1-hydroxyyohimbine and its derivatives: new potent α2-blockers for the treatment of erectile dysfunction

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1-HYDROXYYOHIMBINE AND ITS DERIVATIVES: NEW POTENT α_2-BLOCKERS FOR THE TREATMENT OF ERECTILE DYSFUNCTION[1#]

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Abstract – 1-Hydroxyyohimbine and its various derivatives are prepared for the first time. These novel compounds are found to be potent α_2-blockers comparable to yohimbine itself.

A lot of people are suffering from erectile dysfunction (ED) and waiting for a safe drug. Viagra is a promising drug and has been used for the treatment.[2] However, it has some side-effects[2] to be improved. From the ancient days, yohimbine[3a] (**1**, Scheme 1), a familiar folk medicine, has been widely used as well among people as an α_2-blocker to treat ED.[3b] From the view point of structure-activity relationship, the activity of yohimbine derivatives seem to be sensitive to the change in the stereochemistry of yohimbane nucleus and a substitution on the 1-position, N(1).[4] We have attempted to develop drugs which have desirable characteristics with less toxicity than **1**. Now we wish to report an interesting fact that an introduction of a hydroxy group onto the 1-position does not alter the intrinsic biological activity of **1** and moreover generates a novel family of potent α_2-blockers expected for the treatment of ED.[5]

1-Hydroxyyohimbine (**4**) was given birth for the first time by applying our 1-hydroxyindole synthetic method[6] to 2β,7β- (**2**) and 2α,7α-dihydroyohimbines (**3**). First, we obtained **2** and **3** in 18 and 79% yields, respectively, by the reduction of yohimbine (**1**·free) with $NaBH_3CN$ in CF_3COOH according to the procedure reported by Hannart and co-workers.[7] With the need for the stereoselective production of **3**,

Dedicated to the 70th birthday of Dr. Satoshi Ōmura

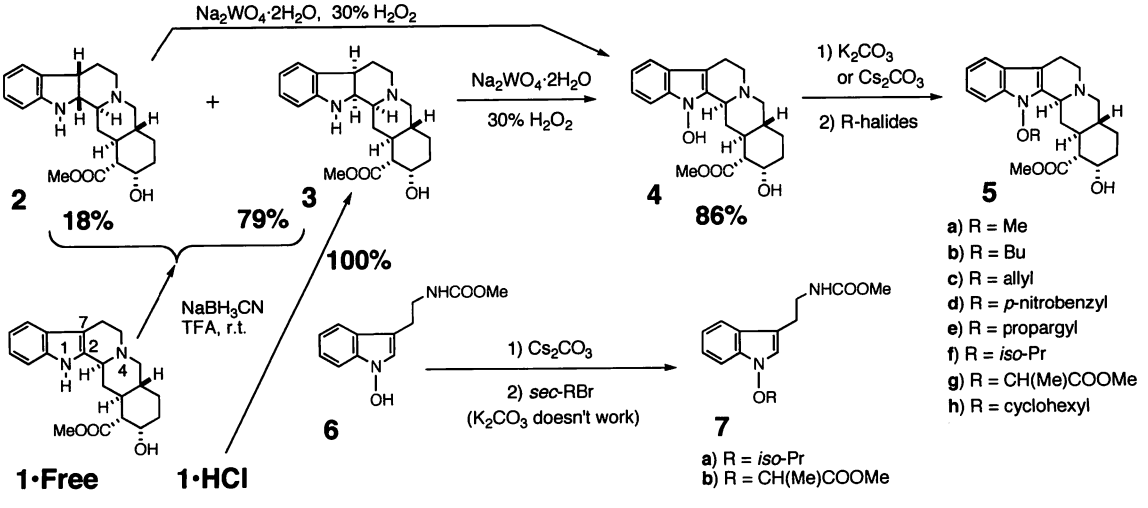
we examined various trials and succeeded in finding the desired reduction conditions. A quantitative production of **3** was attained under the same reaction conditions and with the same reagents simply by employing yohimbine hydrochloride (**1**·HCl) instead of **1**·free as a starting material.

The result is explained as follows. The initial complete protonation of the basic N(4) occurs from the sterically less hindered β-side. The resultant axial N(4)—H bond blocks the β-side and directs the second protonation at the 7-position from the α-side, followed by the α-side hydride attack on the imine C(2).

Oxidation of **3** with $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2 generated a new compound, 1-hydroxyyohimbine (**4**) in a quantitative yield. On the contrary, similar oxidation of **2** afforded **4** in 43% yield with tar formation. A direct procedure for transforming **1** · **HCl** to **4** without isolating **3** is also developed by undergoing $NaBH_3CN$ reduction and Na_2WO_4 catalyzed oxidation consecutively, and now **4** is available in 86% overall yield. Relied on the acidic nature of the 1-hydroxy moiety,[6] the structure of **4** was confirmed by leading it to the corresponding 1-methoxyyohimbine[7] (**5a**) in 77% yield by the reaction with diazomethane.

