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First Total Synthesis of (±)-Oxerine

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Abstract: Total synthesis of (±)-oxerine (**1**), a monoterpene alkaloid, starting from 3-bromopyridine (**7**) is described. The key reaction in this sequence is the samarium iodide (SmI_2)-mediated intramolecular cyclization of γ-ethynyl bromide (**4**).

Many monoterpene alkaloids containing a cyclopentano[*c*]pyridine skeleton are well-known in nature and exhibit unique biological activities. For example, it is known that (-)-actinidine shows the cat-exciting action.[1] Recently, (-)-oxerine (**1**) was isolated from the aerial parts of *Oxera morieri* by R. Benkrief *et al* .(Fig. 1).[2] Since the bark extract of the related species (*Oxera robsta*) is known for its abortive activity,[3] this compound is expected to show interesting biological activities. Until recently, the total effective syntheses of monoterpene alkaloids have not been described except for some reports.[4] Though the transformation of with β–glycosidase in an ammonia solution was reported to give (-)-oxerine, the chemical total synthesis has not been emerged.

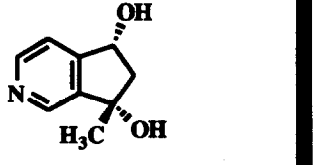
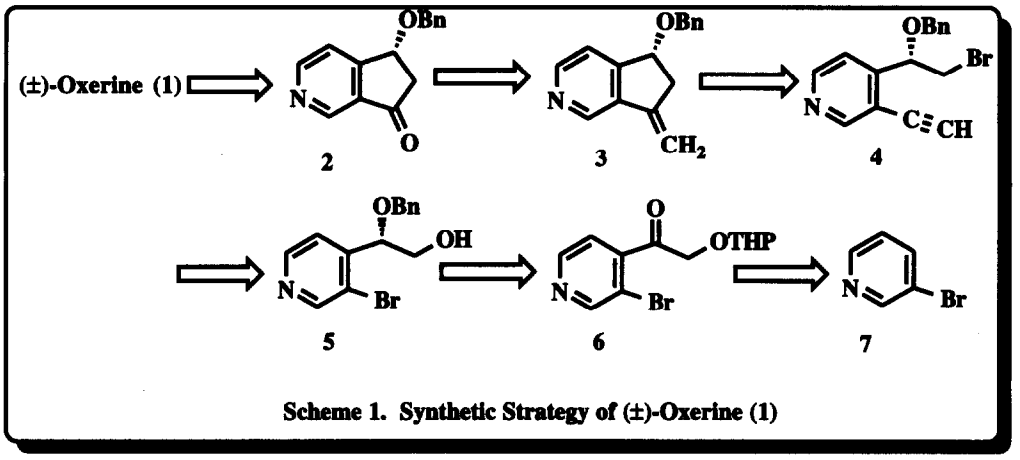


Fig. 1 (-)-Oxerine (**1**)

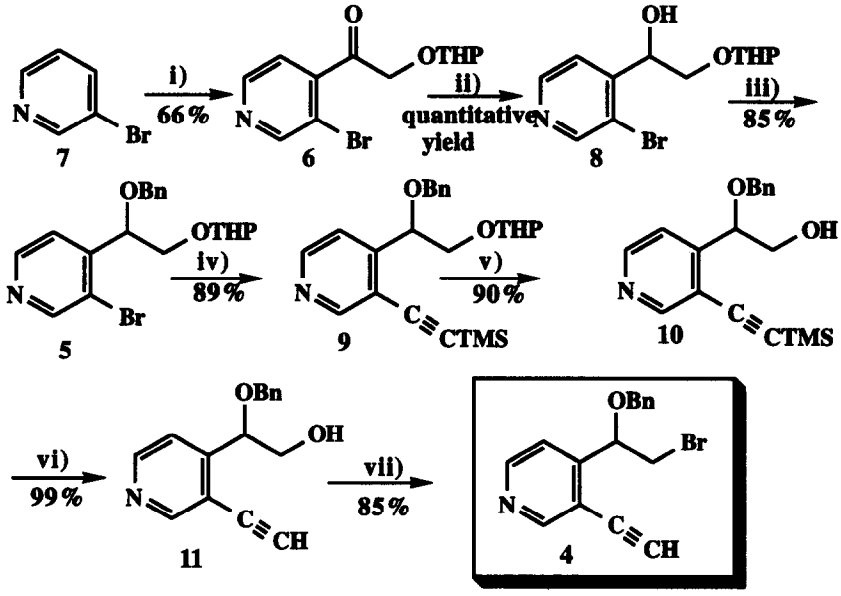
In this paper, we describe the total synthesis of (±)-oxerine (**1**) from 3-bromopyridine (**7**) *via* the samarium iodide (SmI_2)-mediated intramolecular cyclization as the key reaction.

