Supporting Information for the Communication entitled

Highly enantioselective synthesis of rigid, quaternary 1,4-benzodiazepin-2,5-diones derived from proline

Stephanie MacQuarrie-Hunter, Paul R. Carlier*

Department of Chemistry

Virginia Tech

Blacksburg, VA 24061

pcarlier@vt.edu

Table of Contents:

Section	Description	Page
A	Experimental Procedures	1
B	Tabulation of chiral stationary phase HPLC conditions and retention times.	4
C	Computational Details. Absolute Energies, Enthalpy and Entropy corrections.	4
D	Figure S1. Calculated (B3LYP/6-31G*) Geometries and Energies for the conformers of (<i>S</i>)- 7b Figure S2. Calculated (B3LYP/6-31G*) ring inversion transition states 14b* and 15b* .	
E	¹ H and ¹³ C spectra, HPLC Chromatograms	7-33
	¹ H and ¹³ C spectra, HPLC Chromatograms for 6b	7
	¹ H and ¹³ C spectra, HPLC Chromatograms for 7b	11
	¹ H and ¹³ C spectra, HPLC Chromatograms for 8b	15
	¹ H and ¹³ C spectra, HPLC Chromatograms for 9b	19
	¹ H and ¹³ C spectra, HPLC Chromatograms for 10b	23
	¹ H and ¹³ C spectra, HPLC Chromatograms for 11b	27
	¹ H spectra for (<i>S</i>)-(-)- α -methylproline and (<i>R</i>)-(-)- α -benzylproline	31
F	References	33

A. Experimental Procedures

General

THF was distilled from Na/benzophenone immediately before use. (*S*)- and (*R*)-proline were purchased from Across and were used as received. (*S*)- and (*R*)-1,2,3,11a-Tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H)-dione was prepared from (*S*)- and (*R*)-proline and isatoic anhydride according to the literature method^[1]. Isopropyl triflate was prepared according to the literature method^[2] immediately before use and was dispensed as a solution in CCl₄. Enantiomeric excess of all compounds was assessed by HPLC (Chiralcel AD). ¹H NMR Spectra were recorded at 500 and 400 MHz; the corresponding ¹³C NMR resonant frequencies were 125 and 100 MHz respectively. High resolution mass spectra were recorded under FAB conditions (NBA. PEG); in each case the expected molecular formula (M+1) gave the closest match among all possible formulas.

Specific procedure for preparation of *N*-*iPr*-1,4-benzodiazepin-2,5-dione (*S*)-(+)-**6b**

At 0 °C to a stirred solution of (*S*)-1,2,3,11a-Tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H)-dione (299 mg, 1.384 mmol, 1.0 equiv.) in dry THF (5.0 mL) was added NaH (62.0 mg, 1.550 mmol, 1.12 equiv., 60% suspension in mineral oil) in one portion. The resulting solution was stirred at 0 °C for 30 min before the dropwise addition of *i*-PrOTf (800 mg, 4.152 mmol, 3.0 equiv.). The reaction mixture was stirred for a further 20 min at 0 °C, at which point TLC (70EtOAc:30hexanes) indicated the reaction

was complete. The reaction was quenched at 0 °C with 20 ml of saturated aqueous NH_4Cl solution, and extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (70% EtOAc/Hexane) affording 292 mg (82%) of (3*S*)-(+)-**6b** as a white foam.

