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

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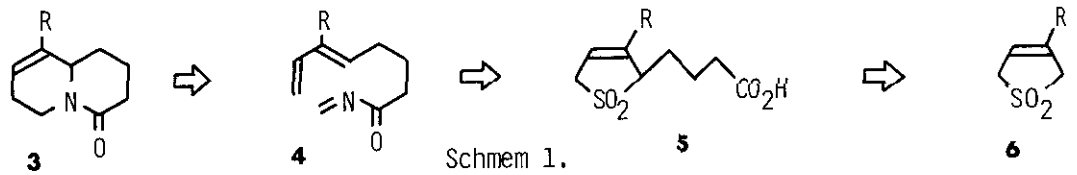
Abstract——The regioselective alkylation of 3-(N,N-dimethylaminomethyl)-3-sulfolene was applied to the synthesis of quinolizidine alkaloids, (±)-lupinine and (±)-epi-lupinine.

We have developed the stereoselective synthesis of conjugated dienes[1a] using direct alkylation of 3-sulfolenes[1b, c] as a key step, and found that substituent effect at the 3-position of 3-sulfolene greatly influences the regioselectivity of the alkylation.[2] 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**).

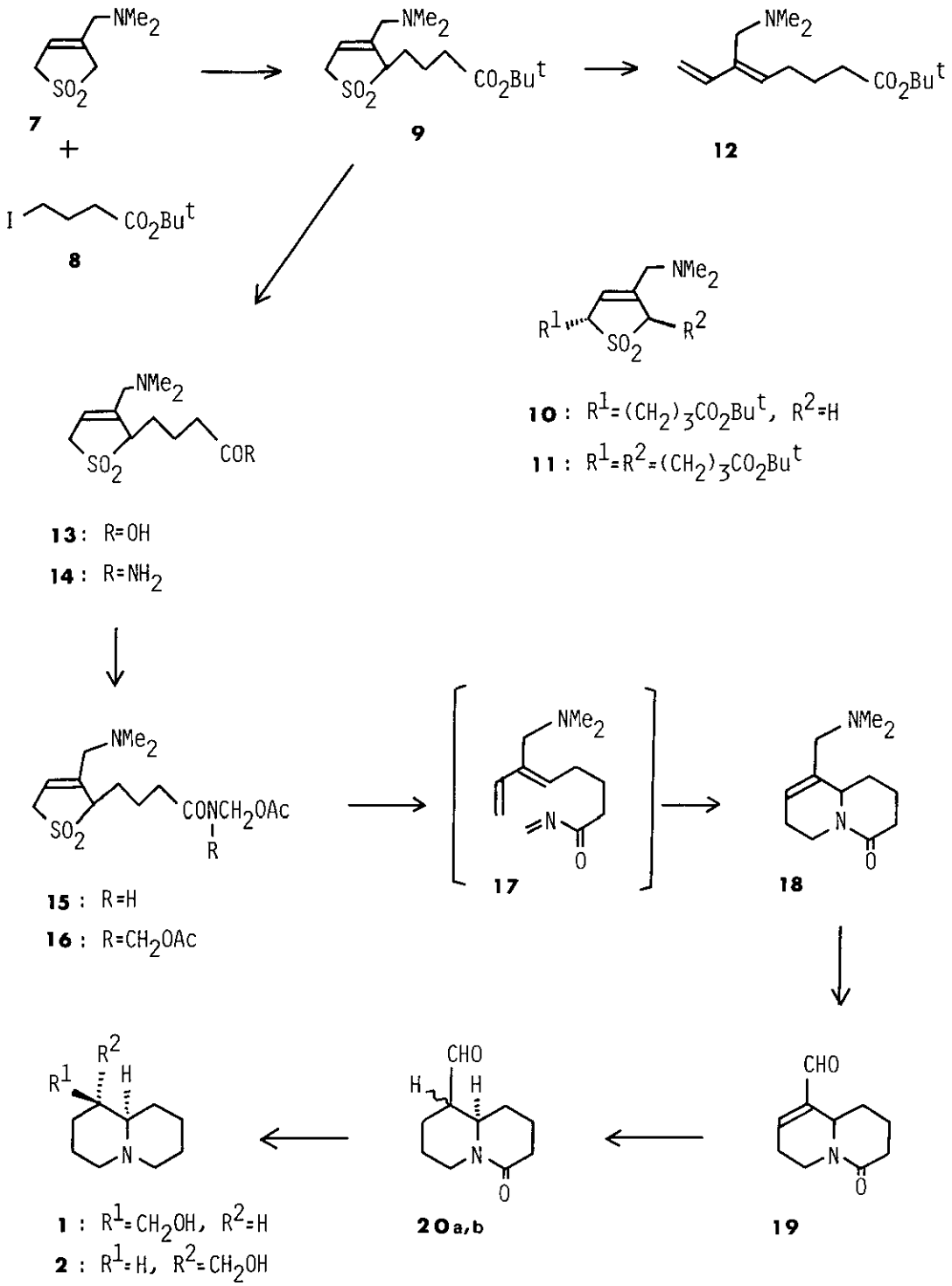
Retrosynthetic analysis of quinolizidine ring system (**3**) starting from 3-sulfolene (**6**) was shown in scheme 1. The quinolizidine (**3**) can be constructed by intramolecular imino Diels-Alder reaction[3] of **4**, and it is obtained by manipulation of the side chain of **5** which would be prepared 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[4] and dimethylamine, was chosen[5] 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-



