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AN EFFICIENT AND HIGHLY REGIOSELECTIVE INTRAMOLECULAR MANNICH-TYPE REACTION: A CONSTRUCTION OF THE AEF RING SYSTEM OF ACONITINE-TYPE DITERPENE ALKALOIDS

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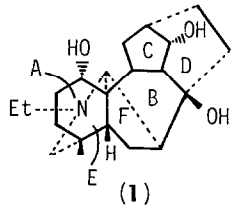
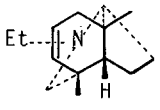
Summary: An efficient and highly regioselective intramolecular Mannich-type reaction has been developed. The utility of the methodology, combined with a stereoselective intramolecular Diels-Alder reaction, for the construction of the AEF ring system of aconitine-type alkaloids has been exemplified.

Aconitine-type diterpene alkaloids[1] are widely distributed throughout the plant world and have long been of interest due to their intriguing chemical structures and their pharmacological activities. In connection with our studies[2] directed towards total synthesis of cardiopetaline (**1**)[3], one of the aconitine-type alkaloids, we planned to develop a new and efficient methodology for constructing the AEF ring system which would be one of the crucial points for the total synthesis. We now wish to report the successful synthesis of the tricyclic enamine (**2**) as a model for the AEF ring system of the diterpene alkaloids using a stereoselective intramolecular Diels-Alder reaction and a subsequent regioselective intramolecular Mannich-type reaction.



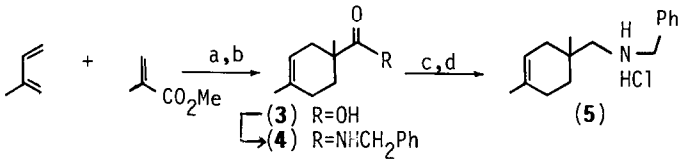
(**1**)



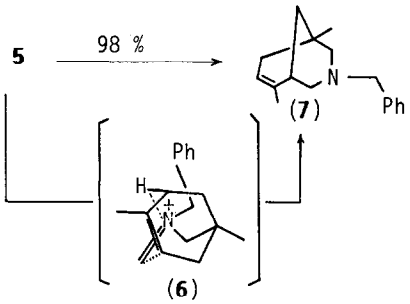
(**2**)

As a preliminary experiment, we tried to construct the E-ring, the piperidine with tertiary amino functionality, by using an intramolecular Mannich-type reaction[4]. Thus, 1,4-dimethylcyclohex-3-enecarboxylic acid (**3**)[5], prepared from the Lewis acid catalyzed Diels-Alder reaction of isoprene and methyl methacrylate followed by basic hydrolysis, was converted into the corresponding benzylamide (**4**) by a standard acid chloride method. Reduction of the amide (**4**) with lithium aluminum hydride(LAH) gave the secondary amine

which was isolated as the hydrochloride (**5**) in 70 % overall yield from methyl methacrylate. On heating a solution of **5** in acetic acid in the presence of formalin at 150°C for 10 h in a sealed tube, the reaction was cleanly completed to give the bicyclic enamine (**7**)[6] as a sole product in 98 % yield. Spectral data, especially ^{1}H and ^{13}CNMR cleanly showed the compound was regiochemically homogeneous and, furthermore, no other isomers were found in the reaction mixture. From the fact that the reaction proceeds quite cleanly and quantitatively in a complete regioselective manner, it was suggested that the conversion would involve a concerted pericyclic process, an unprecedented ene-reaction containing iminium salt[7], which occurs through a fairly stable aza-adamantane-type[8] transition state (**6**). (Scheme 1)



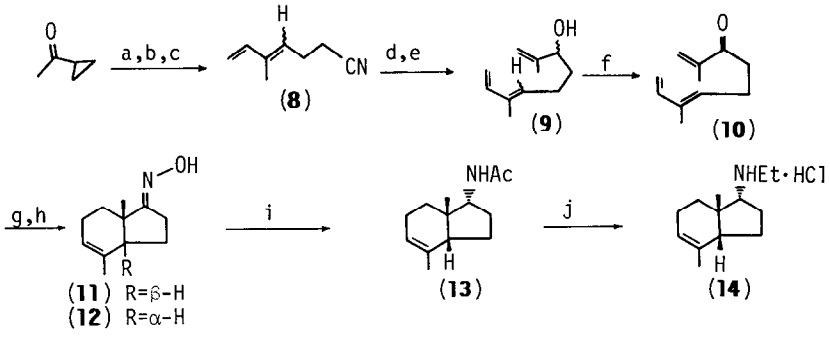
a) $AlCl_3$, PhH, 0°C→rt, 95% b) KOH, aq.EtOH, 92% c) $(COCl)_2$, CH_2Cl_2, rt then $PhCH_2NH_2$, NEt_3, CH_2Cl_2, rt, 95% d) $LiAlH_4$, THF, reflux then HCl in Et_2O, 84%



