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STEREOCONTROLLED SYNTHESIS OF TRICYCLO[6.2.1.$0^{4,9}$]UNDECANE RING SYSTEM OF ACONITIUM ALKALOIDS

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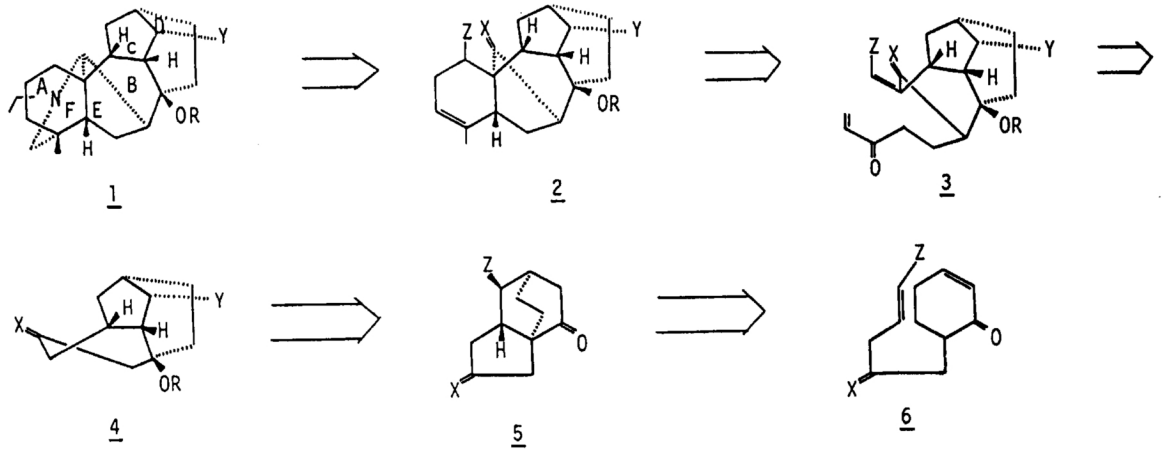
Intramolecular double Michael reaction of the α,β-unsaturated enone ester gave the tricyclo[5.2.2.$0^{1,5}$]undecane derivative, which was stereoselectively converted into the tricyclo[6.2.1.$0^{4,9}$]undecane derivative.

Recently we have developed a novel method, intramolecular double Michael (IDM) reaction[2] and demonstrated its utility for the synthesis of natural products.[1,3] In further continuation of this study, we planned a synthesis of aconitium alkaloids as shown in Scheme 1. Namely rearrangement of the tricyclo[5.2.2.$0^{1,5}$]undecane (5), obtained *via* the IDM reaction of 6, would give the tricyclo[6.2.1.$0^{4,9}$]-undecane (4), which could be transformed into the enone (3). The second IDM reaction of 3 would afford the aconane derivative (2), convertible into the lycoctonine skeleton (1). Here we wish to report a synthesis of 23 as a model experiment for the construction of the tricyclic compound (4), in which the rearrangement was performed in highly stereo- and site-selective manner.[4]