$[\alpha]_{\text{D}}^{26} = +426$ ($c = 1$ in MeOH); ^1H NMR (CDCl_3) δ 1.23 (d, $J = 6.7$ Hz, 3H), 1.50 (d, $J = 7.1$ Hz, 3H), 1.97 (m, 2H), 2.11 (m, 1H), 2.69 (m, 1H), 3.53 (m, 1H), 3.77 (m, 1H), 3.97 (m, 1H), 4.49 (m, 1H), 7.32 (m, unassigned aromatic protons 2H), 7.46 (m, 1H), 7.85 (dd, $J = 9.5$ Hz, $J = 1.6$ Hz 1H); ^{13}C NMR (CDCl_3) δ 14.11, 20.34, 20.95, 21.94, 23.85, 26.37, 46.31, 52.55, 58.09, 60.29, 123.80, 126.23, 129.87, 131.12, 131.83, 165.13, 169.46, 171.02; HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 259.1368, found 259.1462 (+6.0 ppm, +1.6 mmu)

General Sequential Protocol for the C3-alkylation of (3*S*)-(+)-**6b**

At -78 °C or -100 °C under nitrogen, to a stirred solution of (3*S*)-**6b** (0.15mmol, 1.0 equiv) and HMPA (0.90mmol, 6.0 equiv) in anhydrous THF (3.0 mL) was added LDA (0.15 mmol, 1.2 equiv, 1.5 M in hexanes) and the mixture stirred for a further time t . The electrophile (1.5 mmol, 10 equiv.) was then added dropwise via syringe at -78 °C or -100 °C and the reaction was stirred at this temperature until the starting benzodiazepine was consumed (TLC). The reaction was quenched at -78 °C or -100 °C by the addition of saturated aqueous NH_4Cl (5.0 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (70/30 ethyl acetate/hexane). Yields for **7b-11b** are given in Table 2 of the paper.

General In situ Protocol for the C3-alkylation of (3*S*)-(+)-**6b**

At -100 °C under nitrogen, to a stirred solution of (3*S*)-(+)-**6b** (0.15mmol, 1.0 equiv) and HMPA (0.90 mmol, 6.0 equiv) in anhydrous THF (3.0 mL) the electrophile was added (1.5 mmol, 10 equiv.) and the mixture was stirred for 15 min. KHMDs (0.15 mmol, 1.2 equiv, 0.5 M) was then added via syringe and the mixture stirred at -100 °C until the starting benzodiazepine was consumed (TLC). The reaction was quenched at -100 °C by the addition of saturated aqueous NH_4Cl (5.0 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (70/30 ethyl acetate/hexane). Yields for **7b-11b** are given in Table 2 of the paper

N-i-Pr Benzodiazepin-2,5-dione methylation product (3*S*)-(+)-**7b**

$[\alpha]_{\text{D}}^{26} = +137.7$ ($c = 1.0$ in MeOH); ^1H NMR (CDCl_3) δ 1.25 (s, 3H), 1.57 (d, $J = 6.7$ Hz, 3H), 1.77 (d, $J = 7.1$ Hz, 3H), 1.86 (m, 3H), 3.12 (m, 1H), 3.51 (m, 1H), 4.02 (m, 1H), 4.43 (m, 1H), 7.32 (m, unassigned aromatic protons 2H), 7.48 (m, 1H), 7.85 (dd, $J = 9.5$ Hz, $J = 1.6$ Hz 1H); ^{13}C NMR (CDCl_3) δ 20.58, 21.82, 21.98, 22.39, 40.02, 49.04, 54.01, 65.31, 122.92, 126.01, 130.29, 131.48; HRMS (FAB) calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 273.1524, found 273.1592 (-4.0 ppm, -1.1 mmu)

