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DIASTEREOSELECTIVE INTRAMOLECULAR DIELS-ALDER REACTION OF *N*-ALKOXYCARBONYL -1-AZA-1,3-BUTADIENES AND A TOTAL SYNTHESIS OF THE PIPERIDINE ALKALOID, (±)-SEDRIDINE.

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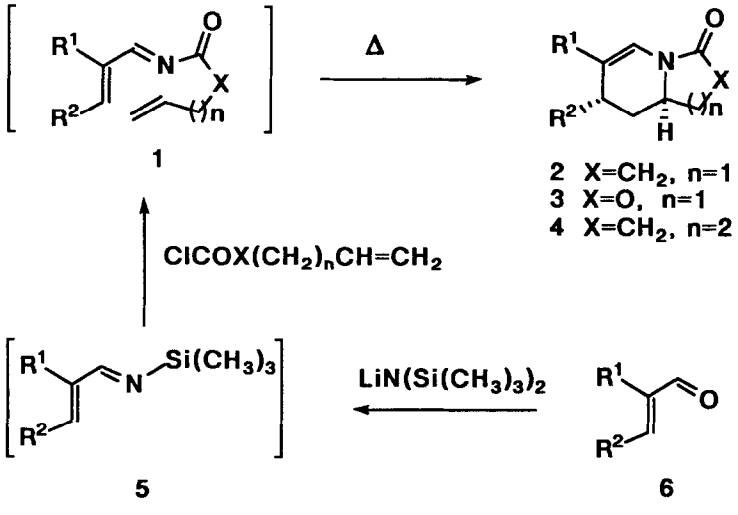
Key Words: Hetrocyclic ring systems; Alkaloids; Cycloaddition; Diastereoselection; Imines.

Abstract: Total synthesis of (±)-sedridine, the piperidine alkaloid, was accomplished on the basis of diastereoselective intramolecular Diels-Alder reaction of the ψ',ω'-unsaturated N-alkoxycarbonyl-1-aza-1,3-butadiene generated in situ from N-trimethylsilyl-1-aza-butadiene and the chloroformate of 4-penten-2-ol.

Intramolecular Diels-Alder reaction of *N*-acyl derivatives of 1-aza-1,3-butadiene (1) is a quite useful method to prepare nitrogen containing heterocyclic compounds, such as 1,7,8,8a-tetrahydro-3(2*H*)-indolizinones (2), the 2-oxa derivatives of 2 (3), and 1,2,3,8,9,9a-hexahydro-4*H*-quinolizin-4-ones (4), and also indolizidine and quinolizidine alkaloids.[1] Very recently, we have presented a new method for generationof *N*-acylimine 1, starting from commercially available α,β-unsaturated aldehydes (6) *via* the corresponding *N*-trimethylsilyl-1-aza-1,3-butadiene (5), and intramolecular Diels-Alder reaction of *N*-acylimine 1 in boiling xylene to give the heterocyclic compounds (2-4).[2] We now report the first entry of 3-oxa-1,2,3,8,9,9a-tetrahydro-4*H*-quinolizin-4-one synthesis by highly diastereoselective intramolecular Diels-Alder reaction and application of this procedure to a total synthesis of the piperidine alkaloid, (±)-sedridine (12).[3]



1

2 X=CH_2, n=1
3 X=O, n=1
4 X=CH_2, n=2

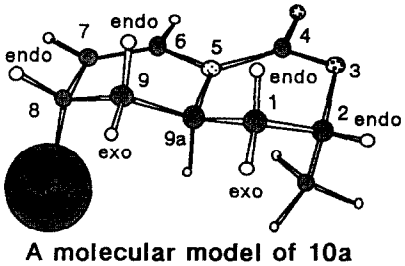
5

6

In spite of extensive studies on intramolecular hetero-Diels-Alder reactions, it is difficult to predict diastereoselectivity of the reaction of new substrates containing unsymmetrically substituted chains.[4] A purpose of this work is to elucidate such diastereoselectivity of the reaction of heterotriene system **9**. Generation of the heterotrienes by the method described previously requires chloroformate **8** and N-trimethylsilylimines **5**.

