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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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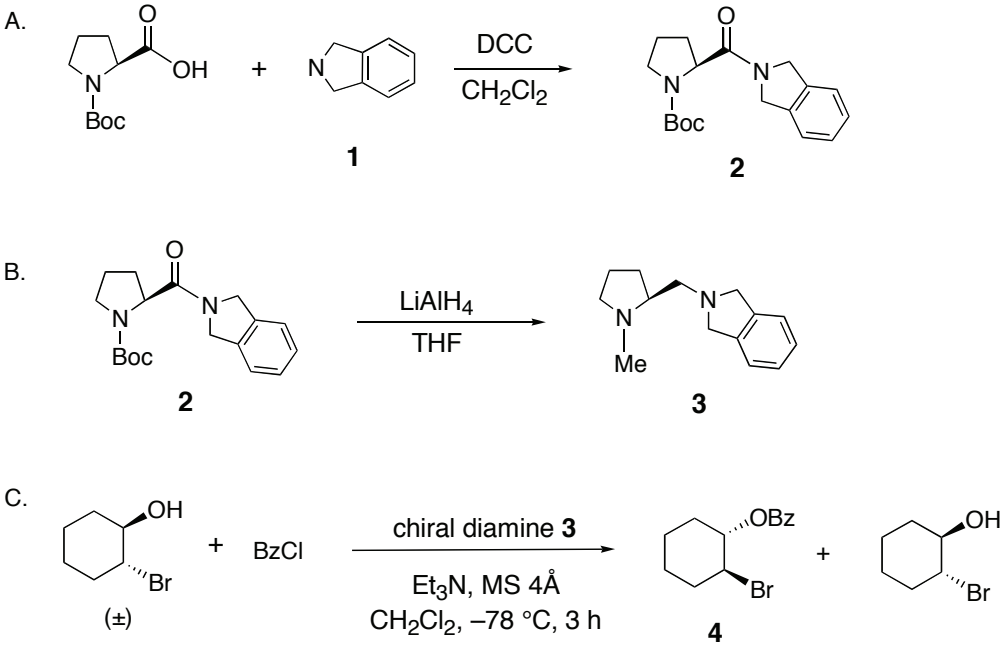
CATALYTIC ASYMMETRIC ACYLATION OF ALCOHOLS USING A CHIRAL 1,2-DIAMINE DERIVED FROM (*S*)-PROLINE: (1*S*,2*S*)-*trans*-1-BENZOYLOXY-2-BROMOCYCLOHEXANE



Submitted by Dai Terakado and Takeshi Oriyama.[1]
Checked by Jing Zhang, Fangzheng Li and Marvin J. Miller.

1. Procedure

A. (S)-N-(N-tert-Butoxycarbonylprolyl)dihydroisoindole (**2**). A dry, 100-mL, two-necked flask equipped with a Teflon-coated magnetic stirring bar and a septum cap is charged with (*S*)-*N*-*tert*-butoxycarbonylproline (5.05 g, 23.5 mmol) (Note 1), dihydroisoindole (2.54 g, 21.3 mmol) (Note 2), and dichloromethane (25 mL) (Note 3) under an argon atmosphere. After cooling to 0 °C with the aid of an ice-water bath, a solution of dicyclohexylcarbodiimide (DCC, 5.1 g, 24.7 mmol) (Note 4) in dichloromethane (20 mL) (Note 3) is added and the reaction mixture is allowed to warm to room temperature while stirring overnight. The mixture is filtered through Celite, concentrated, and purified by column chromatography (Note 5) (ethyl acetate/hexanes:1/3) to afford (*S*)-*N*-(*N*-*tert*-butoxycarbonylprolyl)dihydroisoindole (4.1 g, 61%) as a white

solid (Note 6).

B. (S)-1-Methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (**3**) A dry, 200-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a reflux condenser, a septum cap, and an argon inlet is charged with lithium aluminum hydride (LAH, 0.96 g, 25.3 mmol) in THF (10 mL). After cooling to 0 °C with the aid of an ice-water bath, a solution of (*S*)-*N*-(*N*-*tert*-butoxycarbonylprolyl)dihydroisoindole (3.96 g, 12.5 mmol) in THF (15 mL) was added under an argon atmosphere. The cooling bath is removed and the reaction mixture is refluxed for 3 h. After cooling the mixture to 0 °C, the reaction is quenched carefully by the slow addition of saturated aqueous sodium sulfate (approx 5 mL). The liquid is decanted away from the precipitate, and the precipitate was washed with THF (2 x 20 mL). The combined liquid is dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel (CH_2Cl_2/MeOH/Et_3N:95/5/1), to afford (*S*)-1-methyl-2- [(dihydroisoindol-2-yl)methyl]pyrrolidine (**3**) (1.56 g, 58%) (Note 7).

