Asymmetric Reduction of Cyclic Imines with Chiral Sodium Acyloxyborohydrides

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Asymmetric reduction of prochiral cyclic imines with chiral sodium acyloxyborohydrides (5a—i), which are easily prepared by the reaction of $NaBH_4$ with various *N*-acyl α-amino-acids, has been investigated. Of these new reducing agents, triacyloxyborohydrides (5c—f), derived from $NaBH_4$ (1 equiv.) and (*S*)-*N*-acylproline (3 equiv.), were found to reduce 3,4-dihydropapaverine (2) in tetrahydrofuran to (*S*)-norlaudanosine (3) hydrochloride in 60% optical yield. The *N*-benzyloxycarbonyl derivative (5c) could be isolated as a powder and characterized. The effect of solvents on this asymmetric reduction has been examined by the use of the isolated reagent (5c); halogenated alkane solvents such as CH_2Cl_2 or $CHCl_2CH_3$ gave a better optical yield of compound (3) (70% e.e.). The reagent (5c) also reduced other cyclic imines (6a—c) and (8) to the corresponding alkaloids (7a—c) and (9) in excellent optical yields (70—86% e.e.), providing an effective route to the asymmetric synthesis of these alkaloids. A possible reaction path for this reduction is also presented.

In recent years, asymmetric reduction of prochiral ketones to optically active alcohols with chiral metal hydride reagents has been widely investigated. In contrast the asymmetric reduction of cyclic imines, a reaction which would provide an effective route to various optically active alkaloids, has proved unsuccessful. Grundon and co-workers reported that lithium alkyl(hydro)dipinan-3α-ylborates reduce prochiral cyclic imines asymmetrically in only 4—25% optical yield.[2] Recently, we presented a brief account of the novel asymmetric reduction of cyclic imines by the use of chiral sodium triacyloxyborohydrides.[3] Here, details of this highly effective asymmetric reduction are given.

Results and Discussion

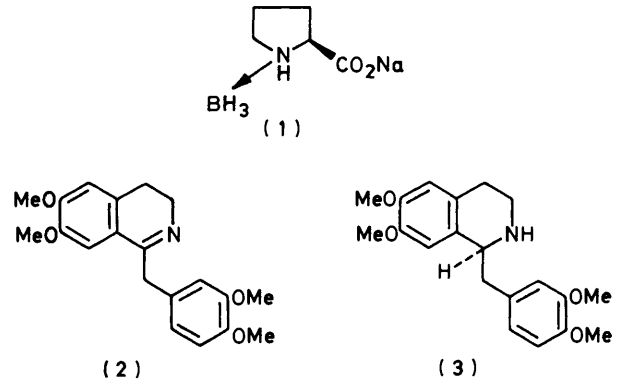
Previously, we reported the convenient asymmetric reduction of various prochiral ketones to optically active alcohols by the use of the sodium (*S*)-prolinate–borane complex (1), prepared by the reaction of $NaBH_4$ (1 equiv.) with (*S*)-proline (1 equiv.)[4] (Scheme 1).

Attempts to reduce 3,4-dihydopapaverine (2) asymmetrically with the complex (1), however, resulted in the formation of racemic tetrahydropapaverine in 78% yield.

However, carboxylic acids are known to react with $NaBH_4$ to form sodium acyloxyborohydrides (4) [equation (1)].

Brown and Subba Rao reported that sodium monopropionyloxyborohydride is obtained by the reaction of $NaBH_4$ (1 equiv.) and propionic acid (1 equiv.) in diglyme.[5] Gribble has shown that the reaction of $NaBH_4$ (1 equiv.) and acetic acid (3.25 equiv.) in benzene leads to the formation of sodium triacetoxyborohydride.[6] Liberatore and co-workers reported that some triacyloxyborohydrides[7] (4; $n = 3$, R = Me, $ClCH_2$, Ph *etc.*) can be isolated. Recently, we described that sodium monoacyloxyborohydrides reduce various functional groups (*e.g.* carboxamides,[8a] carbamates,[8a] nitriles[8b] or oxime ethers[8c]) effectively to the corresponding amines. Hirao *et al.* reported the asymmetric reduction of prochiral aromatic ketones with achiral sodium mono- or di-acyloxyborohydrides in the presence of 1,2:5,6-di-α-*O*-isopropylidene-α-D-glucofuranose.[9] In the present study, we investigated the asymmetric reduction of 3,4-dihydropapaverine (2) with chiral sodium acyloxyborohydrides (5a—i), easily obtained by the reaction of $NaBH_4$ and the *N*-acyl derivatives of optically active α-amino-acids in tetrahydrofuran (THF) [equation (2)].

Reduction of (2) with the reducing agents (5a—i) (1.3 equiv.)



