Communications to the Editor

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THE PARTIAL SYNTHESIS OF ISODELPHININE

Hiromitsu Takayama,[a] Shin-ichiro Sakai,*,[a] Keiichi Yamaguchi,[a] and Toshihiko Okamoto[b]

Faculty of Pharmaceutical Sciences, Chiba University,[a] 1-33, Yayoi-cho, Chiba, 260, Japan and Faculty of Pharmaceutical Sciences, Tokyo University,[b] Hongo, Tokyo, 113, Japan

Formal total synthesis of isodelphinine (1) was achieved. Isodelphonine (3), an alkamine of (1), was synthesized from chasmanine (2), the key intermediates being olefines (8), (13), 15-β-alcohols (10), (14) and 15-ketones (11), (15). And then isodelphonine (3) was converted to isodelphinine (1) by the selective O-acylations.

KEYWORDS—— diterpene alkaloids; chemical conversion; chasmanine; isodelphinine; isodelphonine; 15-epi-isodelphonine

In the course of our synthetic studies of highly oxygenated Aconitum diterpene alkaloids, we made a plan of synthesis of isodelphinine (1) from chasmanine (2),[1] a major alkaloidal component of *Aconitum yesoense* Nakai synthesized by Wiesner *et al.*[2] Isodelphinine (1) is a component of *Aconitum Miyabei* Nakai,[3] and its structure was elucidated by Pelletier using ^{13}C nuclear magnetic resonance (NMR) analysis.[4] In order to synthesize isodelphinine (1), the conversion of the N-Et group in chasmanine (2) to the N-Me group, the introduction of an α-hydroxy group to C-15, and selective O-acylations of the C-8 and C-14 hydroxy groups are required.

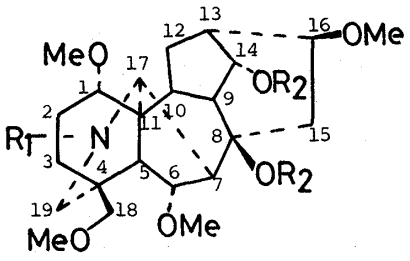
Initially, conversion of chasmanine (2) via the epoxy derivative (9) to isodelphonine (3), an alkamine of isodelphinine (1), was attempted. Oxidation of diacetylchasmanine (5), obtainable from (2), with $KMnO_4$ in aq.acetone[5] gave des-N-ethyl derivative (6) in 89% yield, which upon formylation with $HCOOH$-Ac_2O gave the N-formyl derivative (7) [mp 180-182°C, infrared(IR) spectrum ν_{max}^{KBr} cm^{-1}: 1655, ^1H-NMR[6] δ:8.02(1H,s,N-CHO)] in 72% yield. Pyrolysis of compound (7) under reduced pressure (1.5mmHg/190-200°C,30min) gave the C_8-C_{15} olefinic compound (8) [amorphous, ^1H-NMR δ:5.70 (1H,d,J=6Hz,C-15-H)] in 79% yield, then (8) was converted into the epoxy derivative (9) in 98% yield by exposure to m-CPBA in CH_2Cl_2 at room temperature. The epoxide (9) (mp 197-198°C) was considered to be the β-epimer on the basis of stereomodel and ^1H-NMR spectrum[7] analyses [δ:4.49(1H,t,C_{14}-β-H), 4.44 (1H,d,C_6-β-H)]. Ring opening of the epoxide (9) using formic acid gave rise to the cis diol (10) in 60% yield, rather than the desired trans diol. The configuration of C-15 in compound (10) was confirmed by the X-ray crystallographic study[8] of compound (4) (15-epi-isodelphonine, mp 135-137°C, $[\alpha]_D^{22}$+20.0°) obtainable from (10) by $LiAlH_4$ reduction. Inversion of the C-15 configuration was carried out as follows. The alcohol (10) was oxidized by Swern's method[9] [DMSO-$(CF_3CO)_2O$/CH_2Cl_2

then Et_3N], and the resultant ketone (11) (amorphous, mass(MS) spectrum m/z: 507 (M^+), IR $\nu_{max}^{CHCl_3}$ cm^{-1}:1720) was reduced with $LiAlH_4$ in THF. After purification by flash column chromatography,[10] 8,15-trans diol (3) (isodelphonine) and 8,15-cis diol (4) were obtained in 41% and 35% yield, respectively from (11). The structure of isodelphonine (3) (amorphous, $[\alpha]_D^{19}$+13.0°, high resolution MS Calcd for $C_{24}H_{39}NO_7$:453.2726, Found:453.2710) was deduced by analyses of its 270MHz ^{1}H-NMR [δ:4.37(1H,d,J=6.4Hz,C_{15}-β-H), 4.17(1H,d,J=6.9Hz,C_6-β-H), 4.09(1H,t,J=4.6Hz,C_{14}-β-H), 3.45,3.36,3.30,3.25(each 3H,s,OMex4), 2.35(3H,s,N-Me)] and ^{13}C-NMR spectra.[11]

