Supporting information for

Enantioselective Synthesis of 4-Aminopyrrolidines-2,4-dicarboxylate Derivatives via Ag-Catalyzed Cycloaddition of Azomethine Ylides with Alkylidene Azlactones

María González-Esguevillas, Javier Adrio,* and Juan C. Carretero*

Departamento de Química Orgánica. Facultad de Ciencias. Universidad Autónoma de Madrid. Cantoblanco.28049 Madrid. Spain.

Table of Contents

1. General methods

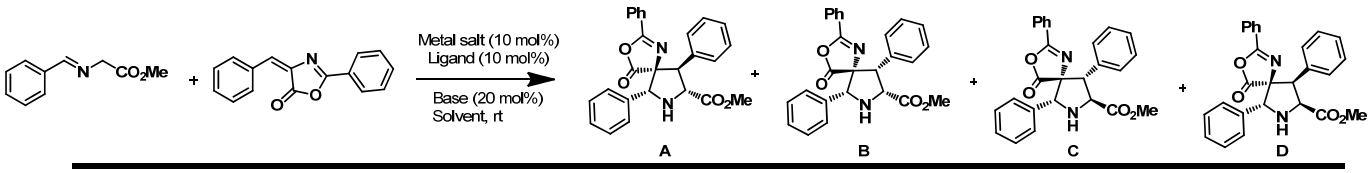
All anaerobic and moisture-sensitive manipulations were carried out in anhydrous solvents and under nitrogen. Dichloromethane, toluene, acetonitrile and tetrahydrofuran were dried over the PureSolv MD purification system. Melting points were taken in open-end capillary tubes. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (230-400 mesh). Flash column chromatographies were performed using silica gel (230-400 mesh). NMR spectra were recorded on AU-300 MHz instrument and calibrated using residual undeuterated solvent ($CDCl_3$, methanol-d_4 or D_2O) as internal reference. MS spectra were recorded on a VG *AutoSpec* mass spectrometer. The HPLC chromatograms of the racemic and enantiomerically enriched cycloadducts are also included.

α-Iminoesters **1a-l** were prepared by condensation of α-aminoesters and the corresponding aldehydes.[1] Due to their lability, all the α-iminoesters precursors of the azomethine ylides, once isolated were immediately used in the 1,3-dipolar cycloaddition without further purification.

Azlactones **2a, 2q, 2u** and **2y** are comercially available. Azlactones **2b-p**, **2r-t** and **2v-x** were prepared according literature procedures.[2]

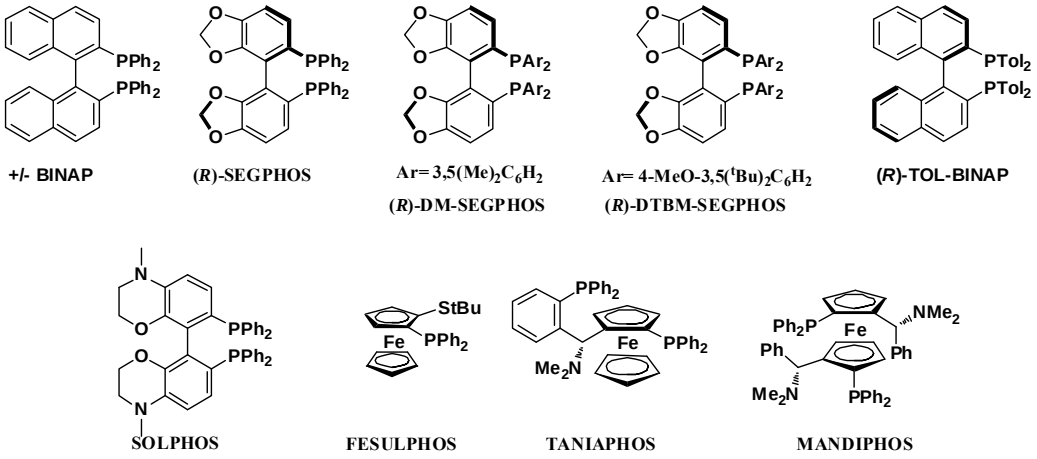
2. Catalyst optimization studies.

The table below shows other chiral catalyst systems tested in the model [3+2] cycloaddition.