Scheme 1

$$NaBH_4 + n\cdot RCO_2H \longrightarrow \underset{(n = 1,2,3)}{NaBH_{4-n}(RCO_2)_n}\ (4) + n\cdot H_2 \quad (1)$$

prepared *in situ*, was carried out in THF at −30 °C (Table 1).

As can be seen from Table 1, the triacyloxyborohydrides (5c—f) derived from $NaBH_4$ (1 equiv.) and (*S*)-*N*-acylproline (3 equiv.), provided good optical yields (55—60% e.e.) of (*S*)-norlaudanosine (3) hydrochloride (entries 3—6). The size of the *N*-acyl groups of these derivatives had little effect on the optical yields. The triacyloxy-derivatives (5g—i), derived from other α-amino-acids, were found to be less effective. The reducing agent (5c), isolated as a colourless powder in high yield, had an elemental analysis consistent with the structure assigned to it. It can be stored at 5—10 °C for over a month and is readily soluble and stable in various aprotic solvents. The effect of solvents on this asymmetric reduction was thus examined by the use of the isolated reagent (5c). The imine (2) was reduced with (5c) (1.5 equiv.) at −30 °C in various solvents, in which a halogenated alkane such as dichloromethane or 1,1-dichloroethane afforded a better optical yield of (3) (70% e.e.) (Table 2).

This simple and highly effective asymmetric reduction of (2) by the use of (5c) could also be applied to various other cyclic imines. Thus, 1-substituted 3,4-dihydroisoquinoline derivatives (6a—c) were reduced with the isolated reagent (5c) (2.5 equiv.) in CH_2Cl_2 at room temperature during 22 h to give the corresponding (*S*)-amines [salsolidine (7a),[10] norcryptostyline I (7b),[11] and norcryptostyline II (7c),[11] respec-

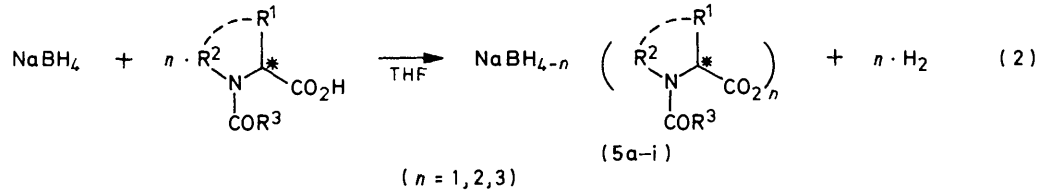


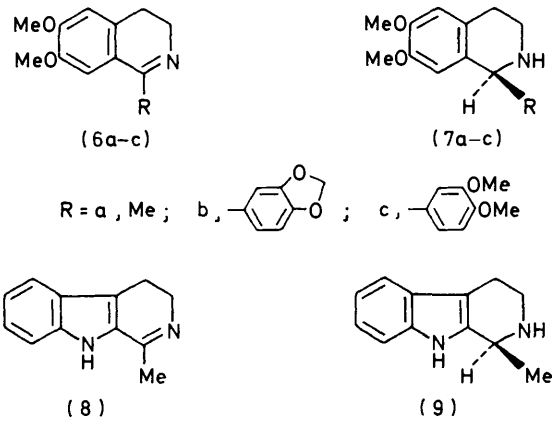
Table 1. Asymmetric reduction of (2) to (3) [a] with chiral reducing agents (5a—i)

Entry	Reducing agent	R^1	R^2	R^3	n	Reaction time (h)	Chem. yield (%)	$[\alpha]_D^{20}$/° (c 1, H_2O)	Opt. yield (% e.e.)
1	(5a)	$-[CH_2]_3-$		OCH_2Ph	1	20	54	0	0
2	(5b)	$-[CH_2]_3-$		OCH_2Ph	2	20	46	+6.8	18
3	(5c)	$-[CH_2]_3-$		OCH_2Ph	3	12	68	+22.7	60
4	(5d)	$-[CH_2]_3-$		Me	3	12	72	+21.0	55
5	(5e)	$-[CH_2]_3-$		Ph	3	12	68	+22.7	60
6	(5f)	$-[CH_2]_3-$		OBu^t	3	9	57	+22.2	58
7	(5g)	Me	H	OCH_2Ph	3	7	64	+6.1	16
8	(5h)	$CHMe_2$	H	OCH_2Pn	3	9	54	+3.8	10
9	(5i)	CH_2Ph	H	OCH_2Ph	3	6	83	+3.0	8

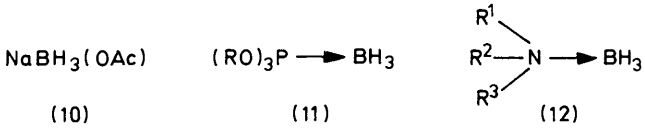
[a] $[\alpha]_D$ +38° (c 1, H_2O) for (*S*)-(+)-norlaudanosine·HCl (3): H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, 1956, **39**, 889.

