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Chiral Synthesis of Novel α-Yohimbane Alkaloids (-)-Nitraraine and (-)-Dihydronitraraine

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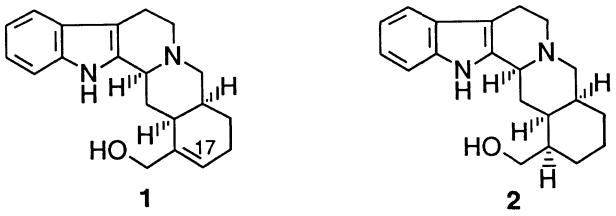
Chiral synthesis of α-yohimbane alkaloids (-)-nitraraine and (-)-dihydronitraraine has been achieved employing the Claisen-Cope rearrangement as the key step. Comparison of the physical and spectral data, however, did not establish identity between the synthetic and natural substances, respectively.

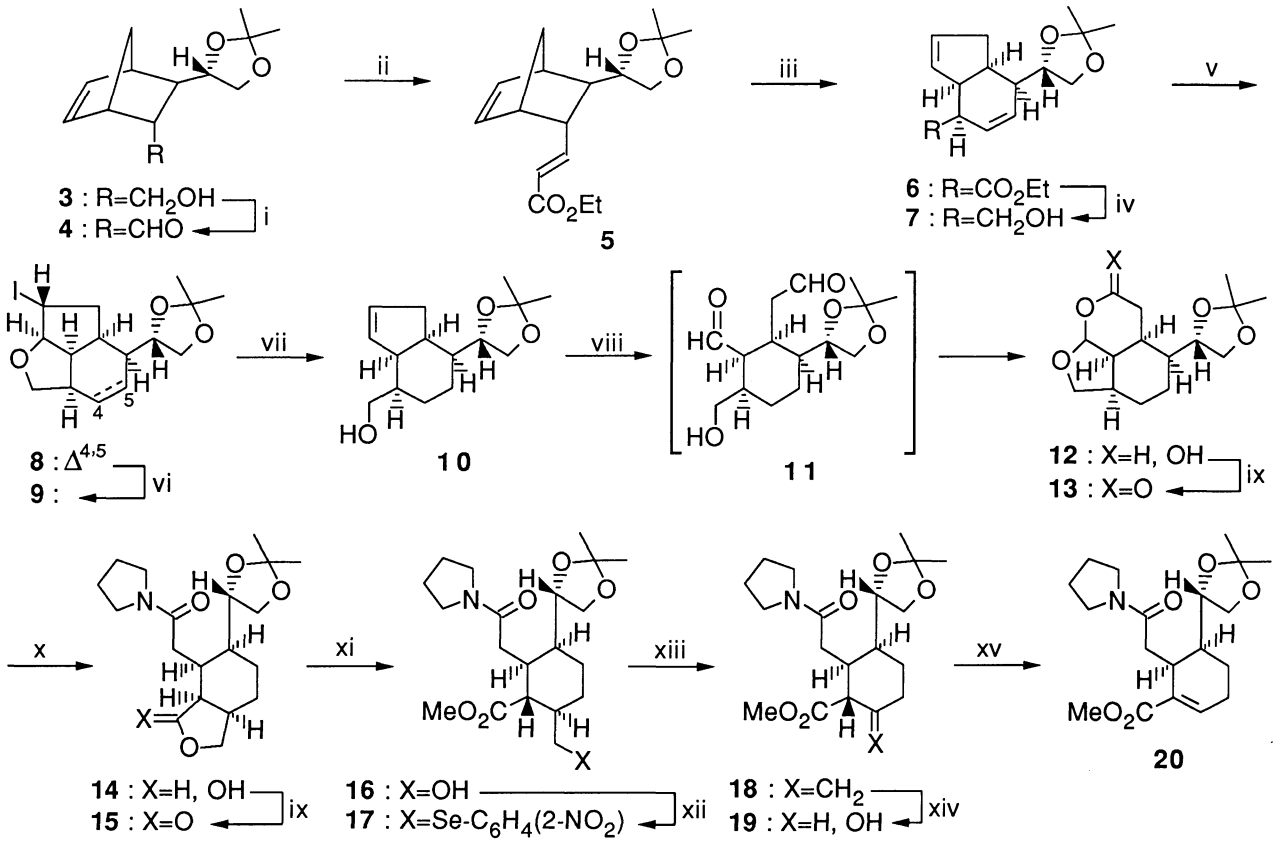
Two novel α-yohimbane alkaloids nitraraine[1] (**1**) and dihydronitraraine[2] (**2**) were isolated from Nitraria schoberi in 1985. They are particularly interesting because they are not only new members of a rare series of the yohimbane alkaloids,[3] but also possess no optical rotations.



1 **2**

Fig. 1.

