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Enantiospecific synthesis of an indolizidine alkaloid, (+)-ipalbidine

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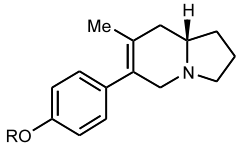
Abstract—Enantiospecific total synthesis of an indolizidine alkaloid, ipalbidine, was achieved starting from (−)-pyroglutamic acid by employing an intramolecular McMurry coupling reaction with a low-valent titanium, as a key step.

Ipalbidine **1**, isolated from the seeds of *Ipomoea alba* L. as the aglycone of ipalbine **2** (Fig. 1), is a naturally occurring indolizidine alkaloid, which contains a 1-azabicyclo[4.3.0]-non-3-ene system with a phenolic substituent at the 3-position.[1]

Ipalbidine **1** was known as a nonaddictive analgesic, and caused analgesia in mice which was not antagonized by naloxone.[2] This alkaloid also showed inhibitory effects on respiratory burst of leukocyte and scavenged oxygen-free radicals.[3]

Although a number of total synthesis for racemic ipalbidine have appeared by application of newly developed synthetic strategies or methodologies,[4] only one chiral synthesis has been reported to date,[5] where, however, the optical purity of the target compound has not been mentioned, unfortunately.[6] In the course of our work on the synthesis of analgesic agents, we are interested in a chiral synthesis of ipalbidine by forming a carbon–carbon double bond as a crucial step.

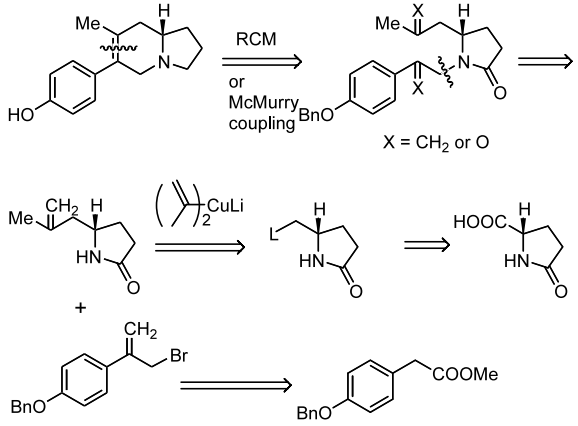


1 Ipalbidine (R = H)
2 Ipalbine (R = **D**-glucose)

Figure 1.

In order to construct the desired carbon–carbon double bond, we first planned to utilize an intramolecular ring-closing metathesis[7] along with our retrosynthetic analysis as depicted in Scheme 1, where the optically active key precursor might be prepared from (−)-pyroglutamic acid in relatively short steps.

Thus, the alcohol **3**,[8] readily accessible from pyroglutamic acid methyl ester, was reacted with *p*-toluenesulfonyl chloride to give the tosylate **4**, which, on treatment with a higher-order cuprate reagent afforded the desired olefinic amide **5** in 93% yield. The bromide **9** was prepared from the ester **6** by condensation with paraformaldehyde in the presence of tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1),[9] followed by



Scheme 1. Retrosynthetic route for (+)-ipalbidine.

Keywords: (+)-ipalbidine; McMurry coupling; indolizidine alkaloid; ring-closing metathesis; chiral synthesis.

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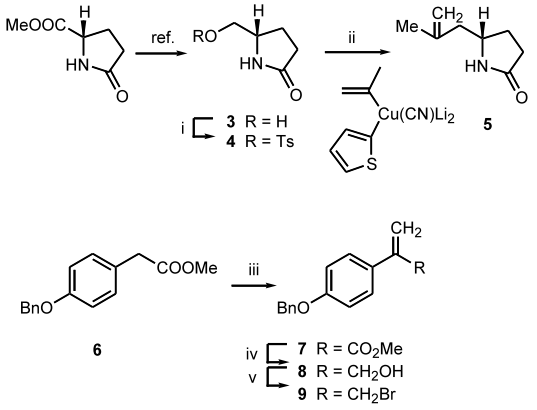


Scheme 2. *Reagents and conditions*: (i) TsCl, Et_3N, DMAP, CH_2Cl_2, rt (88%); (ii) THF–Et_2O, −78 to 0°C (93%); (iii) $(CH_2O)_n$, Cs_2CO_3, TDA-1, toluene, 85°C (54%); (iv) DIBAL, CH_2Cl_2, −78°C; (v) CBr_4, PPh_3, CH_2Cl_2, rt (71% from **7**).

