ASYMMETRIC SYNTHESIS OF PIPERIDINE ALKALOIDS UTILIZING DIASTEREOSELECTIVE REACTION OF 1,3-OXAZOLIDINE WITH GRIGNARD REAGENTS†

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Abstract ——— A facile method of synthesizing enantiomerically pure piperidine alkaloids, (*R*)-(−)-coniine and (2*R*,6*S*)-(−)-dihydropinidine, has been explored by employing the highly diastereoselective reaction of a 1,3-oxazolidine with Grignard reagents.

In the previous paper,[1] we described the highly diastereoselective addition reaction of *N*-substituted chiral 1,3-oxazolidines. The reaction with Grignard reagents gave chiral amines having a newly created chiral center after cleavage of the 1,3-oxazolidine ring in a good yield. It occurred to us that this procedure could be extended to total synthesis of naturally occurring alkaloids. Herein, we wish to report the application of this methodology to the enantioselective synthesis of piperidine alkaloids, (−)-coniine and (−)-dihydropinidine.

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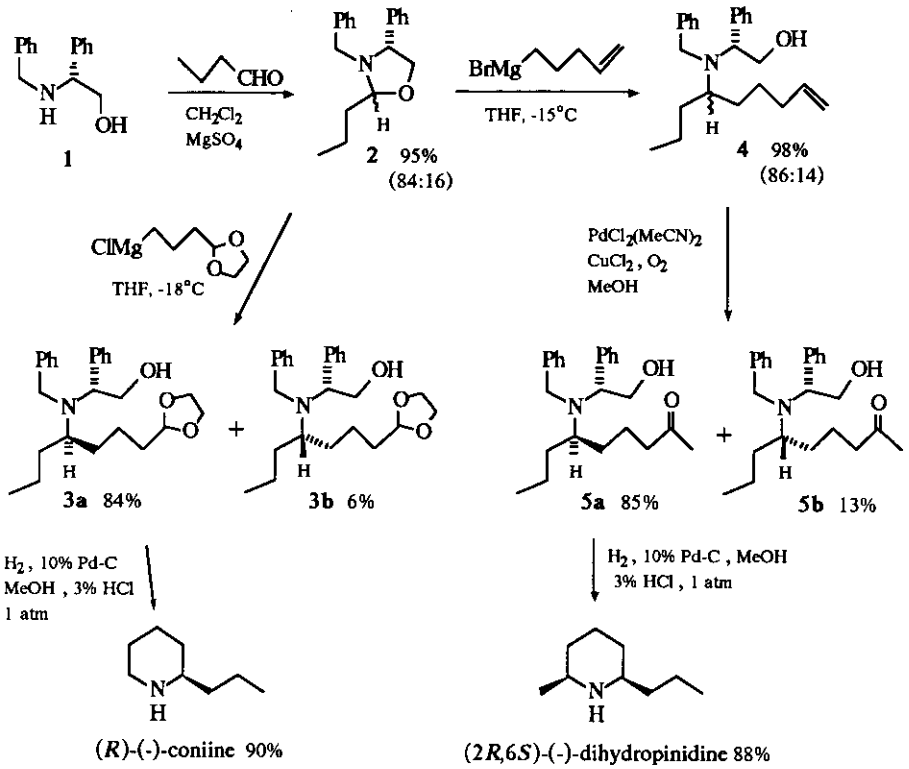
†.Dedicated to Dr. Masatomo Hamana on the occasion of his 75th birthday.



The starting 1,3-oxazolidine(2) was readily prepared by the condensation of chiral *N*-benzylphenylglycinol(1) with butyraldehyde in CH_2Cl_2 in the presence of anhydrous $MgSO_4$. The 1,3-oxazolidine(2) was formed in 95% yield; oil, bp(bulb-to-bulb) 165°C (2.7 mmHg) as a 84:16 mixture of the C-2 epimeric oxazolidines. However, it was not possible to isolate the major product due to facile cleavage of the 1,3-oxazolidine ring during column chromatography, and thus the oxazolidine was used for the subsequent reaction without further purification. The reaction of the 1,3-oxazolidine(2) with the Grignard reagent, which was prepared from 2-(3-chloropropyl)-1,3-dioxolane[2] in THF, afforded pairs of the diastereomeric adducts in a quantitative yield. The isomer ratio (93:7)