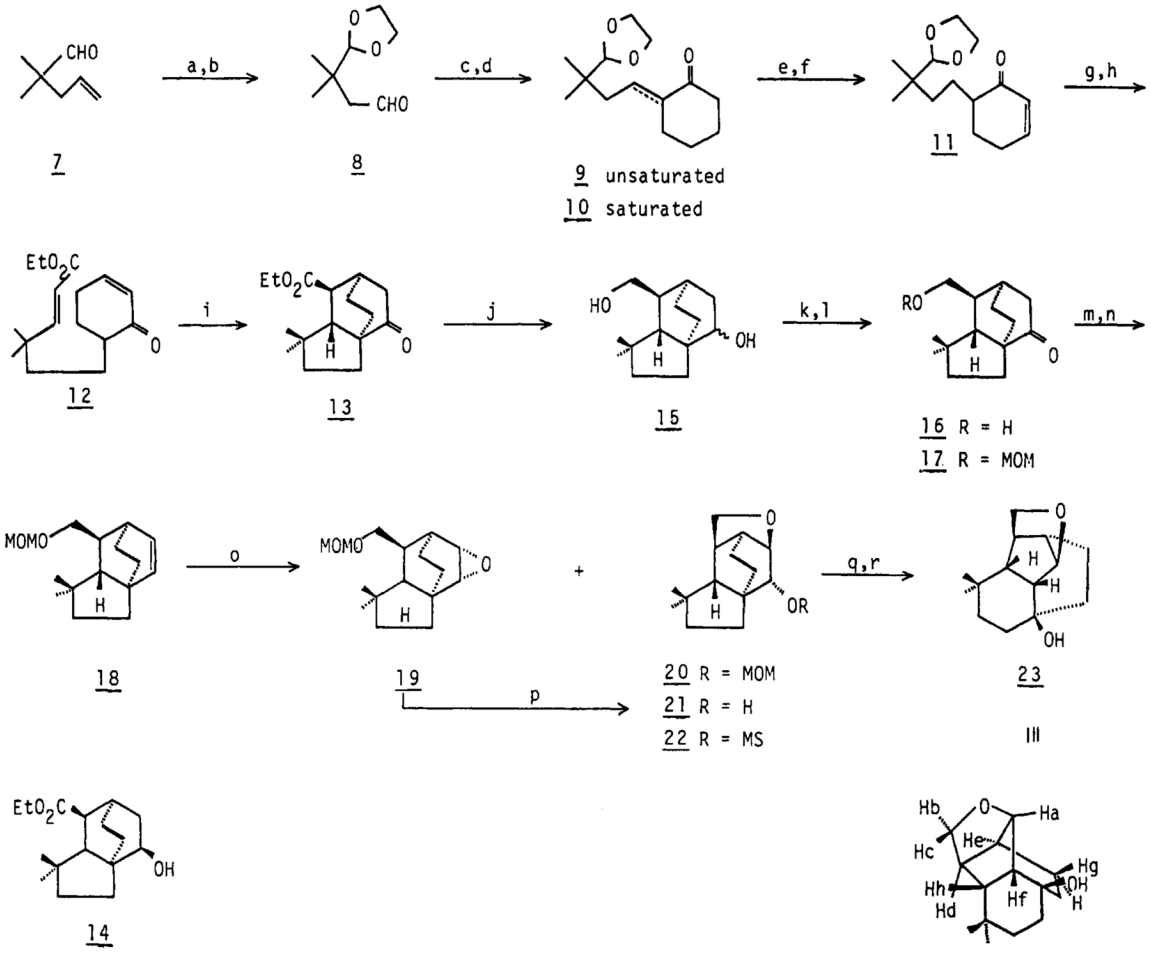


Scheme 1.

Protection(95% yield) of 2,2-dimethyl-4-pentenal (7),[5] followed by oxidation of the double bond with osmium tetroxide and sodium metaperiodate[6] afforded the aldehyde (8), which was condensed with cyclohexanone in a hot aqueous potassium hydroxide solution to give the α,β-unsaturated ketone (9)[7] in 67% yield from 8. After catalytic hydrogenation(81% yield) of 9, the ketone (10),[7] was silylated under the kinetically controlled conditions and then oxidized with palladium(II) acetate and 1,4-benzoquinone[8] to the enone (11)[7] in 90% yield. Deprotection of 11 with dilute perchloric acid in tetrahydrofuran followed by Emmons reaction formed the α,β-unsaturated enone ester (12)[7] in 76% yield from 11. The IDM reaction of 12 was conducted with lithium hexamethyldisilazide in hexane-ether (5 : 1 v/v) at -78 °C for 2 h and at room temperature for 0.5 h to produce the tricyclic compound (13)[7] in 64% yield as a single product. The stereochemistry of 13 was determined on the basis of the consideration of the reaction mechanism[2] and the spectral evidences; particularly due to the chemical shifts of two geminal methyl groups of 13 and the corresponding alcohol (14)[7] which was gained by reduction of 13 with L-selectride.

