Total synthesis of an indolizidine alkaloid, (+)-ipalbidine, by means of an intramolecular McMurry coupling reaction†

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This paper is dedicated to Professor Keiichiro Fukumoto on the occasion of his 70th birthday

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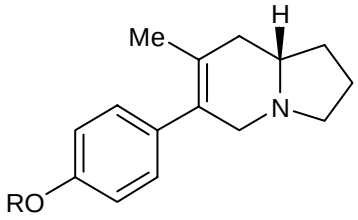
Abstract
An indolizidine alkaloid, (+)-ipalbidine, exhibiting a non-addictive analgesic activity, was synthesized in an optically active form, by employing an intramolecular McMurry coupling reaction as a key step.

Keywords: Indolizidine alkaloid, (+)-ipalbidine, McMurry coupling, ring closing metathesis, analgesic activity

Introduction

Indolizidine alkaloids, a large class of natural products, are popular synthetic targets because they exhibit attractive biological activity and also provide further opportunities for developing new synthetic methods and strategies for the nitrogen-heterocyclic ring systems. Among them, (+)-ipalbidine **1**, isolated from the seeds of *Ipomoea alba* L. as the aglycone of ipalbine **2**, has a relatively simple structural feature, which contains a 1-azabicyclo-[4.3.0]-non-3-ene system with a phenolic substituent at the 3-position[1] (Figure 1). Ipalbidine **1** is known to be a non-addictive analgesic, and caused analgesia in mice which was not antagonized by naloxone.[2] This alkaloid also showed inhibitory effects on respiratory burst of leukocytes and scavenged oxygen-free radicals.[3] Owing to its interesting biological activity, a number of total syntheses for racemic ipalbidine has been reported by several groups.[4] On the other hand, only one chiral synthesis for ipalbidine has appeared to date,[5] where, however, the specific optical rotation of the synthesized compound $[\alpha]_D$ +54.1 (*c*=1, EtOH) was found to be much different from that of the optically resolved compound $[\alpha]_D$ +190.5 (*c*=1, MeOH).[4b] As an extension of our work on the synthesis of analgesic agents, we are interested in a total synthesis of (+)-ipalbidine in an optically pure form

starting from a readily accessible chiral source, (-)-pyroglutamic acid, in which we planned to utilize a carbon–carbon double bond formation as a crucial step.

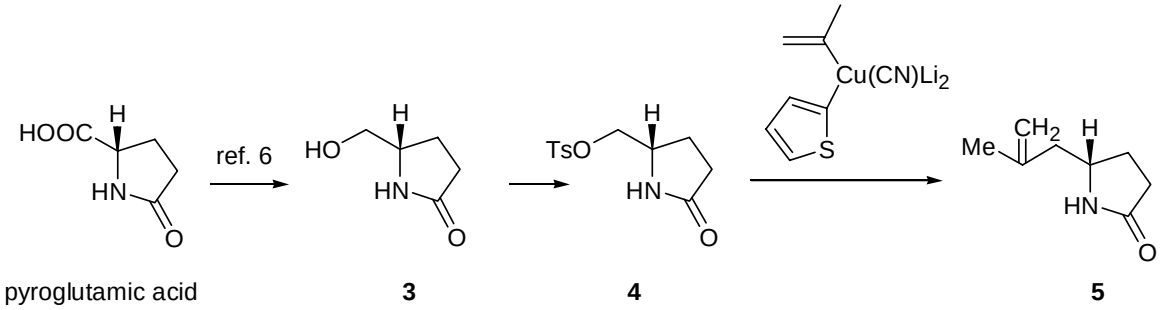


1 Ipalbidine (R = H)
2 Ipalbine (R = **D**-glucose)

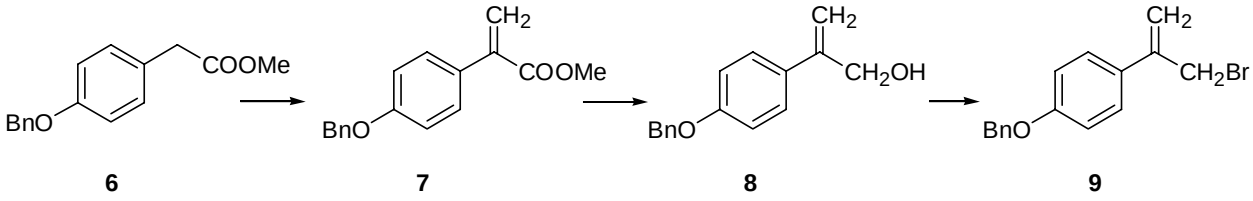
Figure 1. The structures of ipalbidine and ipalbine.

