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Synthesis of (+)-Ipalbidine Based on 6-*exo-trig* Radical Cyclization of a *β*-Amino Radical

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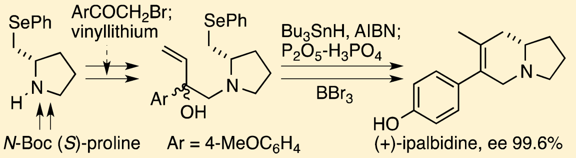
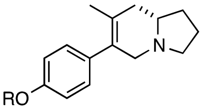
Supporting Information

ABSTRACT: *N*-Boc (*S*)-proline was converted into (2*S*)-2-[(phenylselanyl)methyl]pyrrolidine, which was alkylated on nitrogen with 2-bromo-1-(4-methoxyphenyl)ethan-1-one. Reaction with vinyllithium, 6-*exo-trig* radical cyclization (Bu_3SnH, AIBN, PhMe, 110 °C), dehydration (P_2O_5, H_3PO_4), and demethylation (BBr_3) gave (+)-ipalbidine with ee >99%.



INTRODUCTION

The hexahydroindolizine alkaloid ipalbine (**1**) and its aglycone (**2**) were each isolated many years ago from seeds of *Ipomoea alba* L.,[1,2] and subsequently, the aglycone was obtained from *Ipomoea hardwickii* Hemsl.[3] and *Ipomoea muricata*.[4] Compound **2** is reported to be a nonaddictive analgesic,[5] has anti-inflammatory properties,[6] exerts an inhibitory effect on the respiratory burst of leucocytes, and also scavenges oxygen free radicals.[7] It is likely that ipalbine from some sources is a mixture of *β*-D-glycosides of racemic ipalbidine.[8,9]



1 R = β-glucosyl
2 R = H

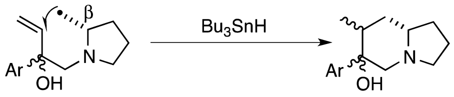
Numerous syntheses (including formal syntheses) of racemic ipalbidine have been described,[8,10] and in one case[8] the material was resolved by *O*-acetylation and formation of diastereoisomeric salts with (+)- and with (−)-di-*O*-*p*-toluoyl tartaric acid. The isomers of ipalbidine were crystallized from a mixture of benzene and cyclohexane, but the crystals tenaciously retain some of these solvents. However, solvent-free (−)-ipalbidine was obtained as a glass by distillation (150 °C, 0.1 Torr) and it then had $[\alpha]^{25}_{D}$ −237 (*c* 1, $CHCl_3$) and $[\alpha]^{25}_{D}$ −190.5 (*c* 1, MeOH).[8]

Five syntheses of (+)-ipalbidine have been reported,[11] but some of the observed optical rotations ($[\alpha]_D$ +158.6 (*c* 0.8, MeOH);[11b] $[\alpha]_D$ +189.4 (*c* 1, $CHCl_3$);[11b] $[\alpha]_D$ +202 (*c* 1, $CHCl_3$);[11c] $[\alpha]^{23}_{D}$ +199 (*c* 1.00, $CHCl_3$);[11d] $[\alpha]^{20}_{D}$ +213.1 (*c* 1, $CHCl_3$)[11e]) differ significantly[12] from the above numerical value measured[8] on distilled material. However, mechanistic considerations support the conclusion that the ee values of the products from these syntheses were very high. Only in two cases[11c,d] have the synthetic compounds been evaluated by chiral HPLC, indicating for (+)-ipalbidine with $[\alpha]_D$ +202 (*c* 1, $CHCl_3$) an ee of 96%[11c] and for (+)-ipalbidine with $[\alpha]^{23}_{D}$ +199 (*c* 1.00, $CHCl_3$) an ee of 94%.[11d]

RESULTS AND DISCUSSION

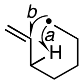
We report a synthesis of (+)-ipalbidine based on 6-*exo-trig* radical cyclization (**3** → **4**) as a key step (Scheme 1).

