Asymmetric Synthesis of *cis*-2,5-Disubstituted Pyrrolidine, the Core Scaffold of β_3-AR Agonists

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Supporting Information

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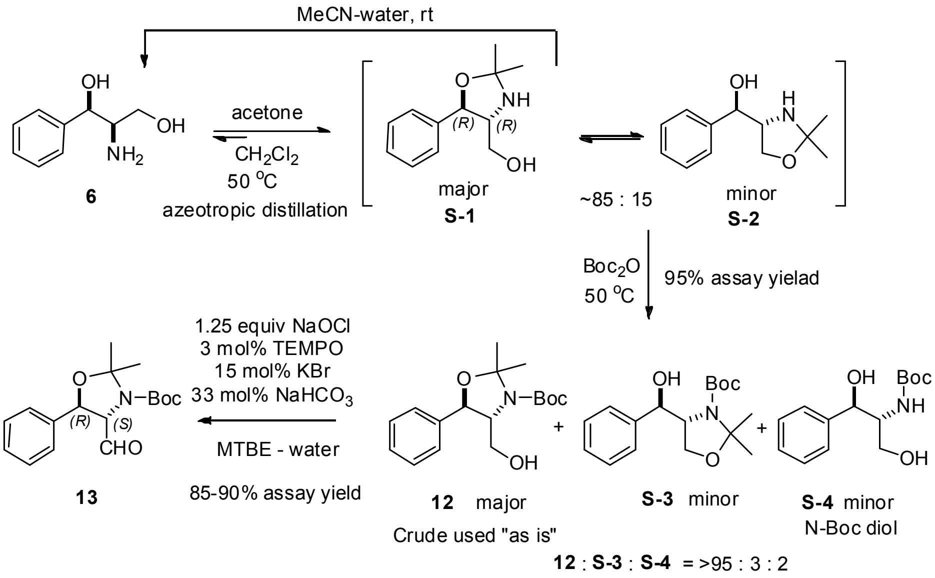
1. Alternative synthesis of aldehyde 13

Alternative preparation of aldehyde **13** from (1R,2R)-2-amino-1-phenylpropane-1,3-diol (**6**) is depicted in Scheme S-1. Protection of diol **6** resulted in a mixture of acetonides **S-1** and **S-2**. The solvent-dependent ratio of **S-1** and **S-2** was a result of thermodynamic equilibrium between **S-1** and **S-2** under the reaction conditions. Typically, by heating **6** in a mixture of acetone and dichloromethane or toluene under Dean–Stark conditions, a 85:15 mixture of **S-1**/**S-2** in favor of **S-1** was obtained. The resulting reaction solution was then treated with 1.1 equiv of Boc$_2$O at ambient temperature to 45 ºC to afford *N*-Boc oxazolidine **12** in 95% assay yield, albeit the ratio of the Boc protection products was 95:3:2 (**12** : **S-3** : **S-4**). Benefiting from the equilibration between acetonide alcohols **S-1** and **S-2**, the ratio of Boc protected acetonides (**12** : **S-3**) was improved because the major isomer **S-1** reacted with Boc$_2$O faster than the minor isomer **S-2**. In addition, the removal of water was important to achieve higher conversion for the acetonide formation and therefore to minimize the formation of *N*-Boc diol byproduct **S-4**.

Scheme S-1. Preparation of aldehyde **13**

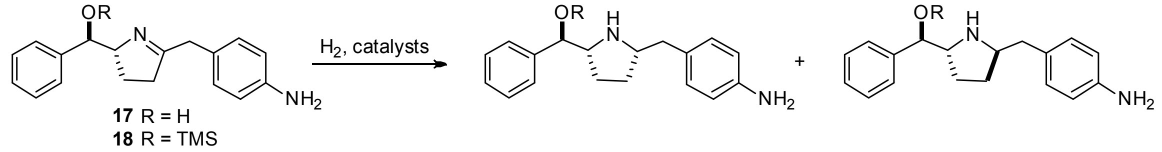


The crude Boc protected reaction mixture (in MTBE) after work-up was used directly "as-is" in the TEMPO oxidation to give aldehyde **13** in 85-95% assay yield.

Attempts to use 2,2-dimethoxypropane instead of acetone (10 mol% TsOH in toluene at up to 80 °C) for the oxazolidine formation gave only ~20% conversion. Similarly, an attempt to reverse the order of acetonide and Boc protection, by forming *N*-Boc amino diol **S-4** first followed by treating with 2,2-dimethoxypropane, in the presence of a catalytic amount of TsOH, afforded an unsatisfactory mixture of desired **12** and regioisomer **S-3**.

2. Diastereoselective hydrogenation of imines 17 and 18

Table S-1. Selected Results of Hydrogenation of Imines **17** and **18**[a]



17 R = H
18 R = TMS

entry	substrates	catalysts	Solvents	additives	conv (%)[b]	cis/trans[b]
1	**17**	Pd/C	*i*-PrOH		64	60:40
2	(R = H)	Pt/C	*i*-PrOH	Na_2CO_3		71:29
3		Pd/C	EtOH		93	56:44
4		$Pd(OH)_2$	*i*-PrOH			60:40
5		Pd/Al_2O_3	MeOH			44:55
6		Pd/Al_2O_3	MeOH	Na_2CO_3		44:55
7		Rh/Al_2O_3	MeOH		94	61:39
8		Rh/Al_2O_3	MeOH	Na_2CO_3		76:24
9		Pt/Al_2O_3	*i*-PrOH		>99	84:16
10		Pt/Al_2O_3	EtOH			73:27
11		Pt/Al_2O_3	MeOH			77:23
12		Pt/Al_2O_3	H_2O			81:19
13		Pt/Al_2O_3	CF_3CH_2OH			66:34
14		Pt/Al_2O_3	DMF			81:19
15		Pt/Al_2O_3	THF	Na_2CO_3		87:13
16		Ru/C	*i*-PrOH		61	84:16
17		Ru/C	EtOAc			79:21
18		PtO_2	EtOH		69	66:33
19		Raney Ni[c]	MeOH		>99	96:4[c]
20		Raney Ni[d]	MeOH		>99	92:8[d]
21	**18**	Pt/Al_2O_3	DMF		>99	96:4
22	(R = TMS)	Pt/C	THF		>99	96:4
23		Rh/Al	THF		72	98:2
24		Pd/C	THF		78	91:9
25		Pd/Al	THF		37	95: 5

[a] Unless otherwise mentioned, all reactions were carried out at 25 °C, 15–40psi H_2 with 10–25 wt% catalyst loading.

[b] Determined by HPLC analysis: Waters Xbridge C18 column, 3.5µm particle size, 150 × 4.6mm; mobile phase: 0.1% aqueous NH_4OH adjust to pH 9.5 with HCl / acetonitrile, 1ml/min flow rate, 25 °C, detection at 210 nm.

[c] 75 °C, 40psi H_2, 100 wt% Raney Ni.

[d] 50 °C, 40psi H_2, 100 wt% Raney Ni.

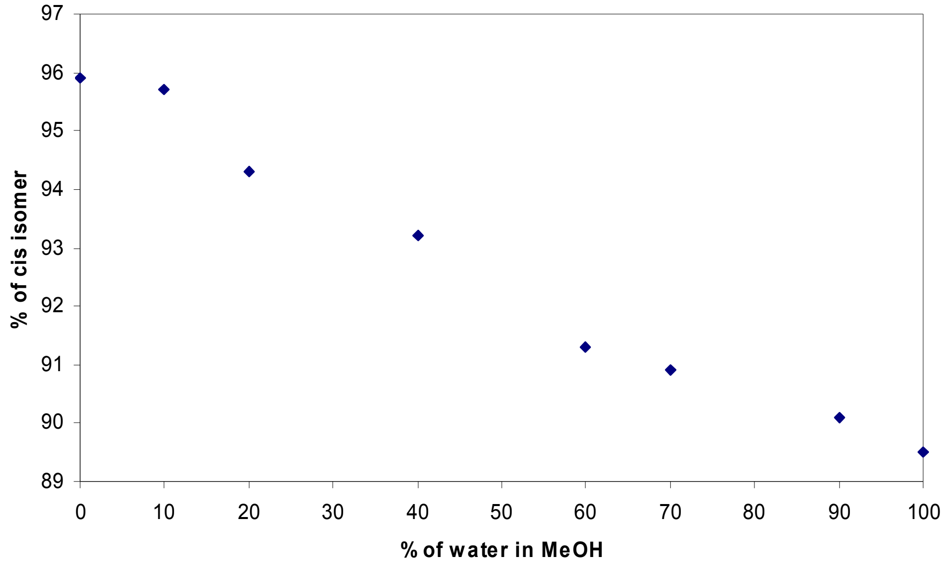
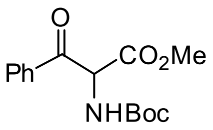


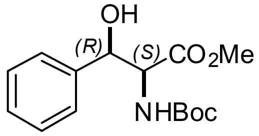
Figure S-1. Hydrogenation of alcohol imine **17** in the presence of Raney Ni: Water effect on diastereoselectivity. Reaction conditions: 75 °C, 40psi H_2, 100wt% Raney Ni with various ratios of MeOH–water.