Results and Discussion

(-)-Pyroglutamic acid was first converted into the corresponding alcohol **3** according to the known procedure.[6] Treatment of **3** with *p*-toluenesulfonyl chloride gave the tosylate **4**, which was further coupled with a higher-order cuprate reagent to afford the desired olefinic amide **5** in 93% yield (Scheme 1).



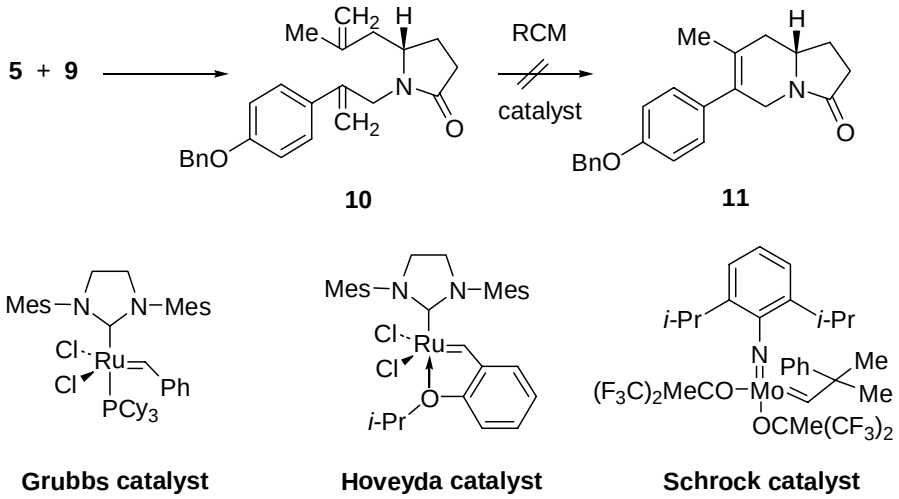
Scheme 1. Functionalization of pyroglutamic acid.



Scheme 2. Preparation of the allylic bromide **9.**

Preparation of the bromide **9**, as an *N*-substituent for **5**, was achieved starting from methyl 4-benzyloxyphenylacetate **6** by condensation with paraformaldehyde in the presence of tris-[2-(2-methoxyethoxy)ethyl]amine (TDA-1),[7] followed by reduction of the ester **7** with diisobutylaluminum hydride and bromination of the resulting alcohol **8** with CBr_4 and Ph_3P as shown in Scheme 2.

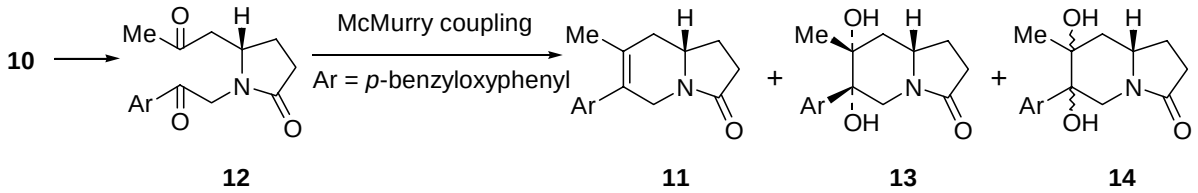
Condensation of the amide **5** with the bromide **9** was carried out in THF–HMPA in the presence of sodium hydride as the base to give the diene **10** in 90% yield. Since the key material for the desired carbon–carbon double bond formation was thus synthesized, we attempted an intramolecular ring-closing metathesis (RCM)[8] by using Grubbs catalyst[9] or Hoveyda catalyst[10] under various reaction conditions; however, no cyclization product **11** could be isolated, unfortunately. For constructing a tetra-substituted alkene system by RCM, the Schrock catalyst[11] is recognized to be more effective than Grubbs catalyst; however, none of the desired product could be obtained even by the use of the active catalyst (Scheme 3).



Scheme 3. Attempted RCM for the diketone **10**.