Scheme 1. Synthetic Plan



3 **4**

Cyclization of alkyl radicals by a 6-*exo-trig* pathway has been applied in synthesis less frequently than the corresponding 5-*exo* process, part of the reason being that, in the general case, allylic hydrogen abstraction (see arrow *a* in **5**) can compete[13] with ring closure (arrow *b*) unless the distal terminus[14] of the double bond carries an electron-withdrawing or radical-stabilizing group. With structures of type **3**, however, such allylic hydrogen abstraction cannot intervene and the geminal substitution (Thorpe−Ingold effect[15]) and presence of the heteroatom[16] may facilitate ring closure.



5

Radical **3** is a *β*-amino radical, and it has been established that such radicals can undergo reversible ring opening and ring closure.[17,18] In particular, the rate constants at 80 °C for opening of radical **6** and closing of the resulting aminyl radical **7** have been determined[17] to be 5.1 × 10^4 and 14.6 × 10^4 s^{-1}, respectively (Scheme 2). While *β*-amino radicals have indeed been used to construct rings,[16,19] we have been unable to locate any reports of their application in situations where reversible ring opening would degrade the optical purity of the starting radical. Consequently, our approach to ipalbidine would test

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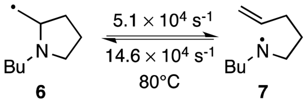
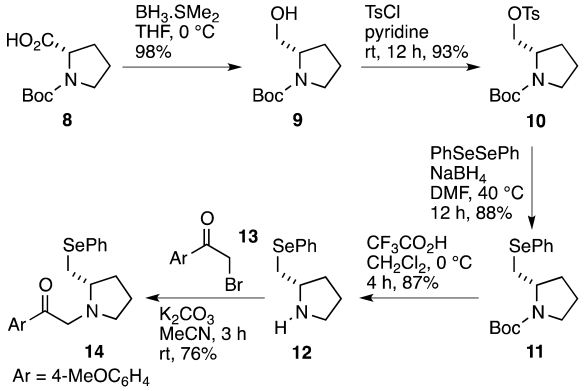
Scheme 2. Reversible Ring Opening of β-Amino Radicals



the relative rates of the desired 6-*exo* closure and the undesired ring-opening and -closing pathways under the normally obligatory cyclization conditions of low stannane concentration—a circumstance that would probably favor the incursion of ring opening. In contrast to the situation for *amines*, cyclization of radicals β to nitrogen to generate optically active products have been reported using substrates in which the nitrogen is part of a *lactam*.[20,21]

Our starting point was commercial *N*-Boc-proline (**8**), which was reduced (98%) with $BH_3{\cdot}SMe_2$ by a literature procedure[22] to the corresponding alcohol (Scheme 3). This was then converted (93%) to its tosylate **10**.[22] When the tosylate was treated with the phenylselenide anion, generated in situ from PhSeSePh and $NaBH_4$ in DMF, the selenide **11**[23] was formed in high yield (87%). The *N*-Boc group was then removed in the standard way (**11** → **12**) and the resulting amine was alkylated with 4-methoxyphenacyl bromide (MeCN, K_2CO_3).[24]

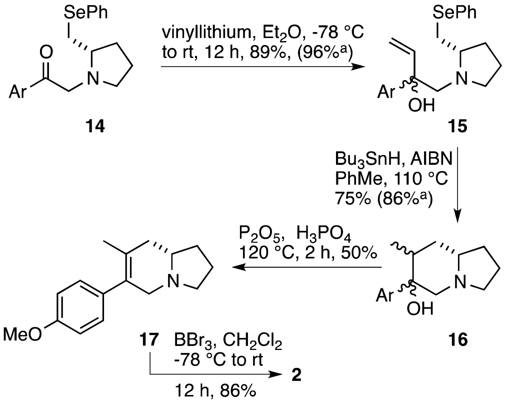
Scheme 3. Construction of Ketone 14



The next step required conversion of ketone **14** into a vinyl alcohol. This was best achieved (89%) by the action of freshly prepared vinyllithium (from tetravinyltin and MeLi)[25] in Et_2O, rather than with vinylmagnesium bromide, so as to obtain the expected mixture of diastereoisomeric alcohols **15** (Scheme 4). Radical cyclization by slow addition of a PhMe solution of Bu_3SnH and AIBN to a refluxing solution of **15** in the same solvent afforded the required cyclization product as a mixture of stereoisomers. One isomer could be isolated in pure form by preparative-layer chromatography and fully characterized. Dehydration of the combined isomers by heating with a mixture of P_2O_5 and 85% H_3PO_4[26] gave *O*-methyl ipalbidine (**17**), which contained an impurity that could not be removed by chromatography. However, demethylation (86%) with BBr_3 in CH_2Cl_2 at −78 °C to room temperature released pure ipalbidine (**2**) and a distilled sample had $[\alpha]^{20}_{D}$ +252.45 (*c* 1.213, $CHCl_3$). HPLC analysis showed the material to have an ee of 99.3%.