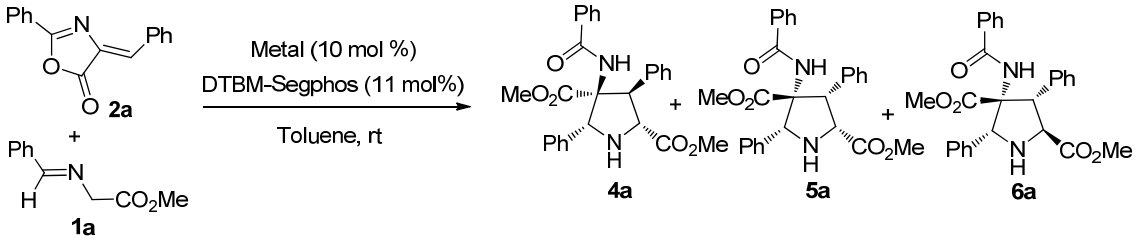


Metal	Ligand	Base	Solvent	A:B:C:D[a,b]
$Cu(CH_3CN)_4PF_6$	± BINAP	Et_3N	THF	18:41:41:0
$Cu(CH_3CN)_4PF_6$	(*R*)-Segphos	Et_3N	THF	40:37:7:16
$Cu(CH_3CN)_4PF_6$	Taniaphos	Et_3N	THF	Complex mixture
$Cu(OAc)_2$	± BINAP	Et_3N	THF	27:48:25:0
$Cu(OTf)_2$	± BINAP	Et_3N	THF	27:55:10:8
$Cu(OTf)_2$	(*R*)-DTBM-Segphos	Et_3N	THF	37:50:12:0
$Cu(OTf)_2$	(*R*)-DTBM-Segphos	----	THF	Complex mixture
AgOAc	± BINAP	Et_3N	THF	8:34:45:13
AgOAc	Fesulphos	Et_3N	THF	11:41:48:0
AgOAc	(*R*)-Segphos	Et_3N	THF	10:28:57:5
AgOAc	(*R*)-DM-Segphos	Et_3N	THF	9:20:50:21
AgOAc	Solphos	Et_3N	THF	14:23:49:14
AgOAc	Mandiphos	Et_3N	THF	34:41:16:9
AgOAc	Taniaphos	Et_3N	THF	38:55:7:0
AgOAc	(*R*)-Tol-Binap	Et_3N	THF	9:28:61:2
AgOAc	(*R*)-DTBM-Segphos	Et_3N	THF	55:25:20:0
AgOTf	(*R*)-DTBM-Segphos	Et_3N	THF	43:46:11:0
$AgClO_4.H_2O$	(*R*)-DTBM-Segphos	Et_3N	THF	51:44:5:0
$AgSbF_6$	(*R*)-DTBM-Segphos	Et_3N	THF	52:42:6:0
AgOAc	(*R*)-DTBM-Segphos	---	THF	57:38:5:0
AgOAc	(*R*)-DTBM-Segphos	Et_3N	ACN	28:52:20:0
AgOAc	(*R*)-DTBM-Segphos	Et_3N	Et_2O	49:41:9:0
AgOAc	(*R*)-DTBM-Segphos	Et_3N	Toluene	60:32:8:0
AgOAc	(*R*)-DTBM-Segphos	^{t}BuOK	Toluene	23:46:32:0
AgOAc	(*R*)-DTBM-Segphos	NaOAc	Toluene	77:20:3:0
AgOAc	(*R*)-DTBM-Segphos	---	Toluene	80:14:6:0

[a] By 1H NMR from the crude reaction mixtures. [b]The spirocyclic adducts can not be purified by silica gel chromatography.



3. Comparative study between silver and copper catalyzed reactions

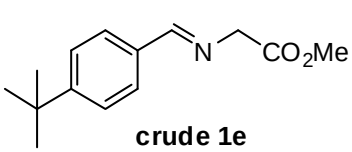


Metal	**4a: 5a: 6a**	Yield **4+5 (%)**[a]	*ee* (%) **4a**[b]
AgOAc	80:20:0	62	95
$Cu(CH_3CN)_4PF_6$	62:20:18	13	93

[a]Yield of the **4a**+**5a** mixture after column chromatography. [b]Determined by chiral HPLC

4. General procedure for the synthesis of α-iminoesters.

Methyl (*E*)-*N*-[(4-*tert*-butylphenyl)methylene]glycinate (1e)



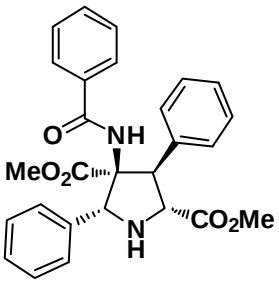
crude 1e

A suspension of methyl glycinate hydrochloride (1.16 g, 9.3 mmol), $MgSO_4$ (0.93 g, 7.7 mmol) and Et_3N (1.3 mL, 9.3 mmol) in dry dichloromethane (8 mL) was stirred at room temperature for 1 h, and 4-*tert*-butylbenzaldehyde (1.0 g, 6.2 mmol) was added. After 12h at room temperature the mixture was filtered off and water (4 mL) was added. The organic layer was separated and the aqueous phase was extracted with dichloromethane (10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to afford methyl (*E*)-*N*-[(4-*tert*-butylphenyl)methylene]glycinate (**1e**) (1.26 g, 88%, yellow solid).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.26 (s, 2H), 3.60 (s, 3H), 1.21 (s, 9H).

5. General procedure for the asymmetric 1,3-dipolar cycloaddition of azomethine ylides.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3,5-diphenylpyrrolidine-2,4-dicarboxylate (4a)



4a

To a solution of (*R*)-DTBM-Segphos (39.0 mg, 33.00 10^{-3} mmol), AgOAc (5.0 mg, 30.10 10^{-3} mmol) and (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (150.0 mg, 0.60 mmol) in toluene (3.0 mL), under nitrogen atmosphere, at -10 ºC, a solution of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (213.0 mg, 1.20 mmol) in toluene (3.0 mL) was added. The mixture was stirred at -10 ºC for 16 h. HCl 3M in methanol (4.0 mL) was added at -10 ºC and the mixture was diluted with dichloromethane and washed with a saturated aqueous of sodium hydrogen carbonate until basic pH. The aqueous phase was then extracted three times with dichloromethane. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (hexane-EtOAc 9:1-8:2) to afford a mixture (98:2) of the cycloadduct **4a** and **5a** (181.5 mg, 66%, colorless solid).

M.p.: 90-93ºC.

$[\alpha]_D^{20}$:+81.7 (c=0.2, $CHCl_3$), >99% *ee*.

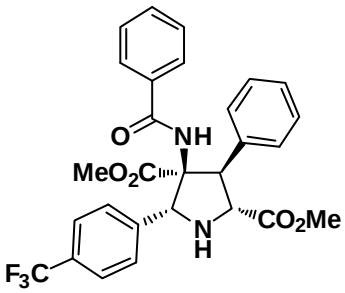
HPLC: Daicel Chiralpak IA, isopropanol-hexane 15-85, flow rate 0.7 mL/min (λ = 254 nm), t_R: 37.3 min (2*R*, 3*S*, 4*S*, 5*R*)-**4a** and 43.6 min (2*S*, 3*R*, 4*R*, 5*S*)-**4a**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 – 7.39 (m, 1H), 7.37 – 7.27 (m, 11H), 7.24-7.22 (m, 2H), 7.18 – 7.13 (m, 1H), 6.60 (s, 1H), 5.18 (s, 1H), 4.79 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 3.29 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 172.0, 167.6, 137.6, 137.2, 134.7, 131.5, 128.9, 128.5, 128.5, 128.3, 128.2, 127.3, 126.6, 126.4, 73.5, 69.1, 64.8, 57.6, 52.6, 52.5.