Since an intramolecular RCM was found to be ineffective for the desired carbon–carbon double bond formation in this synthesis, we decided to utilize an intramolecular McMurry coupling reaction[12] for this purpose. Thus, the diene **10** was converted into the diketone **12** by ozonolysis, followed by reductive work-up with methyl sulfide, in the usual manner. Treatment of **12** with titanium(0), prepared from titanium(III) chloride–THF complex and Zn–Cu couple, in DME at 80°C for 40 h, furnished the desired product **11** in 30% yield together with the *cis*- diol **13** and a stereochemically unidentified compound **14** in 15% and 15% yields, respectively (Scheme 4). The structure of the *cis*- diol **13**, including its absolute stereochemistry, was unambiguously determined by single-crystal X-ray analysis as shown in Figure 2. On the other hand, the compound **14** was also supposed to have diol functions, based on its mass spectrum, and its NMR spectrum was quite similar to that of the *cis*- diol **13**. Although we cannot confirm

its structure at present, a diastereoisomeric β-*cis*- diol structure might reasonably be assumed, based on the reaction mechanism.



12 **11** **13** **14**

Scheme 4. Intramolecular McMurry coupling reaction of **12**.

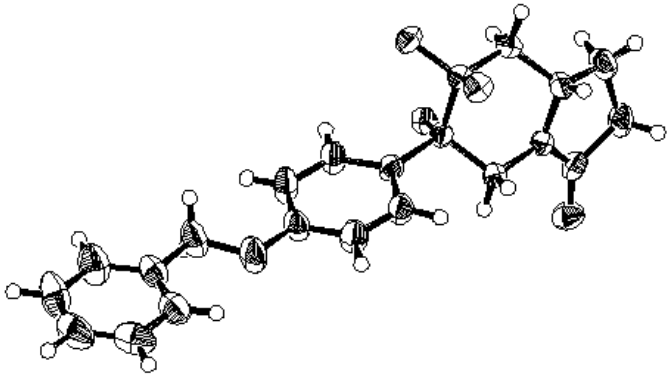
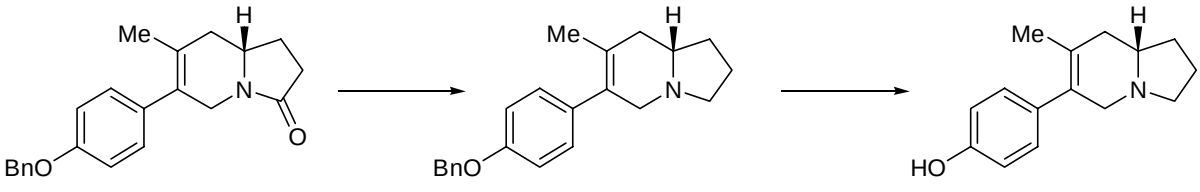


Figure 2. ORTEP Drawing of the *cis*-diol **13**.

When this coupling was carried out under the same reaction conditions for a shorter reaction time (5 h), the *cis*- diol **13** was isolated as the major product, in 66% yield, in addition to the diol **14** (6%). Since we could obtain the desired product **11** by the formation of a carbon–carbon double bond in relatively short steps, its conversion into (+)-ipalbidine **1** was further investigated as follows. Lithium aluminum hydride reduction of **11** afforded the amine **15** in 86% yield, which on debenzylation under hydrogenolysis conditions over 5% palladium hydroxide on carbon in MeOH furnished the natural product **1** (Scheme 5).

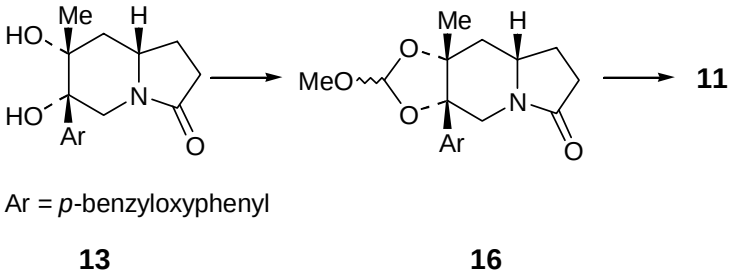


11 **15** **1**

Scheme 5. Synthesis of (+)-ipalbidine **1**.

The spectroscopic data for **1**, mp 76–78°C (from benzene–cyclohexane) (lit.[4b] mp 82–84°C) were in agreement with those reported.[4] Although some difference is observed between the specific optical rotation of the synthesized compound **1** ($[\alpha]_D$ +158.6 (*c*=0.8, MeOH); +189.4 (*c*=1, $CHCl_3$)) and those reported (lit.[4b] $[\alpha]_D$ +190.5 (*c*=1, MeOH); lit.[5] $[\alpha]_D$ +54.1 (*c*=1, EtOH)), and the accurate value is still obscure, we believe that our compound is in almost optically pure form, based on the synthetic strategy.