Scheme 1

Encouraged by this results, we decided to apply the methodology to the synthesis of tricyclic enamine (**2**). The trienone (**10**)[9] was prepared by modifying the literature procedure[9,10]. Thus, cyclopropyl methyl ketone was converted into 5-bromo-3-methylhexa-1,3-diene as a mixture of the olefinic isomers (E/Z=3/1 from ^{1}HNMR) via two-step sequence in 72 % yield. The cyanide (**8**)[10], derived from the bromide with KCN in the presence of 18-crown-6 in 96 % yield, was reduced with diisobutylaluminum hydride to the corresponding aldehyde, which was then treated with isopropenylmagnesium bromide followed by oxidation with activated manganese oxide to give **10** as a mixture of E and Z isomers in 46 % yield from **8**. The thermolysis of a solution of **10** in o-dichlorobenzene at 180°C for 12 h afforded the crude cycloadducts which, without isolation, was treated with hydroxylamine hydrochloride in the presence of pyridine at 100°C to provide a separable mixture of the trans-(**12**) and the cis-fused oxime (**11**) in a ratio of 2.5:1 in 41 % yield. Sequential reduction of **11** with LAH and treatment of the resulting primary amine with acetic anhydride[11] gave the acetamide (**13**) which was then reduced with LAH to

give the secondary amine hydrochloride (**14**) in 54 % yield after treating with hydrogen chloride in ether. (Scheme 2)

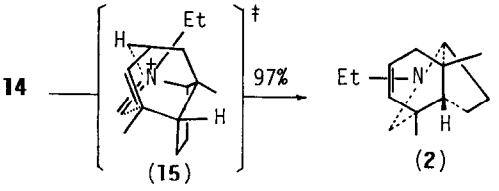


a) MgBr, THF, Et_2O, 76% b) 48%HBr, 0°C, 10min., 95% c) KCN, DMF, 18-crown-6, 96% d) DIBAH, ^{n}hexane, -78°C then SiO_2 e) MgBr, THF, 48% from **8** f) MnO_2, ^{n}hexane, rt, 96% g) o-dichlorobenzene, 180°C, 12h h) $H_2NOH\cdot HCl$, pyridine, 100°C, 41% from **10** i) $LiAlH_4$, Et_2O, reflux then Ac_2O, 80% j) $LiAlH_4$, THF, reflux then HCl in Et_2O, 68%.

Scheme 2

Having the key intermediate (**14**) in hand, the successful completion of our synthetic strategy now depended upon a crucial ring closure by the Mannich-type reaction. Treatment of **14** with the same conditions as in **5**, provided the expected tricycle (**2**), probably via the conformation (**15**) in the transition state, in a complete regioselective manner in 97 % yield as its hydrochloride. The structure of **2**[12] thus prepared was confirmed by ^{13}CNMR, 400 MHz ^{1}HNMR and its decoupling experiment.

This methodology thus developed should provide a basis for the total synthesis of cardiopetaline (**1**).



Scheme 3

Acknowledgement. The authors wish to thank Dr. N. Shoji of Tokushima Bunri University and Dr. Y. Hirai of Toyama Medical and Pharmaceutical University for recording 400 MHz ^{1}HNMR and ^{13}CNMR spectra.

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6) Colorless oil; ^{13}CNMR($CDCl_3$, 50 MHz) δ 22.126(q), 28.761(q), 29.720(t), 37.038(d), 38.409(s), 39,498(t), 54.336(t), 62.333(t), 67.720(t), 122.836(d), 126.510(d), 127.971(d), 128.499(d), 135.169(s), 139.379(s); MS(m/z) 241(M^+).

7) (a) The [3,3]-sigmatropic rearrangement involving iminium salt has been reported, L. E. Overman and M. Kakimoto, J. Am. Chem. Soc., **101**, 1310 (1979), and the references cited therein. (b) The intramolecular iminium ion variation of the Diels-Alder reaction, see S. D. Larsen and P. A. Grieco, J. Am. Chem. Soc., **107**, 1768 (1985).

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12) For the hydrochloride; colorless prisms(MeOH-Et_2O), mp 184°C(decomp.); ^{1}HNMR($CDCl_3$, 400 MHz) δ1.04(3H, s) 1.06(3H, s), 1.46(3H, t, J=7.3 Hz), 1.98-2.09(2H, m), 2.14(1H, d, J=20.0 Hz), 2.30(1H, dd, J=12.7 and 8.8 Hz), 2.93(1H, d, J=12.7 Hz), 3.10(1H, m), 3.23(1H, m), 3.42(1H, d, J=4.9 Hz), 3.46(1H, d, J=20.0 Hz), 5.53(1H, dt, J=9.8 and 2.0 Hz), 6.09(1H, dt, J=9.8 and 3.4 Hz); ^{13}CNMR($CDCl_3$, 25 MHz) δ10.802(q), 20.313(t), 22.309(t), 23.953(q), 26.772(q), 33.875(t), 34.463(s), 42.330(s), 46.029(d), 49.962(t), 55.540(t), 68.221(d), 130.276(d), 132.390(d); MS(m/z) 205(M^+).

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