

Supporting Information

Supporting Information

**Synthesis and Anticonvulsant Activities of *N*-
(4'-Substituted)benzyl (*R*)-2-Acetamido-3-
methoxypropionamides**

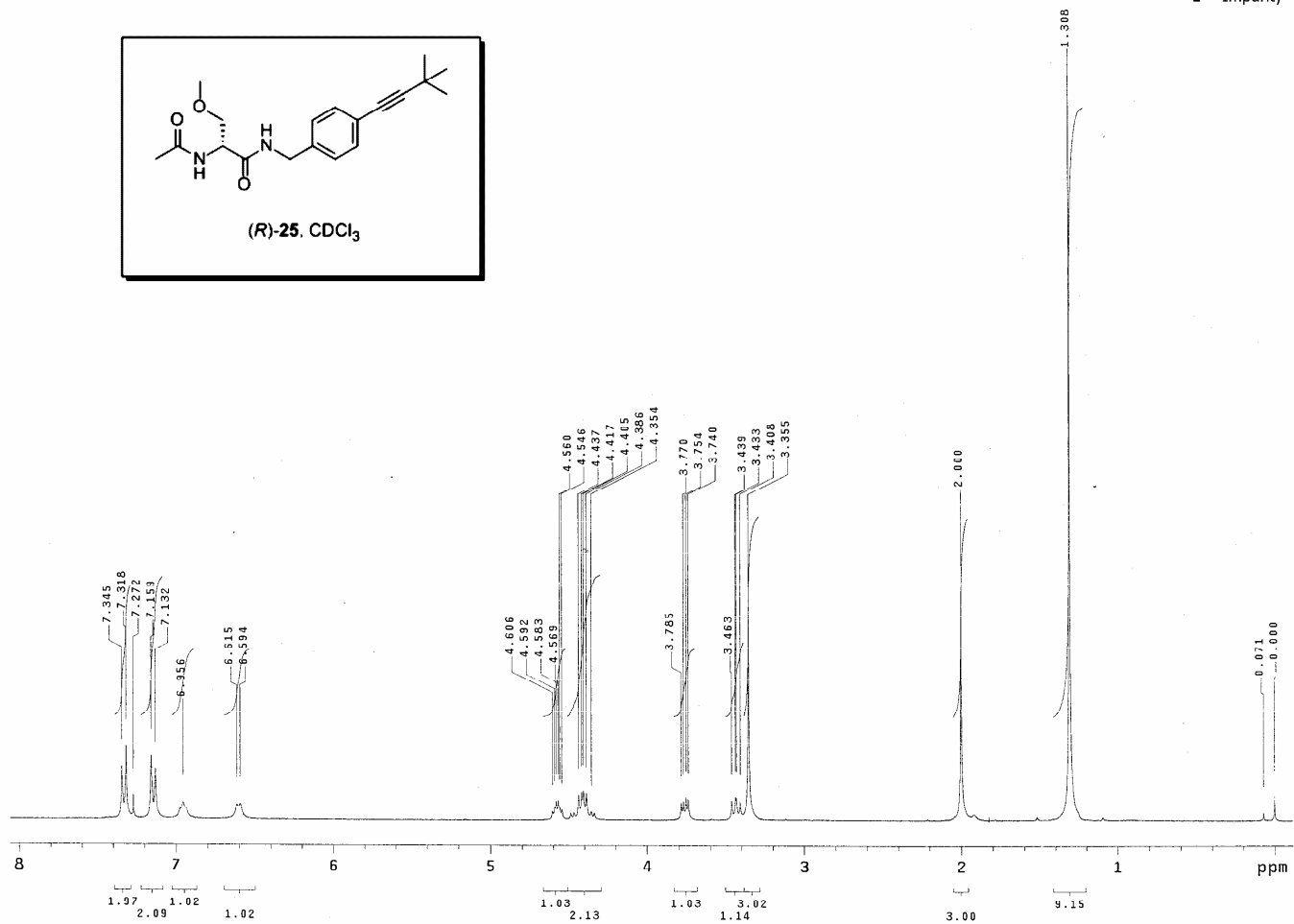
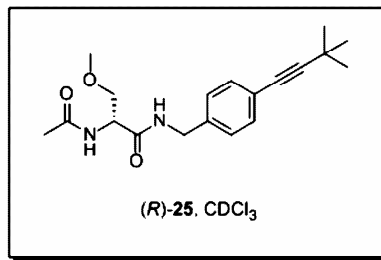
*Christophe Salomé,¹ Elise Salomé-Grosjean,¹ Ki Duk Park,¹ Pierre
Morieux,¹ Robert Swendiman,¹ Erica DeMarco,¹ James P. Stables,² and
Harold Kohn*^{1,3}*

¹Division of Medicinal Chemistry and Natural Products, UNC Eshelman School of Pharmacy,
University of North Carolina, Chapel Hill, North Carolina 27599-7568, USA

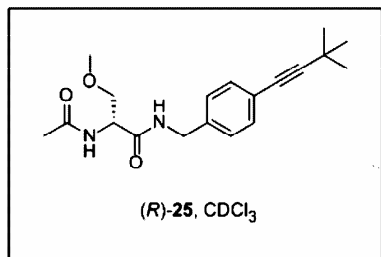
²Anticonvulsant Screening Program, National Institute of Neurological Disorders and Stroke,
National Institutes of Health, 6001 Executive Blvd., Suite 2106, Rockville, MD 20892-9523, USA

³Department of Chemistry,
University of North Carolina, Chapel Hill, North Carolina 27599-3290, USA

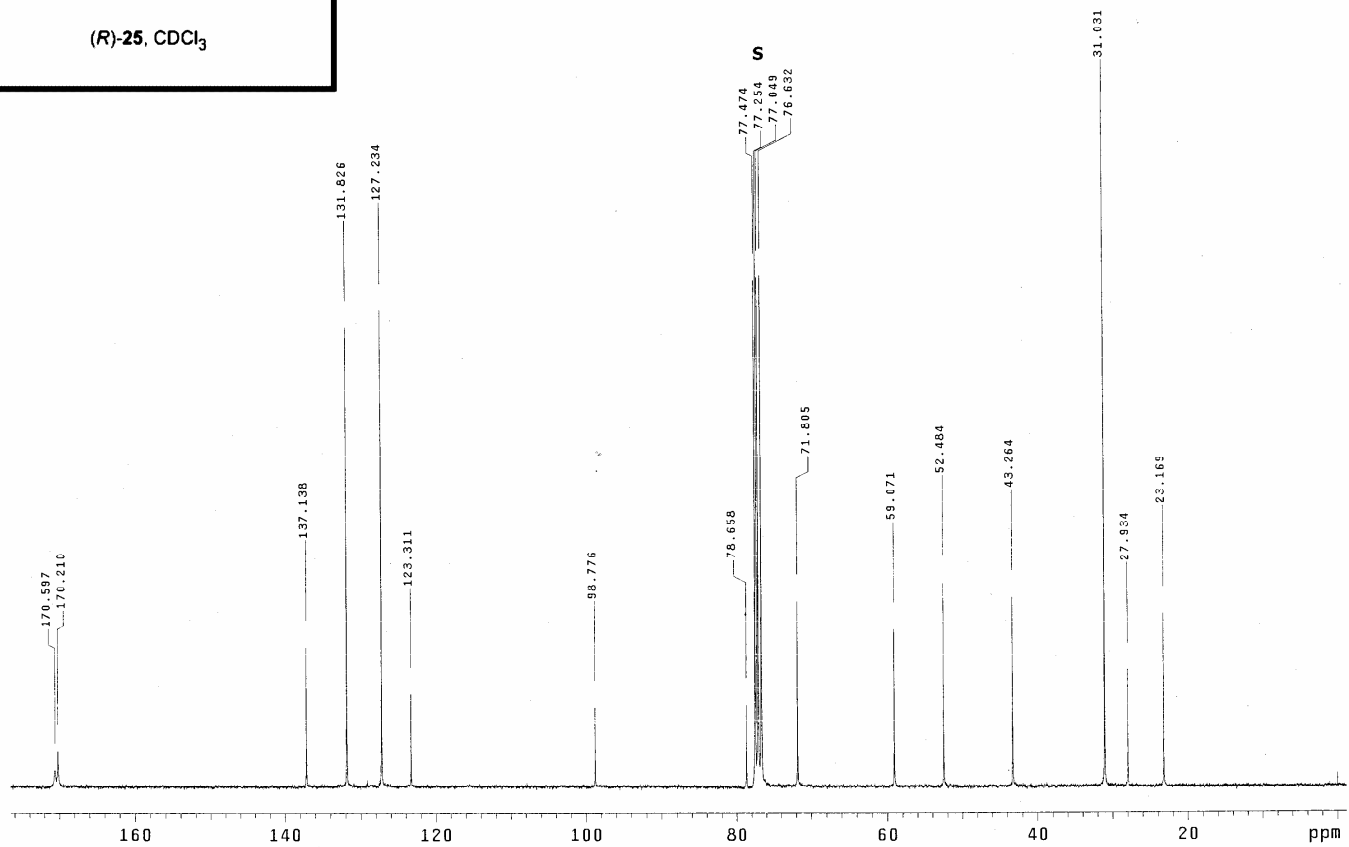
Supporting Information



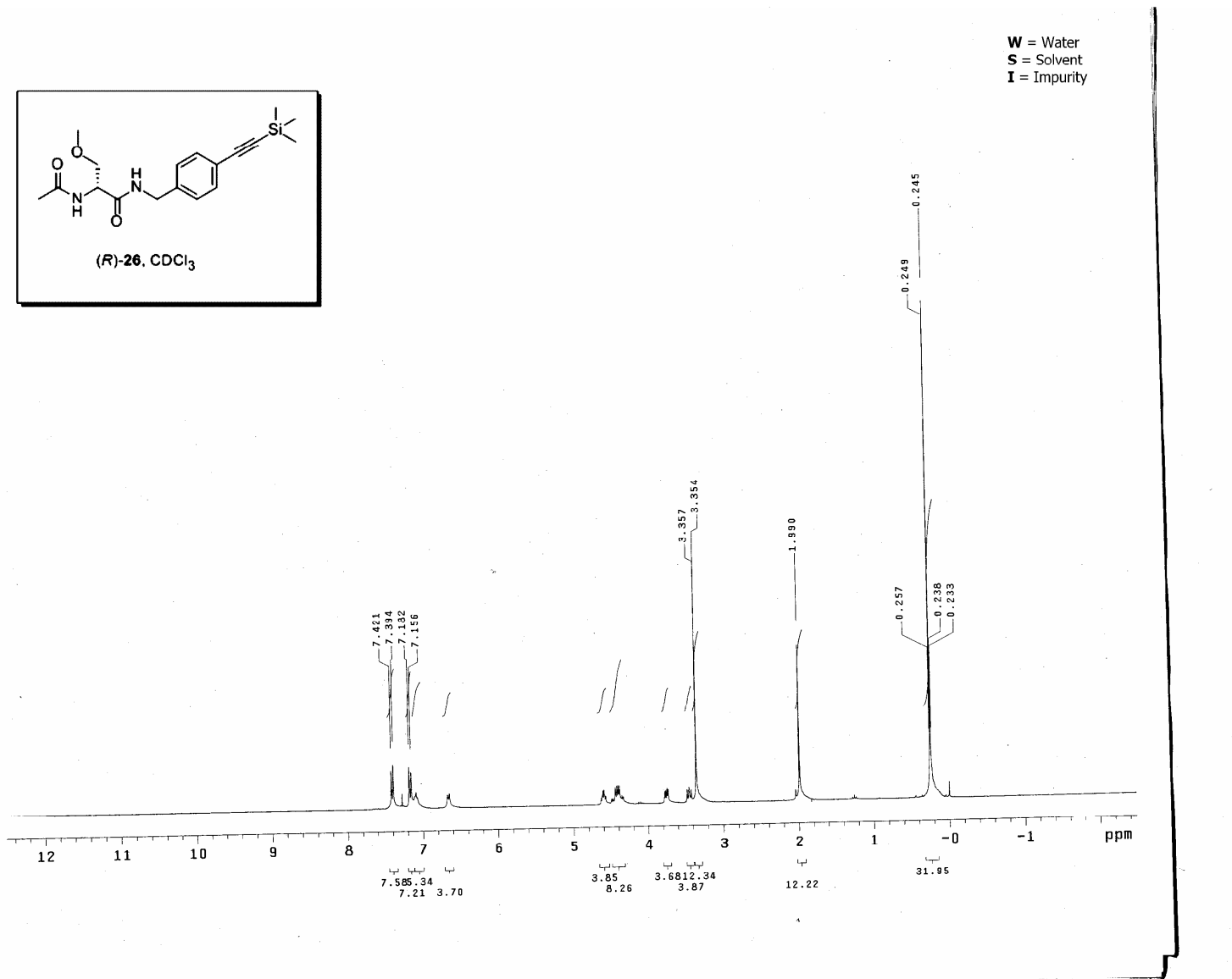
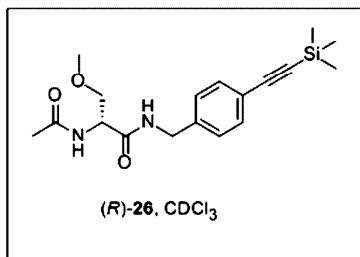
Supporting Information



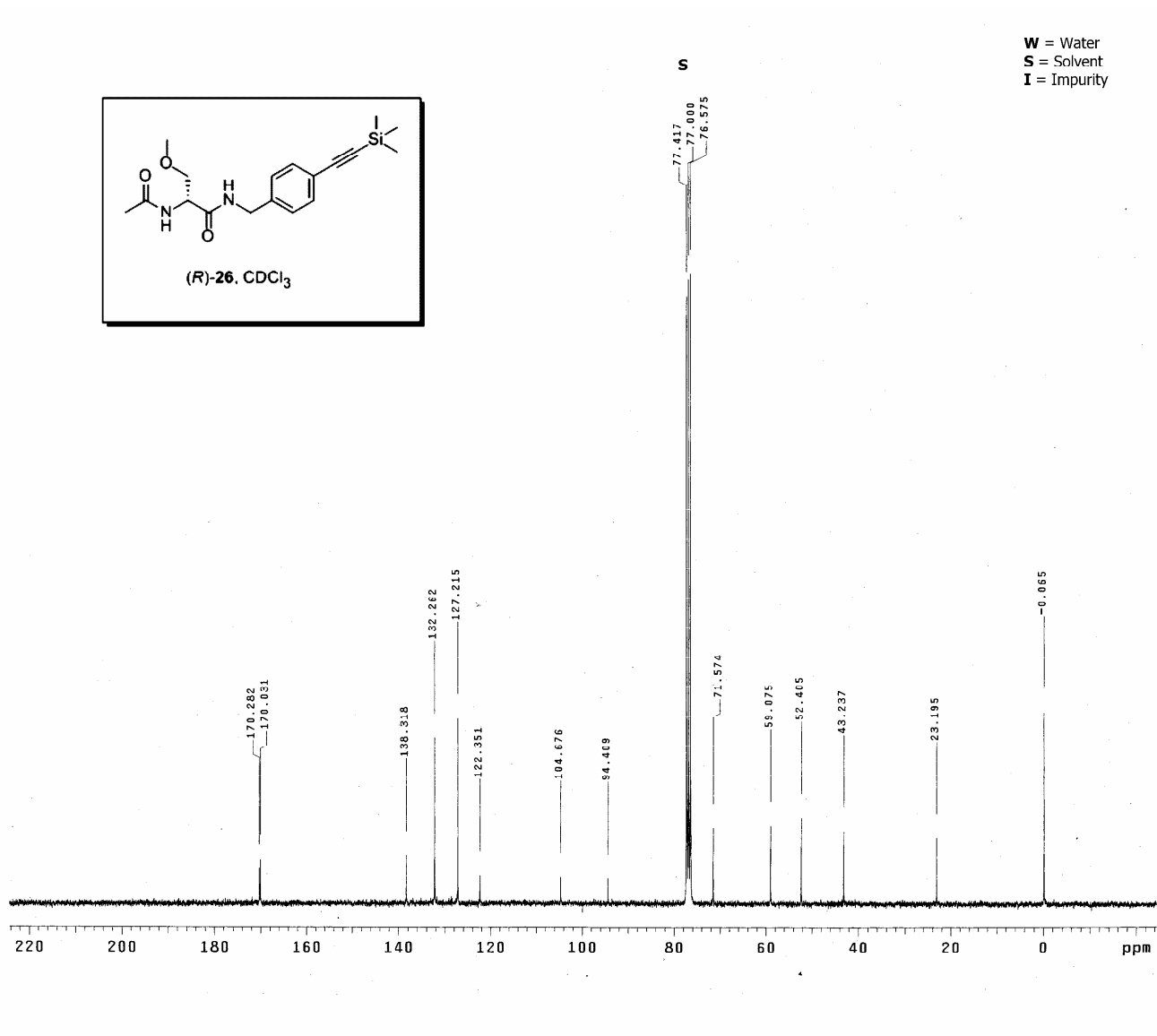
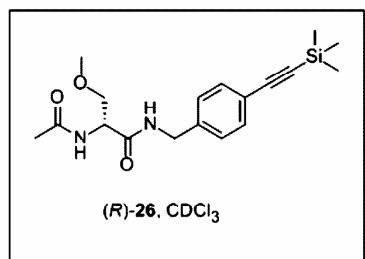
W = Water
S = Solvent
I = Impurity



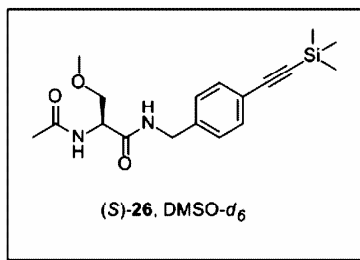
Supporting Information



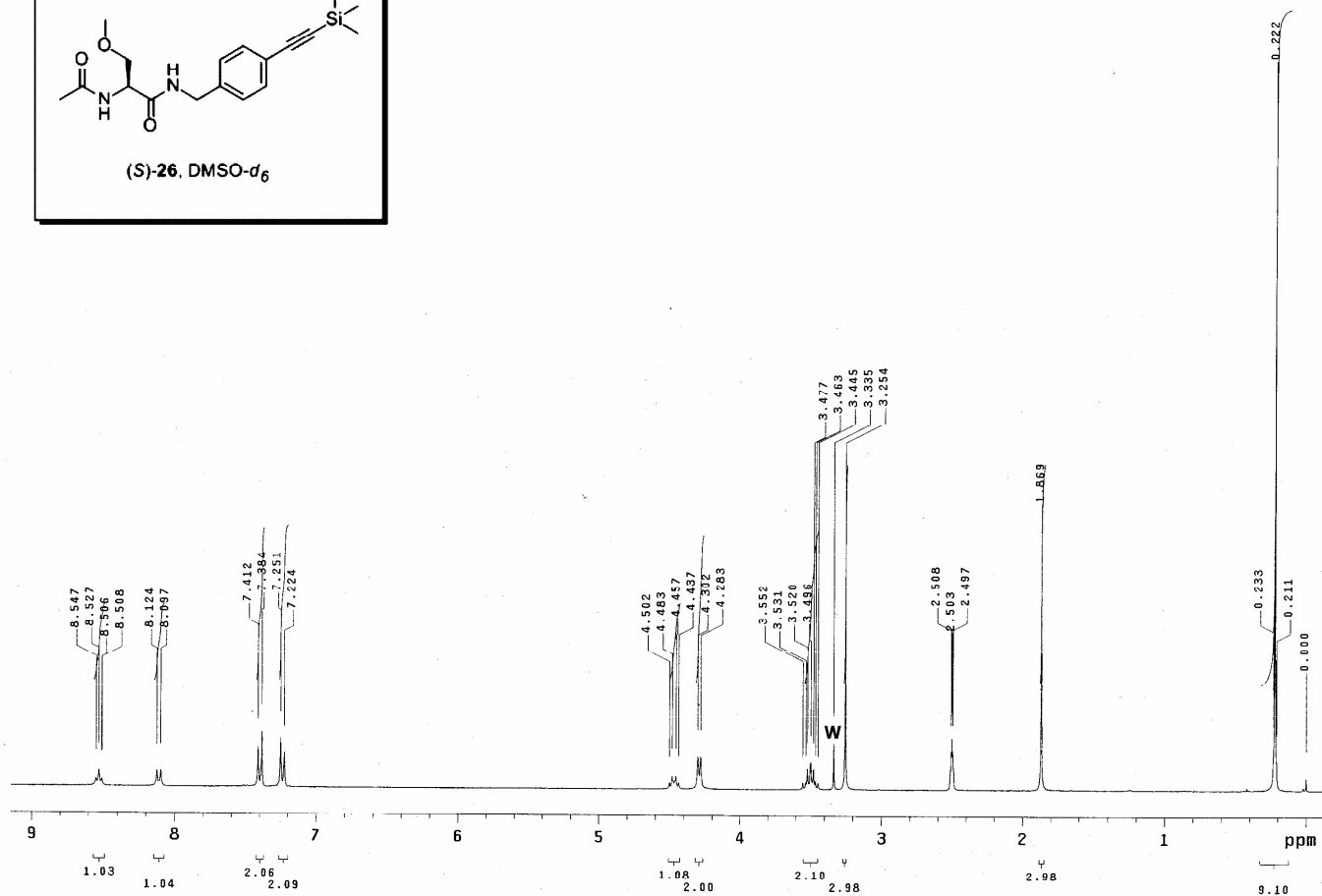
Supporting Information



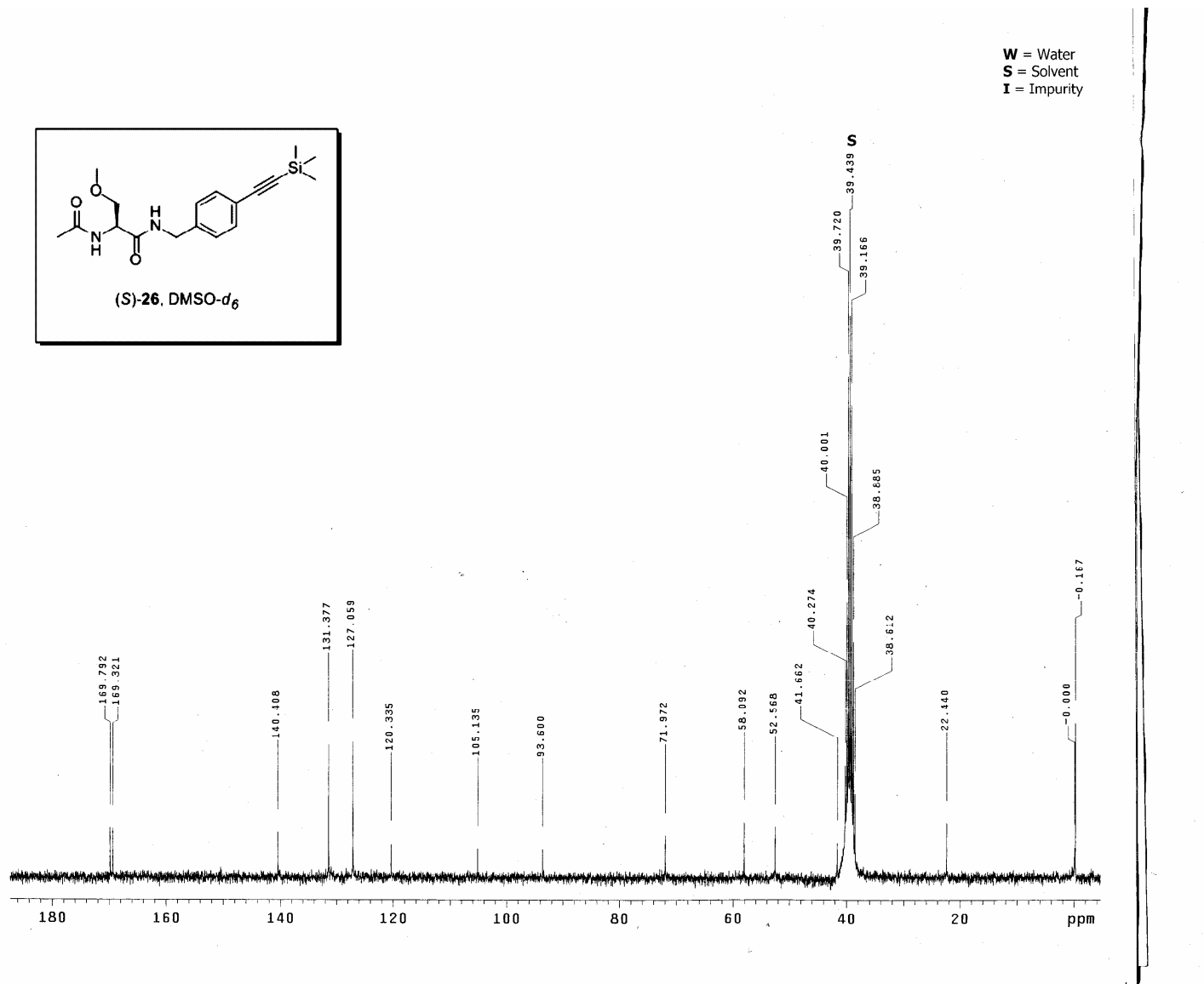
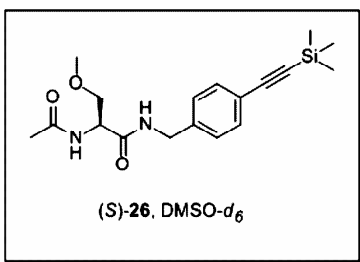
Supporting Information