One interpretation of our results is that ring opening of the intermediate β-amino radical (cf. Scheme 2) does not occur to any significant extent, if at all, and so the optical purity of our starting material was not degraded. However, our experiments do not rule out the possibility that some ring opening occurs and that the resulting radical follows pathways other than ring closure. In either event, it is clear that radical cyclization of β-amino radicals can indeed be used to synthesize compounds of extremely high ee. The present case represents a demanding test, because a 6-*exo-trig* closure of radicals is significantly slower (at 25 °C a 0.023-fold reduction in the case of hexenyl radicals[27]) than the more usual 5-*exo* mode. The rate constant for cyclization of 3-azahex-6-enyl radicals has not been reported.

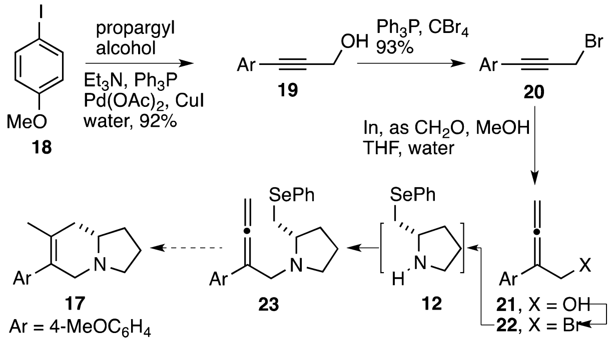
Scheme 4. Elaboration of Ketone 14 to (+)-iIalbidine



[a]Corrected for recovered starting material.

During the course of this work we looked at the possibility of shortening the route along the lines summarized in Scheme 5. The required allenyl bromide **22** was easily prepared, by analogy with literature procedures for related compounds,[28,29] as shown in the scheme.

Scheme 5. Attempted Radical Cyclization onto an Allene



Although the *N*-alkylation step **22** → **23** worked satisfactorily (70%), our attempts to effect radical ring closure (**23** → **17**) by the use of Bu_3SnH invariably led to complex mixtures, notwithstanding the fact that several ring closures of alkyl radicals onto allenes have been reported.[30] Radical cyclization onto allenes is not a highly developed subject, and we did not establish the reasons for the observed outcome with compound **23**.

■ CONCLUSION

The radical cyclization route we have used gives (+)-ipalbidine with ee >99%, and the method establishes that reversible opening of the intermediate β-amino radical does not, in practice, interfere with the process, even though the key ring closure is of the relatively slow 6-*exo* type.

EXPERIMENTAL SECTION

General Procedures. Solvents used for chromatography were distilled before use. Commercial thin-layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230−400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. The symbols s, d, t, and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Solutions were evaporated under water pump vacuum, and the residue was then kept under oil pump vacuum. High-resolution electrospray mass spectrometric analyses were done with an orthogonal time-of-flight analyzer, and electron ionization mass spectra were measured with a double-focusing sector mass spectrometer.

***tert*-Butyl (2*S*)-2-(Hydroxymethyl)pyrrolidine-1-carboxylate (9).**[22] $BH_3 \cdot SMe_2$ (2 M in THF, 6 mL, 12 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *N*-Boc-L-proline (2.0 g, 9.2 mmol) in dry THF (20 mL). When gas evolution ceased, the ice bath was removed and stirring was continued overnight. The solution was cooled to 0 °C, and MeOH (0.3 mL) was added dropwise. The mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated to afford **9** (1.83 g, 98%) as a colorless oil that was used directly in the next step. Characterization data: FTIR (CH_2Cl_2 cast) 3430, 2974, 2932, 2878, 1695, 1672, 1406, 1171 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9 H), 1.76−1.84 (m, 2 H), 1.97−2.04 (m, 1 H), 3.28−3.33 (m, 1 H), 3.42−3.44 (m, 1 H), 3.56−3.67 (m, 2 H), 3.80−4.02 (br, 2 H), 4.70−4.72 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.1 (t), 28.5 (q), 28.8 (s), 47.6 (t), 60.2 (d), 67.8 (t), 80.2 (t), 157.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{10}H_{19}NNaO_3$ (M + Na) 224.1257, found 224.1253.

