Asymmetric Synthesis of 2-Substituted Piperidines. Synthesis of the Alkaloids (−)-Coniine and (+)-Pseudoconhydrine

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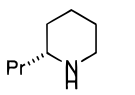
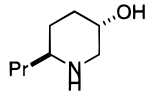
The development of methods for the asymmetric synthesis of piperidines remains an area of considerable interest due to the presence of this heterocyclic ring in a large number of biologically important compounds.[1] We now report a new approach to chiral, nonracemic piperidines, illustrated by the synthesis of the hemlock alkaloids (−)-coniine (**1**)[2] and (+)-pseudoconhydrine (**2**).[3]



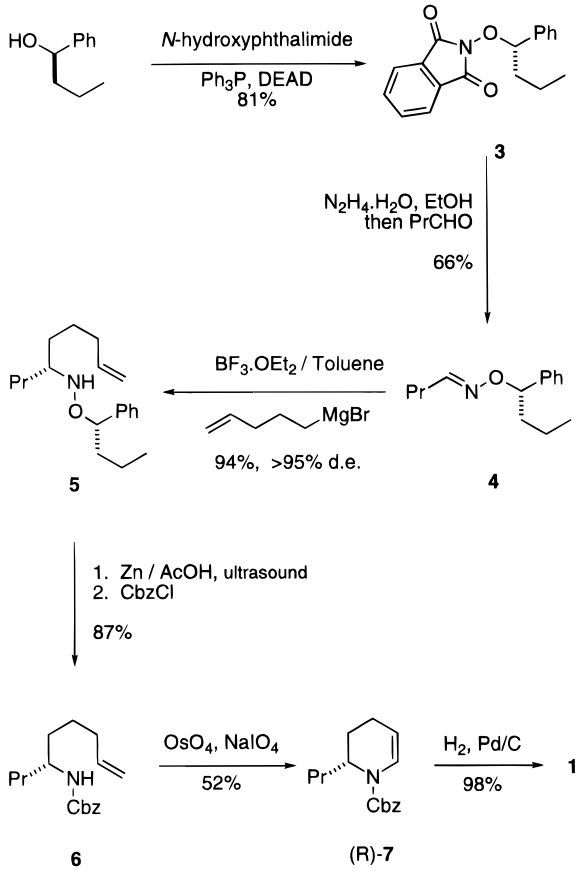
1
(R)-(-)-coniine



2
(2S,5S)-(+)-pseudoconhydrine

The method is based on the addition of pent-4-enylmagnesium bromide to a chiral oxime ether of butyraldehyde. We have previously shown that the addition of a range of organolithium and Grignard reagents to *O*-(1-phenylethyl) aldoximes in the presence of boron trifluoride etherate proceeds in good yield and with modest diastereoselectivity, typically 75%.[4] Our subsequent efforts to improve the levels of 1,4-induction in such additions has resulted in the development of (*R*)- and (*S*)-*O*-(1-phenylbutyl)hydroxylamines (ROPHy and SOPHy) as excellent reagents for the preparation of a range of oxime ethers.[5] The hydroxylamines are readily prepared from the commercial 1-phenylbutanols by Mitsunobu reaction with *N*-hydroxyphthalimide followed by cleavage of the phthaloyl unit with hydrazine hydrate. The resulting oximes undergo addition of organometallic reagents with excellent levels (>90% de) of 1,4-induction.[5]

