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A Novel Asymmetric Reduction of Imines with Chiral Sodium Triacyloxyborohydrides

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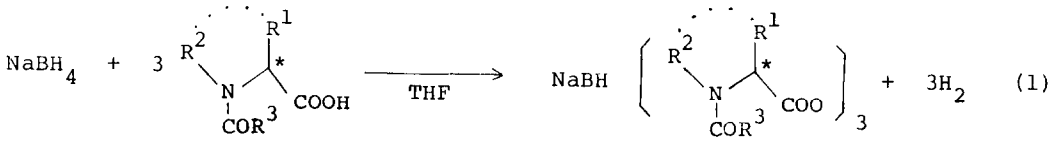
Summary: There has been described a novel and convenient synthesis of optically active alkaloids by the asymmetric reduction of cyclic imines using the chiral sodium triacyloxyborohydrides, easily prepared from the reaction of $NaBH_4$ and N-acyl L-prolines.

In recent years, the asymmetric reduction of prochiral carbonyl compounds with chiral metal hydride reagents to optically active alcohols has been widely investigated. Studies on asymmetric reduction of cyclic imines, however, remain without success,[1] though such reduction would provide an effective entry to various optically active alkaloids.

In 1971, Grundon *et al.* reported that the asymmetric reduction of 3,4-dihydropapaverine (2) with lithium hydro(methyl)dipinan-3α-ylborate followed by treatment with methyl iodide gives (-)-laudanosine methiodide in only 8.9% optical yield.[2]

Recently, Gribble reported that the reaction of $NaBH_4$ (1 equiv.) and acetic acid (3.25 equiv.) in benzene leads to the formation of sodium triacetoxyborohydride [$NaBH(OCOCH_3)_3$].[3] Liberatore described that these reducing agents [$NaBH(OCOR)_3$, R=Me, $ClCH_2$, Ph *etc.*] can be isolated.[4]

We now wish to report a novel and convenient asymmetric reduction of cyclic imines to optically active alkaloids by the use of the chiral sodium triacyloxyborohydrides (1), easily obtained from the reaction of $NaBH_4$ (1 equiv.) and N-acyl derivatives of optically active α-amino acids (3 equiv.) [equation 1].

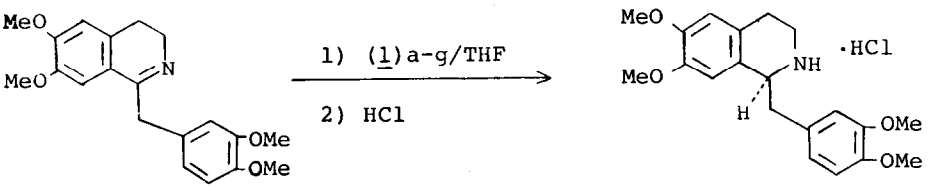


(1)

1a-g

We preliminarily investigated the asymmetric reduction of 3,4-dihydropapaverine (2) to norlaudanosine·HCl (3) in THF at -30° with the various chiral borohydride derivatives (1a-g) (1.3 equiv.), prepared *in situ*.

As shown in Table I, the reducing agents (1d-g), prepared from the reaction of $NaBH_4$ and N-acyl L-prolines, were found to provide good optical yields (55-60%).



2 3

Table I. Asymmetric Reduction of 3,4-Dihydropapaverine (2) with Various Chiral Reducing Agents (1a-g) to *S*-(+)-Norlaudanosine·HCl (3)[a] in THF.

Reducing Agents[b]	R_1	R_2	R_3	Reaction Time	Chemical Yield(%)	$[\alpha]_D^{20}$ (c=1.0,H_2O)	Optical Yield(%)
1a	CH_3	H	OCH_2Ph	7 h	64	+ 6.1°	16
1b	$CH(CH_3)_2$	H	OCH_2Ph	9 h	54	+ 3.8°	10
1c	CH_2Ph	H	OCH_2Ph	6 h	83	+ 3.0°	8
1d	$-(CH_2)_3-$		OCH_2Ph	12 h	68	+22.7°	60
1e	$-(CH_2)_3-$		CH_3	12 h	72	+21.0°	55
1f	$-(CH_2)_3-$		Ph	12 h	68	+22.7°	60
1g	$-(CH_2)_3-$		O-t-Bu	9 h	57	+22.2°	58

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

b) 1a-g were prepared from N-acyl L-amino acids.

