

SYNTHESIS OF (±)-LUPININE AND (±)-EPI-LUPININE USING  
REGIOSELECTIVE ALKYLATION OF FUNCTIONALIZED 3-SULFOLENE

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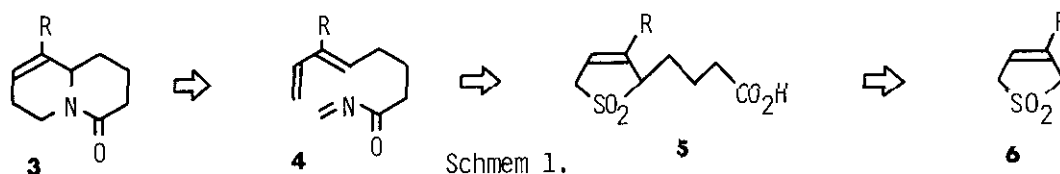
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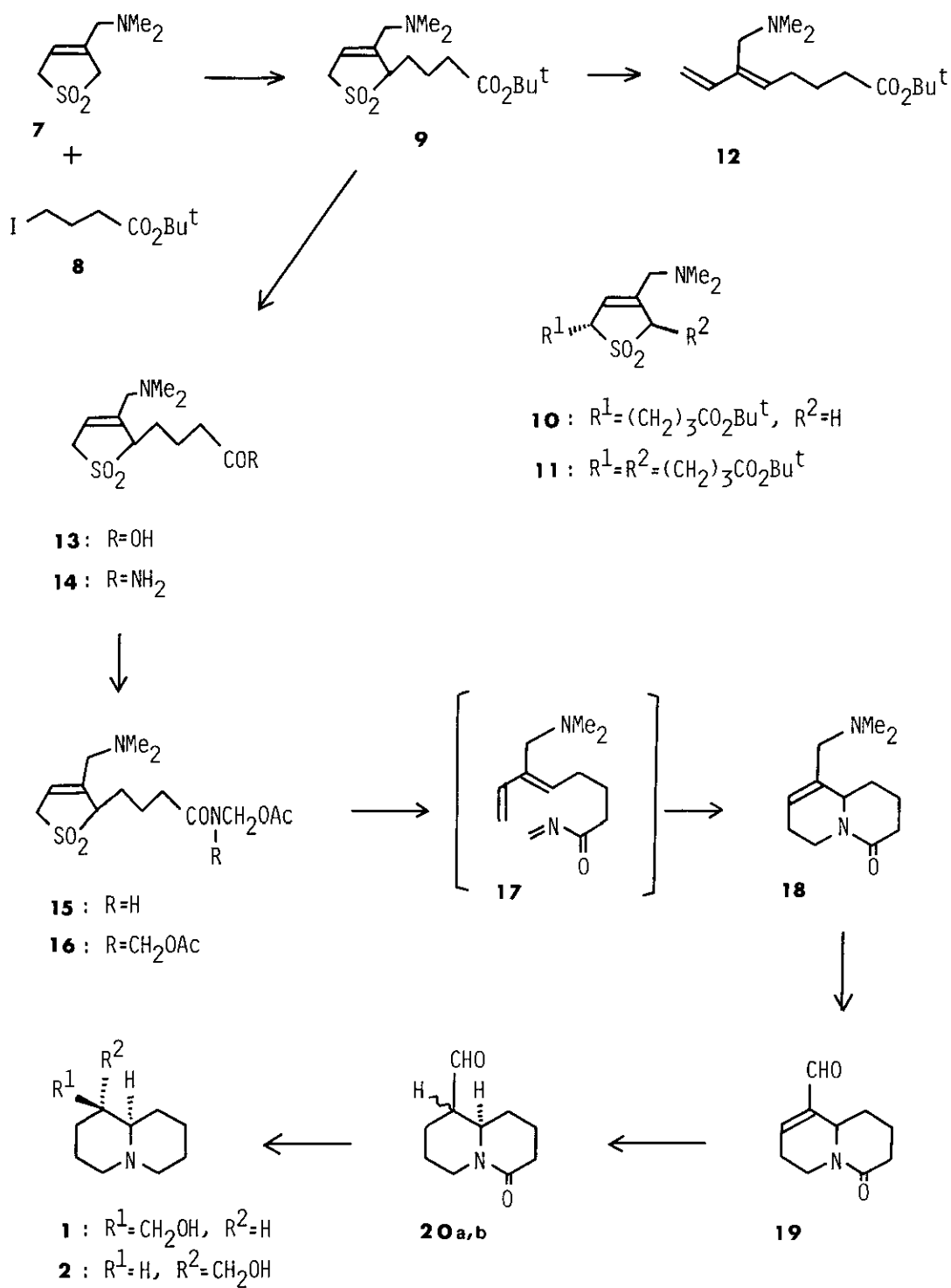
**Abstract**—The regioselective alkylation of 3-(N,N-dimethylaminomethyl)-3-sulfolene was applied to the synthesis of quinolizidine alkaloids, (±)-lupinine and (±)-epi-lupinine.