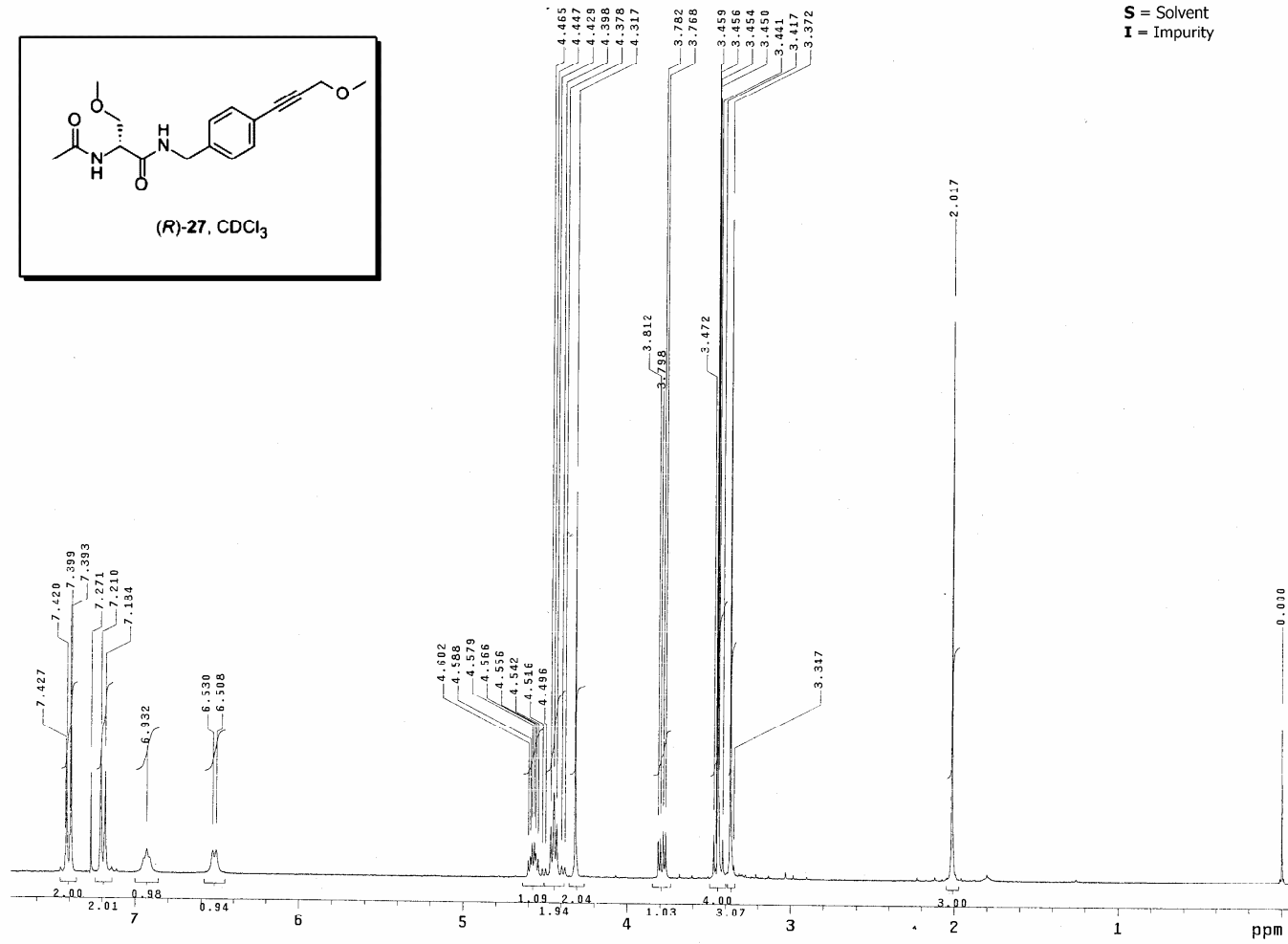
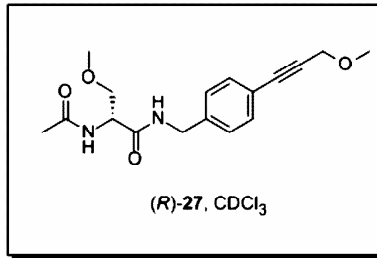
W = Water
S = Solvent
I = Impurity



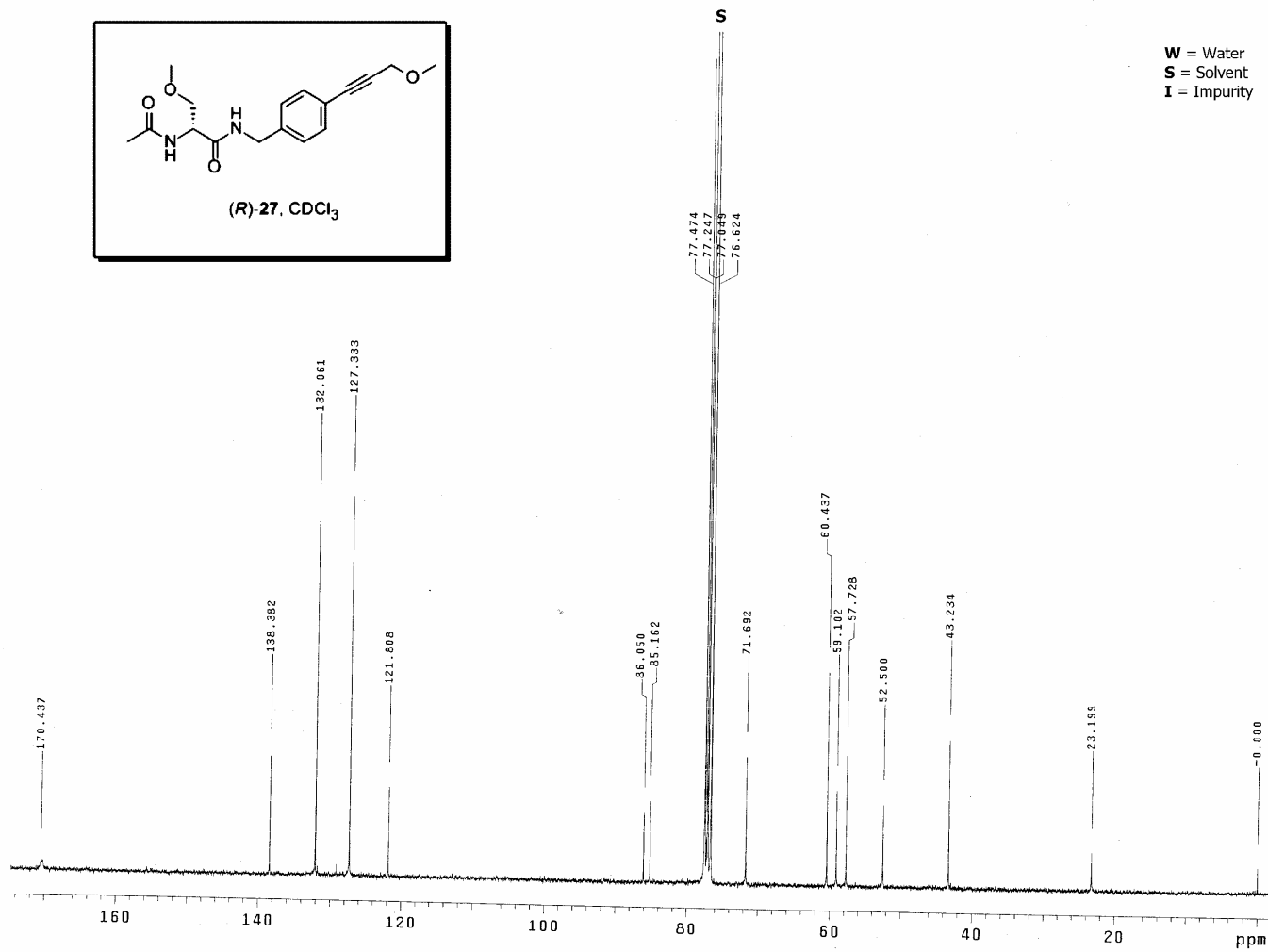
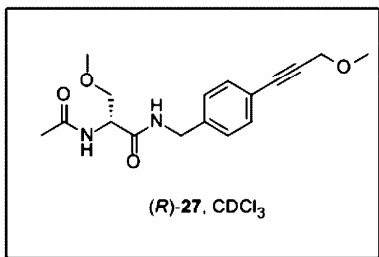
Supporting Information