Our synthetic plan is shown in Scheme 1: A γ-ethynyl bromide (**4**), as a key intermediate, may be prepared from 3-bromopyridine (**7**) *via* several steps. The SmI_2-mediated intramolecular cyclization of the

γ-ethynyl bromide (**4**) will give a cyclopentano[*c*]pyridine (**3**) having an exocyclic methylene group. Then, compound **3** should readily lead to (±)-oxerine (**1**).



Scheme 1. Synthetic Strategy of (±)-Oxerine (1)



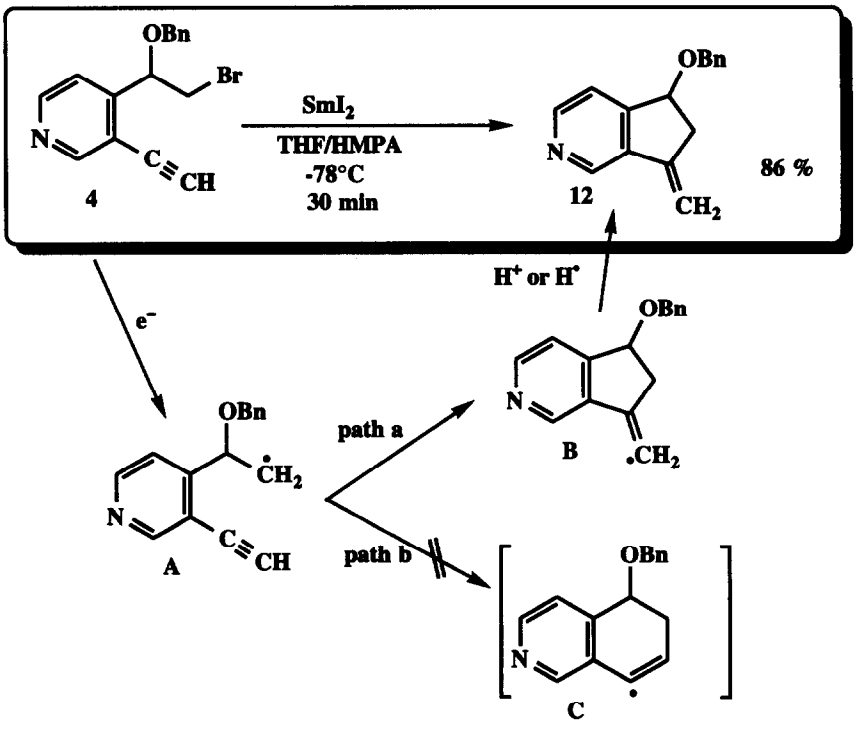
i) a) LDA, -78°C b) $THPOCH_2COOEt$ ii) $NaBH_4$, r.t., in MeOH iii) a) NaH b) BnBr iv) TMS-acetylene, $Pd(PPh_3)_4$, Et_3N v) p-TsOH, in MeOH vi) Bu_4NF, in THF vii) PPh_3, NBS in CH_2Cl_2

Scheme 2. Synthesis of γ-Ethynyl Halide (4)

First, we examined the synthesis of compound **6** *via* the *ortho*-lithiation of compound **7**. The introduction of a formyl group to the 4-position of a pyridine ring using the *ortho*-lithiation of 3-bromopyridine