MS (ESI+): 459.2 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{27}H_{27}N_2O_5$, 459.1914; found, 459.1910.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-phenyl-5-(4-trifluoromethyl)phenyl)pyrrolidine-2,4-dicarboxylate (4b)



4b

Following the general procedure, the reaction of (*E*)-*N*-[4-trifluoromethyl)phenyl)methylene]glycinate (**1b**) (98.4 mg, 0.40 mmol) with (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (50.0 mg, 0.20 mmol) in the presence of (*R*)-DTBM-Segphos (13.0 mg, 11.00 10^{-3} mmol) and AgOAc (1.7 mg, 10.00 10^{-3} mmol) for 5.5 h afforded, after chromatography (hexane-EtOAc 8:2-7:3), the cycloadduct **4b** (72.1 mg, 68%, colorless solid).

M.p.: 84-87ºC.

$[\alpha]_D^{20}$: +40.3 (c=0.8, $CHCl_3$), 98% *ee*.

HPLC: Daicel Chiralpak IC, isopropanol-hexane 15-85, flow rate 0.7 mL/min (λ = 254 nm), t_R: 28.7 min (2*R*, 3*S*, 4*S*, 5*R*)-**4b** and 50.4 min (2*S*, 3*R*, 4*R*, 5*S*)-**4b**.

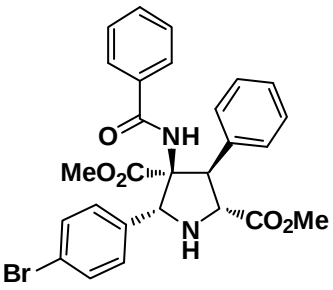
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.32 (m, 1H), 7.30 – 7.23 (m, 4H), 7.23 – 7.14 (m, 4H), 7.15 – 7.06 (m, 1H), 6.68 (s, 1H), 5.37 (s, 1H), 4.88 (d, *J* = 8.0 Hz, 1H), 4.40 (d, *J* = 8.0 Hz, 1H), 3.72 (s, 3H), 3.23 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 171.9, 167.6, 142.2, 136.3, 134.6, 131.6, 130.2 (d, $J_{C\text{-}F}$ = 32.4 Hz), 128.8, 128.5, 128.3, 127.5, 126.8, 126.5, 125.2 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.0 (d, $J_{C\text{-}F}$ = 270.0 Hz), 74.0, 67.5, 64.0, 57.9, 52.7, 52.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ = -62.6.

MS (ESI+): 527.2 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{28}H_{26}N_2O_5F_3$, 527.1788; found, 527.1787.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-phenyl-5-(4-bromophenyl)pyrrolidine-2,4-dicarboxylate (4c)



4c

Following the general procedure, the reaction of (*E*)-*N*-[(4-bromophenyl)methylene]glycinate (**1c**) (102.7 mg, 0.40 mmol) with (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (50.0 mg, 0.20 mmol) in the presence of (*R*)-DTBM-Segphos (13.0 mg, 11.00 10^{-3} mmol) and AgOAc (1.7 mg, 10.00 10^{-3} mmol) for 16 h afforded, after chromatography (hexane-EtOAc 8:2-1:1), the cycloadduct **4c** (75.5 mg, 70%, colorless solid).

M.p.: 102-104ºC.

$[\alpha]_D^{20}$: +68.9 (c=1.1, $CHCl_3$), >99% *ee*.

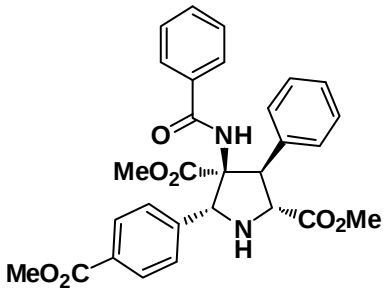
HPLC: Daicel Chiralpak IC, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 210 nm), t_R: 30.5 min (2*R*, 3*S*, 4*S*, 5*R*)-**4c** and 51.6 min (2*S*, 3*R*, 4*R*, 5*S*)-**4c**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.2 Hz, 2H), 7.27 – 7.03 (m, 12H), 6.57 (s, 1H), 5.18 (s, 1H), 4.78 (d, *J* = 7.5 Hz, 1H), 4.43 (d, *J* = 7.4 Hz, 1H), 3.71 (s, 3H), 3.28 (s, 3H), 2.98 (bs, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 171.9, 167.6, 136.8, 136.8, 134.6, 131.5, 131.5, 128.8, 128.5, 128.3, 128.1, 127.4, 126.5, 122.0, 73.6, 67.8, 64.2, 57.6, 52.7, 52.5.

MS (ESI+): 537.1 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{28}H_{26}N_2O_5Br$, 537.1019; found, 537.0999.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-phenyl-5-(4-methoxycarbonylphenyl)pyrrolidine-2,4-dicarboxylate (4d)



4d

Following the general procedure, the reaction of (*E*)-*N*-[4-methoxycarbonyl)phenyl)methylene]glycinate (**1d**) (94.4 mg, 0.40 mmol) with (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (50.0 mg, 0.20 mmol) in the presence of (*R*)-DTBM-Segphos (13.0 mg, 11.00 10^{-3} mmol) and AgOAc (1.7 mg, 10.00 10^{-3} mmol) for 14 h afforded, after chromatography (hexane-EtOAc 8:2-6:4), the cycloadduct **4d** (59.5 mg, 57%, colorless solid).

M.p.: 100-103ºC.

$[\alpha]_D^{20}$: +73.6 (c=0.5, $CHCl_3$), 95% *ee*.