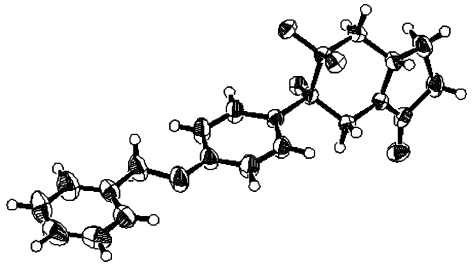


Figure 2. ORTEP drawing of the diol **13**.

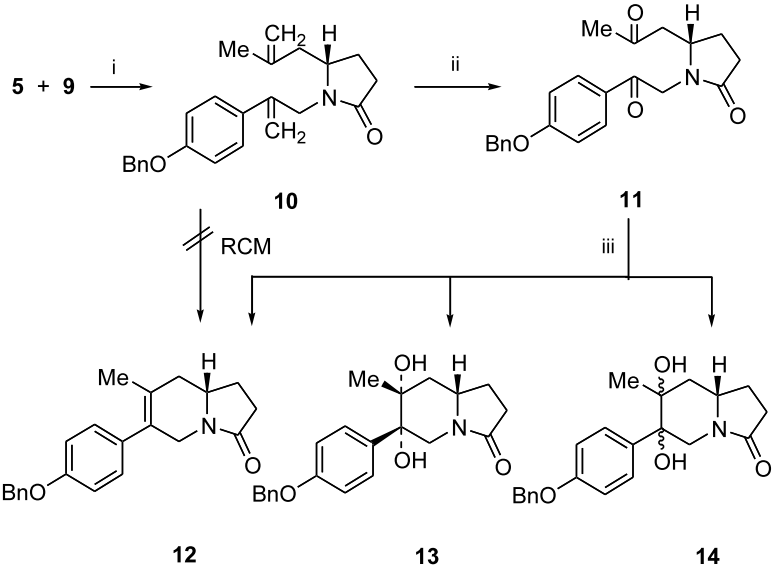
reduction of the ester **7** with diisobutylaluminum hydride and bromination of the resulting alcohol **8** with CBr_4 and Ph_3P as shown in Scheme 2. Condensation of the amide **5** with the bromide **9** was carried out in THF–HMPA in the presence of NaH to give the diene **10** in 90% yield.

With the pivotal starting material in hand, we attempted a ring-closing metathesis (RCM) for the diene **10** using Grubbs catalyst[10] or Hoveyda catalyst[11] under various reaction conditions; however, no cyclization product could be isolated, unfortunately. It is recognized that the Schrock catalyst is usually more effective than the Grubbs catalyst in the construction of a poly-substituted olefin system in RCM; however, none of the desired product could be obtained even by the use of the Schrock catalyst.[12]

We therefore turned our attention to McMurry coupling[13] for constructing a tetra-substituted olefin system. Ozonolysis of the diene **10**, followed by reductive work-up with methyl sulfide, provided the corresponding diketone **11**, which, on treatment with titanium(0), prepared from titanium(III) chloride THF complex and Zn–Cu couple, in DME at 80°C for 48 h furnished the desired product **12**[14] in 30% yield together with the *cis*-diol **13** and stereochemically unidentified diol **14** in 15 and 15% yields, respectively. The structure of the *cis*-diol **13** was determined by X-ray analysis unambiguously as depicted in Figure 2.[15]

Unidentified compound **14** seemed to have diol functions based on consideration of the spectroscopic data.[16] Although we could not confirm its structure at present, unfortunately, a diastereoisomeric β-*cis*-diol structure would be assumed reasonably based on the reaction mechanism. When this coupling was carried out under the same reaction conditions for 5 h, the *cis*-diol **13** was isolated in 66% yield in addition to the diol **14** (6%) (Scheme 3).

For completion of the synthesis of (+)-ipalbidine, reduction of the amide function for **12** was achieved by using lithium aluminum hydride to furnish the amine **15** in 86% yield.