Further modification of the 1-hydroxy group of **4** with primary alkyl halides in DMF was readily attained. For example, the reaction of **4** with *n*-butyl iodide in the presence of K_2CO_3 gave 1-*n*-butyloxyyohimbine (**5b**) as expected in 93% yield. Under similar reaction conditions, **4** reacted with allyl, *p*-nitrobenzyl, and propargyl bromides to afford 1-allyloxy- (**5c**), 1-*p*-nitrobenzyloxy- (**5d**), and 1-propargyloxyyohimbines (**5e**) in 99, 90, and 99% yields, respectively.

Scheme 1



Upon the reaction of **4** with *sec*- and *tert*-alkyl halides, we have encountered much trouble in the preparation of the desired yohimbine derivatives. To overcome the problem, we examined various

reaction conditions using 1-hydroxy-*N*-methoxycarbonyltryptamine (**6**) as a substrate. In the presence of K_2CO_3 in DMF, **6** did not react at all with 2-bromopropane and (*dl*)-methyl 2-bromopropionate. We have finally succeeded in the preparation of *N*-methoxycarbonyl-1-isopropyloxy- (**7a**) and -(*dl*)-1-(1-methoxycarbonyl)ethoxytryptamine (**7b**) in 83 and 97% yields, respectively, by finding a novel procedure: the initial formation of the cesium salt of the 1-hydroxy group, followed by its reaction with 2-bromopropane and (*dl*)-methyl 2-bromopropionate in DMF.

The above reaction conditions worked well in the case of 1-hydroxyyohimbine (**4**). When 2-bromopropane and (*dl*)-methyl 2-bromopropionate were allowed to react with **4**, the corresponding 1-isopropyloxy- (**5f**) and (*dl*)-1-(1-methoxycarbonyl)ethoxyyohimbine (**5g**) were obtained in 99 and 99% yields, respectively. However, even under the improved reaction conditions, cyclohexyl bromide reacted poorly with **4** giving an 11% yield of 1-cyclopropyloxyyohimbine (**5h**). We have not yet succeeded in the reaction of **4** with *tert*-alkyl halides.

Table 1. Effects of yohimbine derivatives on the contraction induced by clonidine in rat thoracic aorta.

Compound	n	Tension (g)		Relaxant response (%)[b]
		80 mM KCl	Clonidine (10^{-7} or 10^{-6} M)[a]	
4	3	1.36 ± 0.12	1.35 ± 0.03	101.9 ± 3.7
5a	3	1.60 ± 0.20	1.09 ± 0.05	98.2 ± 1.8
5b	3	1.46 ± 0.37	0.98 ± 0.11	101.8 ± 1.8
5c	3	1.38 ± 0.24	1.10 ± 0.15	101.5 ± 1.5
5d	3	1.54 ± 0.24	1.15 ± 0.15	101.5 ± 1.5

[a]Clonidine-induced contraction was attained by 10^{-7} M or 10^{-6} M in the presence of N^G-nitro-L-arginine methyl ester (L-NAME, 10^{-4} M).

[b]Responses to yohimbine derivatives are expressed as % relaxation to the maximum relaxation by 10^{-5} M yohimbine.

Results are represented as mean ± S.E.M. of n number of experiments.

With various derivatives in hand, we have evaluated the relaxant potencies of yohimbine derivatives (**4**, **5a**, **5b**, **5c**, and **5d**). Table 1 shows clearly that all the compounds exhibited almost the same extent of the vascular relaxation as yohimbine (**4**) produced in the muscle contracted with clonidine. These results strongly suggest that these yohimbine derivatives possess at least the same and/or more potent antagonistic effect on vascular smooth muscle α_2-AR.

In conclusion, we have succeeded in finding new leads for the treatment of ED.

MATERIALS AND METHOD

Animals: Male Wistar rats were used in the present study. Animals were housed under controlled conditions (21–22°C, relative humidity 50±5%). Food and water were freely available to all animals. This study was performed according to the Guideline for the Care and Use of Laboratory Animals of Toho University School of Pharmaceutical Sciences (which is accredited by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan), and the protocol of this study was approved by the Institutional Animal Care and Use Committee.

Preparation of rat thoracic aortic rings: Rats were killed by cervical dislocation and exsanguinated from the common carotid arteries. A section of the thoracic aorta between aortic arch and diaphragm was carefully removed and immersed in oxygenated Krebs-HEPES solution of the following composition (in mM): NaCl, 126.9; KCl, 5.9; $CaCl_2$, 2.36; $MgCl_2$, 1.18; HEPES, 10.03 and glucose, 11.8 (pH=7.4). The aorta was cleaned of loosely adhering fat and connective tissues and cut into ring segments about 2 mm in length. In this series of experiments, the endothelium was not removed.