N-i-Pr Benzodiazepin-2,5-dione allylation product (3*R*)-(+)-**8b**

$[\alpha]_{\text{D}}^{26} = +389.7$ ($c = 1.0$ in MeOH); ^1H NMR (CDCl_3) δ 1.33 (d, $J = 7.1$ Hz, 3H), 1.54 (d, $J = 6.7$ Hz, 3H), 1.88 (m, 2H), 1.99 (m, 3H), 3.09 (m, 1H), 3.25 (m, 1H), 4.09 (m, 1H), 4.49 (m, 1H), 4.77 (dd, $J = 18.7$ Hz, $J = 1.9$ Hz, 1H), 5.02 (ddd, $J = 11.9$ Hz, $J = 1.9$ Hz, $J = 1.1$ Hz, 1H), 7.32 (m, unassigned aromatic protons 2H), 7.51 (m, 1H), 7.88 (dd, $J = 9.5$ Hz, $J = 1.6$ Hz 1H); ^{13}C NMR (CDCl_3) δ 20.49, 21.78, 21.85, 21.88, 37.01, 38.65, 49.53, 54.02, 68.32, 119.67, 122.84, 126.07, 130.47, 130.84, 131.29, 131.59, 138.92, 165.36, 170.41; HRMS (FAB) calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 299.1681, found 299.1762 (+0.9 ppm, +0.3 mmu)

***N*-i-Pr Benzodiazepin-2,5-dione benzylation product (3*R*)-(+)-9b**

$[\alpha]_D^{26} = +259.4$ ($c = 1.0$ in MeOH); $^1\text{H NMR}$ (CDCl_3) δ 1.33 (d, $J = 7.1$ Hz, 3H), 1.55 (d, $J = 5.1$ Hz, 3H), 1.65 (m, 1H), 1.73 (m, 1H), 1.95 (m, 1H), 2.46 (d, $J = 13.5$ Hz, 2H), 2.59 (d, $J = 13.5$ Hz, 2H), 2.92 (m, 1H), 3.39 (m, 1H), 4.04 (m, 1H), 4.51 (m, 1H), 6.89 (d, $J = 7.5$ Hz, 2H), 7.18 (m, unassigned aromatic protons 4H), 7.35 (m, 1H), 7.54 (m, 1H), 7.98 (d, $J = 7.9$ Hz, 1H); $^{13}\text{C NMR}$ (CDCl_3) δ 20.40, 21.75, 36.85, 39.66, 49.65, 49.65, 54.20, 123.06, 126.28, 127.08, 128.42, 129.59, 130.46, 131.20, 131.78, 135.45, 139.06, 159.19, 165.43, 170.23; HRMS (FAB) calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 349.1837, found 349.1923 (+2.0 ppm, +0.7 mmu)

***N*-i-Pr Benzodiazepin-2,5-dione 4-methyl benzylation product (3*R*)-(+)-10b**

$[\alpha]_D^{26} = 98.6$ ($c = 1.0$ in MeOH); $^1\text{H NMR}$ (CDCl_3) δ 1.33 (d, $J = 7.1$ Hz, 3H), 1.54 (d, $J = 6.7$ Hz, 3H), 1.65 (m, 1H), 1.72 (m, 1H), 1.95 (m, 1H), 2.27 (s, 3H), 2.40 (d, $J = 13.9$ Hz, 1H), 2.54 (d, $J = 13.5$ Hz, 1H), 2.87 (m, 1H), 3.41 (m, 1H), 4.03 (m, 1H), 4.50 (m, 1H), 6.77 (d, $J = 7.9$ Hz, 2H), 7.01 (d, $J = 7.5$ Hz, 2H), 7.36 (m, unassigned aromatic protons 2H), 7.53 (m, 1H), 7.95 (dd, $J = 9.1$ Hz, $J = 1.1$ Hz, 1H); $^{13}\text{C NMR}$ (CDCl_3) δ 20.36, 20.47, 20.97, 21.14, 21.71, 36.75, 39.14, 49.62, 54.11, 69.54, 123.01, 126.19, 129.07, 129.39, 130.41, 131.70, 132.25, 136.64, 139.05, 165.39, 170.30; HRMS (FAB) calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 363.1994, found 363.2076 (+1.0 ppm, +0.4 mmu)