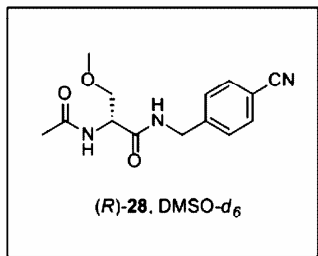
Supporting Information



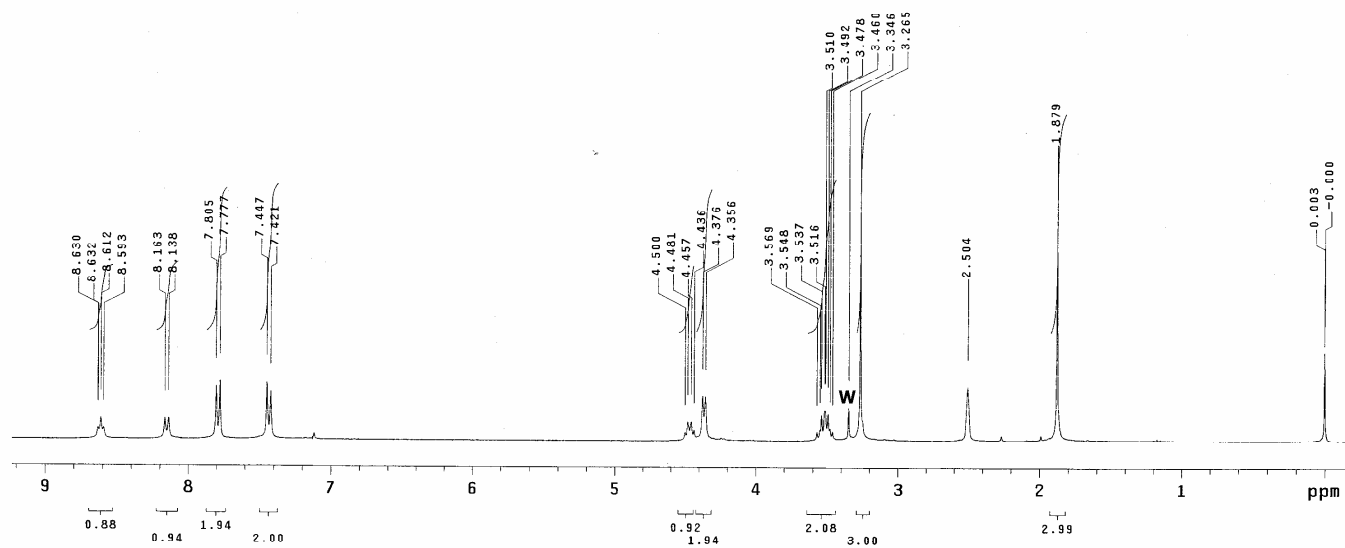
Supporting Information



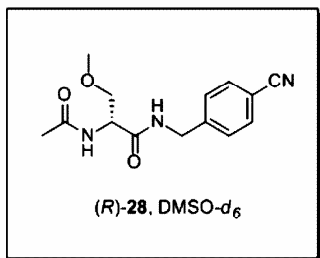
Supporting Information



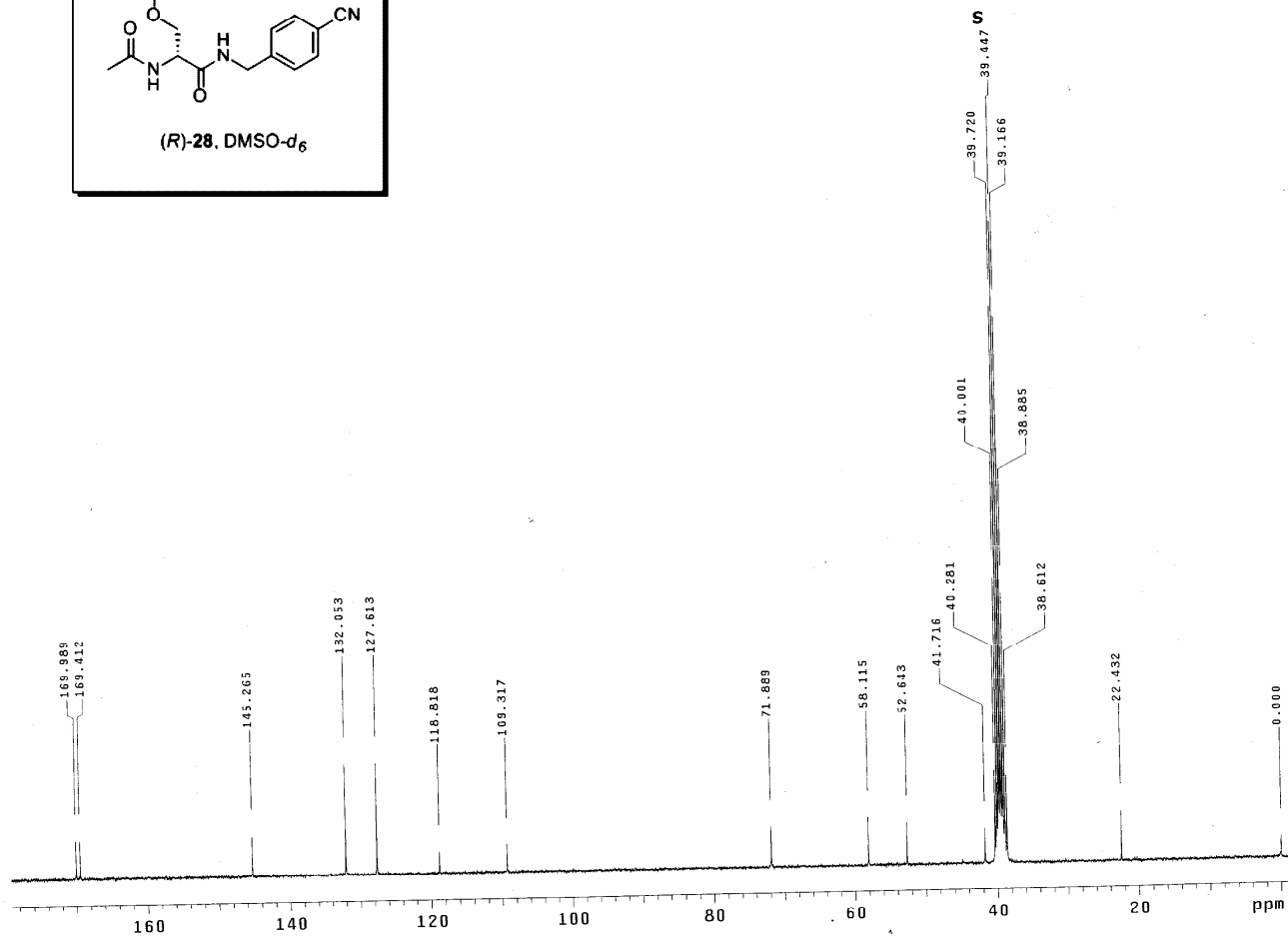
W = Water
S = Solvent
I = Impurity



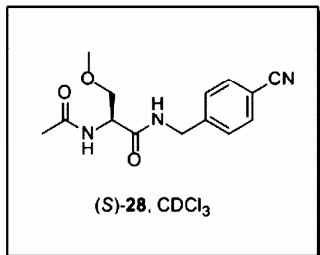
Supporting Information



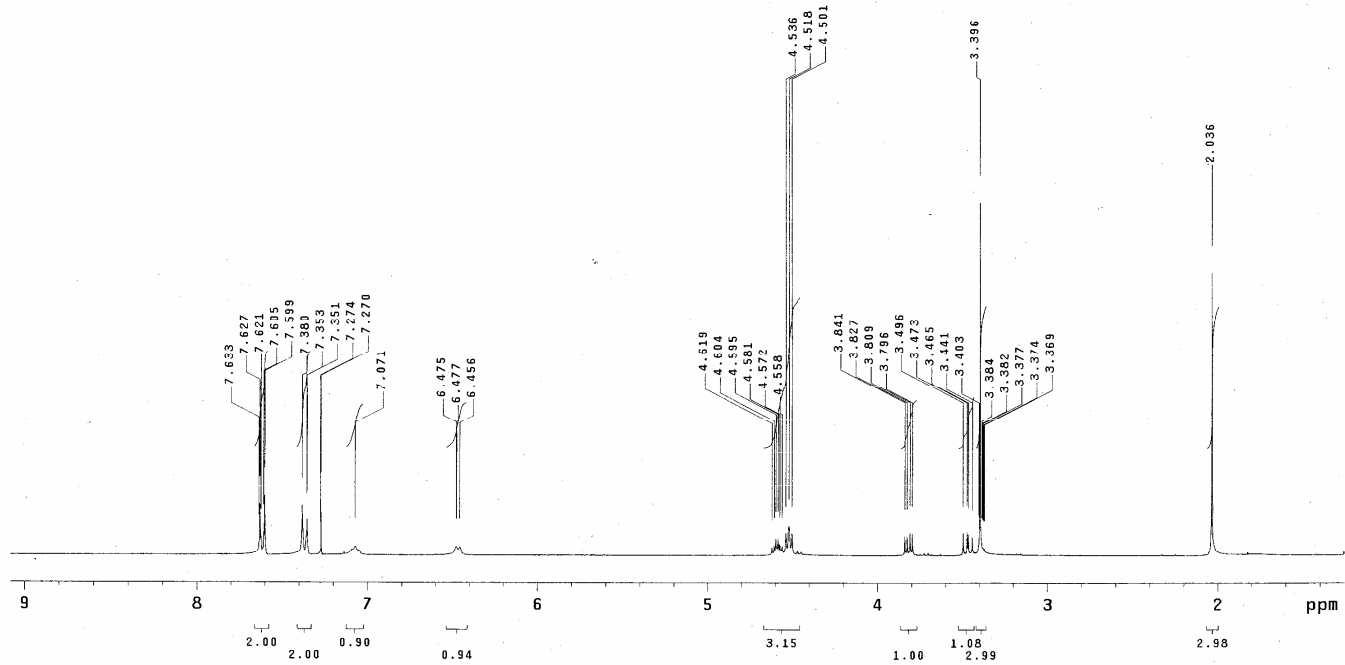
W = Water
S = Solvent
I = Impurity



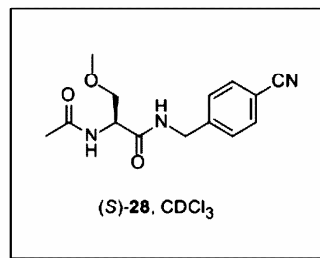
Supporting Information



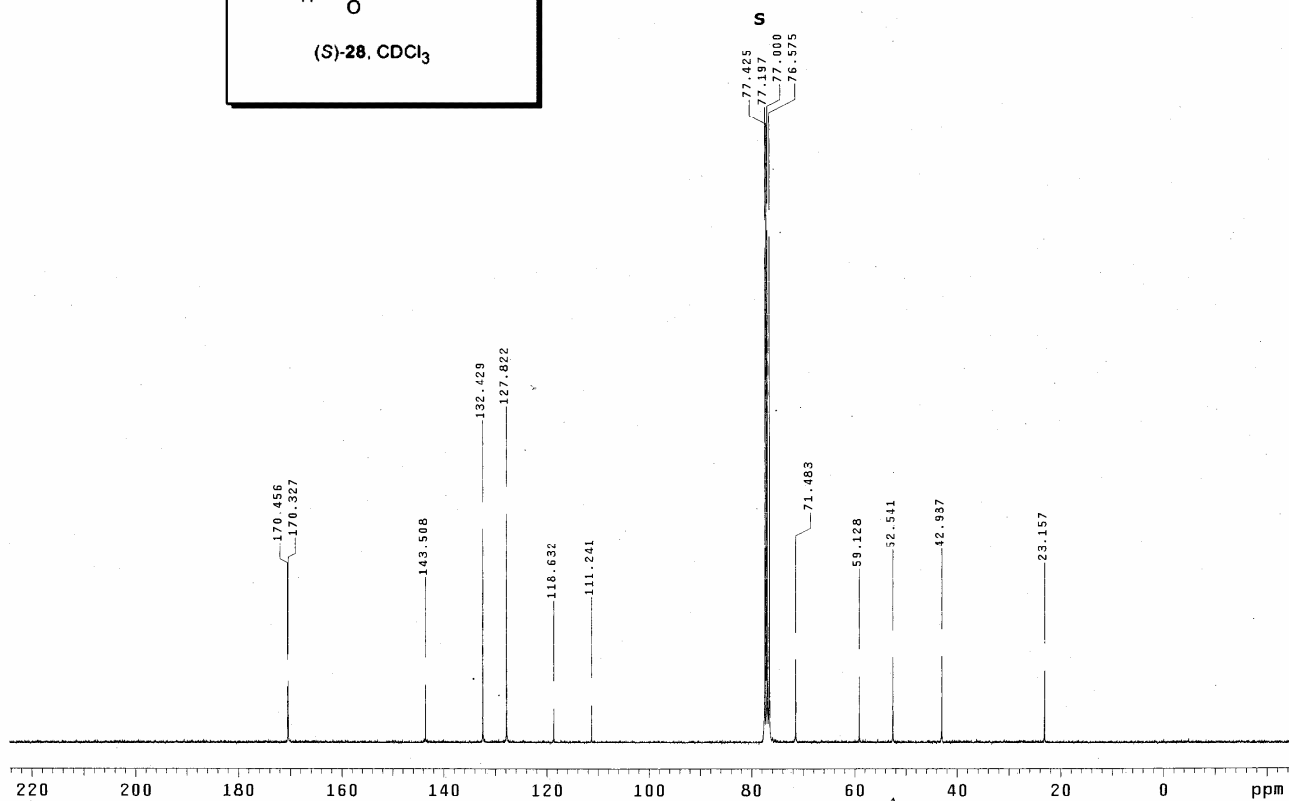
W = Water
S = Solvent
I = Impurity



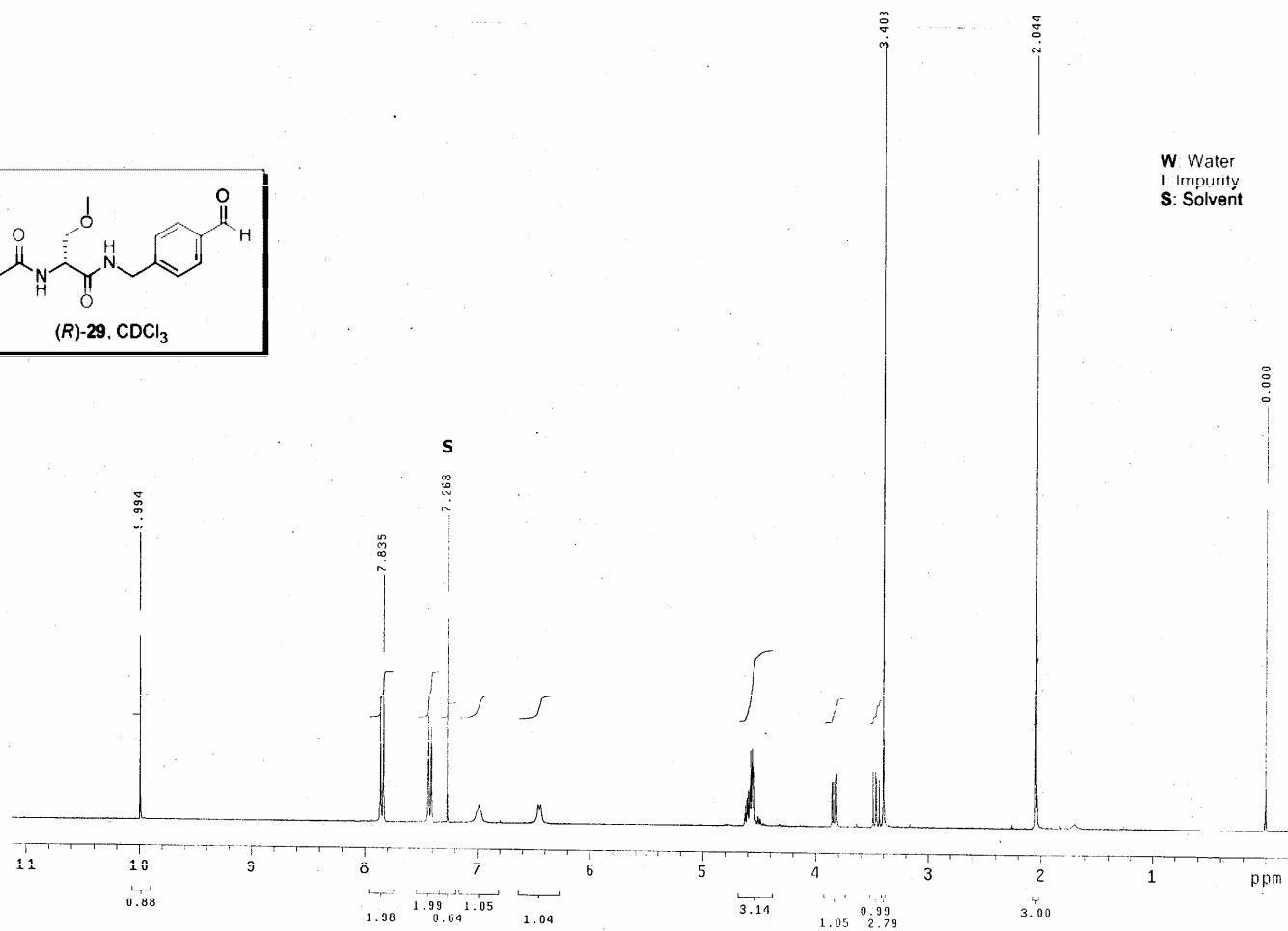
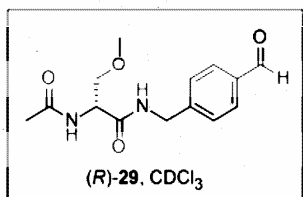
Supporting Information



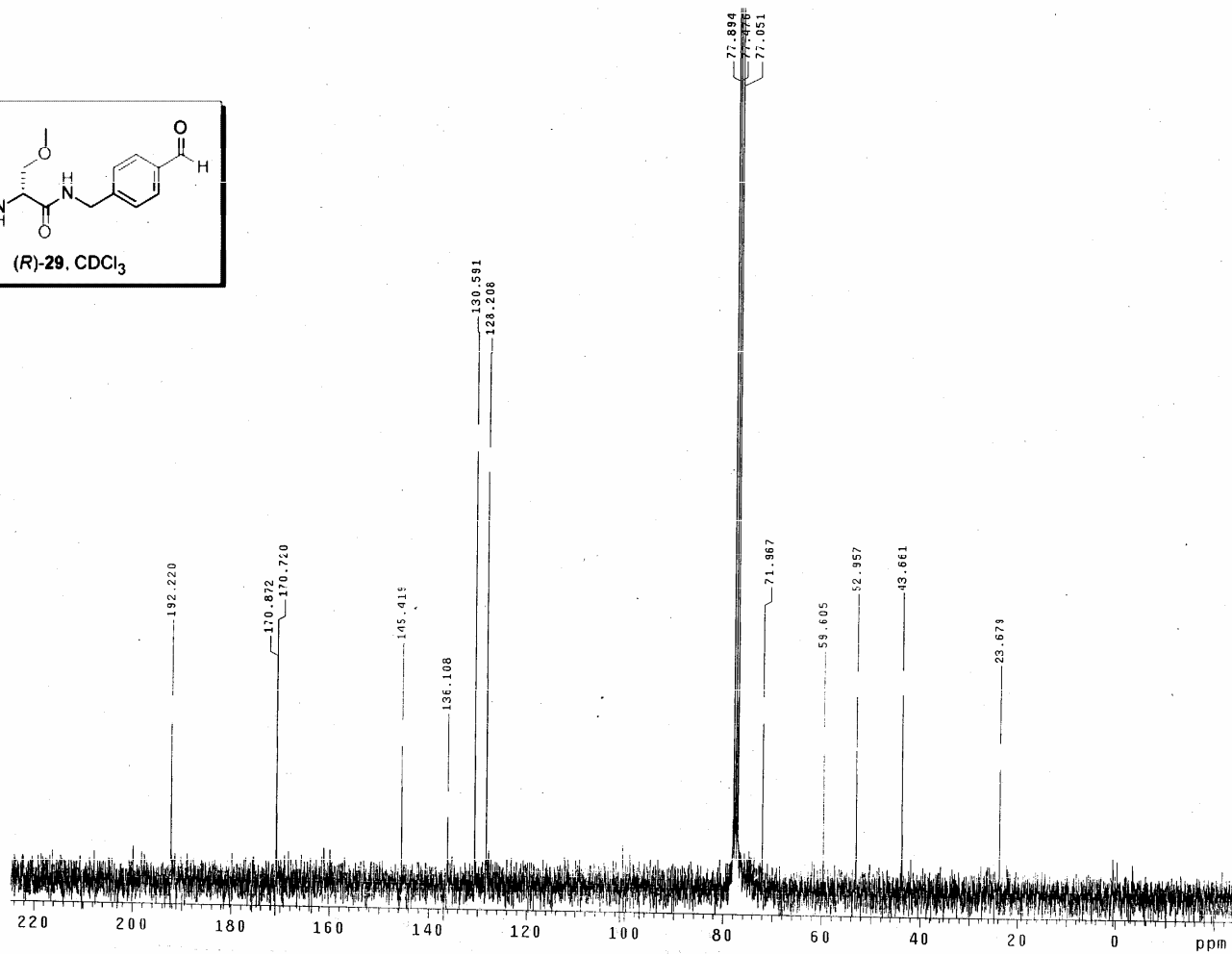
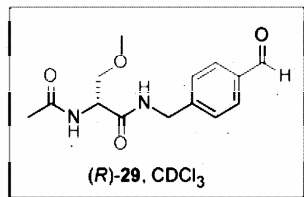
W = Water
S = Solvent
I = Impurity



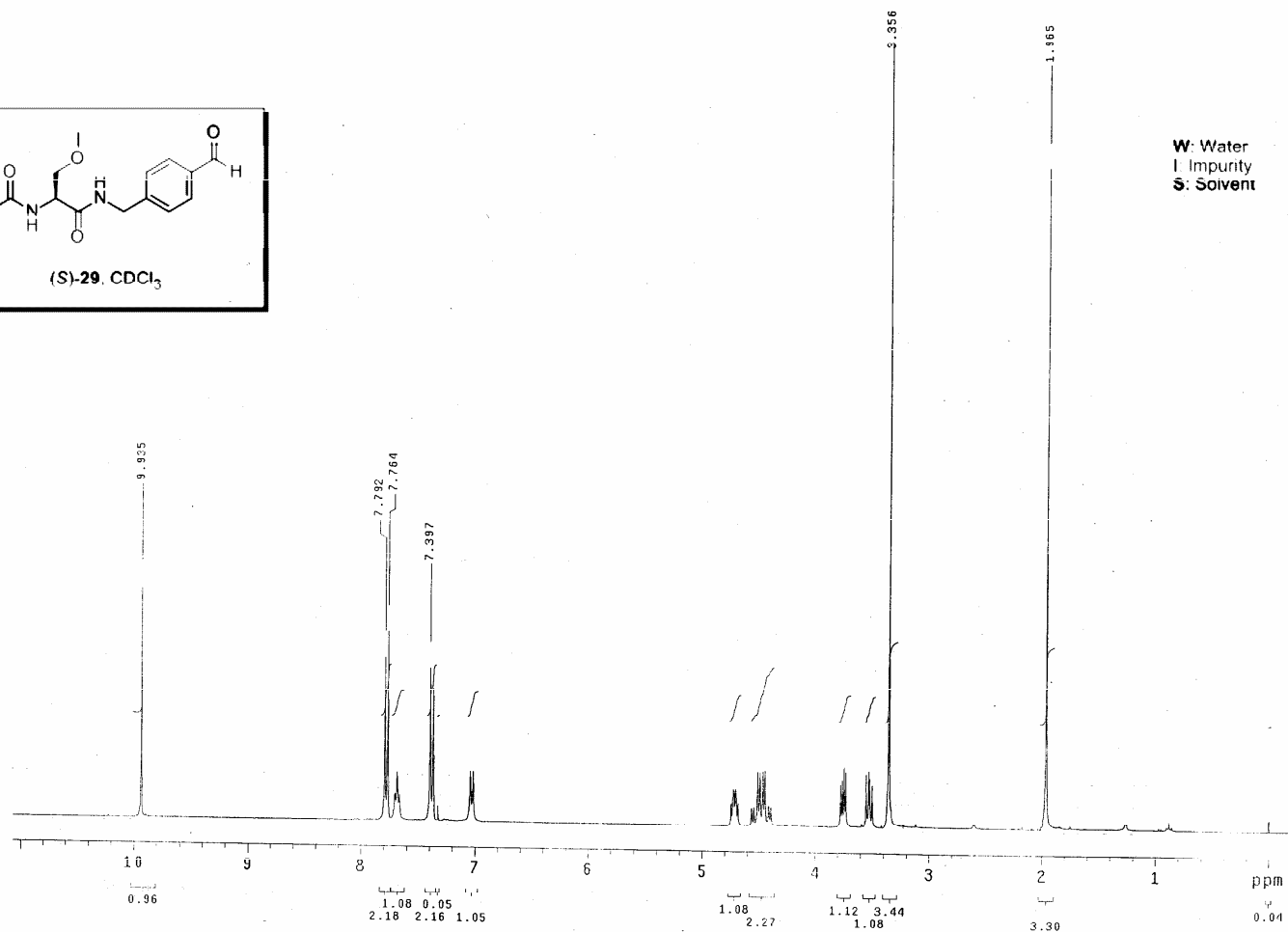
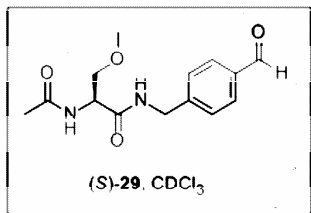
Supporting Information



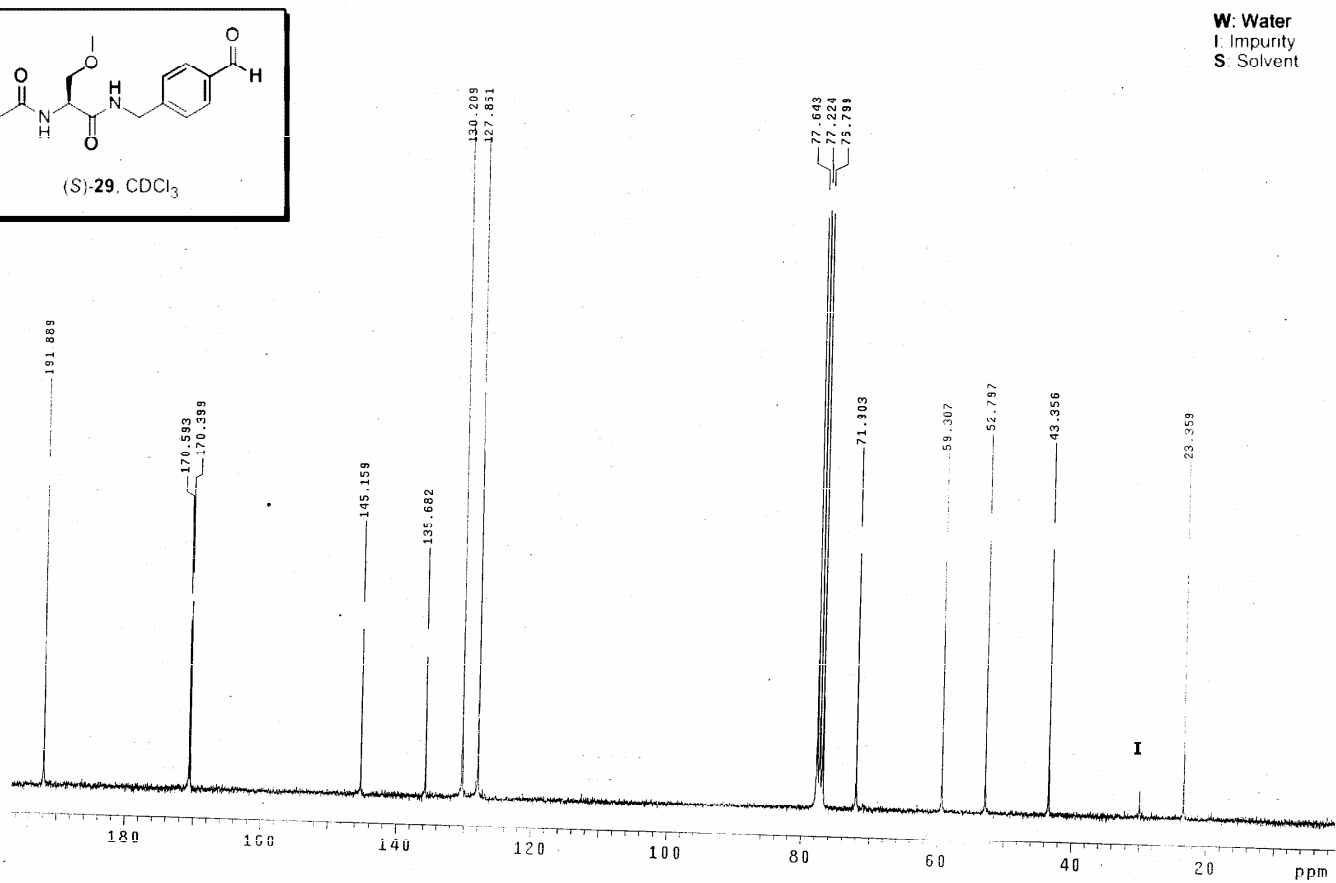
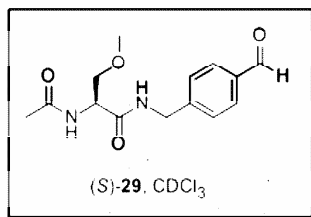
Supporting Information



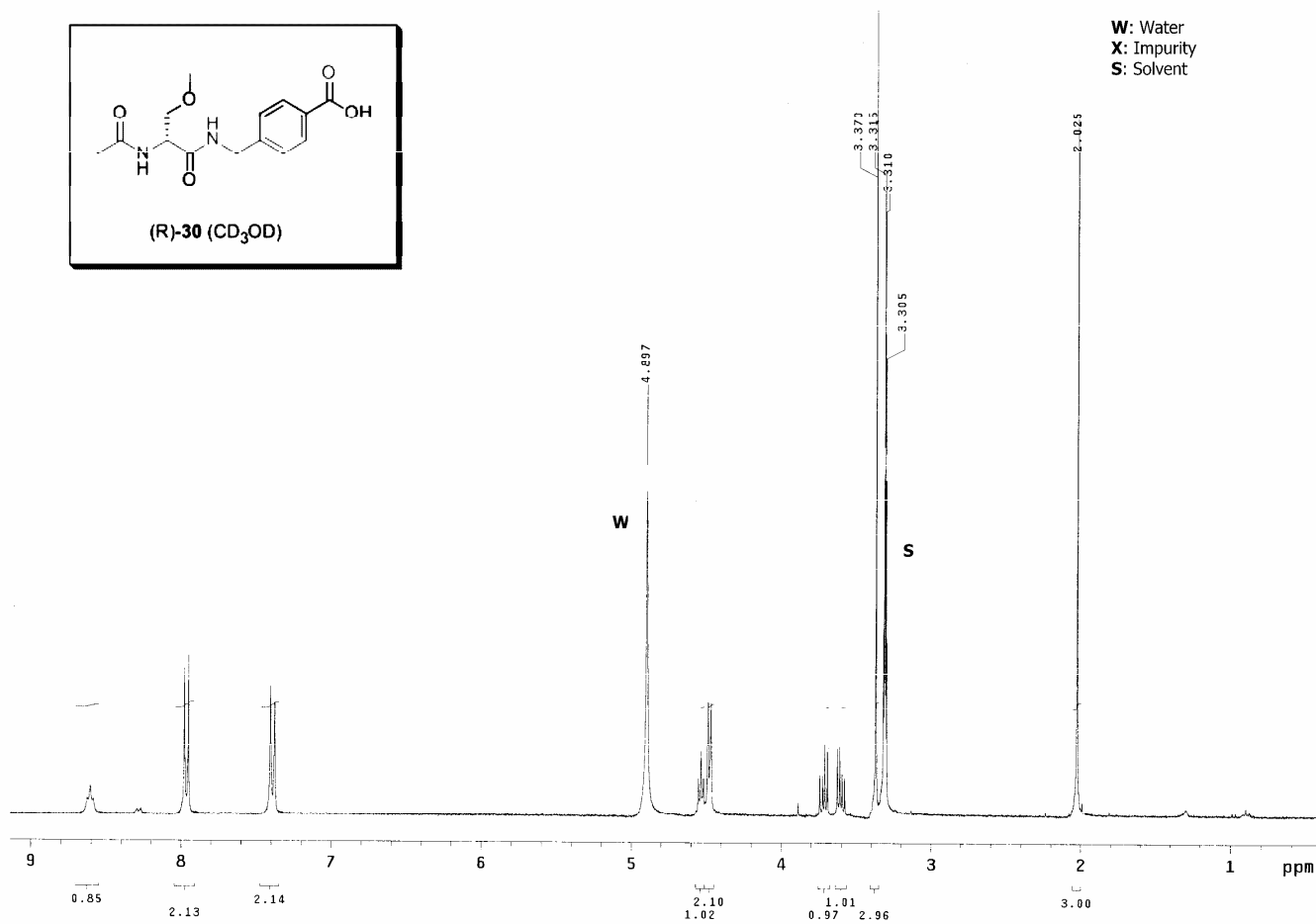
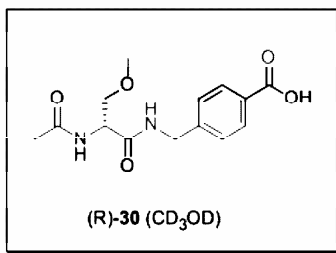
Supporting Information