Although the direct formation of the alkene function from the diketone **12** by employing McMurry coupling as the key step gave the desired product, which led to the chiral synthesis of the target natural product, the yield was found to be unsatisfactory. We therefore investigated an alternative synthetic path to (+)-ipalbidine, in which elimination of the *vic*-diol function in **13** was involved as the key reaction. Thus, the reaction of the diol **13** obtained in 66% yield from **12** by McMurry coupling with a shorter reaction time, with trimethyl orthoformate and PPTS, afforded the orthoformate **16**, which on treatment with acetic anhydride[13] brought about the desired elimination reaction to provide the olefin **11** in 75% yield from **13** (Scheme 6).



Ar = *p*-benzyloxyphenyl

13 **16**

Scheme 6. Alternative synthesis of the alkene **11**.

In summary, we have succeeded in an alternative total synthesis of optically active (+)-ipalbidine **1**, in which intramolecular McMurry coupling of the diketone **12** with Ti(0) was employed as the key reaction, forming a carbon–carbon double bond directly. Elimination of the *vic*-diol of **13**, obtained as the major product from the McMurry coupling of **12** under different reaction conditions, also afforded the desired product efficiently. The synthetic strategy developed here would be applicable to the synthesis of other biologically active phenanthroindolizidine and phenanthroquinolizidine alkaloids.

Experimental Section

General Procedures. 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 a JEOL LAMBDA-270 (^{1}H-NMR: 270 MHz, ^{13}C-NMR: 67.8 MHz) instrument for solutions in $CDCl_3$, and chemical shifts are reported on the δ scale from internal TMS. ^{13}C multiplicities were determined with the aid of an APT sequence,

separating methylene and quaternary carbons = up, from methyl and methine carbons = down. Mass spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed using a Yanaco-MT5 instrument.

5-(Tosyloxymethyl)pyrrolidin-2-one (4). To a stirred solution of **3** (2.30 g, 20.0 mmol) in CH_2Cl_2 (100 mL) were added Et_3N (3.35 mL, 24.0 mmol), 4-dimethylaminopyridine (DMAP) (977 mg, 8.00 mmol) and *p*-TsCl (4.19 g, 22.0 mmol) at 0°C, and the resulting solution was stirred at room temperature for a further 1.5 h. After treatment with saturated aqueous NH_4Cl solution, the mixture was extracted with CH_2Cl_2, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with $CHCl_3$–MeOH (15:1, v/v) as the eluent to afford the tosylate (**4**) (4.71 g, 88%) as a colorless solid. Mp 128.5–130°C (CH_2Cl_2–hexane); $[\alpha]_D$ -7.1 (*c*=1.0, EtOH); IR $\nu_{max.}$ 3430, 1705 cm^{-1}; ^{1}H-NMR δ 1.65–2.40 (4H, m), 2.45 (3H, s), 3.85–4.10 (3H, m), 5.95 (1H, br s), 7.40 (2H, d, *J*=8.2 Hz), 7.85 (2H, d, *J*=8.2 Hz); ^{13}C-NMR δ up 22.7, 29.2, 71.9, 132.3, 145.3, 177.8; down 21.6, 52.5, 127.8, 130.0.

5-(2-Methyl-2-propenyl)pyrrolidin-2-one (5). To a stirred solution of 2-bromopropene (7.99 mL, 90.0 mmol) in Et_2O (180 mL) was slowly added 1.49 *M tert*-BuLi in pentane (113 mL, 180 mmol) over a period of 1 h at -78°C under argon. After being stirred for 3 h at the same temperature, 0.25 *M* lithium 2-thienylcyanocuprate in THF (360 mL, 90.0 mmol) was added to the solution, and the whole was stirred for a further 1 h at the same temperature. To this solution was added a solution of the tosylate (**4**) (8.07 g, 30.0 mmol) in THF (120 mL) over a period of 30 min at -78°C, and the resulting mixture was gradually warmed to 0°C and stirred for further 12 h at the same temperature. The mixture was treated with saturated aqueous NH_4Cl solution, and the insoluble materials were removed by filtration through a pad of Celite. The filtrate was extracted with Et_2O, and the extract 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 EtOAc–MeOH (70:1, v/v) gave the olefin (**5**) (3.89 g, 93%) as a pale yellowish oil. $[\alpha]_D$ +13.6 (c=1.0, $CHCl_3$); IR $\nu_{max.}$ 3228, 1699 cm^{-1}; ^{1}H NMR δ 1.75 (3H, s), 1.68–1.81 (1H, m), 2.11–2.43 (5H, m), 3.78–3.88 (1H, m), 4.76 (1H, s), 4.85 (1H, s), 5.86 (1H, br. s); ^{13}C NMR δ up 27.1, 30.2, 45.1, 113.1, 141.7, 177.8; down 22.4, 52.0. HRMS *m/z* (EI): Calcd for $C_8H_{13}NO$: 139.0997. Found: 139.1005. Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.91; H, 9.55; N, 10.03%.