3. Experimental Procedure

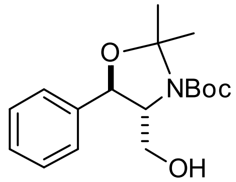


Methyl 2-((tert-butoxycarbonyl)amino)-3-oxo-3-phenylpropanoate (9). To a mixture of Na_2CO_3 (110 g, 1.034 mol) in water (600 mL) and EtOAc (600 mL) at 0-5 ^{o}C was added glycine methyl ester hydrochloride (119 g, 0.948 mol) in portions over 30 min. The resulting slurry was aged for additional 15-30 min, PhCOCl (100 mL, 0.862 mol) was then added dropwise over 1.5 h at 0-5 ^{o}C. After aging additional 1 h at 0-5 ^{o}C, the reaction mixture was warmed to 25 ^{o}C and formed a homogenous biphasic solution. The separated organic phase was azeotropically concentrated and solvent switched to MeCN at a final volume of ~600 mL. DMAP (43.1 mmol, 5.26 g) was added. A solution of Boc_2O (0.948 mol, 207 g) in MeCN (200 mL) was added at ambient temperature dropwsie over 2-3 h. After the reaction solution was stirred at ambient temperature for ~6 h, the batch was vacuum degassed with N_2 to remove CO_2 generated in the amidation step. THF (540 mL) was added. Then, a solution of *t*-BuOK (1.12 mol, 128 g, 97%) in THF (670 ml) was added at 0-10 ^{o}C dropwise over 1-2 h. After aging at 0-5 ^{o}C for additional 1 h, a solution of 15 wt% citric acid in water (0.431 mol, 91 g citric acid in 515 mL H_2O) was added at <10 ^{o}C. The organic phase was washed with 480 mL of half saturated aqueous NaCl, and solvent switched to *i*-PrOH at a final volume of ~1.25 L containing ~10% water at < 45 ^{o}C. Water (1.25 L) was added dropwise at 40-50 ^{o}C over 2 h. Then, the slurry was cooled to ambient temperature and aged for 1-2 h before filtration. The wet cake was displacement washed with 30% *i*-PrOH in water (640 mL x 2), and vacuum oven dried at < 50 ^{o}C to give 227 g of white crystalline solid **9**. 90% yield. m.p. 96-97 °C; ^{1}H NMR (400 MHz, d_6-DMSO): major rotomer:

δ 7.95 (d, J = 7.6 Hz, 2 H), 7.86 (d, J = 8.4 H, 1 H), 7.69 (m, 1 H), 7.55 (m, 2 H), 5.89 (d, J = 8.4 Hz, 1 H), 3.67 (s, 3 H), 1.38 (3, 9 H); ^{13}C NMR (100 MHz, *d*$_6$-DMSO): major rotomer: δ 192.9, 168.3, 155.5, 134.5, 133.9, 128.74, 128.68, 79.1, 59.1, 52.4, 28.0; HRMS calc'd for $C_{15}H_{19}NO_5$ $[M+Na]^+$ 316.1155, found 316.1156.



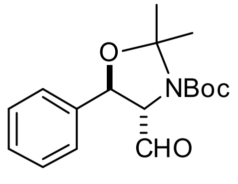
Methyl (2S,3R)-2-((tert-butoxycarbonyl)amino)-3-hydroxy-3-phenylpropanoate (10). To a solution of K_2HPO_4 (141 g) in water (800 mL) at ambient temperature was added dextrose (98 g, 0.49 mol) followed by NADP (3.6 g), GDH-105 (1.15 g), CDX-018 (2.9 g). The resulting homogenous solution was pH adjusted to a minimum of 7.5 with 2M NaOH prior to use. A solution of ketone **9** (120 g, 0.409 mol) in DMSO (360 mL) was added over 4 h at 30 °C with vigorous agitation, while 2M NaOH (~2.1 L total) was added dropwise to maintain the reaction mixture at pH = 7.3–7.7. Once 90% (~1.9 L) of 2M NaOH solution was added, the reaction temperature was raised to 35 °C until >95% conversion was achieved. *i*-PrOH (0.9 L) followed by MTBE (0.49 L) were added and the organic phase was separated. The aqueous phase was extracted with *i*-PrOH:MTBE (1.4 L, *i*-PrOH:MTBE = 20:80). The combined organic phase was washed with brine (0.5 L, 10% w/v brine) and the crude product containing compound **10** was directly used for the next step. 90-92% assay yield.



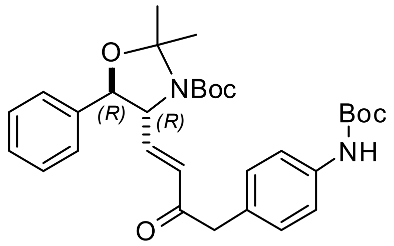
***tert*-Butyl (4*R*,5*R*)-4-(hydroxymethyl)-2,2-dimethyl-5-phenyl-1,3-oxazolidine-3-carboxylate (12).** To a toluene solution of ester **10** (35.9 mmol, 10.6 g, in ~25 to 30 mL toluene, crude solution from previous DKR step) were added acetone (50 mL) and 2,2-dimethoxy propane (20 mL). A solution of $BF_3{\cdot}$etherate (3.59 mmol, 0.43 mL) in toluene (2 mL) was then added via a syringe pump at ambient temperature over 2 h. The reaction solution was aged at ambient temperature for 15h. Et_3N (3.59 mmol, 0.5 mL) was added dropwise. After aging for additional 15 min, the solution was solvent switched to toluene (~30 mL) while most of the acetone was removed in vacuum. MTBE (60 mL) was added and the organic phase was washed with 5% $NaHCO_3$/brine (40 mL). The organic phase was azeotropically dried and solvent switched to toluene at a final volume of ~35-40 mL (95% assay yield of **11**).

The above solution was added to a mixture of $LiBH_4$ (44.3 mmol, 966 mg) in THF (60 mL) over 30 min. The reaction mixture was aged for 15 h at 35 °C. The reaction solution was cooled to ambient temperature and added to a solution of 10% NH_4Cl (40 mL) below 5 °C with external cooling. The quenched solution was aged at ambient temperature for 2-3 h or until the evolution of H_2 gas ceased. MTBE (100 mL) was added. The separated organic layer was solvent switched to toluene at a final volume of ~40 mL, which was directly used in the subsequent oxidation step. 92% assay yield of **12**.

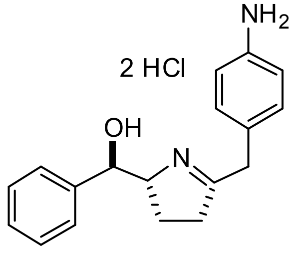
An analytically pure sample of **12** was obtained by crystallization from toluene/heptane: m.p. 69-72 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (m, 2 H), 7.37 (m, 3 H), 4.78 (br s, 1 H), 4.58 (br s, 1 H), 3.82 (br s, 2 H), 3.70 (br m, 1 H), 1.71 (s, 3 H), 1.59 (s, 3 H), 1.53 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3, 137., 129.0, 128.9, 127.5, 94.9, 81.6, 78.6, 67.9, 63.7, 28.6, 27.9, 26.2; Anal. Calcd. for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56; Found: C, 66.33; H, 8.43; N, 4.59.