Chloroformylation of alcohols had been carried out by treatment with phosgene generated from trichloromethyl chloroformate (TCF) or bis(trichloromethyl) carbonate.[5] Treatment of the secondary alcohol (**7**) with TCF and an amine, general conditions for such chloroformylation, however, gave a mixture of chloroformate **8** and a large amount of the dialkenyl carbonate. After several attempts, we developed the two step procedure for preparation of chloroformate **8**. The first step is treatment of alcohol **7** with 2 equiv. of TCF in boiling dichloromethane to give a 1 : 1 mixture of chloroformate **8** and trichloromethyl 4-penten-2-yl carbonate. The second step is conversion of the latter into chloroformate **8** by treatment of the mixture with a catalytic amount of pyridine (0.05 equiv) in dichloromethane. After careful evaporation of the solvent, the residue was soaked in dry pentane and then pyridinium hydrochloride was removed by filtration. Chloroformate **8** was obtained in 78% yield after distillation *in vacuo* (bp 75°C / 66 mmHg).

N-Trimethylsilylimine **5a** derived form aldehyde **6a** (3 mmol) in THF was treated with chloroformate **8** (3.4 mmol) for 1 h and then the mixture was diluted with freshly distilled xylene (50 ml). Tetrahydrofuran was removed by distillation and the resulting solution was heated under reflux for 36 h. Chromatography of the reaction mixture gave heterocyclic compound **10a** (40% yield) as the only cycloaddition product.[6] The stereostructure of product **10a** was determined on the basis of its ^{1}H-NMR spectra.[7] The large values of $J_{9a,9\text{-}endo}$ and $J_{9a,1\text{-}endo}$ (12.0 and 10.4 Hz, respectively) indicate that each of the 1-*endo*-H, 9-*endo*-H, and 9a-H is axial or pseudoaxial. The relatively small value of $J_{8,9\text{-}endo}$ (6.2 Hz) suggests that the 8-H is the equatorial (*endo*) proton and the phenyl group is the *exo* substituent. The 3% nuclear Overhauser effect at 9a-H upon irradiation of the methyl protons reflects the 2-methyl group is at the *exo* position.