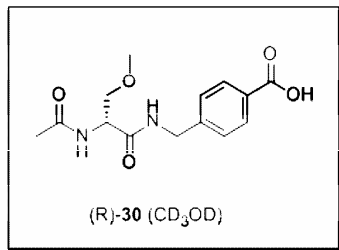
Supporting Information



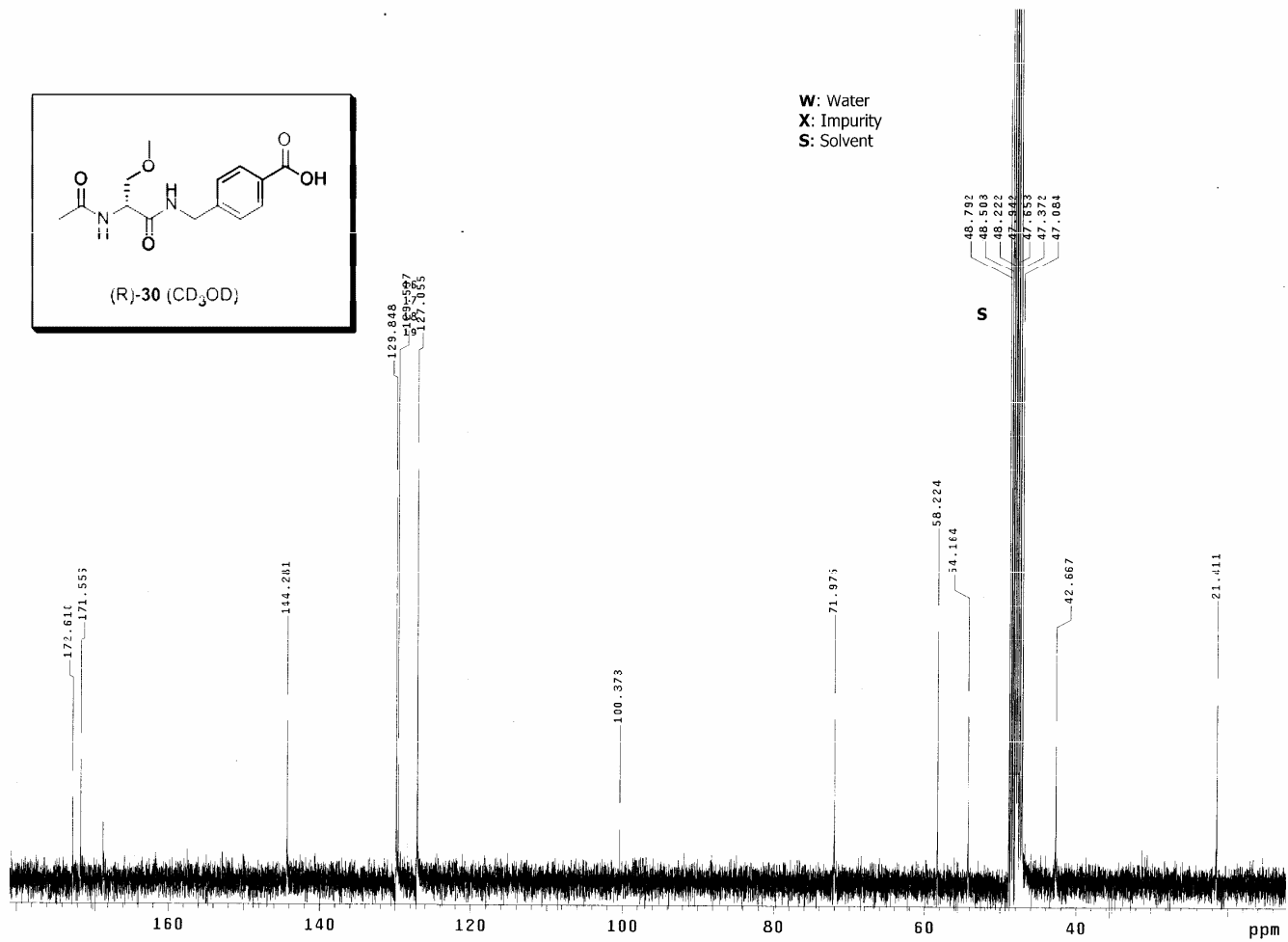
Supporting Information



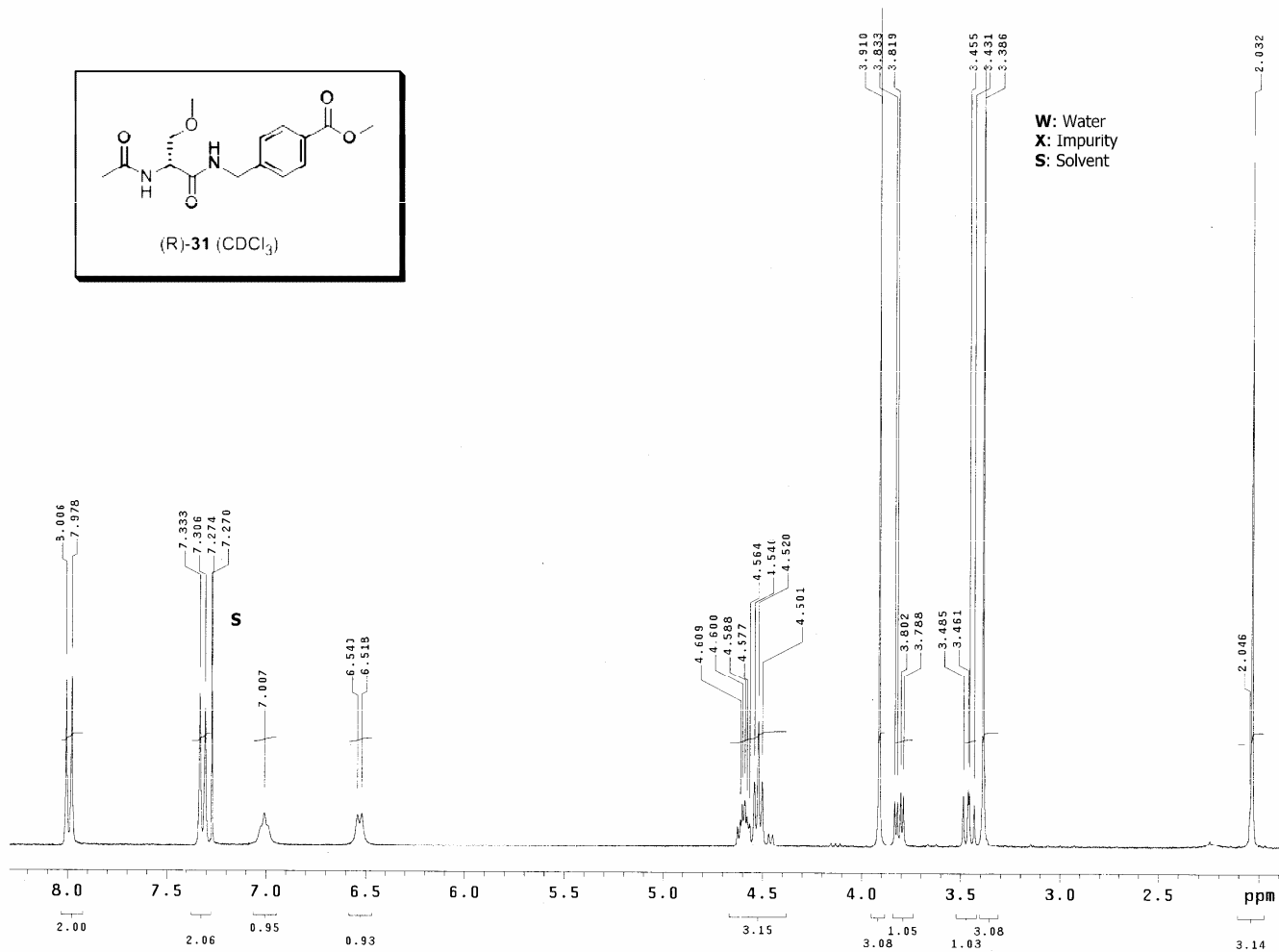
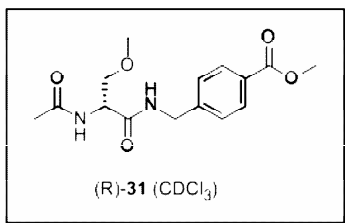
Supporting Information



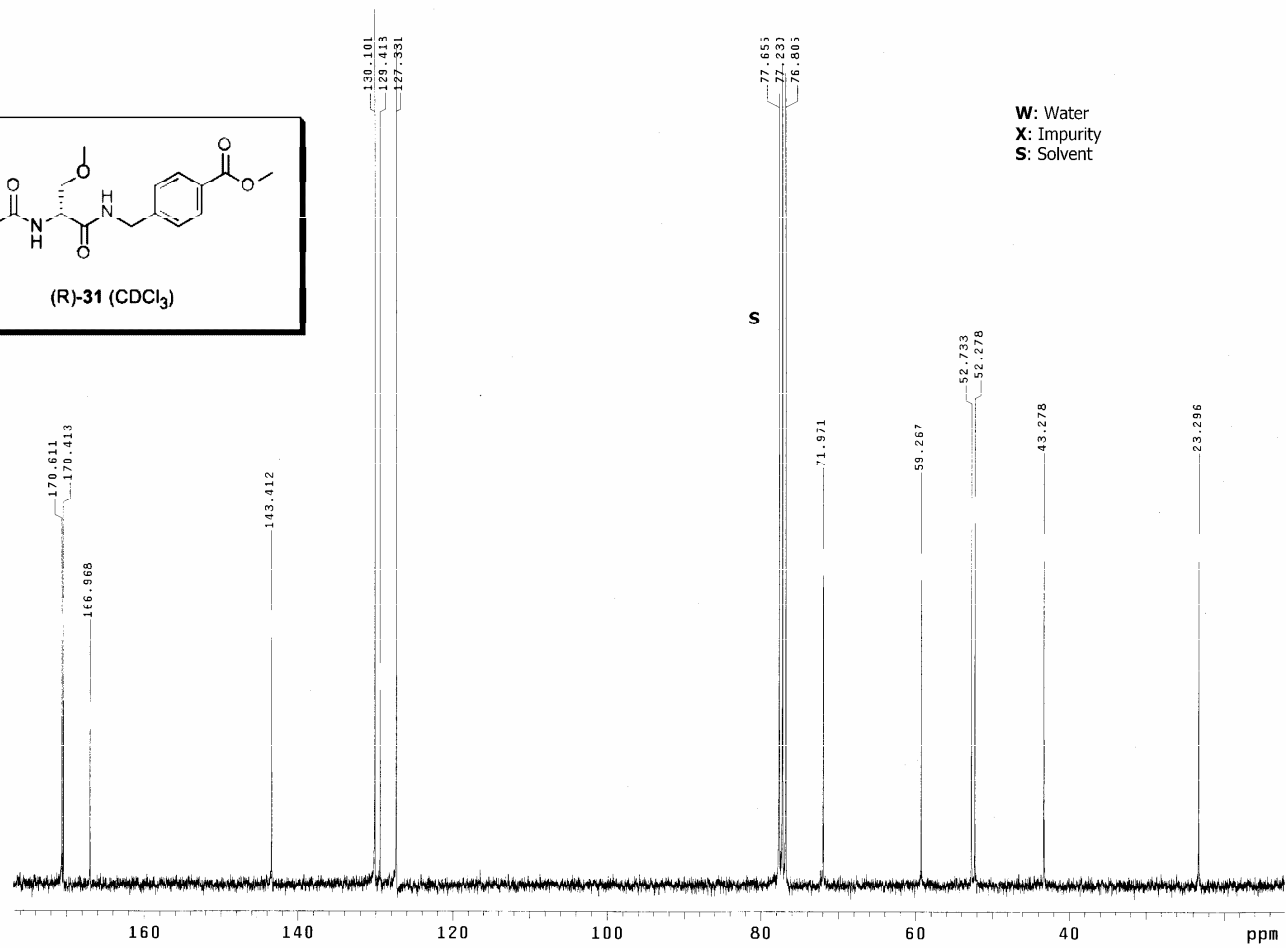
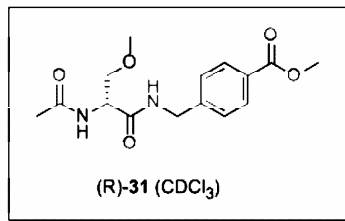
W: Water
X: Impurity
S: Solvent



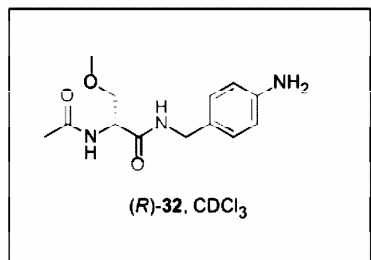
Supporting Information



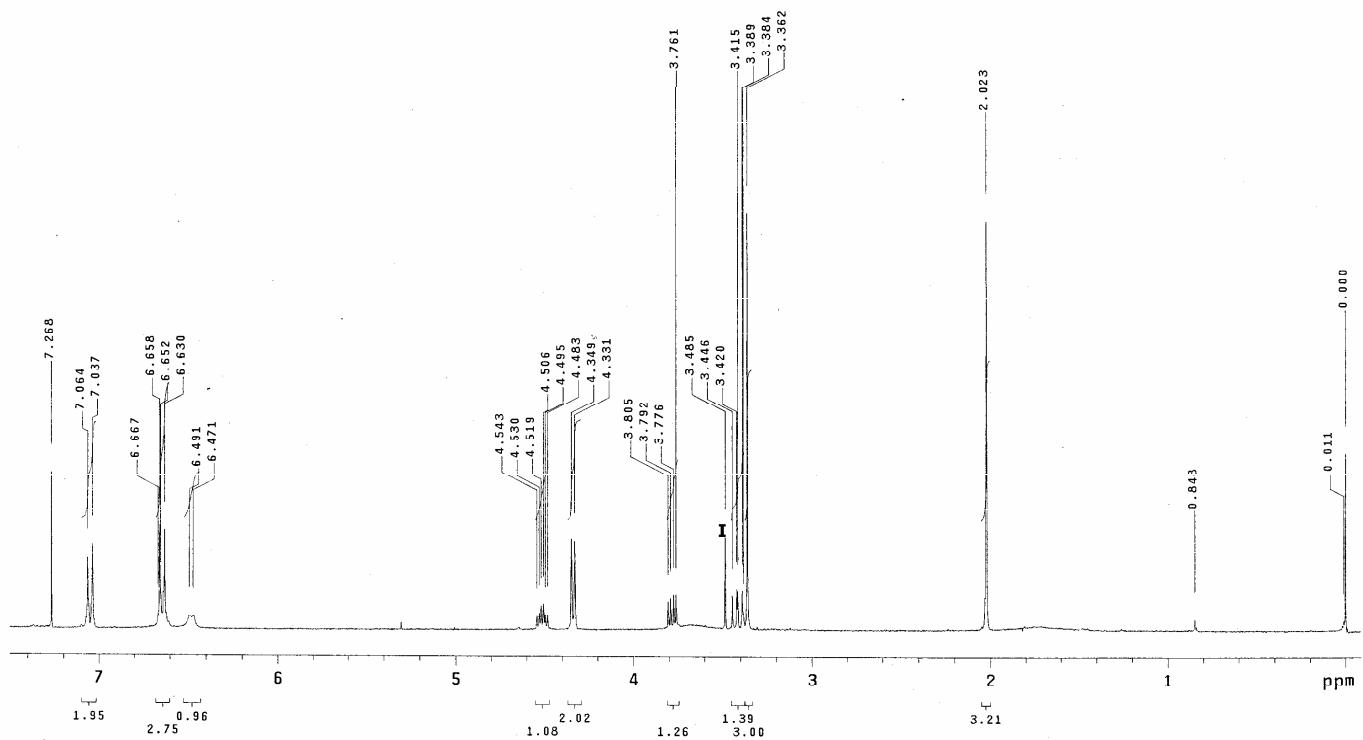
Supporting Information



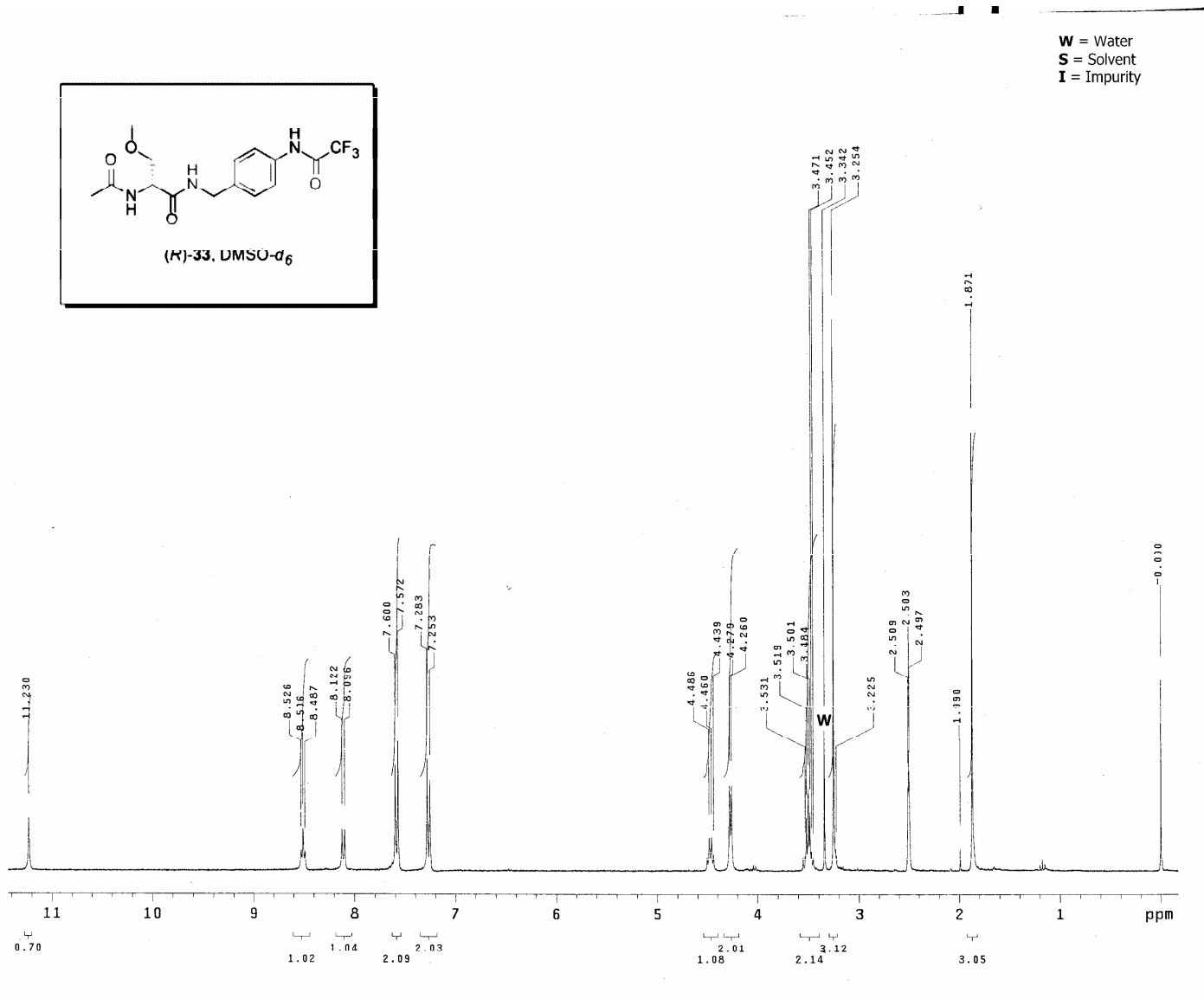
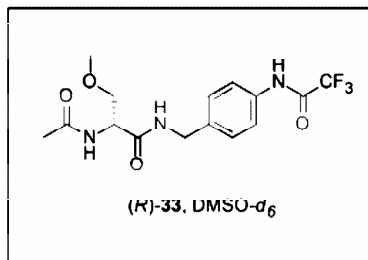
Supporting Information



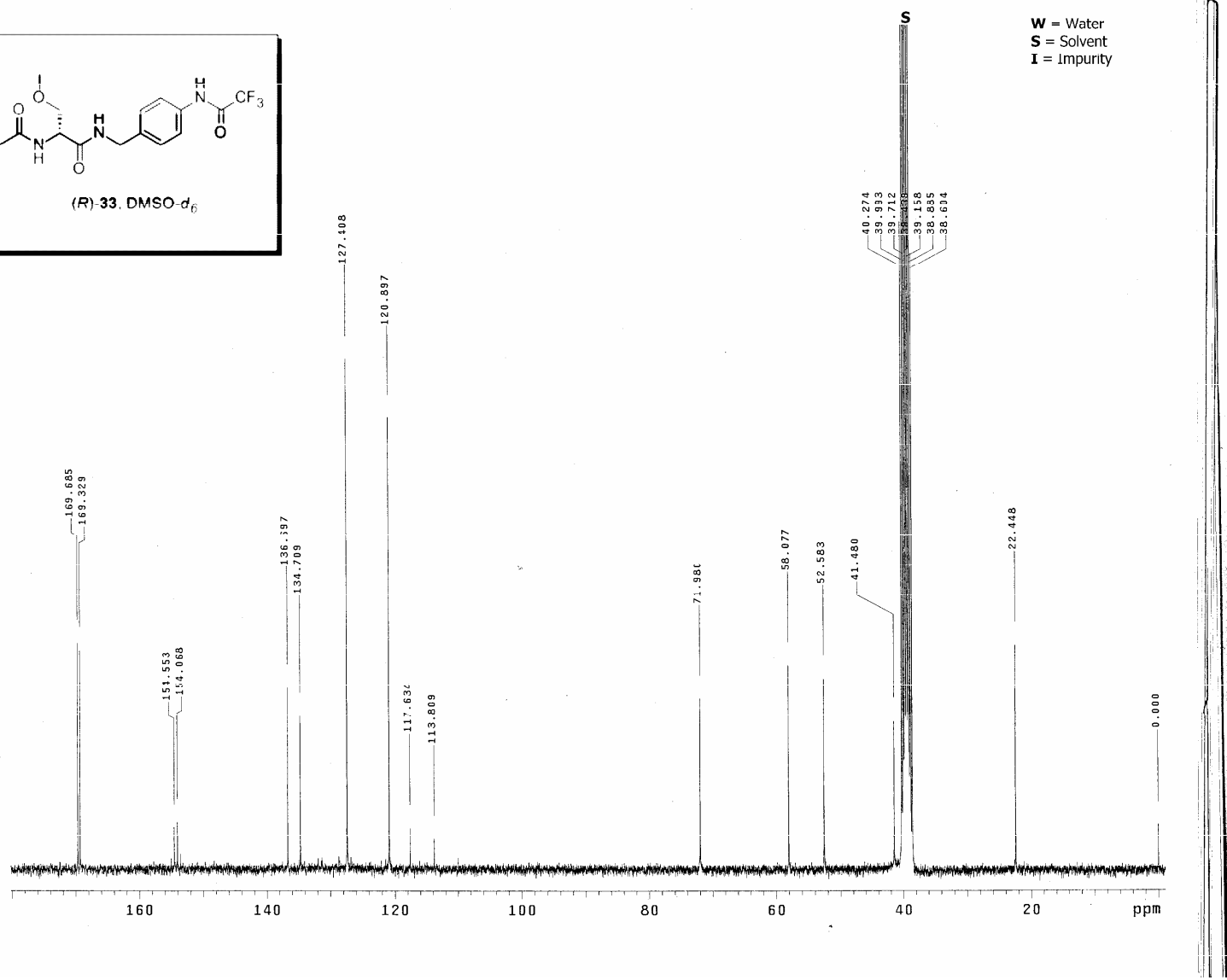
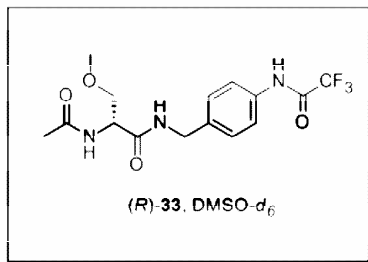
W = Water
S = Solvent
I = Impurity



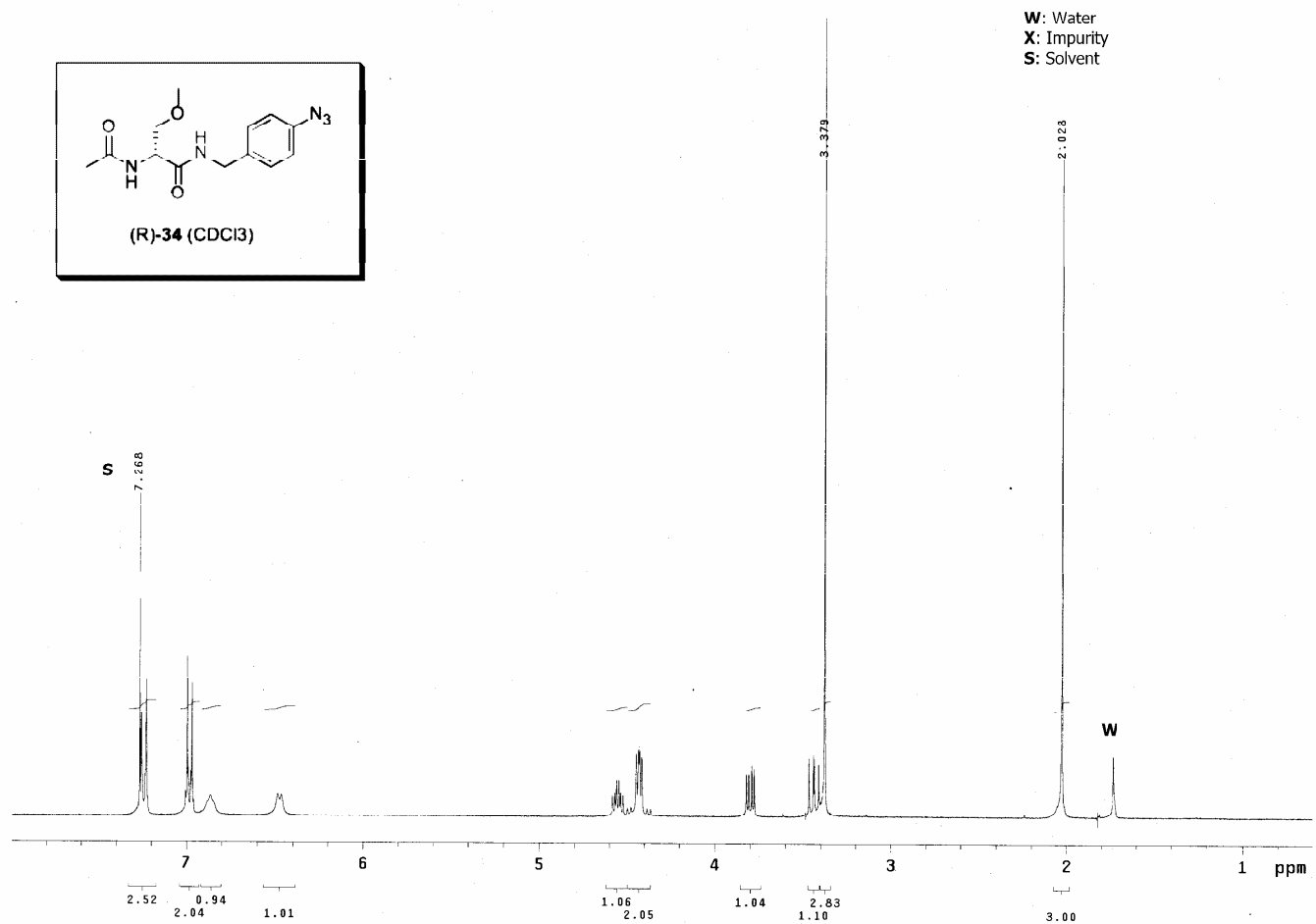
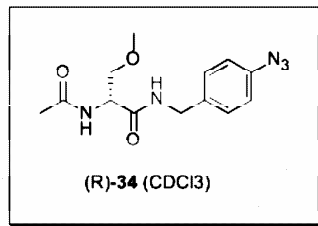
Supporting Information