C. (1S,2S)-trans-1-Benzoyloxy-2-bromocyclohexane (**4**). A 100-mL, two-necked flask equipped with a Teflon-coated magnetic stirring bar and a septum cap is charged with 1 g of molecular sieves 4 Å (Note 8), and flame-dried under reduced pressure. After being allowed to warm to ambient temperature, the apparatus is flushed with argon. The flask is charged with (*S*)-1-methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (65 mg, 0.28 mmol) in dichloromethane (5 mL) (Note 3), triethylamine (5.56 g, 55 mmol) (Note 9) in dichloromethane (15 mL), and racemic *trans*-2-bromocyclohexanol (17.91 g, 100 mmol) (Note 10) in dichloromethane (40 mL) by means of an oven-dried syringe and needle. After cooling to –78 °C by immersion in a dry-ice bath, benzoyl chloride (9.14 g, 65 mmol) (Note 11) in dichloromethane (20 mL) is added slowly over 30 min by means of an oven-dried syringe and needle. The solution is stirred for 3 h at –78 °C, and then quenched with a phosphate buffer (pH 7) (Note 12). The layers are separated and the aqueous layer extracted with diethyl ether (3 x 50 mL). The combined organic phase is washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated under

vacuum. The crude products are purified by column chromatography (Note 13) (ethyl acetate/hexanes:1/50) to give (1*S*, 2*S*)-*trans*-1-benzoyloxy-2-bromocyclohexane (14.25 g, 50%) (Note 14) and unreacted alcohol (1*R*, 2*R*)-*trans*-2-bromocyclohexanol (6.60 g, 37%) (Note 15).

2. Notes

1. The checkers purchased (*S*)-*N*-*tert*-butoxycarbonylproline from Aldrich Chemical Company.

2. The checkers purchased dihydroisoindole (isoindoline) from Aldrich Chemical Company.

3. Dichloromethane was purchased by the submitters as anhydrous solvent from Kanto Chemical Company, Inc., and used without further purification. The dichloromethane used by the checkers was purchased from Fisher Scientific and distilled from CaH_2 prior to use.

4. Dicyclohexylcarbodiimide (DCC) used by the submitters was purchased from Tokyo Kasei Kogyo Co. The checkers used DCC purchased from Aldrich Chemical Co. The submitters reversed the addition by adding the substrates to the DCC mixture. However, the checkers found that the substrates were incompletely soluble in methylene chloride and that transfer was then incomplete.

5. Column chromatography was performed (38 mm x 600 mm column) on Wakogel C-200 that purchased from Wako Chemical Company, Inc. The checkers used Merck silica gel with a 45 mm x 200 mm column.

6. The submitters reported 100% yield. The analytical and spectral data of (*S*)-*N*-(*N*-*tert*-butoxycarbonylprolyl)dihydroisoindole are as follows: mp 150–152 °C (decompose), $[\alpha]_D^{24}$ –18.4 (*c* 1.0, EtOH). The checkers obtained $[\alpha]_D$ –19.8 (*c* 1.0, EtOH); The NMR spectra show the presence of two rotameric forms in an approximate 1:1 ratio. Resonances for both rotamers are included in the following characterization data. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (s, 9 H), 1.46 (s, 9 H), 1.82–2.02 (m, 4 H), 2.08–2.29 (m, 4 H), 3.42–3.68 (m, 4 H), 4.47 (dd, 1 H, *J* = 8.1, 4.8 Hz), 4.59 (dd, 1 H, *J* = 7.7, 3.3 Hz), 4.72–4.91 (m, 6 H), 4.99 (d, 1 H, *J* = 13.6 Hz), 5.18 (d, 1 H, *J* = 13.6 Hz), 7.22–7.32 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.94 (CH_2), 24.55 (CH_2), 28.50 (CH_3), 28.63 (CH_3), 29.64 (CH_2), 30.49 (CH_2), 46.82 (CH_2), 47.03 (CH_2), 52.35 (CH_2), 52.46 (CH_2), 52.56 (CH_2), 57.55 (CH), 57.89 (CH), 79.69 (C), 79.77 (C), 122.70 (CH), 122.75 (CH), 123.02

