Asymmetric Reduction of Aromatic Ketones. I. Enantioselective Synthesis of Denopamine

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Asymmetric reduction of the *N*-protected amino ketone (2) with several chiral reducing agents, i.e., (*R*)-(+)-2-amino-3-methyl-1,1-diphenylbutanol (6)-borane complex (method A), (*S,S'*)-*N,N'*-dibenzoylcystine (7)-LiBH₄-ROH complex (method B), and sodium (*S*)-prolinat-borane complex (8) (method C), was investigated in an attempt to synthesize denopamine (1) enantioselectively. Reduction of 2f by method B in tetrahydrofuran at 2–3°C gave the best result (88% ee with 95% chemical yield).

Keywords denopamine; asymmetric reduction; sodium (*S*)-prolinat-borane complex; amino ketone; LiBH₄; *N,N'*-dibenzoylcystine

Denopamine (1), (*R*)-(-)- α -[(3,4-dimethoxyphenethyl)-amino]methyl-4-hydroxybenzyl alcohol was the first orally active and long-acting positive inotropic agent with a selective β_1 -adrenoceptor agonistic activity to be brought into clinical use.²⁾ Potent positive inotropic activity was found to reside only in the (*R*)-(-)-isomer (denopamine), its (*S*)-(+)-isomer being much less active (approximately 1% as potent as denopamine).²⁾

Optical resolution of the precursor of denopamine^{3a)} and successful inversion of the hydroxyl group of the unwanted

(*S*)-(+)-carbinol ((+)-5) to the desired (*R*)-(-)-5 have been reported.⁴⁾ Several attempts to synthesize denopamine from chiral precursors such as (*R*)-(-)-mandelic acid^{3b)} and (*R*)-(-)-(*p*-hydroxyphenyl)glycine^{3c)} suffered from low overall yield and insufficient optical purity of the final product. A practical enantioselective synthesis of denopamine, therefore, is still required. In our previous paper,⁵⁾ as part of our studies on the asymmetric reduction of various ketones with sodium salts of α -amino acid borane complex, we reported the synthesis of denopamine *via* the reduction

Chart 1

Chart 2

Dedicated to the memory of Professor S. Sugawara.

of the intermediate ketone (**2a**) with (*S*)-proline-borane complex (**8**) in moderate optical yield. Recently, Corey and Link⁶) reported a synthesis of denopamine involving the highly enantioselective reduction of 1-[4-(*tert*-butyldimethylsilyloxy)phenyl]-2-ethanone with BH_3 in the presence of a catalytic amount of (*R*)-oxazaborolidine.⁷⁾

In this paper, we wish to report the results of detailed studies on the enantioselective reduction of the aminoacetophenone derivatives (**2**) with several chiral metal hydride complexes. The key intermediate ketone (**2**) was obtained from the amino ketone (**3**)^{3a)} by acylation in the usual manner.

Initially, we applied the reagent⁸⁾ prepared from (*R*)-(+)-2-amino-3-methyl-1,1-diphenylbutanol (**6**) and borane to the reduction of the *N*-carbobenzyloxy (Cbz) derivative (**2a**) (method A). Reaction of **2a** with the reagent prepared from 1 eq of **6** and 2 eq of borane-oxathiane in tetrahydrofuran (THF) at 3–5 °C for 1.5 h, followed by reductive removal of the *O*-benzyl and *N*-Cbz groups gave (*R*)-(–)-denopamine (**1**) with high optical purity (96% ee) in 66% overall yield. Compound **2** with an *N*-acyl protective group was not a suitable substrate in this reduction, since the reagent concomitantly reduced the amide group.