Table 2. Effect of solvents in the asymmetric reduction of (2) with the isolated reagent (5c)

Solvent	Reaction time (h)	Chem. yield (%)	$[\alpha]_D^{20}$/° (c 1, H_2O)	Opt. yield (% e.e.)
Et_2O	8	35	+25.1	66
DME	144	60	+16.1	42
MeCN	144	60	+18.4	48
$PhCH_3$	8	53	+24.6	65
AcOEt	44	74	+23.8	63
CH_2Cl_2	6	70	+26.9	71
$CHCl_2Me$	44	79	+26.4	70
$CHCl_2CHCl_2$	30	89	+22.9	60



Scheme 2



Scheme 3

tively] in high yield (85—90%) with excellent enantioselectivities (70—86% e.e.). The asymmetric reduction of 1-methyl-3,4-dihydro-β-carboline (8) also proceeded smoothly to furnish tetrahydroharman (9) [12] in 79% optical yield (85% chemical yield) (Scheme 2).

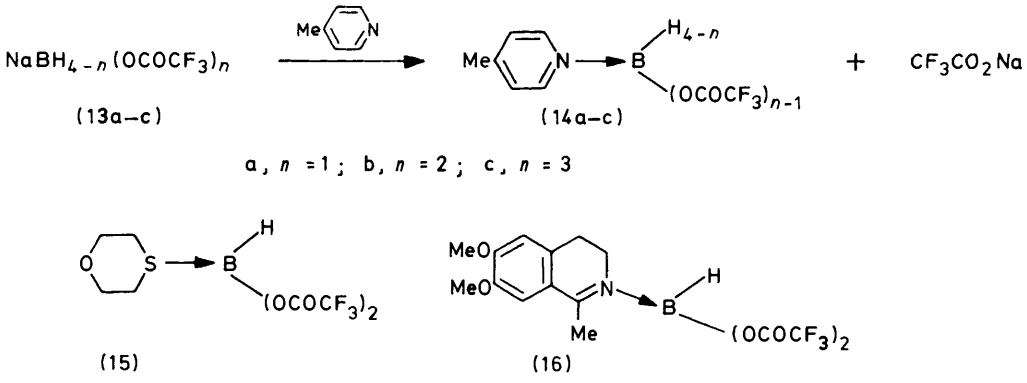
Since these cyclic imines, (6a—c) and (8), are easily accessible by the Bishler-Napieralski reaction, the discovery of the new reducing agent (5c) provides a very effective route to various optically active alkaloids. Moreover, the reagent (5c) is quite inexpensive since (*S*)-*N*-benzyloxycarbonylproline can be recovered in nearly quantitative yield after the reduction.

Finally, we investigated the reaction course of this asymmetric reduction. Reetz reported that trialkyl phosphites react with sodium monoacetoxyborohydride [$NaBH_3(OAc)$] (10) in THF to give trialkyl phosphite–borane complexes (11).[13] The present authors also found that the reaction of various amines with the reagent (10) affords the corresponding amine–borane complexes (12) in good yield (Scheme 3).

On the basis of these observations, we assumed that the reduction of cyclic imines proceeds *via* an imine–borane complex. To gain greater insight into this problem, we examined the reaction of γ-picoline with sodium trifluoroacetoxyborohydrides [$NaBH_{4-n}(OCOCF_3)_n$] (13a—c); the latter are easily prepared by the reaction of $NaBH_4$ (1 equiv.) and CF_3CO_2H (i—3.5 equiv.) in THF, as a model experiment (Scheme 4).

As expected, the reagents (13a—c) reacted with γ-picoline to give the amine–borane complexes (14a—c) in 59, 54, and 52% yields, respectively. The amine–borane complex (14a) thus obtained, when treated with CF_3CO_2H (1.5 equiv.) in CH_2Cl_2 at 0 °C, gave the monoacyloxy-complex (14b) in 60% yield which, in turn, was converted into the diacyloxy-complex (14c) in 37% yield by reaction with an excess of CF_3CO_2H at 40—50 °C for 0.5 h. Alternatively, and in order to establish its identity, the complex (14c) was obtained by the reaction of γ-picoline and the sulphide–borane complex (15) * [prepared

* The formation of a bis(trifluoroacetoxy)borane–dimethyl sulphide complex has been reported by Maryanoff *et al.*[14]



Scheme 4

Table 3. Physical data of γ-picoline-borane complexes (14a—c)