(CH), 123.20 (CH), 127.53 (CH), 127.73 (CH), 127.83 (CH), 128.07 (CH), 136.13 (C), 136.26 (C), 136.42 (C), 136.50 (C), 153.92 (C), 154.71 (C), 171.73 (C), 171.89 (C); IR (neat) cm^{-1}: 2967, 2867, 1694, 1653, 1405, 1358, 1163, 1127, 888, 755; MS (FAB) exact mass, (*m/z*) Calcd for $C_{18}H_{24}N_2O_3$ 317.1865, Found 317.1862; Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.16; H, 7.60; N, 8.65.

7. The submitters reported 60% yield after distillation under reduced pressure. The checkers had difficulty with reproducibility using distillation. The yield obtained by the checkers after chromatography varied between 58% and 65%. The checkers used Merck silica gel with a 45 mm x 200 mm column. The analytical and spectral data of (*S*)-1-methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine are as follows: bp 112–114 °C / 0.6 mmHg, $[\alpha]_D^{24}$ –70.4 (*c* 1.1, EtOH), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.58–1.84 (m, 3 H), 1.94–2.06 (m, 1 H), 2.16 (dt, 1 H, *J* = 9.6, 7.8 Hz), 2.30 (m, 1 H), 2.40 (s, 3 H), 2.62 (dd, 1 H, *J* = 11.7, 7.8 Hz), 2.88 (dd, 1 H, *J* = 12, 4.8 Hz), 3.03 (m, 1 H), 3.89 (s, 4 H), 7.11 (s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.60 (CH_2), 30.53 (CH_2), 41.35 (CH_3), 57.67 (CH_2), 59.96 (CH_2), 60.94 (CH_2), 64.96 (CH), 122.04 (CH), 126.50 (CH), 140.28 (C); IR (neat) cm^{-1}: 2938, 2771, 1463, 1149, 742; MS (FAB) exact mass (*m/z*) Calcd for $C_{14}H_{20}N_2$ 217.1705, Found 217.1701. Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.72; H, 9.32; N, 12.95. Found: C, 77.34; H, 9.53; N, 12.83.

8. Molecular sieves 4Å were purchased from Wako Chemical Company, Inc., and dried at 100 °C for 3 h as a powder under reduced pressure before use. The checkers used molecular sieves purchased from Aldrich Chemical Company.

9. Triethylamine was purchased from Tokyo Kasei Kogyo Co., and distilled before use. The triethylamine used by the checkers was purchased from Aldrich Chemical Company and was distilled from CaH_2 prior to use.

10. *trans*-2-Bromocyclohexanol was prepared from cyclohexene oxide and hydrobromic acid according to the following procedure: A 200-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with hydrobromic acid (47%, 40 mL, 346 mmol) and cooled at 0 °C by immersion in an ice-water bath. Cyclohexene oxide (20 mL, 198 mmol) is added dropwise and the mixture is stirred at room temperature for 8 h. After being cooled to 0 °C, the solution is neutralized by addition of saturated aqueous Na_2CO_3 (approx 30 mL) (*Caution: slow addition of the Na_2CO_3 solution is recommended due to excessive bubbling of the solution*), and extracted with diethyl ether (3 x 30 mL). The combined

organic phases are dried over anhydrous sodium sulfate, filtered, concentrated, and distilled under reduced pressure to give *trans*-2-bromocyclohexanol (30.0 g, 85%) (bp 92 °C / 11 mmHg).

11. BzCl was purchased from Tokyo Kasei Kogyo Co., and distilled before use.

12. The buffer was prepared by dissolving 33.4 g of disodium hydrogenphosphate dodecahydrate and 6.4 g of potassium dihydrogenphosphate into 300 mL of water. The buffer solution was diluted to a final volume of 700 mL and stored in a glass bottle.

