SYNTHESIS OF DEPYRROLO ANALOGUE OF RESERPINE

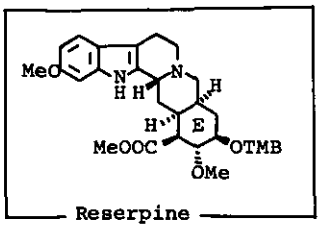
Okiko Miyata, Etsuko Doi, Takeaki Naito, and Ichiya Ninomiya*
Kobe Women's College of Pharmacy, Motoyamakita, Higashinada,
Kobe 658, Japan

Abstract—— Depyrrolo analogue (19) of reserpine was synthesized via the route involving hydrocyanation reaction of the β-methoxyenone (7) followed by the Michael reaction of the α,β-unsaturated nitrile (11) with sodium methoxide.

As an extension of our synthetic study[1] on reserpine alkaloids and related biologically active compounds, we report here the synthesis of the depyrrolo analogue of reserpine via the route involving hydrocyanation reaction[2] of the β-methoxyenone and the Michael addition of methoxide anion to α,β-unsaturated nitrile system, thereby established a potential synthetic route to the parent alkaloid. Since the stereochemical inversion of 3α-hydrogen into 3β-hydrogen in the pentacyclic structure of reserpine has been well documented[3] in the chemistry of reserpine type alkaloids, our attention has focused on the stereoselective construction of E ring which contains five chiral centers. Reductive photocyclization[4] of the dimethoxy-substituted enamide (1),[5] which was readily prepared from 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline and 3,5-dimethoxybenzoyl chloride, in the presence of sodium borohydride in benzene-methanol afforded the unstable tetracyclic lactam (2)[5] which without purification was subjected to acid hydrolysis to give the cis- and trans-methoxyenones (6)[5,6] and (5)[5,6] in 44 and 16% yields, respectively. Although attempts to improve the yield of the cis-lactam (6) by adoption of the various solvent system such as tetrahydrofuran-methanol and acetonitrile-methanol for the reductive photocyclization were unsuccessful as shown in Table, a combination of lithium borohydride[7] as a reducing agent and teterahydrofuran-methanol as a solvent system afforded the cis-amine (7)[5] in 45% yield in addition to two lactams (6)(10%) and (5)(10%) upon acid hydrolysis of the crude photocyclized products (2) and (3).

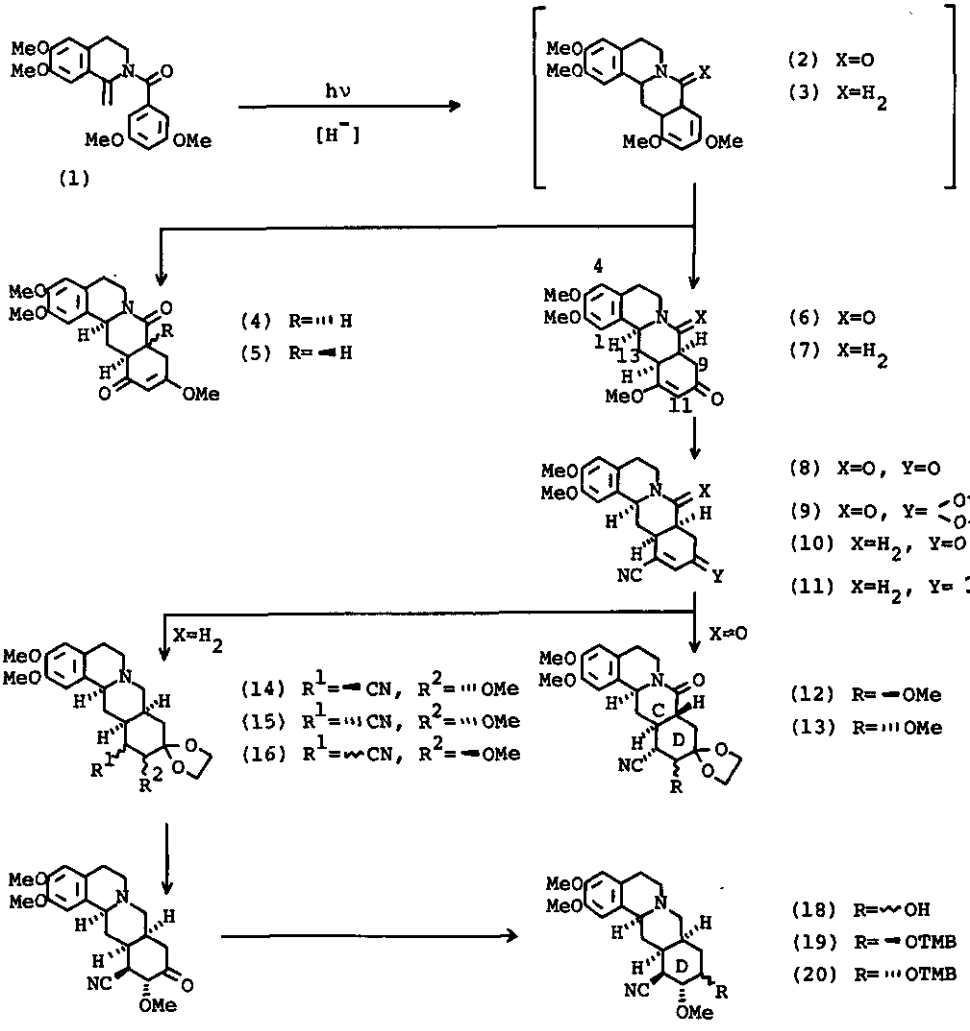
Introduction of a nitrile group as C_1-unit into 12-position was then undertaken by applying the addition-elimination reaction involving hydrocyanation reaction developed by Nagata, et al.,[2] to the β-methoxyenone system. Hydrocyanation reaction of two methoxyenones (6) and (7) with diethylaluminum cyanide at 60°C proceeded smoothly to give the desired nitriles (8)[5,6] and (10)[5] in 61 and 68% yields, respectively. On the other hand, treatment of the lactam (6) with cyanotrimethylsilane[8] in the presence of triethylaluminum in refluxing tetrahydrofuran afforded the same nitrile (8) in 61% yield while the amine (7) did not give any nitrile, instead with the full recovery of 7.