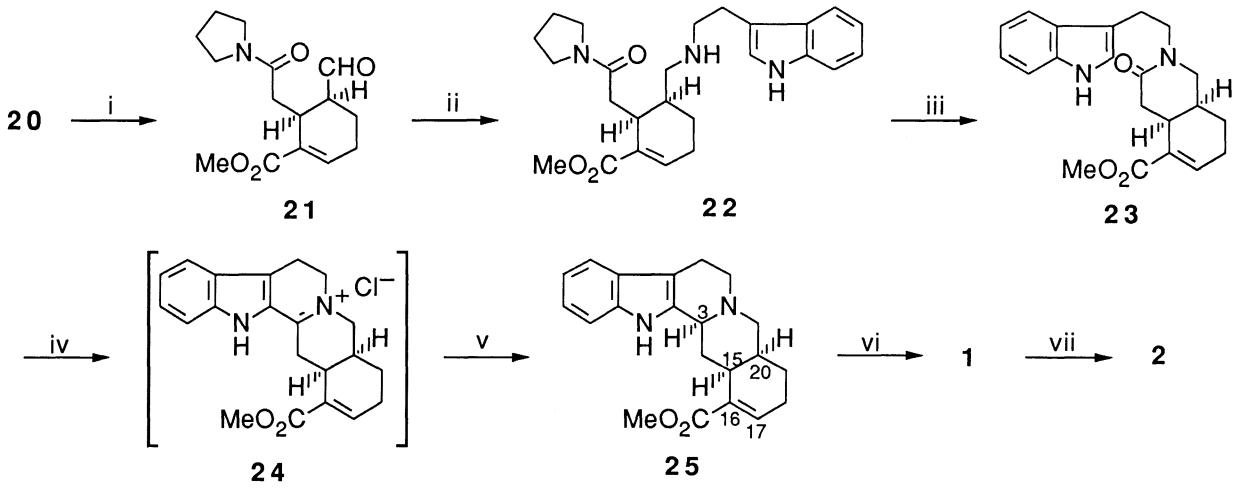
In this communication we describe the chiral synthesis of (-)-(**1**) and (-)-(**2**) starting from the known optically active alcohol[4] (**3**) employing the Claisen-Cope rearrangement as the key step. Modified Swern oxidation[5] of **3**, obtained in 68% overall yield from ethyl (S)-4,5-O-isopropylidene-2-pentenoate,[6] followed by Wittig reaction of the resulting aldehyde **4** afforded the unsaturated ester[7] **5** in 73% overall yield. Refluxing **5** in o-dichlorobenzene (10%) allowed to undergo smooth Claisen-Cope rearrangement[8] within 2 h to give the expected hydrindane derivative **6** in 78% yield.[9] After reduction of **6** with lithium aluminum hydride the resulting alcohol **7** (86%) was exposed to iodine to discriminate two double bonds. The resulting single iodo-ether **8** (84%) was hydrogenated over Adams catalyst to give the cyclohexane **9** which, on treatment with zinc powder, regenerated the cyclopentene ring to give **10** in 92% overall yield. Oxidative cleavage[10] of **10** yielded the dialdehyde **11** which isolable as the cyclic hemiacetal **12** (95%) was oxidized with silver carbonate on Celite[11] to afford δ-lactone **13** in 86% yield.



Scheme 1.

i, CCl_3OCOCl, DMSO, Et_3N, CH_2Cl_2, -70 - -60 °C; ii, $Ph_3P=CHCO_2Et$ (3 equiv.), CH_2Cl_2, r.t., 2 days; iii, o-dichlorobenzene, reflux, 2 h; iv, LAH, THF, 0 °C; v, I_2 (2 equiv.), THF-sat. aq. $NaHCO_3$ (4:1), 0 °C; vi, H_2, PtO_2, AcOEt, r.t.; vii, Zn (5 equiv.), MeOH, r.t.; viii, cat. OsO_4, 1-methylmorphorine-1-oxide, THF, 0 °C - r.t., then $NaIO_4$, H_2O, 0 °C; ix, Ag_2CO_3 on Celite, benzene, reflux; x, $Me_2AlN(CH_2)_4$, benzene, 0 °C - r.t., 2 h; xi, K_2CO_3 (0.2 equiv.), MeOH, 50 °C, 9 h; xii, $2\text{-}NO_2C_6H_4SeCN$ (1.5 equiv.), $^nBu_3P$ (1.5 equiv.), THF, r.t.; xiii, 30% H_2O_2 (10 equiv.), THF, 0 °C - r.t.; xiv, O_3, MeOH, -68 °C, then $NaBH_4$ (10 equiv.), -68 - 0 °C; xv, I_2 (3 equiv.), PPh_3 (3 equiv.), imidazole (3 equiv.), DBU (10 equiv.), $Et_2O\text{-}CH_3CN$ (3:1), 50 °C, 2 h.