3 **4** **5** **6**

Schmem 1.


NMe2
SO2
7
+
I
CO2Bu^t
8
9
12
10 : R^1=(CH2)3CO2Bu^t, R^2=H
11 : R^1=R^2=(CH2)3CO2Bu^t
13 : R=OH
14 : R=NH2
15 : R=H
16 : R=CH2OAc
CONCH2OAc
R
17
18
19
CHO
20a,b
1 : R^1=CH2OH, R^2=H
2 : R^1=H, R^2=CH2OH

Scheme 2.

graphic purification, the desired ester (**9**)[6] was obtained as a main product in 33% yield accompanied by **10**[6] (6%) and the dialkylated compound (**11**)[6] (5%). The regiochemistry of **9** was confirmed by converting it to the corresponding diene (**12**)[6] by thermal desulfonylation. Treatment of the ester (**9**) with TFA in CH_2Cl_2 at room temperature afforded the corresponding carboxylic acid (**13**), which without isolation was converted to the amide (**14**)[6] in 70% yield ($ClCO_2Et$, Et_3N in CH_2Cl_2 then conc. NH_4OH)[7]. 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**)[8] (77%) and N,N-diacetoxymethylated compound (**16**) (13%). Thermolysis of **15** in toluene containing $NaHCO_3$ (5 equiv.) in a sealed tube at 200°C for 2 h gave the lactam (**18**) [m/e 208 (M^+); IR (neat) 1630 cm^{-1}] 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_2Cl_2 followed by treatment with acid anhydride (Ac_2O or TFAA) to yield the aldehyde (**19**) [m/e 179 (M^+); ^1H NMR ($CDCl_3$) 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^{-1}] in 65% yield. Catalytic hydrogenation of **19** gave **20a, b** and subsequent lithium aluminum hydride reduction provided (±)-lupinine (**1**) [m/e 169 (M^+); ^1H NMR ($CDCl_3$) 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 (±)-epilupinine (**2**) [m/e 169 (M^+); ^1H NMR ($CDCl_3$) 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.[9]

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2. a) Preliminary results were presented at The 105th Annual Meeting of Pharmaceutical Society of Japan, Kanazawa, April 1985, Abstracts p 662 and details on these will be reported in the near future; b) S. Yamada, H. Naito, T. Nomoto, and H. Takayama, Chem. Pharm. Bull., submitted ; c) Recently other group reported independently regioselective alkylation of 3-

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5. It can be assumed that alkylation of **7** occurs at 2-position,[2a] and when 3-bromomethyl-3-sulfolene was subjected to alkylation reaction, elimination of hydrogen bromide occurred immediately.
6. **9**: ^{1}H NMR ($CDCl_3$) 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**: ^{1}H NMR ($CDCl_3$) 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**: ^{1}H NMR ($CDCl_3$) 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**: ^{1}H NMR ($CDCl_3$) 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**: ^{1}H NMR ($CDCl_3$) 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^{-1}.
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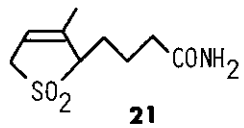
8. In the case of acetoxymethylation of amide (**21**), **22** (R=Me) was isolated as minor product in 6% yield. Although ^{1}H NMR spectra of **15** suggested the existance of 22 ($R=CH_2NMe_2$) (8%), it was inseparable by column chromatography.



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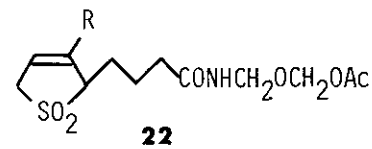

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