Methyl α-(4-benzyloxyphenyl)acrylate (7). To a stirred solution of methyl 4-benzyloxyphenylacetate (**6**) (1.28 g, 5.00 mmol) in toluene (50 mL) were added paraformaldehyde (1.50 g, 50.0 mmol), cesium carbonate (6.52 g, 20.0 mmol) and tris-[2-(2-methoxyethoxy)ethyl]amine (TDA-1) (0.16 mL, 0.50 mmol) at room temperature under argon. The whole mixture was heated at 85°C for 3 h, and the insoluble materials were removed by filtration through a pad of Celite. The filtrate was washed with water 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 (8:1, v/v) gave the acrylate (**7**) (720 mg, 54%) as a

colorless oil. IR $\nu_{max.}$ 1722, 1607, 1510, 1174 cm^{-1}; ^{1}H-NMR δ 3.78 (3H, s), 5.81 (1H, d *J*=1.2 Hz), 6.25 (1H, d *J*=1.2 Hz), 6.94 (2H, d *J*=8.9 Hz), 7.26–7.43 (7H, m); ^{13}C-NMR δ up 69.9, 125.3, 129.2, 136.7, 140.5, 158.7, 167.4; down 52.0, 114.4, 127.3, 127.9, 128.5, 129.4. HRMS *m/z* (EI): Calcd for $C_{17}H_{16}O_3$: 268.1099. Found: 268.1073.

2-(4-Benzyloxyphenyl)-3-bromoprop-1-ene (9). To a stirred solution of the ester (**7**) (1.12 g, 4.18 mmol) in CH_2Cl_2 (20 mL) was added 0.95 *M* DIBAL in hexane (9.68 mL, 9.19 mmol) at -78°C under argon, and the resulting mixture was stirred for a further 1 h at the same temperature. After treatment with saturated aqueous NH_4Cl solution, the mixture was stirred for 1 h at room temperature, and the precipitated material was filtered off using a pad of Celite. The filtrate was concentrated to give the crude alcohol (**8**) (966 mg), which without further purification was used in the next reaction. To a stirred solution of the above crude alcohol (**8**) in CH_2Cl_2 (40 mL) were added Ph_3P (1.27 g, 4.83 mmol) and CBr_4 (2.00 g, 6.04 mmol) at ambient temperature, and the resulting mixture was stirred for 5 min. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and 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–Et_2O (20:1, v/v) gave the bromide (**9**) (895 mg, 71%) as a colorless solid. IR $\nu_{max.}$ 1606, 1514, 1454, 1247, 1182 cm^{-1}; ^{1}H-NMR δ 4.36 (2H, s), 5.09 (2H, s), 5.40 (1H, s), 5.48 (1H, s), 6.98 (2H, d, *J*= 8.9 Hz), 7.33–7.46 (7H, m); ^{13}C-NMR δ 34.4, 70.0, 115.6, 130.1, 136.8, 143.5, 158.9; down 114.8, 127.3, 127.5, 128.2, 128.6. HRMS *m/z* (EI): Calcd for $C_{16}H_{15}OBr$: 302.0306. Found: 302.0308.