***N*-i-Pr Benzodiazepin-2,5-dione 2-phenyl benzylation product (3*R*)-(+)-11b**

$[\alpha]_D^{26} = +198.6$ ($c = 1.0$ in MeOH); $^1\text{H NMR}$ (CDCl_3) δ 1.32 (d, $J = 7.1$ Hz, 3H), 1.25 (m, 1H), 1.49 (m, 2H), 1.55 (d, $J = 6.7$ Hz, 3H), 2.64 (m, 1H), 2.67 (dd, 2H), 3.29 (m, 1H), 3.84 (m, 1H), 4.50 (m, 1H), 6.97 (m, 1H), 7.1-7.4 (m, unassigned aromatic protons 11H), 7.54 (m, 1H), 7.91 (dd, $J = 9.5$ Hz, $J = 1.6$ Hz, 1H); $^{13}\text{C NMR}$ (CDCl_3) δ 20.39, 21.42, 21.77, 34.61, 35.62, 49.49, 54.15, 70.13, 123.09, 126.34, 126.83, 127.09, 127.46, 128.38, 129.09, 129.57, 130.40, 130.64, 131.30, 131.79, 133.28, 138.92, 141.30, 143.02; HRMS (FAB) calcd for $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 425.2150, found 425.2228 (-0.2 ppm, -0.1 mmu)

General procedure for hydrolysis of *N*-i-Pr-1,4-benzodiazepin-2,5-diones to the corresponding quaternary amino acids.

The benzodiazepin-2,5-dione to be hydrolyzed (0.1 mmol) was combined with hydrochloric acid (6.0M, 2.0mL) in a pressure tube (Teflon screw cap) and heated at 140 °C (bath temperature) for 3 days. Water (2.0 mL) was then added and the mixture was extracted with EtOAc (3 x 3mL) to remove the aminobenzophenone. The water layer was separated, concentrated *in vacuo* and the residue dissolved in EtOH (2.0 mL). Propylene oxide (0.3 mL) was added, and the resulting solution was heated at reflux for 30 minutes. Upon cooling the precipitated solid was collected and washed with ethyl acetate and acetone, affording the corresponding free amino acid.

(*S*)-(-)- α -methylproline

27.2 mg (0.1 mmol) of (3*S*)-(+)-7b was treated as above to afford (*S*)- α -methylproline (78%). $^1\text{H NMR}$ (CD_3OD) δ 1.72 (s, 3H), 2.08 (m, 2H), 2.20 (m, 1H), 2.47 (m, 1H), 3.48 (m, 2H); $[\alpha]_D^{18} = -76.2$ ($c = 1$, H_2O). Acros (*S*)- α -methylproline is: $[\alpha]_D^{18} = -83.1^\circ$, ($c = 1$, H_2O). We thus assign (*S*)-stereochemistry to our synthesized amino acid.

(*R*)-(-)- α -benzylproline

34.8 mg (0.1 mmol) of (3*S*)-(+)-9b was treated as above to afford (*R*)- α -benzylproline (85%). $^1\text{H NMR}$ (D_2O) δ 1.80 (m, 1H), 1.97 (m, 2H), 2.19 (m, 1H), 2.94 (d, $J = 14.3$ Hz

1H), 3.26 (m, 1H), 3.38 (d, $J = 14.7$ Hz, 1H); $[\alpha]_D^{25} = -18.15$ ($c = 1.2$, H_2O). Literature rotation value for (*R*)- α -benzylproline is $[\alpha]_D = -19.25$ °C, ($c = 1.2(H_2O)$, 25°C)

B. Tabulation of HPLC Conditions and Retention Times

Reported retention times are determined from racemic and enantiomerically enriched/pure samples on a Chiralcel AD column.