13. The checkers used Merck silica gel with a 70 mm x 200 mm column.

14. The checkers obtained 13.65 g (48%) of the benzoate (**4**) and 7.59 g (42%) of the alcohol. The submitters determined the enantiomeric excess of the benzoate (95% *ee*) by HPLC analysis using a Daicel CHIRALCEL OD column (*i*-PrOH:hexanes = 1:1000, 1.0 mL/min, 254 nm). The retention times for the (1*S*,2*S*)-*trans*-1-benzoyloxy-2-bromocyclohexane are 14.6 min ((+)-1*S,*2*S*) and 16.7 min ((–)-1*R,*2*R*). The checkers determined the enantiomeric excess of the benzoate to be 90% using a 25 x 0.46 cm Daicel CHIRALPAK AD-H column (*i*-PrOH:hexanes = 1:9, 1.0 mL/min, 254 nm). The retention times are 5.05 and 5.31 min. The analytical and spectral data of pure (1*S*, 2*S*)-*trans*-1-benzoyloxy-2-bromocyclohexane are as follows: $[\alpha]_D^{24}$ +104.6 (*c* 1.0, $CHCl_3$, 90.0% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35–1.44 (m, 1 H), 1.48–1.57 (m, 2 H), 1.75–1.85 (m, 2 H), 1.91–1.99 (m, 1 H), 2.25–2.33 (m, 1 H), 2.39–2.45 (m, 1 H), 4.16 (m, 1 H), 5.14 (dt, 1 H, *J* = 9.0, 4.5 Hz), 7.46 (t, 2 H, *J* = 7.5 Hz), 7.57 (m, 1 H), 8.07 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.5 (CH_2), 25.6 (CH_2), 31.3 (CH_2), 35.7 (CH_2), 52.8 (CH), 76.5 (CH), 128.5 (CH), 129.9 (CH), 130.4 (C), 133.2 (CH), 165.8 (C); IR (neat) cm^{-1}: 2941, 1720, 1450, 1274, 1104, 1027, 945, 711; MS (FAB) exact mass (*m/z*) Calcd for $C_{13}H_{15}BrO_2$ 283.0334, Found 283.0308. The submitters report that the product gave the following elemental anlysis: Anal. Calcd for $C_{13}H_{15}BrO_2$: C, 55.14; H, 5.34. Found: C, 55.05; H, 5.42.

15. The enantiomeric excess was determined by the submitters to be >99% by HPLC analysis using Daicel CHIRALCEL OD (*i*-PrOH:hexanes = 1:1000, 1.0 mL/min, 254 nm) after conversion to the corresponding benzoate. The retention times for the (1*R*, 2*R*)-*trans*-1-benzoyloxy-2-bromocyclohexane are 14.3 min ((+)-1*S*,2*S*) and 16.8 min ((–)-1*R*,2*R*). The analytical and spectral data of (1*R*, 2*R*)-*trans*-2-bromocyclohexanol are

as follows: $[\alpha]_D^{24}$ –33.0 (*c* 1.0, $CHCl_3$, 99.3% ee); ^1H NMR (500 MHz, $CDCl_3$) δ: 1.22–1.40 (m, 3 H), 1.65–1.70 (m, 1 H), 1.77–1.86 (m, 2 H), 2.10–2.16 (m, 1 H), 2.30–2.36 (m, 1 H), 2.62 (brs, 1 H), 3.60 (dt, 1 H, *J* = 9.9, 4.5 Hz), 3.89 (ddd, 1 H, *J* = 12.1, 9.5, 4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.26 (CH_2), 26.8 (CH_2), 33.7 (CH_2), 36.4 (CH_2), 61.96 (CH), 75.4 (CH); IR (neat) cm^{-1}: 3350, 2835, 1450, 1070, 955.

Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Asymmetric acylation of alcohols is divided into two types of reactions. These are kinetic resolution of racemic alcohols and desymmetrization of meso-polyols. Although most methods reported so far employ an enzyme such as a lipase or an esterase,[2] some outstanding asymmetric acylations of alcohols by using organocatalysts[3] have recently emerged as reliable alternatives to the well established enzyme-catalyzed reactions.

Kinetic resolution of racemic alcohols via asymmetric acylation has been widely used to construct various useful chiral building blocks in the synthesis of complex natural products.[4] The submitters have demonstrated highly enantioselective desymmetrization of *meso*-diols[5] and highly efficient kinetic resolution of racemic secondary alcohols[6] catalyzed by a chiral 1,2-diamine derived from (*S*)-proline.