As an alternative method, we next examined the reduction of **2** with the reagent prepared from LiBH_4 , *N,N'*-dibenzoylcystine and *tert*-BuOH⁹⁾ (method B). Soai and his coworkers⁹⁾ reported that reduction of α -amino ketones with this complex using (*R,R'*)-*N,N'*-dibenzoylcystine gave β -amino alcohols with (*S*)-configuration. To obtain the desired (*R*)-alcohol (**4**), therefore, reduction of **2a** at room temperature with the complex prepared from (*S,S'*)-*N,N'*-dibenzoylcystine (**7**) in THF was conducted, followed by hydrolytic removal of the *N*-Cbz group to give the (*R*)-(–)-alcohol [(–)-**5**] in 71% ee. The effects of modifying metal borohydride, solvent and added alcohol were then examined, and the results are summarized in Tables I and II.

Substitution of LiBH_4 with NaBH_4 or a change of the

TABLE I. Enantioselective Reduction of **2a** with (*S,S'*)-*N,N'*-Dibenzoylcystine-Metal Borohydride-*tert*-BuOH Complex (Method B)

Entry	MBH ₄	Solvent	Yield of 1 (%)	Optical purity ^{a)} (% ee)	Configuration
1	LiBH_4	THF	74	71	<i>R</i>
2	LiBH_4	CH_2Cl_2	62	27	<i>R</i>
3	NaBH_4	THF	74	30	<i>R</i>

a) Based on the maximum value $[\alpha]_{\text{D}} - 27.7^\circ$ ($c=1$, MeOH).²⁾

TABLE II. Effect of the Added Alcohol in Enantioselective Reduction of **2a** with LiBH_4 and **7**

Entry	ROH	Yield of 5 ·HCl (%)	Optical purity ^{a)} (% ee)	Configuration
1	<i>tert</i> -Butanol	99	58	<i>R</i>
2	cyclo- $\text{C}_6\text{H}_{11}\text{OH}$	96	57	<i>R</i>
3	$\text{PhC}(\text{CH}_3)_2\text{OH}$	98	60	<i>R</i>
4	$\text{CF}_3\text{CH}_2\text{OH}$	89	52	<i>R</i>
5	$\text{PhCH}(\text{CH}_3)\text{OH}$	98	44	<i>R</i>

a) Based on the maximum value $[\alpha]_{\text{D}} - 30.1^\circ$ ($c=1$, MeOH).³⁾

solvent from THF to CH_2Cl_2 resulted in a decrease in enantioselectivity. Replacement of *tert*-BuOH with various alcohols did not give favorable results. Since the steric bulkiness of the *N*-protective group of **2** may play an important role in the enantioselectivity in this reduction, the effect of modifying this group was examined next (Table III).

The reduction of *N*-acetyl or benzoyl derivatives (**2b**, **c**) showed rather low enantioselectivity, while the *N*-pivaloyl derivative (**2f**) gave the best result (80% ee, 95% yield, at room temperature). At lower temperature (2–3 °C), 88% ee of the product was achieved in the reduction of **2f** (entry 6). The 2,4,6-trimethylbenzoyl derivative (**2g**) also showed good selectivity, but the removal of this group by alkaline hydrolysis was unsuccessful. These results indicate that the amino ketone (**2**) with sterically bulkier *N*-substituents gave higher optical yield.

In view of the relative inaccessibility of the chiral auxiliary (**6** or **7**) described above from unnatural amino acids ((*R*)-valine or *S,S'*-cystine), we further explored the reduction of **2** with sodium (*S*)-proline-borane complex (**8**)⁵⁾ (method C). Previously, reduction of the *N*-Cbz derivative (**2a**) with this reducing agent gave, after removal of the protective groups, (*R*)-(–)-denopamine in 62% ee.⁵⁾ In view of the favorable effect of the bulky *N*-protective group on the asymmetric reduction by method B, we examined the reduction of the *N*-pivaloyl derivative (**2f**) by

TABLE III. Effect of Modifying the *N*-Protective Group of **2** in the Enantioselective Reduction by Method B

