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Synthetic Applications of Sulfur-Substituted Indolizidines and Quinolizidines

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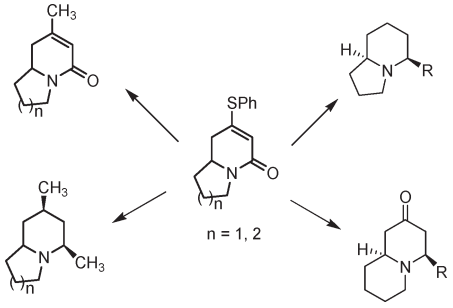
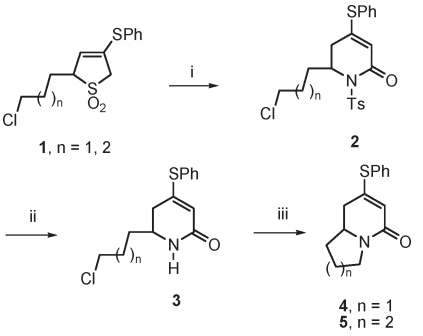
Received October 22, 2010



Starting from the sulfur-substituted indolizidines and quinolizidines, a few useful synthetic transformations have been developed and the synthesis of some natural products including indolizidine 209D, epimyrtine, lasubine II, 8a-*epi*-dendroprimine, and 5-*epi*-cermizine C has been accomplished.

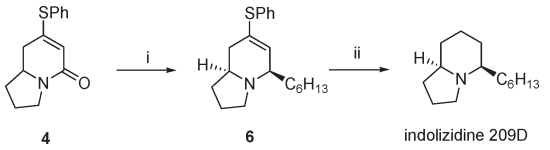
Some alkaloids have the indolizidine or quinolizidine structures, which often show interesting biological activities.[1] Many methods have been developed for the synthesis of these novel compounds,[2] but those which can be applied both to the synthesis of indolizidines and quinolizidines are most useful.[3] We have reported a new aza-Diels−Alder reaction of thio-substituted 3-sulfolenes with *p*-toluenesulfonyl isocyanate (PTSI) to synthesize sulfur-substituted piperidine derivatives,[4] and have used this method to prepare some indolizidines and quinolizidines.[5] For example, 3-sulfolenes **1**[6] reacted with PTSI to generate dihydropyridinones **2**, which upon detosylation and intramolecular cyclization gave the sulfur-substituted indolizidine **4** and quinolizidine **5** (Scheme 1).[5b]

SCHEME 1. Synthesis of Indolizidine 4 and Quinolizidine 5[a]



[a]Reagents and conditions: (i) (a) Ts—N=C=O (3 equiv), HQ (cat.), $NaHCO_3$ (1 equiv), Tol, 110 °C, 4.5 h; (b) Et_3N; (ii) Bu_3SnH (1.2 equiv), AIBN (0.2 equiv × 3), Tol, reflux, 4.5 h; (iii) NaH (1.5 equiv), THF, reflux, 3 h.

SCHEME 2. Synthesis of Indolizidine 209D[a]



[a]Reagents and conditions: (i) (a) $C_6H_{13}MgBr$ (4 equiv), THF, rt, 2 h; (b) HOAc (4 equiv), 0 °C, 5 min; (c) $NaBH_4$ (10 equiv), MeOH, 0 °C, 30 min, 71%; (ii) Ra-Ni (10 equiv), 95% EtOH, reflux, 2 h, 71%.

We now report some new synthetic applications of compounds **4** and **5**. Reaction of compound **4** with hexylmagnesium bromide at room temperature, followed by treatment sequentially with acetic acid and $NaBH_4$/MeOH, gave the vinyl sulfide **6**. The stereochemistry of compound **6** was established by NOESY spectrum, and was further confirmed by its subsequent conversion to indolizidine 209D by reacting with Ra-Ni in refluxing EtOH (Scheme 2).[7]

Similar reactions of compound **5** with methylmagnesium bromide, acetic acid, and $NaBH_4$ yielded the corresponding vinyl sulfide **7**. Hydrolysis of compound **7** with concentrated hydrobromic acid provided (±)-epimyrtine (Scheme 3), the spectral data of which were in agreement with the literature report.[8]

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(2) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139–165. and other reviews in these series.