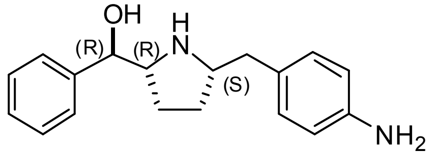
***tert*-Butyl (4S,5R)-4-formyl-2,2-dimethyl-5-phenyloxazolidine-3-carboxylate (13).** To a solution of alcohol **12** in toluene (65.07 mmol, 20 g assay, ~60 mL) was added acetonitrile (120 mL) at ambient temperature. KBr (9.76 mmol, 1.16 g), $NaHCO_3$ (21.48 mmol, 1.8 g) and water (40 mL) were then charged. The biphasic mixture was cooled to 5 °C and TEMPO (1.95 mmol, 305 mg) was added. Then, 6 wt% NaOCl solution (81.38 mmol, 101 g) was added dropwise at 0-5 °C over 2 h. After addition, the reaction was stirred at 5 °C for additional 30 min. The reaction was quenched by dropwise addition of 10% sodium sulfite (50 mL) at 5 °C. The organic layer was separated and directly used for the subsequent HWE coupling step without further purification. The assay yield of **13** was 17.5 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$): **12** exists as a mixture of two rotomers. Overlap of signals does not permit unequivocal assignment of each rotomers. δ 9.62-9.50 (br d, 1 H), 7.5-7.4 (m, 5 H), 4.99 (d, 1 H), 4.3-4.1 (br m, 1 H), 1.8-1.7 (m, 6 H), 1.55-1.47 (m, 9 H); Selected data of ^{13}C NMR (100 MHz, $CDCl_3$): Some ^{13}C signals are too broad to be assigned due to a mixture of rotomers at 20 °C. δ 197.2, 136.7, 129.1, 129.0, 126.7, 96.2, 81.9, 76.3, 71.5, 28.4, 26.4, 25.5.



***tert*-Butyl (4R,5R)-4-((E)-4-(4-((tert-butoxycarbonyl)-amino)-phenyl)-3-oxobut-1-en-1-yl)-2,2-dimethyl-5-phenyloxazolidine-3-carboxylate (14).** To a solution of aldehyde **13** in wet toluene/acetonitrile (57.3 mmol, 17.5 g assay; 10.81 wt%, 162 g crude stream solution) obtained above at -10 °C were added acetonitrile (140 mL), phosphonate **4** (68.8 mmol, 24.6 g) and LiBr (171.9 mmol, 14.9 g) while the internal temperature was maintained below 0 °C. Then, Hunig's base (171.9 mmol, 22.2 g) was added at 0-5 °C dropwise over 2 h. The resulting reaction mixture was stirred at 0-5 °C for 2-4 h followed by at ambient temperature for 12 h. The slurry was cooled to 5 °C, and a 10% aqueous solution of citric acid (39.1 mmol, ~75 g) was added dropwise to adjust the pH to 6.5-7.0 while maintaining the batch temperature at 0-5 °C. The organic layer was washed with saturated $NaHCO_3$ (57 mL) and H_2O (57 mL) successively. The organic phase was solvent switched to *i*-PrOH at a final volume of ~190 mL. The product was gradually crystallized during the distillation. Water (16.4 mL) was added and the slurry was heated to 49 °C to give a homogeneous solution. The resulting solution was cooled to 40 °C and seeded (0.27 g). After aging at 40 °C for 2 h to establish a seed bed, H_2O (93 mL) was charged dropwise at 40 °C over 3 h. After aging at 40 °C for additional 1 h, the slurry was gradually cooled to 5-10 °C and agitated at 5-10 °C for additional 2 h before filtration. The wet cake was washed with 50% H_2O/ *i*-PrOH (a 164 mL displacement wash followed by a 110 mL slurry wash). Suction dried under nitrogen gave the product as an off-white solid (24.9 g, >99% purity). 80% isolated yield. m.p. 134-135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 5 H), 7.23 (m, 2 H), 7.07 (d, J = 8.4 Hz, 2 H), 6.76 (dd, J = 15.7, 8.0 Hz, 1 H), 6.50 (s, 1 H), 5.93 (d, J = 15.7 Hz, 1 H), 4.65 (d, J = 8.2 Hz, 1 H), 4.30-4.02 (br m, 1 H), 3.71 (s, 2 H), 1.74 (s, 3 H), 1.63 (s, 3 H), 1.53 (s, 9 H), 1.32 (br s, 9 H); Selected data of ^{13}C NMR (100 MHz, $CDCl_3$): Some ^{13}C signals are too broad to be assigned due to a mixture of rotomers at 20 °C. δ 196.8, 152.9, 137.7, 136.8, 130.1, 129.5, 128.9, 128.8, 127.0, 119.0, 80.9, 66.4, 48.0, 28.54, 28.50, 26.5, 26.0; Anal. Calcd. for $C_{31}H_{40}N_2O_6$: C, 69.38; H, 7.51; N, 5.22. Found: C, 69.11; H, 7.58; N, 5.24.