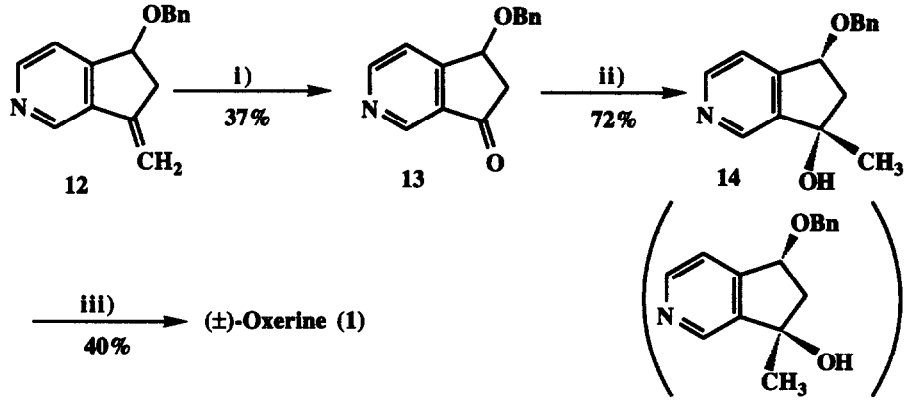
was reported by E. J. Corey.[5] Therefore, we treated 3-bromopyridine (**7**) with lithium diisopropylamide (LDA) at -78°C, followed by the addition of several *O*-protected glycolic acid ethyl esters (*i.e.*, *O*-THP, *O*-TBDMS, or *O*-TBDPS). When ethyl 2-tertahydropyranyloxyacetate was used, the product (**6**), which was easily separated from 3-bromopyridine (**7**) by medium-pressure liquid chromatography (MPMC), was obtained in the best yield (66 %). Hydride reduction of compound **6** with sodium borohydride ($NaBH_4$) in MeOH afforded an alcohol (**8**) in quantitative yield. Benzylation of a hydroxy group was accomplished in the usual manner (NaH / BnBr). Introduction of an acethylenic group to the 3-position of the pyridine ring was carried out using the palladium-catalyzed cross coupling reactions of aryl halides with trimethylsilylacetylene.[6] The protecting groups were successively removed *via* 2 steps (overall yield 89%). The alcohol was converted to the γ-ethynyl bromide (**4**) using *N*-bromosuccinimide (NBS)-triphenylphosphine systems[7] in 85% (Scheme 2).

Next, the SmI_2-mediated intramolecular cyclization of the γ-ethynyl bromide (**4**) was examined. The SmI_2-promoted intramolecular cyclization reactions of aromatic halides with olefins [8] and the coupling reaction between aliphatic halides and unsaturated bonds[9] have been reported. As expected, only cyclized product **12**, a cyclopentano[2,3-*c*]pyridine having an exocyclic methylene group, was obtained in 86% yields,[12] when the γ-ethynyl bromide (**4**) was treated with SmI_2 in the presence of *N,N,N,N',N',N'*-hexamethylphophoramide (HMPA) at -78°C for 0.5 h.



Scheme 3. SmI_2-Mediated Intramolecular Cyclization of γ-Ethynyl Bromide (4)

Finally, the conversion of **12** to (±)-oxerine (**1**) was scrutinized. After ozonolysis of compound **12**, the reductive treatment afforded a ketone (**13**). Treatment of compound **13** with methylmagnesium bromide gave an alcohol **14**. The relative configuration of **14** was elucidated by a ^1H-^1H NOESY experiment as shown in Fig. 2: the hydroxyl group and the benzyloxy group of **14** are arranged with *syn*-configuration.



i) a) O_3, in MeOH b) $(CH_3)_2S$ ii) MeMgBr iii) TMSI

Scheme 4. Synthesis of (±)-Oxerine (1)

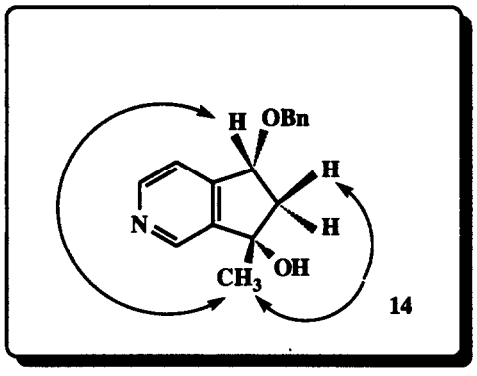


Fig. 2 Result of ^1H-^1H NOE of Compound (14)

Reductive debenzylation of compound **14** with H_2/Pd-C was unsuccessful. Trimethylsilyl iodide (TMSI) was effective for removing the benzyl group (Scheme 4). The physical data of synthetic (±)-oxerine (**1**) were identical with those of the specimen, which was provided by Prof. F. Tillequin. In this way, total synthesis of (±)-oxerine (**1**) was accomplished.