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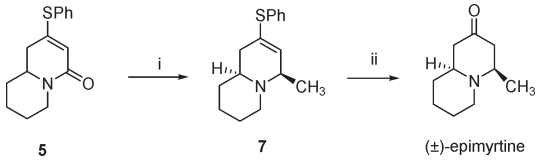
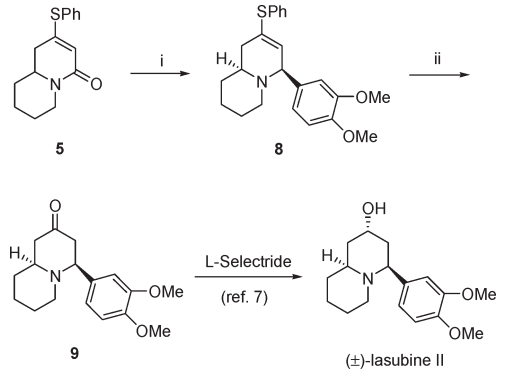
Published on Web 12/17/2010 DOI: 10.1021/jo102092b

SCHEME 3. Synthesis of Epimyrtine[a]



[a]Reagents and conditions: (i) (a) MeMgBr (4 equiv), THF, 70 °C, 2.5 h; (b) HOAc (5 equiv), 0 °C, 10 min; (c) $NaBH_4$ (10 equiv), CH_3OH, 0 °C, 30 min, 86%; (ii) concd HBr (excess), 95% EtOH, 75 °C, 2.5 h, 91%.

SCHEME 4. Formal Synthesis of Lasubine II[a]

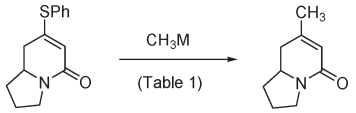


[a]Reagents and conditions: (i) (a) 3,4-dimethoxyphenylmagnesium bromide (5 equiv), THF, 70 °C, 2.5 h; (b) HOAc (5 equiv), 0 °C, 10 min; (c) NaBH4 (10 equiv), MeOH, 0 °C, 30 min, 59%; (ii) concd HBr ('xs), 95 % EtOH, 70 °C, 3 h, 80%.

Reaction of compound **5** with 3,4-dimethoxyphenylmagnesium bromide, followed by treatment with acetic acid and $NaBH_4$/MeOH, gave the vinyl sulfide **8**, which was hydrolyzed by concentrated hydrobromic acid to yield the ketone **9**. It has been reported that ketone **9** can be stereoselectively reduced to lasubine II by L-Selectride.[9] Thus we have achieved a formal synthesis of (±)-lasubine II (Scheme 4).

We have also studied various reaction conditions to convert the phenylthio-substituted compound **4** to the methyl-substituted product **10** (Table 1). From our previous studies,[4] we expected an organocopper reagent might accomplish this transformation. We found that the reaction of compound **4** with lithium dimethylcuprate (entry 1) gave only the recovered starting material. We then used $BF_3 \cdot Et_2O$ to activate the reaction of compound **4** with lithium dimethylcuprate (entry 2),[10] lithium dimethylcopper (entry 3), or methyllithium in the presence of a catalytic amount of CuI (entry 4),[11] still there were no reactions observed. Attempted reaction of compound **4** with MeMgBr in the presence of a nickel catalyst (entry 5),[12] or with MeLi/CuCN·2LiCl/$BF_3 \cdot Et_2O$ (entry 6)[13] also failed to give any desired product

TABLE 1. Conversion of Compound 4 to Compound 10[a]



entry	reagents (equiv)	additive (equiv)	**10** (%)
1	MeLi (7), CuI (3.5)	none	NR[b]
2	MeLi (6), CuI (3)	$BF_3 \cdot Et_2O$ (3)	NR[b]
3	MeLi (3.5), CuI (3.5)	$BF_3 \cdot Et_2O$ (5.5)	NR[b]
4	MeLi (3.5), CuI (cat.)	$BF_3 \cdot Et_2O$ (5.5)	NR[b]
5	MeMgBr (2.2)	$NiCl_2(PPh_3)_2$ (0.03)	NR[b]
6	MeLi (6), CuCN·2LiCl (3)	$BF_3 \cdot Et_2O$ (5)	NR[b]
7	MeLi (6), CuCN (3)	$BF_3 \cdot Et_2O$ (5)	39[c]
8	MeLi (6), CuI (3)	$BF_3 \cdot Et_2O$ (5)	65[d]
9	MeLi (7), CuI (3.5)	$BF_3 \cdot Et_2O$ (5.5)	74
10	MeMgBr (7), CuI (3.5)	$BF_3 \cdot Et_2O$ (5.5)	78
11[e]	MeLi (7), CuI (3.5)	$BF_3 \cdot Et_2O$ (5.5)	96