Scheme 1



The starting material for the synthesis of (*R*)-coniine was the SOPHy oxime **4** of butyraldehyde. This was prepared from (*R*)-1-phenylbutanol *via* the alkoxyphthalimide **3**, as shown in Scheme 1, and isolated in 66% yield as the pure (*E*)-oxime after chromatographic separation from the (*Z*)-isomer. Addition of the pentenyl Grignard reagent (3 equiv) to a solution of the oxime **4** and boron trifluoride etherate (3 equiv) in toluene at −92 °C gave the hydroxylamine **5** in excellent yield. The diastereoselectivity is estimated at >95% since only one diastereomer is observed in the ^{1}H NMR spectrum; the configuration at the new chiral center is assigned as *R* on the basis of our previous model for the addition reactions,[4] and by the subsequent conversion of **5** into (*R*)-(−)-coniine as follows. The N−O bond was cleaved using the zinc/acetic acid/ultrasound method,[6] and the resulting amine was protected *in situ* to give the benzyl carbamate **6**. Oxidative cleavage of the double bond was followed by immediate cyclization and dehydration to give the enecarbamate **7** in modest yield. Finally, hydrogenation over palladium-on-charcoal gave (*R*)-(−)-coniine, $[\alpha]^{20}_D$ −8.1° (*c* = 2, $CHCl_3$) (lit.,[2b] $[\alpha]^{24}_D$ −7.9° (*c* = 0.52, $CHCl_3$)); hydrochloride salt, mp 212−213 °C, $[\alpha]^{20}_D$ −7.6° (*c* = 1, EtOH) (lit.,[2b] mp 217−218 °C, $[\alpha]^{24}_D$ −6.3° (*c* = 0.62, EtOH)). In order to confirm the enantiomeric purity, a sample of coniine was treated with 2-methoxy-2-(trifluoromethyl)phenylacetyl chloride to give the corresponding amide (57%), the NMR of which established the optical purity of the sample as 95%.

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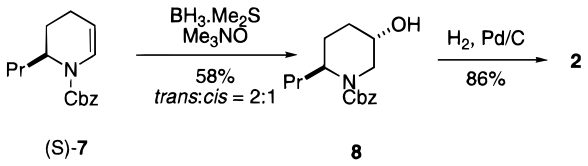
S0022-3263(96)01843-9 CCC: $14.00

Scheme 2



For the preparation of (+)-pseudoconhydrine, the enantiomeric enecarbamate (*S*)-**7**, prepared from the ROPHy oxime (*R*)-**4** in an identical manner was converted into the β-hydroxypiperidine **8** (58%) by hydroboration under similar conditions to those described by Oppolzer.[3c] The hydroxypiperidine **8** was formed as a 2:1 mixture of diastereomers with the *trans*-isomer predominating as expected on the basis of the literature precedent. Hydrogenolysis of the benzyloxycarbonyl group gave (+)-pseudoconhydrine in excellent yield, mp 102−103 °C, $[\alpha]^{20}_D$ +17.4° (*c* = 0.62, $CHCl_3$) (lit.,[3e] mp 102−104 °C, $[\alpha]^{25}_D$ +11.1° (*c* = 1, EtOH)) (Scheme 2).

Experimental Section

General. General experimental details are given in ref 4.

General Method for Alkoxyphthalimides. Diethyl azodicarboxylate (6.4 mL, 40.4 mmol) was added to a solution of *N*-hydroxyphthalimide (6 g, 37 mmol), triphenylphosphine (9.63 g, 37 mmol) and the substituted benzyl alcohol (37 mmol), in THF (200 mL) at 0 °C. The resulting solution was warmed to 50 °C and stirred for 3 days. The solution was evaporated, and ether (200 mL) and saturated Na_2CO_3 solution (200 mL) were added and the layers separated. The ether layer was washed with further portions of Na_2CO_3 solution (2 × 100 mL) which were combined and back extracted with ether (2 × 100 mL). The combined ether portions were evaporated, and the residue was purified by column chromatography on silica gel with ether−petroleum ether as eluent.

(*S*)-(−)-*N*-(1-Phenylbutoxy)phthalimide (3). Obtained from the Mitsunobu reaction of (*R*)-(+)-1-phenylbutanol with *N*-hydroxyphthalimide (81%), >96% ee, as determined by NMR in the presence of (−)-TFAE, as a crystalline solid: mp 80−81 °C; $[\alpha]_D$ −185.1° (*c* = 2, CH_2Cl_2); IR (Nujol) 2922, 1789, 1727, 698 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.45 (m, 2H), 7.29 (m, 3H), 5.34 (t, 1H, *J* = 7.0 Hz), 2.16 (m, 1H), 1.91 (m, 1H), 1.47 (m, 2H), 0.97 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.8, 137.9, 134.1, 128.8, 128.8, 128.2, 128.0, 123.2, 89.0, 36.8, 18.9, 13.8; LRMS EI *m*/*z* (%) 163 (3), 133 (52), 117 (8), 104 (9), 91 (100), 76 (11); HRMS calcd for $C_{18}H_{17}NO_3$ 295.1208, found 295.1211.