Measurement of tension changes: The aortic tissue was then mounted using stainless steel hooks (outer diameter, 200 μm) under the resting tension of 2.0 g in a 5 mL organ bath (UC-5, UFER Medical Instrument, Kyoto, Japan) containing normal Tyrode's solution (mM): NaCl, 158.3; KCl, 4.0; $NaHCO_3$, 10.0; NaH_2PO_4:, 0.42; $CaCl_2$, 2.0; $MgCl_2$, 1.05 mM, glucose, 5.6), which was continuously gassed with 95% O_2–5% CO_2 being kept at 37±1°C (pH=7.4). Tension changes of the muscle preparation were isometrically recorded with a force-displacement transducer (T7-8-240; Orientec, Tokyo, Japan; TB-612T, Nihon Kohden, Tokyo, Japan) connected to a carrier amplifier (AP-600G/AP-621G, Nihon Kohden, Tokyo, Japan; Signal Conditioner: Model MSC-2, Labo Support, Suita-City, Japan). Vascular preparations were equilibrated for 90 min in normal Tyrode's solution, which was exchanged every 20–30 min. Before starting assessment of yohimbine derivatives, aortic preparations were contracted with isotonic high-KCl (80 mM) Tyrode's solution (mM: NaCl, 82.3; KCl, 80.0; $CaCl_2$, 2.0; $MgCl_2$, 1.05; NaH_2PO_4, 0.42; $NaHCO_3$, 10.0 and glucose, 5.6), in order to confirm the muscle normal contractility. After washing out, experiments were started after a subsequent 30 min equilibration period.

Assessment of relaxant potencies of yohimbine derivatives: Aortic ring preparations were contracted with an a_2-adrenoceptor (α_2-AR) agonist clonidine (10^{-7}–10^{-6} M) in the presence of an NO synthase inhibitor nitro-L-arginine methylester (L-NAME, 10^{-4} M). When the sustained contraction induced by

clonidine reached a steady-state level, yohimbine derivatives (10^{-5} M) were applied to the bath solution. When the relaxant effects of yohimbine derivatives reached their maximum level, yohimbine at 10^{-5} M was applied. The steady-state tension level before application of each yohimbine derivative and the tension level corresponding to yohimbine-induced maximum relaxation were defined as 0% and 100% relaxation, respectively. Relaxant potency of tested yohimbine derivatives was expressed as percentage relaxation to the maximum response to 10^{-5} M yohimbine.

Drugs: The following drugs were used in the present study: clonidine hydrochloride (Sigma-Aldrich, St. Louis, MO, USA); yohimbine hydrochloride (Wako Pure Chemical Industries, Ltd., Osaka, Japan); N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME) (Dojindo Laboratories, Kumamoto, Japan). Yohimbine derivatives tested in this study were dissolved in pure dimethyl sulfoxide (DMSO) at 10^{-2} M. Final DMSO concentrations in the bath medium did not exceed 0.1%, which did not affect the vascular responses. Other drugs were dissolved/diluted in/with distilled water. All drugs are expressed in molar concentrations (mol/L, M) in bathing solution.

Statistics: Data are presented as means±S.E.M. and n refers to the number of experiments.

SYNTHESIS OF CHEMICALS

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 spectrophotometer, and ^{1}H-NMR spectra with a JEOL GSX-500 spectrometer, with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102A spectrometer. Column chromatography was performed on silica gel (SiO_2, 100—200 mesh, from Kanto Chemical Co. Inc.).

2β,7β- (2) and 2α,7α-Dihydroyohimbine (3) from Yohimbine (1·Free) — General Procedure: $NaBH_3CN$ (610.7 mg, 9.72 mmol) was added to a solution of **1·Free** (1056.4 mg, 2.98 mmol) in CF_3COOH (20.0 mL) at 0°C. The mixture was stirred at rt for 3 h. After evaporation of the solvent, the whole was made alkaline with initially aq. 8% and then 0.8% NaOH under ice cooling, and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with AcOEt–$CHCl_3$–MeOH–28% aq. NH_3 (51.5:46:5:0.5, v/v) to give **3** (843.3 mg, 79%) and **2** (189.1 mg, 18%) in the order of elution. **2**: mp 191—193.5°C (pale yellow needles, recrystallized from AcOEt–hexane). IR (KBr): 3502, 1722, 1608, 754 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (1H, q, *J*=11.5 Hz), 1.30—1.53 (5H, m), 1.60—1.78 (4H, m), 1.90—1.96 (1H, m), 2.06 (1H, dt, *J*=3.9, 11.5 Hz), 2.15—2.27 (2H, m), 2.25 (1H, dd, *J*=11.5, 2.0 Hz), 2.60 (1H, dt, *J*=11.5, 3.4 Hz), 2.71 (1H, dd, *J*=11.5, 2.7 Hz), 3.00 (1H, br s, disappeared on addition of