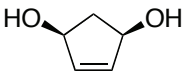
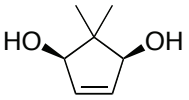
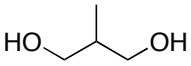
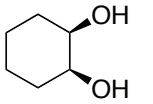
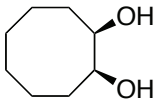
Chiral diamine catalysts can be readily prepared in three steps from (*S*)-proline. This type of a 1,2-diamine is frequently used in important and fundamental asymmetric syntheses.[7] This diamine has an advantage in that the non-proline amine portion can be easily modified to include, for example, cyclic pyrrolidine, piperidine, indoline skeletons, or the acyclic benzyl-methylamino skeleton. More efficient reactions and higher enantioselectivities during asymmetric acylation of alcohols are achieved by

using a chiral diamine containing a dihydroisoindole or a benzyl-methylamino component. Representative results of asymmetric acylation of alcohols catalyzed by chiral 1,2-diamines are shown in Tables I and II. (1*S*,2*S*)-*trans*-1-Benzoyloxy-2-bromocyclohexane is a valuable synthetic precursor for allylic alcohol derivatives. An enantio-enriched allylic benzoate can be provided via β-elimination. Treatment of **4** with DBN (1,5-diazabicyclo[4.3.0]non-5-ene) in refluxing toluene gives the corresponding allylic benzoate, (*S*)-1-benzoyloxy-2-cyclohexene, without loss of enantio-purity.[6c]

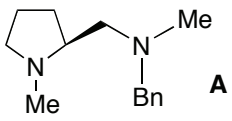
We have presented a promising small organocatalyst for asymmetric acylation of various alcohols including racemic secondary alcohols and *meso*-1,2-, 1,3-, and 1,4-diols. Catalytic asymmetric acylation of alcohols by using a chiral 1,2-diamine has the following distinguishing synthetic features: 1) high enantioselectivity, 2) high efficiency, 3) operational simplicity, 4) widespread applicability, and 5) the absence of a metal.

TABLE II

CHIRAL 1,2-DIAMINE CATALYZED ASYMMETRIC DESYMMETRIZATION OF *meso*-DIOLS[a]

Entry	*meso*-Diol	Amine	Solvent	Monoester Yield[b] / %	Monoester ee[c] / %
1[d]		Et_3N	PrCN	38	98
2[d,e]		Et_3N	PrCN	87	>99
3[f]		*i*-Pr_2NEt	CH_2Cl_2 - DMF (9 : 1)	57	>99
4		*i*-Pr_2NEt	PrCN	33	96
5[g,h]		Et_3N	CH_2Cl_2	92	98
6[g,h]		Et_3N	CH_2Cl_2	92	99

a) Reaction conditions : MS 4Å (40 mg), chiral 1,2-diamine (0.0015 mmol), amine (0.45 mmol), diol (0.3 mmol), *p*-*t*-BuC_6H_4COCl (0.45 mmol), –78 °C, 3 h. b) Isolated yield of purified product. c) Determined by chiral HPLC analysis. d) 0.51 mmol of BzCl and Et_3N were used. e) Reaction was performed for 8 h. f) Chiral 1,2-diamine **A** was used. g) 0.003 mmol of chiral 1,2-diamine and 0.3 mmol of Et_3N were used and silylation of monoalcohol was performed in one-pot after acylation for 3 h. h) *p*-$CH_3C_6H_4COCl$ was used instead of *p*-*t*-BuC_6H_4COCl.



A

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);

Di-*tert*-butyl dicarbonate: Formic acid, oxydi-, di-*tert*-butyl ester; Dicarbonic acid, bis(1,1-dimethylethyl)ester; (24424-99-5)

tert-Butoxycarbonyl-L-proline: 1,2-Pyrrolidinedicarboxylic acid, 1-(1,1-dimethylethyl)ester, (*S*)-*tert*-Butoxycarbonyl-L-proline (15761-39-4)

Isoindoline, 1,3-Dihydroisoindole: 1*H*-Isoindole, 2,3-dihydro-; (496-12-8)

Dicyclohexylcarbodiimide: Carbodiimide, dicyclohexyl-; Cyclohexanamine, *N,N′*-methanetetraylbis-; (538-75-0)

(*S*)-*N*-(*N*-*tert*-Butoxycarbonylprolyl)dihydroisoindole (188122-39-6)

(*S*)-1-Methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (159497-37-7)

trans-2-Bromocyclohexanol; (2425-33-4)

(1*S*, 2*S*)-1-Benzoyloxy-2-bromocyclohexane; Cyclohexanol, 2-bromo-, benzoate, (1*S*,2*S*)-; (222851-77-6)