General Method for *O*-Alkyloximes. The *N*-alkoxyphthalimide (3.31 mmol) and EtOH (10 mL) were added to a round bottomed flask, and the suspension was heated until the phthalimide dissolved. Hydrazine hydrate (0.18 mL, 3.64 mmol) was added at this elevated temperature, and the solution was allowed to cool to rt. The aldehyde (0.37 g, 3.5 mmol) was added and the mixture stirred overnight. The solvent was evaporated and CCl_4 (30 mL) and $MgSO_4$ were added to the residue. The resulting suspension was filtered, the filtrate evaporated, and the residue purified by column chromatography (5% ether−petroleum ether).

(*S*)-(−)-*O*-(1-Phenylbutoxy)butyraldoxime (4). Obtained from the cleavage of (*S*)-(−)-*N*-(1-phenylbutoxy)phthalimide (**3**) and subsequent condensation of the hydroxylamine with butyraldehyde (66%) as a colorless oil: $[\alpha]_D$ −4.6° (*c* = 0.78, CH_2Cl_2); IR (film) 2959, 2934, 1454, 933 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.42 (t, 1H, *J* = 6.2 Hz), 7.31 (m, 5H), 5.02 (t, 1H, *J* = 6.8 Hz), 2.10 (dt, 2H, *J* = 7.0, 14.2 Hz), 1.90 (m, 1H), 1.70 (m, 1H), 1.40 (m, 4H), 0.91 (t, 3H, *J* = 7.3 Hz), 0.87 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 151.0, 142.9, 128.1, 127.1, 126.6, 84.4, 38.4, 31.3, 20.1, 18.8, 13.9, 13.4; LRMS EI *m*/*z* (%) 220 (MH^+, 100), 178 (74), 133 (96), 91 (94), 43 (36); HRMS calcd for $C_{14}H_{21}NO$ 219.1623, found 219.1626.

(6*R*,1′*S*)-(−)-*N*-(1-Phenylbutoxy)-6-non-1-enylamine 5. (*S*)-(−)-*O*-(1-Phenylbutoxy)butyraldoxime (**4**) (2.62 g, 12 mmol) was dissolved in dry toluene (40 mL) under nitrogen. The resulting solution was cooled to −92 °C, boron trifluoride etherate (4.43 mL, 36 mmol) was added, and the solution was stirred for 15 min. An ether solution of pent-4-enylmagnesium bromide (2 M; 18 mL, 36 mmol) was added dropwise to the cooled toluene solution over 30 min. After addition the solution was stirred for 30 min at −92 °C followed by the addition of water (1 mL). The mixture was allowed to warm to rt, and the solvent was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The layers were separated, and the aqueous layer was washed with further portions of CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine and then dried ($MgSO_4$), filtered, and evaporated. Column chromatography of the residue on silica gel (ether−petroleum ether 1:20) gave the *title compound* (94%, 95% de) as a colorless oil: $[\alpha]_D$ −61.9° (*c* = 0.62, CH_2Cl_2); IR (film) 2958, 2933, 1641, 1455, 910 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.78 (m, 1H), 5.04 (br s, 1H), 4.96 (m, 2H), 4.52 (dd, 1H, *J* = 5.6, 7.5 Hz), 2.79 (m, 1H), 2.04 (m, 2H), 1.54 (m, 12H), 0.91 (t, 3H, *J* = 7.2 Hz), 0.85 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 143.4, 138.9, 128.2, 127.2, 126.5, 114.3, 85.1, 60.0, 38.7, 34.0, 33.9, 31.7 (2 carbons), 25.0, 19.2, 14.2, 14.0; LRMS EI *m*/*z* (%) 157 (12), 133 (54), 114 (21), 91 (100); HRMS calcd for $C_{19}H_{31}NO$ 289.2405, found 289.2404.