***tert*-Butyl (2*S*)-2-{[(4-Methylbenzenesulfonyl)oxy]methyl}-pyrrolidine-1-carboxylate (10).**[22] TsCl (0.84 g, 4.0 mmol) was added as a solid to a stirred solution of *N*-Boc-L-prolinol (**9**; 0.81 g, 4.0 mmol) in dry pyridine (0.8 mL). The mixture was stirred overnight at room temperature, diluted with EtOAc, and washed with ice-cold hydrochloric acid (1 N, 27 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 3/7 EtOAc/hexane, gave **10** (1.32 g, 93%) as a colorless oil: $[\alpha]^{20}_{D}$ −37.65 (*c* 1.07600, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2976, 2932, 1694, 1177 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38−1.42 (m, 9 H), 1.80−2.00 (m, 4 H), 2.50 (s, 3 H), 3.29−3.35 (m, 2 H), 3.90−4.00 (m, 2 H), 4.10−4.12 (m, 1 H), 7.40 (br s, 2 H), 7.79 (d, *J* = 7.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6 (q), 22.9 (t), 23.8 (t), 27.7 (t), 28.4 (q), 28.5 (t), 46.5 (t), 46.9 (t), 55.6 (d), 70.0 (s), 79.6 (t), 79.9 (t), 127.9 (d), 129.9 (d), 133.0 (s), 144.7 (s), 144.8 (s), 154.0 (s), 154.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{25}NNaO_5S$ (M + Na) 378.1346, found 378.1342.

***tert*-Butyl (2*S*)-2-[(Phenylselanyl)methyl]pyrrolidine-1-carboxylate (11).**[31] $NaBH_4$ (0.20 g, 5.6 mmol) was added to a stirred and warmed (40 °C) solution of PhSeSePh (0.87 g, 2.8 mmol) in dry DMF (8 mL). After 30 min a solution of **10** (1.54 g, 4.3 mmol) in DMF (8 mL) was added and stirring at 40 °C was continued overnight. The mixture was cooled, poured into water, and extracted with Et_2O. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using increasing amounts of EtOAc in hexane from 5% EtOAc to 30% EtOAc in hexane, gave **11** (1.3 g, 88%) as a yellow oil: $[\alpha]^{20}_{D}$ −17.79 (*c* 1.07200, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3070, 2973, 2929, 1693, 1392 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) (rotamers) δ 1.30−1.40 (m, 9 H), 1.70−2.10 (m, 4 H), 2.92−2.96 (m, 1 H), 3.22−3.52 (m, 3 H), 3.97−4.11 (m, 1 H), 7.25−7.28 (m, 3 H), 7.55−7.56 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8 (t), 23.7 (t), 28.6 (q), 30.4 (t), 30.9 (t), 31.1 (s), 31.9 (s), 46.7 (t), 47.2 (t), 57.1 (d), 79.2 (t), 79.6 (t), 126.5 (d), 127.0 (d), 129.1 (d), 129.9 (s), 130.5 (s), 131.8 (d), 132.9 (d), 154.3 (s), 154.4 (s); exact mass (electron impact) *m*/*z* calcd for $C_{16}H_{23}N^{80}SeO_2$ 341.0894, found 341.0896.

