A SYNTHESIS OF (±)-IPALBIDINE USING SULFUR-CONTROLLED 6-*EXO* SELECTIVE RADICAL CYCLIZATION OF α-PHENYLTHIO AMIDE

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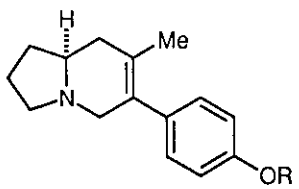
Abstract — A synthesis of (±)-ipalbidine (**1**) has been achieved using Bu_3SnH-mediated 6-*exo* selective radical cyclization of 2-[3-(phenylthio)prop-2-enyl]-*N*-[α-(*p*-methoxyphenyl)-α-(phenylthio)acetyl]pyrrolidine (**15**) as a key step.

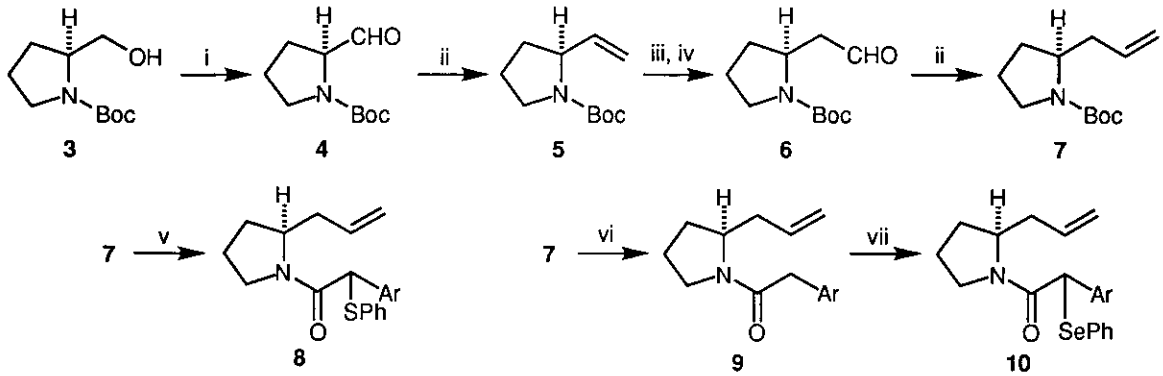
(+)-Ipalbidine (**1**) is the aglycone of ipalbine (**2**), an indolizidine alkaloid isolated from seeds of *Ipomoea alba* L.[1] A number of methods have so far been reported for the construction of the indolizidine skeleton,[2] and several efforts have culminated in the total synthesis of racemic[3] and optically active[4] 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 Bu_3SnH (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 stating material (**8**) even when an additional amount of Bu_3SnH 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 Bu_3SnH (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).

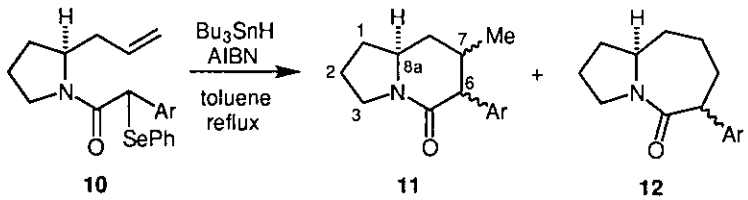
Scheme 1



Ar = *p*-methoxyphenyl

Reagents and conditions: i, SO_3-pyridine, Et_3N, DMSO, quant.; ii, $Ph_3P^+Me\ Br^-$, NaH, DMSO, 73% for **5**, 50% for **7**; iii, Sia_2BH, THF then H_2O_2, NaOH, quant.; iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, quant.; v, CF_3CO_2H, 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

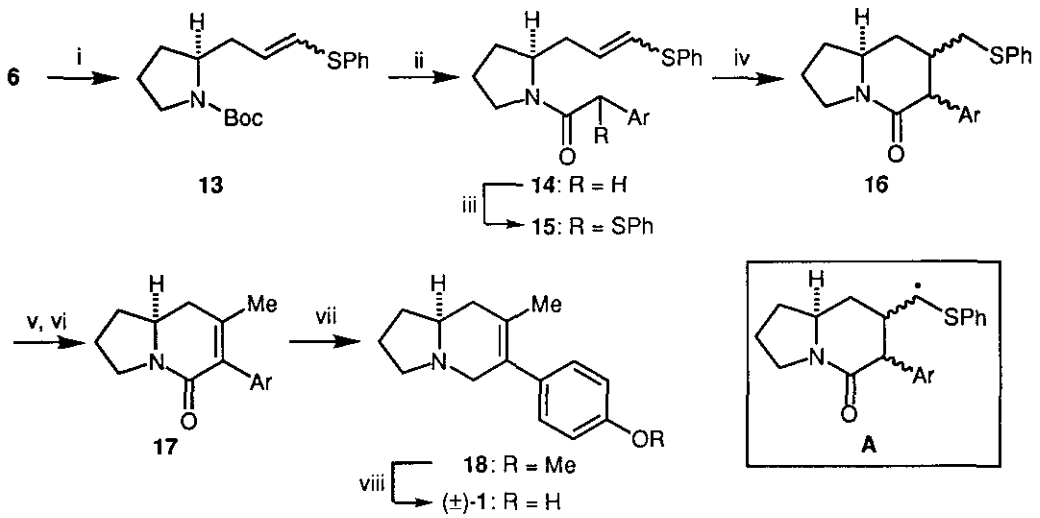


Previously we demonstrated that the regiochemistry of radical cyclization can be controlled by the sulfur-substitution on the alkenic bond. For example, the 5-*endo-trig* mode of cyclization of the *N*-vinylic α-halo amides can be shifted to the 4-*exo-trig* mode by introducing the phenylthio group(s) at the teminus of the *N*-vinylic 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)phophine 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.* 1:2[7] 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

Scheme 3



Ar = *p*-methoxyphenyl

Reagents and conditions: i, $Ph_2P(O)CH_2SPh$, NaH, DMSO, 76%; ii, Me_3SiI, MeCN then *p*-methoxyphenylacetyl chloride, Et_3N, CH_2Cl_2, 57%; iii, LDA then $(PhS)_2$, 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 ($[\alpha]^{25}_D$) 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.

ACKNOWLEDGMENT

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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 ^{1}H 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 ^{1}H 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. ^{1}H NMR ($CDCl_3$, 270 MHz) spectrum of **13** exhibited the signals due to =C*H*(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. ^{1}H 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 specfic 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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