(*R*)-(−)-*N*-(Benzyloxycarbonyl)-6-non-1-enylamine (6). Zinc dust (28.5 g, 443 mmol) was added to a solution of chiral hydroxylamine **5** (3.2 g, 11.1 mmol) in acetic acid and water (20 mL, 1:1). The mixture was placed in a sonic bath at 40 °C for 2 h. The solution was filtered, ether (50 mL) and water (50 mL) were added, the layers were separated, and the aqueous layer was washed with further portions of ether and CH_2Cl_2. The combined organic extracts were evaporated, and THF/water (100 mL, 1:1) was added to the residue. Solid Na_2CO_3 (1.27 g, 12 mmol) was added, the mixture was cooled to 0 °C, benzyl chloroformate (1.6 mL, 11.1 mmol) was then added dropwise, and the mixture was allowed to warm to rt and was stirred for 2 h. The THF was removed *in vacuo*, ether (50 mL) was added, the layers were separated, and the aqueous layer was washed with further portions of ether. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Column chromatograpy of the residue on silica gel (ether−petroleum ether 1:6) gave the *title compound* (87%) as a colorless solid: mp 71−73 °C; $[\alpha]_D$ −1.5° (*c* = 1, CH_2Cl_2); IR (Nujol) 3312, 2925, 1687, 1547, 1462 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.70 (m, 1H), 5.08 (s, 2H), 4.95 (m, 2H), 4.50 (br d, 1H, *J* = 9 Hz), 3.63 (br s, 1H), 2.04 (m, 2H), 1.42 (m, 8H), 0.90 (br t, 3H, *J* = 6.9 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.2, 138.5, 136.4, 128.4, 128.1, 128.0, 114.6, 66.4, 50.9, 37.6, 34.8, 33.5, 25.0, 18.9, 13.9; LRMS EI *m*/*z* (%) 232 (10), 162 (18), 91 (100); HRMS calcd for $C_{17}H_{25}NO_2$ 275.1885, found 275.1892.

(*R*)-(−)-1-(Benzyloxycarbonyl)-1,2,3,4-tetrahydro-2-propylpyridine (7). Osmium tetraoxide (1 mol %, 14 mg, 0.06 mmol) was added to a solution of the alkene **6** (1.65 g, 6 mmol) in THF/water (40 mL, 3:1), and the mixture was stirred at rt for 5 min. The solution changed from colorless to brown, and sodium periodate (2.35 g, 11 mmol) was then added portionwise over 20 min. The reaction mixture was stirred for a further 20 min. Water (30 mL) and ether (50 mL) were added , the ether layer was separated, and the aqueous layer was washed with further portions of ether (4 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Column chromatograpy of the residue on silica gel (CH_2Cl_2) gave the *title compound* (52%) as a colorless oil: $[\alpha]_D$ −69.2° (*c* = 0.5, CH_2Cl_2); IR (film) 2958, 2933, 1705, 1416, 1327 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) major rotamer δ 7.25 (m, 5H), 6.67 (br d, 1H, *J* = 8 Hz), 5.11 (br s, 2H), 4.76 (br m, 1H), 4.26 (br m, 1H), 2.01−1.24 (m, 8H), 0.83 (br t, 3H), minor rotamer δ 6.75 (br d, 1H, *J* = 8 Hz), 4.80 (br m, 1H), 4.18 (br m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) both rotamers δ 153.4, 136.9, 128.9, 128.4, 128.4, 128.0, 124.0, 106.3, 67.7, 50.7, 33.1, 24.4, 19.5, 18.0, 14.4; LRMS EI *m*/*z* (%) 259 (M^+, 9), 172 (20), 91 (100); HRMS calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1579.

(*R*)-(−)-2-Propylpiperidine (coniine) 1 and Coniine Hydrochloride 1·HCl. Palladium on charcoal (10%; 70 mg) was added to a solution of tetrahydropyridine **7** (1.68 g, 6.5 mmol) in MeOH (20 mL), and the mixture was hydrogenated (41 psi H_2) for 12 h. The solution was filtered through Celite and half the filtrate evaporated to give the *title compound* (0.4 g, 97%) as a colorless oil: $[\alpha]_D$ −8.1° (*c* = 2, $CHCl_3$) (lit.,[2b] $[\alpha]_D$ -7.9° (*c* =

1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 2.98 (m, 1H), 2.55 (dt, 1H, $J = 3.0, 11.7$ Hz), 2.37 (m, 1H), 1.75−0.86 (m, 11H), 0.84 (t, 3H, $J = 6.6$ Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.5, 47.1, 39.6, 32.9, 26.6, 24.8, 18.9, 14.1.