compound	Column	solvent, flowrate	fast enantiomer (config) retention time	slow enantiomer (config) retention time
6b	AD	20% isopropanol-hexane, 1mL/min	7.0 min (3 <i>R</i>)	9.4 min (3 <i>S</i>)
7b	AD	20% isopropanol-hexane, 1mL/min	6.1 min (3 <i>R</i>)	8.6 min (3 <i>S</i>)
8b	AD	20% isopropanol-hexane, 1mL/min	6.4 min (3 <i>S</i>)	8.5 min (3 <i>R</i>)
9b	AD	20% isopropanol-hexane, 1mL/min	7.7 min (3 <i>S</i>)	10.4 min (3 <i>R</i>)
10b	AD	20% isopropanol-hexane, 1mL/min	7.1 min (3 <i>S</i>)	9.9 min (3 <i>R</i>)
11b	AD	20% isopropanol-hexane, 1mL/min	6.9 min (3 <i>R</i>)	9.1 min (3 <i>S</i>)

C. Computational details for calculated structures 6b, 7b, 12b and 12b*.

Structure	Energy basis	ϵ_0 (nimag) ^a (hartrees)	Corr ZPVE ^b (hartrees)	$G_{corr}(T)$ ^c (hartrees)	$G(T)$ ^c (hartrees)	$\Delta G(T)$ ^c (kcal/mol)
(<i>M</i>)-(<i>S</i>)- 7b	6-31G*	-881.734819 (0)	0.333882	0.289159	-881.445660	0.0
(<i>P</i>)-(<i>S</i>)- 7b	6-31G*	-881.692183 (0)	0.332856	0.287567	-881.404616	25.8
(<i>M</i>)-(<i>S</i>)- 12b	6-31G*	-1126.684672 (1)	0.464055	0.436840	-1126.247832	0.0
	6-31+G*	-1126.716452	0.464055	0.436840	-1126.279612	0.0
(<i>P</i>)-(<i>S</i>)- 12b	6-31G*	-1126.665622 (1)	0.464585	0.436722	-1126.228900	11.9
	6-31+G*	-1126.697438	0.464585	0.436722	-1126.260716	11.9
(<i>M</i>)-(<i>S</i>)- 13b	6-31G*	-1436.774273 (1)	0.624710	0.590772	-1436.183501	0.0
	6-31+G*	-1436.813602	0.624710	0.590772	-1436.222830	0.0
(<i>P</i>)-(<i>S</i>)- 13b	6-31G*	-1436.758723 (1)	0.625265	0.590427	-1436.168296	9.5
	6-31+G*	-1436.797744	0.625265	0.590427	-1436.207317	9.7
(<i>M</i>)- 14b	6-31G*	-841.820306 (0)	0.291016	0.270099	-841.550207	0.0
	6-31+G*	-841.864176	0.291016	0.270099	-841.594077	0.0
(<i>M</i>)- 14b * ^d	6-31G*	-841.8032099 (1)	0.291285	0.270543	-841.532666	11.0
	6-31+G*	-841.845129	0.291285	0.270543	-841.574586	12.2
(<i>M</i>)- 15b	6-31G*	-1314.510547 (0)	0.536242	0.504102	-1314.006445	0.0
	6-31+G*	-1314.549748	0.536242	0.504102	-1314.045646	0.0
(<i>M</i>)- 15b * ^d	6-31G*	-1314.487770 (1)	0.536846	0.505978	-1313.981792	15.5
	6-31+G*	-1314.526140	0.536846	0.505978	-1314.020162	16.0

^aGeometry optimizations and frequency calculations were performed using Gaussian03^[4] at B3LYP/6-31G*; B3LYP electronic energies (ϵ_0) were calculated at the indicated basis set. Stationary points were identified as minima (nimag=0) or transition structures (nimag=1). The displacement of the imaginary frequencies corresponded to the expected molecular motion for deprotonation and ring inversion transition structures. ^bVibrational frequencies were corrected by a factor of 0.9804 to calculate zero point vibrational energy (ZPVE) and the Gibbs free energy correction G_{corr} . Gibbs free energy $G(T)$ is defined as the sum of ϵ_0 and $G_{corr}(T)$. ^cThermodynamic corrections at 173K, except for **7b**, which were calculated at 298K. ^dOne of a pair of enantiomeric ring inversion transition states.

