v/v/v) gave **21** (67 mg, 66%) as a colorless oil. $[\alpha]_D^{26}$ +34.10 (*c* 1.00, $CHCl_3$); IR: ν_{max} 3308, 2950, 2869 cm^{-1}; ^1H NMR: δ 2.99 (d, *J*=12.7 Hz, 1H), 2.92 (dd, *J*=12.7, 3.9 Hz, 1H), 2.84 (dd, *J*=13.0, 4.2 Hz, 1H), 2.16 (dd, *J*=12.3, 11.2 Hz, 1H), 2.11 (br s, 1H), 2.01–1.90 (m, 2H), 1.75–1.65 (m, 1H), 1.56–1.45 (m, 2H), 1.34–1.26 (m, 2H), 1.24–1.17 (m, 1H), 0.96 (d, *J*=6.3 Hz, 3H), 0.79 (d, *J*=6.5 Hz, 3H); ^{13}C NMR: δ 53.4, 47.1, 45.9, 45.6, 33.2, 32.7, 32.2, 28.0, 19.5, 17.7; HRMS *m*/*z* (CI) calcd for $C_{10}H_{20}N$ (M^++H) 154.1596, found 154.1587. The spectroscopic data were identical with those reported.[4b]

4.14. (+)-α-Skytanthine 1

N-Methylation of **21** was carried out by using the previously reported procedure to provide (+)-α-skytanthine.

$[\alpha]_D^{28}$ +66.5 (*c* 1.40, CH_2Cl_2) {lit:[4a] $[\alpha]_D^{20}$ +79}; IR: ν_{max} 3370, 2925, 2854 cm^{-1}; ^1H NMR: δ 2.83 (d, *J*=11.8 Hz, 1H), 2.69 (dd, *J*=7.6, 1.7 Hz, 1H), 2.24 (s, 3H), 2.07 (dd, *J*=11.7, 3.9 Hz, 1H), 2.11–2.00 (m, 1H), 1.97–1.88 (m, 1H), 1.76–1.66 (m, 1H), 1.53 (t, *J*=10.6 Hz, 1H), 1.52–1.37 (m, 4H), 1.21–1.12 (m, 1H), 0.96 (d, *J*=6.5 Hz, 3H), 0.82 (d, *J*=6.0 Hz, 3H); ^{13}C NMR: δ 63.3, 55.6, 48.1, 46.8, 44.9, 33.7, 32.8, 32.3, 27.5, 19.5, 17.9; HRMS *m*/*z* (EI) calcd for $C_{11}H_{21}N$ (M^+) 167.1674, found 167.1667. The spectroscopic data obtained were superimposable with those previously reported.[4b]

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