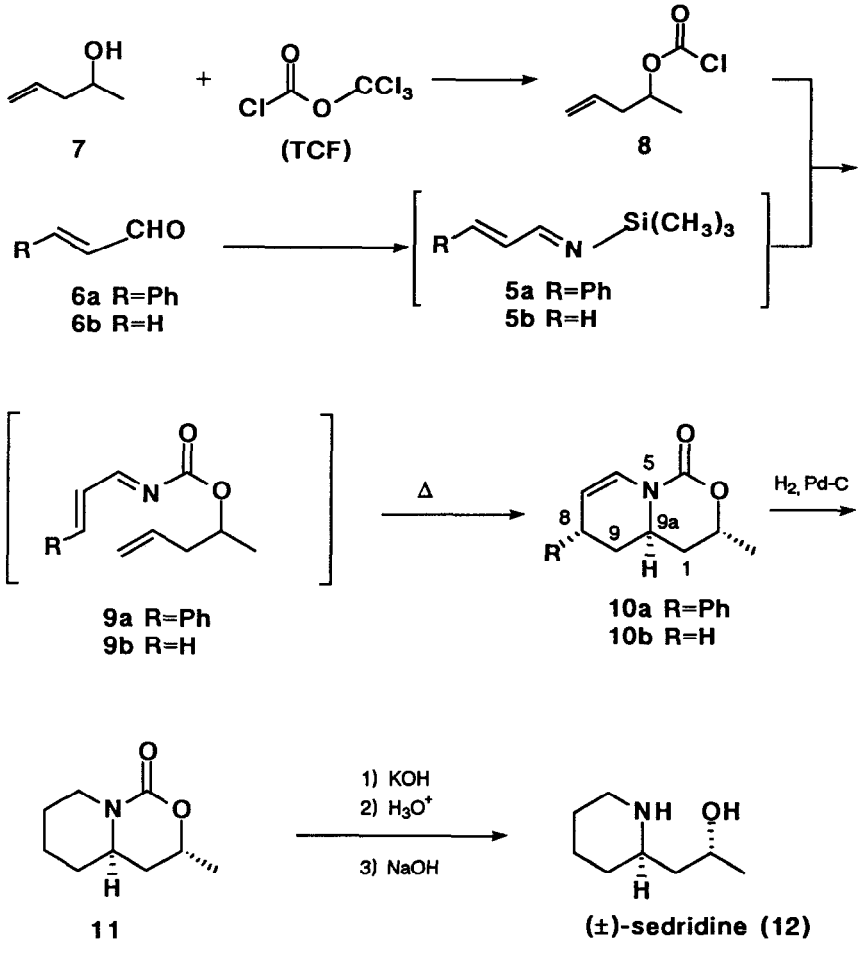
A molecular model of 10a

This stereochemical outcome indicates that the intramolecular hetero-Diels-Alder reaction proceeds *via* the *exo* transition state and the diastereoselectivity on the basis of the absolute configuration of the homoallyl alcohol is excellent. Therefore, we made a plan for a total synthesis of (±)-sedridine (**12**) using acrolein (**6b**) as the starting α,β-unsaturated aldehyde (*vide infra*). (±)-Sedridine itself is a natural piperidine alkaloid isolated from *Sedum acre* (Crassulaceae).[3,8]

In order to generate *N*-alkoxycarbonyl-1-aza-1,3-butadiene **9b**, a solution of acrolein (9 mmol) in THF was treated successively with lithium hexamethylsilazide (10 mmol, -78°C, then 20°C, 1 h), trimethylchlorosilane (10.6 mmol, 0°C, then 20°C, 1 h), and chloroformate **8** (9.8 mmol, 20°C, 30 min). The reaction mixture was diluted with xylene (100 ml) and THF was removed by distillation and the xylene solution was heated under reflux for 63 h. After removal of the solvent, chromatography of the residue gave the desired 3-oxa-1,2,3,8,9,9a-tetrahydro-4*H*-quinolizin-4-one (**10b**, 2.7 mmol, 30% yield).[9] Catalytic hydrogenation of **10b** gave octahydro-4*H*-quinolizin-4-one **11** in an excellent yield. Transformation of this cyclic carbamate into amino alcohol **12** was carried out in 69% yield (from **10b**) by successive treatment with a boiling aqueous KOH solution, diluted hydrochloric acid, and a 10% NaOH solution. Aminoalcohol (**12**) was isolated by ether extraction and purified by sublimation followed by recrystallization. The spectral characteristics of the *N,O*-acetal of the aminoalcohol prepared by a reaction with *p*-bromobenzaldehyde were identical with those reported previously.[3b,10]

In conclusion, a 3-oxa-1,2,3,8,9,9a-tetrahydro-4*H*-quinolizin-4-one, a potent synthetic precursor for a piperidine alkaloid, can be prepared by highly diastereoselective intramolecular Diels-Alder reaction of an *N*-(4'-penten-2'-oxy)carbonyl-1-aza-1,3-butadiene derived in one pot from an α,β-unsaturated aldehyde, lithium hexamethyldisilazide, and the homoallyl chloroformate.

Acknowledgement. We gratefully acknowledge Hodogaya Chemical Co.,Ltd. for the generous gift of TCF.



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(4) Recent reviews, see: (a) Ciganek, E. *Org. Reaction*, 1984, **32**, 1. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic press: San Diego 1987.