Complex	Yield (%)	M.p. (°C)	Mass (*m/z*)	I.r. (Nujol) (cm^{-1})	N.m.r. ($CDCl_3$) (δ)	Elemental analysis (%) Found (Calc.)
(14a; *n* = 1)	59	73—73.5 (72—73) [a]	106 ($M^+ - 1$) 93	2 350 2 290	2.50 (3 H, s) 7.29 (2 H, d, *J* 6 Hz) 8.41 (2 H, d, *J* 6 Hz)	
(14b; *n* = 2)	54	61—62	218 ($M^+ - 1$) 142 124 106 93	2 450 1 750	2.59 (3 H, s) 7.48 (2 H, d, *J* 6 Hz) 8.52 (2 H, d, *J* 6 Hz)	C 43.75 (43.88) H 4.1 (4.14) N 6.35 (6.40) F 26.1 (26.03)
(14c; *n* = 3)	52	60.5—61.5	330 ($M^+ - 1$) 236 218 142 124 93	2 500 1 760	2.64 (3 H, s) 7.60 (2 H, d, *J* 6 Hz) 8.57 (2 H, d, *J* 6 Hz)	C 36.15 (36.29) H 2.4 (2.44) N 4.2 (4.23) F 34.2 (34.44) B 3.2 (3.27)

[a] J. A. Bigol, T. J. Deboar, and F. L. J. Sixma, *Recl. Trav. Chim. Pays-Bas*, 1975, **76**, 996.

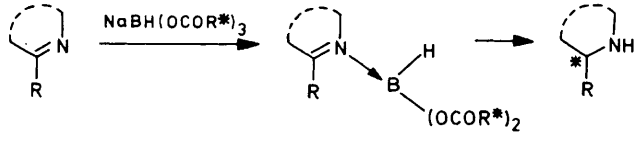
from borane-1,4-oxathian and CF_3CO_2H (2 equiv.)]. Further evidence for the structure of (14c) was its acidic hydrolysis with evolution of 1 mol equiv. of hydrogen. The spectral and analytical data for the complexes (14a—c), compatible with their assigned structures, are summarized in Table 3.

The above results indicate that the reaction of amines with sodium mono-, di-, or tri-acyloxyborohydrides leads to the formation of the corresponding amine–borane complexes with expulsion of a sodium carboxylate.

Thus, the formation of similar imine–borane complexes is expected in the course of the reaction of cyclic imines with trifluoroacetoxyborohydrides. In fact, when treated with the reagent (13c) in THF at 0 °C, the imine (6a) afforded the imine–borane complex (16) in 80% yield. Heating of (16) in THF for 48 h led to the formation of the reduction product (racemic salsolidine) in 30% yield along with 45% yield of the recovered imine (6a) after hydrolytic work up.

Although the precise mechanism of the present asymmetric reduction of cyclic imines is not clear, the reduction thus proceeds almost certainly through a stepwise process (Scheme 5): (1) formation of an imine–borane complex and (2) intra- or inter-molecular hydride reduction of the imine group.

Further studies on the asymmetric reduction of imines with chiral sodium acyloxyborohydrides are in progress.



Scheme 5

Experimental

M.p.s are uncorrected. I.r. spectra were recorded on a Hitachi IR-215 spectrometer and ^1H n.m.r. on JEOL PMX-60 or FX-100 spectrometer with trimethylsilane in $CDCl_3$ and sodium 3-(trimethylsilyl)propionate in D_2O as the internal standard. Mass spectra were recorded on a Hitachi RMU-6M spectrometer. Optical rotations were measured at 20 °C with a Union Giken PM-201 polarimeter. T.l.c. and preparative t.l.c. were carried out on Silica Gel 60F-254 (Merck) and $60GF_{254}$ (Merck), respectively. Column chromatography were performed on silica gel 60 (70—230 mesh ASTM) (Merck). Throughout ether refers to diethyl ether.

Materials.—The following (*S*)-*N*-acylamino-acids were prepared by known methods: (*S*)-*N*-acetylproline, m.p.