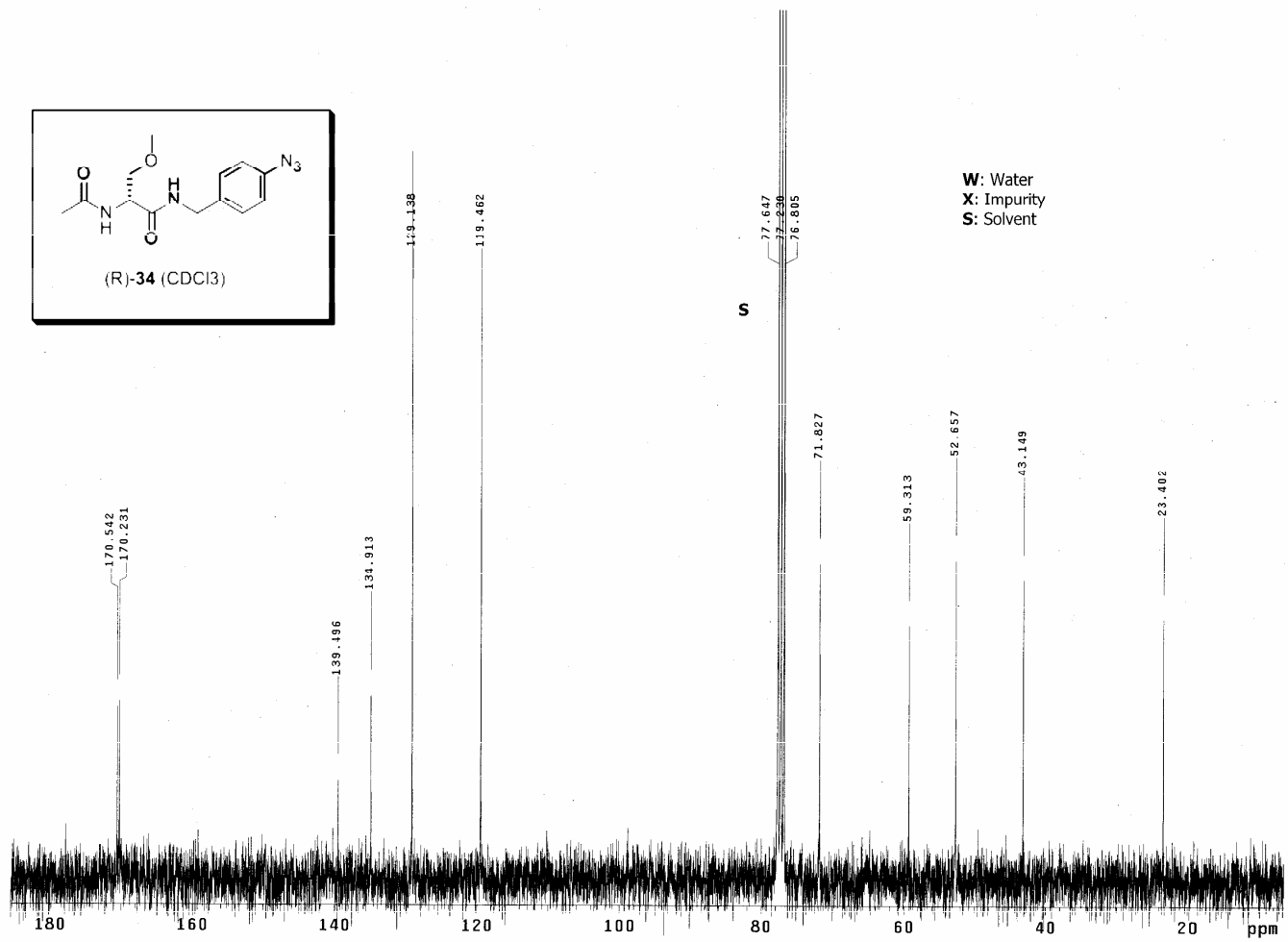
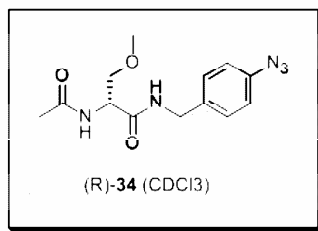
Supporting Information



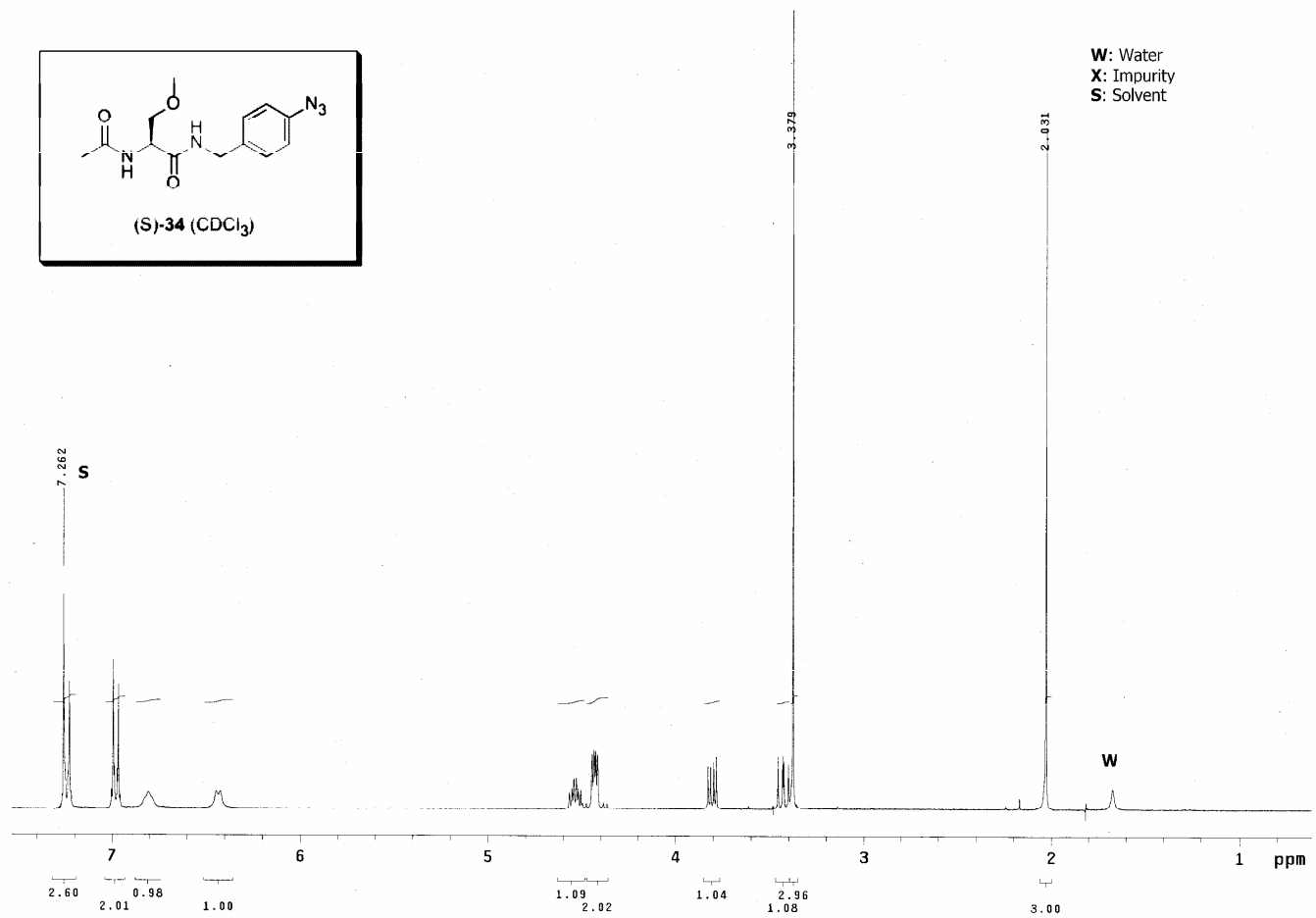
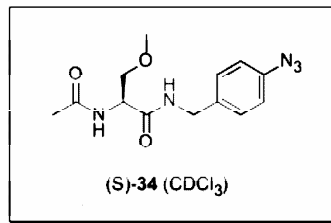
Supporting Information



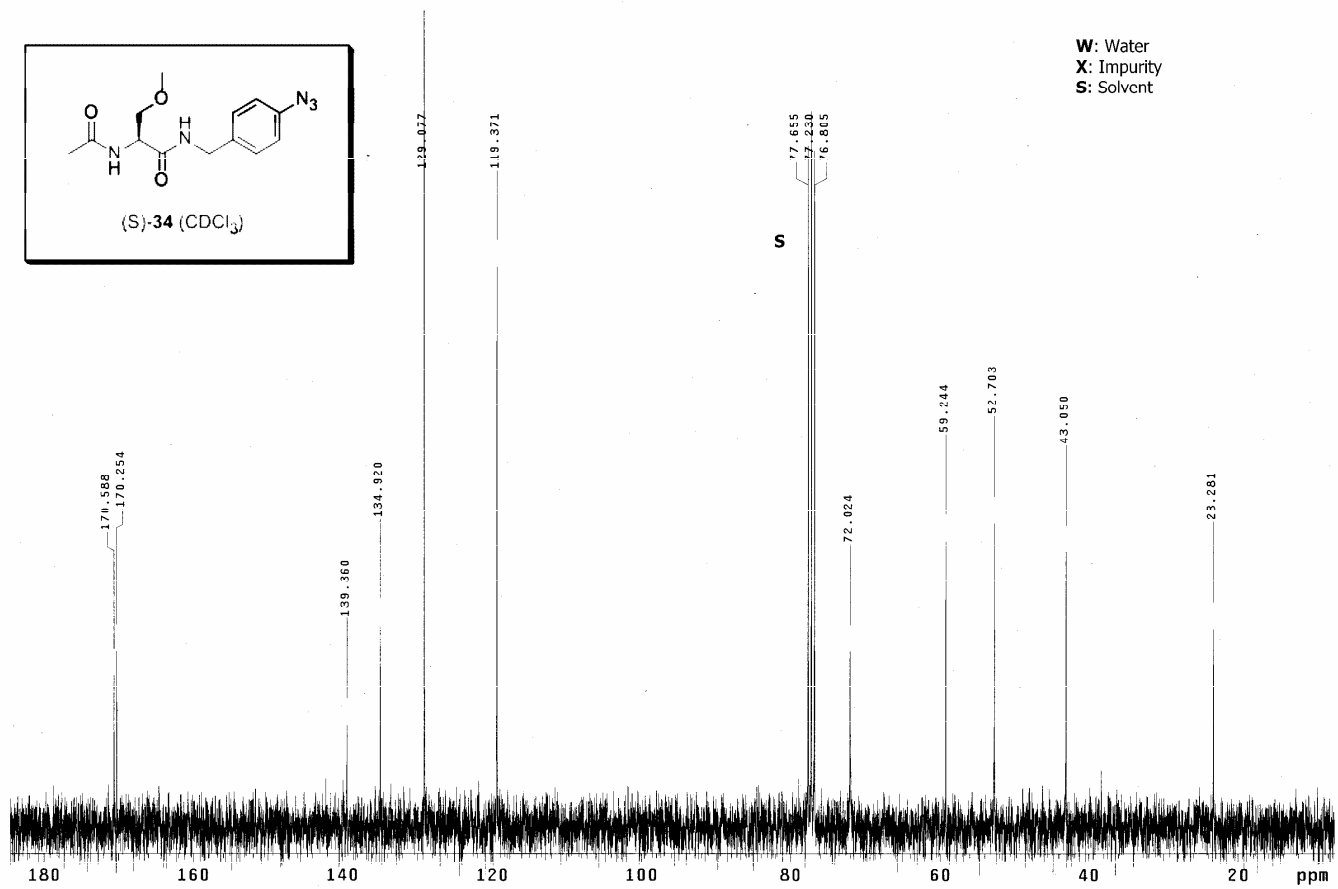
Supporting Information



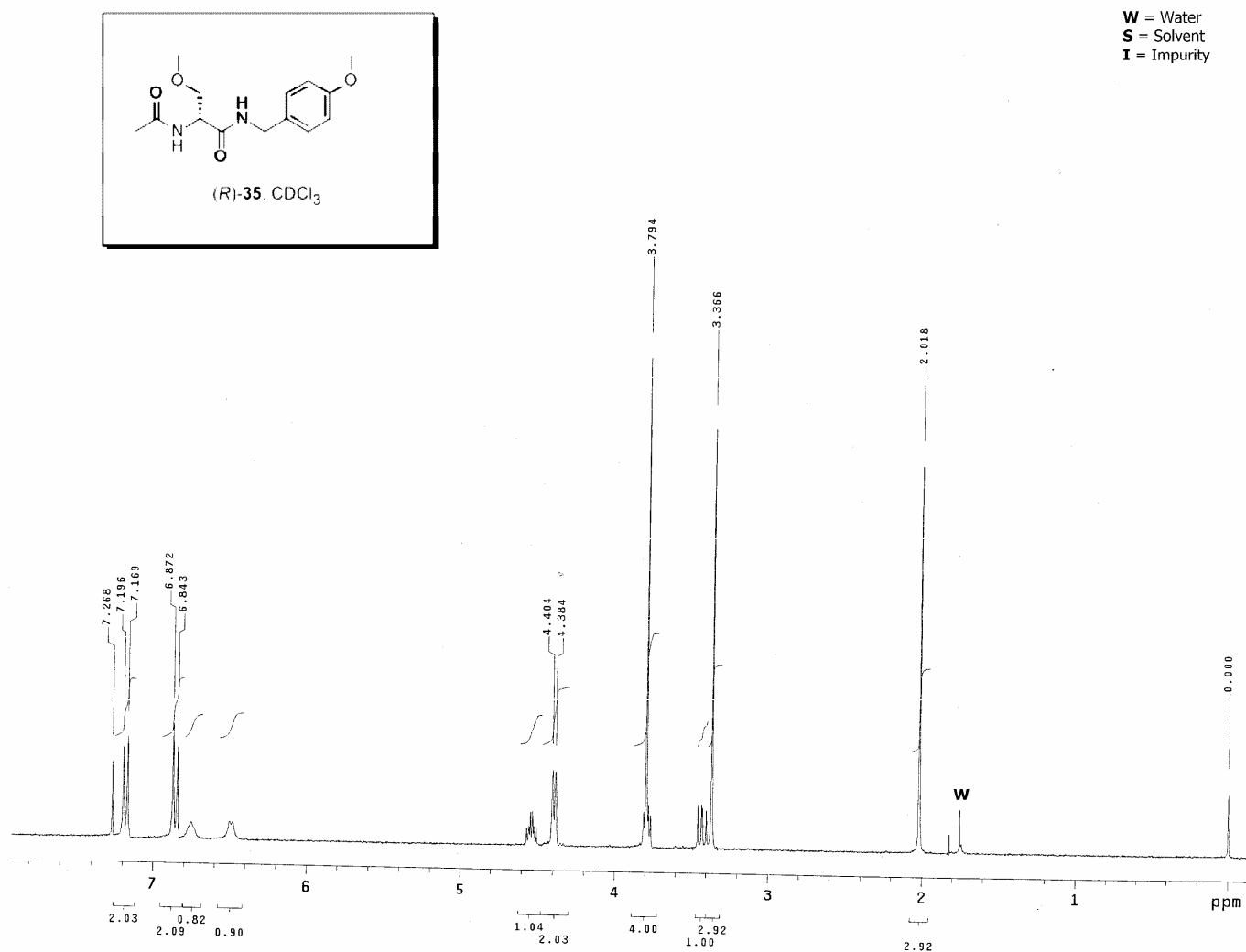
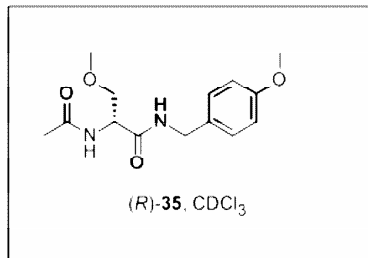
Supporting Information



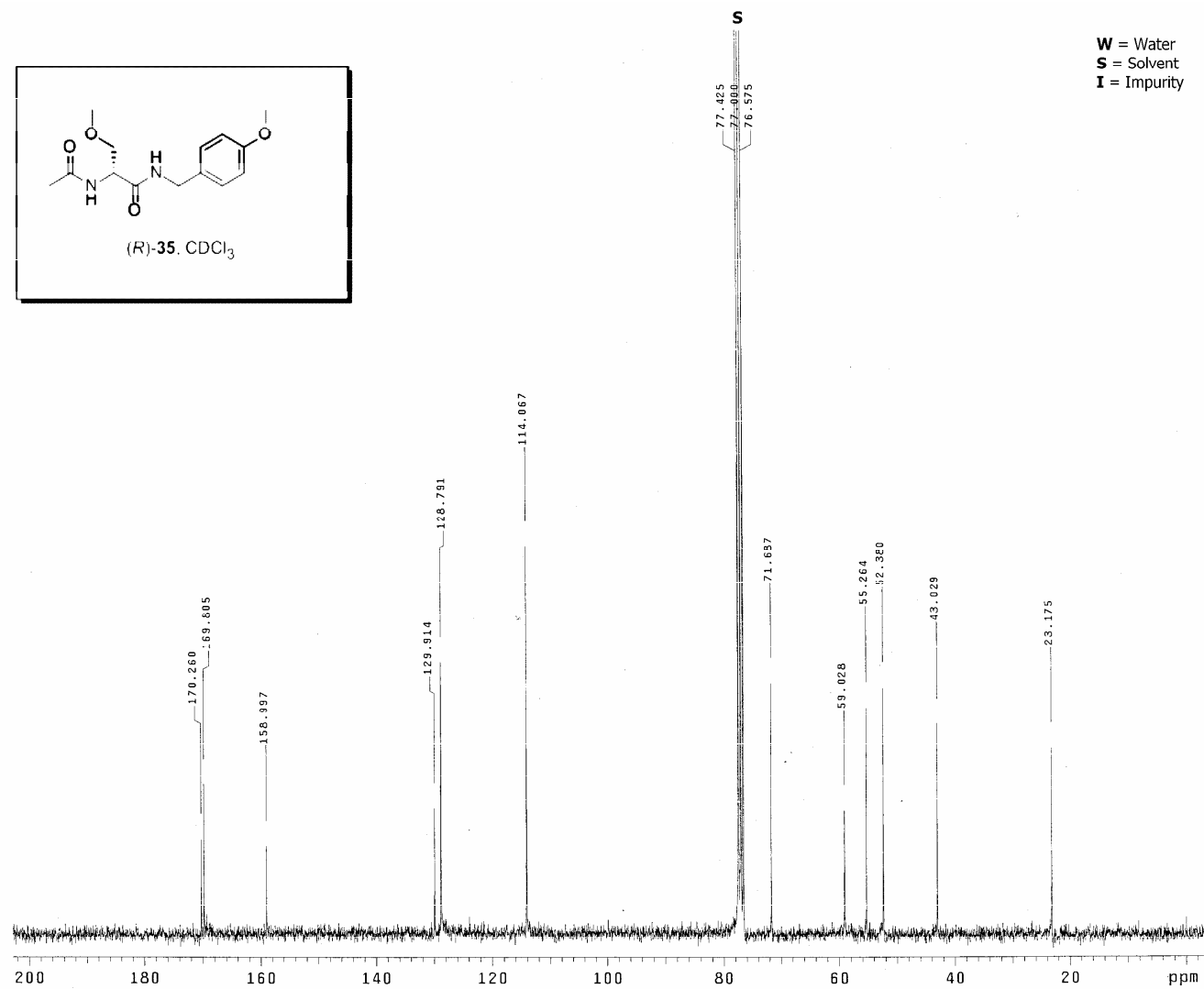
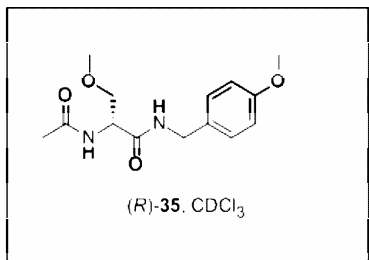
Supporting Information