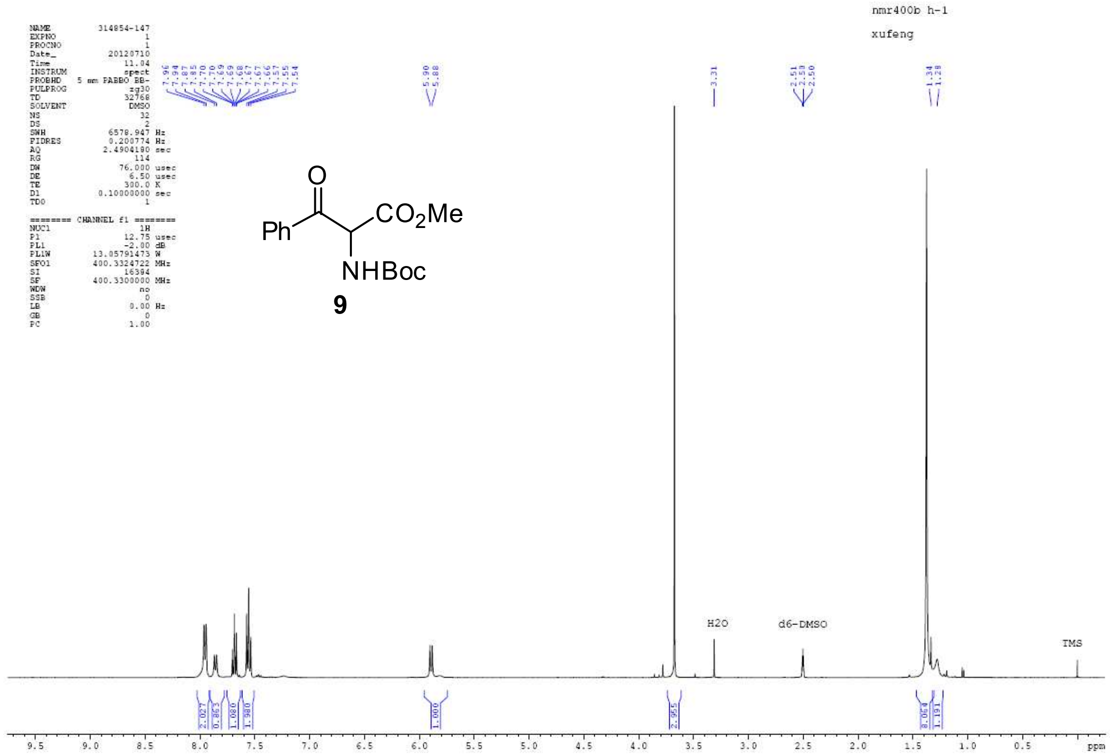


(R)-((R)-5-(4-aminobenzyl)-3,4-dihydro-2H-pyrrol-2-yl)-(phenyl)methanol bis hydrochloric acid salt monohydrate (17). A mixture of enone **14** (0.354 mol, 190.0 g) and 10% Palladium on 10% Pd/C (9.5 g) in THF (0.85 Kg) was hydrogenated under 20 psig H_2 for 90 min at 25 ^oC until uptake of hydrogen had ceased. The catalyst was removed through filtration of a bed of solka floc. The filtered residues were washed with THF (0.85 Kg). The combined filtrate was solvent switched to *i*-PrOH at a final volume of ~1.4 L. 4N HCl in *i*-PrOH (1.5 L) at ambient temperature. The reaction mixture was stirred at 20-25 ˚C for 24 h. The batch was distilled under reduced pressure, at constant volume by charging *i*-PrOH up to one batch volume, to remove HCl. The batch was then concentrated to a final volume of ~1.5 L. The resulting slurry was heated to 45°C, and *i*-PrOAc (2.5 L) was slowly added to the batch over 2-3 h. The slurry was then cooled to ~20 °C over 1-2 h and aged overnight. The batch was filtered, and the cake was washed with a 1:2 mixture of *i*-PrOH / *i*-PrOAc (0.8 L) followed by *i*-PrOAc (0.8 L). The wet cake was dried at 45 ˚C in vacuum under nitrogen sweep to give the cyclic imine bis-HCl salt **17** (124 g, >97% purity). 94% yield. m.p. 220-226 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.16 (br s, 2 H), 7.47-7.28 (m, 9 H), 4.74 (d, J = 6.8 Hz, 1 H), 4.63 (br m, 1 H), 4.21 (AB q, J = 22.1, 14.5 Hz, 2 H), 2.89 (m, 1 H), 2.78 (m, 1 H), 1.96 (m, 1 H), 1.86 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.7, 140.5, 132.5, 131.7, 130.7, 128.3, 137.9, 126.9, 123.5, 73.2, 72.1, 36.2, 36.1, 22.3; HRMS calc'd for $C_{18}H_{20}N_2O$ $[M+H]^+$ 281.1654, found 281.1645.



(R)-((2R,5S)-5-(4-aminobenzyl)pyrrolidin-2-yl)-(phenyl)methanol (1). To a mixture of imine dihydrochloride **17** (0.318 mol, 120.0 g, 98.5 wt%) and THF (0.9 L) under nitrogen was charged hexamethyldisilazane (0.679 mol, 109.5 g) while maintaining the batch temperature below 25 °C. The resulting slurry was stirred vigorously at ambient temperature for 2 h. The slurry was transferred to an 3 L autoclave charged with a suspension of 5% platinum on alumina (6.05 g) in THF (240 mL). The transfer line was flushed with THF (85 mL). The resulting mixture was stirred at ambient under hydrogen (40 psig) until the hydrogen uptake ceased (~12 h). The catalyst was filtered through a pad of Solka Floc, and washed with THF (1 L). The combined filtrate was stirred with 0.5 M hydrochloric acid (1.3 L) at ambient temperature for 1 h. The aqueous layer was separated and *i*-PrOAc (400 mL) was added. Sodium hydroxide (5 N, ~150 mL) was added to adjust the pH to 10.0. The organic phase was treated with carbon (AquaGuard® powder, Meadwestvaco; 25 g) at ambient temperature for 2 h. The mixture was filtered through a pad of Solka Floc and was washed with 2-propanol (180 mL). The combined filtrate was concentrated to ~700 mL. The solution was distilled at the constant volume by feeding a total of 1.4 L of 2-propanol, maintaining the batch temperature at 33-35 °C in vacuum. The resulting solution was then concentrated to 340 mL and heated to 50 °C, followed by addition of H_2O (65 mL). The resulting solution was cooled to 41-43 °C and seeded with pyrrolidine aniline hemihydrate (0.4 g). The resulting mixture was aged at 41-43 °C for 1 h to establish a seed bed. H_2O (610 mL) was charged at 41-43 °C over 6 h, and the resulting mixture was cooled to 10 °C over 3 h, followed by aging at 10 °C for 2 h before filtration. The wet cake was displacement washed with 25% 2-propanol/H_2O (1:3 v/v, 500 mL). The wet cake was suction-dried at ambient temperature under nitrogen to afford 76.8 g of pyrrolidine aniline as hemihydrate in 99% purity. 80% isolated yield. m.p. 88-89 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.27 (m, 4 H), 7.17 (m, 1 H), 6.81 (d, J = 8.1, 2 H), 6.45 (d, J = 8.1 Hz, 2 H), 5.07 (s, br, 1 H), 4.75 (s, 2 H), 4.18 (d, J = 7.0 Hz, 1 H), 3.05 (m, 2 H), 2.47 (dd, J = 13.0, 6.7 Hz, 1 H), 2.40 (dd, J = 13.0, 6.6 Hz, 1 H), 1.53 (m, 1 H), 1.34 (m, 1 H0, 1.22 (m, 2 H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 146.5, 144.3, 129.2, 127.8, 127.4, 126.8, 126.7, 114.0, 76.8, 64.4, 60.1, 42.1, 30.2, 27.2. HRMS calc'd for $C_{18}H_{22}N_2O$ $[M+H]^+$ 283.1810, found 283.1805.

4. ^1H and ^{13}C NMR spectra



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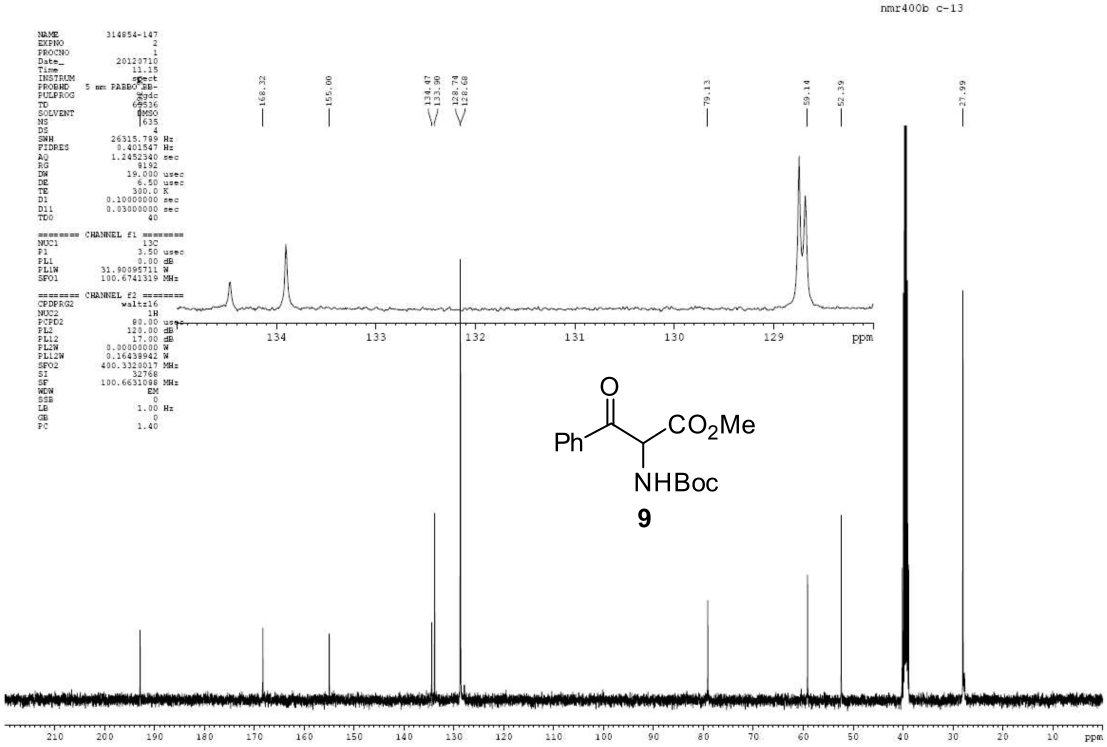