Treatment of **13** with dimethylaluminum pyrrolidide[12] followed by oxidation[11] of the resulting amido-hemiacetal **14** (74%) furnished the γ-lactone **15** (81%) as a 2:1 mixture of two epimers. When the mixture was stirred in warm methanol (50 °C) containing potassium carbonate spontaneous methanolysis and epimerization occurred to give the seco-ester **16** as a single epimer. The observed facile methanolysis and epimerization may be due to steric congestion embraced in the contiguously cis-tetra-substituted cyclohexane framework. Dehydration[13] of **16** via the selenide **17** yielded the exo-olefin **18** (59% overall from **15**) which was transformed into the secondary alcohol **19** (71%, epimeric mixture) on sequential one-flask ozonolysis and reduction. Upon exposure to a mixture of iodine, triphenylphosphine, imidazole,[14] and DBU at 50 °C, **19** furnished the α,β-unsaturated ester **20** in 89% yield as a single epimer.



Scheme 2.

i, HIO_4 (1.5 equiv.), THF-5% HCl (1:1), 0 °C - r.t.; ii, tryptamine (1.0 equiv.), MeOH, 1 h, then $NaBH_4$ (1.5 equiv.), 0 °C; iii, toluene, reflux; iv, $POCl_3$ (10 equiv.), CH_3CN, 90 °C, 1 h; v, $NaBH_4$ (15 equiv.), aq. MeOH, 0 °C; vi, DIBAL (3.6 equiv.), THF, 0 °C; vii, H_2, PtO_2, AcOEt, r.t.

Removal of the acetonide group of **20** was found to be very difficult. However, treatment of **20** with periodic acid in a mixture of 5% hydrochloric acid and THF (1:1 v/v) allowed direct formation of the aldehyde **21** by spontaneous hydrolytic removal of the acetonide group and oxidative cleavage of the 1,2-glycol moiety generated. Reductive condensation of **21** with tryptamine yielded the secondary amine **22** which on reflux in toluene[15] afforded the δ-lactam **23** in 55% yield. Bischler-Napieralski cyclization of **23**, followed by reduction of the crude salt **24** with sodium borohydride afforded apo-α-yohimbine (**25**), mp 209 °C, $[\alpha]_D^{22}$ -101.30° (c 0.922, $CHCl_3$) (racemic **25**:[16] mp 195-197 °C), selectively, in 75% overall yield. It showed apparent Bohlmann bands in its ir spectrum which ruled out the formation of the alternative 3β-epimer (**25**: 3epi) since the latter isomer possesses cis-C/D conformation.[3,16] Moreover, it was also confirmed that no epimerization at C_{20} center took place during the reaction sequence since the product was not identical with an authentic apo-yohimbine (**25**: 20epi) which is only possible enantiomer showing Bohlmann bands in the apo-series of the yohimbine alkaloids.[3]

Having obtained optically active apo-α-yohimbine (**25**), we first treated it with diisobutylaluminum hydride to give nitraraine (**1**). The product obtained in 95% was then hydrogenated over Adams catalyst to give dihydronitraraine (**2**) in 75% yield. Comparison of the reported physical and spectral data of the natural substances with the synthetic materials, however, were not identical with one another, respectively. Thus, both synthetic **1** and **2** possess optical rotations, $[\alpha]_D^{23}$ -175.86° (c 0.754, $CHCl_3$) and $[\alpha]_D^{23}$ -70.28° (c 0.350, $CHCl_3$), and possess different melting points, 114-116 °C (reported[1]: 280 °C) and 154-157 °C (reported[2]: 285-287 °C), respectively. More striking discrepancy was chemical shift of 17-proton of **1**[17]: the synthetic **1** showed the signal at δ 5.60 while the natural **1** at δ 5.22.

In conclusion, the present synthesis raised considerable doubt to the proposed structures of nitraraine (**1**) and dihydronitraraine (**2**). The present synthesis, however, may have potential utility for the enantioselective construction of medicinally important α-yohimbane alkaloids represented by reserpine.

References

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9) A small amount of a readily separable ethyl (S)-6,7-O-isopropylidene-2,4-heptadienoate was also obtained as a by-product (≈14%): $[\alpha]_D^{24}$ +31.1° (c 1.268, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, J=7.3 Hz), 1.41 (s, 3H), 1.44 8s, 3H), 3.63 (dd, 1H, J=7.6 and 8.3 Hz), 4.15 (dd, J=6.1 and 8.1 Hz), 4.21 (q, 2H, J=7.3 Hz), 4.62 (q, 1H, J=6.3 Hz), 5.91 (d, 1H, J=15.1 Hz), 6.04 (dd, 1H, J=5.9 and 14.9 Hz), 6.44 (dd, 1H, J=10.5 and 15.5 Hz), 7.27 (dd, 1H, J=10.5 and 15.4 Hz).
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17) The corresponding isomeric alcohol (**1**: 20epi) obtained from apo-yohimbine (**25**: 20epi) by reduction with diisobutylaluminum hydride shows its 17-proton at δ 5.57.

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