STANDARD 1H OBSERVE

exp1 s2pul

SAMPLE		DEC. & VT	
date	Apr 28 2004	dfrq	299.948
solvent	cdcl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	299.948	dm	nnn
tn	H1	dmm	c
at	4.096	dmf	200
np	32768	dseq	
sw	4000.0	dres	1.0
fb	2200	homo	n
bs	4	PROCESSING	
tpwr	59	wtfile	
pw	14.0	proc	ft
d1	0.100	fn	65536
tof	0	math	f
nt	16		
ct	16	werr	
alock	n	wexp	proc_H
gain	not used	wbs	
FLAGS		wnt	
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	215.1		
wp	2222.1		
vs	134		
sc	0		
wc	250		
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is	172.84		
rfl	500.1		
rfp	0		
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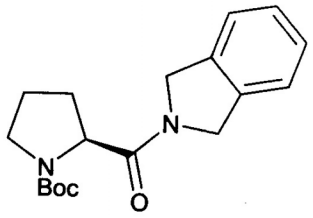
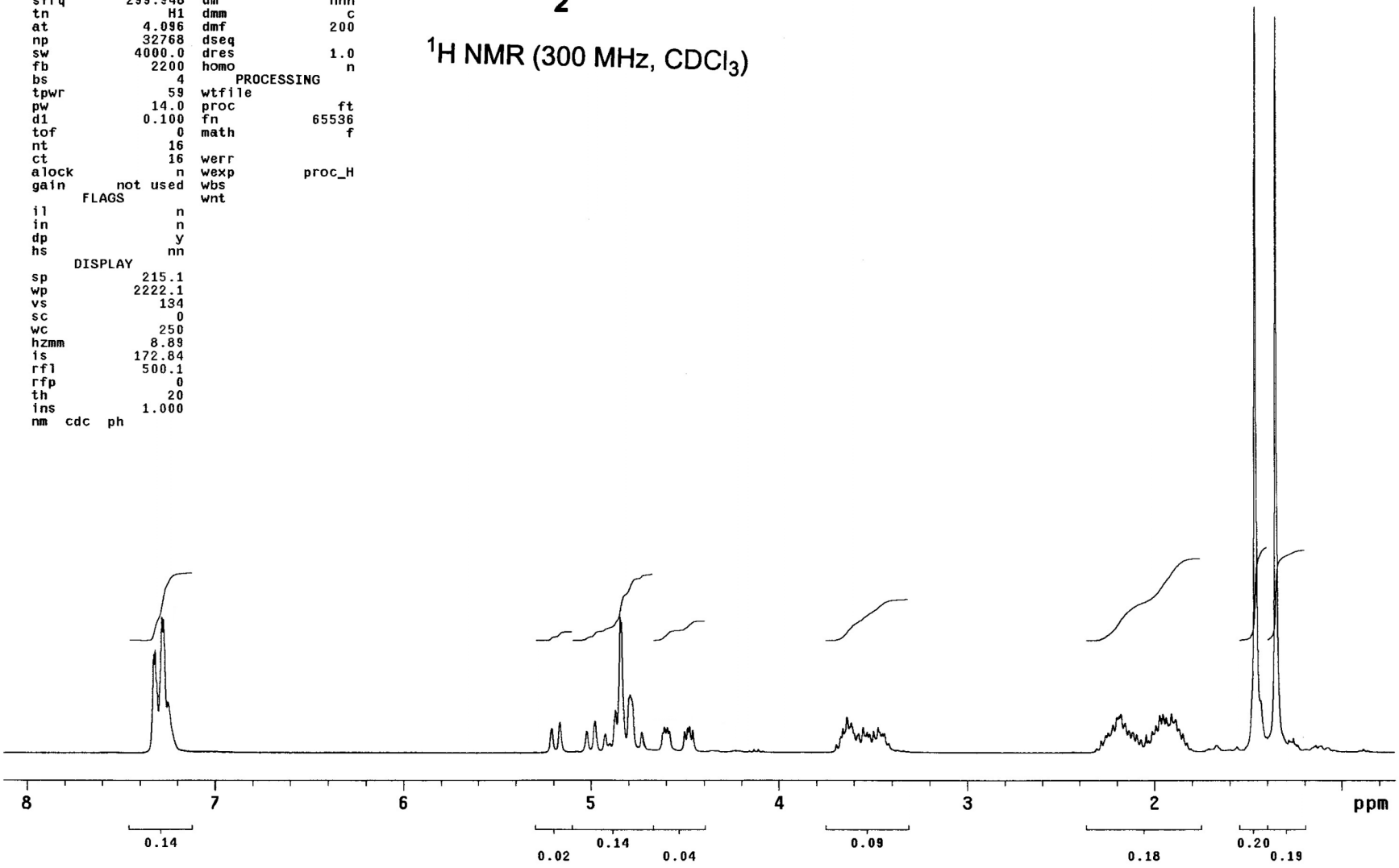
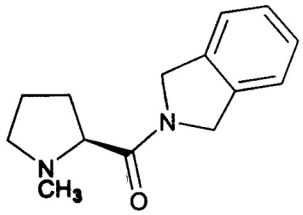
nm cdc ph			