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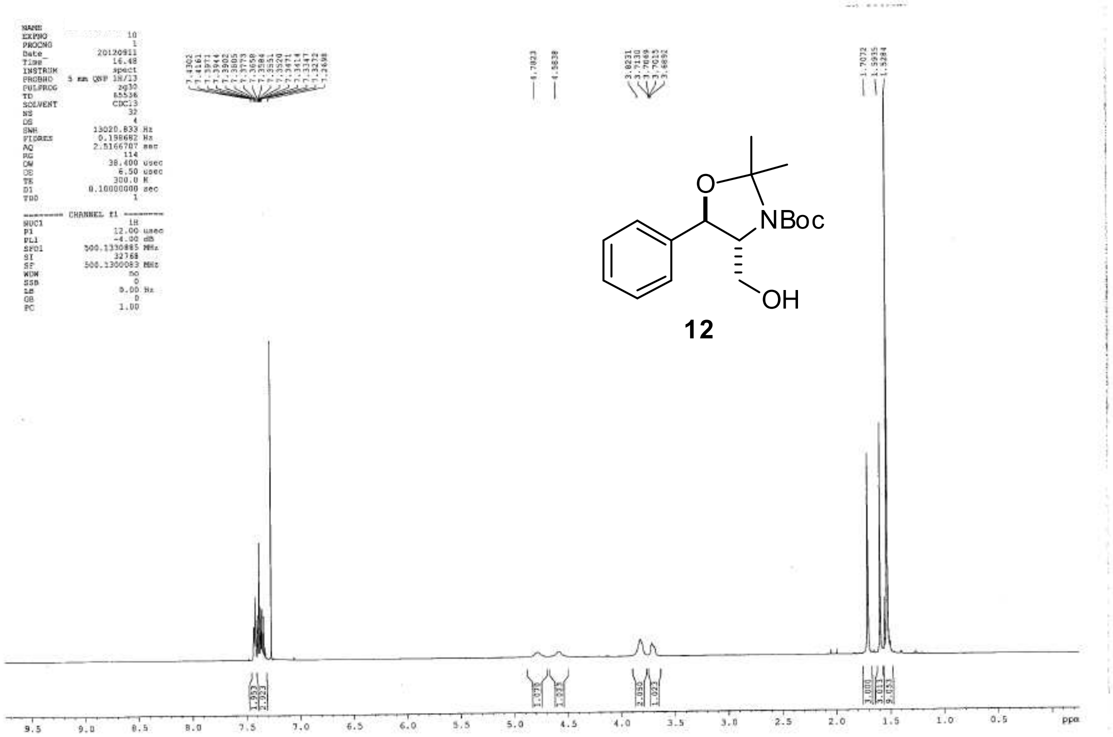

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12

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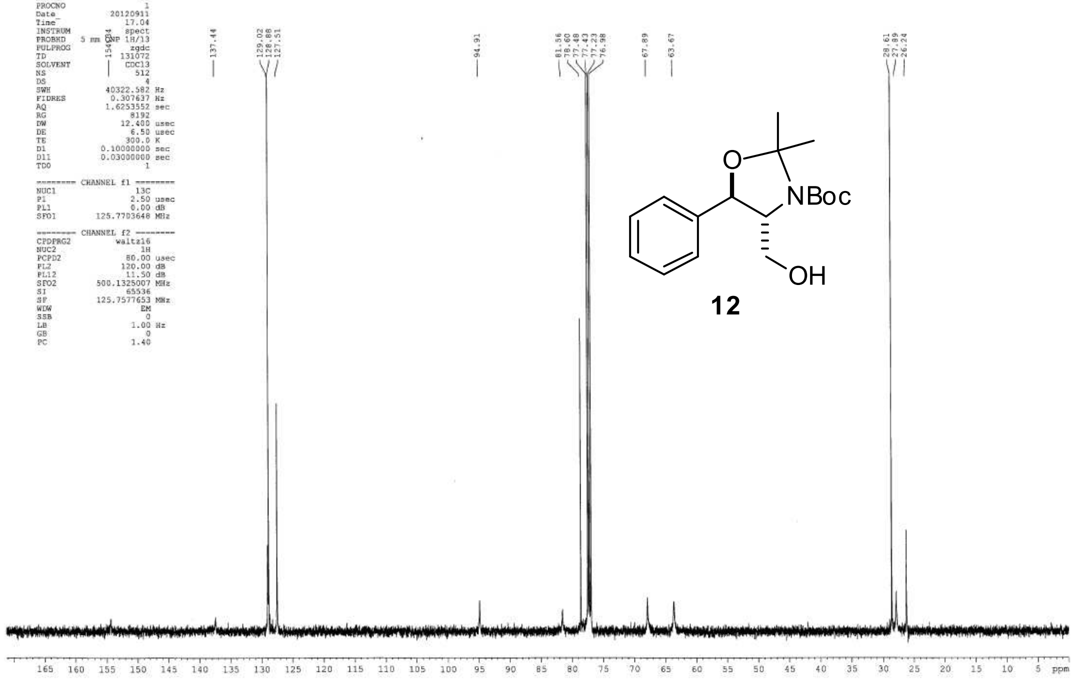

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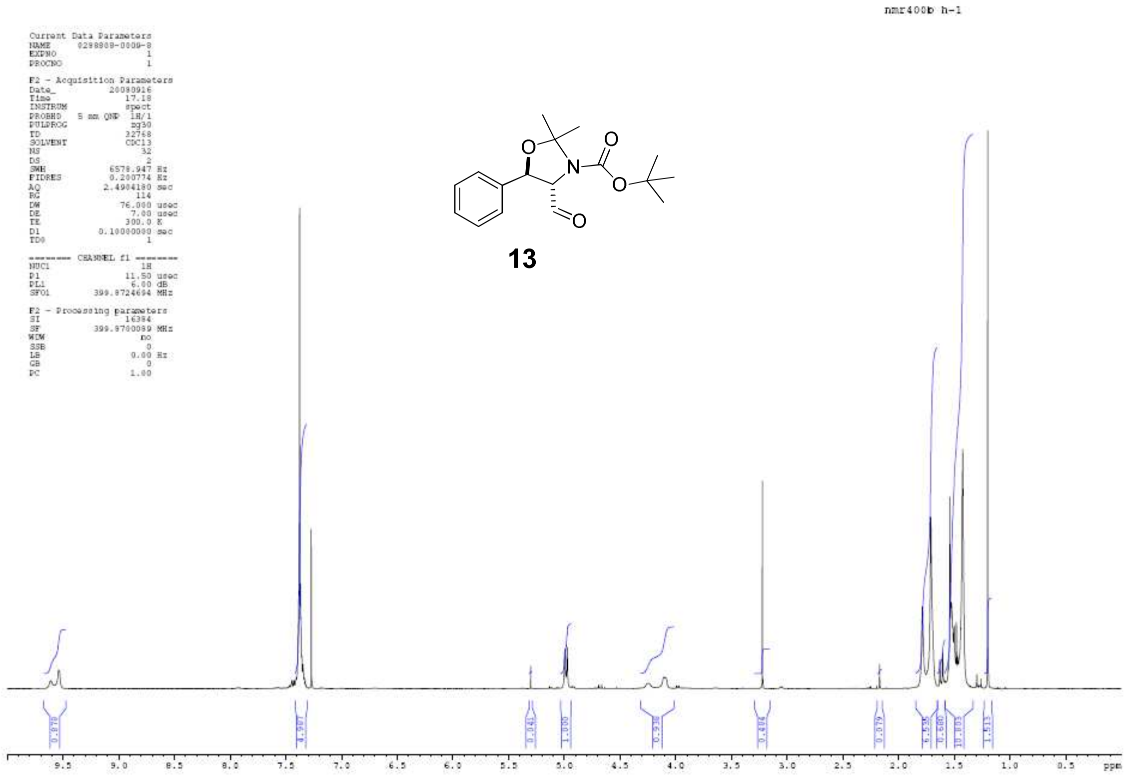
NS                      512
DS                        4
SWH              40322.582 Hz
FIDRES            0.307637 Hz
AQ               1.6253552 sec
RG                     8192
DW                   12.400 usec
DE                     6.50 usec
TE                    300.0 K
D1               0.10000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     2.50 usec
PL1                    0.00 dB
SFO1            125.7703648 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                  120.00 dB
PL12                  11.50 dB
SFO2            500.1325007 MHz
SI                    65536
SF              125.7577653 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