We have developed the stereoselective synthesis of conjugated dienes<sup>1a</sup> using direct alkylation of 3-sulfolenes<sup>1b, c</sup> as a key step, and found that substituent effect at the 3-position of 3-sulfolene greatly influences the regioselectivity of the alkylation.<sup>2</sup> In this paper, we wish to describe application of the regioselective alkylation of functionalized 3-sulfolene to the synthesis of quinolizidine alkaloids, (±)-lupinine (1) and (±)-epi-lupinine (2).

Retrosynthetic analysis of quinolizidine ring system (3) starting from 3-sulfolene (6) was shown in scheme 1. The quinolizidine (3) can be constructed by intramolecular imino Diels-Alder reaction<sup>3</sup> of 4, and it is obtained by manipulation of the side chain of 5 which would be prepared using regioselective alkylation of functionalized 3-sulfolene (6). In this case, 3-(N,N-dimethylaminomethyl)-3-sulfolene (7), which was readily prepared from 3-bromomethyl-3-sulfolene<sup>4</sup> and dimethylamine, was chosen<sup>5</sup> as the synthetic equivalent of 3-formyl-3-sulfolene which would be available for the synthesis of many natural products.

To a solution of 3-(N,N-dimethylaminomethyl)-3-sulfolene (7) (1.5 equiv.), ester iodide (8) (1 equiv.), and HMPA (4 equiv.) in THF was added a solution of LiHMDS (1.1 equiv.) in THF in one portion at -78°C. After general work up and chromato-





Scheme 2.