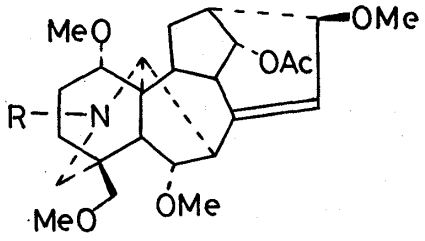
A more efficient synthetic route to isodelphonine (3) was also studied. Des-N-ethyl-diacetylchasmanine (6) was methylated with CH_2O-$NaBH_3CN$ in aq.CH_3CN (pH 4) to give the N-methyl derivative (12)[^{1}H-NMR δ:2.29(3H,s,N-Me)] in 80% yield. Compound (12) was converted in 94% yield by pyrolysis under reduced pressure (2mmHg/195-205°C,12-15min.) into the C_8-C_{15} olefinic compound (13) [ultraviolet spectrum $\lambda_{max}^{ethanol}$ nm:241, ^{1}H-NMR δ:5.45(1H,d,J=6Hz,C-15-H)]. Compound (13) was treated successively with OsO_4 in pyridine-THF and with $NaHSO_3$-H_2O to give the cis diol (14) (MS m/z:495(M^+)) in 70% yield after purification by Al_2O_3 column chromatography. Inversion of the C-15 configuration of the cis diol was accomplished by carrying out oxidation according to Swern's method and reduction of the resultant ketone (15) (amorphous, MS m/z:493(M^+)) with $LiAl(OMe)_3H$ in dry THF (-72°C to room temperature), giving rise to the desired trans diol (3) (isodelphonine) in 79% yield.

The selective O-acylations of isodelphonine (3) into natural isodelphinine (1) was carried out as follows. Isodelphonine (3) was treated with 1.3 equivalent benzoylchloride in dry pyridine-CH_2Cl_2(1:1) at -70°C to 0°C to give 14-monobenzoate (16) in 98% yield. The ^{1}H-NMR spectrum showed a triplet at δ5.07 ppm which was typical of a β proton on C-14 having α-benzoyloxy group. On acetylation with AcCl at room temperature for two weeks, (16) gave diacetate (17) [colorless prisms, mp 184-186°C, $C_{35}H_{47}NO_{10}$, ^{1}H-NMR δ:5.93(1H,d,J=6Hz,C_{15}-β-H), 2.11 and 1.33 (each 3H, s,-OCOC$\underline{H}_3$x2)]. On the other hand, the C-15 hydroxy group in compound (16) was protected with βββ-trichloroethoxycarbonyl group to give (18) [^{1}H-NMR δ:5.88(1H,d, J=6Hz,C_{15}-β-H), 4.95 and 4.64(each 1H,d,J=12Hz,-OCOOC$\underline{H}_2$$CCl_3$)] in 88% yield, and then the remaining tertiary hydroxy group at C-8 was acetylated with AcCl at room temperature for 12 days to give (19) [IR $\nu_{max}^{CHCl_3}$ cm^{-1}:1770,1720. ^{1}H-NMR δ:1.37(3H,s, OCOC$\underline{H}_3$)] in 96% yield. Treatment of (19) with Zn in AcOH afforded isodelphinine (1) in 88% yield. (1):colorless solid, mp 158-160°C,$[\alpha]_D^{29}$+17.4°, $C_{33}H_{45}NO_9$, IR ν_{max}^{KBr} cm^{-1}:3490,1720,1705. 270MHz ^{1}H-NMR δ: aromatic H(5H), 5.05(1H,t,J=4.3Hz,C_{14}-β-H), 4.41(1H,d,J=2.8Hz,-O$\underline{H}$), 4.35(1H,dd,J_1=5.7Hz,J_2=2.6Hz,C_{15}-β-H), 4.04(1H,d, J=6.8Hz,C_6-β-H), 3.52(3H,s),3.29(6H,s),3.19(3H,s)-OMex4, 2.35(3H,s,N-Me), 1.44(3H, s,-OCOC$\underline{H}_3$).