Figure S1. B3LYP/6-31G* Geometries and Energies for the Conformers of (*S*)-**7b**.

Figure S2. B3LYP/6-31G* Geometries of solvated deprotonation transition structures (*M*)-(*S*)- and (*P*)-(*S*)-**13b**, and enolate ring inversion transition states (*M*)-**14b*** and **15b***.

1H OBSERVE

Pulse Sequence: s2pul1
 Solvent: CDCl3
 Ambient temperature
 INOVA-400 "inova400"
 Relax. delay 1.000 sec
 Pulse 26.1 degrees
 Acq. time 3.700 sec
 Width 6387.7 Hz
 12 repetitions
 OBSERVE H1, 399.9418232 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FT size 65536
 Total time 2 min, 30 sec
 Jul 14 2003
 VA Tech Chemistry NMR Lab

sim-v-139
 pad=2 run with findz0 before acquisition
 Archive directory: /export/home/robot/vnmrs
 Sample directory: sim-v-139_t0c14_2005-04-2
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Acq. temperature
 File: CARBON_01
 INOVA-400 "Inova400alt"
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.199 sec
 Width 25141.4 Hz
 F2 500.136 MHz
 F1 125.761 MHz
 OBSERVE C13, 5660286 MHz
 DECOUPLE H1, 399.9461188 MHz
 Power 46 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 1.0 Hz
 F2 500.136 MHz
 Total time 1 hr, 32 min, 0 sec
 Apr 27 2005
 VA Tech Chemistry NMR Lab

VA TECH

Project Name: Steph
Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name: slm-IV-113-1-21-04
Sample Type: Unknown
Vial: 1
Injection #: 1
Injection Volume: 10.00 ul
Run Time: 20.00 MinutesAcquired By: Steph
Date Acquired: 1/22/04 2:36:45 AM
Acq. Method: 20% isopropanol
Date Processed: 1/22/04 2:50:42 AM
Channel Name: 2487Channel 1
Sample Set Name: Steph

	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	7.036	14499063	18.86	1153732	25.79
2	9.419	62374296	81.14	3319476	74.21

VA TECH

Project Name: Steph

Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name: slm-IV-L-17-03

Acquired By: Steph

Sample Type: Unknown

Date Acquired: 12/18/03 1:07:20 AM

Vial: 1

Acq. Method: 20% isopropanol

Injection #: 1

Date Processed: 12/18/03 1:19:08 AM

Injection Volume: 10.00 ul

Channel Name: 2487Channel 1

Run Time: 20.00 Minutes

Sample Set Name: Steph

	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	10.039	1368508	100.00	82502	100.00

3N-III-177-8-8-1

VA TECH

Project Name: Steph

Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name: ¹⁰⁹slm-IV-D/L-01-19-04

Sample Type: Unknown

Vial: 1

Injection #: 1

Injection Volume: 10.00 ul

Run Time: 20.00 Minutes

Acquired By: Steph

Date Acquired: 1/19/04 2:27:12 AM

Acq. Method: 20% isopropanol

Date Processed: 1/19/04 2:38:21 AM

Channel Name: 2487Channel 1

Sample Set Name: Steph

	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	6.173	14122135	48.72	1347350	57.25
2	8.615	14861849	51.28	1005979	42.75

VA TECH

Project Name: Steph
Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name:	slm-IV-109-exp1-AD-1-8-04	Acquired By:	Steph
Sample Type:	Unknown	Date Acquired:	1/8/04 1:38:58 AM
Vial:	1	Acq. Method:	20% isopropanol
Injection #:	1	Date Processed:	1/8/04 1:53:07 AM
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	20.00 Minutes	Sample Set Name	Steph

	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	8.733	14901542	100.00	1006870	100.00

SLM-V-23

Archive directory: /export/home/robot/vnmr/vars/data
 Sample directory:

Pulse Sequence: s2pul
 Solvent: CDCl₃
 Temperature:
 File: CARBON_01
 INOVA-400 "Inova400"

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.199 sec
 Width 25141.4 Hz
 Observed F1: 399.8438386 MHz
 OBSERVE C13: 100.5654514 MHz
 DECOUPLE H1: 399.8438386 MHz
 Power 45 dB
 continuously on
 VAL72-16 modulated
 Data processing:
 FT size 65536
 Time processing 1.0 Hz
 Total time 1 hr, 13 min, 36 sec
 Jun 18 2004
 VA Tech Chemistry NMR Lab

VA TECH

Project Name: Steph

Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name: slm-IV-135
Sample Type: Unknown
Vial: 1
Injection #: 1
Injection Volume: 10.00 ul
Run Time: 60.00 Minutes

Acquired By: Steph
Date Acquired: 4/26/05 4:02:34 AM
Acq. Method: 20% isopropanol
Date Processed: 4/26/05 4:19:31 AM
Channel Name: 2487Channel 1
Sample Set Name: Steph

	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	6.486	82445334	47.01	3862528	52.32
2	8.564	92930675	52.99	3520109	47.68

VA TECH

Project Name: Steph

Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name: slm-IV-163
Sample Type: Unknown
Vial: 1
Injection #: 1
Injection Volume: 10.00 ul
Run Time: 60.00 Minutes

Acquired By: Steph
Date Acquired: 4/26/05 3:38:47 AM
Acq. Method: 20% isopropanol
Date Processed: 4/26/05 4:24:07 AM
Channel Name: 2487Channel 1
Sample Set Name: Steph

	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	6.509	202194	0.57	14836	0.98
2	8.616	35304598	99.43	1498598	99.02

(3R)-(+)-9b

sim-iv-23
 pad=2.5 run with findz0 before acquisition
 Archive directory: /export/home/robot/vnmrsys/data
 Sample directory: sim-iv-23_loc2_2003-11-27

Pulse Sequence: s2pul
 Solvent: CDCl₃
 Ambient temperature
 File: PROTON
 INOVA-400 "inova400"

Relax. delay 1.00 sec
 Pulse 45.0 degrees
 Width 6536 Hz
 32 repetitions
 OBSERVE H1, 399.9418373 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FT size 65536
 Total time 2 min, 50 sec
 Nov 26 2003
 VA Tech Chemistry NMR Lab

sim-iv-23

Project Name: Steph_Chiral
Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name:	slm-IV-23-8-28-03-AD	Acquired By:	Steph
Sample Type:	Unknown	Date Acquired:	8/28/03 4:36:39 PM
Vial:	1	Acq. Method:	20% B Isopropanol
Injection #:	1	Date Processed:	8/28/03 4:50:17 PM
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	20.00 Minutes	Sample Set Name:	Steph

	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	7.744	6716790	50.09	501138	58.37
2	10.467	6693843	49.91	357369	41.63

VA TECH

Project Name: Steph

Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name: slm-IV-bn-AD
Sample Type: Unknown
Vial: 1
Injection #: 1
Injection Volume: 10.00 μ l
Run Time: 30.00 Minutes

Acquired By: Steph
Date Acquired: 11/27/03 3:15:35 AM
Acq. Method: 20% isopropanol
Date Processed: 11/27/03 3:31:30 AM
Channel Name: 2487Channel 1
Sample Set Name: Steph

	RT (min)	Area (μ V*sec)	% Area	Height (μ V)	% Height
1	10.950	23137421	100.00	1192804	100.00

Archive directory: /export/home/robot/vnmrsys/data
Sample directory:

Solvent: CDCl₃

Ambient temperature
File: PPTON 01

0
0
+
5
4
0
=

0
0
T
I
4
0
=

Pulse 45.0 degrees

width 6399.0 Hz
16 repetitions

DATA PROCESSING

Total time 1 min, 15 sec

VA Tech Chemistry NMR Lab

SLM-IV-153

Archive directory: /export/home/robot/vnmrSYS/data
 Sample directory:

