APPLICATION OF THE OXYGENATIVE NUCLEOPHILE INTRODUCTION REACTION TO 1-ALKOXYCARBONYL-2-ALKYNYL-1,2-DIHYDROPYRIDINES A FACILE SYNTHESIS OF (±)-SEDACRYPTINE

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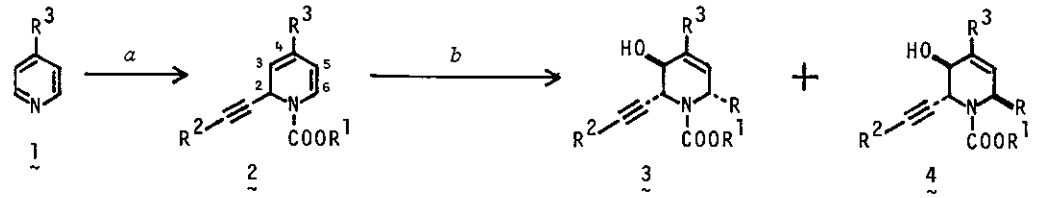
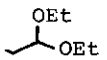
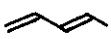
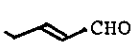
Abstract — A *Sedum* alkaloid, (±)-sedacryptine (17) was effectively synthesized from the compound (3g), one of the products (3a-3l) derived from 2-alkynyl-1,2-dihydropyridine derivatives (2) by application of our oxygenative nucleophile introduction reaction.

The $SnCl_2$-mediated ring opening reaction of *endo*-peroxides, accompanied by introduction of carbon nucleophiles[1] (oxygenative nucleophile introduction reaction) has been proved to be a powerful method for regio- and stereoselective formation of variously substituted piperidine derivatives suitable to the starting materials for natural product synthesis. Preparation of 1,2-dihydropyridine derivatives having a functionalized alkyl group at the C-2 position is necessary for the extension of applicability of the above reaction and in this communication, we wish to report i) the predominant formation of 1-alkoxycarbonyl-2-alkynyl-1,2-dihydropyridines (2), ii) application of these compounds to our oxygenative nucleophile introduction reaction to furnish highly functionalized piperidine derivatives (3), and iii) a facile total synthesis of a *Sedum* alkaloid, (±)-sedacryptine (17) starting from 3g.

According to the established method for preparation of 1-alkoxycarbonyl-2-alkyl-1,2-dihydropyridines,[2] Grignard reagents obtained from 1-alkyns and EtMgBr were reacted with pyridine or 4-methylpyridine in the presence of chloro alkylformates in THF under ice-cooling. Addition of HMPA as a co-solvent assisted a smooth and homogeneous reaction to afford mainly 1-alkoxycarbonyl-2-alkynyl-1,2-dihydropyridines (2) in high yields, whose structures were readily determined by ^{1}H-nmr spectra exhibiting each olefinic proton in an asymmetric fashion [2g, δ: 1.82 (d,



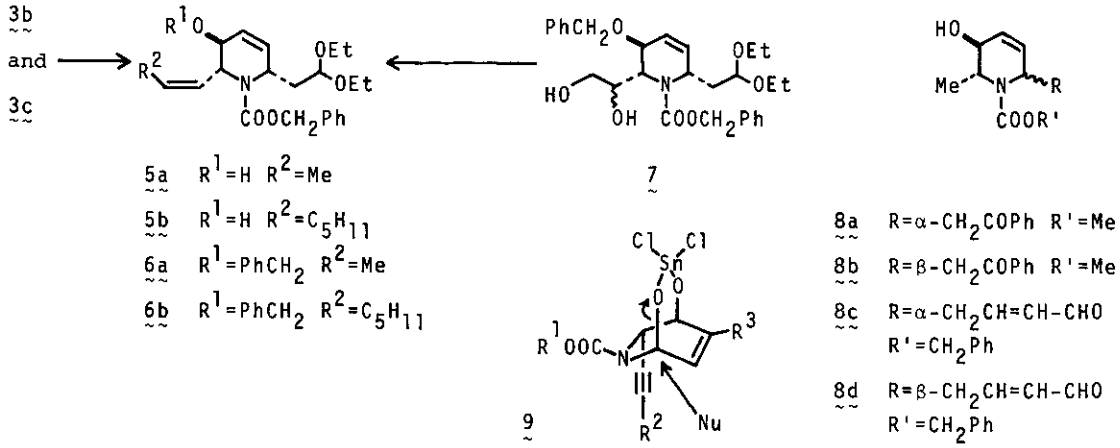
a: R^2-≡-MgBr, $ClCOOR^1$, THF-HMPA, 0°C. *b*: (i) O_2, 500 W halogen lamp, methylene blue, CH_2Cl_2, −55—50°C; (ii) nucleophile, $SnCl_2$ suspended in EtOAc, −50°C→ice-NaCl cooling.

