

A Synthesis of (\pm)-Ipalbidine Using Sulfurcontrolled 6-Exo Selective Radical Cyclization of α -Phenylthio Amide

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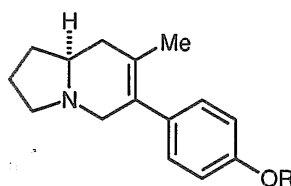
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Abstract — A synthesis of (±)-ipalbidine (**1**) has been achieved using Bu₃SnH-mediated 6-*exo* selective radical cyclization of 2-[3-(phenylthio)prop-2-enyl]-N-[α-(*p*-methoxyphenyl)-α-(phenylthio)acetyl]pyrrolidine (**15**) as a key step.

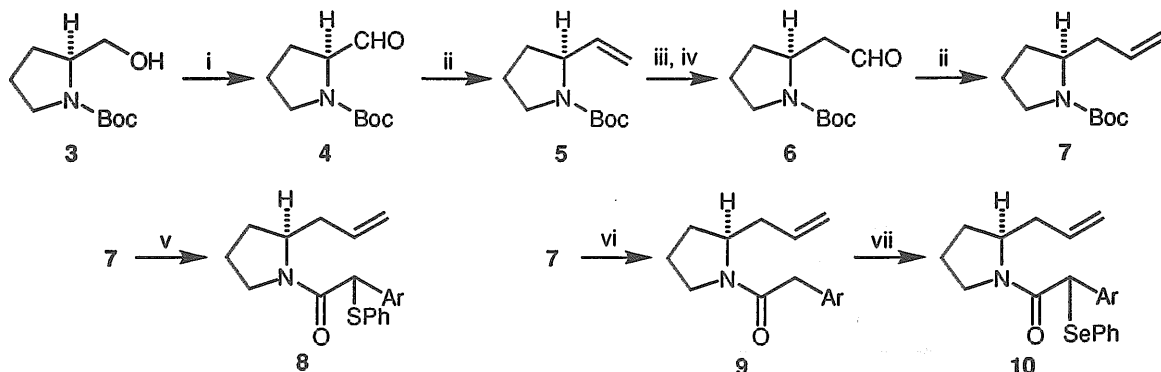
(+)-Ipalbidine (**1**) is the aglycone of ipalbine (**2**), an indolizidine alkaloid isolated from seeds of *Ipomoea alba* L.¹ A number of methods have so far been reported for the construction of the indolizidine skeleton,² and several efforts have culminated in the total synthesis of racemic³ and optically active⁴ ipalbidine. Herein we wish to report a new synthesis of (±)-ipalbidine using sulfur-controlled 6-*exo* selective radical cyclization of α-phenylthio amide as a key step.



1: R = H
2: R = β-D-glucosyl

We initiated our investigation by examining the radical cyclization of the 2-(prop-2-enyl)-N-[(phenylthio)acetyl]pyrrolidine (**8**), which was prepared from *N*-Boc-(*S*)-prolinol (**3**) as illustrated in Scheme 1. A toluene solution of Bu₃SnH (1.1 equiv.) and AIBN (0.1 equiv.) was added slowly to a boiling solution of **8** in toluene during 3 h and the mixture was heated under reflux for several hours to give only the starting material (**8**) even when an additional amount of Bu₃SnH was added. Therefore, we turned our attention to the α-phenylselenenyl congener (**10**) prepared as shown in Scheme 1. When the compound (**10**) was treated slowly with Bu₃SnH (1.1 equiv.) in a manner similar to that described above for **8**, the expected 6-*exo-trig* cyclization product (**11**)⁵ was obtained, but the yield of **11** was rather low (21%) and the undesired 7-*endo-trig* cyclization product (**12**)⁵ was also obtained in 16% yield (Scheme 2).

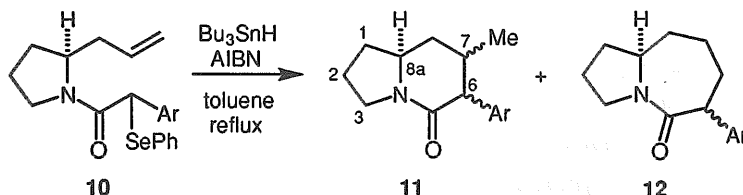
Scheme 1



Ar = *p*-methoxyphenyl

Reagents and conditions: i, SO_3 -pyridine, Et_3N , DMSO, quant.; ii, $\text{Ph}_3\text{P}^+\text{Me Br}^-$, NaH, DMSO, 73% for 5, 50% for 7; iii, Si_2BH , THF then H_2O_2 , NaOH, quant.; iv, $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , quant.; v, $\text{CF}_3\text{CO}_2\text{H}$, CH_2Cl_2 then α -(*p*-methoxyphenyl)- α -(phenylthio)acetyl chloride, Et_3N , DMAP, CH_2Cl_2 , 67%; vi, Me_3SiI , MeCN then α -(*p*-methoxyphenyl)acetyl chloride, Et_3N ; vii, LDA then PhSeCl , THF, 51% from 7