(2*S*)-2-[(Phenylselanyl)methyl]pyrrolidine (12).[23] CF_3CO_2H (5.7 mL was added dropwise over 1 h to a stirred and cooled (0 °C) solution of **11** (0.57 g, 1.6 mmol) in CH_2Cl_2 (5.7 mL). After the addition, stirring at 0 °C was continued for 4 h and then saturated aqueous $NaHCO_3$ was added dropwise until the pH of the solution was 8−9 (indicator paper). The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 1/19 MeOH/CH_2Cl_2, gave material that was partitioned between Et_2O and 10% w/v aqueous NaOH. The organic extract was dried and evaporated to give **12** (0.36 g, 87%) as an amber oil: $[\alpha]^{20}_{D}$ +24.94 (*c* 1.496, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3052, 2960, 2869, 1679, 1478, 1437, 1400, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45−1.52 (m, 1 H), 1.75−1.91 (m, 2 H), 1.94−2.01 (m, 1 H), 2.92−2.96 (m, 2 H), 3.02−3.10 (m, 3 H), 3.35 (quintet, *J* = 6.9 Hz, 1 H), 7.23−7.29 (m, 3 H), 7.52−7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.3 (t), 31.7 (t), 34.0 (t), 46.3 (t), 58.5 (d), 127.0 (d), 129.1 (d), 130.1 (s), 132.7 (d); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{16}N^{80}Se$ 242.0442 [M + H], found 240.0442.

2-Bromo-1-(4-methoxyphenyl)ethan-1-one (13).[24] A solution of Br_2 (0.3 mL, 6.5 mmol) in $CHCl_3$ (10 mL) was added slowly to a stirred solution of *p*-methoxyacetophenone (1.0 g, 6.79 mmol) in $CHCl_3$ (10 mL). The mixture was then stirred overnight, diluted with Et_2O (10 mL), and washed with water. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using increasing amounts of EtOAc in hexane from 0% to 5% EtOAc in hexane, gave **13** (1.14 g, 73%) as a white solid: mp 69−70 °C; FTIR (CH_2Cl_2 cast) 3078, 3061, 3011, 2943, 2844, 1685, 1602, 1206 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.90 (s, 3 H), 4.41 (s, 2 H), 6.96−7.02 (m, 2 H), 7.97−8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.7 (t), 55.6 (q), 114.1 (d), 127.0 (s), 131.4 (d), 164.2 (d), 190.0 (d); exact mass (electrospray) *m*/*z* calcd for $C_9H_9{}^{79}BrNaO_2$ (M + Na) 250.9678, found 250.9678.

1-(4-Methoxyphenyl)-2-{(2*S*)-2-[(phenylselanyl)methyl]-pyrrolidin-1-yl}ethan-1-one (14). K_2CO_3 (5.5 g, 4.0 mmol) was added to a stirred solution of amine **12** (580 mg, 2.40 mmol) in dry MeCN (17 mL), followed by bromide **13** (450 mg, 2.0 mmol) (N_2 atmosphere). Stirring at room temperature was continued for 3 h, and then water was added. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 1/1 EtOAc/hexane, gave **14** (710 mg, 76%) as a tan oil containing minor impurities (^{1}H NMR and ^{13}C NMR). (We obtained a pure sample of the corresponding racemic material; see the Supporting Information for copies of the NMR spectra.) The compound is unstable and should be used within 1 day: $[\alpha]^{20}_{D}$ −18.66 (*c* 1.0200, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3055, 2925, 2853, 1712, 1601, 1256 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70−1.90 (m, 3 H), 2.04−2.10 (m, 1 H), 2.43 (q, *J* = 9.1 Hz, 1 H), 2.90−2.97 (m, 1 H), 3.00−3.09 (m, 1 H), 3.13−3.18 (m, 1 H), 3.21−3.25 (m, 1 H), 3.87 (s, 3 H), 3.97 (AB q, *J* = 15.9, $\Delta\nu_{AB}$ = 235.7 Hz, 2 H), 6.91−6.95 (m, 2 H), 7.22−7.28 (m, 3 H), 7.47−7.51 (m, 2 H), 8.00−8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9 (t), 31.2 (t), 32.9 (t), 54.6 (t), 55.5 (d), 60.3 (t), 63.8 (q), 113.7 (d), 126.7 (d), 129.1 (s), 129.2 (d), 130.6 (d), 130.9 (s), 132.3 (d), 163.6 (s), 196.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{24}NO_2{}^{80}Se$ (M + H) 390.0968, found 390.0961.