[a]Unless otherwise indicated, the reaction conditions were as follows: **4** (1 equiv) in THF was added at −78 °C to a mixture of an organometallic reagent w/o additives. The reaction mixture was slowly warmed to room temperature, stirred for another 1.5 h, and then quenched with saturated ammonium chloride. [b]No reaction was observed. [c]Compound **4** was recovered in 50%. [d]Compound **4** was recovered in 7%. [e]The reaction mixture was stirred at room temperature for 24 h.

10. However, when $BF_3 \cdot Et_2O$ was used in combination with MeLi/CuCN (2:1, entry 7), compound **10** was obtained in low yield. Replacement of CuCN with CuI (entry 8) increased the yield of product **10** significantly, but a small amount of the starting material **4** remained. Increasing the amount of the organocuprate (entry 9) completed the reaction. The use of MeMgBr/CuI/$BF_3 \cdot Et_2O$ (entry 10) also achieved the transformation. Finally, stirring the reaction mixture at room temperature for 24 h (entry 11) provided the product **10** in 96% yield.

By comparing the results in entries 2 and 8, it can be seen that the use of the same equivalent of $BF_3 \cdot Et_2O$ as that of Me_2CuLi (entry 2) did not give any product **10**, whereas the use of excess equivalent of $BF_3 \cdot Et_2O$ than that of Me_2CuLi (entry 8) resulted in 65% yield of the product **10**. This seems to indicate that $BF_3 \cdot Et_2O$ first forms a 1:1 complex with Me_2CuLi, and then the excess $BF_3 \cdot Et_2O$ activates its reaction with compound **4** by complexing with the amido group of compound **4**. Furthermore, the structure of the copper reagents used in entries 6, 7, and 8 has a significant impact on the reaction; CuI is more efficient than CuCN, while CuCN·2LiCl is totally inactive.

Compound **10** was hydrogenated to give the cis-product **11**, which has identical spectral data with the literature values.[14] Compound **11** further reacted with methyllithium, acetic acid, and $NaBH_4$ to give 8a-*epi*-dendroprimine (Scheme 5),[15] which shows a Bohlmann band at 2793 cm^{-1} in the IR spectrum indicating that the lone pair electrons of nitrogen as well as the H_5 and H_{8a} are at the axial position.

Compound **5** was also smoothly converted to the methyl-substituted compound **12** by $Me_2CuLi/BF_3 \cdot Et_2O$. Since

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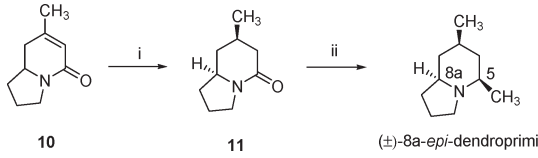
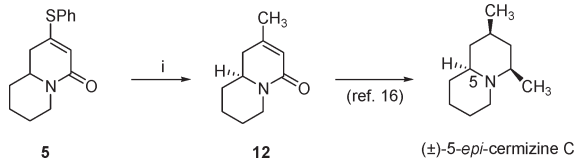
(15) The hydrochloride salt, but not the free base of (−)-8a-*epi*-dendroprimine, has been reported in ref 14b.

SCHEME 5. Synthesis of 8a-*epi*-Dendroprimine[a]



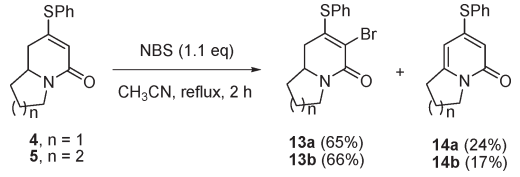
[a]Reagents and conditions: (i) H_2 (1 atm), PtO_2 (10 mol %), EtOAc, rt, 28 h, 96%; (ii) (a) CH_3Li (3 equiv), THF, rt, 5 h; (b) HOAc (excess), 0 °C, 10 min; (c) $NaBH_4$ (10 equiv), CH_3OH, 0 °C, 3 h, 68%.