Entry	2	R	Reduction temperature (%)	Yield of (–)- 5 ·HCl (%)	Optical purity ^{a)} (% ee)	Con- figuration
1	2a	OCH_2Ph	22–26	93	68	<i>R</i>
2	2b	Ph	r.t.	99	54	<i>R</i>
3	2c	CH_3	r.t.	92	49	<i>R</i>
4	2d	OCH_2CCl_3	22–26	82	71 ^{b)}	<i>R</i>
5	2e	$\text{OC}(\text{CH}_3)_3$	22–26	91	62	<i>R</i>
6	2e	$\text{OC}(\text{CH}_3)_3$	2–3	87	78	<i>R</i>
7	2f	$\text{C}(\text{CH}_3)_3$	22–26	93	80	<i>R</i>
8	2f	$\text{C}(\text{CH}_3)_3$	2–3	95	88	<i>R</i>
9	2g		20–24	q. ^{d)}	81 ^{c)}	<i>R</i>

a) See Table II, footnote a. b) The $\text{N-CO}_2\text{CH}_2\text{CCl}_3$ group was removed by treatment with $\text{Zn}-1\text{N NH}_4\text{OAc}$. c) Enantiomeric excess was determined by comparison of $[\alpha]_{\text{D}}$ with that of an authentic sample obtained from pure (–)-**5** and 2,4,6-trimethylbenzoyl chloride. d) Yield of **7g**.

TABLE IV. Asymmetric Reduction of **2f** Using Sodium (*S*)-Proline-Borane Complex (**8**) (Method C)

Entry	Equivalent of 8	Reduction condition	(–)- 5 ·HCl yield, (%)	Optical purity ^{a)} (% ee)	Con- figuration
1	2	r.t. 12.5 d	68 ^{b)}	81	<i>R</i>
2	2	ca. 50 °C 24 h	91	73	<i>R</i>
3	2	Reflux 15 h	90	62	<i>R</i>
4	5	r.t. 3.5 d	51 ^{c)}	61	<i>R</i>
5	5	Reflux 16 h	86	70	<i>R</i>

a) See Table II, footnote a. b) Starting material **2f** was recovered (20%). c) Starting material **2f** was recovered (37%).

the use of the reagent (**8**).

As shown in Table IV, much improved enantioselectivity (81% ee) was obtained after prolonged reaction in THF at room temperature. At higher temperatures, the reaction was accelerated, with decreased enantioselectivity. Increase of the molar ratio of the reagent (**8**) to the substrate resulted in a decrease in optical yield.

Although the exact mechanisms of the asymmetric reductions described above are not clear, the steric bulkiness of the *N*-substituents of **2** apparently plays an important role in the enantioselective approach of hydride of the reducing agent to the carbonyl group.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrophotometer. Proton magnetic resonance (¹H-NMR) spectra were recorded on a JEOL PMX-60, PS-100, FX-200, or a Hitachi RH-90H spectrometer with tetramethylsilane as the internal standard. Optical rotations were measured at 20 °C with a Union Giken PM-201 polarimeter. Mass spectra (MS) were recorded on a Hitachi RMU-6M spectrometer. The characterization of the products was performed by comparison of IR, NMR and mass spectra and thin-layer chromatographic behavior with those of authentic samples.