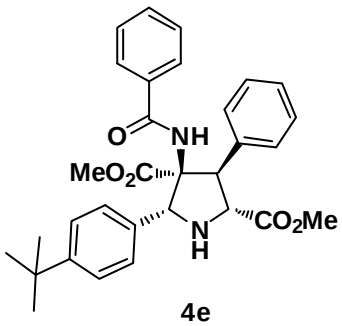
HPLC: Daicel Chiralpak IA, isopropanol-hexane 30-70, flow rate 0.7 mL/min (λ = 254 nm), t_R: 16.6 min (2*S*, 3*R*, 4*R*, 5*S*)-**4d** and 36.0 min (2*R*, 3*S*, 4*S*, 5*R*)-**4d**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.34 – 7.32 (m, 1H), 7.28 – 7.01 (m, 9H), 6.68 (s, 1H), 5.34 (s, 1H), 4.85 (d, *J* = 7.7 Hz, 1H), 4.40 (d, *J* = 7.7 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.22 (s, 3H), 3.03 (bs, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 172.0, 167.6, 166.7, 143.1, 136.6, 134.6, 131.5, 129.8, 129.6, 128.9, 128.5, 128.3, 127.4, 126.5, 126.4, 73.9, 67.8, 64.2, 58.0, 52.7, 52.5, 52.1.

MS (ESI+): 517.2 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{29}H_{29}N_2O_7$, 517.1969; found, 517.1972.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-phenyl-5-(4-*tert*-butylphenyl)pyrrolidine-2,4-dicarboxylate (4e)



4e

Following the general procedure, the reaction of (*E*)-*N*-[4-*tert*-butyl-phenyl)methylene]glycinate (**1e**) (93.6 mg, 0.40 mmol) with (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (50.0 mg, 0.20 mmol) in the presence of (*R*)-DTBM-Segphos (13.0 mg, 11.00 10^{-3} mmol) and AgOAc (1.7 mg, 10.00 10^{-3} mmol) for 17 h afforded, after chromatography (hexane-EtOAc 8:2-1:1), a mixture (98:2) of cycloadducts **4e** and **5e** (69.2 mg, 67%, colorless solid).

M.p.: 98-101ºC.

[α]$_D^{20}$: +81.0 (c=0.3, $CHCl_3$), 98% *ee*.

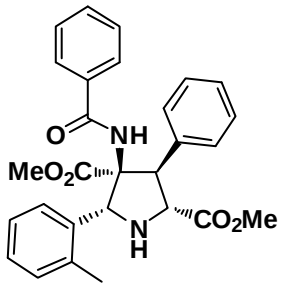
HPLC: Daicel Chiralpak IA, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 210 nm), t_R: 18.2 min (2*R*, 3*S*, 4*S*, 5*R*)-**4e** and 24.6 min (2*S*, 3*R*, 4*R*, 5*S*)-**4e**.

^{1}H NMR (300 MHz, $CDCl_3$): δ ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36 – 7.04 (m, 14H), 6.42 (s, 1H), 5.00 (s, 1H), 4.65 (d, *J* = 6.4 Hz, 1H), 4.51 (d, *J* = 6.3 Hz, 1H), 3.75 (s, 3H), 3.18 (s, 3H), 1.22 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 172.0, 167.5, 151.4, 138.0, 134.7, 134.1, 131.4, 128.9, 128.4, 128.2, 127.2, 126.6, 126.0, 125.3, 73.4, 69.3, 65.1, 57.3, 52.5, 52.3, 34.6, 31.3.

MS (ESI+): 515.3 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{31}H_{35}N_2O_5$, 515.2540; found, 515.2560.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-phenyl-5-(2-methylphenyl)pyrrolidine-2,4-dicarboxylate (4f)



4f

Following the general procedure, the reaction of (*E*)-*N*-[2-methyl-phenyl)methylene]glycinate (**1f**) (76.7 mg, 0.40 mmol) with (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (50.0 mg, 0.20 mmol) in the presence of (*R*)-DTBM-Segphos (13.0 mg, 11.00 10^{-3} mmol) and AgOAc (1.7 mg, 10.00 10^{-3} mmol) for 17 h afforded, after chromatography (hexane-EtOAc 8:2-1:1), a mixture (98:2) of cycloadducts **4f** and **5f** (75.6 mg, 89%, pale yellow solid).

M.p.: 80-83ºC.

[α]$_D^{20}$: +33.2 (c=0.3, $CHCl_3$), 98% *ee*.

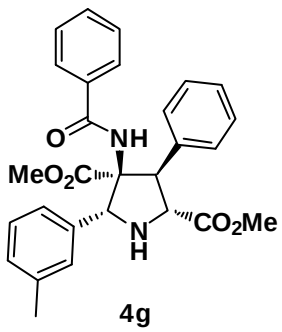
HPLC: Daicel Chiralpak AD, isopropanol-hexane 10-90, flow rate 0.7 mL/min (λ = 254 nm), t_R: 37.7 min (2*R*, 3*S*, 4*S*, 5*R*)-**4f** and 41.1 min (2*S*, 3*R*, 4*R*, 5*S*)-**4f**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.50 – 7.02 (m, 13H), 6.74 (s, 1H), 5.68 (s, 1H), 5.07 (d, *J* = 8.4 Hz, 1H), 4.63 (d, *J* = 8.4 Hz, 1H), 3.77 (s, 3H), 3.32 (s, 3H), 3.02 (bs, 1H), 2.32 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 172.0, 167.4, 136.7, 136.0, 134.8, 131.4, 130.6, 128.8, 128.5, 128.2, 127.8, 127.2, 126.8, 126.5, 125.8, 75.0, 64.5, 64.1, 57.3, 52.6, 52.4, 20.1.

MS (ESI+): 473.2 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{28}H_{29}N_2O_5$, 473.2070; found, 473.2082.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-phenyl-5-(3-methylphenyl)pyrrolidine-2,4-dicarboxylate (4g)



4g

Following the general procedure, the reaction of (*E*)-*N*-[3-methyl-phenyl)methylene]glycinate (**1g**) (122.7 mg, 0.64 mmol) with (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (80.0 mg, 0.32 mmol) in the presence of (*R*)-DTBM-Segphos (20.8 mg, 18.00 10^{-3} mmol) and AgOAc (2.7 mg, 16.00 10^{-3} mmol) for 30 h afforded, after chromatography (hexane-EtOAc 9:1-7:3), a mixture (98:2) of cycloadducts **4g** and **5g** (97.2 mg, 64%, pale

yellow solid).