SCHEME 6. Formal Synthesis of 5-*epi*-Cermizine C[a]

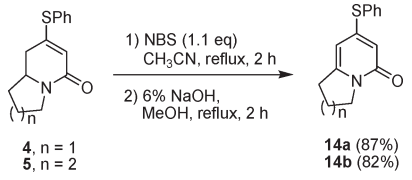


[a]Reagents and conditions: (i) MeLi (7 equiv), CuI (3.5 equiv), THF, $BF_3 \cdot Et_2O$ (5.5 equiv), −78 °C to rt, 1.5 h, 84%.

SCHEME 7. Preparation of Vinyl Bromides 13



SCHEME 8. Preparation of Elimination Products 14



compound **12** has been selectively transformed into 5-*epi*-cermizine C,[16] our method constitutes a formal synthesis of racemic 5-*epi*-cermizine C (Scheme 6).

Compounds **4** and **5** also reacted with *N*-bromosuccinimide (NBS) in refluxing acetonitrile to give the vinyl bromides **13a** and **13b**, together with the corresponding elimination products **14a** and **14b** (Scheme 7). Varying the reaction solvent or temperature still led to a mixture of compounds **13** and **14**, which were effectively separated by column chromatography. We also found that reaction of compounds **4** and **5** with NBS at reflux followed by treatment with NaOH/MeOH afforded the elimination products **14a** and **14b** in good yield (Scheme 8). This indicates that compounds **14a** and **14b** derived from further elimination of compounds **13a** and **13b**, which involves the isomerization of the double bond of compounds **13** followed by 1,4-elimination of HBr.

Vinyl bromides **13a** and **13b** were successfully converted by Suzuki coupling reactions with phenylboronic acid to give

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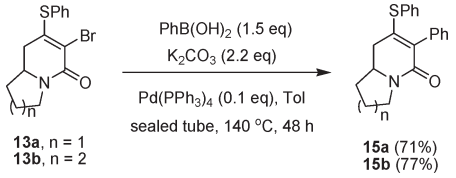
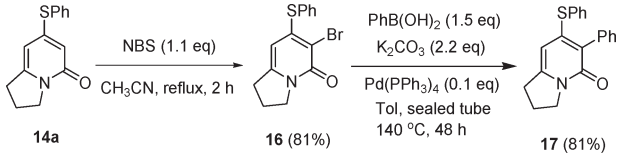
SCHEME 9. Suzuki Coupling Reactions of Compounds 13



SCHEME 10. Bromination and Suzuki Coupling of 14a



the phenylated products **15a** and **15b**, respectively, in good yield (Scheme 9).

Compound **14a** also reacted with NBS to give the vinyl bromide **16**, which underwent Suzuki coupling reaction with phenylboronic acid to afford the phenylated product **17** in good yield (Scheme 10).

In summary, we have developed a few useful synthetic transformations of sulfur-substituted indolizidine **4** and quinolizidine **5** to the vinyl bromides **13a**, **13b**, and **16**, aromatic compounds **14a** and **14b**, and Suzuki coupling products **15a**, **15b**, and **17**. We have also accomplished the synthesis of some natural products including indolizidine 209D, epimyrtine, lasubine II, 8a-*epi*-dendroprimine, and 5-*epi*-cermizine C.

Experimental Section

Indolizidine 209D. A mixture of compound **6** (34 mg, 0.107 mmol) and a W-2 Ra-Ni (91 mg) in 95% EtOH (5 mL) was heated at reflux under nitrogen for 2 h. The solid was filtered off, and the residue was evaporated under vacuum in an ice bath. The crude product was purified by flash chromatography using Et_3N/ethyl acetate/hexanes (1:1:20) as eluent to give indolizidine 209D (15 mg, 71%) as a colorless liquid, the spectral data of which were identical with the literature values.[7]

Epimyrtine. To a solution of compound **7** (50 mg, 0.19 mmol) in 95% EtOH (4 mL) was added dropwise a 50% HBr (3 mL). The mixture was heated at 70 °C under nitrogen for 2.5 h. The solvent and excess HBr solution were removed under vacuum, and saturated sodium bicarbonate was slowly added. The solution was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexanes (1:8) containing 5% Et_3N as eluent to give epimyrtine as a colorless oil (29 mg, 91%), the spectral data of which are identical with the literature values.[8]