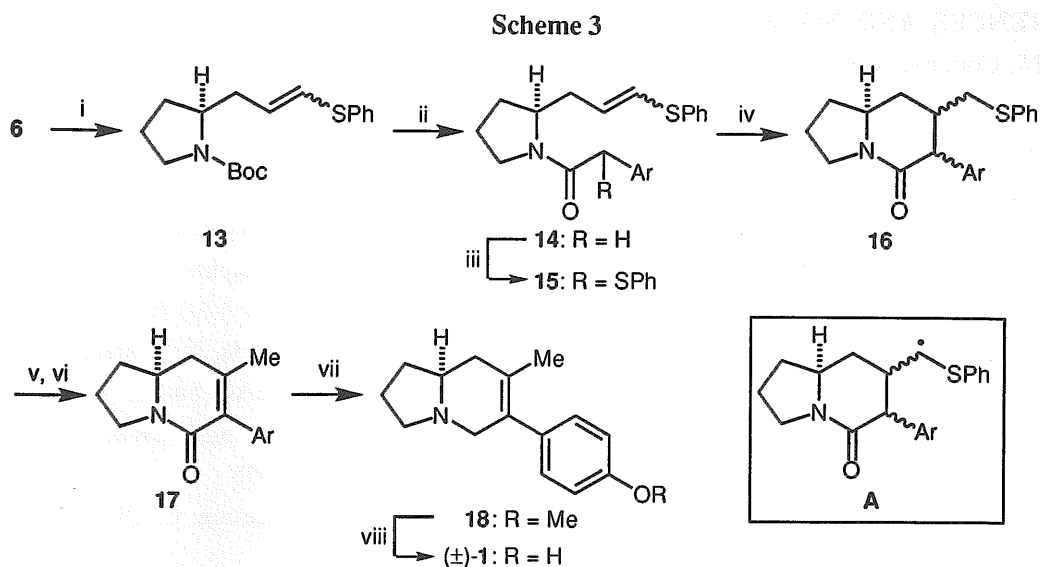
Scheme 2



Previously we demonstrated that the regiochemistry of radical cyclization can be controlled by the sulfur-substitution on the alkenic bond. For example, the 5-*endo-trig* mode of cyclization of the *N*-vinyllic α -halo amides can be shifted to the 4-*exo-trig* mode by introducing the phenylthio group(s) at the terminus of the *N*-vinyllic bond.⁶ This is probably because the sulfur substituent stabilizes the cyclized intermediacy of radical. So, we next examined the cyclization of 2-[3-(phenylthio)prop-2-enyl]pyrrolidine (15).

Compound (15) was prepared as illustrated in Scheme 3. Thus, treatment of aldehyde (6) with diphenyl(phenylthiomethyl)phosphine oxide in DMSO in the presence of NaH gave vinyl sulfide (13) as a mixture of the (*E*)- and (*Z*)-isomers in a ratio of *ca.* 1:2⁷ and in 76% combined yield. Deprotection of the *N*-Boc group with trimethylsilyl iodide followed by *N*-acylation of the resulting amine with *p*-methoxyphenylacetyl chloride gave amide (14) in 57% yield from 13. Treatment of 14 with LDA followed by diphenyl disulfide gave 15 in 81% yield.