2-[(Benzyloxycarbonyl)(3,4-dimethoxyphenethyl)amino]-1-(4-benzyloxyphenyl)ethanone (2a) A solution of carbobenzoxy chloride (14.07 g, 82.5 mmol) in CH₂Cl₂ (50 ml) was added to a vigorously stirred mixture of 2-(3,4-dimethoxyphenethyl)amino-1-(4-benzyloxyphenyl)ethanone hydrochloride (**3**, 33.15 g, 75 mmol)²¹ in CH₂Cl₂ (400 ml) and NaHCO₃ (25.2 g, 300 mmol) in H₂O (500 ml) at 0–2 °C during a period of 20 min. The reaction mixture was stirred at 0–5 °C for 20 min and then at room temperature for 1 h. The CH₂Cl₂ layer was separated and the aqueous layer was extracted with CH₂Cl₂. The CH₂Cl₂ layer were combined, washed with aqueous NaCl, dried over MgSO₄, and concentrated. The residual yellow oil was triturated with *n*-hexane and recrystallized from EtOAc–*n*-hexane to give **2a** (37.88 g, 91.1%) as yellow fine needles, mp 102.5–103.5 °C. MS *m/z*: 539 (M⁺). IR (Nujol) cm^{−1}: 1690. ¹H-NMR (CDCl₃) δ: 2.66–2.97 (2H, m), 3.41–3.70 (2H, m), 3.75 (3H, s), 3.83 (3H, s), 4.49, 4.59 (2H, s each, rotational isomers), 5.12, 5.16 (4H, s each, rotational isomers), 6.53–6.83 (3H, m), 6.98 (2H, d, *J* = 8.6 Hz), 7.15–7.50 (10H, m), 7.84 (2H, m). *Anal.* Calcd for C₃₃H₃₃NO₆: C, 73.45; H, 6.16; N, 2.60. Found: C, 73.37; H, 6.22; N, 2.76.

2b–g were prepared by the same procedure as described for **2a**.

2b: mp 102.0–103.5 °C. MS *m/z*: 509 (M⁺). IR (Nujol) cm^{−1}: 1685, 1635. ¹H-NMR (CDCl₃) δ: 2.55–3.10 (2H, m), 3.37–3.64 (2H, m), 3.73 (3H, s), 3.82 (3H, s), 4.42, 4.90 (2H, s each, rotational isomers), 5.13 (2H, s), 6.30–6.85 (3H, m), 7.02 (2H, d, *J* = 8.6 Hz), 7.3–7.4 (10H, m), 7.5–8.1 (2H, m). *Anal.* Calcd for C₃₃H₃₁NO₅: C, 75.42; H, 6.13; N, 2.75. Found: C, 75.21; H, 6.02; N, 2.81.

2c: mp 87.5–89.5 °C. MS *m/z*: 447 (M⁺). IR (neat) cm^{−1}: 1680. ¹H-NMR (CDCl₃) δ: 2.02 (3H, s), 2.80 (2H, t, *J* = 7 Hz), 3.60 (2H, t, *J* = 7 Hz), 3.8–3.9 (6H, m, rotational isomers), 4.55–4.85 (2H, m), 5.11 (2H, s), 6.7–7.1 (5H, m), 7.37 (5H, m), 7.75–8.0 (2H, m). *Anal.* Calcd for C₂₇H₂₉NO₅: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.35; H, 6.57; N, 3.22.

2d: mp 126–127.5 °C. MS *m/z*: 580 (M⁺). IR (Nujol) cm^{−1}: 1720, 1680. ¹H-NMR (CDCl₃) δ: 2.7–3.1 (2H, m), 3.4–4.0 (2H, m), 3.84 (6H, s), 4.58 (2H, s), 4.70, 4.81 (2H, s each, rotational isomers), 5.13 (2H, s), 6.76 (3H, s), 7.00 (2H, d, *J* = 8.8 Hz), 7.39 (5H, s), 7.86 (2H, m). *Anal.* Calcd for C₂₈H₂₈Cl₃NO₆: C, 57.90; H, 4.86; Cl, 18.31; N, 2.41. Found: C, 57.75; H, 4.77; Cl, 18.45; N, 2.39.

2e: Oil. MS *m/z*: 505 (M⁺). IR (neat) cm^{−1}: 1690. ¹H-NMR (CDCl₃) δ: 1.37, 1.48 (9H, s each, rotational isomers), 2.67–2.96 (2H, m), 3.35–3.66 (2H, m), 3.84 (6H, s), 4.42, 4.52 (2H, s each, rotational isomers), 5.12 (2H, s), 6.76 (3H, s), 6.99 (2H, d, *J* = 8.6 Hz), 7.39 (5H, s), 7.89 (2H, d, *J* = 8.6 Hz).