M.p.: 94-97ºC.

$[\alpha]_D^{20}$: +87.3 (c=0.7, $CHCl_3$), >99% *ee*.

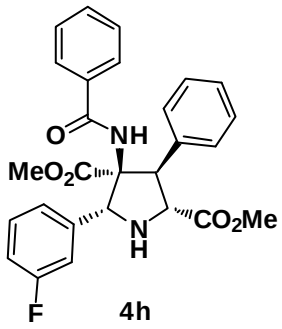
HPLC: Daicel Chiralpak AD, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 254 nm), t_R: 20.3 min (2*R*, 3*S*, 4*S*, 5*R*)-**4g** and 40.7 min (2*S*, 3*R*, 4*R*, 5*S*)-**4g**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 – 7.05 (m, 14H), 6.56 (s, 1H), 5.12 (s, 1H), 4.78 (d, *J* = 6.5 Hz, 1H), 4.61 (d, *J* = 6.4 Hz, 1H), 3.84 (s, 3H), 3.35 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 172.0, 167.6, 138.2, 137.9, 136.9, 134.7, 131.4, 129.1, 128.9, 128.4, 128.4, 128.2, 127.2, 127.0, 126.6, 123.5, 73.4, 69.2, 65.0, 57.5, 52.5, 52.4, 21.5.

MS (ESI+): 473.2 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{28}H_{29}N_2O_5$, 473.2070; found, 473.2083.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-phenyl-5-(3-fluorophenyl)pyrrolidine-2,4-dicarboxylate (4h)



4h

Following the general procedure, the reaction of (*E*)-*N*-[3-fluoro-phenyl)methylene]glycinate (**1h**) (78.3 mg, 0.40 mmol) with (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (50.0 mg, 0.20 mmol) in the presence of (*R*)-DTBM-Segphos (13.0 mg, 11.00 10^{-3} mmol) and AgOAc (1.7 mg, 10.00 10^{-3} mmol) for 40 h afforded, after chromatography (hexane-EtOAc 8:2-1:1), the cycloadduct **4h** (47.8 mg, 50%, colorless solid).

M.p.: 87-90ºC.

$[\alpha]_D^{20}$: +45.4 (c=0.1, $CHCl_3$), 99% *ee*.

HPLC: Daicel Chiralpak IC, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 210 nm), t_R: 32.8 min (2*R*, 3*S*, 4*S*, 5*R*)-**4h** and 42.4 min (2*S*, 3*R*, 4*R*, 5*S*)-**4h**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 1H), 7.29 – 7.02 (m, 12H), 6.96 – 6.87 (m, 1H), 6.62 (s, 1H), 5.24 (s, 1H), 4.81 (d, *J* = 7.6 Hz, 1H), 4.42 (d, *J* = 7.6 Hz, 1H), 3.73 (s, 3H), 3.28 (s, 3H).

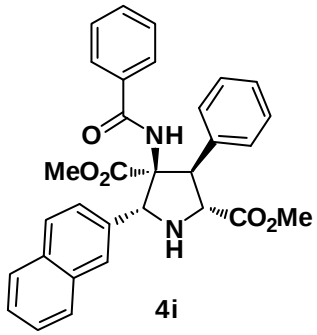
^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 172.0, 167.6, 162.8 (d, $J_{C\text{-}F}$ = 246.7 Hz), 140.5 (d, $J_{C\text{-}F}$ = 6.9 Hz), 136.7, 134.6, 131.5, 129.9 (d, $J_{C\text{-}F}$ = 8.1 Hz), 128.8, 128.5, 128.3, 127.4, 126.5, 122.0 (d, $J_{C\text{-}F}$ = 2.9 Hz), 115.0 (d, $J_{C\text{-}F}$ = 21.1 Hz), 113.6 (d, $J_{C\text{-}F}$ = 22.4 Hz), 73.7, 67.7, 64.2, 57.7, 52.7, 52.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -112.5.

MS (ESI+): 477.2 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{27}H_{26}N_2O_5F$, 477.1820; found, 477.1836.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-phenyl-5-(2-naphthyl)pyrrolidine-2,4-dicarboxylate (4i)

Following the general procedure, the reaction of (*E*)-*N*-[2-naphtyl-methylene]glycinate (**1i**) (91.2 mg, 0.40 mmol) with (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (50.0 mg, 0.20 mmol) in the presence of (*R*)-DTBM-Segphos (13.0 mg, 11.00 10^{-3} mmol) and AgOAc (1.7 mg, 10.00 10^{-3} mmol) for



4i

117 h afforded, after chromatography (hexane-EtOAc 9:1-1:1), a mixture (90:10) of cycloadducts **4i** and **5i** (66.4 mg, 65%, pale yellow solid).

M.p.: 135-138ºC.

$[\alpha]_D^{20}$: +8.5 (c=1.3, $CHCl_3$), >99% *ee*.

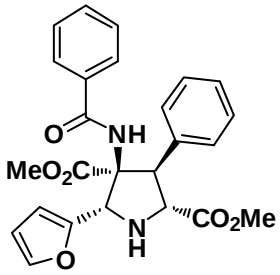
HPLC: Daicel Chiralpak IA, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 210 nm), t_R: 29.4 min (2*R*, 3*S*, 4*S*, 5*R*)-**4i** and 52.9 min (2*S*, 3*R*, 4*R*, 5*S*)-**4i**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.97 – 7.84 (m, 3H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.53 – 7.18 (m, 12H), 6.85 (s, 1H), 6.32 (s, 1H), 5.13 (d, *J* = 7.9 Hz, 1H), 4.76 (d, *J* = 7.8 Hz, 1H), 3.86 (s, 3H), 3.19 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 171.7, 167.6, 137.0, 134.8, 133.8, 133.8, 131.7, 131.5, 129.2, 128.9, 128.6, 128.5, 128.3, 127.3, 126.6, 126.4, 125.6, 125.1, 124.6, 122.5, 74.8, 64.2, 63.0, 57.0, 52.5, 52.4.