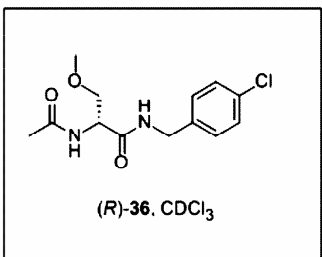
Supporting Information



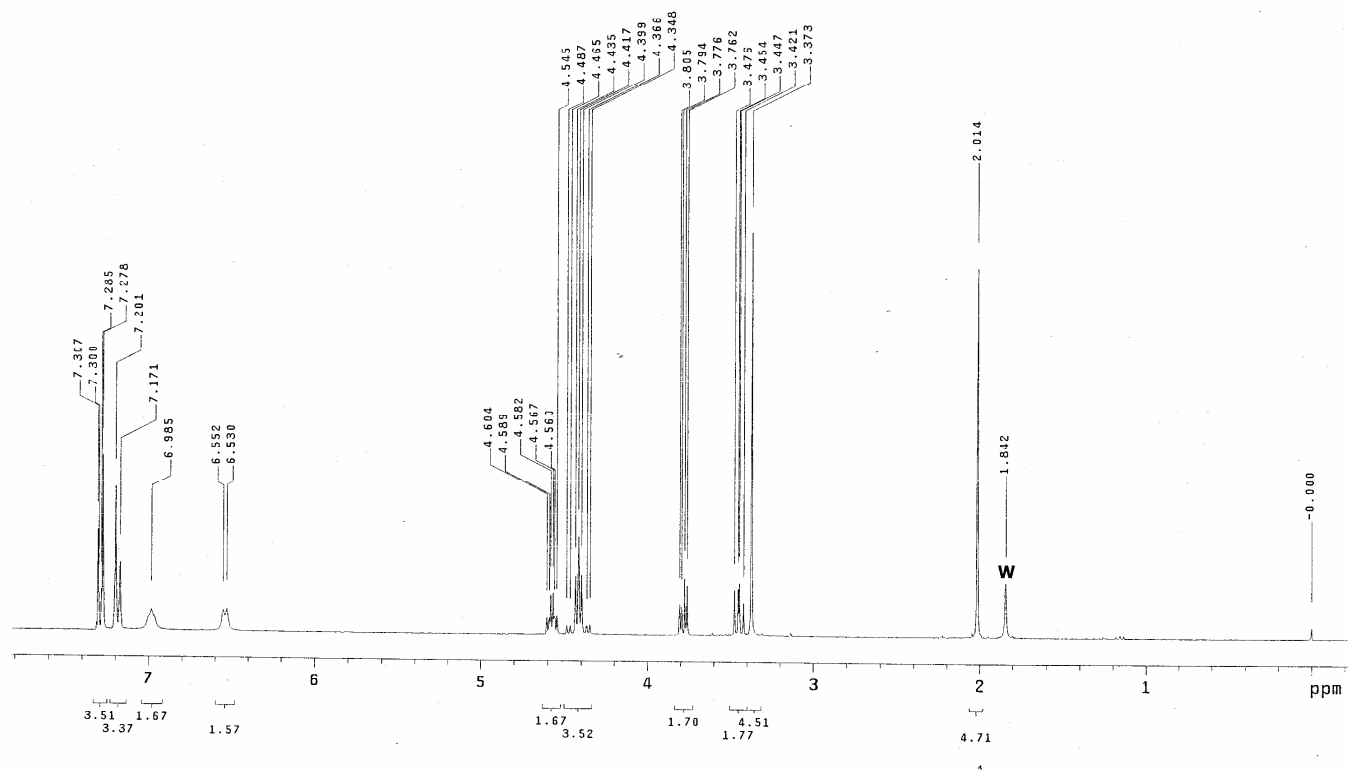
Supporting Information



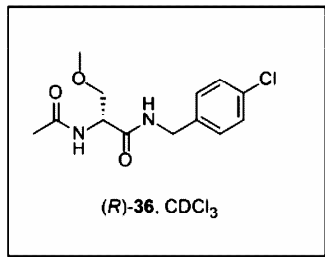
Supporting Information



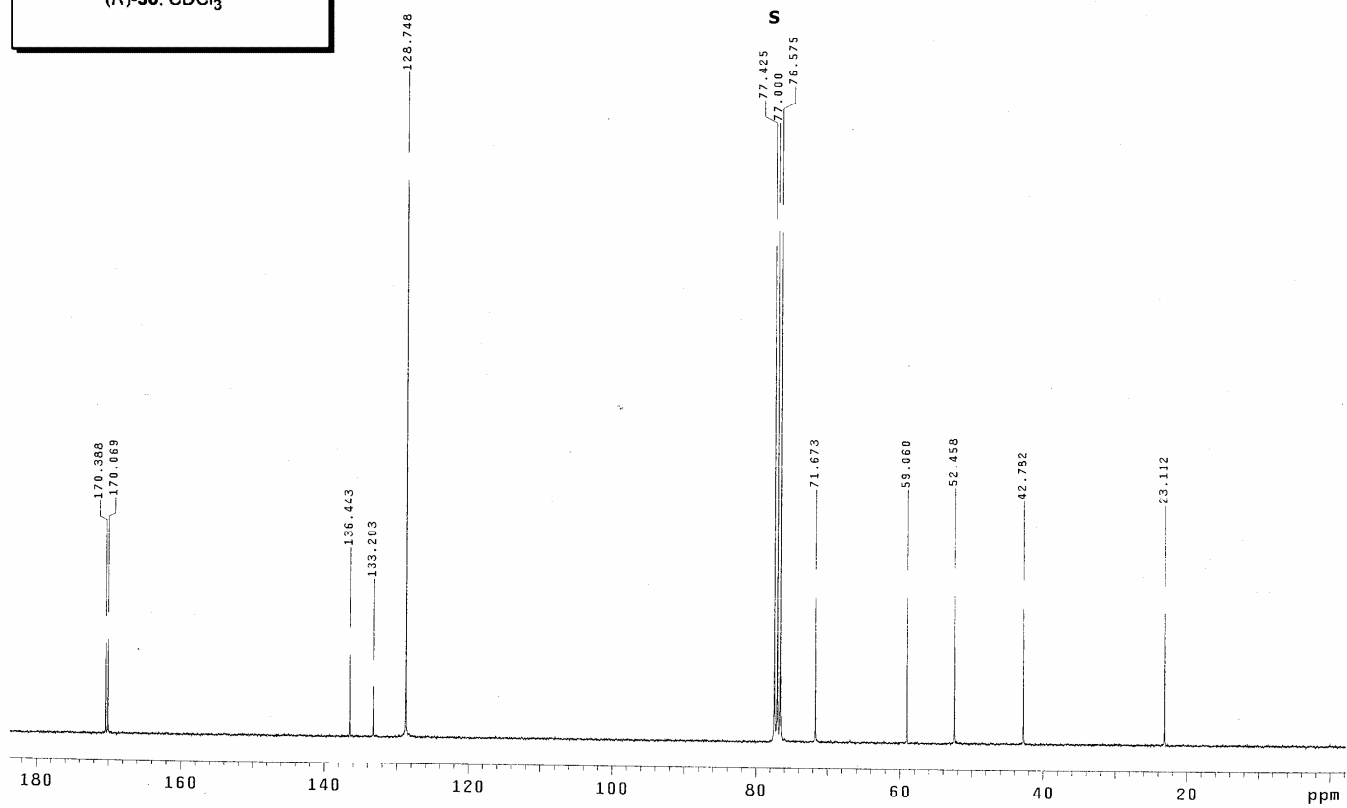
W = Water
S = Solvent
I = Impurity



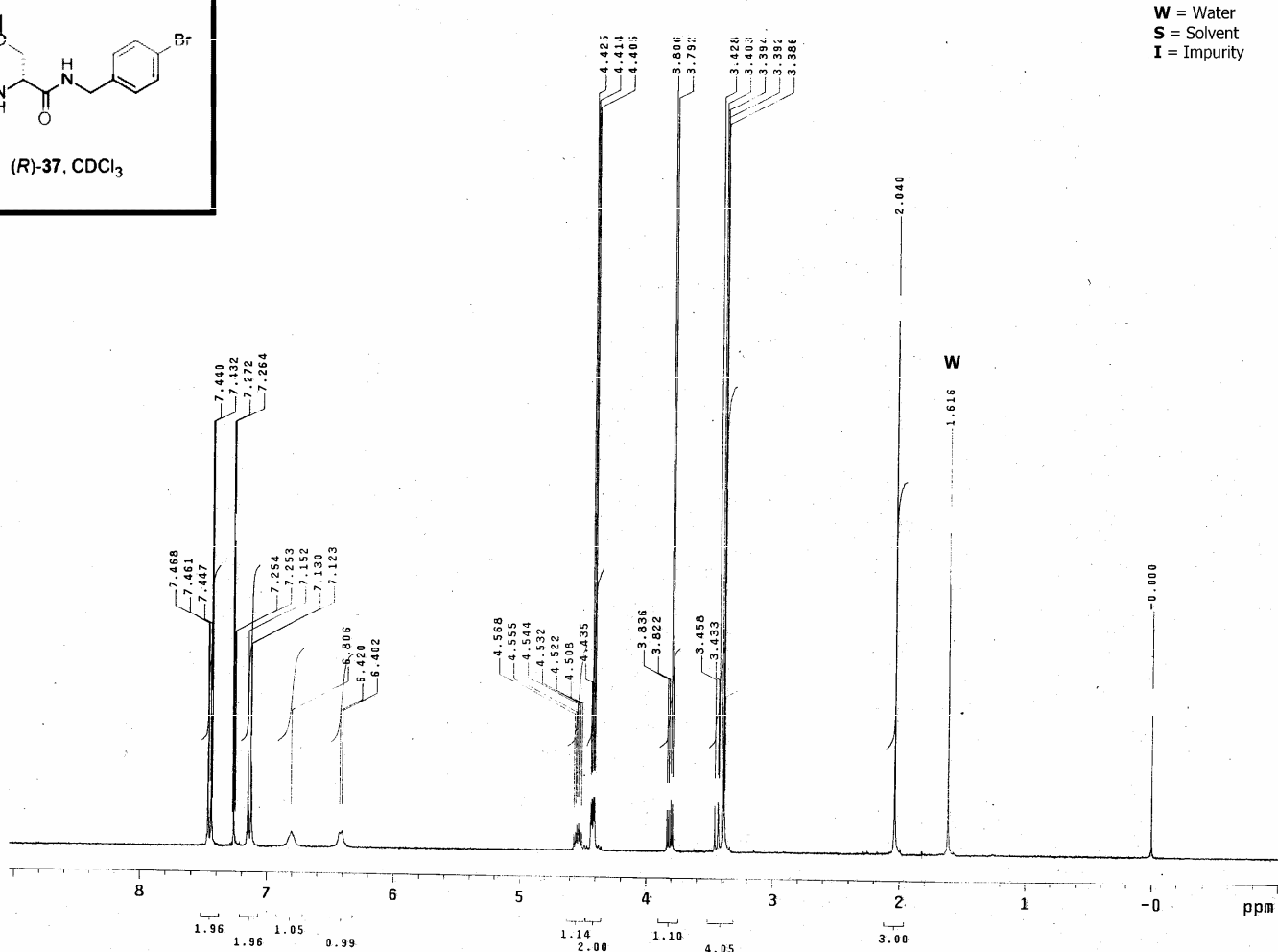
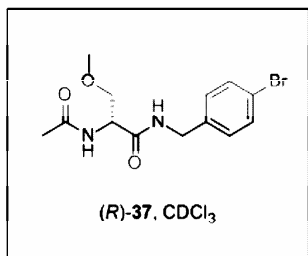
Supporting Information



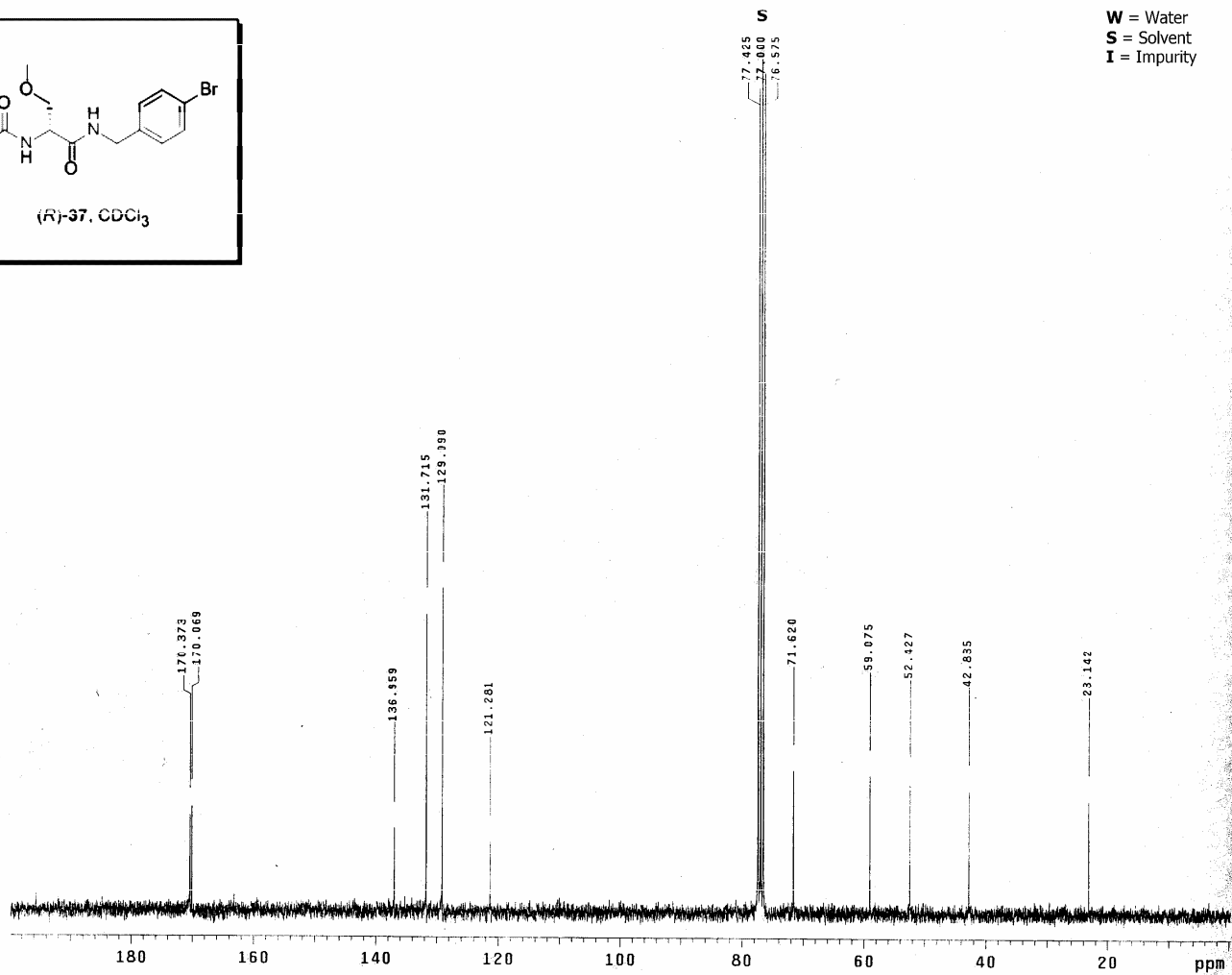
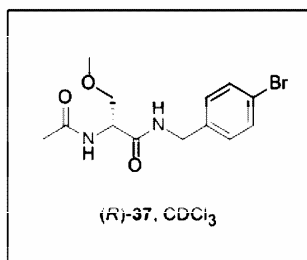
W = Water
S = Solvent
I = Impurity