2f: Oil. MS *m/z*: 489 (M⁺). IR (neat) cm^{−1}: 1690, 1620. ¹H-NMR (CDCl₃) δ: 1.32 (9H, s), 2.74–2.98 (2H, m), 3.54–3.93 (2H, m), 3.84 (6H, s), 4.65 (2H, s), 5.13 (2H, s), 6.63–6.79 (3H, m), 7.00 (2H, d, *J* = 9.0 Hz), 7.39 (5H, s), 7.91 (2H, d, *J* = 9.0 Hz).

2g: Oil. MS *m/z*: 551 (M⁺). IR (Nujol) cm^{−1}: 1690, 1630. ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.28 (3H, s), 2.33 (3H, s), 2.4–4.0 (4H, m), 3.70 (3H, s), 3.79 (3H, s), 4.36, 4.96 (2H, s each, rotational isomers), 5.14 (2H,

s), 6.2–8.1 (14H, m).

Asymmetric Reduction of 2a Using Diphenylvalinol (6) and Conversion to 1 i) A solution of borane–oxathiane (3 g, 20 mmol) in THF (15 ml) was added to a stirred solution of (*R*)-(+)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**6**, 2.55 g, 10 mmol) in THF (15 ml) at 0 °C during a period of 2–3 min and the mixture was stirred at room temperature for 16.5 h. A solution of **2a** (4.31 g, 8 mmol) in THF (25 ml) was added to the reaction mixture at 0 °C during a period of 10 min. The mixture was stirred at 3–5 °C for 1 h, decomposed by addition of ice-water and aqueous 10% HCl, and then extracted with AcOEt. The extracts were combined, washed with saturated aqueous NaHCO₃ and aqueous NaCl successively, dried over MgSO₄, and concentrated. The residue was purified by silica gel column chromatography (eluted with CHCl₃) to afford **4a** as a colorless oil (4.165 g, 96%).

ii) A solution of **4a** (0.5 g, 0.92 mmol) in MeOH (15 ml) was hydrogenated in the presence of 10% Pd–C (184 mg) at room temperature and ordinary pressure. After removal of Pd–C and MeOH, the residual oil was recrystallized from EtOH–H₂O to give **1** (204 mg, 69%), mp 165–167 °C (dec.) (lit.^{2a}) mp 167 °C (dec.). [α]_D −26.7° (*c* = 1, MeOH), 96% ee based on the maximum value [α]_D −27.7° (*c* = 1, MeOH).^{2a}

Asymmetric Reduction of 2f by Method B and Conversion to (−)-5·HCl (Chart 2) i) A solution of 2 M LiBH₄ in THF (3.6 ml, 7.2 mmol) was added to a stirred suspension of (*S*,*S'*)-*N,N'*-dibenzoylcystine (**7**, 1.076 g, 2.40 mmol) and *tert*-BuOH (237 mg, 3.2 mmol) in THF (8 ml) at room temperature and the mixture was heated under reflux for 30 min. A solution of **2f** (979 mg, 2 mmol) in THF (5 ml) was added to the stirred reaction mixture at 2–3 °C during a period of 10 min. After stirring at 2 °C for 10 min, ice-water and saturated aqueous NaHCO₃ (10 ml) were added to the reaction mixture and the obtained mixture was extracted with CH₂Cl₂. The CH₂Cl₂ layers were combined, washed with aqueous NaCl and dried over MgSO₄, and concentrated *in vacuo*. The residual oil was purified by silica gel column chromatography (eluted with CHCl₃–MeOH (100:1)) to give **4f** (1.014 g) as a colorless oil.