Introduction of 11α-methoxyl group was accomplished via the route involving the Michael reaction of the α,β-unsaturated nitrile system (10). Recently, Szántay, et al.[9] has reported the synthesis of deserpidine in which the Michael reaction of the α,β-unsaturated ester was applied for the introduction of 17α-methoxyl group though in poor (10%) yield even after long reaction time (72 h). After protection of the enone carbonyl group in 8 with ethylene glycol, the α,β-unsaturated nitrile (9) was subjected to the Michael reaction with sodium methoxide in absolute methanol at 60°C for 2 h to give two adducts (12)[5] and (13)[5] in 58 and 29% yields, respectively, which were however proved to be the undesirable C/D-trans isomers from their nmr spectra, suggesting that isomerization occurred at the 8a-position under basic reaction condition. On the other hand, the Michael reaction of the amine (11), prepared by protection of the enone (10) with ethylene glycol, proceeded slowly (24 h) to afford three adducts (14),[5] (15),[5] and (16)[5] in 20, 6, and 6% yields, respectively, together with the recovered starting nitrile (11) in 42% yield. Unfortunately, attempts to improve the yield of the desired adduct (14) by either changing the concentration of the donor (NaOMe) or employing 15-crown-5 to enhance reactivity of methoxide ion were all unsuccessful. Deprotection of the ketal group in 14 with hydrochloric acid, followed by sodium borohydride reduction of the resulting ketone (17),[5] and acylation with 3,4,5-trimethoxybenzoyl chloride afforded a mixture of two esters (19)[5] and (20)[5] in 22 and 17% yields from 14, respectively. The former ester (19) was proved to be the desired depyrroloreserpine analogue which has the same stereostructure of the D ring as that of the ring E in reserpine, upon comparison with their nmr spectra.[10]



Table

Hydride	Solvent	Yield (%) (4)	(5)	(6)	(7)
$NaBH_4$	C_6H_6-MeOH	--	16	44	--
$NaBH_4$	THF-MeOH	1	46	47	--
$NaBH_4$	MeCN-MeOH	5	--	17	--
$LiBH_4$	THF-MeOH	trace	10	10	45



TMB=3,4,5-trimethoxybenzoyl

Thus, we have established a new synthetic route for reserpine type alkaloids by preparing its depyrrolo analogue (19) which is expected to show the analogous biological activities of the parent alkaloids.[11]

ACKNOWLEDGEMENTS

We are grateful to Drs. W. Nagata and M. Yoshioka (Shionogi Research Laboratory, Shionogi & Co., Ltd. Japan) for gift of diethylaluminum cyanide and the Ministry of Education, Sciences, and Cultures, Japan for a research grant. Thanks are also extended to Misses K. Yasuoka and N. Miwa for technical assistance.

REFERENCES AND NOTES

1 O. Miyata, Y. Hirata, T. Naito, and I. Ninomiya, Heterocycles, 1984, 22, 1041.

2 W. Nagata and M. Yoshioka, " Organic Reactions," Vol. 25, ed. by W. G. Dauben, John Wiley and Sons, Inc., New York, 1977, p. 255.

3 R. T. Brown, " The Chemistry of Heterocyclic Compounds," Vol. 25, (Indoles, Part 4, ed. by J. E. Saxton), ed. by A. Weissberger and E. C. Taylor, John Wiley and Sons, Inc., New York, 1983, p. 147.

4 T. Naito, Y. Tada, Y. Nishiguchi, and I. Ninomiya, J. Chem. Soc., Perkin Trans. 1, 1985, 487.

5 All new compounds reported herein gave ir, nmr, and mass spectral data consistent with the assigned structures.

6 The position of the methoxyl or nitrile group was confirmed by the fact that the products (5), (6), and (8) were converted into the known lactams[12,13] by $NaBH_4$ reduction and subsequent thermal dehydration and dehydrogenation.

7 K. Soai, A. Ookawa, and H. Hayashi, J. Chem. Soc., Chem. Commun., 1983, 668.

8 K. Utimoto, M. Obayashi, Y. Shishiyama, M. Inoue, and H. Nozaki, Tetrahedron Lett., 1980, 21, 3389.

9 C. Szántay, G. Blaskó, K. Honty, E. Baitz-Gács, J. Tamás, and L. Töke, Justus Liebigs Ann. Chem., 1983, 1292.

10 M. Lounasmaa, A. Tolvanen, and S-K. Kan, Heterocycles, 1985, 23, 371.

11 I. Tóth, L. Szabó, G. Bozsár, C. Szántay, L. Szekeres, and J. G. Papp, J. Med. Chem., 1984, 27, 1411.

12 T. Naito, K. Katsumi, Y. Tada, and I. Ninomiya, Heterocycles, 1983, 20, 775.

13 T. Naito, Y. Tada, and I. Ninomiya, Heterocycles, 1983, 20, 853.

Received, 1st April, 1987