115—116 °C, $[\alpha]_D$ −116° (*c* 2.0, H_2O) [lit.,[15] m.p. 118 °C, $[\alpha]_D^{23}$ −115° (*c* 2.0, H_2O)]; (*S*)-*N*-benzoylproline, m.p. 156—157 °C, $[\alpha]_D$ −99.5° (*c* 0.2, EtOH) [lit.,[16] m.p. 158—159 °C, $[\alpha]_D^{25}$ −100.5° (*c* 0.2, EtOH)]; (*S*)-*N*-t-butyloxycarbonylproline, m.p. 134—136 °C, $[\alpha]_D$ −60.3° (*c* 2.01, AcOH) [lit.,[17] m.p. 136—137 °C $[\alpha]_D^{25}$ −60.2° (*c* 2.01, AcOH)]; (*S*)-*N*-benzyloxycarbonylproline, m.p. 72—73 °C, $[\alpha]_D$ −41.1° (*c* 1, EtOH) [lit.,[18] m.p. 77 °C, $[\alpha]_D^{20}$ −40.6° (*c* 2, EtOH)]; (*S*)-*N*-benzyloxycarbonylphenylalanine, m.p. 83—83.5 °C, $[\alpha]_D$ +5.5° (*c* 2.01, EtOH) [lit.,[18] m.p. 88—89 °C, $[\alpha]_D^{22}$ +5.1° (*c* 2, EtOH)]; (*S*)-*N*-benzyloxycarbonylvaline, m.p. 58—60 °C, $[\alpha]_D$ −5.0° (*c* 2, AcOH) [lit.,[19] m.p. 57—61 °C, $[\alpha]_D^{23}$ −4.3° (*c* 2, AcOH)]; (*S*)-*N*-benzyloxycarbonylalanine, m.p. 82—83 °C, $[\alpha]_D$ −15.0° (*c* 2.03, AcOH) [lit.,[20] m.p. 87 °C, $[\alpha]_D^{27}$ −13.9° (*c* 2, AcOH)].

The following imines were prepared from the corresponding amides by a Bischler-Napieralski reaction: 3,4-dihydropapaverine (2), m.p. 96—98 °C (from Et_2O–hexane) (lit.,[21] an oil); 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (6a), m.p. 103—104 °C (lit.,[22] m.p. 104—105 °C); 6,7-dimethoxy-1-(3,4-methylenedioxyphenyl)-3,4-dihydroisoquinoline (6a), m.p. 110—111 °C (lit.,[23] m.p. 109—110 °C); 6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-3,4-dihydroisoquinoline (6c),[24] m.p. 168—169 °C; 1-methyl-3,4-dihydro-β-carboline (Harmalan, 8), m.p. 171—175 °C (lit.,[25] m.p. 180—181 °C).

Reduction of 3,4-*Dihydropapaverine* (2) *with Sodium* (S)-*Prolinate–Borane Complex* (1).—A solution of the imine (2) (170 mg, 0.5 mmol) in THF (10 ml) was added to a stirred suspension of sodium (*S*)-prolinate–borane complex (2), prepared from $NaBH_4$ (113 mg, 3 mmol) and (*S*)-proline (345 mg, 3 mmol) in THF (10 ml) at room temperature for 4 h; the whole was then stirred at room temperature for 10 days under an argon atmosphere. The reaction mixture was treated with saturated brine and extracted with AcOEt. The AcOEt extracts were washed with saturated brine, dried (Na_2SO_4), and evaporated. The residual oil was treated with 10% methanolic HCl and crystallized from MeOH–Et_2O to afford (±)-(3)·HCl (149 mg, 78%) as colourless prisms, m.p. 210—212 °C (lit.,[21] m.p. 215 °C), $[\alpha]_D$ 0° (*c* 0.4, EtOH), $\nu_{max.}$ (Nujol) 3 100, 2 740—2 350, and 1 590 cm^{-1}; δ(D_2O) 3.63 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.86 (6 H, s, 2 × OMe), 6.39 (1 H, s, ArH), 6.7—7.0 (4 H, m, 4 × ArH); *m*/*z* 192, 151.

Asymmetric Reduction of 3,4-*Dihydropapaverine* (2) *with Various Sodium Acyloxyborohydrides* (5a—i) (1.3 *Equiv.*) *in THF*.—Entry 3 in Table 1 is representative. A solution of (*S*)-*N*-benzyloxycarbonylproline (1.12 g, 4.5 mmol) in THF (10 ml) was added, with cooling, to a stirred suspension of $NaBH_4$ (57 mg, 1.5 mmol) in THF (3 ml). The mixture was stirred at room temperature for 2 h after which time a solution of (2) (392 mg, 1.15 mmol) in THF (10 ml) was added at −30 °C; the whole was then stirred at −30 °C for 12 h. The reaction mixture was quenched with 5% aqueous HCl, heated at 60—70 °C for 0.5 h, and concentrated under reduced pressure. The aqueous residue was made basic with K_2CO_3, and extracted with AcOEt. The AcOEt extracts were washed with 20% aqueous K_2CO_3, dried ($MgSO_4$), and concentrated. The residue was purified by preparative t.l.c. ($CHCl_3$–MeOH, 20 : 1 v/v) and treated with 10% ethanolic HCl to afford *S*-(3)·HCl (295 mg, 68%) (from MeOH–Et_2O) as a colourless powder, m.p. 135(sint.)−204 °C, $[\alpha]_D$ +22.7° (*c* 1, H_2O) (60% e.e.). $\nu_{max.}$ (Nujol) 3 090, 2 750—2 450, 1 610, and 1 595 cm^{-1}. N.m.r. and mass spectra of this sample were identical with (±)-(3)·HCl.