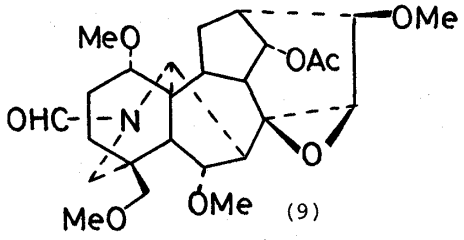
Since we could not obtain an authentic sample of isodelphinine (1), we investigated the basic fraction I[12] of *Aconitum Miyabei* Nakai in order to make direct comparison of synthetic isodelphinine (1) with the natural compound. 14-Benzoylisodelphonine (16) (8-O-deacetylisodelphinine) was separated from this fraction[13] by the combination of SiO_2 column chromatography and Al_2O_3 preparative TLC, but (1) was not detected on TLC. Natural (16), which was identical with (16) synthesized from chasmanine (2), was acylated and converted into isodelphinine (1) according to the above mentioned method. Isodelphinine (1) (mp 158.5-160°C,



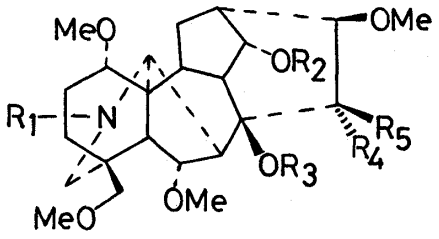
R_1=Et, R_2=H, chasmanine (2)
R_1=Et, R_2=Ac, (5)
R_1=H, R_2=Ac, (6)
R_1=CHO, R_2=Ac, (7)
R_1=Me, R_2=Ac, (12)



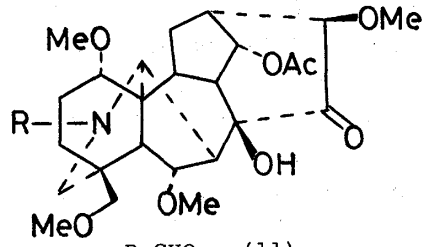
R=CHO, (8)
R=Me, (13)



(9)



R_1=Me, R_2=Bz, R_3=Ac, R_4=OH, R_5=H, isodelphinine (1)
R_1=Me, R_2=R_3=R_5=H, R_4=OH, isodelphonine (3)
R_1=Me, R_2=R_3=R_4=H, R_5=OH, (4)
R_1=CHO, R_2=Ac, R_3=R_4=H, R_5=OH, (10)
R_1=Me, R_2=Ac, R_3=R_4=H, R_5=OH, (14)
R_1=Me, R_2=Bz, R_3=R_5=H, R_4=OH, (16)
R_1=Me, R_2=Bz, R_3=Ac, R_4=OAc, R_5=H, (17)
R_1=Me, R_2=Bz, R_3=R_5=H, R_4=$OCOOCH_2CCl_3$, (18)
R_1=Me, R_2=Bz, R_3=Ac, R_4=$OCOOCH_2CCl_3$, R_5=H, (19)



R=CHO, (11)
R=Me, (15)

$[\alpha]_D^{26}$+19.5°) derived from *Aconitum Miyabei* Nakai was indistinguishable from synthetic (1) by TLC in several solvent systems, IR, ^{1}H and ^{13}C-NMR, MS spectrometry, and mixture melting point test. Thus, the formal total synthesis of isodelphinine (1) and the procedure for the introduction of the C-15-α-hydroxy group[14] were established.

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6) Throughout the present work, NMR spectra were measured in $CDCl_3$.
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8) Orthorhombic systems, space group $P2_12_12_1$, R=0.073 : Details will be described in a full paper.
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11) ^{13}C-NMR of isodelphonine (3) δ^{CDCl_3} : 85.5(C_1), 26.3(C_2), 34.6(C_3), 39.4(C_4), 48.1(C_5), 83.6(C_6), 45.9(C_7), 78.4(C_8), 49.8(C_9), 41.2(C_{10}), 50.3(C_{11}), 30.4 (C_{12}), 46.9(C_{13}), 75.9(C_{14}), 80.2(C_{15}), 90.7(C_{16}), 62.8(C_{17}), 80.6(C_{18}), 56.6 (C_{19}), 42.8(N-Me), 56.4(OMe 1'), 57.4(OMe 6'), 57.8(OMe 16'), 59.2(OMe 18').
12) Prof. N. Katsui, Hokkaido University, kindly sent us basic fraction I, from which isodelphinine (1) was isolated as described in ref. 3).
13) This is a long standing sample of over 20 years. The smooth hydrolysis of the C-8 acetyl ester group in aconite alkaloids is well known.
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