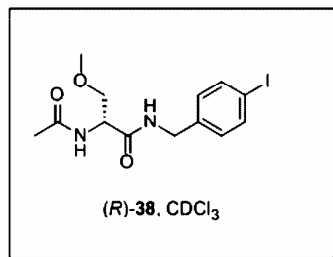
Supporting Information



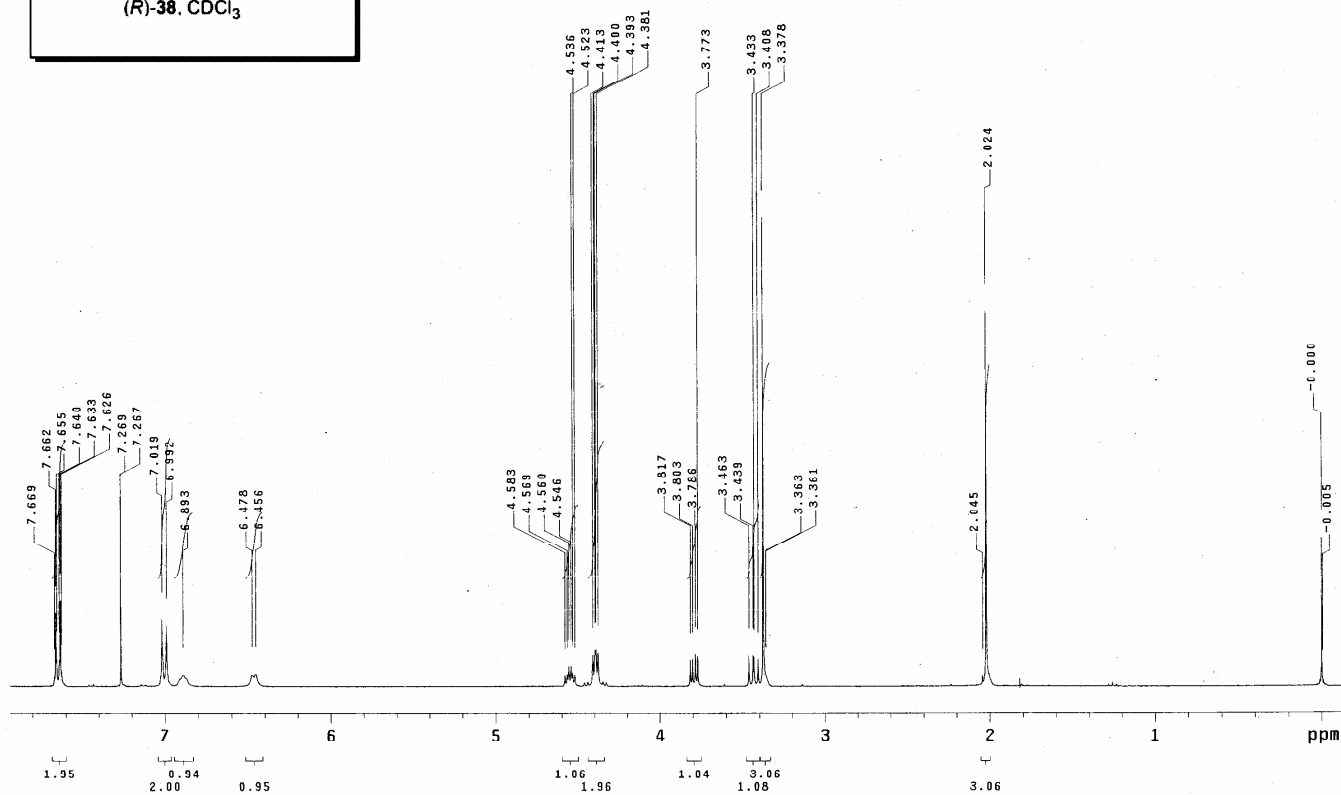
Supporting Information



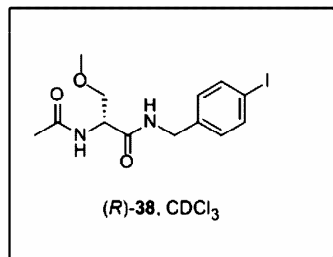
Supporting Information



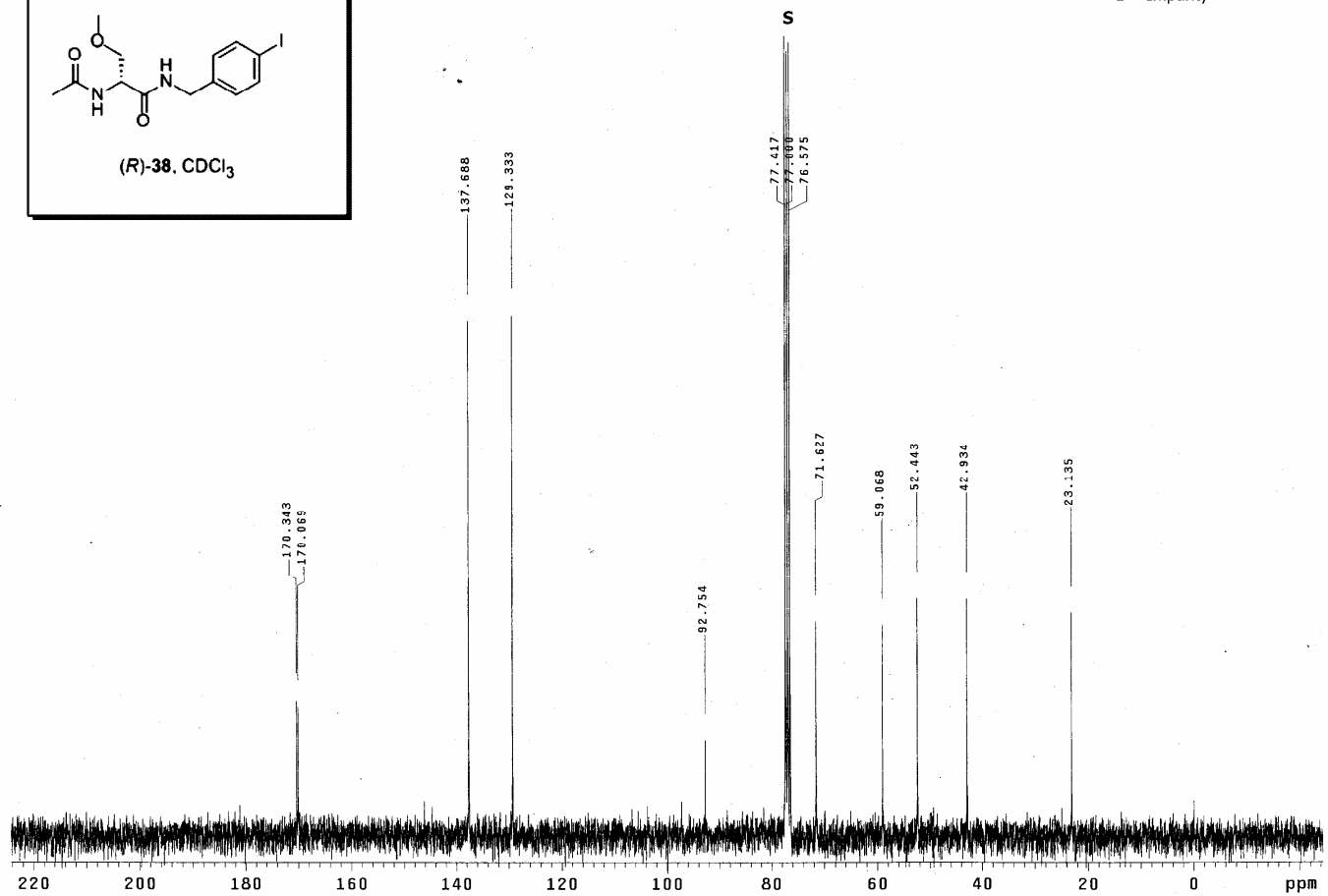
W = Water
S = Solvent
I = Impurity



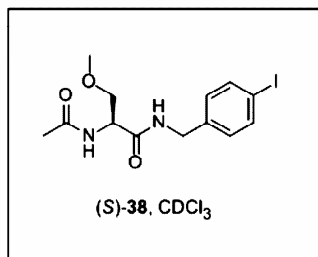
Supporting Information



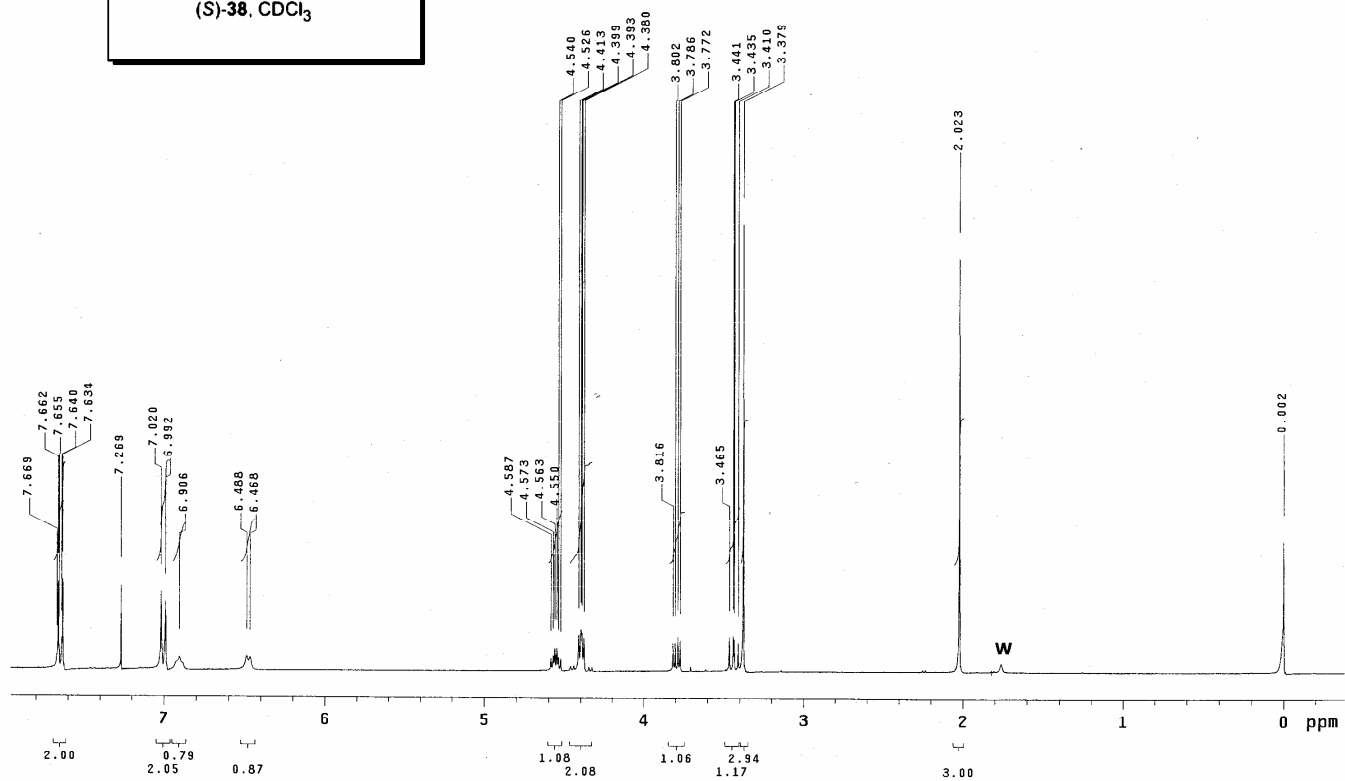
W = Water
S = Solvent
I = Impurity



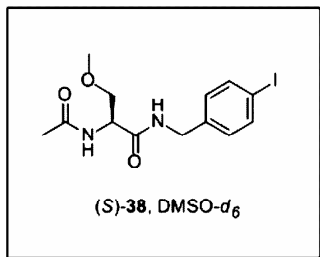
Supporting Information



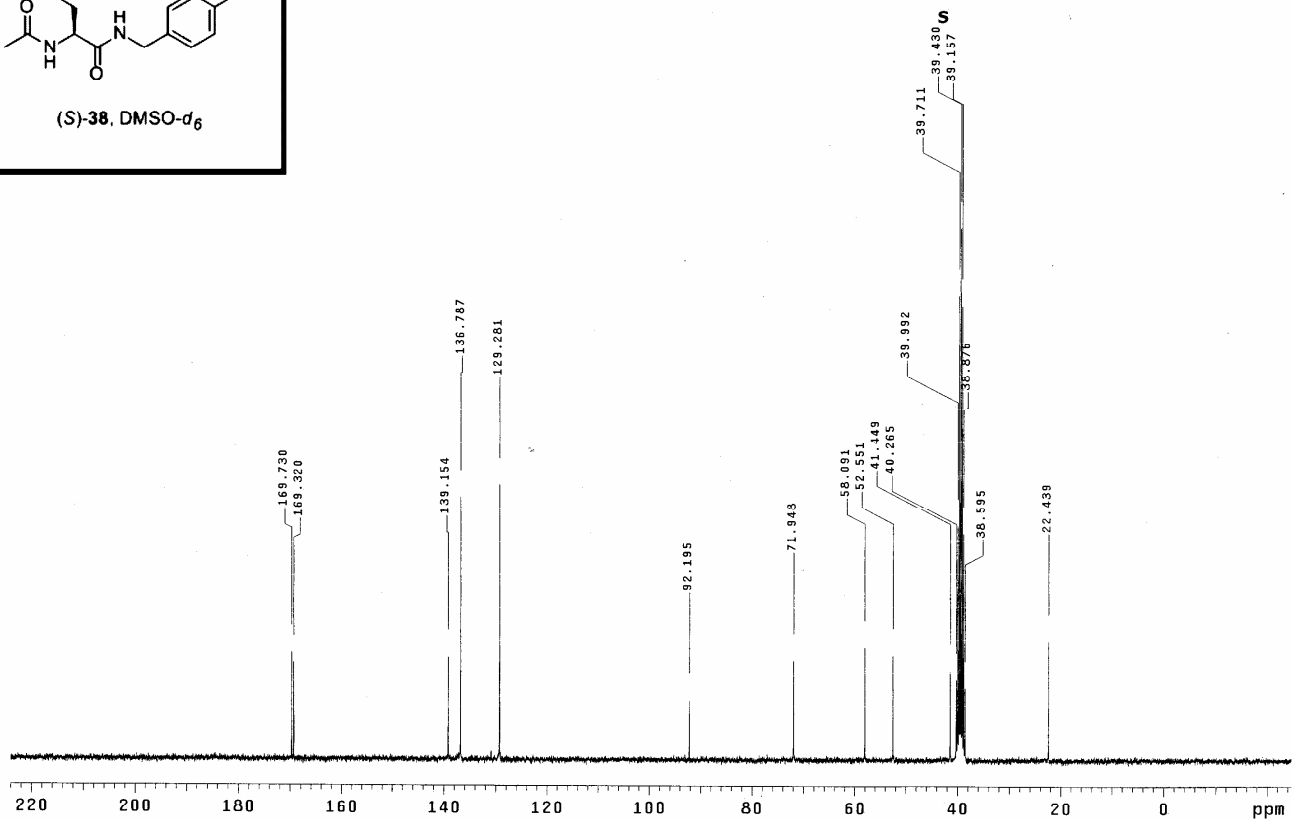
W = Water
S = Solvent
I = Impurity



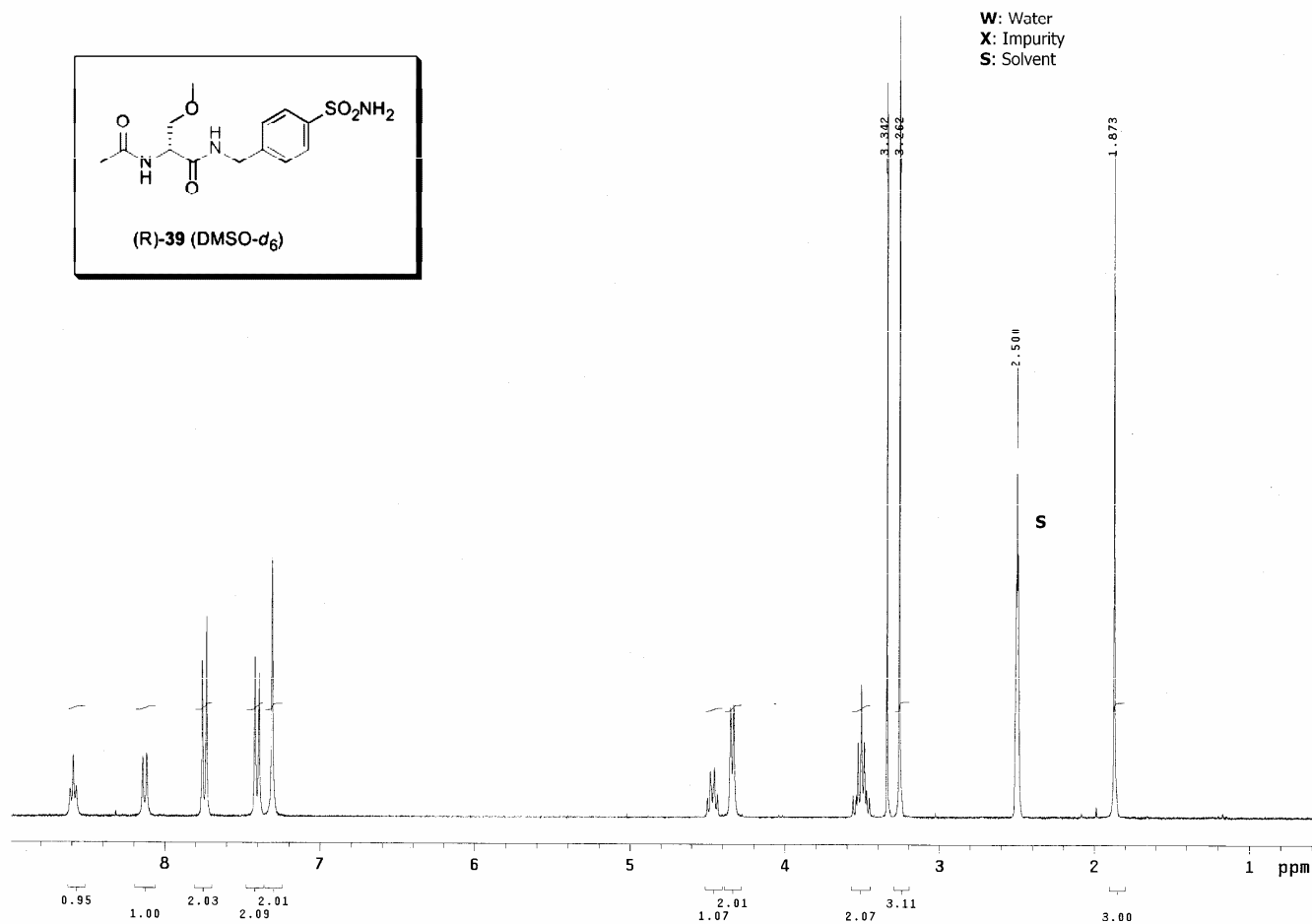
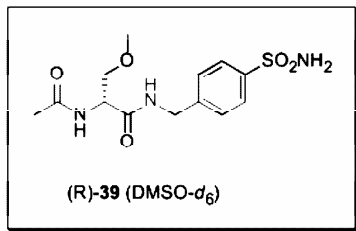
Supporting Information



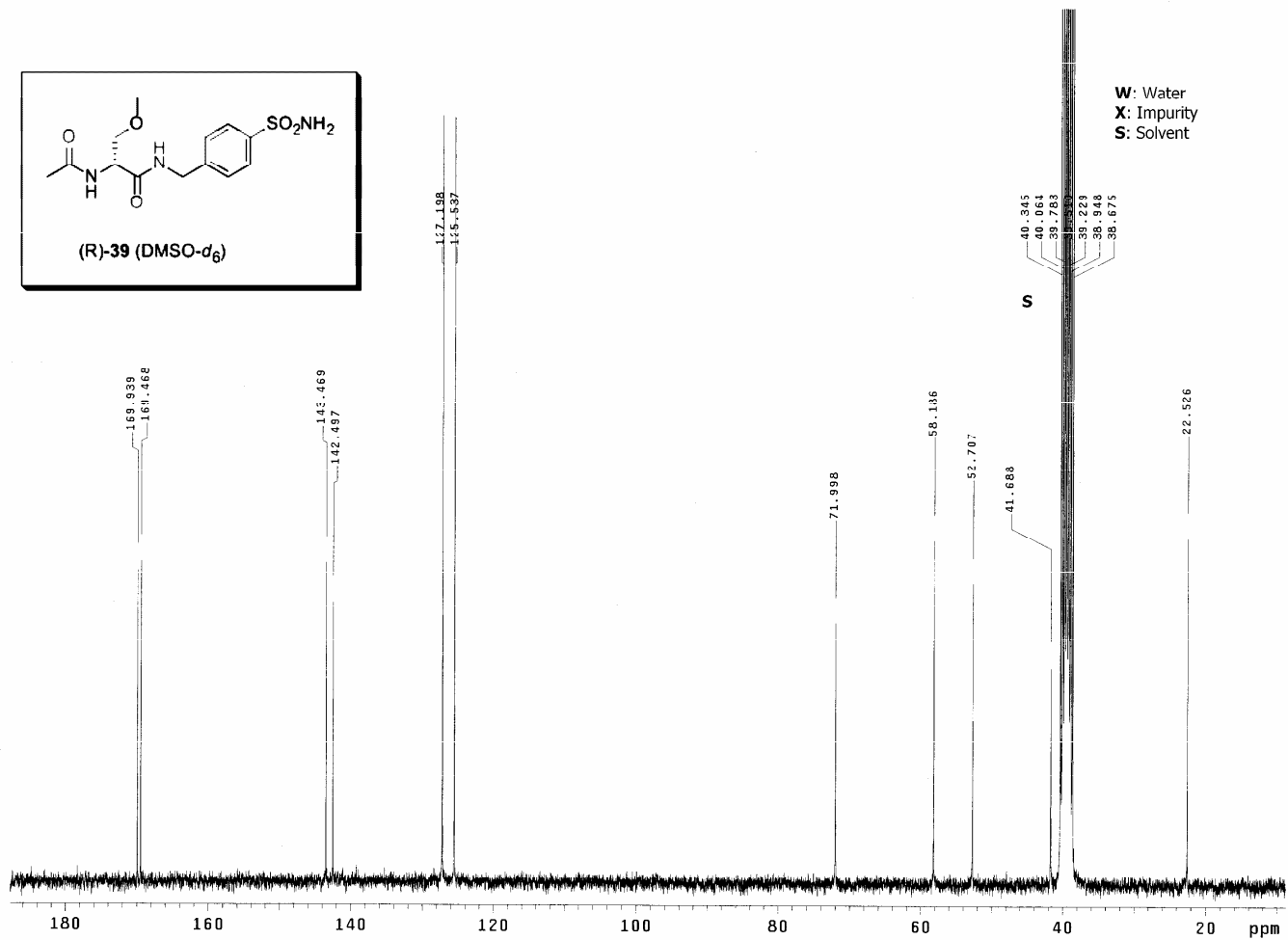
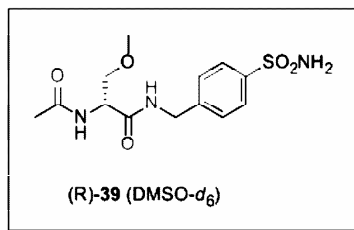
W = Water
S = Solvent
I = Impurity



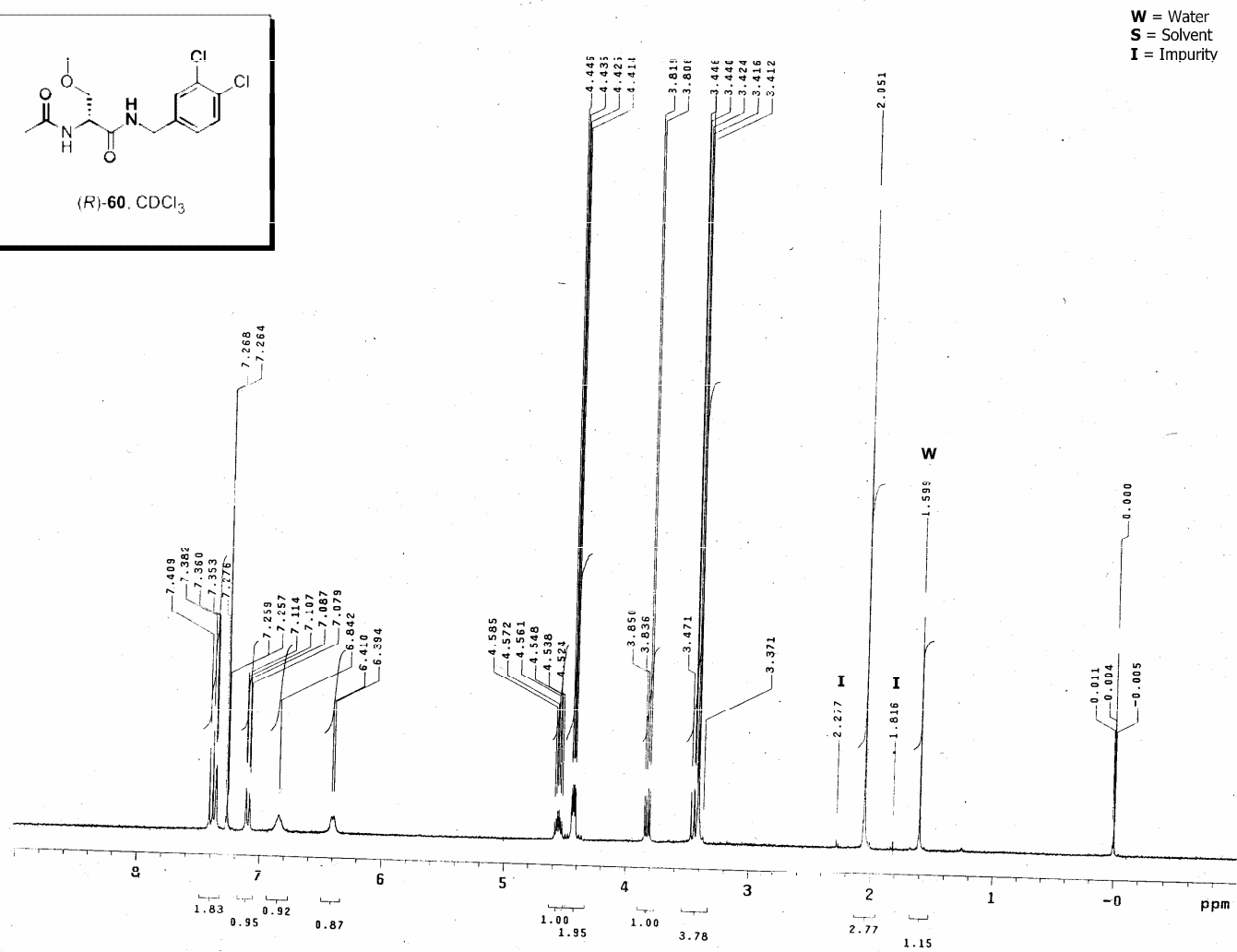
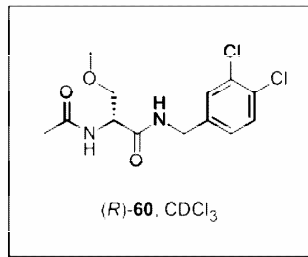
Supporting Information



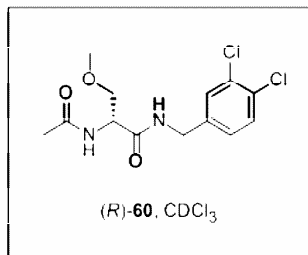
Supporting Information



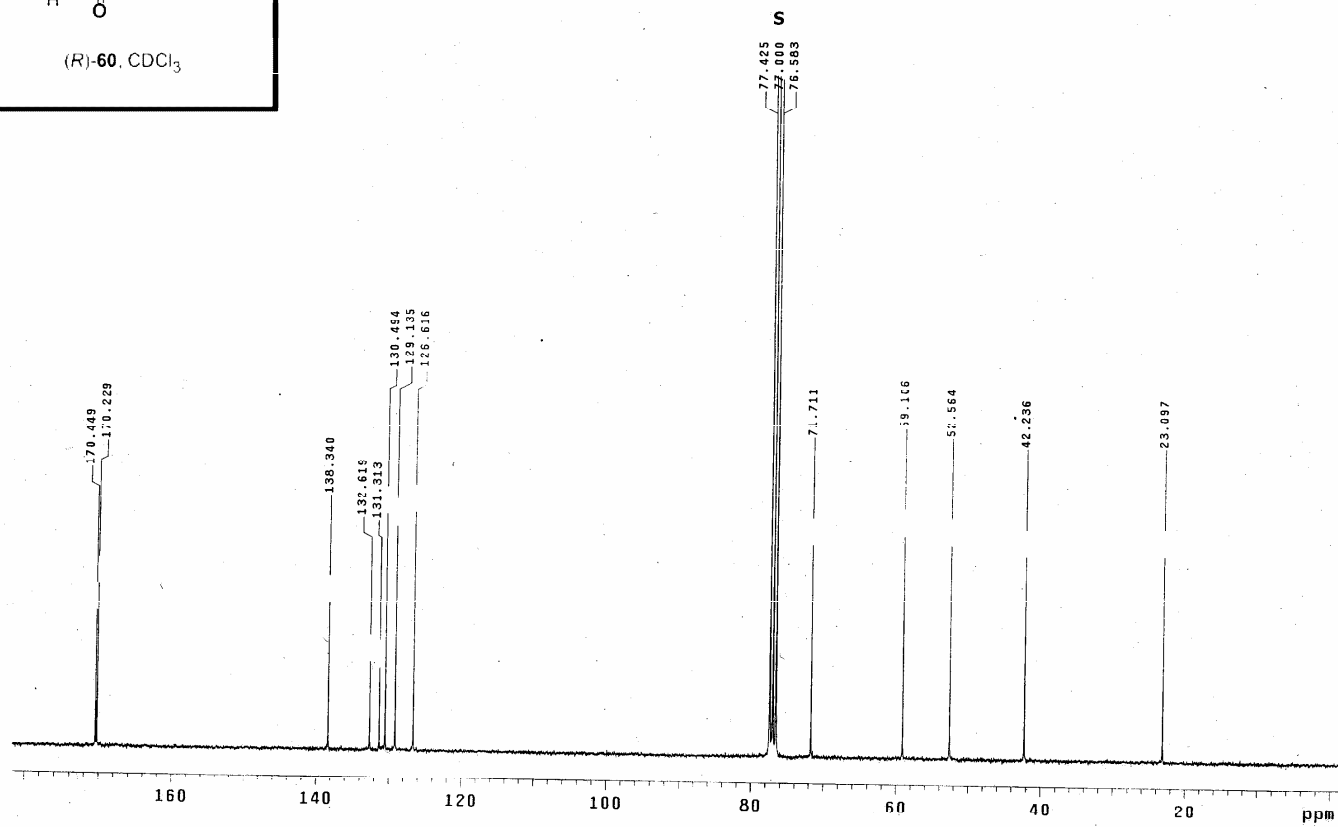
Supporting Information



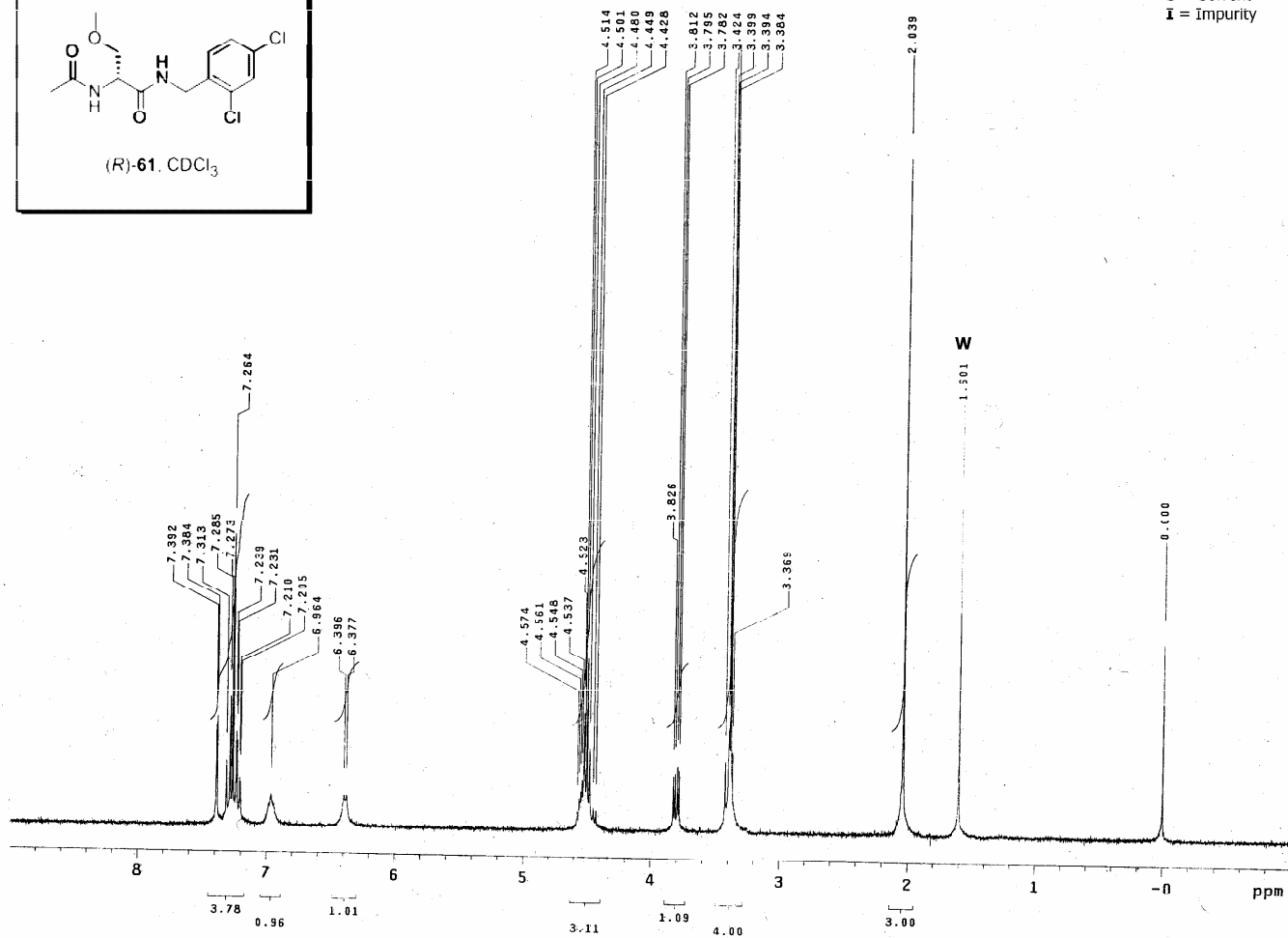
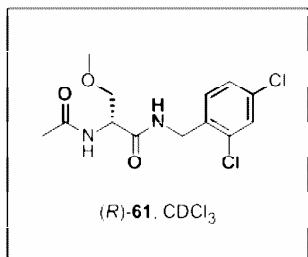
Supporting Information