***cis*-4-(3,4-Dimethoxyphenyl)hexahydro-1*H*-quinolizin-2(6*H*)-one (9).** The procedure was the same as that for the preparation of epimyrtine from compound **7**. Starting from compound **8** (20 mg, 0.07 mmol), product **9** (12 mg, 80%) was obtained as a colorless oil, the spectral data of which are identical with the literature values.[9]

7-Methyl-1,2,3,5,8,8a-hexahydro-5-indolizinone (10). To a mixture of CuI (271 mg, 1.43 mmol) in THF (6 mL) at 0 °C was added dropwise a solution of MeLi (2.2 M in diethyl ether, 1.30 mL, 2.86 mmol). After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C, and $BF_3 \cdot OEt_2$ (0.28 mL, 2.24 mmol) was added and stirred for 5 min. Then a solution of compound **4** (100 mg, 0.41 mmol) in THF (6 mL) precooled at −78 °C was

added dropwise. The reaction mixture was slowly warmed to room temperature, stirred for another 24 h, and quenched with saturated ammonium chloride. The aqueous solution was extracted with CH_2Cl_2, combined with the organic layer, dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexanes (2:1) and then ethyl acetate as eluent to give product **10** (59 mg, 96%) as a colorless oil: IR (neat) 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (1H, q, J = 1.2 Hz), 3.74−3.59 (2H, m), 3.50−3.40 (1H, m), 3.31 (1H, dd, J = 16.8, 5.4 Hz), 2.24−2.11 (2H, m), 2.06−1.98 (1H, m), 1.91 (3H, s), 1.88−1.71 (1H, m), 1.66−1.53 (1H, m); ^{13}C NMR ($CDCl_3$) δ 164.0, 149.6, 121.0, 56.3, 43.7, 35.9, 33.4, 22.9, 22.7; EI-MS (rel intensity) m/z 151 (M^+, 100), 150 (43), 96 (44), 82 (94), 70 (77); HRMS m/z calcd for $C_9H_{13}NO$ 151.0997, found 151.0996.

***cis*-7-Methyl-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (11).** A mixture of compound **10** (54.2 mg, 0.36 mmol) and PtO_2 (12 mg) in ethyl acetate (2 mL) was stirred vigorously under a balloon of hydrogen at room temperature for 24 h. The mixture was diluted with ethyl acetate, filtered through Celite, dried ($MgSO_4$), and evaporated under vacuum to give product **11** (52.5 mg, 96%) as a colorless liquid. Its spectral data are identical with the literature values.[14]

8a-*epi*-Dendroprimine. To a solution of compound **11** (33.3 mg, 0.22 mmol) in THF (3 mL) at room temperature was added slowly another solution of MeLi (2.2 M in hexane, 0.30 mL, 0.66 mmol). The reaction mixture was stirred at room temperature for 5 h, and then cooled in an ice bath. Acetic acid (0.06 mL, 1.1 mmol) was then added dropwise. The mixture was stirred for 10 min, and $NaBH_4$ (82.3 mg, 2.2 mmol) and methanol (2 mL) were added sequentially. After stirring for 3 h, the solvent was removed under vacuum, and saturated sodium bicarbonate was added. The mixture was extracted with ethyl acetate, dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography on silica gel using ethyl acetate/hexanes (1:4) as eluent to give 8a-*epi*-dendroprimine (22.6 mg, 68%) as a colorless oil: IR (neat) 2793 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.25 (1H, td, J = 8.4, 2.1 Hz), 2.10−1.40 (11H, m), 1.10 (3H, d, J = 6.3 Hz), 1.05−0.85 (m, 1H), 0.90 (3H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 64.8, 58.2, 51.4, 43.1, 39.4, 31.4, 30.4, 22.0, 21.0, 20.8; EI-MS (rel intensity) m/z 153 (M^+, 44), 152 (47), 138 (100), 136 (17), 133 (18), 132 (16), 119 (31), 105 (31), 91 (34), 70 (34), 55 (35), 43 (37), 41 (40); HRMS m/z calcd for $C_{10}H_{19}N$ 153.1517, found 153.1513.

Acknowledgment. Financial support of this work by the National Science Council of the Republic of China (NSC 97-2113-M-030-001-MY3) and Fu Jen Catholic University (9991A15/10973104995-4) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for compounds **2**−**8** and **12**−**17** and ^1H and ^{13}C NMR spectra for compounds **2**−**17** and 8a-*epi*-dendroprimine. This material is available free of charge via the Internet at http://pubs.acs.org.