Pulse Sequence: s2pul

Solvent: CDCl₃

Ambient temperature

File: 0806031

INOVA-400 "Inova400"

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq time 1.19 sec

Width 2541.19 sec

320 repetitions

OBSERVE C13, 100.5654572 MHz

DECOUPLE H1, 399.9438386 MHz

Power 45 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Mar 10 2004

Total time 36 min, 48 sec

VA Tech Chemistry NMR Lab

Project Name: Steph_Chiral
Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name:	slm-IV-67-10-18-03	Acquired By:	Steph
Sample Type:	Unknown	Date Acquired:	10/18/03 2:43:20 PM
Vial:	1	Acq. Method:	20% B Isopropanol
Injection #:	1	Date Processed:	10/18/03 3:13:56 PM
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	25.00 Minutes	Sample Set Name:	Steph

	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	7.181	5324228	15.11	416774	20.72
2	9.986	29901739	84.89	1595039	79.28

VA TECH

Project Name: Steph
Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name:	slm-IV-153-3-8-04	Acquired By:	Steph
Sample Type:	Unknown	Date Acquired:	3/8/04 3:18:03 AM
Vial:	1	Acq. Method:	20% isopropanol
Injection #:	1	Date Processed:	3/8/04 3:30:22 AM
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	20.00 Minutes	Sample Set Name	Steph

	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	6.605	245383	0.41	18471	0.57
2	9.337	59545831	99.59	3247107	99.43

Project Name: Steph_Chiral
Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name: ~~slm-IV-60~~-AD-10-24-03
Sample Type: Unknown
Vial: 1
Injection #: 1
Injection Volume: 10.00 ul
Run Time: 120.00 Minutes

Acquired By: Steph
Date Acquired: 10/24/03 11:37:37 AM
Acq. Method: 20% B Isopropanol
Date Processed: 10/24/03 11:49:18 AM
Channel Name: 2487Channel 1
Sample Set Name: Steph

	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	6.896	12653243	50.35	963228	58.53
2	9.132	12476756	49.65	682356	41.47

Project Name: Steph_Chiral
Reported by User: Steph

Breeze

SAMPLE INFORMATION

Sample Name:	slm-IV59-AD-10-24-03	Acquired By:	Steph
Sample Type:	Unknown	Date Acquired:	10/24/03 11:51:08 AM
Vial:	1	Acq. Method:	20% B Isopropanol
Injection #:	1	Date Processed:	10/24/03 12:03:45 PM
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	120.00 Minutes	Sample Set Name:	Steph

	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	6.959	30676205	97.79	2363127	98.48
2	9.150	692845	2.21	36541	1.52

1H OBSERVE

Pulse Sequence: s2pu1
Solvent: CD300
Ambient temperature
File: slm-III-121-6-11-03
INOVA-400 "Inova400"

Relax. delay 1.000 sec
Pulse 26.1 degrees
Acq. time 3.700 sec
Width 6387.7 Hz
16 repetitions
OBSERVE H1, 399.9433990 MHz
DATA PROCESSING
Line broadening 0.2 Hz
F1 size 65536
Total time 2 min, 30 sec
Jun 11 2003
VA Tech Chemistry NMR Lab

F. References

- [1] W. Wright, H. Brabander, E. Greenblatt, I. Day, R. Hardy, *J. Med. Chem.* **1978**, *21*, 1087-1089.
- [2] C. V. Beard, K. Baum, V. Grakaskas, *J. Org. Chem.* **1973**, *38*, 3673.
- [3] D. Seebach, M. Boes, R. Naef, B. Schweizer, *J. Am. Chem. Soc.* **1983**, *105*, 5390.
- [4] Gaussian 03, Revision B.05, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 2003.