ii) The obtained oil was treated with a solution of 86% KOH (580 mg) in EtOH (20 ml) and H₂O (2 ml) under reflux for 30 min. The reaction mixture was concentrated to remove EtOH, diluted with water, and extracted with CHCl₃. The extracts were combined and washed with 5% HCl (10 ml). The aqueous layer was extracted with CHCl₃ several times. The CHCl₃ layer was combined, dried over MgSO₄, and concentrated *in vacuo*, and the residual solid was triturated with EtOH–iso-Pr₂O to give (−)-5·HCl, 847 mg (95% from **2f**) as a colorless powder, mp 169–173 °C (dec.) (lit.³) mp 174–174.5 °C (dec.). [α]_D −26.4° (*c* = 0.587, MeOH), 88% ee based on maximum value [α]_D −30.1° (*c* = 1, MeOH).³

Asymmetric Reduction of 2f by Method C and Transformation to (−)-5·HCl A mixture of (*S*)-proline (1.151 g, 10 mmol) and NaBH₄ (378 mg, 10 mmol) in THF (20 ml) was stirred at room temperature for 3 h. A solution of **2f** (2.498 g, 5 mmol) in THF (5 ml) was added to the stirred suspension at room temperature and the mixture was stirred at room temperature for 12.5 d. The reaction mixture was decomposed by addition of 10% HCl (5 ml) and extracted with Et₂O. The Et₂O layer were combined, washed with 10% NaOH and then with saturated aqueous NaCl, dried over MgSO₄, and concentrated. The residual oil was purified by silica gel column chromatography (eluted with CHCl₃–MeOH (100:1)) to give **4f** (3.765 g) as a colorless oil and **2f** (500 mg, 20%). The obtained oil **4f** was hydrolyzed with KOH (2.9 g) in EtOH (25 ml) and H₂O (5 ml) under reflux for 30 min. After concentration *in vacuo*, the reaction mixture was worked up in the same manner as described above to give (−)-5·HCl, (1.30 g, 68%), mp 172–174.5 °C (dec.) as a colorless powder. [α]_D −24.15° (*c* = 0.593, MeOH), 81% ee.

Removal of the *N*-Protective Group of 4d Zn powder (4 g, 6.1 mmol) was added to a solution of **4d** (1.21 g, 2.07 mmol) in 1 N aqueous AcONH₄ (4 ml)–THF (20 ml) and the mixture was stirred at room temperature for 18 h. After removal of Zn by filtration, the filtrate was concentrated and extracted with CHCl₃. The extracts were worked up in the same manner as described above to give (−)-5·HCl, (756 mg, 82%), mp 172–174 °C (dec.). [α]_D −21.4° (*c* = 0.588, MeOH), 71.4% ee.

(*R*)-(−)-4-Benzyloxy- α [(3,4-dimethoxyphenethyl)(2,4,6-trimethylbenzoyl)amino]methylbenzyl Alcohol (4g) 2,4,6-Trimethylbenzoyl chloride (548 mg, 3 mmol) in AcOEt (2 ml) was added to a mixture of optically pure (−)-5·HCl^{3a)} (888 mg, 2 mmol), NaHCO₃ (2 g), AcOEt (15 ml), and H₂O (10 ml) under vigorous stirring at 5 °C. The reaction mixture was stirred for 3 h, then worked up in the usual manner to give **4g** (1.065 g, 96.2%) as an oil. [α]_D −9.87° (*c* = 1.033, MeOH). IR (Nujol) cm^{−1}: 3285, 1607. MS *m/z*: 535 (M⁺ − H₂O), 371, 164, 148 (base peak). ¹H-NMR (DMSO-*d*₆) δ: 2.04, 2.05, 2.09, 2.11 (total 6H, s each, rotational isomers,

CH₃), 2.23 (3H, s, CH₃), 2.4—3.9 (6H, m, CH₂), 3.60, 3.66, 3.73, 3.77 (total 6H, s each, rotational isomers, OCH₃), 4.2—5.0 (1H, m, CHOH), 5.03, 5.10 (total 2H, s each, PhCH₂), 5.25 (1H, d each, rotational isomers, *J*=4.2 Hz, OH) 6.2—7.5 (14H, m, aromatic H).

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