D_2O), 3.31 (1H, t, *J*=8.1 Hz), 3.42 (1H, br s), 3.78 (3H, s), 4.16 (1H, br s), 6.65 (1H, d, *J*=7.8 Hz), 6.77 (1H, dd, *J*=7.6, 7.3 Hz), 7.02—7.06 (2H, m). High-resolution MS *m/z*: calcd for $C_{21}H_{28}N_2O_3$: 356.2100, found 356.2096. $[\alpha]^{29}_D$ –69.9° (c=0.33, MeOH). **3**: mp 190—193°C (colorless fine needles, recrystallized from AcOEt–hexane). IR (KBr): 3471, 2906, 1707, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36—1.61 (7H, m), 1.68 (1H, br s, disappeared on addition of D_2O), 1.71—1.77 (1H, m), 1.83—2.06 (4H, m), 2.18 (1H, dt, *J*=11.5, 2.7 Hz), 2.30 (1H, dd, *J*=11.5, 2.2 Hz), 2.77 (1H, ddd, *J*=11.5, 3.4, 3.2 Hz), 2.83 (1H, dd, *J*=11.5, 2.2 Hz), 2.93 (1H, dt, *J*=6.6, 2.7 Hz), 3.10 (1H, s, disappeared on addition of D_2O), 3.57 (1H, dd, *J*=6.6, 2.7 Hz), 3.76 (3H, s), 4.19 (1H, br s), 6.68 (1H, dd, *J*=7.8, 1.0 Hz), 6.72 (1H, ddd, *J*=7.6, 7.3, 1.0 Hz), 7.01 (1H, ddd, *J*=7.8, 7.6, 1.0 Hz), 7.08 (1H, dd, *J*=7.3, 1.0 Hz). High-resolution MS *m/z*: calcd for $C_{21}H_{28}N_2O_3$: 356.2100, found: 356.2111. *Anal.* Calcd for $C_{21}H_{28}N_2O_3 \cdot 1/8H_2O$: C, 70.31; H, 7.94; N, 7.81. Found: C, 70.30; H, 7.93; N, 7.78. $[\alpha]^{25}_D$ +90.64° (*c*=0.20, $CHCl_3$).

2α,7α-Dihydroyohimbine (3) from Yohimbine hydrochloride (1·HCl) — According to the general procedure, $NaBH_3CN$ (36.4 mg, 0.55 mmol), **1·HCl** (107.6mg, 0.28 mmol), and CF_3COOH (2.0 mL) were used. After column-chromatography on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46:3:0.3, v/v), **3** (98.0 mg, 100%) was obtained.

1-Hydroxyyohimbine (4) from Yohimbine hydrochloride (1·HCl) — According to the general procedure, $NaBH_3CN$ (85.5 mg, 1.3 mmol), **1·HCl** (101.0mg, 0.26 mmol), and CF_3COOH (2.0 mL) were used. The resultant oil, obtained after general procedure, was dissolved in MeOH (9.0 mL). A solution of $Na_2WO_4 \cdot 2H_2O$ (17.0 mg, 0.05 mmol) in H_2O (1.0 mL) and 30% H_2O_2 (0.59 mL, 5.2 mmol) were added to the solution. The mixture was stirred at 0°C for 1 h. After addition of H_2O, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46:5:0.5, v/v) to give **4** (82.1 mg, 86%). **4**: mp 224—226°C (decomp., colorless fine needles, recrystallized from MeOH). IR (KBr): 3505, 2945, 1711, 751 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.19 (1H, q, *J*=11.5 Hz), 1.33—1.39 (1H, m), 1.43—1.57 (2H, m), 1.65 (1H, br t, *J*=13.4 Hz), 1.91 (1H, dq, *J*=13.4, 2.7 Hz), 1.99 (1H, dq, *J*=2.7, 11.5 Hz), 2.31 (1H, br d, *J*=11.5 Hz), 2.40 (1H, t, *J*=11.5 Hz), 2.63—2.76 (2H, m), 2.88—2.98 (3H, m), 3.10—3.15 (1H, m), 3.62 (1H, d, *J*=11.5 Hz), 3.73 (3H, s), 4.22 (1H, q, *J*=2.7 Hz), 6.98 (1H, t, *J*=7.6 Hz), 7.09 (1H, t, *J*=7.6 Hz), 7.29 (1H, d, *J*=7.6 Hz), 7.37 (1H, d, *J*=7.6 Hz). MS *m/z*: 370 (M^+), 354 (M^+–O), 353 (M^+–OH). *Anal.* Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.97; H, 7.13; N, 7.60. $[\alpha]^{30}_D$ +7.75° (*c*=0.20, DMF).