12



```
nmr400b h-1
```

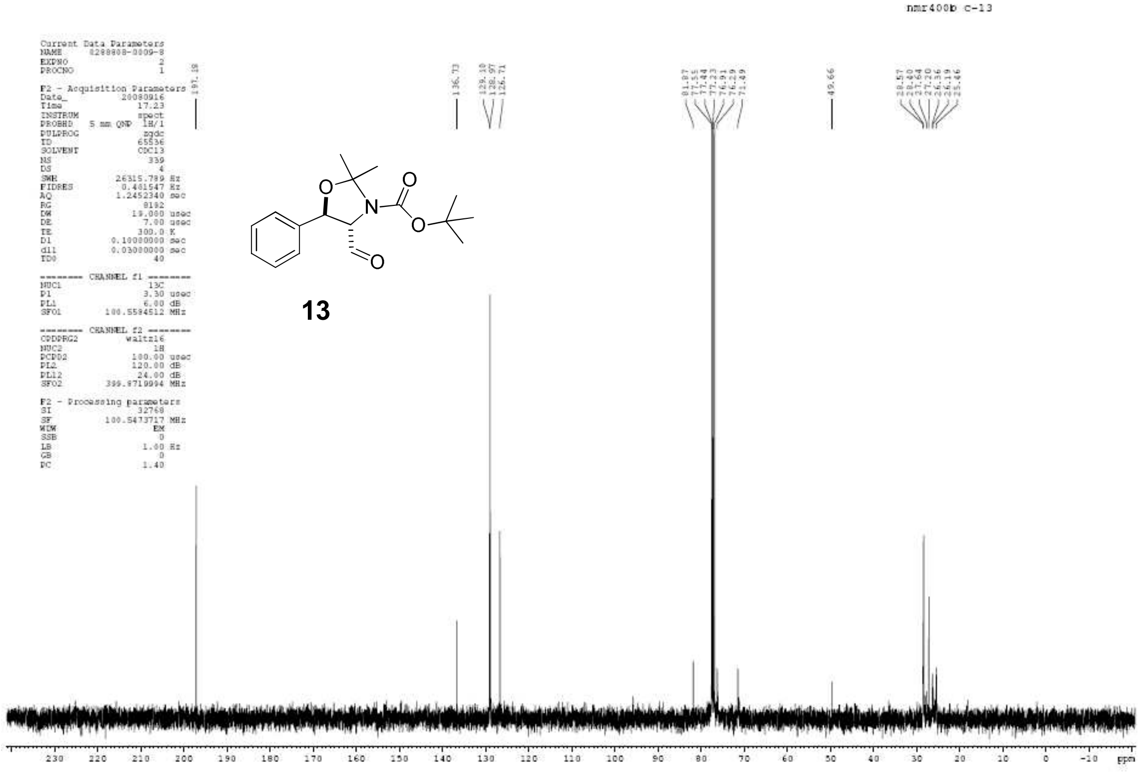
```
Current Data Parameters
NAME     0298808-0009-8
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20080916
Time              17.18
INSTRUM           spect
PROBHD   5 mm QNP  1H/1
PULPROG            zg30
TD                32768
SOLVENT           CDCl3
NS                   32
DS                    2
SWH            6578.947 Hz
FIDRES         0.200774 Hz
AQ            2.4904180 sec
RG                  114
DW               76.000 usec
DE                 7.00 usec
TE                300.0 K
D1           0.10000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                11.50 usec
PL1                6.00 dB
SFO1        399.8724694 MHz

F2 - Processing parameters
SI                16384
SF          399.8700089 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00
```

13



```
nmr400b c-13
```

```
Current Data Parameters
NAME     0288808-0009-8
EXPNO                 2
PROCNO                1

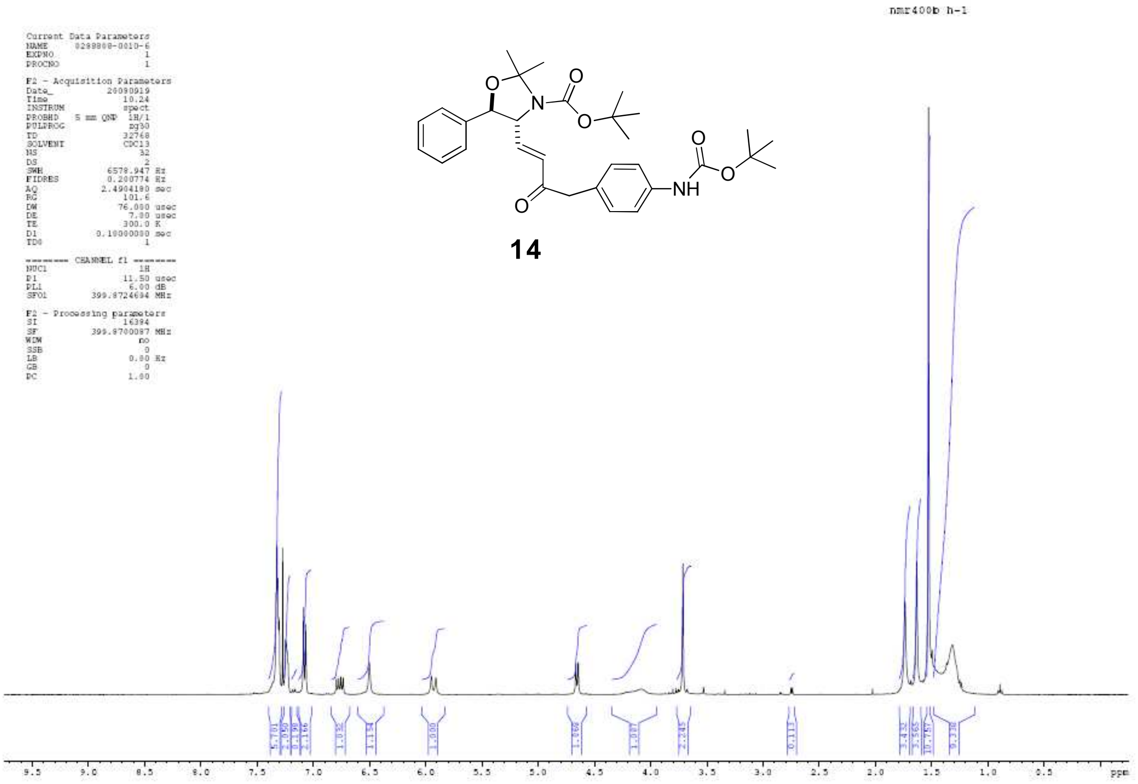
F2 - Acquisition Parameters
Date_          20080916
Time              17.23
INSTRUM           spect
PROBHD   5 mm QNP  1H/1
PULPROG            zgdc
TD                65536
SOLVENT           CDCl3
NS                  339
DS                    4
SWH           26315.789 Hz
FIDRES         0.401547 Hz
AQ            1.2452340 sec
RG                 8192
DW               19.000 usec
DE                 7.00 usec
TE                300.0 K
D1           0.10000000 sec
d11          0.03000000 sec
TD0                  40

======== CHANNEL f1 ========
NUC1                13C
P1                 3.30 usec
PL1                6.00 dB
SFO1        100.5594512 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2              120.00 dB
PL12              24.00 dB
SFO2        399.8719994 MHz

F2 - Processing parameters
SI                32768
SF          100.5473717 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

13



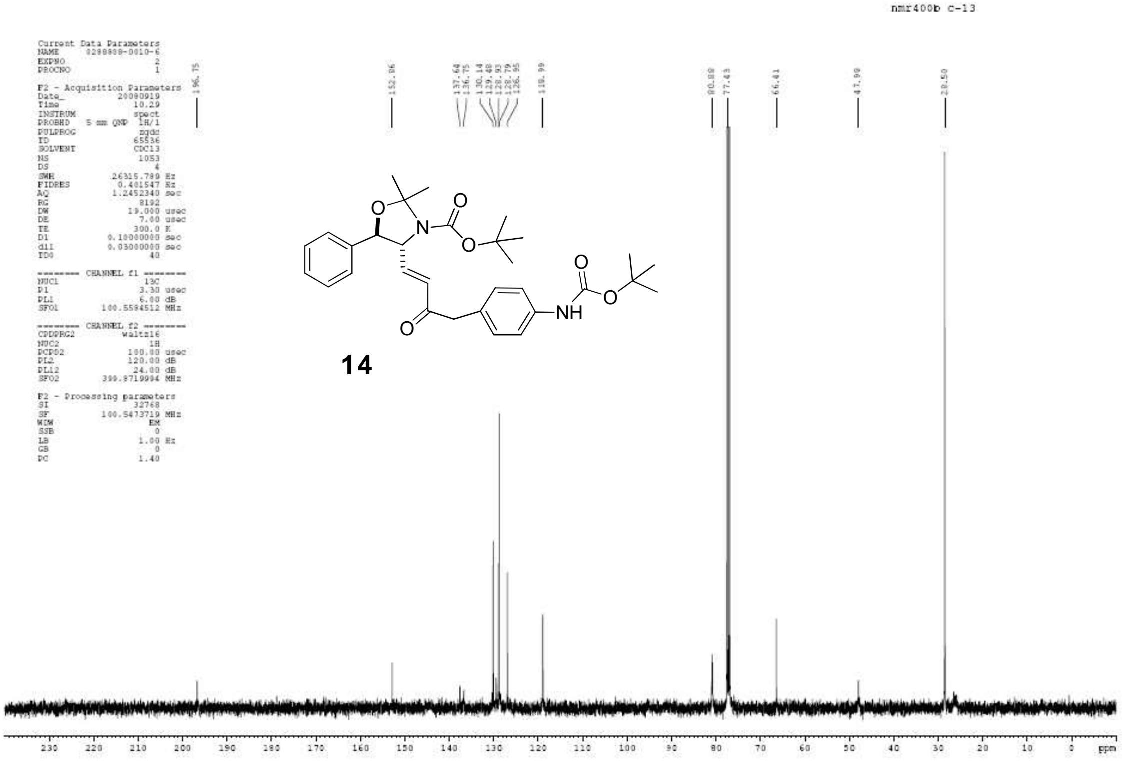
14