Acknowledgement: We are very grateful to Professor Dr. F. Tillequin, Laboratoire de Pharmacognosie, URA au C. N. R. S. n° 1310, who gave us a sample of (-)-oxerine.

EXPERIMENTAL

Infrared spectra were measured using a JASCO A-100 spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard on a Varian Gemini 300 or a Bruker AM-400 instrument. Medium-pressure column liquid chromatography (MPLC) was conducted using a UVILOG ALPC-100 as the pump, UVILOG-5IIIa as the UV detector (Oyo Bunko Kiki Co. Ltd., Tokyo) and Kiesel gel 60 (Merk AG, Darmstadt) as the packing material. Mass spectral data were obtained with a Hitachi M-80 (Hitachi Co. Ltd.) or a VG Auto Spec (Fisons Co. Ltd.). High-Resolution MS were measured with a VG Auto Spec (Fisons Co. Ltd.) . 0.1 M SmI_2 in THF was purchased from Aldrich Chemical Co, Ltd.

3-Bromo-4-(2-tetrahydropyranyloxyacetyl)pyridine (6). To a THF solution (30 mL) of LDA , prepared from diisopropylamine (6.4 mL, 45.6 mmol) and 1.6 M ^{n}BuLi in hexane (26 mL, 41.6 mmol), 3-bromopyridine (6.0 g, 38.0 mmol) in dry THF solution (30 mL) was added dropwise at -78°C in an Ar atmosphere. The resulting solution was stirred for 15 min at this temperature. A dry THF solution (20 mL) of ethyl 2-(tetrahydropyranyloxy)acetate (7.9 g, 42 mmol) was the added. After the mixture was stirred for 2 h, sat.NH_4Cl (50 mL) was carefully added. The resulting solution was diluted with Et_2O (100 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (50 mL x 2). The combined organic solution was washed with sat. NaCl (100 mL x 3) and dried with Na_2SO_4. The solvent was evaporated under reduced pressure to give a residue. The residue was purified with MPLC (Hexane-AcOEt = 2:1) to afford 7.5 g (66 %) of **6** as a solid, which was crystallized from ^{i}Pr$_2$O to give colorless needles, mp. 65-66°C. IR (KBr): 1725 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.82 (1H, s), 8.53 (1H, d, J = 5 Hz), 7.30 (1H, d, J = 5 Hz), 4.73 (1H, t, J = 3 Hz), 4.68 (2H, s), 3.85-3.78 (1H, m), 3.56-3.49 (1H, m), 1.82-1.51 (6H, m); MS (m/z): 300 (M^+); Anal. Calcd for $C_{12}H_{14}NO_3Br$: C, 48.02; H, 4.67; N, 4.70. Found: C, 48.21; H, 4.65; N, 4.71.

3-Bromo-4-(1-hydroxy-2-tetrahydropyranyloxyethyl)pyridine (8) (*Diastereomixture*). To a MeOH solution (5 mL) of **6** (0.05 g, 0.17 mmol), $NaBH_4$ (0.06 mg, 0.17 mmol) was added portionwise at 0°C. After generation of H_2 gas ceased, the reaction mixture was stirred for 0.25 h at room temperature. The solvent was evaporated *in vacuo* to afford a residue, which was dissolved in Et_2O (10 mL). The organic solution was washed with sat. NaCl (10 mL x 3) and dried with Na_2SO_4. The solvent was distilled *in vacuo* to give a residue. The residue was purified with MPLC (Hexane-AcOEt = 1:1) to give compound **8** as an oil (0.05 g, quantitative yield). IR (neat): 3400 (OH) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.63 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.61 (0.5H, d, J = 5 Hz), 7.55 (0.5H, d, J = 5 Hz), 5.15 (0.5H, m), 5.13 (0.5H, m), 4.76 (1H, brs), 4.62-4.53 (1H, m), 4.04-3.88 (2H, m), 3.66 (0.5H, dd, J = 11 and 7 Hz), 3.60- 3.52 (1H, m), 3.47 (0.5H, dd, J = 11 and 8 Hz), 1.86-1.52 (6H, m) ppm; MS (m/z): 302 (M^+); HRMS Calcd for $C_{12}H_{16}NO_3Br$: 301.0314. Found: 301.0332.