2-(4-Methoxyphenyl)-1-{(2*S*)-2-[(phenylselanyl)methyl]-pyrrolidin-1-yl}but-3-en-2-ol (15). MeLi (1.6 M in Et_2O, 5.2 mL, 8.2 mmol) was added dropwise to a stirred and cooled (0 °C) solution of tetravinyltin (0.37 mL, 2.04 mmol) in Et_2O (40 mL).[25] Stirring was continued for 1 h, and the solution was then cooled to −78 °C. A solution of ketone **14** (200 mg, 0.51 mmol) in Et_2O (10 mL) was added dropwise at −78 °C, the cold bath was left in place, but not recharged, and stirring was continued overnight. The mixture was cooled to 0 °C, quenched with water, and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 16 cm), using 1/1 EtOAc/hexane, gave **15** (190 mg, 89%, or 96% corrected for recovered **14** (15 mg)) as a pale yellow oil which was a mixture of isomers: FTIR (CH_2Cl_2 cast) 3418, 3070, 3056, 2953, 2834, 1610, 1510, 1248, 1199 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55−1.85 (m, 4 H), 1.92−2.03 (m, 1 H), 2.35−2.40 (m, 1 H), 2.87−3.00 (m, 3 H), 3.05−3.08 (m, 0.5

H), 3.14−3.18 (m, 0.5 H), 3.30−3.42 (m, 1 H), 3.81−3.82 (two s, 3 H), 4.34−4.48 (two br s, 1 H), 5.11 (ddd, *J* = 20.4, 10.4, 1.4 Hz, 1 H), 5.26 (dd, *J* = 16.9, 1.4 Hz, 0.5 H), 5.48 (dd, *J* = 17.1, 1.4 Hz, 0.5 H), 6.10 (dd, *J* = 16.9, 10.4 Hz, 0.5 H), 6.24 (dd, *J* = 16.9, 10.4 Hz, 0.5 H), 6.86−6.89 (m, 2 H), 7.22−7.30 (m, 3 H), 7.38−7.42 (m, 2 H), 7.48−7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.7 (t), 23.8 (t), 30.2 (t), 30.5 (t), 33.81 (t), 33.89 (t), 55.2 (q), 56.0 (t), 56.9 (t), 65.0 (d), 65.3 (d), 65.7 (t), 66.6 (t), 74.0 (t), 112.9 (s), 113.2 (s), 113.4 (d), 113.6 (d), 126.2 (d), 126.7 (d), 126.8 (d), 126.9 (d), 129.0 (d), 129.1 (d), 130.4 (s), 132.67 (d), 132.70 (d), 132.74 (d), 137.62 (s), 137.68 (s), 143.5 (d), 144.5 (d), 158.3 (s), 158.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{27}NO_2{}^{80}Se$ (M + H) 418.1280, found 418.1279.

(8a*S*)-6-(4-Methoxyphenyl)-7-methyloctahydroindolizin-6-ol (16). A solution of Bu_3SnH (0.2 mL, 0.76 mmol) and AIBN (6 mg, 0.03 mmol) in PhMe (2 mL) was added via syringe pump over 8 h to a stirred and heated (110 °C) solution of **15** (mixture of isomers) (160 mg, 0.38 mmol). Stirring at 110 °C was continued for 2 h after the addition, and the solvent was then evaporated at room temp (water pump vacuum). Flash chromatography of the residue over 10% KF on silica gel[32] (2 × 16 cm) using 1/19 MeOH/EtOAc gave **16** (75 mg, 75% or 85.9% corrected for recovered **15** (20 mg)) as a light brown oil which appeared to be a mixture of at least two isomers. Preparative TLC (20 × 20 × 0.215 mm), using 1/4 *i*-PrOH/CH_2Cl_2, allowed isolation of one isomer, which had the following characterization data: FTIR (CH_2Cl_2 cast) 3483, 2962, 2930, 2799, 1512, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.69 (d, *J* = 6.4 Hz, 3 H), 1.23−1.32 (m, 1 H), 1.42−1.50 (m, 1 H), 1.68−1.94 (m, 6 H), 1.95−2.06 (m, 1 H), 2.21 (q, *J* = 8.8 Hz, 1 H), 2.57 (AB q, *J* = 11.2, $\Delta\nu_{AB}$ = 223.8 Hz, 2 H), 2.96 (dt, *J* = 2.3, 8.5 Hz, 1 H), 3.47 (s, 1 H), 3.82 (s, 3 H), 6.87−6.91 (m, 2 H), 7.38−7.42 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.0 (q), 21.5 (t), 30.6 (t), 35.9 (t), 39.0 (d), 53.3 (t), 55.2 (q), 64.1 (d), 65.5 (t), 73.6 (s), 113.4 (d), 126.1 (d), 136.7 (s), 158.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{16}H_{24}NO_2$ (M + H) 262.1802, found 262.1804.