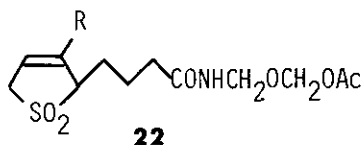
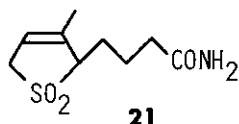
graphic purification, the desired ester (**9**)<sup>6</sup> was obtained as a main product in 33% yield accompanied by **10**<sup>6</sup> (6%) and the dialkylated compound (**11**)<sup>6</sup> (5%). The regiochemistry of **9** was confirmed by converting it to the corresponding diene (**12**)<sup>6</sup> by thermal desulfonylation. Treatment of the ester (**9**) with TFA in CH<sub>2</sub>Cl<sub>2</sub> at room temperature afforded the corresponding carboxylic acid (**13**), which without isolation was converted to the amide (**14**)<sup>6</sup> in 70% yield (ClCO<sub>2</sub>Et, Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> then conc. NH<sub>4</sub>OH)<sup>7</sup>. The amide (**14**) was treated with paraformaldehyde (1.1 equiv.) and cesium carbonate in THF, and the crude product was acetylated with acetic anhydride/pyridine to yield the acetate (**15**)<sup>8</sup> (77%) and N,N-diacetoxymethylated compound (**16**) (13%). Thermolysis of **15** in toluene containing NaHCO<sub>3</sub> (5 equiv.) in a sealed tube at 200°C for 2 h gave the lactam (**18**) [m/e 208 (M<sup>+</sup>); IR (neat) 1630 cm<sup>-1</sup>] in 80% yield via desulfonylation and subsequent intramolecular Diels-Alder reaction of **17**. The lactam (**18**) was treated with MCPBA (1.1 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> followed by treatment with acid anhydride (Ac<sub>2</sub>O or TFAA) to yield the aldehyde (**19**) [m/e 179 (M<sup>+</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.04-2.10 (9H, m), 4.36, 4.98, and 7.02 (each 1H, m), 9.45 (1H, s); IR (KBr) 1680, 1625 cm<sup>-1</sup>] in 65% yield. Catalytic hydrogenation of **19** gave **20a, b** and subsequent lithium aluminum hydride reduction provided (±)-lupinine (**1**) [m/e 169 (M<sup>+</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.20-2.40 (15H, m), 2.70-2.95 (2H, m), 3.71 (1H, d, J=11.0 Hz), 4.18 (1H, dd, J=11.0, 5.0 Hz)] and (±)-epi-lupinine (**2**) [m/e 169 (M<sup>+</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.10-2.30 (15H, m), 2.65-2.95 (2H, m), 3.35-3.80 (2H, m)] in 28% and 50% yield from **19**, respectively. The spectroscopic properties of **1** and **2** thus obtained were identical with those reported.<sup>9</sup>

## REFERENCES AND NOTES

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5. It can be assumed that alkylation of **7** occurs at 2-position,<sup>2a</sup> and when 3-bromomethyl-3-sulfolene was subjected to alkylation reaction, elimination of hydrogen bromide occurred immediately.
6. **9**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.46 (9H, s), 1.70-2.00 (4H, m), 2.19 (6H, s), 2.20-2.48 (2H, m), 2.76 (1H, d, J=14 Hz), 3.20 (1H, d, J=14 Hz), 3.74 (3H, m), 5.90 (1H, m); **10**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.46 (9H, s), 1.65-2.10 (4H, m), 2.20 (6H, s), 2.15-2.45 (2H, m), 2.98 (2H, s), 3.76 (3H, s), 5.88 (1H, m); **11**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.46 (18H, s), 1.70-2.00 (8H, m), 2.19 (6H, s), 2.20-2.40 (4H, m), 2.73 (1H, d, J=14 Hz), 3.17 (1H, d, J=14 Hz), 3.68 (2H, m), 5.84 (1H, m); **12**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.45 (9H, s), 1.60-1.90 (2H, m), 2.20 (6H, s), 2.10-2.40 (4H, m), 3.04 (2H, s), 5.03 (1H, dd, J=11.0, 1.5 Hz), 5.36 (1H, dd, J=17.5, 1.5 Hz), 5.66 (1H, t, J=7.5 Hz), 6.32 (1H, dd, J=17.5, 11.0 Hz); **14**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.75 - 2.05 (4H, m), 2.20 (6H, s), 2.34 (2H, t, J=6 Hz), 2.77 (1H, d, J=14 Hz), 3.20 (1H, d, J=14 Hz), 3.76 (3H, m), 5.50-5.80 (2H, br. s), 5.91 (1H, m); IR (neat) 3600-3100, 1665 cm<sup>-1</sup>.
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8. In the case of acetoxymethylation of amide (**21**), **22** (R=Me) was isolated as minor product in 6% yield. Although <sup>1</sup>H NMR spectra of **15** suggested the existence of **22** (R=CH<sub>2</sub>NMe<sub>2</sub>) (8%), it was inseparable by column chromatography.



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