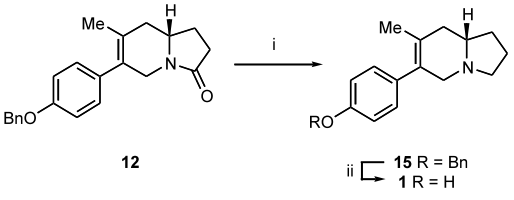


Scheme 3. *Reagents and conditions*: (i) NaH, THF–HMPA, rt (90%); (ii) O_3, MeOH, −78°C, then Me_2S, −78°C to rt (99%); (iii) $TiCl_3(thf)_3$, Zn–Cu, DME, 80°C (30% for **12**, 15% for **13**, 15% for **14**).

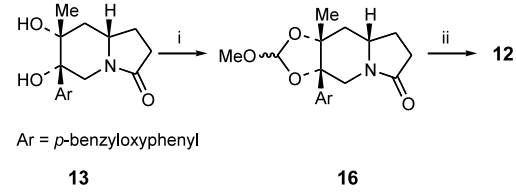
Finally, debenzylation of **15** under hydrogenolysis conditions over 5% palladium hydroxide on carbon in MeOH afforded the natural product **1**. The spectroscopic data of **1**, mp 76–78°C (from benzene–cyclohexane) (lit.,[4b] mp 82–84°C), were in agreement with those reported.[4] Although some difference 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 at present, we believe that our compound has an almost optically pure form based on the synthetic strategy (Scheme 4).

Since the direct formation of the alkene function from the diketone **11** by the McMurry coupling was found to be insufficient in terms of the yield, we 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 from **11** by the McMurry coupling with a shorter reaction time in 66% yield, with trimethyl orthoformate and PPTS afforded the orthoformate **16**, which, on treatment with acetic anhydride[17] brought about the desired elimination reaction to provide the olefin **12** in 75% yield from **13** (Scheme 5).

In summary, we have disclosed an alternative total synthesis of optically active (+)-ipalbidine **1**, in which intramolecular McMurry coupling of the diketone **11** 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 **11** under different reaction conditions, also afforded the desired product, successfully. The synthetic strategy developed here would be applicable to the synthesis of biologically active phenanthroindolizidine and phenanthroquinolizidine alkaloids.



Scheme 4. *Reagents and conditions*: (i) $LiAlH_4$, THF, rt (86%); (ii) H_2, 5% $Pd(OH)_2$–C, MeOH, rt (100%).



Scheme 5. *Reagents and conditions*: (i) $CH(OMe)_3$, PPTS, CH_2Cl_2, rt; (ii) Ac_2O, 140°C (75% from **13**).

Acknowledgements

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14. Selected data for **12**: mp 109–111°C (recrystallized from benzene–hexane); $[\alpha]_D$ +186.1 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.63 (3H, s), 1.73 (1H, m), 2.13 (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 (2H, d, $J=8.7$ Hz), 7.30–7.47 (5H, m); ^{13}C NMR ($CDCl_3$) δ 20.4, 24.9, 29.9, 38.2, 44.3, 52.9, 69.9, 114.4, 126.9, 127.4, 127.8, 128.2, 128.5, 129.7, 132.0, 136.8, 157.7, 173.7; IR (thin film) 1786, 1606, 1510, 1453, 1421, 1240 cm^{-1}; HRMS *m*/*z* found: 333.1749 (calcd for $C_{22}H_{23}NO_2$: 333.1729).
15. Crystal data for **13**: mp 167–168°C (recrystallized from EtOAc). $C_{22}H_{25}NO_4/3H_2O$, $M=421.49$, orthorhombic, space group $P2_12_12_1$, $a=7.666(1)$, $b=42.539(5)$, $c=6.7407(9)$ Å, $V=2198.2(5)$ $Å^3$, $Z=4$, $D_{calcd}=1.27$ 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 ($I<10.0\sigma(I)$) were rescanned (maximum of seven 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. $R=0.049$, $Rw=0.056$.
16. Selected data for **14**: ^1H NMR ($CDCl_3$) δ 0.99 (3H, s), 1.41 (1H, d, $J=1.6$ Hz), 1.67 (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), 2.24 (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 ($CDCl_3$) δ 23.8, 24.6, 30.4, 41.2, 46.3, 52.8, 69.9, 72.9, 75.0, 114.1, 127.5, 127.9, 128.0, 128.5, 133.3, 136.9, 158.1, 175.2; IR (thin film) 3392, 1664, 1608, 1508, 1454, 1246, 1178 cm^{-1}; HRMS *m*/*z* found: 367.1784 (calcd for $C_{22}H_{25}NO_4$: 367.1783).
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