MS (ESI+): 509.2 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{31}H_{29}N_2O_5$, 509.2070; found, 509.2061.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-phenyl-5-(2-furyl)pyrrolidine-2,4-dicarboxylate (4j)



4j

Following the general procedure, the reaction of (*E*)-*N*-[2-furyl-methylene]glycinate (**1j**) (187.6 mg, 1.12 mmol) with (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (70.0 mg, 0.28 mmol) in the presence of (*R*)-DTBM-Segphos (18.2 mg, 15.00 10^{-3} mmol) and AgOAc (2.3 mg, 14.00 10^{-3} mmol) for 45 h afforded, after chromatography (hexane-EtOAc 9:1-1:1), the cycloadduct **4j** (88.9 mg, 70%, yellow-brown solid).

M.p.: 85-88ºC.

$[\alpha]_D^{20}$: +96.6 (c=0.3, $CHCl_3$), >99% *ee*.

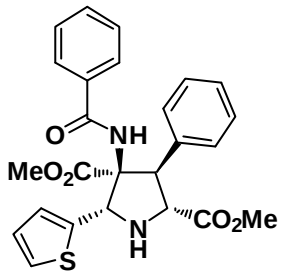
HPLC: Daicel Chiralpak AD, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 210 nm), t_R: 16.2 min (2*R*, 3*S*, 4*S*, 5*R*)-**4j** and 30.3 min (2*S*, 3*R*, 4*R*, 5*S*)-**4j**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 – 7.01 (m, 11H), 6.48 (s, 1H), 6.47 – 6.43 (m, 1H), 6.40 – 6.39 (m, 1H), 4.94 (s, 1H), 4.74 (d, *J* = 4.9 Hz, 1H), 4.50 (d, *J* = 5.0 Hz, 1H), 3.85 (s, 3H), 3.49 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 171.3, 167.7, 150.1, 142.6, 138.8, 134.3, 131.4, 128.9, 128.4, 128.3, 127.3, 126.7, 110.5, 107.4, 71.9, 66.0, 64.4, 56.3, 52.8, 52.6.

MS (ESI+): 449.17 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{25}H_{25}N_2O_6$, 449.1707; found, 449.1724.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-phenyl-5-(2-thiophenyl)pyrrolidine-2,4-dicarboxylate (4k)



4k

Following the general procedure, the reaction of (*E*)-*N*-[2-thioophenyl-methylene]glycinate (**1k**) (73.5 mg, 0.40 mmol) with (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (50.0 mg, 0.20 mmol) in the presence of (*R*)-DTBM-Segphos (13.0 mg, 11.00 10^{-3} mmol) and AgOAc (1.7 mg, 10.00 10^{-3} mmol) for 5 h afforded, after chromatography (hexane-EtOAc 8:2-1:1), a mixture (91:9) of cycloadducts **4k** and **5k** (83.8 mg, 90%, yellow-brown solid).

M.p.: 94-97ºC.

$[\alpha]_D^{20}$: +45.7 (c=0.2, $CHCl_3$), >99% *ee*.

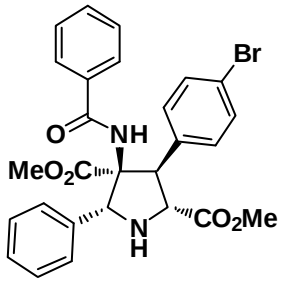
HPLC: Daicel Chiralpak IB, isopropanol-hexane 10-90, flow rate 0.7 mL/min (λ = 210 nm), t_R: 41.9 min (2*R*, 3*S*, 4*S*, 5*R*)-**4k** and 47.8 min (2*S*, 3*R*, 4*R*, 5*S*)-**4k**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 – 7.16 (m, 11H), 7.11 – 7.07 (m, 1H), 7.03 – 7.01 (m, 1H), 6.63 (s, 1H), 5.42 (s, 1H), 4.77 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 3.48 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 171.7, 167.6, 140.3, 137.4, 134.6, 131.5, 128.9, 128.4, 128.2, 127.3, 127.0, 126.6, 124.7, 124.3, 73.5, 65.2, 64.8, 57.2, 52.8, 52.5.

MS (ESI+): 465.15 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{25}H_{25}N_2O_5S$, 465.1478; found, 465.1479.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(4-bromophenyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4m)



4m

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (107.9 mg, 0.61 mmol) with (Z)-4-(4-bromobenzylidene)-2-phenyloxazol-5(4H)-one (**2m**) (100.0 mg, 0.30 mmol) in the presence of (*R*)-DTBM-Segphos (19.8 mg, 16.00 10^{-3} mmol) and AgOAc (2.5 mg, 15.00 10^{-3} mmol) for 40 h afforded, after chromatography (hexane-EtOAc 9:1-8:2), a mixture (92:8) of cycloadducts **4m** and **5m** (87.2 mg, 53%, colorless solid).

M.p.: 100-103ºC.

$[\alpha]_D^{20}$: +61.0 (c=0.3, $CHCl_3$), >99% *ee*.

HPLC: Daicel Chiralpak IB, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 254 nm), t_R: 16.3 min (2*R*, 3*S*, 4*S*, 5*R*)-**4m** and 18.9 min (2*S*, 3*R*, 4*R*, 5*S*)-**4m**.

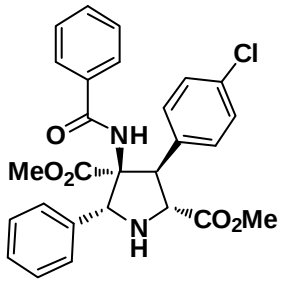
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.35 (m, 1H), 7.33 – 7.22 (m, 10H), 7.19 – 7.18 (m, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 6.61 (s, 1H), 5.06 (s, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 4.41 (d, *J* = 7.0 Hz, 1H), 3.74 (s, 3H), 3.22 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 171.9, 167.4, 137.0, 136.5, 134.4, 131.7, 131.2, 130.7, 128.6, 128.5, 128.4, 126.5, 126.3, 121.2, 73.5, 69.0, 64.7, 57.1, 52.6, 52.6.