1-Hydroxyyohimbine (4) from 2β,7β-Dihydroyohimbine (2) — A solution of $Na_2WO_4 \cdot 2H_2O$ (6.8 mg, 0.03 mmol) in H_2O (0.3 mL) and 30% H_2O_2 (0.10 mL, 0.80 mmol) were added to a solution of **2** (28.2 mg, 0.80 mmol) in MeOH (3.0 mL). The mixture was stirred at rt for 2 h. After addition of H_2O, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and

evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46:5:0.5, v/v) to give **4** (12.7mg, 43%).

1-Methoxyyohimbine (5a) from 4 — An excess amount of ethereal CH_2N_2 was added to a solution of **4** (52.6 mg, 0.14 mmol) in MeOH (20.0 mL) and the whole was stirred at 0°C for 1 h. The solution was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% aq. NH_3 (46:3:0.3, v/v) to give **5a** (42.2 mg, 77%). **5a**: mp 201—203°C (decomp., colorless prisms, recrystallized from acetone. Lit.[8] mp 198—201°C). IR (KBr): 3145, 1737, 743 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36—1.45 (2H, m), 1.49—1.62 (3H, m), 1.97—2.09 (2H, m), 2.32—2.39 (2H, m), 2.46 (1H, ddd, *J*=12.7, 3.2, 2.9 Hz), 2.63 (1H, dt, *J*=4.2, 11.2 Hz), 2.66—2.71 (1H, m), 2.89—2.98 (2H, m), 3.03—3.08 (1H, m), 3.36 (1H, br s, disappeared on addition of D_2O), 3.49 (1H, br d, *J*=11.2 Hz), 3.77 (3H, s), 3.89 (3H, s), 4.21 (1H, br s), 7.09 (1H, ddd, *J*=7.8, 7.1, 1.0 Hz), 7.19 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.34 (1H, dd, *J*=8.1, 1.0 Hz), 7.44 (1H, dd, *J*=7.8, 1.0 Hz). MS *m/z*: 384 (M^+), 353 (M^+–OMe). *Anal.* Calcd for $C_{22}H_{28}N_2O_4$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.65; H, 7.35; N, 7.23. $[\alpha]^{29}_D$ +20.54° (*c*=0.20, $CHCl_3$).

1-Allyloxyyohimbine (5b) from 4 — General procedure: K_2CO_3 (59.2 mg, 0.43 mmol) and a solution of allyl bromide (24.7 mL, 0.3 mmol) in DMF (1.0 mL) were successively added to a solution of **4** (52.8 mg, 0.14 mmol) in DMF (4.0 mL) and the whole was stirred at rt for 30 min. After addition of H_2O, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (95:5, v/v) to give **5b** (54.6 mg, 93%). **5b**: mp 150—152°C (decomp., colorless fine needles, recrystallized from hexane). IR (KBr): 3464, 2935, 1738, 1151, 737 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, *J*=7.3 Hz), 1.34—1.43 (2H, m), 1.48—1.63 (5H, m), 1.65—1.79 (2H, m), 1.97—2.07 (2H, m), 2.34 (1H, dd, *J*=11.2, 2.0 Hz), 2.36 (1H, t, *J*=11.2 Hz), 2.53 (1H, dt, *J*=12.9, 2.9 Hz), 2.63 (1H, dt, *J*=4.2, 11.2 Hz), 2.66—2.72 (1H, m), 2.90—2.98 (1H, m), 2.96 (1H, dd, *J*=11.2, 2.9 Hz), 3.05 (1H, ddd, *J*=11.2, 5.6, 2.0 Hz), 3.29 (1H, s, disappeared on addition of D_2O), 3.48 (1H, d, *J*=11.2 Hz), 3.76 (3H, s), 3.98 (1H, dt, *J*=6.6, 8.5 Hz), 4.06 (1H, dt, *J*=6.6, 8.5 Hz), 4.20 (1H, br s), 7.07 (1H, ddd, *J*=8.1, 7.8, 1.0 Hz), 7.17 (1H, dt, *J*=1.0, 8.1 Hz), 7.31 (1H, dd, *J*=8.1, 1.0 Hz), 7.43 (1H, dd, *J*=7.8, 1.0 Hz). MS *m/z*: 426 (M^+), 353 (M^+–O*n*-Bu). *Anal.* Calcd for $C_{25}H_{34}N_2O_4$: C, 70.39; H, 8.03; N, 6.57. Found: C, 70.26; H, 8.12; N, 6.48. $[\alpha]^{32}_D$ +21.46° (*c*=0.21, $CHCl_3$).