3-Bromo-4-(1-benzyloxy-2-tetrahydropyranyloxyethyl)pyridine (5) (*Diastereomixture*). To a dry THF (10 mL) suspension of 60 % NaH (0.335 mg, 8.4 mmol), compound **8** (2.1 g, 7.0 mml) in dry THF (20 mL) was added at room temperature under Ar. After the mixture was stirred for 1 h, BnBr (1.24 mL, 10.5 mmol) was added dropwise. The resulting mixture was stirred at room temperature overnight. The mixture

was cooled in ice bath. The reaction was quenched with sat. NH_4Cl (20 mL). The resulting solution was diluted with Et_2O (30 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (20 mL x 2). The combined organic layer was treated in usual manner to give an oil, which was purified with MPLC (Hexane: Et_2O = 2:1) to afford compound **5** (2.34 g, 85 %) as an oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.68 (1H, s), 8.53 (1H, d, J = 5 Hz), 7.56 (0.5H, d, J = 5 Hz), 7.53 (0.5H, d, J = 5 Hz), 7.35-7.29 (5H, m), 5.00 (0.5H, dd, J = 7 and 3 Hz), 4.95 (0.5H, d, J = 6 and 3 Hz), 4.69-4.64 (1H, m), 4.58 (1H, d, J = 12 Hz), 4.46 (0.5H, d, J = 12 Hz), 4.44 (0.5H, d, J = 12 Hz), 3.89-3.83 (1H, m) 3.76-3.49 (2H, m), 3.49-3.40 (1H, m), 1.81 (6H, m): MS: m/z 392 (M^+): HRMS Calcd for $C_{19}H_{23}NO_3{}^{81}Br$ (M^++1): 394.084084. Found: 394.087174.

4-(1-Benzyloxy-2-tetrahydropyranyloxyethyl)-3-trimethylsilylethynylpyridine (9) (*Diastereomixture*). The mixture of compound **5** (705 mg, 1.33 mmol), tetrakis(triphenylphosphine)-palladium (146 mg, 10 mol%), TMS-acetylene (0.5 ml, 3.6 mmol), and Et_3N (10 mL) was heated at 100 °C for 6 h in a sealed tube. The solvent was removed *in vacuo*. To the residue, H_2O (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (20 mL x 3). After the organic layer was dried with Na_2SO_4, the solvent was evaporated under reduced pressure to give an oil. The oil was purified with MPLC (Hexane:Et_2O = 2:1) to give compound **9** as a pale yellow oil (681 mg, 89 %). IR (neat): 2160 (triple bond) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.65 (1H, s), 8.54 (1H, d, J = 5Hz), 7.53 (0.5H, d, J = 5Hz), 7.33 (0.5H, d, J = 5Hz), 7.36-7.27 (5H, m), 5.07 (0.5H, dd, J = 7 and 3Hz), 5.03 (0.5H, dd, J = 7 and 3Hz), 4.69-4.64 (1H, m), 4.59 (1H, d, J = 12 Hz), 4.43 (0.5H, d, J = 12 Hz), 4.42 (0.5H, d, J = 12 Hz), 3.89-3.83 (1H, m), 3.77-3.49 (2H, m), 3.48-3.39 (1H, m), 1.90-1.45 (6H, m), 0.24 (4.5H, s), 0.21 (4.5H, s) ppm; CI-MS: m/z 410 (M^++1); HRMS Calcd for $C_{24}H_{31}NO_3Si$: 409.207323. Found: 409.203122.

4-(1-Benzyloxy-2-hydroxy)-3-trimethylsilylethynylpyridine (10). The mixture of compound **9** (2.2 g, 5.5 mmol) and p-TsOH• H_2O (1.14 g, 6.1 mmol) in MeOH (40 ml) was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure. Sat.$NaHCO_3$ was then added to make the solution alkaline. The aqueous phase was extracted with Et_2O (20 ml x 3). The organic layer was dried with Na_2SO_4. The solvent was evaporated *in vacuo* to give the residue. The residue was purified with MPLC (Hexane: AcOEt = 1:1) to give compound **10** (1.6 g, 90 %) as a colorless oil. IR (neat): 3300 (OH), 2160 (triple bond) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.67 (1H, s), 8.56 (1H, d, J = 5 Hz), 7.45 (1H, d, J = 5 Hz), 7.38-7.32 (5H, m), 4.98 (1H, dd, J = 7.4 and 3.3 Hz), 4.57 (1H, d, J = 11 Hz), 4.41 (1H, d, J = 11 Hz), 3.82 (1H, dd, J = 12 and 3.5 Hz), 3.64 (1H, dd, J = 12 and 8 Hz), 2.18 (1H, brs), 0.25 (9H, s) ppm. MS: m/z 325 (M^+). HRMS Calcd for $C_{19}H_{23}NO_2Si$: 325.149808. Found: 325.149882.