The other half of the methanolic filtrate was treated with HCl in ether (6 mL, 6 mmol), the mixture was stirred for 5 min, and the solvent was then evaporated *in vacuo*. The resulting residue was triturated with ether to provide coniine hydrochloride (0.43 g, 80%) as a colorless solid: mp 212−213 °C (lit.,[2b] 217−218 °C), $[\alpha]_D$ −7.6° ($c = 1$, EtOH) (lit.,[2b] $[\alpha]_D$ −6.3° ($c = 0.62$, EtOH)); ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (br s, 1H), 9.21 (br s, 1H), 3.49 (m, 1H), 2.95 (m, 1H) 2.83 (m, 1H), 2.02-1.44 (m, 10H), 0.97 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 57.6, 45.1, 35.7, 28.6, 22.8, 22.6, 19.0, 14.1.

(2*S*,5*S*)-(+)-1-(Benzyloxycarbonyl)-5-hydroxy-2-propylpiperidine (8). (*S*)-(+)-1-(Benzyloxycarbonyl)-1,2,3,4-tetrahydro-2-propylpyridine (**7**) was treated with borane−dimethyl sulfide complex in THF at −78 °C, and the mixture was allowed to warm to rt and stirred for 2 days. Trimethylamine *N*-oxide was added and the solution heated to reflux for 12 h. The solution was cooled, water (30 mL) and ether (30 mL) were added, the layers were separated, and the aqueous layer was washed with ether (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Column chromatography on silica gel with EtOAc−light petroleum ether (2:1) as eluent gave the pure *trans* isomer (40%) as a colorless oil: $[\alpha]_D$ +15.7° ($c = 1.4$, MeOH) (lit.,[3b] $[\alpha]_D$ +15.8° ($CHCl_3$); IR (film) 3434, 2942, 1693, 1429, 1243, 1151 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.13 (dd, 2H, $J = 12.5, 15.8$ Hz), 4.30 (br m, 1H), 4.10 (br d, 1H, $J = 14.5$ Hz), 3.91 (br s, 1H), 3.03 (dd, 1H, $J = 1.4, 14.3$ Hz), 2.04 (m, 2H), 1.68 (m, 2H), 1.31 (m, 4H), 0.90 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.0, 136.8, 128.4, 127.8, 127.7, 67.1, 64.5, 50.4, 44.8, 31.3, 25.4, 22.1, 19.4, 13.9.

(2*S*,5*S*)-(+)-5-Hydroxy-2-propylpiperidine (pseudoconhydrine) (2). Palladium on charcoal (7 mg, 10 mol %, 10% on charcoal) was added to a solution of tetrahydropyridine **8** (0.07 g, 0.25 mmol) in MeOH (7 mL), and the mixture was hydrogenated (45 psi H_2) for 3 h. The solution was filtered through Celite and the filtrate evaporated to give the *title compound* (98%) as a colorless solid: mp 102−103 °C, (lit.,[3e] 102−104 °C); $[\alpha]_D$ +17.4° ($c = 0.62$, $CHCl_3$) (lit.,[3e] $[\alpha]_D$ +11.1° ($c = 1$, EtOH); ^1H NMR (250 MHz, $CDCl_3$) δ 3.60 (m, 1H), 3.18 (m, 1H), 2.43 (t, 1H, $J = 10.8$ Hz) 2.37 (br s, 1H), 2.06−1.69 (m, 3H), 1.37−1.07 (m, 7H), 0.88 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 66.7, 53.6, 52.1, 36.7, 32.3, 29.4, 17.5, 12.3.

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Supporting Information Available: Copies of the ^{13}C NMR spectra of compounds **1**−**8** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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