2

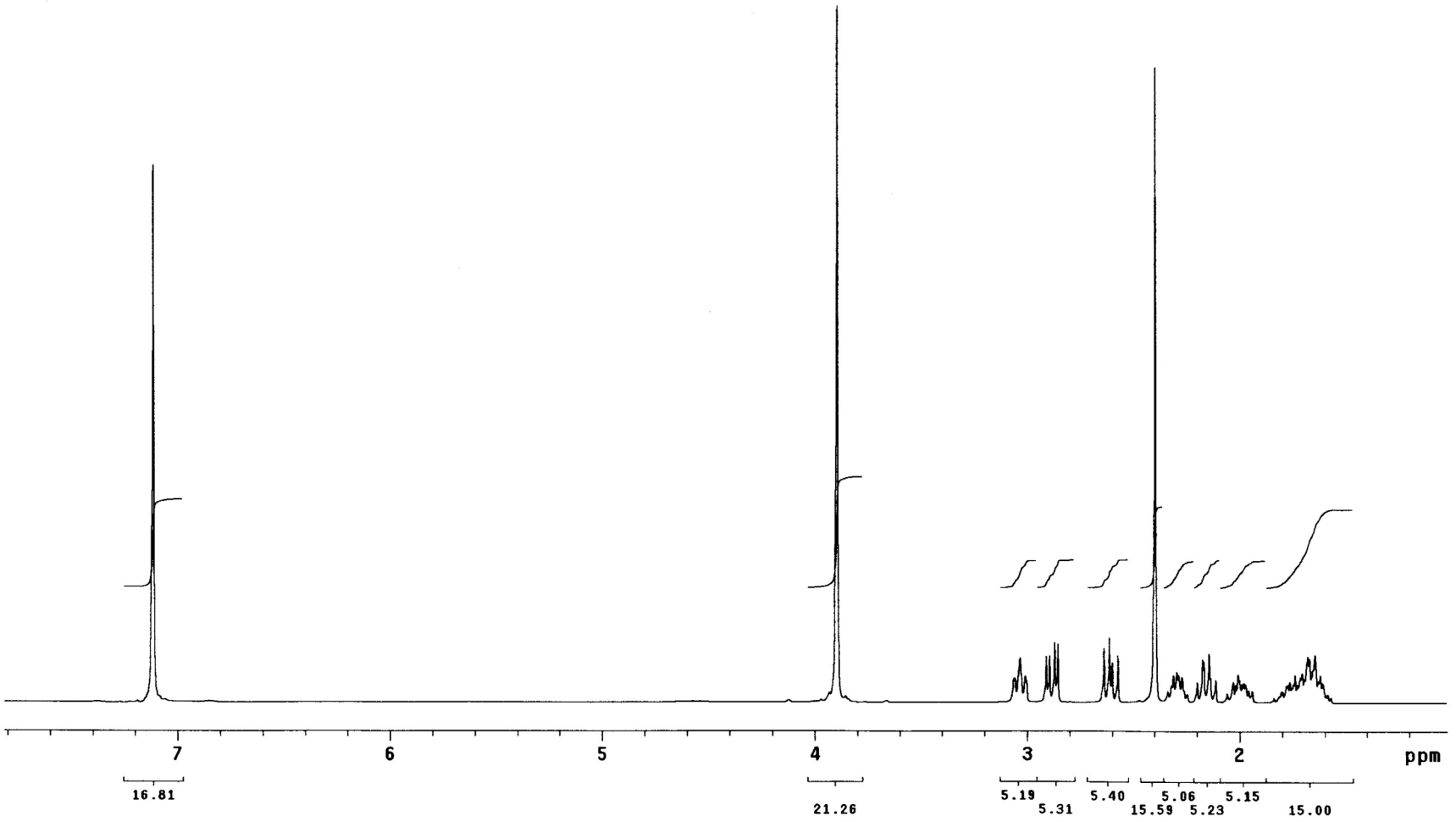
^{1}H NMR (300 MHz, $CDCl_3$)