As expected, the radical cyclization of 15 proceeded in a regioselective manner to give only the desired lactam (16)⁸ in 65% yield as a mixture of two diastereoisomers in a ratio of *ca.* 1:1.⁹ Treatment of 16 with sodium metaperiodate followed by heating the resulting sulfoxide in chlorobenzene at 160 °C in a sealed tube gave unsaturated lactam (17) through isomerization of the initially formed *exo*-methylene intermediate. Finally, according to the procedure reported by Danishefsky and Vogel,^{3f} compound (17) was reduced by



Reagents and conditions: i, $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{SPh}$, NaH, DMSO, 76%; ii, Me_3SiI , MeCN then *p*-methoxyphenylacetyl chloride, Et_3N , CH_2Cl_2 , 57%; iii, LDA then $(\text{PhS})_2$, THF, 81 %; iv, Bu_3SnH , AIBN, benzene, reflux, 65%; v, NaIO_4 , MeOH- H_2O , 77%; vi, chlorobenzene, 160 °C, 53%; vii, LiAlH_4 , AlCl_3 , THF, reflux, 86%; viii, BBr_3 , CH_2Cl_2 , 51%

alane and the resulting amine (**18**) was demethylated with boron tribromide to furnish ipalbidine as an oil. At this time, we believed that the present sequence of the reactions starting from *N*-Boc-(*S*)-prolinol (**3**) might provide optically pure (+)-ipalbidine, but the picrate of this compound showed a specific rotation of nearly zero and its melting point (163-165 °C) was identical to that (163-165 °C) reported for the picrate of racemic ipalbidine^{3b} [mp of picrate of (+)-ipalbidine: lit.,¹ 178 °C or lit.,^{3b} 183-185 °C]. The intermediate *O*-methylipalbidine (**18**), however, showed a specific rotation ($[\alpha]^{25}_{\text{D}}$) of +22.5 (*c* 0.75, EtOH)}. These results suggest that ipalbidine herein obtained is not optically pure,¹⁰ though it has some degree of optical activity. It is reasonable to assume that the partial racemization might occur in the Wittig olefination of aldehyde (**4**) giving **5**. Indeed, no reproducible values of the specific rotation of **5** were obtained, especially in its mass production. Therefore, in order to synthesize optically pure (+)-ipalbidine, an alternative method for the synthesis of the key intermediate **15** is required.

Thus, we revealed a new synthesis of indolizidine skeleton using sulfur controlled 6-*exo* selective radical cyclization of α -phenylthio amide. The application of this methodology to the synthesis of more complex indolizidine alkaloids is now in progress.

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4. For the asymmetric synthesis of (+)-ipalbidine, see: L. Zhujin, L. Renrong, C. Qi, H. Hai, *Acta Chimica Sinica*, 1985, **43**, 992.
5. The ^1H NMR spectrum of **11** showed it to be a single stereoisomer, though the exact stereochemistry is unknown [δ (CDCl_3 , 270 MHz) 1.13 (3 H, d, $J = 6.9$ Hz, CMe), 1.41-2.19 (7 H, m, 1- H_2 , 2- H_2 , 7-H, 8- H_2), 3.32 (1 H, d, $J = 3.6$ Hz, 6-H), 3.41-3.80 (3 H, m, 3- H_2 , 8a-H), 3.77 (3 H, s, OMe), 6.83 (2 H, d, $J = 8.6$ Hz, ArH), 7.03 (2 H, d, $J = 8.6$ Hz, ArH)]. The diastereoisomeric ratio of **12** is unknown because of complexity of its ^1H NMR spectrum [δ (CDCl_3 , 270 MHz) 1.38-2.35 (10 H, m), 3.35-3.45 (1 H, m), 3.55-3.75 (2 H, m), 3.79 (3 H, s, OMe), 3.85-3.98 (1 H, m), 6.85 (2 H, d, $J = 8.6$ Hz, ArH), 7.13 (2 H, d, $J = 8.6$ Hz, ArH)].
6. H. Ishibashi, C. Kameoka, H. Iriyama, K. Kodama, T. Sato, and M. Ikeda, *J. Org. Chem.*, 1995, **60**, 1276. See also: H. Ishibashi, H. Kawanami, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1997, 817 and references cited therein.
7. ^1H NMR (CDCl_3 , 270 MHz) spectrum of **13** exhibited the signals due to =CH(SPh) at δ 6.19 (d, $J = 14.8$ Hz) and 6.28 (d, $J = 9.2$ Hz) for the (*E*)- and (*Z*)-isomers, respectively.
8. ^1H NMR (C_6D_6 , 270 MHz) spectrum of **16** exhibited the signals due to 6-H for two stereoisomers at δ 3.56 (d, $J = 4.3$ Hz) and 3.84 (d, $J = 5.6$ Hz), respectively.
9. The reason why the α -phenylthio group of **8** did not work as a leaving group is not clear at the moment.
10. It has been reported that (+)-ipalbidine forms hexagonal crystals from benzene/cyclohexane, but the specific rotation of this material is not reproducible and depends upon the drying conditions because the crystals contain some benzene and cyclohexane. See ref. 3b.

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