MS (ESI+): 537.10 ([M+H], 75). **HRMS** (ESI+): Calculated for $C_{27}H_{26}N_2O_5Br$, 537.1019; found, 537.1026.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(4-chlorophenyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4n)

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (62.4 mg, 0.35 mmol) with (Z)-4-(4-chlorobenzylidene)-2-phenyloxazol-5(4H)-one (**2n**) (50.0 mg, 0.18 mmol) in the presence of (*R*)-DTBM-Segphos (11.4 mg, 9.7 10^{-3} mmol) and AgOAc (1.4 mg, 8.80 10^{-3} mmol) for 13 h afforded, after chromatography (hexane-EtOAc 9:1-8:2), a mixture (94:6) of cycloadducts **4n** and **5n** (57.7 mg, 66%, colorless solid).



4n

M.p.: 94-97ºC.

[α]$_D^{20}$: +66.5 (c=0.4, $CHCl_3$), >99% *ee*.

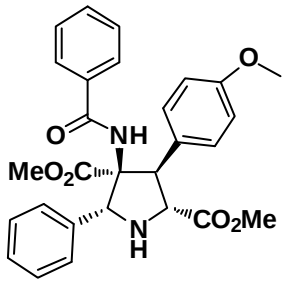
HPLC: Daicel Chiralpak IA, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 210 nm), t_R: 23.6 min (2*R*, 3*S*, 4*S*, 5*R*)-**4n** and 43.3 min (2*S*, 3*R*, 4*R*, 5*S*)-**4n**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 – 7.33 (m, 10H), 7.32 – 7.14 (m, 4H), 6.73 (s, 1H), 5.16 (s, 1H), 4.78 (d, *J* = 6.8 Hz, 1H), 4.55 (d, *J* = 6.9 Hz, 1H), 3.85 (s, 3H), 3.33 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 171.9, 167.4, 137.1, 136.0, 134.4, 133.1, 131.7, 130.4, 128.6, 128.5, 128.3, 128.3, 126.5, 126.3, 73.5, 69.0, 64.8, 57.0, 52.6, 52.5.

MS (ESI+): 493.15 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{27}H_{26}N_2O_5Cl$, 493.1524; found, 493.1516.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(4-methoxyphenyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4o)



4o

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (126.8 mg, 0.71 mmol) with (Z)-4-(4-methoxybenzylidene)-2-phenyloxazol-5(4H)-one (**2o**) (100.0 mg, 0.36 mmol) in the presence of (*R*)-DTBM-Segphos (23.2 mg, 19.7 10^{-3} mmol) and AgOAc (3.0 mg, 18.0 10^{-3} mmol) for 21 h afforded, after chromatography (hexane-EtOAc 9:1-8:2), the cycloadduct **4o** (159.7 mg, 91%, colorless solid).

M.p.: 88-91ºC.

[α]$_D^{20}$: +66.3 (c=0.6, $CHCl_3$), 99% *ee*.

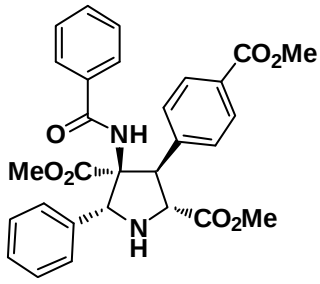
HPLC: Daicel Chiralpak IA, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 254 nm), t_R: 32.2 min (2*R*, 3*S*, 4*S*, 5*R*)-**4o** and 40.4 min (2*S*, 3*R*, 4*R*, 5*S*)-**4o**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 – 7.31 (m, 10H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.1 Hz, 2H), 6.68 (s, 1H), 5.21 (s, 1H), 4.78 (d, *J* = 7.1 Hz, 1H), 4.54 (d, *J* = 6.9 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.32 (s, 3H), 2.81 (bs, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 172.1, 167.6, 158.7, 137.4, 134.7, 131.5, 130.0, 129.5, 128.5, 128.2, 126.6, 126.3, 113.7, 73.7, 68.9, 65.0, 57.0, 55.2, 52.5, 52.4.

MS (ESI+): 489.20 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{28}H_{29}N_2O_6$, 489.2020; found, 489.2018.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(4-methoxycarbonylphenyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4p)



4p

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (115.2 mg, 0.65 mmol) with (*Z*)-4-(4-(methoxycarbonyl)benzylidene)-2-phenyloxazol-5(4H)-one (**2p**) (100.0 mg, 0.33 mmol) in the presence of (*R*)-DTBM-Segphos (21.1 mg, 18.0 10^{-3} mmol) and AgOAc (2.7 mg, 16.0 10^{-3} mmol) for 4 h afforded, after chromatography (hexane-EtOAc 9:1-7:3), the cycloadduct **4p** (115.5 mg, 69%, colorless solid).

M.p.: 101-104ºC.

$[\alpha]_D^{20}$: +64.6 (c=0.6, $CHCl_3$), >99% *ee*.

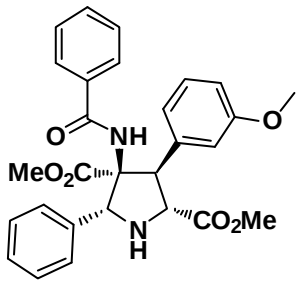
HPLC: Daicel Chiralpak IB, etanol-hexane 10-90, flow rate 0.7 mL/min (λ = 210 nm), t_R: 21.3 min (2*R*, 3*S*, 4*S*, 5*R*)-**4p** and 29.6 min (2*S*, 3*R*, 4*R*, 5*S*)-**4p**.