```
Current Data Parameters
NAME     0298808-0010-6
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20090919
Time              10.24
INSTRUM           spect
PROBHD   5 mm QNP  1H/1
PULPROG            zg30
TD                32768
SOLVENT           CDCl3
NS                   32
DS                    2
SWH            6578.947 Hz
FIDRES         0.200774 Hz
AQ            2.4904180 sec
RG                101.6
DW               76.000 usec
DE                 7.00 usec
TE                300.0 K
D1           0.10000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                11.50 usec
PL1                6.00 dB
SFO1        399.8724694 MHz

F2 - Processing parameters
SI                16384
SF          399.8700087 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00
```



14

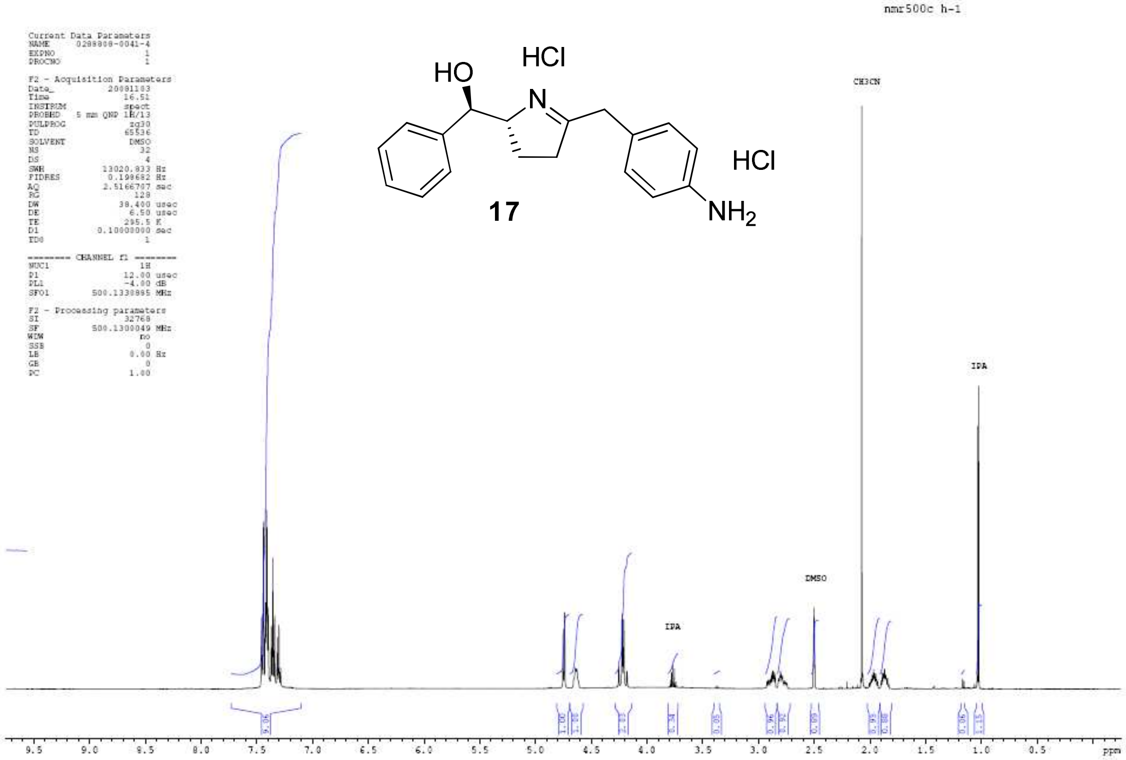
```
Current Data Parameters
NAME     0298808-0010-6
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20090919
Time              10.29
INSTRUM           spect
PROBHD   5 mm QNP  1H/1
PULPROG            zgdc
TD                65536
SOLVENT           CDCl3
NS                 1053
DS                    4
SWH           26315.789 Hz
FIDRES         0.401547 Hz
AQ            1.2452340 sec
RG                 8192
DW               19.000 usec
DE                 7.00 usec
TE                300.0 K
D1           0.10000000 sec
d11          0.03000000 sec
TD0                  40

======== CHANNEL f1 ========
NUC1                13C
P1                 3.30 usec
PL1                6.00 dB
SFO1        100.5594512 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2              120.00 dB
PL12              24.00 dB
SFO2        399.8719994 MHz

F2 - Processing parameters
SI                32768
SF          100.5473719 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

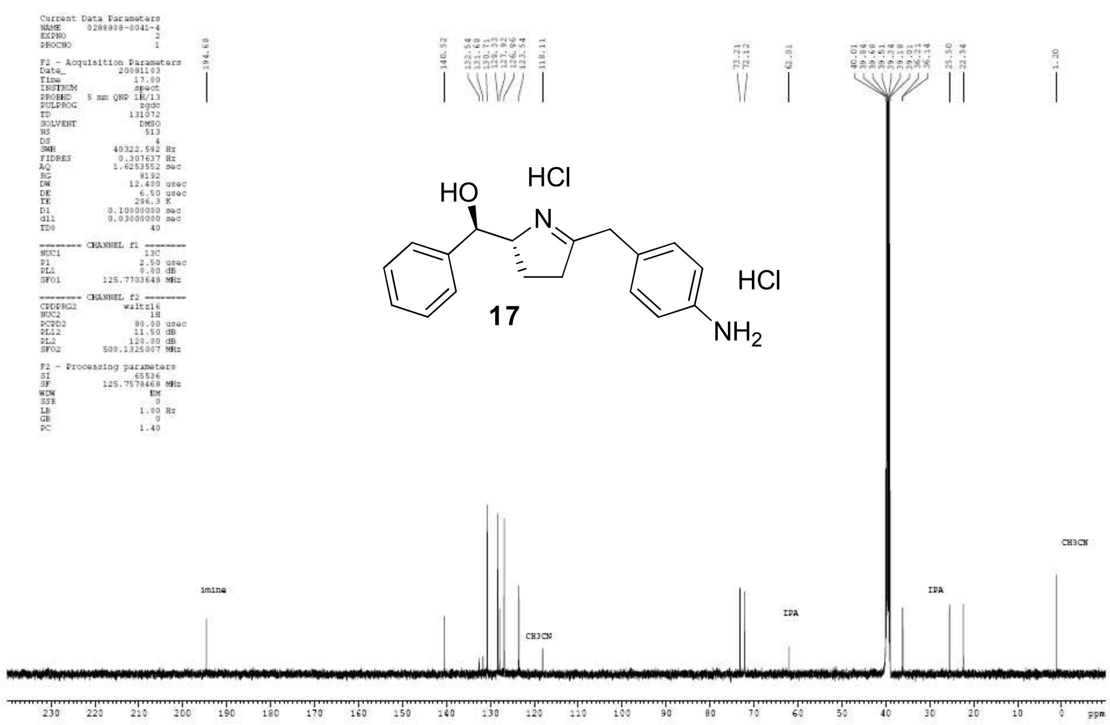


```
Current Data Parameters
NAME      0288808-0041-4
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20081103
Time               16.51
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    32
DS                     4
SWH            13020.833 Hz
FIDRES          0.198682 Hz
AQ             2.5166707 sec
RG                   128
DW                38.400 usec
DE                  6.50 usec
TE                 295.5 K
D1            0.10000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 12.00 usec
PL1                -4.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                 32768
SF           500.1300049 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```



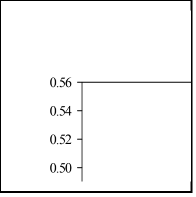
```
Current Data Parameters
NAME      0288808-0041-4
EXPNO                  2
PROCNO                 1