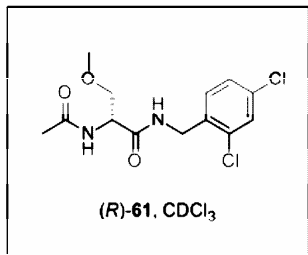
W = Water
S = Solvent
I = Impurity



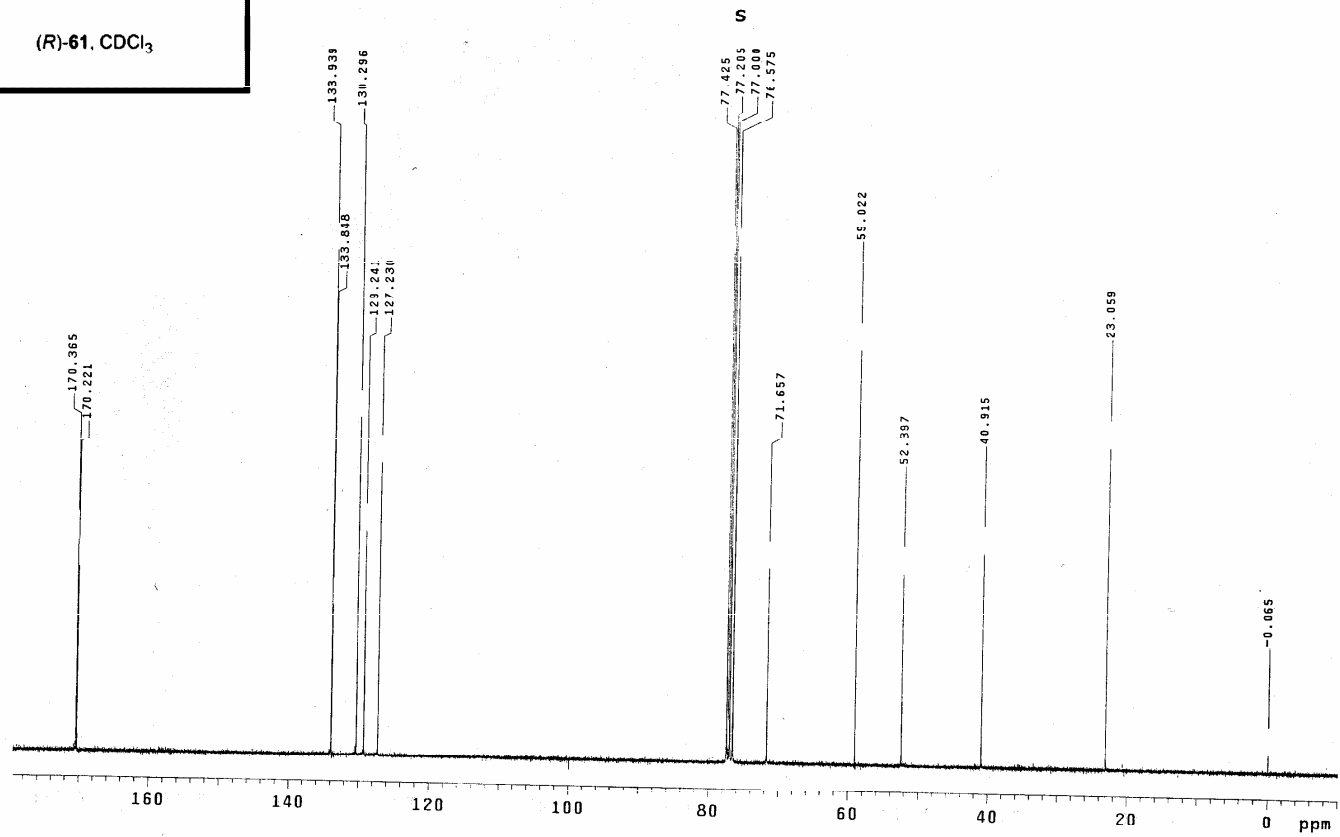
Supporting Information



Supporting Information



W = Water
S = Solvent
I = Impurity



Supporting Information

Table S1. Elemental Analysis of Newly Prepared Compounds.

No.	Formula	Calcd.							Found						
		C	H	N	F	Cl	Br	I	C	H	N	F	Cl	Br	I
(R)-62	C ₁₅ H ₂₁ FN ₂ O ₄	57.68	6.78	8.97	6.08				57.63	6.87	9.01	5.92			
(R)-63	C ₁₆ H ₂₃ FN ₂ O ₄	58.88	7.10	8.58	5.82				59.15	7.20	8.52	5.78			
(R)-4	C ₁₃ H ₁₇ FN ₂ O ₃	58.20	6.63	10.44	7.08				58.12	6.40	10.41	6.96			
(R)-64	C ₁₉ H ₁₉ F ₃ N ₂ O ₅	55.34	4.64	6.79	13.82				55.27	4.62	6.74	13.80			
(R)-65	C ₂₀ H ₂₁ F ₃ N ₂ O ₅	56.34	4.96	6.57	13.37				56.30	4.98	6.89	13.22			
(R)-7	C ₁₄ H ₁₇ F ₃ N ₂ O ₄	50.30	5.13	8.38	17.05				50.28	5.21	8.18	17.30			
(R)-66	C ₁₉ H ₁₉ F ₃ N ₂ O ₃	55.34	4.64	6.79	13.82				55.44	4.59	6.79	13.66			
(R)-67	C ₂₀ H ₂₁ F ₃ N ₂ O ₅	56.34	4.96	6.57	13.37				56.15	4.86	6.48	13.23			
(R)-8	C ₁₄ H ₁₇ F ₃ N ₂ O ₄	50.30	5.13	8.38	17.05				50.25	5.07	8.17	16.78			
(R)-68	C ₁₉ H ₁₉ F ₃ N ₂ O ₅	55.34	4.64	6.79	13.82				55.06	4.61	6.74	13.70			
(R)-69	C ₂₀ H ₂₁ F ₃ N ₂ O ₅	56.34	4.96	6.57	13.37				56.34	4.97	6.63	13.28			
(R)-9	C ₁₄ H ₁₇ F ₃ N ₂ O ₄	50.30	5.13	8.38	17.30				50.45	5.13	8.39	17.18			
(R)-70	C ₁₉ H ₂₂ N ₂ O ₄	66.65	6.48	8.18					66.49	6.53	8.07				
(R)-71	C ₂₀ H ₂₄ N ₂ O ₄	67.40	6.79	7.86					67.22	6.82	7.82				
(R)-10	C ₁₄ H ₂₀ N ₂ O ₃	63.62	7.63	10.60					63.44	7.68	10.60				
(R)-72	C ₂₀ H ₂₄ N ₂ O ₄	67.40	6.79	7.86					67.31	6.81	7.88				
(S)-72	C ₂₀ H ₂₄ N ₂ O ₄	67.40	6.79	7.86					67.40	6.78	7.86				
(R)-73	C ₂₁ H ₂₆ N ₂ O ₄	68.09	7.07	7.56					67.86	7.10	7.59				
(S)-73	C ₂₁ H ₂₆ N ₂ O ₄ •0.05H ₂ O	67.91	7.08	7.54					67.66	7.18	7.59				
(R)-11	C ₁₅ H ₂₂ N ₂ O ₃	64.73	7.97	10.06					64.52	7.98	10.05				
(S)-11	C ₁₅ H ₂₂ N ₂ O ₃	64.73	7.97	10.06					64.73	7.98	10.04				
(R)-12	C ₁₆ H ₂₄ N ₂ O ₃	65.73	8.27	9.58					66.01	8.24	9.36				
(R)-74	C ₂₁ H ₂₆ N ₂ O ₄	68.09	7.07	7.56					67.82	6.98	7.47				
(R)-75	C ₂₂ H ₂₈ N ₂ O ₄	68.73	7.34	7.29					68.71	7.40	7.29				

Supporting Information

(R)-13	C ₁₆ H ₂₂ N ₂ O ₃	65.73	8.27	9.58					65.46	8.21	9.48			
(R)-76	C ₂₂ H ₂₈ N ₂ O ₄	68.73	7.34	7.29					68.60	7.36	7.26			
(R)-77	C ₂₃ H ₃₀ N ₂ O ₄	69.32	7.59	7.03					69.15	7.64	7.03			
(R)-14	C ₁₇ H ₂₆ N ₂ O ₃	66.64	8.55	9.14					66.61	8.49	9.09			
(R)-78	C ₂₄ H ₃₁ N ₃ O ₆	63.00	6.83	9.18					62.99	6.70	9.16			
(R)-79	C ₂₅ H ₃₃ N ₃ O ₆	63.68	7.05	8.91					63.61	7.12	8.88			
(R)-16	C ₁₉ H ₂₉ N ₃ O ₅	60.14	7.70	11.07					60.11	7.83	11.02			
(R)-15	C ₂₀ H ₂₄ ClN ₂ O ₄ •0.49HCl	50.38	6.79	12.59					50.15	6.90	12.29			
(R)-83	C ₂₀ H ₂₄ N ₂ O ₅ •0.25H ₂ O	63.73	6.55	7.43					63.35	6.43	7.29			
(R)-84	C ₂₁ H ₂₆ N ₂ O ₅	65.27	6.78	7.25					65.27	6.79	7.38			
(R)-17	C ₁₅ H ₂₂ N ₂ O ₄	61.21	7.45	9.52					60.88	7.45	9.35			
(R)-85	C ₁₉ H ₁₉ F ₃ N ₂ O ₄ •0.08C ₄ H ₈ O ₂	57.52	4.91	6.93	14.11				57.14	4.82	6.99	13.71		
(R)-18	C ₁₄ H ₁₇ N ₂ O ₃	52.83	5.38	8.80	17.91				52.84	5.30	8.78	17.67		
57	C ₁₀ H ₁₅ NO•0.12THF	72.38	9.25	8.04					72.78	9.25	7.65			
(R)-19	C ₁₆ H ₂₄ N ₂ O ₄	62.32	7.84	9.08					62.33	7.69	9.12			
(R)-20	C ₁₇ H ₂₆ N ₂ O ₄	63.33	8.13	8.69					63.12	8.13	8.64			
(R)-87	C ₁₇ H ₂₄ N ₂ O ₄	63.73	7.55	8.74					63.45	7.60	8.70			
(S)-87	C ₁₇ H ₂₄ N ₂ O ₄	63.73	7.55	8.74					63.55	7.63	8.57			
(R)-88	C ₁₈ H ₂₆ N ₂ O ₄	64.65	7.84	8.38					64.51	7.88	8.33			
(S)-88	C ₁₈ H ₂₆ N ₂ O ₄	64.65	7.84	8.38					64.73	7.98	8.25			
(R)-21	C ₁₅ H ₂₀ N ₂ O ₃	65.20	7.30	10.14					65.17	7.33	10.02			
(S)-21	C ₁₅ H ₂₀ N ₂ O ₃ •0.10H ₂ O	64.78	7.32	10.07					64.83	7.31	10.00			
(R)-89	C ₂₁ H ₂₆ N ₂ O ₄	68.09	7.07	7.56					68.09	7.14	7.48			
(R)-90	C ₂₂ H ₂₈ N ₂ O ₄	68.73	7.34	7.29					68.52	7.48	7.24			
(R)-91	C ₁₇ H ₂₁ ClN ₂ O ₂	63.64	6.60	8.73		11.05			63.42	6.65	8.64		11.04	
(R)-22	C ₁₉ H ₂₂ N ₂ O ₃ •0.10H ₂ O	69.54	6.82	8.54					69.23	6.76	8.42			
(R)-26	C ₁₈ H ₂₆ N ₂ O ₃ Si	62.39	7.56	8.08					62.41	7.60	7.99			
(S)-26	C ₁₈ H ₂₆ N ₂ O ₃ Si	62.39	7.56	8.08					62.10	7.67	7.93			
(R)-23	C ₁₅ H ₁₈ N ₂ O ₃	65.68	6.61	10.21					65.39	6.58	10.08			
(S)-23	C ₁₅ H ₁₈ N ₂ O ₃ •0.25H ₂ O	64.62	6.69	10.05					64.60	6.57	9.99			

Supporting Information

(R)-24	C ₁₆ H ₂₀ N ₂ O ₃ ●0.20H ₂ O	65.62	7.06	9.57					65.98	7.02	9.17			
(R)-25	C ₁₉ H ₂₆ N ₂ O ₃ ●0.20H ₂ O	68.32	7.97	8.39					68.25	7.96	8.33			
(R)-27	C ₁₇ H ₂₂ N ₂ O ₄ ●0.33H ₂ O	62.95	7.04	8.64					62.98	6.78	8.47			
(R)-92	C ₁₉ H ₁₉ N ₃ O ₄ ●0.25H ₂ O	63.77	5.49	11.74					64.01	5.37	11.73			
(S)-92	C ₁₉ H ₁₉ N ₃ O ₄	64.58	5.42	11.89					64.20	5.38	11.70			
(R)-93	C ₂₀ H ₂₁ N ₃ O ₄ ●0.25H ₂ O	64.59	5.83	11.30					64.61	5.79	11.01			
(S)-93	C ₂₀ H ₂₁ N ₃ O ₄ ●0.25H ₂ O	64.59	5.83	11.30					64.63	5.70	11.51			
(R)-28	C ₁₄ H ₁₇ N ₃ O ₃ ●0.25H ₂ O	60.09	6.30	15.02					60.17	6.22	14.66			
(S)-28	C ₁₄ H ₁₇ N ₃ O ₃	61.08	6.22	15.16					61.02	6.35	15.08			
(R)-97	C ₂₁ H ₂₄ N ₂ O ₆	62.99	6.04	7.00					62.86	6.05	7.06			
(S)-97	C ₂₁ H ₂₄ N ₂ O ₆	62.99	6.04	7.00					63.00	6.03	6.97			
(R)-98	C ₂₂ H ₂₆ N ₂ O ₆ ●0.25H ₂ O	63.07	6.38	6.69					63.09	6.37	6.64			
(S)-98	C ₂₂ H ₂₆ N ₂ O ₆ ●0.25H ₂ O	63.07	6.38	6.69					63.18	6.38	6.70			
(R)-99	C ₁₄ H ₂₀ N ₂ O ₄ ●0.25CH ₄ O	59.36	7.34	9.72					59.33	7.14	9.45			
(S)-99	C ₁₄ H ₂₀ N ₂ O ₄ ●0.25CH ₄ O	59.36	7.34	9.72					59.28	7.14	9.52			
(R)-53	C ₁₆ H ₂₂ N ₂ O ₅	59.61	6.88	8.69					59.50	6.90	8.56			
(S)-53	C ₁₆ H ₂₂ N ₂ O ₅	59.61	6.88	8.69					59.51	6.90	8.58			
(R)-29	C ₁₄ H ₁₈ N ₂ O ₄	60.42	6.52	10.07					60.40	6.57	9.90			
(S)-29	C ₁₄ H ₁₈ N ₂ O ₄	60.42	6.52	10.07					60.13	6.49	9.91			
(R)-100	C ₂₀ H ₂₂ N ₂ O ₆	62.17	5.74	7.25					62.02	5.78	7.22			
(R)-31	C ₁₅ H ₂₀ N ₂ O ₅	58.43	6.54	9.09					58.40	6.43	8.91			
(R)-30	C ₁₄ H ₁₈ N ₂ O ₅	57.13	6.16	9.52					57.10	6.18	9.30			
(R)-102	C ₁₅ H ₂₁ N ₃ O ₆	53.09	6.24	12.38					52.99	6.35	11.98			
(R)-103	C ₁₆ H ₂₃ N ₃ O ₆	54.38	6.56	11.89					54.54	6.60	11.70			
(R)-33	C ₁₅ H ₁₈ F ₃ N ₃ O ₄	49.86	5.02	11.63	15.77				49.79	4.91	11.56	15.66		
(R)-51	C ₁₂ H ₁₇ N ₃ O ₃	57.36	6.82	16.72					57.13	6.87	16.55			
(S)-51	C ₁₂ H ₁₇ N ₃ O ₃	57.36	6.82	16.72					57.12	6.84	16.43			
(R)-52	C ₁₂ H ₁₅ N ₅ O ₃	51.98	5.45	25.26					51.93	5.47	24.98			
(S)-52	C ₁₂ H ₁₅ N ₅ O ₃	51.98	5.45	25.26					52.08	5.51	25.00			
(R)-34	C ₁₃ H ₁₇ N ₅ O ₃	53.60	5.88	24.04					53.72	5.91	23.84			

Supporting Information

(S)-34	C ₁₃ H ₁₇ N ₅ O ₃	53.60	5.88	24.04					53.76	5.97	24.22			
(R)-104	C ₁₉ H ₂₂ N ₂ O ₅	63.51	6.20	7.80					63.24	6.26	7.72			
(R)-105	C ₂₀ H ₂₄ N ₂ O ₅	64.50	6.50	7.52					64.25	6.50	7.52			
(R)-35	C ₁₄ H ₂₀ N ₂ O ₄	59.99	7.19	9.99					60.04	7.32	9.86			
(R)-106	C ₁₅ H ₂₁ ClN ₂ O ₄	54.79	6.44	8.52		10.78			54.96	6.28	8.66		10.91	
(R)-107	C ₁₆ H ₂₃ ClN ₂ O ₄	56.06	6.77	8.17		10.34			56.19	6.77	8.17		10.07	
(R)-36	C ₁₃ H ₁₇ ClN ₂ O ₃	54.84	6.02	9.84		12.45			54.71	5.95	9.76		12.37	
(R)-108	C ₁₅ H ₂₁ BrN ₂ O ₄	48.27	5.67	7.51			21.41		48.08	5.63	7.44			21.41
(R)-109	C ₁₆ H ₂₃ BrN ₂ O ₄	49.62	5.99	7.23			20.63		49.82	6.09	7.15			20.60
(R)-110	C ₁₁ H ₁₆ BrClN ₂ O ₂	40.83	4.98	8.66		10.96	24.69		40.71	4.97	8.71		11.06	24.74
(R)-37	C ₁₃ H ₁₇ BrN ₂ O ₃	47.43	5.21	8.51			24.27		47.47	5.31	8.41			24.11
(R)-111	C ₁₅ H ₂₁ IN ₂ O ₄	42.87	5.04	6.67				30.20	43.13	5.14	6.71			29.96
(S)-111	C ₁₅ H ₂₁ IN ₂ O ₄	42.87	5.04	6.67				30.20	43.08	5.10	6.62			29.94
(R)-112	C ₁₆ H ₂₃ IN ₂ O ₄	44.25	5.34	6.45				29.22	44.51	5.34	6.41			28.99
(S)-112	C ₁₆ H ₂₃ IN ₂ O ₄	44.25	5.34	6.45				29.22	44.54	5.38	6.35			28.92
(R)-38	C ₁₃ H ₁₇ IN ₂ O ₃	41.51	4.55	7.45				33.73	41.70	4.49	7.39			33.69
(S)-38	C ₁₃ H ₁₇ IN ₂ O ₃	41.51	4.55	7.45				33.73	41.37	4.52	7.37			33.47
(R)-116	C ₆ H ₁₁ N ₂ O ₄	44.72	6.88	8.69					44.71	6.74	8.66			
(R)-117	C ₁₅ H ₂₀ Cl ₂ N ₂ O ₄	49.60	5.55	7.71		19.52			49.62	5.54	7.70		19.65	
(R)-118	C ₁₆ H ₂₂ Cl ₂ N ₂ O ₄ •0.05C ₅ H ₁₁ O ₂	50.98	5.92	7.34		18.57			51.36	5.95	7.35		18.20	
(R)-60	C ₁₃ H ₁₆ Cl ₂ N ₂ O ₃	48.92	5.05	8.78		22.21			49.14	5.01	8.80		22.12	
(R)-120	C ₁₅ H ₂₀ Cl ₂ N ₂ O ₄	49.60	5.55	7.71		19.52			49.63	5.62	7.64		19.65	
(R)-121	C ₁₆ H ₂₂ Cl ₂ N ₂ O ₄	50.94	5.88	7.43		18.79			51.15	6.02	7.35		18.92	
(R)-122	C ₁₁ H ₁₅ Cl ₂ N ₂ O ₂ •0.08H ₂ O	41.95	4.85	8.89		33.77			41.72	4.76	8.74		33.39	
(R)-61	C ₁₃ H ₁₆ Cl ₂ N ₂ O ₃	48.92	5.05	8.78		22.21			48.99	4.98	8.69		22.36	

No.	Formula	Calcd.				Found			
		C	H	N	S	C	H	N	S
(R)-39	C ₁₃ H ₂₀ N ₃ O ₅ S	47.71	5.81	12.76	9.74	47.43	5.95	12.77	9.77

Supporting Information

Table S2. Mass Spectra Data of Select Compounds.

No.	Formula	Calcd.	Found
81	C ₈ H ₆ NO ⁺	132.0443	132.0443
82	C ₉ H ₁₃ NOH ⁺	152.1075	152.1075
<i>(R)</i> - 86	C ₂₀ H ₂₁ F ₃ N ₂ O ₄ H ⁺	411.1538	411.1531
<i>(R)</i> - 115	C ₇ H ₁₄ NO ₄ H ⁺	176.0918	176.0923
<i>(R)</i> - 119	C ₁₁ H ₁₄ Cl ₂ N ₂ O ₂ H ⁺	277.08	277.05