	R^1	R^2	R^3	Yield (%) of 2	Nu	R	Yield (%) 3	Yield (%) 4
a	CH_2Ph	H	H	83	 †		77	0
b	"	Me	"	93	"	"	71	0
c	"	n-C_5H_{11}	"	97	"	"	66	0
d	"	Ph	"	95	"	"	77	0
e	"	THP-OCH_2	"	87	"	"	73§	0
f	"	H	"				68	0
g	Me	Me	"	88	"	"	54	10
h	"	Ph	"	98	"	"	53	7
i	"	H	"	86			72	4
j	"	"	Me	92			65	0
k	CH_2Ph	"	H				70	0
l	"	"	"		indole		85	0

† Work-up with addition of EtOH.

§ Isolated in the form of $-CH_2OH$ derivative.

J=2 Hz, Me), 3.83 (s, COOMe), 5.30 (dd, *J*=7.5, 5.5 Hz, H-5), 5.41-5.71 (2H, m, H-2 and H-3), 5.94 (dd, *J*=8, 5.5 Hz, H-4), and 6.72 ppm (br. d, *J*=7.5 Hz, H-6)]. Dihydropyridine derivatives (2) thus produced were subjected to the sensitized photooxygenation, followed by the $SnCl_2$-mediated reaction with various nucleophiles such as enol ethers and indole to furnish in good yields piperidine derivatives (3a-3l) possessing a variety of functions on the piperidine ring, where the triple



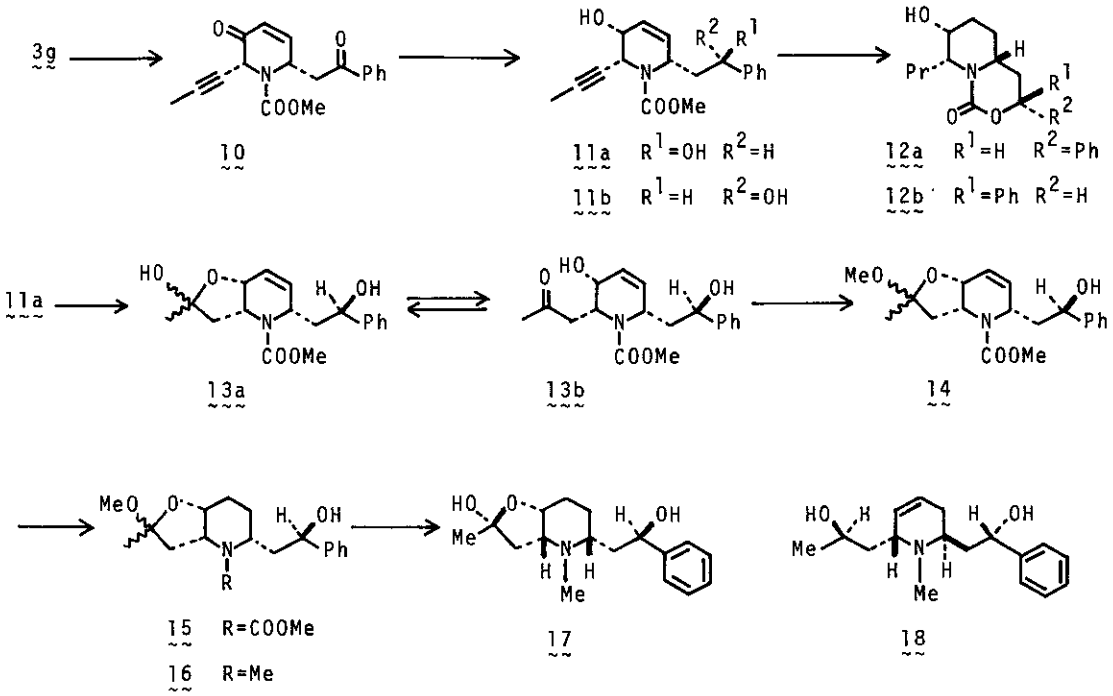
5a R^1=H R^2=Me
5b R^1=H R^2=C_5H_{11}
6a R^1=$PhCH_2$ R^2=Me
6b R^1=$PhCH_2$ R^2=C_5H_{11}

8a R=α-CH_2COPh R'=Me
8b R=β-CH_2COPh R'=Me
8c R=α-CH_2CH=CH-CHO R'=CH_2Ph
8d R=β-CH_2CH=CH-CHO R'=CH_2Ph

bond of the side chain remained intact.