Isolation of the Chiral Reducing Agent Sodium Tris[(S)-N-*benzyloxycarbonylprolyoxy*]*hydroborate* (5c).—(*S*)-*N*-Benzyloxycarbonylproline (1.49 g, 6 mmol) was added to a stirred suspension of $NaBH_4$ (76 mg, 2 mmol) in THF (10 ml) at 5—10 °C. After vigorous hydrogen evolution ceased, the mixture was stirred at room temperature for 3 h and then concentrated under reduced pressure. The residue was digested with n-hexane and filtered to give (5c) as a colourless powder (1.46 g, 94%), m.p. 55—65 °C (decomp.) (Found: C, 59.55; H, 5.7; N, 5.15; Na, 3.1. $C_{39}H_{43}BN_3NaO_{12}$ requires C, 60.09; H, 5.56; N, 5.39; Na, 2.95%); $\nu_{max.}$ (Nujol) 2 460 (BH) and 1 700 cm^{-1}.

Effect of Solvents on the Asymmetric Reduction of 3,4-*Dihydropapaverine* (2) *with the Isolated Reagent* (5c) (1.5 *Equiv.*).—Dichloromethane is representative. A solution of (2) (392 mg, 1.15 mmol) in CH_2Cl_2 (16 ml) was added to a stirred solution of (5c) (1.35 g, 1.73 mmol) in CH_2Cl_2 (10 ml) at −30 °C. After being stirred at −30 °C for 6 h, the reaction mixture was quenched with 5% aqueous HCl. Work-up as described above gave (3)·HCl (305 mg, 70%) as a colourless solid, m.p. 141(sint.)−200 °C, $[\alpha]_D$ +26.9° (*c* 1, H_2O) (71% e.e.).

Asymmetric Reduction of (6a—c) *and* (8) *to* (7a—c) *and* (9) *with* (5c) *in* CH_2Cl_2.—(S)-(−)-*Salsolidine* (7a). A solution of (6a) (308 mg, 1.5 mmol) in CH_2Cl_2 (15 ml) was added to a stirred solution of (5c) (2.93 g, 3.76 mmol) in CH_2Cl_2 (20 ml), and the whole was stirred at room temperature for 22 h. After removal of the solvent, the residue was treated with 5% aqueous HCl (at 60 °C for 1 h), made basic with K_2CO_3, and extracted with AcOEt. The AcOEt extracts were washed with 20% aqueous K_2CO_3, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by preparative t.l.c. ($CHCl_3$–MeOH, 20 : 1, v/v) to afford (7a) (263 mg, 85%) as a slightly yellowish oil, $[\alpha]_D$ −41.5° (*c* 1.71, EtOH) (70% e.e.) [lit.,[10] $[\alpha]_D^{22}$ −59.5° (*c* 4.39, EtOH)], $\nu_{max.}$ ($CHCl_3$) 1 605 cm^{-1}; δ($CDCl_3$) 1.45 (3 H, d, *J* 6.6 Hz, Me), 2.25 (1 H, s, NH, exchanges with D_2O), 4.07 (1 H, q, *J* 6.6 Hz, 1-H), 3.84 (6 H, s, 2 × OMe), 6.57 and 6.62 (1 H each, s, 2 × ArH); *m*/*z* 207 (M^+) and 192 (base).

(S)-(−)-*Norcryptostyline I* (7b). The imine (6b) (311 mg, 1.0 mmol) was reduced with (5c) (1.95 g) in a similar manner as described above and purified by preparative t.l.c. ($CHCl_3$–MeOH, 20 : 1, v/v) to afford (7b) (281 mg, 90%) as a colourless solid, m.p. 117—122 °C, $[\alpha]_D$ −19.7° (*c* 1, $CHCl_3$) (86% e.e.) [lit.,[11] m.p. 122—123 °C, $[\alpha]_D^{25}$ −23° (*c* 1, $CHCl_3$)], $\nu_{max.}$ (Nujol) 3 250 cm^{-1}; δ($CDCl_3$) 2.02 (1 H, s, NH, exchanges with D_2O), 3.66 and 3.85 (3 H each, s, 2 × OMe), 4.96 (1 H, s, 1-H), 5.90 (2 H, s, OCH_2O), 6.27 and 6.59 (1 H each, s, 2 × ArH), and 6.71 (3 H, s, 3 × ArH); *m*/*z* 313 (M^+), 312, 192.