4-(1-Benzyloxy-2-hydroxy)-3-ethynylpyridine (11). To a THF solution (20 mL) of compound **10** (1.6 g, 4.9 mmol), 1.0 M Bu_4NF in THF (7.4 mL, 7.4 mmol) was added dropwise at 0°C under an Ar atmosphere. The mixture was stirred at room temperature for 14 h. To the solution, sat. NH_4Cl (10 mL) was added. The aqueous layer was extracted with Et_2O (20 mL x 3). The organic layer was dried with Na_2SO_4. The organic solvent was distilled *in vacuo* to afford an oil, which was purified with MPLC (Hexane:AcOEt = 1:1) to give compound **11** (1.23 g, 99 %) as a colorless oil. IR (neat): 3300 (OH), 2120 (triple bond) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.73 (1H, s), 8.61 (1H, d, J = 5 Hz), 7.49 (1H, d, J = 5 Hz), 7.41-7.33 (5H, m), 5.03 (1H, dd, J = 8 and 3 Hz), 4.57 (1H, d, J = 11 Hz), 4.44 (1H, d, J = 11 Hz), 3.84 (1H, dd, J = 11 and 3

Hz), 3.66 (1H, dd, J = 11 and 8 Hz) ppm; MS: m/z 253 (M^+); HRMS Calcd for $C_{16}H_{15}NO_2$: 253.110279. Found: 253.110694.

4-(1-Benzyloxy-2-bromo)-3-ethynylpyridine (4). To a suspension of NBS (705 mg, 4.0 mmol) in dry CH_2Cl_2 (18 mL), a solution of triphenylphosphine (968 mg, 3.7 mmol) in dry CH_2Cl_2 (9 mL) was added dropwise. The resulting solution was stirred at room temperature for 5 min. Compound **11** (336 mg, 1.32 mmol) in dry CH_2Cl_2 (9 mL) was then slowly added. The mixture was stirred at room temperature overnight. To the mixture, sat. $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (20 mL x 3). The organic layer was treated in the usual manner to give an oil, which was purified with MPLC (Hexane:Et_2O = 3:1) to give compound **4** (353 mg, 85 %) as a colorless oil. IR (neat): 2100 (triple bond) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.73 (1H, s), 8.62 (1H, d, J = 5 Hz), 7.50 (1H, d, J = 5 Hz), 7.37-7.31 (5H, m), 5.06 (1H, dd, J = 7 and 3 Hz), 4.57 (1H, d, J = 11 Hz), 4.49 (1H, d, J = 11 Hz), 3.68 (1H, dd, J = 11 and 4 Hz), 3.54 (1H, dd, J = 11 and 7 Hz), 3.49 (1H, s) ppm; MS: m/z 316 (M^+); HRMS Calcd for $C_{16}H_{14}NOBr$: 315.0259. Found: 315.0278.

1-Benzyloxy-4-methylenecyclopentano[2,3-*c*]pyridine (12). To a mixture of 0.1 M SmI_2 in THF (27.5 mL, 2.75 mmol) and HMPA (1.9 mL), a THF solution (30mL) of compound **4** (340mg, 1.1 mmol) was added dropwise at -78 °C for 0.5 h. After sat. NH_4Cl (15 mL) was added to the solution, a resulting deposit was filtered off on ®Celite. The filtrate was extracted with Et_2O (20 mL x 3). The combined organic layer was washed with sat. NaCl (20 mL x 3) and dried using Na_2SO_4. The solvent was evaporated under reduced pressure to give a residue, which was purified with MPLC (Hexane:Et_2O=1:1) to yield compound **12** (224 mg, 86 %) as an oil. Bp 150 °C (oil bath temp.); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.82 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.40-7.28 (6H, m), 5.64 (1H, t, J = 2 Hz), 5.20 (1H, t, J = 2 Hz), 5.10 (1H, dd, J = 7 and 4 Hz), 4.69 (1H, d, J = 12 Hz), 4.63 (1H, d, J = 12 Hz), 3.10 (1H, ddt, J = 16, 7, and 2 Hz), 2.82 (1H, ddt, J = 16, 4, and 7 Hz) ppm; MS: m/z 237 (M^+); HRMS Calcd for $C_{16}H_{15}NO$: 237.1154. Found: 2371151.