1-[2-(4-Benzyloxyphenyl)prop-1-en-3-yl]-5-(2-methyl-2-propenyl)pyrrolidin-2-one (10). To a stirred solution of the lactam (**5**) (371 mg, 2.67 mmol) in THF (6.9 mL) in the presence of NaH (60% in mineral oil, 160 mg, 4.00 mmol) were added HMPA (0.70 mL, 4.00 mmol) and a solution of the bromide (**9**) (809 mg, 2.67 mmol) in THF (2 mL) at 0°C under argon, and the resulting mixture was stirred for 2 h further at ambient temperature. After treatment with saturated aqueous NH_4Cl solution, the mixture was extracted with Et_2O, and the extract 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 (2:1, v/v) gave the lactam (**10**) (871 mg, 90%) as a colorless oil. $[\alpha]_D$ +185.4 (c=1.0, $CHCl_3$); IR $\nu_{max.}$ 1686, 1608, 1512, 1246, 1182 cm^{-1}; ^{1}H-NMR δ 1.57–1.69 (1H, m), 1.69 (3H, s), 1.75–1.89 (1H, m), 1.93 (1H, dd, *J*=10.1 and 13.5 Hz), 2.18 (1H, ddd, *J*=5.6, 9.6 and 17.1 Hz), 2.41 (1H, ddd, *J*=7.8, 9.2 and 17.1 Hz), 2.52(1H, dd, *J*=3.8 and 13.5 Hz), 3.50 (1H, dddd, *J*=3.8, 7.7, 7.9 and 10.1 Hz), 3.76 (1H, d, *J*=15.5 Hz), 4.71 (1H, s), 4.81 (1H, s), 5.01 (1H, d, *J*=15.5 Hz), 5.06 (2H, s), 5.13 (1H, s), 5.44 (1H, s), 6.94 (2H, d, *J*=8.9 Hz), 7.32–7.45 (7H, m); ^{13}C-NMR δ up 23.4, 29.7, 41.1, 44.2, 69.9, 113.4, 113.6, 130.6, 136.8, 141.4, 142.6, 158.7, 174.7; down 22.5, 55.0, 114.7, 127.3, 127.5, 128.0, 128.6. HRMS *m/z* (EI): Calcd for $C_{24}H_{27}NO_2$: 361.2042. Found: 361.2053.

1-[2-Oxo-2-(4-benzyloxyphenyl)ethyl]-5-(2-oxopropyl)pyrrolidin-2-one (12). A solution of the olefin (**10**) (100 mg, 0.28 mmol) in MeOH (5 mL) was saturated with ozone at -78°C. the solution was stirred for 30 min at the same temperature, and ozone was removed by exchange with argon. To this solution was added methyl sulfide (67.7 μL, 0.61 mmol), and the resulting mixture was allowed to warm to room temperature, and stirred for further 12 h. After

evaporation of the solvent, the residue was purified by column chromatography on silica gel with hexane–EtOAc (1:3, v/v) as the eluent to give the ketone (**12**) (99.1 mg, 99%) as a colorless solid. Mp 101–103°C (EtOAc–hexane); $[\alpha]_D$ +2.0 (c=1.0, $CHCl_3$); IR $\nu_{max.}$ 1713, 1693, 1682, 1600, 1232, 1170 cm^{-1}; ^{1}H-NMR δ 1.65–1.75 (1H, m), 2.10 (3H, s), 2.34–2.57 (3H, m), 2.57 (1H, dd, *J*=6.4 and 17.6 Hz), 2.98 (1H, dd, *J*=6.3 and 17.6 Hz), 4.20 (1H, dddd, *J*=4.8, 6.3, 6.4 and 12.7 Hz), 4.57 (1H, d, *J*=17.5 Hz), 4.78 (1H, d, *J*=17.5 Hz), 5.14 (2H, s), 7.01 (1H, d, *J*=9.1 Hz), 7.33–7.45 (5H, m), 7.91 (2H, d, *J*=9.1 Hz); ^{13}C-NMR δ up 25.5, 29.5, 47.9, 48.1, 70.1, 128.0, 135.9, 163.0, 175.7, 192.5, 206.4; down 30.3, 54.5, 114.7, 127.4, 128.2, 128.6, 130.2. HRMS *m/z* (EI): Calcd for $C_{22}H_{23}NO_4$: 365.1627. Found: 365.1618. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.30; H, 6.34; N, 3.82%.