1-*n*-Butyloxyyohimbine (5c) from 4 — According to the general procedure for **5b**, K_2CO_3 (56.7 mg, 0.41 mmol), *n*-butyl iodide (30.8 mg, 0.17 mmol), and **4** (50.5 mg, 0.14 mmol) were used. After column-chromatography, **5c** (57.8 mg, 99%) was obtained. **5c**: mp 126—128.5°C (decomp., colorless fine needles, recrystallized from hexane). IR (KBr): 3458, 2920, 1739, 1151, 737 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34—1.43 (2H, m), 1.48—1.64 (3H, m), 1.97—2.06 (2H, m), 2.34 (1H, dd, *J*=11.5, 2.2 Hz), 2.35 (1H, t,

J=11.5 Hz), 2.55 (1H, dt, *J*=12.9, 2.9 Hz), 2.62 (1H, dt, *J*=4.2, 10.7 Hz), 2.66—2.72 (1H, m), 2.90—2.98 (1H, m), 2.96 (1H, dd, *J*=11.5, 2.9 Hz), 3.05 (1H, ddd, *J*=11.5, 5.6, 2.2 Hz), 3.30 (1H, s, disappeared on addition of D_2O), 3.51 (1H, dd, *J*=11.5, 2.2 Hz), 3.75 (3H, s), 4.20 (1H, d, *J*=1.2 Hz), 4.49 (1H, dddd, *J*=11.0, 6.6, 1.2, 1.0 Hz), 4.55 (1H, dddd, *J*=11.0, 6.1, 1.2, 1.0 Hz), 5.39 (1H, ddd, *J*=10.7, 1.2, 1.0 Hz), 5.44 (1H, dq, *J*=17.1, 1.2 Hz), 6.05 (1H, dddd, *J*=17.1, 10.7, 6.6, 6.1 Hz), 7.08 (1H, ddd, *J*=8.1, 7.8, 1.0 Hz), 7.18 (1H, dt, *J*=1.0, 8.1 Hz), 7.34 (1H, ddd, *J*=8.1, 1.0, 0.7 Hz), 7.43 (1H, br d, *J*=7.8 Hz). MS *m/z*: 410 (M+), 353 (M^+–$OCH_2CH=CH_2$). *Anal.* Calcd for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.13; H, 7.50; N, 6.57. $[\alpha]^{30}_D$ +18.4° (*c*=0.21, $CHCl_3$).

1-*p*-Nitrobenzyloxyyohimbine (5d) from 1-Hydroxyyohimbine (4) — According to the general procedure for **5b**, K_2CO_3 (56.8 mg, 0.41 mmol), *p*-nitrobenzyl bromide (35.4 mg, 0.16 mmol), and **4** (50.3 mg, 0.14 mmol) were used. After column-chromatography, **5d** (61.7 mg, 90%) was obtained. **5d**: mp 148—149°C (decomp., yellow fine needles, recrystallized from AcOEt–hexane). IR (KBr): 3430, 2924, 1734 and 1703 (collapsed to 1710 in $CHCl_3$), 1523, 1348, 739 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33—1.43 (2H, m), 1.50—1.61 (3H, m), 1.94—2.03 (2H, m), 2.28 (1H, br t, *J*=11.0 Hz), 2.33 (1H, dd, *J*=11.7, 2.2 Hz), 2.54 (1H, dt, *J*=12.7, 2.9 Hz), 2.57 (1H, dt, *J*=4.2, 11.0 Hz), 2.66—2.72 (1H, m), 2.89—2.98 (2H, m), 3.01—3.07 (1H, m), 3.04 (1H, s, disappeared on addition of D_2O), 3.23 (1H, br d, *J*=11.0 Hz), 3.59 (3H, s), 4.21 (1H, br s), 5.02 (1H, d, *J*=10.6 Hz), 5.07 (1H, d, *J*=10.6 Hz), 7.12 (1H, ddd, *J*=8.1, 7.8, 1.0 Hz), 7.21 (1H, dt, *J*=1.0, 8.1 Hz), 7.32 (1H, dd, *J*=8.1, 1.0 Hz), 7.46 (1H, dd, *J*=7.8, 1.0 Hz), 7.59—7.62 (2H, A_2 part of A_2B_2), 8.29—8.33 (2H, B_2 part of A_2B_2). *Anal.* Calcd for $C_{28}H_{31}N_3O_6$: C, 66.52; H, 6.18; N, 8.31. Found: C, 66.40; H, 6.22; N, 8.18. $[\alpha]^{31}_D$ +48.77° (*c*=0.20, $CHCl_3$).