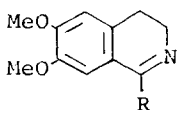
Of these N-acyl L-proline derivatives, 1d (mp 55-65° (dec.)) and 1f (mp 125-140° (dec.)) could be isolated in high yields. The compound (1d) is readily soluble in various solvents, thus making it possible to examine the effect of solvents in the asymmetric reduction of 2. The reduction of 2 with the isolated reagent (1d) (1.5 equiv.) at -30° was examined in various solvents, in which a halogenated alkane such as dichloromethane or 1,1-dichloroethane gave an excellent optical yield of 3 (Table II).

Table II. Effect of Solvents in the Asymmetric Reduction of 2 with the Reducing Agent (1d)

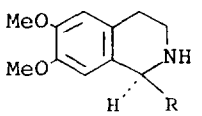
Solvent	Reaction Time	Chemical Yield(%)	$[\alpha]_D^{20}$ (c=1,H_2O)	Optical Yield(%)
Et_2O	8 h	35	+25.1°	66
DME	6 days	60	+16.1°	42
CH_3CN	6 days	60	+18.4°	48
$PhCH_3$	8 h	53	+24.6°	65
AcOEt	44 h	74	+23.8°	63
CH_2Cl_2	6 h	70	+26.9°	71
$CHCl_2CH_3$	44 h	79	+26.4°	70
$CHCl_2CHCl_2$	30 h	87	+22.9°	60

This simple and highly effective asymmetric reduction of 2 by the use of 1d could be applicable also to various other cyclic imines.

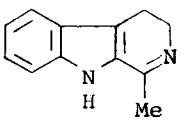
Thus, 1-substituted 3,4-dihydroisoquinoline derivatives (4a-c) were reduced with the isolated reagent (1d) (2.5 equiv.) in CH_2Cl_2 at room temperature for 22 h to give salsolidine (5a)[5] [85%, $[\alpha]_D^{20}$-41.5° (c=1.71, EtOH) (70% ee)], norcryptostyline I (5b)[6] [90%, $[\alpha]_D^{20}$-19.7° (c=1, $CHCl_3$) (86% ee)], and norcryptostyline II (5c)[7] [87%, $[\alpha]_D^{20}$-24.7° (c=1, $CHCl_3$) (73% ee)], respectively, in high chemical yields and in excellent optical yields. The asymmetric reduction of 1-methyl-3,4-dihydro-β-carboline (6) also proceeded smoothly to furnish



4a-c



5a-c



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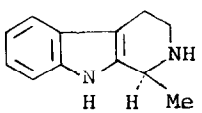
a; R=methyl

b; R=3,4-methylenedioxyphenyl

c; R=3,4-dimethoxyphenyl



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tetrahydroharman (7)[8] [85%, $[\alpha]_D^{20}$-41.0°(c=2.38, EtOH)] in 79% optical yield.

The procedure for the reduction of the 3,4-dihydroisoquinoline derivative (4b) with the isolated reagent (1d) is illustrative.

Isolation of 1d. N-Benzyloxycarbonyl-L-proline (1.49 g, 6 mmol) was added to a stirred suspension of $NaBH_4$ (0.076 g, 2 mmol) in THF (10 ml) at 5-10°. After hydrogen evolution, the mixture was stirred at room temperature for 3 h and then concentrated *in vacuo*. The residue was digested with n-hexane and filtered to give 1d as a colorless powder (1.46 g, 94%), mp 55-65° (dec.).

Reduction of 4b. A solution of 4b (311 mg, 1 mmol) in CH_2Cl_2 (13 ml) was added to a stirred solution of 1d (2.0 g, 2.5 mmol) in CH_2Cl_2 (10 ml). After stirring at room temperature for 22 h, the reaction mixture was treated with aq. $(CO_2H)_2$, made alkaline with K_2CO_3, and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative TLC [silica gel 60 GF_{254} (Merck)] to afford 5b (281 mg, 90%) as a colorless solid, mp 117-122°, $[\alpha]_D^{20}$-19.7° (c=1, $CHCl_3$) (86 % ee) [lit.[6] for pure *s*-enantiomer (5b) mp 122-123°].

The scope and limitation of the asymmetric reduction of cyclic imines by the use of chiral sodium triacyloxyborohydrides, are being continued.

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References and Notes.

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6) $[\alpha]_D^{25}$-23°(c=1, $CHCl_3$) for *s*-(-)-norcryptostyline I (5b); A. Brossi and S. Teitel, Helv. Chim. Acta, 54, 1564 (1971).
7) $[\alpha]_D^{25}$-34° (c=1, $CHCl_3$) for *s*-(-)-norcryptostyline II (5c); See reference 5.
8) $[\alpha]_D^{25}$-52° (c=2.0, EtOH) for *s*-(-)-tetrahydroharman (7); H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, Chem. Pharm. Bull. 22, 2614 (1974).

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