Regio- and stereostructure of 3 was confirmed by transformation of 3b and 3c into 6a and 6b [(i) H_2, Lindlar catalyst, MeOH, 3b→5a: 64%, 3c→5b: 74%; (ii) NaH, $PhCH_2Cl$, HMPA-THF, 5a→6a: 88%, 5b→6b: 84%], which were respectively identical with the products derived from the structure definite compound[3] (7) [(i) $NaIO_4$, MeOH-H_2O; (ii) Ph_3P=CH-Me or Ph_3P=CH-C_5H_{11}, THF, 7→6a: 64%, 7→6b: 88% (Z olefin was the sole product in either case)]. Compared with the previous observation that the oxygenative nucleophile introduction reaction on 1-alkoxycarbonyl-2-methyl-1,2-dihydropyridine using α-trimethylsilyloxystyrene or 1-trimethylsilyloxy-1,3-butadiene as a nucleophile afforded 8a and 8b in 22% and 21% yields or 8c and 8d in 34% and 9% yields,[4] predominant formation of 3g, 3h, and 3i with enhanced yields was remarkable in cases of the alkynyl substituents, and this fact was reasonably explained by the preferential S_N2 attack of nucleophiles from the back side of the leaving oxygen atom in 9, where alkynyl groups with sp character exerted less steric effect towards the incoming nucleophiles than alkyl groups, so that formation of 4 was inversely suppressed since 4 was considered to be generated by the S_N1 mechanism. Ready access to highly functionalized piperidine derivatives (3) with specific stereochemical arrangement made possible to execute the synthesis of various kinds of natural products and an example is shown in the following as a facile total synthesis of a minor alkaloid, sedacryptine[5] (17) of *Sedum acre*, which is well-known to contain a main constituent, sedinine[6] (18) having the *Lobelia* alkaloid structure.[7]

The compound (3g) was oxidized with Jones reagent in acetone under ice-MeOH cool-



ing and a very unstable α,β-unsaturated ketone derivative (10) was directly reduced with $LiBH_4$ in MeOH at 0°C to afford two products (11a) and (11b) in 36% and 13% yields, respectively. In order to confirm configuration of the hydroxyl group, both compounds were converted to the corresponding cyclic carbamates (12a) and (12b) [(i) H_2, Pt, DME, r.t., (ii) NaH, HMPA, r.t., 64% yield each], and nmr signals of the protons adjacent to the phenyl group [a double doublet at 5.11 ppm for 12a (J=12, 2.5 Hz) and a double doublet at 5.44 ppm for 12b (J=6, 4.5 Hz)] suggested the configuration as shown. In addition to this fact, it was already experienced that the borohydride reduction of an α,β-unsaturated ketone group produced a single allyl alcohol, whose hydroxyl function was oriented in the *cis* relationship with respect to the substituents located at 2- and/or 6-positions,[8] and therefore, the major reduction product (11a) was concluded to be a suitable compound for the sedacryptine synthesis.

Hydration of the triple bond in 11a was performed by catalysis of $HgSO_4$ in diluted acidic DME-H_2O solution at 0°C for a short period to afford in 84% yield a *ca.* 1:1 mixture of 13a and 13b, the ratio being estimated by inspection of the singlet signals of the methyl protons at 1.47 and 2.13 ppm. Preliminary experments suggested that intramolecular assistance of the hydroxyl group on the

piperidine ring was essential to this reaction, since no successful result was obtained in cases of compounds having the opposite configuration of the hydroxyl group. The ketone group in 13 was next protected in the form of hemiketal methyl ether by treatment of the mixture of 13a and 13b with p-TsOH in MeOH at room temperature, and the compound (14) obtained in 93% yield was hydrogenated over Pt in DME at atmospheric pressure (94% yield, overreduction took place otherwise to eliminate the benzylic hydroxyl group), followed by reduction of 15 with $LiAlH_4$ in refluxing THF to give in quantitative yield the compound (16), whose ^{1}H-nmr spectrum revealed that 16 was actually a mixture of isomers in the ratio of 4:1 originating from the hemiketal orientation of unknown stereochemistry. Hydrolysis of the methoxyl group was carried out readily by acid treatment of 16 [5% HCl in DME-H_2O (1:1), r.t.] and the crystalline product (17), mp 99-101°C (benzene-cyclohexane), thus obtained in 92% yield, was identified with sedacryptine by comparison of tlc, ms, ir (CCl_4), and ^{1}H-nmr spectra.

ACKNOWLEDGEMENT The authors are grateful to Dr. C. Hootelé, Université Libre de Bruxelles, for generous gift of sedacryptine and its spectral data.

REFERENCES

1) M. Natsume, Y. Sekine, M. Ogawa, H. Soyagimi, and Y. Kitagawa, *Tetrahedron Lett.*, 1979, 3473.

2) G. Fraenkel. T.W. Cooper, and C.M. Fink, *Angew. Chem.*, 82, 518 (1970).

3) M. Natsume and M. Ogawa, *Heterocycles*, 16, 973 (1981).

4) M. Natsume and M. Ogawa, *Heterocycles*, 14, 615 (1980).

5) C. Hootelé, B. Colau, and F. Halin, *Tetrahedron Lett.*, 21, 5061 (1980).

6) (a) B. Franck, *Chem. Ber.*, 91, 2803 (1958); 92, 1001 (1959). (b) C. Hootelé, B. Colau, and F. Halin, *Tetrahedron Lett.*, 21, 5063 (1980).

7) W.A. Ayer and T.E. Habgood, "The Alkaloids," Vol. XI, ed. by R.H.F. Manske, Academic Press, New York, 1968, p. 459.

8) M. Natsume and M. Ogawa, *Heterocycles*, 14, 169 (1980).

Received, 14th January, 1983