(S)-(−)-*Norcryptostyline II* (7c). The imine (6c) (327 mg, 1 mmol) was reduced with (5c) (1.95 g) in a similar manner as described above and purified by preparative t.l.c. ($CHCl_3$–MeOH, 20 : 1, v/v) to afford (7c) (285 mg, 87%) as a colourless solid, m.p. 107—111 °C $[\alpha]_D$ −24.7° (*c* 1, $CHCl_3$) (73% e.e.) [lit.,[11] m.p. 114—115 °C, $[\alpha]_D^{25}$ −34° (*c* 1, $CHCl_3$)], $\nu_{max.}$ (Nujol) 3 250 cm^{-1}; δ($CDCl_3$) 2.15 (1 H, s, NH, exchanges with D_2O), 3.68 and 3.85 (3 H, each, s, 2 × OMe), 3.89 (6 H, s, 2 × OMe), 4.99 (1 H, s, 1-H), 6.32 and 6.55 (1 H, each, s, 2 × ArH), 6.82 (3 H, s, 3 × ArH); *m*/*z* 329 (M^+), 328, and 192.

(S)-(−)-*Tetrahydroharman* (9). The imine (8) (276 mg, 1.5 mmol) was reduced with (5c) (2.93 g) in a manner similar to that described above; the product was purified by preparative t.l.c. ($CHCl_3$–MeOH–28% aqueous NH_3, 100 : 10 : 1, v/v) to afford (9) (238 mg, 85%) as a pale yellow solid, m.p. 149(sint.)—168 °C, $[\alpha]_D$ −41° (*c* 2.38, EtOH) (79% e.e.) [lit.,[12] m.p. 177 °C, $[\alpha]_D^{25}$ −52° (*c* 2.0, EtOH)], δ($CDCl_3$)

1.43 (3 H, d, *J* 6.7 Hz, Me), 2.19 (1 H, s, NH, exchanges with D_2O), 2.6—2.9 (2 H, m), 3.0—3.5 (2 H, m), 4.15 (1 H, q, *J* 6.7 Hz, 1-H), 7.0—7.6 (4 H, m) and 8.0 (1 H, bs, NH, exchanges with D_2O); *m/z* 186 (M^+), 176 (base), and 157.

γ-Picoline–Borane Complex (14a) *from* $NaBH_3(OCOCF_3)$ (13a).—A solution of γ-picoline (1.77 g, 19 mmol) in THF (15 ml) was added to a THF solution of (13a), prepared from $NaBH_4$ (760 mg, 20 mmol) and CF_3CO_2H (2.28 g, 20 mmol) in THF (35 ml) at 5 °C for 0.5 h; the whole was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue extracted with $CHCl_3$. The $CHCl_3$ extracts were concentrated and the residual solid was purified by column chromatography ($CHCl_3$–hexane, 1 : 1, v/v) to afford (14a) (1.20 g, 59%) as colourless needles, m.p. 73—73.5 °C (from benzene–hexane). The physical data for (14a) are shown in Table 3.

γ-Picoline–Trifluoroacetoxyborane Complex (14b).—(i) *From* $NaBH_2(OCOCF_3)_2$ (13b). A solution of γ-picoline (880 mg, 9.5 mmol) in THF (10 ml) was added to a THF solution of (13b), prepared from $NaBH_4$ (380 mg, 10 mmol) and CF_3CO_2H (2.28 g, 20 mmol) in THF (35 ml) at 5 °C for 1 h; the whole was stirred at room temperature overnight. The mixture was worked up as described above for the isolation of (14a) and purified by column chromatography ($CHCl_3$–hexane, 3 : 2, v/v) to afford (14b) (1.11 g, 54%) as colourless scales, m.p. 61—62 °C (from benzene–hexane). The physical data for (14b) are shown in Table 3.

(ii) *From* (14a). A solution of CF_3CO_2H (855 mg, 1.5 mmol) in CH_2Cl_2 (7 ml) was added to a stirred solution of (14a) (535 mg, 1 mmol) in CH_2Cl_2 (10 ml) at −5 °C. After being stirred at 0 °C for 1 h, the reaction mixture was concentrated under reduced pressure at 0 °C. The residue was purified by short-column chromatography ($CHCl_3$) to afford (14b) (655 mg, 60%) as a colourless solid, m.p. 61—62 °C, identical with an authentic sample obtained by method (i).

γ-Picoline–Bis(trifluoroacetoxy)borane Complex (14c).—(i) *From* $NaBH(OCOCF_3)_3$ (13c). γ-Picoline (1.26 g, 13.5 mmol) was added to a solution of (13c) in THF (30 ml), prepared from $NaBH_4$ (570 mg, 15 mmol) and CF_3CO_2H (5.99 g, 52.5 mmol) in THF (40 ml) at room temperature overnight. After removal of THF, benzene (40 ml) was added to the residue and the whole was refluxed for 1.5 h. The reaction mixture was concentrated and submitted to column chromatography ($CHCl_3$) to afford (14c) (2.34 g, 52%) as colourless prisms, m.p. 60.5—61.5 °C (from benzene–hexane). The physical data for (14c) are shown in Table 3.