McMurry coupling reaction of 12 (Method 1). A mixture of $TiCl_3(thf)_3$ (8.89 g, 24.0 mmol), zinc–copper couple (5.02 g, 76.8 mmol), and DME (20 mL) was stirred at 80°C for 4 h. To this solution was added slowly a solution of the ketone (**12**) (1.10 g, 3.00 mmol) in DME (30 mL) over a period of 5 h, and the resulting mixture was stirred for further 40 h at the same temperature. After being cooled to room temperature, the mixture was diluted with Et_2O, and the organic layer was filtered through a pad of Celite to remove insoluble materials. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–EtOAc (1:2, v/v) gave **11** (300 mg, 30%), as a colorless solid. Mp 109–111°C (benzene–hexane); $[\alpha]_D$ +186.1 (c=1.0, $CHCl_3$); IR $\nu_{max.}$ 1687, 1606, 1510, 1240 cm^{-1}; ^{1}H-NMR δ 1.63 (3H, s), 1.68–1.80 (1H, m), 2.07–2.18 (1H, m), 2.25–2.48 (4H, m), 3.58 (1H, d, *J*=18.2 Hz), 3.74 (1H, dddd, *J*=5.1, 7.4, 10.4 and 12.5 Hz), 4.47 (1H, d, *J*=18.2 Hz), 5.07 (2H, s), 6.95 (2H, d, *J*=8.7 Hz), 7.10 (1H, d, *J*=8.7 Hz), 7.30–7.47 (5H, m); ^{13}C-NMR δ up 24.9, 29.9, 38.2, 44.3, 69.9, 126.9, 128.2, 132.0, 136.8, 157.7, 173.7; down 20.4, 52.9, 114.4, 127.4, 127.8, 128.5, 129.7. HRMS *m/z* (EI): Calcd for $C_{22}H_{23}NO_2$: 333.1729. Found: 333.1749. Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.41; H, 7.22; N, 4.21%.

Further elution with the same solvent system afforded the *cis*-diol (**13**) (164 mg, 15%) as a colorless solid. Mp 167–168°C (EtOAc); $[\alpha]_D$ +44.9 (c=1.0, $CHCl_3$); IR $\nu_{max.}$ 3372, 1666, 1512, 1452, 1248, 1181 cm^{-1}; ^{1}H-NMR δ 1.11 (3H, s), 1.67–1.77 (1H, m), 1.77 (1H, dd, *J*=3.8 and 12.5 Hz), 2.01 (1H, dd, *J*=12.0 and 12.5 Hz), 2.20–2.33 (1H, m), 2.38–2.59 (2H, m), 2.41 (1H, s), 2.99 (1H, s), 3.45 (1H, d, *J*=14.1 Hz), 3.74 (1H, dddd, *J*= 3.8, 4.9, 7.9 and 12.0 Hz), 4.10 (1H, d, *J*=14.1 Hz), 5.07 (2H, s), 6.95 (2H, d, *J*=8.9 Hz), 7.30–7.46 (5H, m), 7.35 (2H, d, *J*=8.9 Hz); ^{13}C-NMR δ up 24.0, 30.1, 43.4, 46.4, 69.9, 73.4, 75.2, 132.9, 136.9, 158.2, 175.2; down 22.1, 55.0, 114.0, 127.4, 128.0, 128.1, 128.6. HRMS *m/z* (EI): Calcd for $C_{22}H_{25}NO_4$: 367.1783. Found: 367.1791.

Finally, compound **14** (161 mg, 15%) was obtained as the third fraction. IR $\nu_{max.}$ 3392, 1664, 1608, 1508, 1454, 1246, 1178 cm^{-1}; ^{1}H- NMR δ 0.99 (3H, s), 1.41 (1H, d, *J*=1.6 Hz), 1.61–1.73 (1H, m), 1.70 (1H, dd, *J*=3.8 and 13.3 Hz), 1.96 (1H, ddd, *J*=1.6, 11.7 and 13.3 Hz), 2.17–2.31 (1H, m), 2.43 (1H, s), 2.43–2.51 (2H, m), 3.77 (1H, d, *J*=13.8 Hz), 3.84 (1H, d, *J*=13.8 Hz), 4.00 (1H, dddd, *J*=3.8, 4.9, 8.7 and 11.7 Hz), 5.07 (2H, s), 6.97 (2H, d, *J*=9.1 Hz), 7.30–7.49 (7H, m); ^{13}C- NMR δ up 23.8, 30.4, 41.2, 46.3, 69.9, 72.9, 75.0, 133.3, 136.9, 158.1, 175.2; down 24.6,

52.8, 114.1, 127.5, 127.9, 128.0, 128.5. HRMS *m/z* (EI): Calcd for $C_{22}H_{25}NO_4$: 367.1783. Found: 367.1784.