Now our attention was focused on the stereocontrolled rearrangement accompanied with an introduction of two oxygen functional groups. Therefore transformation of the ethoxycarbonyl group to a more hindered group as the methoxymethyloxymethyl group and a rearrangement *via* an epoxide intermediate were examined. Thus 13 was reduced with diisobutylaluminum hydride to provide in 99% yield the corresponding epimeric alcohols (15),[7] whose secondary hydroxyl group was selectively oxidized with sodium bromate in the presence of ceric ammonium nitrate[9] to the keton(16) in 80% yield. The primary alcohol (16)[7] was blocked using methoxymethyl chloride and diisopropylethylamine to give the ether (17)[7] in 83% yield. Conversion of 17 into the olefin (18)[7] was carried out in 53% yield according to the Shapiro's procedure.[10] Reaction of 18 with m-chloroperbenzoic acid afforded two products. The major product obtained in 65% yield was shown to be the desired epoxide (19),[7] but the more polar compound, gained in 4% yield, appeared to have the structure 20[7,11] on the basis of ^{1}H-NMR spectrum. Interestingly, treatment of the epoxide (19) with 10% perchloric acid in tetrahydrofuran produced the tetracyclic alcohol (21),[7] mp 93 -94 °C, in 71% yield. Acidic treatment of the above 20 also yielded 21. Furthermore reaction of 19 with boron trifluoride etherate in anhydrous dichloromethane formed 20[11] and 21 in 33% and 36% yields. It was considered that the tetracyclic alcohol (21) possessed ideal characteristics for the rearrangement; the correct stereochemistry of the hydroxyl group and the limitation of rearranged products due to the existence of the tetrahydrofuran ring. Mesylation of 21 (66% yield), followed by solvolysis, which was conducted by heating the mesylate (22)[7] for 15 h in a mixture of acetone and water (2 : 1 v/v), furnished the required product (23)[7] in 65% yield. The structure of 23 was determined by spectroscopic methods including INEPT ^{13}C-NMR and 400 MHz two-dimentional (2D) correlated NMR (H,H-COSY) techniques.

Highly stereocontrolled construction of the partial structure of aconitium alkaloids was thus achieved and an application of this methodology for the synthesis of the natural products is in progress.



a) HO~OH, p-TsOH b) OsO_4, $NaIO_4$ c) cyclohexanone, KOH d) H_2, Pd-C
e) LDA; TMSCl, Et_3N f) $Pd(OAc)_2$, quinone g) dil. $HClO_4$ h) $(EtO)_2POCH_2CO_2Et$, NaH
i) $LiN(TMS)_2$ j) DIBAL k) $NaBrO_3$, CAN l) MOMCl, $^iPr_2NEt$ m) $TsNHNH_2$, $BF_3 \cdot Et_2O$
n) ^{n}BuLi, TMEDA o) mCPBA p) dil. $HClO_4$ p) MsCl, Et_3N r) Δ, H_2O

Scheme 2.

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7) New compounds have been characterized by elemental analyses and/or high resolution mass spectra. Significant spectral data are recorded below: 13 : IR νmax ($CHCl_3$) 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 1.00 and 1.11 (each 3H, each s, 2 Me); MS m/e 264 (M^+). 14 : IR ν max ($CHCl_3$) 3580 (OH), 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 1.02 (6H, s, 2 Me), 3.65 (1H, m, >CHOH); MS m/e 266 (M^+). 20 : ^{1}H-NMR ($CDCl_3$) 1.03 and 1.08 (each 3H, each s, 2 x Me), 3.11 (1H, s, >CHOMOM), 3.34 (1H, d, J = 6 Hz, >CHO-), 3.35 (3H, s, OMe), 3.67 (1H, dd, J = 6 and 2 Hz, 1/2-CH_2O-), 3.77 (1H, d, J = 6 Hz, 1/2-CH_2O-), 4.59 and 4.74 (each 1H, each d, each J = 6 Hz, OCH_2O); MS m/e 266 (M^+). 21 : IR νmax ($CHCl_3$) 3600 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$) 1.03 and 1.09 (each 3H, each s, 2 x Me), 3.19 (1H, s, >CHOH), 3.33 (1H, d, J = 6 Hz, >CHO-), 3.63 (1H, d, J = 2 Hz, 1/2-CH_2O-), 3.69 (1H, dd, J = 2 and 1 Hz, 1/2-CH_2O-); MS m/e 222 (M^+). (23) IR νmax ($CHCl_3$) 3600 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$) 1.03 and 1.10 (each 3H, each s, 2 Me), 1.78 (1H, d, J = 8.3 Hz, H_h), 1.90 - 2.00 (1H, m, H_g), 2.20 (1H, d, J = 8.3 Hz, H_f), 2.21 - 2.25 (1H, m, H_e), 2.28 (1H, br s, H_d), 3.41 (1H, d, J = 6.3 Hz, H_c), 3.66 (1H, dd, J = 6.3 and 1.4 Hz, H_b), 4.44 (1H, br s, H_a); ^{13}C-NMR ($CDCl_3$) 22.04 (t), 29.41 (s), 30.34 (q), 33.33 (q), 34.56 (t), 35.43 (t), 37.86 (t), 41.02 (d), 44.50 (d), 51.49 (d), 52.98 (d), 73.55 (s), 77.99 (t), 78.14 (d); MS m/e 222 (M^+).

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11) It is considered that the migration of MOM group is due to the formation of $MeO^{\oplus}=CH_2$ in anhydrous conditions.

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