(ii) *From* (14b). A solution of (14b) (530 mg, 2.42 mmol) in CF_3CO_2H (6 ml) was heated at 40—50 °C for 0.5 h. After removal of CF_3CO_2H, the residue was purified by column chromatography ($CHCl_3$) to afford (14c) (297 mg, 37%) as a colourless solid, m.p. 60.5—61.5 °C, identical with an authentic sample obtained by method (i).

(iii) *From bis(trifluoroacetoxy)borane–1,4-oxathian complex* (15). γ-Picoline (651 mg, 7 mmol) was added to a stirred solution of (15), prepared from a 7.8M-solution of borane–1,4-oxathian complex (7.7 mmol) (Aldrich Chemical Co.) and CF_3CO_2H (1.85 g, 16.2 mmol) in THF at room temperature for 4 h, at 0 °C. After removal of the solvent, the residue was purified by column chromatography ($CHCl_3$–hexane, 3 : 2, v/v) to afford (14c) (1.23 g, 53%) as colourless prisms, m.p. 60.5—61.5 °C, identical with an authentic sample obtained by method (i).

Hydrolysis of (14c).—A solution of 10% aqueous HCl (10 ml) and EtOH (10 ml) was added to (14c) (1.66 g, 5.0 mmol) with stirring at 25 °C. Hydrogen evolution (125 ml, 5.1 mmol) ceased after 2 h.

Isolation of the Imine Bis(trifluoroacetoxy)borane Complex (16).—A solution of the imine (6a) (2.20 g, 10.8 mmol) in THF (10 ml) was added to a stirred solution of $NaBH(OCOCF_3)_3$ (13c) in THF (10 ml), prepared from $NaBH_4$ (532 mg) and CF_3CO_2H (5.58 g) as described above, at 0 °C. The mixture was concentrated under reduced pressure at 0 °C and extracted with cold CH_2Cl_2 (MeOH free). The CH_2Cl_2 extracts were concentrated under reduced pressure, and the residue was digested with CH_2Cl_2–hexane to afford (16) (3.82 g, 80%) as an amorphous solid, m.p. 83—86 °C (decomp.), $\nu_{max.}$ (Nujol) 2 500 (BH), 1 770, 1 750 (C=O), and 1 645 (C=N) cm^{-1}; δ($CDCl_3$) 2.73 (3 H, bs, Me), 2.8—3.2 (2 H, m, 2 × 4-H), 3.7—4.1 (2 H, m, 2 × 3-H), 3.88 and 3.94 (3 H each, s, 2 × OMe), and 6.90 and 7.22 (1 H each, s, 2 × ArH); *m/z* 442 ($M^+ - 1$), 348, 330, 288, 274, 254, 236, 205, 192, and 190.

Hydrolysis of (16).—A solution of 10% aqueous HCl (5 ml) and THF (5 ml) was added to (16) (886 mg, 2 mmol), and the mixture was heated at 40 °C. Hydrogen evolution (39 ml, 1.6 mmol) ceased after 2 h. The mixture was concentrated under reduced pressure, and the residue was recrystallized from MeOH–Et_2O to afford (6a)·HCl (403 mg, 84% recovery) as colourless needles, m.p. 197—197.5 °C.

Conversion of (16) *into* (±)-*Salsolidine* (7a) *in Refluxing THF*.—A solution of (16) (868 mg, 1.96 mmol) in THF (15 ml) was refluxed for 48 h. The reaction mixture was treated with 10% aqueous HCl (7 ml). After removal of THF, the aqueous solution was made basic with K_2CO_3 and extracted with AcOEt. The AcOEt extracts were dried ($MgSO_4$) and concentrated. The residue was purified by preparative t.l.c. ($CHCl_3$–MeOH, 40 : 3, v/v). From the upper band, the imine (6a) (182 mg, 45%) was recovered as a pale yellow solid, m.p. 92—99 °C. From the lower band, the amine [(±)-(7a)] was obtained as an oil, which was treated with 10% ethanolic HCl to afford (±)-(7a)·HCl (142 mg, 30%) as colourless needles, m.p. 185—188 °C (from MeOH–Et_2O) (lit.,[26] m.p. 196—197 °C) (Found: C, 59.15; H, 7.45; Cl, 14.55; N, 5.75. $C_{12}H_{18}NO_2Cl$ requires C, 58.63; H, 7.41; Cl, 14.75; N, 5.76%), δ(D_2O) 1.73 (3 H, d, *J* 7 Hz, Me), 2.9—3.3 (2 H, m), 3.4—4.3 (2 H, m), 3.86 (6 H, s, 2 × OMe), and 6.90 (2 H, s, 2 × ArH); *m/z* 207 (M^+) and 192 (base).

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