1-Benzyloxy-4-oxocyclopentano[2,3-*c*]pyridine (13). A MeOH solution (7 mL) of γ-ethynyl bromide (**4**) (25 mg, 0.11 mmol) was ozonized at -78 °C until KI-starch testing paper showed blue. Me_2S (0.6 mL) was added to the reaction mixture, which was slowly warmed to room temperature. The solvent was then evaporated in reduced pressure to give a residue. To the residue, H_2O (20 mL) was added. The aqueous layer was extracted with Et_2O (20 mL x 3), and combined organic layer was treated with usual manner to give an oil, which was purified with MPLC (Hexane:AcOEt = 1:1) to afford a ketone (**13**) (13 mg, 37 %) as a colorless oil. IR (neat): 1720 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 9.04 (1H, s), 8.83 (1H, d, J = 5 Hz), 7.65 (1H, d, J = 5 Hz), 7.41-7.34 (5H, m), 5.18 (1H, dd, J = 7 and 3 Hz), 4.78 (1H, d, J = 12 Hz), 4.70 (1H, d, J = 12 Hz), 3.03 (1H, dd, J = 19 and 7 Hz), 2.74 (1H, dd, J = 19 and 3 Hz) ppm; CI-MS: m/z 240 (M^++1); HRMS Calcd for $C_{15}H_{13}NO_2$-Bn: 148.0399. Found: 148.0388.

(1S*,4R*)-1-Benzyloxy-4-hydroxy-4-methylcyclopentano[2,3-c]pyridine (14). To a dry THF solution (5 mL) of compound (**13**) (85 mg, 0.36 mmol), 1.0M MeMgBr in THF (0.43 ml, 0.43 mmol) was added dropwise at room temperature. The resulting solution was stirred at room temperature for 15 h. Sat. NH_4Cl (10 mL) was then added to the reaction mixture. The resulting precipitant was removed off the ®Celite.

The filtrate was extracted with Et_2O (15mL x 3). The organic layer was dried with Na_2SO_4. The solvent was evaporated *in vacuo* to give an pale yellow colorles oil, which was purified with MPLC (CH_2Cl_2:MeOH = 20:1) to give compound **14** (66mg, 72 %) as a pale yellow colorles oil. IR (neat): 3225 and 3350 (OH) cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz): δ 8.72 (1H, s), 8.57 (1H, d, J = 5 Hz), 7.37-7.30 (6H, m), 4.86 (1H, dd, J = 6 and 4 Hz), 4.69 (1H, d, J = 12 Hz), 4.64 (1H, d, J = 12 Hz), 2.48 (1H, dd, J = 14 and 6 Hz), 2.31 (1H, dd, J = 14 and 4 Hz), 1.80 (1H, brs), 1.61 (3H, s) ppm; MS: m/z 240 (M^+-CH_3); HRMS Calcd for $C_{16}H_{17}NO_2$-Bn: 147.0684. Found: 147.0676.

(±)-Oxerine (1). A $CHCl_3$ solution (0.5 mL) of compound **14** (30 mg, 0.12 mmol) was ultrasonically irradiated at room temperature for 0.5 h. The solvent was then evaporated *in vacuo* to give the residue, which was purified with PTLC ($CHCl_3$:MeOH = 20:1) to give compound **1** (8 mg, 40 %) as a colorless crystals, whose physical data was identified with that of an authentic sample, which was provided by Professor F. Tillequin.

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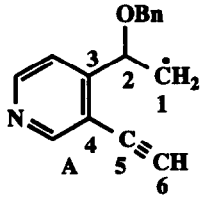
12. The geometries for the intermediate radical spiecies (**A**, **B**, and **C**) were estimated by the full geometry optimization in the MNDO method in order to determine the frontier orbital energies and coefficients. As the result of the calculation, it was found that two π-orbitals of the alkyne and C-1 have the same phase and the coefficients of C-5 is larger than that of C-6. Further, the distance between C-1 and C-5 is shorter than that between C-1 and C-6.



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