McMurry coupling reaction of 12 (Method 2). When the McMurry coupling reaction was carried out for 5 h under the same reaction condition as described above, the *cis*-diol (**13**) was obtained as a major product in 66% yield, together with **11** and **14** in 5 and 6% yields, respectively.

X-Ray analysis of the *cis*-diol (13). $C_{22}H_{25}NO_4.3H_2O$, *M*=421.49, orthorhombic, space group $P2_12_12_1$, *a*=7.666(1), *b*=42.539(5), *c*=6.7407(9) Å, *V*=2198.2(5) Å ^{3}, *Z*=4, *Dc*=1.27 g/cm^3; The data were collected at a temperature of 23±1°C using the ω scan technique to a maximum 2θ value of 136.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.18° with a take-off angle of 6.0°. Scans of (1.68+0.30 tan θ)° were made at a speed of 16.0°/min (in ω). The weak reflections (I < 10.0σ (I)) were rescanned (maximum of 7 scans) and the counts were accumulated to ensure good counting statistics. Of the 4267 reflections that were collected, 4228 were unique ($R_{int.}$ = 0.000); equivalent reflections were merged. The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied. The structure was solved using MALTAN88. *R*=0.049, *Rw*=0.056.

***O*-Benzylipalbidine (15).** To a stirred suspension of $LiAlH_4$ (168 mg, 4.43 mmol) in THF (3.7 mL) was added a solution of the lactam (**11**) (246 mg, 0.74 mmol) in THF (2 mL) at 0°C, and the resulting mixture was stirred at room temperature for 1 h. After quenching the reaction by addition of 10% NaOH solution, the insoluble material was removed by filtration, and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–Et_2O (1:1, v/v) gave the amine (**15**) (204 mg, 86%) as a colorless solid. Mp 80–81°C (hexane–Et_2O); $[\alpha]_D$ +134.4 (c=1.0, $CHCl_3$); IR $\nu_{max.}$ 1606, 1508, 1238, 1174 cm^{-1}; ^{1}H- NMR δ 1.42–1.57 (1H, m), 1.60 (3H, s), 1.69–2.31 (7H, m), 2.90 (1H, ddd, *J*=2.3, 2.5 and 15.3 Hz), 3.21 (1H, dddd, *J*= 2.1, 2.3, 8.4 and 8.7 Hz), 3.61 (1H, d, *J*=15.3 Hz), 5.05 (2H, s), 6.93 (2H, d, *J*=8.9 Hz), 7.10 (2H, d, *J*=8.9 Hz), 7.28–7.46 (5H, m); ^{13}C- NMR δ up 21.4, 30.8, 38.5, 54.1, 57.8, 69.9, 127.9, 130.3, 134.0, 137.1, 157.4; down 20.0, 60.1, 114.3, 127.5, 127.9, 128.5, 129.8. HRMS (EI): Calcd for $C_{22}H_{25}NO$: 319.1936. Found: 319.1942. Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.83; H, 8.10; N, 4.39%.

(+)-Ipalbidine (1). A solution of the amine (**15**) (165 mg, 0.52 mmol) in MeOH (2.6 mL) in the presence of $Pd(OH)_2$ on carbon (16.5 mg) was stirred under an atmospheric pressure of hydrogen for 1 h. After removal of the catalyst by filtration, the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with EtOAc–MeOH (5:1, v/v) gave ipalbidine (**1**) (118 mg, 100%) as a colorless solid. Mp 76–78°C (benzene–cyclohexane); $[\alpha]_D$ +146.9 (c=0.75, EtOH); The spectroscopic data were identical with those reported.[4]

Conversion of the *cis*- diol into the lactam 11. A solution of the diol (**13**) (64.0 mg, 0.17 mmol), trimethyl orthoformate (95.3 μL, 0.87 mmol) and PPTS (21.9 mg) in CH_2Cl_2 (0.7 mL) was stirred for 24 h at room temperature. The mixture was filtered through a short column on

silica gel, and the crude filtrate was dissolved into acetic anhydride (0.5 mL). The solution was heated at 140°C for 24 h. After treatment with saturated aqueous NH_4Cl solution, the mixture was extracted with EtOAc, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–EtOAc (1:2, v/v) as the eluent to afford the lactam (**11**) (43.6 mg, 75%) as a colorless solid. The lactam obtained here was identical with the authentic specimen.

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