1-Propargyloxyyohimbine (5e) from 4 — According to the general procedure for **5b**, K_2CO_3 (223.6 mg, 1.62 mmol), propargyl bromide (70.8 mg, 0.60 mmol), and **4** (200.1 mg, 0.54 mmol) were used. After column-chromatography with AcOEt–hexane (1:1, v/v), **5e** (57.8 mg, 99%) was obtained. **5e**: mp 158—161°C (decomp., colorless fine needles, recrystallized from AcOEt–hexane). IR (KBr): 3565, 1720, 1265, 742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.43 (2H, m), 1.51—1.63 (3H, m), 1.97—2.07 (2H, m), 2.34 (1H, dd, *J*=11.5, 2.2 Hz), 2.36 (1H, d, *J*=11.2 Hz), 2.55 (1H, dt, *J*=12.7, 3.4 Hz), 2.60-2.71 (3H, m), 2.89—2.96 (1H, m), 2.96 (1H, dd, *J*=11.2, 3.4 Hz), 3.05 (1H, ddd, *J*=11.2, 6.1, 1.7 Hz), 3.46 (1H, br s, disappeared on addition of D_2O), 3.58 (1H, dd, *J*=11.2, 1.7 Hz), 3.79 (3H, s), 4.21 (1H, d, *J*=1.2 Hz), 4.63 (1H, dd, *J*=15.1, 2.4 Hz), 4.71 (1H, dd, *J*=15.1, 2.4 Hz), 7.09 (1H, dt, *J*=1.0, 7.8 Hz), 7.19 (1H, dt, *J*=1.0, 7.8 Hz), 7.38 (1H, d, *J*=7.8 Hz), 7.43 (1H, d, *J*=7.8 Hz). MS *m/z*: 408 (M^+). *Anal.* Calcd for $C_{24}H_{28}N_2O_4 \cdot 1/2H_2O$: C, 69.04; H, 7.00; N, 6.71. Found: C, 68.99; H, 6.82; N, 6.56. $[\alpha]^{24}_D$ +96.19° (*c*=0.21, MeOH).

***N*-Methoxycarbonyl-1-isopropyloxytryptamine (7a) from 1-Hydroxy-*N*-methoxycarbonyltryptamine (6) — General procedure**: 1-Hydroxytryptamine (**6**, 50.9 mg, 0.22 mmol)

was added to a solution of Cs_2CO_3 (83.9 mg, 0.23 mmol) in MeOH (2.0 mL) and the whole was stirred at rt for 20 min. To the resultant residue obtained after evaporation of the solvent under reduced pressure, a solution of isopropyl bromide (160.0 mg, 1.32 mmol) in DMF (3.0 mL) was added and the whole was stirred at rt for 1 h. After addition of H_2O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$ to give **7a** (49.7 mg, 83%). **7a**: colorless oil. IR (film): 1710 (br), 740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, d, *J*=6.2 Hz), 1.37 (3H, d, *J*=6.2 Hz), 2.93 (2H, t, *J*=6.6 Hz), 3.49 (2H, br q, *J*=6.6 Hz, collapsed to t on addition of D_2O), 3.66 (3H, s), 4.52 (1H, sep, *J*=6.2 Hz), 4.74 (1H, br s, disappeared on addition of D_2O), 7.06 (1H, s), 7.09 (1H, dt, *J*=0.8, 7.7 Hz), 7.22 (1H, dt, *J*=0.8, 7.7 Hz), 7.38 (1H, dd, *J*=7.7, 0.8 Hz), 7.55 (1H, dd, *J*=7.7, 0.8 Hz). High-resolution MS *m/z*: calcd for $C_{15}H_{20}N_2O_3$: 276.1482, found: 276.1474.

(*dl*)-*N*-Methoxycarbonyl-1-(1-methoxycarbonyl)ethoxytryptamine (7b) from 6 — According to the general procedure for **7a**, **6** (49.1 mg, 0.21 mmol), Cs_2CO_3 (76.0 mg, 0.23 mmol), and (*dl*)-methyl 2-bromopropionate (212.8 mg, 1.3 mmol) were used. After column-chromatography with AcOEt–hexane (1:2, v/v), **7b** (64.9 mg, 97%) was obtained. **7b**: colorless oil. IR (film): 3405, 1749, 1716 (br), 742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, d, *J*=7.0 Hz), 2.89 (2H, t, *J*=6.6 Hz), 3.47 (2H, br q, *J*=6.6 Hz, collapsed to t on addition of D_2O), 3.66 (3H, s), 3.77 (3H, s), 4.73 (1H, br s, disappeared on addition of D_2O), 4.85 (1H, q, *J*=7.0 Hz), 7.12 (1H, dt, *J*=0.7, 7.6 Hz), 7.21 (1H, s), 7.24 (1H, dt, *J*=0.7, 7.6 Hz), 7.40 (1H, d, *J*=7.6 Hz), 7.54 (1H, d, *J*=7.6 Hz). High-resolution MS *m/z*: calcd for $C_{16}H_{20}N_2O_5$: 320.1372, found: 320.1371.