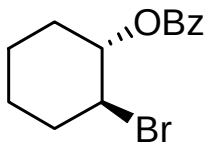




3

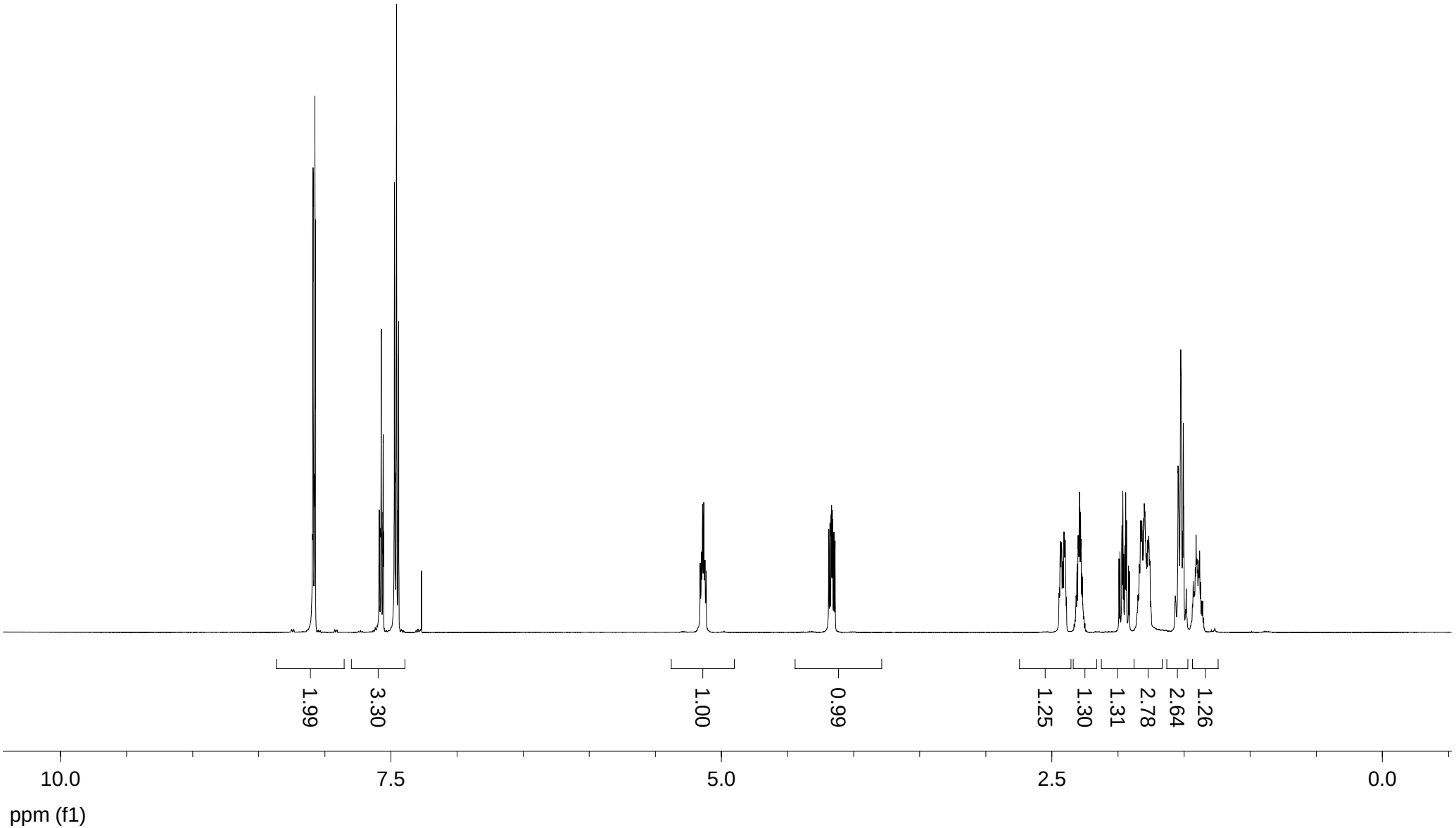
^{1}H NMR (300 MHz, $CDCl_3$)

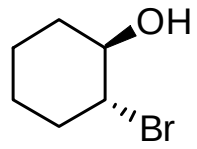




4

^{1}H NMR (500 MHz, $CDCl_3$)





^{1}H NMR (500 MHz, $CDCl_3$)