(5) Recent reviews, see: (a) Kawaguchi, T. *J. Synth. Org. Chem.*, **1989**, 47, 384-385. (b) Imagawa, T.*ibid.*, **1990**, 48, 1058-1059.

(6) All new compounds gave satisfactory analytical and high-resolution mass data.

(7) **10a**: Mp 110-111°C (hexane-EtOH); IR (KBr) 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ=7.31 (6-H, dd, *J*=8.4 and 1.4 Hz), 5.21 (7-H, ddd, *J*=8.4, 5.2, and 1.7 Hz), 4.59 (2-*endo*-H, qdd, *J*=6.7, 4.7, and 3.4 Hz), 3.59 (8-*endo*-H, dddd, *J*=6.2, 5.2, 3.4, and 1.4 Hz), 3.57 (9a-H, dddd, *J*=12.0, 10.4, 5.0, and 2.3 Hz), 2.03 (9-*endo*-H, ddd, *J*=12.3, 12.0, and 6.2 Hz), 1.95 (1-*endo*-H, ddd, *J*=14.0, 10.4, and 4.7 Hz), 1.90 (9-*exo*-H, dddd, *J*=13.2, 3.4, 2.3, and 1.7 Hz), 1.77 (1-*exo*-H, ddd, *J*=14.0, 5.0, and 3.4 Hz), and 1.36 (CH_3, d, *J*=6.7 Hz).

(8) A total synthesis of (±)-sedridine, see: Tufariello, J. J.; Ali, S. A. *Tetrahedron Lett.*, **1978**, 4647-4650.

(9) **10b**: Mp 60-60.5°C (hexane-ether); IR (KBr) 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ=6.99 (6-H, ddd, *J*=8.4, 2.4 and 1.5 Hz), 5.07 (7-H, dddd, *J*=8.4, 5.6, 2.4 and 1.5 Hz), 4.59 (2-*endo*-H, qdd, *J*=6.6, 4.5, and 3.7 Hz), 3.66 (9a-H, dddd, *J*=11.7, 10.0, 5.4, and 2.2 Hz), 2.19 (8-*exo*-H, ddddd, *J*=17.9, 11.8, 6.2, 2.4, and 2.4 Hz), 2.12 (8-*endo*-H, ddddd, *J*=17.9, 6.2, 5.2, 3.4, and 1.4 Hz), 1.99 (1-*endo*-H, ddd, J=13.9, 10.0, and 4.5 Hz), 1.93 (9-*exo*-H, m), 1.93 (1-*exo*-H, m), 1.64 (9-*endo*-H, dddd, *J*=13.9, 11.7, 11.7 and 6.2 Hz), and 1.42 (CH_3, d, *J*=6.6 Hz).

(10) We have not yet found complete spectral data of (±)-sedridine in literature; **12**: Mp 73.5-74.5°C (pentane) (listd[3a] 75°C); IR (KBr) 3280, 3140 (broad), 3045, 3040, 2970, 2940, 2870, 2830, 1480, 1370, 1335, 1320, 1150, 1125, 1105, 1085, 1055, 955, 885, and 870 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ=4.11 (1H, qdd, *J*=6.2, 3.1, and 3.1 Hz), 3.05 (1H, broad d, *J*=11.8 Hz, $W_{1/2}$=7 Hz), 2.87-2.50 (1H, m), 2.56 (1H, ddd, *J*=11.8 and 2.7 Hz), 1.83-1.79 (1H, m), 1.60-1.54 (3H, m), 1.44 (1H, ddd), *J*=14.5, 8.7, and 3.3 Hz), 1.42-1.34 (3H, m), and 1.17 (3H, d, *J*=6.2 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ=65.2 (2'), 54.9 (2), 47.0 (6), 43.9 (1'), 31.5 (3), 26.2 (5), 24.8 (4), and 23.6 (3').

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