1-Isopropyloxyyohimbine (5f) from 4 — a) Cs_2CO_3 Method: According to the general procedure for **7a**, **4** (29.4 mg, 0.08 mmol), Cs_2CO_3 (28.6 mg, 0.09 mmol), and isopropyl bromide (29.3 mg, 0.24 mmol) were used. After column-chromatography with $CHCl_3$–MeOH–28% aq. NH_3 (46:1:0.1, v/v), **5e** (32.3 mg, 99%) was obtained. **5e**: pale brown viscous oil. IR (film): 3456, 2922, 1734 (br), 750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, d, *J*=6.1 Hz), 1.31 (3H, d, *J*=6.1 Hz), 1.41—1.64 (4H, m), 1.95—2.07 (2H, m), 2.38 (1H, dd, *J*=11.6, 2.0 Hz), 2.64—2.77 (3H, m), 2.97—3.07 (2H, br s), 3.07—3.17 (2H, br s), 3.55—3.65 (1H, br), 3.76 (3H, s), 4.23 (1H, br s), 4.50 (1H, sep, *J*=6.1 Hz), 4.72 (2H, br s, disappeared on addition of D_2O), 7.02 (1H, t, *J*=7.3 Hz), 7.19 (1H, t, *J*= 7.3 Hz), 7.30 (1H, d, *J*=7.9 Hz), 7.43 (1H, d, *J*=7.3 Hz). MS *m/z*: 412 (M^+), 353 (M^+–$OCHMe_2$). High-resolution MS *m/z*: calcd for $C_{24}H_{32}N_2O_4$: 412.2362, found: 412.2366. $[\alpha]^{25}_D$ +16.45° (*c*=0.15, $CHCl_3$).

b) K_2CO_3 Method: According to the general procedure for **5b**, K_2CO_3 (18.9 mg, 0.14 mmol), isopropyl bromide (19.8 mg, 0.16 mmol), and **4** (16.8 mg, 0.05 mmol) were used. After work-up, **5e** (13.3 mg, 71%) was obtained.

(*dl*)-**1-(1-Methoxycarbonyl)ethoxyyohimbine (5g) from 4** — According to the general procedure for **7a**, **4** (30.3 mg, 0.08 mmol), Cs_2CO_3 (29.4 mg, 0.09 mmol), and (*dl*)-methyl-2-bromopropionate (41.0 mg, 0.25 mmol) were used. After column-chromatography with AcOEt, **5g** (37.0 mg, 99%) was obtained. **5g**: pale brown viscous oil. IR (film): 3509, 2923, 1739, 1710, 752 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30—1.45 (2H, m), 1.52—1.61 (3H, m), 1.55 (3H, d, *J*=6.8 Hz), 1.95—2.07 (2H, m), 2.34 (1H, dd, *J*=11.6, 2.0 Hz), 2.37—2.44 (1H, m), 2.52 (1H, dt, *J*=13.2, 2.7 Hz), 2.61—2.71 (2H, m), 2.86—2.95 (1H, m), 2.98 (1H, dd, *J*=11.6, 2.7 Hz), 3.01—3.08 (1H, m), 3.16 (1H, br s, disappeared on addition of D_2O), 3.53 (1H, d, *J*=10.0 Hz), 3.66 (3H, s), 3.77 (3H, s), 4.20 (1H, br s), 4.66 (1H, q, *J*=6.8 Hz), 7.06 (1H, t, *J*=7.8 Hz), 7.16 (1H, t, *J*=7.8 Hz), 7.39 (1H, d, *J*=7.8 Hz), 7.44 (1H, d, *J*=7.8 Hz). High-resolution MS *m/z*: calcd for $C_{25}H_{32}N_2O_6$: 456.2260, found: 456.2263. $[\alpha]^{26}_D$ –22.11° (*c*=0.015, $CHCl_3$).

1-Cyclohexyloxyyohimbine (5h) from 4 — According to the general procedure for **7a**, **4** (30.0 mg, 0.08 mmol), and Cs_2CO_3 (29.1 mg, 0.09 mmol) were used. The reaction time with cyclohexyl bromide (40.7 mg, 0.25 mmol) was prolonged to 130 min. After column-chromatography with $CHCl_3$–MeOH–28% aq. NH_3 (46:0.5:0.05, v/v), **5h** (4.0 mg, 11%) and unreacted **4** (20 mg, 67%) were obtained. **5h**: pale brown viscous oil. IR (film): 3446, 2927, 1738 (br), 739 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.25—1.41 (8H, m), 1.46—1.71 (5H, m), 1.77—2.08 (6H, m), 2.35 (1H, dd, *J*=11.7, 2.7 Hz), 2.45 (1H, br t, *J*=11.0 Hz), 2.68—2.79 (2H, m), 2.90—3.02 (3H, m), 3.09—3.18 (1H, m), 3.73 (3H, s), 4.12—4.19 (1H, m), 4.20—4.25 (1H, m), 7.01 (1H, t, *J*=7.8 Hz), 7.13 (1H, t, *J*=8.3 Hz), 7.30 (1H, d, *J*=8.3 Hz), 7.39 (1H, d, *J*=7.8 Hz). High-resolution MS (EI) *m/z*: calcd for $C_{27}H_{34}N_2O_4$: 452.2675, found: 452.2677. $[\alpha]^{25}_D$ +8.46° (*c*=0.14, $CHCl_3$).

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