(8a*S*)-6-(4-Methoxyphenyl)-7-methyl-1,2,3,5,8,8a-hexahydroindolizine (17). P_2O_5 (8.4 mg, 0.06 mmol) was added to a solution of **16** (42 mg, 0.16 mmol) in 85% H_3PO_4 (12.6 mL),[26] and the mixture was heated at 120 °C for 2 h, cooled, poured onto ice, and basified to pH 12 with powdered KOH. The resulting mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.1 × 15 cm), using 1/19 MeOH/EtOAc, gave **17** (20 mg, 50%) as a colorless oil containing trace impurities (^{1}H NMR): $[\alpha]^{20}_{D}$ +133.76 (*c* 0.676, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3033, 2956, 2930, 1511 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49−1.57 (m, 1 H), 1.61 (s, 3 H), 1.76−2.35 (m, 7 H), 2.91−2.95 (m, 1 H), 3.24 (dt, *J* = 8.3, 2.0 Hz, 1 H), 3.64 (d, *J* = 15.4 Hz, 1 H), 3.81 (s, 3 H), 6.86−6.89 (m, 2 H), 7.09−7.13 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.1 (q), 21.4 (t), 30.8 (t), 38.4 (t), 54.1 (t), 55.2 (q), 57.8 (t), 60.2 (d), 113.5 (d), 128.0 (s), 129.8 (d), 130.3 (s), 133.7 (s), 158.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{16}H_{22}NO$ (M + H) 244.1696, found 244.1696.

4-[(8a*S*)-7-Methyl-1,2,3,5,8,8a-hexahydroindolizin-6-yl]-phenol ((+)-Ipalbidine) (2). BBr_3 (1 M in CH_2Cl_2, 0.24 mL) was added to a stirred and cooled (−78 °C) solution of **17** (20 mg, 0.08 mmol) in dry CH_2Cl_2 (1.0 mL).[11c,d] The cold bath was left in place but not recharged, and stirring was continued overnight. The mixture was cooled to 0 °C and quenched by addition of water. The mixture was stirred, and saturated aqueous $NaHCO_3$ was added until all the dark gummy material dissolved. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.1 × 15 cm), using 1/19 MeOH/CH_2Cl_2, gave **2** (16 mg, 86%) as a semisolid: FTIR (CH_2Cl_2 cast) 3030, 2966, 2914, 2878, 2829, 2791, 1609, 1585, 1513, 1445, 1267 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62 (s, 3 H), 1.64−1.68 (m, 1 H), 1.81−1.86 (m, 1 H), 1.98−2.11 (m, 2 H), 2.20−2.33 (m, 3 H), 2.40−2.49 (m, 1 H), 3.10 (d, *J* = 15.4 Hz, 1 H), 3.30 (dt, *J* = 1.5, 9.0 Hz, 1 H), 3.53 (d, *J* = 15.5 Hz), 6.79−6.82 (m, 2 H), 7.00−7.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.1 (q), 21.2 (t), 30.2 (t), 37.6 (t), 54.1 (t), 57.7 (t), 60.7 (d), 115.5 (d), 128.3 (s), 129.7 (d), 129.8 (s), 132.1 (s), 155.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{19}NO$ (M + H) 230.1539, found 230.1542. Kugelrohr distillation of a sample (140 °C, 0.005 mmHg) gave (+)-ipalbidine as a glass: $[\alpha]^{20}_{D}$ +252.45 (*c* 1.21300, $CHCl_3$) (lit.[8] $[\alpha]^{25}_{D}$ +233.5 (*c* 1, $CHCl_3$)). Chiral HPLC analysis (RegisPack CLA-1, 250 × 4.6 cm, hexane/ethanol (90/10) + 0.1% Et_2NH, 1 mL per min, wavelength 254 nm) established the ee as 99.3%. For comparison purposes racemic ipalbidine was made the same way as the optically active compound, starting with racemic proline.