was determined by means of ^{1}H-nmr spectra before purification. After separation of the two isomers[3] by silica gel column chromatography (n-hexane:ether, 1:1), the alcohol(3a) (84% from 2) was treated under catalytic hydrogenation conditions (H_2, 10% Pd-C, MeOH, 3% HCl, 1 atm). Under these conditions, the hydrogenolysis of the *N*-substituted benzyl group and liberation of the formyl function were followed by formation of the imine, which was reduced to the desired piperidine system in 90% yield. Synthetic (*R*)-(-)-coniine $[\alpha]_D$-8.82°(c=1.01,$CHCl_3$) having the unnatural configuration exhibited spectral data identical with those of an authentic specimen.[4]

Since a short and novel synthesis of (-)-coniine has been accomplished in 72% overall yield from **1**, we next envisioned the application of this methodology to an enantioselective synthesis of (-)-dihydropinidine. Thus, treatment of the 1,3-oxazolidine(**2**) with 4-pentenylmagnesium bromide in THF at -15°C furnished the alcohol(**4**) in 98% yield as an inseparable diastereomeric mixture (86:14), which was subjected to the Wacker procedure [$PdCl_2(MeCN)_2$,$CuCl_2$,O_2,MeOH] to form a mixture of the methyl ketones(**5a-b**)[5] in a quantitative yield. The methyl ketone(5a) was isolated from this mixture by silica gel column chromatography (n-hexane:ether,3:1) in 85% yield. Subsequent ring formation of 5a by catalytic hydrogenation provided exclusively (2*R*,6*S*)-(-)-dihydropinidine having the unnatural configuration in 88% yield [HCl salts $[\alpha]_D$-12.85° (c=1.09,EtOH)].[6]

Thus, the simple and novel synthesis of piperidine alkaloids, (-)-coniine and (-)-dihydropinidine, has been achieved by using the diastereoselective reaction of a 1,3-oxazolidine with Grignard reagents as a key reaction, and this type of reaction would provide a useful route to the synthesis of other naturally occurring alkaloids.

REFERENCES AND NOTES

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2. R. B. Loftfield, *J. Am. Chem. Soc.*, 1951, **73**, 1365.
3. **3a**: $[\alpha]_D$−56.2°(c=1.44,EtOH);^{1}H−nmr δ(270 MHz,$CDCl_3$) 0.59(t,J=7.3 Hz, 3H), 0.67−1.73(m,10H), 2.46(br s,1H), 2.65(m,1H), 3.46−3.51(m,1H), 3.55(d,J=14.0 Hz,1H), 3.78−4.01(m,7H), 4.87(t,J=4.9 Hz,1H), 7.24−7.42(m,10H).
3b: $[\alpha]_D$−62.2°(c=1.05,EtOH);^{1}H−nmr δ(270 MHz,$CDCl_3$) 0.90(t,J=7.3 Hz, 3H), 0.70−1.70(m,10H), 2.50(br s,1H), 2.63−2.70(m,1H), 3.45−3.52(m, 1H), 3.55(d,J=14.0 Hz,1H), 3.72−3.97(m,7H), 4.64(t,J=4.9 Hz,1H), 7.24−7.40(m,10H).
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5. **5a**: $[\alpha]_D$−63.2°(c=1.09,EtOH);^{1}H−mnr δ(270 MHz,$CDCl_3$) 0.61(t,J=6.7 Hz, 3H), 0.79−2.00(m,8H), 2.12(s,3H), 2.35(t,J=6.7 Hz,2H), 2.46(br s,1H), 2.62(m,1H), 3.48−3.58(m,2H), 3.81−3.93(m,3H), 7.26−7.42(m,10H).
5b: $[\alpha]_D$−54.8°(c=1.09,EtOH);^{1}H−mnr δ(270 MHz,$CDCl_3$) 0.91(t,J=6.7 Hz, 3H), 0.69−1.66(m,8H), 2.01(s,3H), 2.01−2.07(m,2H), 2.46(br s,1H), 2.65(m,1H), 3.46−3.57(m,2H), 3.78−3.94(m,3H), 7.26−7.38(m,10H).
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Received, 7th August, 1991