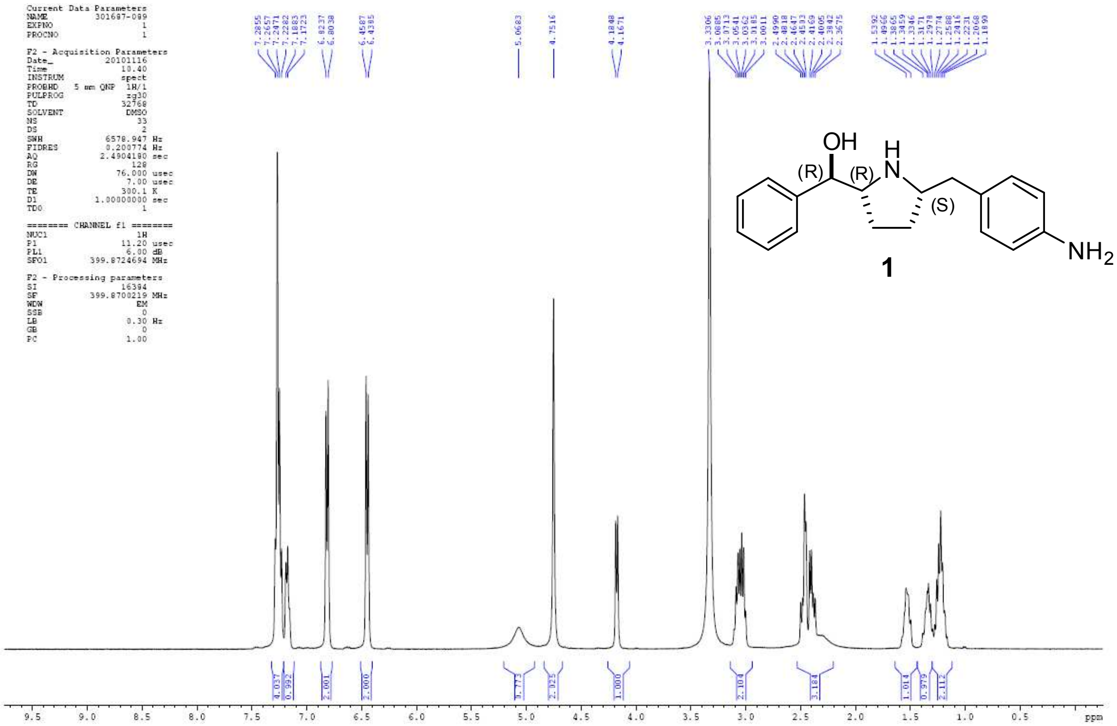
F2 - Acquisition Parameters
Date_           20081103
Time               17.00
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG             zgdc
TD                131072
SOLVENT             DMSO
NS                   513
DS                     4
SWH            40322.582 Hz
FIDRES          0.307637 Hz
AQ             1.6253552 sec
RG                  8192
DW                12.400 usec
DE                  6.50 usec
TE                 296.3 K
D1            0.10000000 sec
d11           0.03000000 sec
TD0                   40

======== CHANNEL f1 ========
NUC1                 13C
P1                  2.50 usec
PL1                 0.00 dB
SFO1         125.7703648 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL12               11.50 dB
PL2               120.00 dB
SFO2         500.1325007 MHz

F2 - Processing parameters
SI                 65536
SF           125.7578468 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```





```
Current Data Parameters
NAME          301687-089
EXPNO                  1
PROCNO                 1

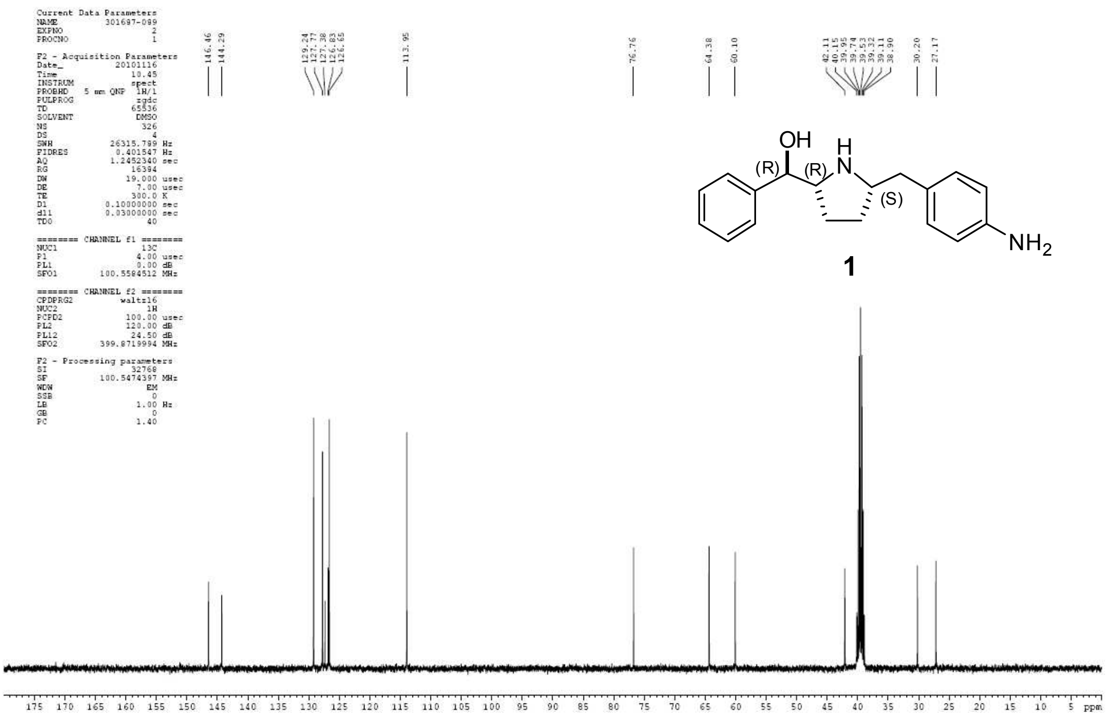
F2 - Acquisition Parameters
Date_           20101116
Time               10.40
INSTRUM            spect
PROBHD   5 mm QNP  1H/1
PULPROG             zg30
TD                 32768
SOLVENT             DMSO
NS                    33
DS                     2
SWH             6578.947 Hz
FIDRES          0.200774 Hz
AQ             2.4904180 sec
RG                   128
DW                76.000 usec
DE                  7.00 usec
TE                 300.1 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 11.20 usec
PL1                 6.00 dB
SFO1         399.8724694 MHz

F2 - Processing parameters
SI                 16384
SF           399.8700219 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

1

SM in DMSO 400NMR



```
Current Data Parameters
NAME          301687-089
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20101116
Time               10.45
INSTRUM            spect
PROBHD   5 mm QNP  1H/1
PULPROG             zgdc
TD                 65536
SOLVENT             DMSO
NS                   326
DS                     4
SWH            26315.789 Hz
FIDRES          0.401547 Hz
AQ             1.2452340 sec
RG                 16384
DW                19.000 usec
DE                  7.00 usec
TE                 300.0 K
D1            0.10000000 sec
d11           0.03000000 sec
TD0                   40

======== CHANNEL f1 ========
NUC1                 13C
P1                  4.00 usec
PL1                 0.00 dB
SFO1         100.5584512 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2               120.00 dB
PL12               24.50 dB
SFO2         399.8719994 MHz

F2 - Processing parameters
SI                 32768
SF           100.5474397 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

1