2-(4-Methoxyphenyl)buta-2,3-dien-1-ol (21).[29] Formaldehyde (37% aqueous solution, 0.32 mL, 3.2 mmol) was added to a vigorously stirred solution of 1-(3-bromoprop-1-yl)-4-methoxybenzene[28] (**20**; 0.82 g, 3.6 mmol) in 1/1 THF/water (16.4 mL). Indium powder (0.62 g, 5.4 mmol) was added quickly, and vigorous stirring was continued for 12 h. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.8 × 16 cm), using a gradient of hexane to 5% CH_2Cl_2 in hexane, gave **21** (0.52 g, 82%) as a white solid: mp 65−67 °C; FTIR (CH_2Cl_2 cast) 3367, 3039, 2935, 1940 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.62 (t, *J* = 6.0, 1 H), 3.83 (s, 3 H), 4.55−4.57 (m, 2 H), 5.24 (t, *J* = 2.5, 2 H), 6.89−6.92 (m, 2 H), 7.35−7.39 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.3 (q), 61.7 (t), 80.3 (s), 105.6 (t), 114.2 (d), 126.0 (s), 127.3 (s), 158.9 (s), 207.2 (s); exact mass (electron impact) *m*/*z* calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0837.

1-(1-Bromobuta-2,3-dien-2-yl)-4-methoxybenzene (22).[28] CBr_4 (2.74 g, 0.0081 mol) was added to a stirred solution of **21** (1.2 g, 0.0068 mol) and Ph_3P (2.14 g, 0.0081 mol) in CH_2Cl_2 (25 mL), and stirring was continued at room temperature for 6 h. Evaporation of solvent and flash chromatography of the residue over silica gel (2 × 16 cm), using 1/20 EtOAc/hexane, gave **22** (1.2 g, 73.8%) as a yellow solid: mp 41−45 °C; FTIR (CH_2Cl_2 cast) 3038, 2956, 1934, 1512, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.85 (s, 3 H), 4.43 (s, 2 H), 5.20 (s, 2 H), 6.92−6.94 (m, 2 H), 7.40−7.42 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.0 (t), 55.3 (q), 79.3 (t), 103.0 (s), 114.1 (s), 125.1 (d), 127.4 (d), 159.1 (s), 209.2 (s); exact mass (electron impact) *m*/*z* calcd for $C_{11}H_{11}O^{79}Br$ 237.9993, found 237.9995.

(2*S*)-1-[2-(4-Methoxyphenyl)buta-2,3-dien-1-yl]-2-[(phenylselanyl)methyl]pyrrolidine (23). K_2CO_3 (2.76 g, 20.0 mmol) was added to a stirred solution of amine **12** (300 mg, 1.2 mmol) in dry MeCN (8.6 mL), followed by bromide **22** (230 mg, 1.0 mmol) (N_2 atmosphere). Stirring at room temperature was continued for 3 h, and then water was added. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 3/7 EtOAc/hexane, gave **23** (280 mg, 70%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3056, 2963, 2832, 1940, 1510, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.66−1.76 (m, 3 H), 1.98−2.03 (m, 1 H), 2.30−2.37 (m, 1 H), 2.79−2.83 (m, 1 H), 2.99−3.04 (m, 1 H), 3.06−3.15 (m, 1 H), 3.15−3.19 (m, 1 H), 3.21−3.25 (br d, 1 H), 3.80 (s, 3 H), 3.82−3.86 (m, 1 H), 4.96−5.03 (m, 2 H), 6.85−6.88 (m, 2 H), 7.22−7.27 (m, 3 H), 7.46−7.51 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.6 (t), 31.3 (t), 33.3 (t), 54.4 (t), 55.3 (q), 55.6 (t), 63.7 (d), 102.5 (t), 113.8 (d), 126.5 (d), 127.68 (s), 127.71 (d), 129.0 (d), 131.2 (s), 132.4 (d), 158.6 (s), 209.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{26}NO^{80}Se$ (M + H) 400.1174, found 400.1171.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01890.

NMR spectra of all compounds, chiral HPLC measurements, and a complete list of references for the synthesis of racemic ipalbidine (PDF)

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Notes

The authors declare no competing financial interest.

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