^{1}H NMR (300 MHz, $CDCl_3$): 7.88 (d, *J* = 8.1 Hz, 2H), 7.54 – 7.21 (m, 12H), 6.84 (s, 1H), 5.15 (s, 1H), 4.78 (d, *J* = 6.5 Hz, 1H), 4.66 (d, *J* = 6.3 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.31 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 171.7, 167.4, 166.8, 143.2, 137.0, 134.2, 131.6, 129.3, 129.1, 128.9, 128.5, 128.5, 128.5, 128.4, 126.6, 126.4, 73.4, 69.3, 64.9, 57.1, 52.5, 52.0.

MS (ESI+): 517.20 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{29}H_{29}N_2O_7$, 517.1969; found, 517.1980.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(3-methoxyphenyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4q)



4q

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (63.4 mg, 0.36 mmol) with (*Z*)-4-(3-methoxybenzylidene)-2-phenyloxazol-5(4H)-one (**2q**) (50.0 mg, 0.18 mmol) in the presence of (*R*)-DTBM-Segphos (11.6 mg, 9.9 10^{-3} mmol) and AgOAc (1.5 mg, 8.9 10^{-3} mmol) for 22 h afforded, after chromatography (hexane-EtOAc 9:1-7:3), the cycloadduct **4q** (62.7 mg, 72%, colorless solid).

M.p.: 102-105ºC.

$[\alpha]_D^{20}$: +71.2 (c=0.2, $CHCl_3$), >99% *ee*.

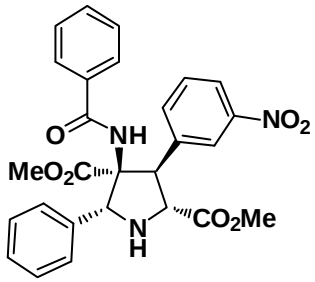
HPLC: Daicel Chiralpak AS-H, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 254 nm), t_R: 15.9 min (2*S*, 3*R*, 4*R*, 5*S*)-**4q** and 21.4 min (2*R*, 3*S*, 4*S*, 5*R*)-**4q**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 – 7.15 (m, 10H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.90 – 6.78 (m, 2H), 6.70 – 6.55 (m, 1H), 6.45 (s, 1H), 5.05 (s, 1H), 4.65 (d, *J* = 6.2 Hz, 1H), 4.50 (d, *J* = 6.2 Hz, 1H), 3.75 (s, 3H), 3.61 (s, 3H), 3.20 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 171.8, 167.6, 159.4, 139.5, 137.3, 134.6, 131.5, 129.3, 128.5, 128.4, 128.3, 126.6, 126.4, 121.1, 114.8, 113.0, 73.4, 69.2, 64.9, 57.3, 55.2, 52.5, 52.4.

MS (ESI+): 489.2018 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{28}H_{29}N_2O_6$, 489.2020; found, 489.2018.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(3-nitrophenyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4r)



4r

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (96.2 mg, 0.54 mmol) with (*Z*)-4-(3-nitrobenzylidene)-2-phenyloxazol-5(4H)-one (**2r**) (80.0 mg, 0.27 mmol) in the presence of (*R*)-DTBM-Segphos (17.6 mg, 15.0 10^{-3} mmol) and AgOAc (2.3 mg, 14.0 10^{-3} mmol) for 24 h afforded, after chromatography (hexane-EtOAc 9:1-7:3), a mixture (95:5) of cycloadducts **4r** and **5r** (71.7 mg, 52%, pale yellow solid).

M.p.: 165-167ºC.

$[\alpha]_D^{20}$: +85.6 (c=0.4, $CHCl_3$), >99% *ee*.

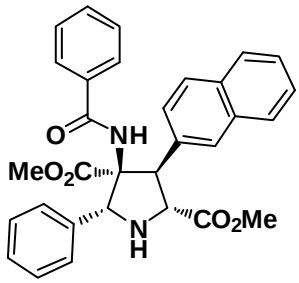
HPLC: Daicel Chiralpak IB, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 230 nm), t_R: 21.4 min (2*R*, 3*S*, 4*S*, 5*R*)-**4r** and 30.1 min (2*S*, 3*R*, 4*R*, 5*S*)-**4r**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.23 (m, 11H), 6.79 (s, 1H), 5.11 (s, 1H), 4.79 (d, *J* = 7.3 Hz, 1H), 4.69 (d, *J* = 7.3 Hz, 1H), 3.83 (s, 3H), 3.32 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 171.4, 167.2, 147.9, 139.8, 136.7, 135.74, 133.7, 131.9, 128.9, 128.6, 128.6, 128.6, 126.5, 126.4, 123.8, 122.3, 73.4, 69.6, 64.9, 56.5, 52.7, 52.6.

MS (ESI+): 504.18 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{27}H_{26}N_3O_7$, 504.1765; found, 504.1767.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(2-naphtyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4s)



4s

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (118.3 mg, 0.67 mmol) with (*Z*)-4-(naphthalene-2-ylmethylene)-2-phenyloxazol-5(4H)-one (**2s**) (100.0 mg, 0.33 mmol) in the presence of (*R*)-DTBM-Segphos (21.7 mg, 18.0 10^{-3} mmol) and AgOAc (2.8 mg, 17.0 10^{-3} mmol) for 13 h afforded, after chromatography (hexane-EtOAc 9:1-7:3), a mixture (87:13) of the cycloadduct **4s** and **5s** (133.5 mg, 79%, pale yellow solid).

M.p.: 75-78ºC.

$[\alpha]_D^{20}$: +94.5 (c=0.3, $CHCl_3$), >99% *ee*.

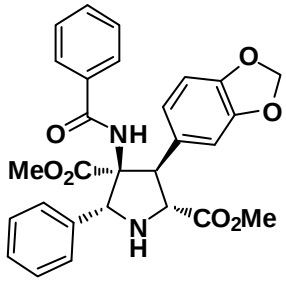
HPLC: Daicel Chiralpak AD, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 254 nm), t_R: 31.2 min (2*R*, 3*S*, 4*S*, 5*R*)-**4s** and 54.5 min (2*S*, 3*R*, 4*R*, 5*S*)-**4s**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.85 – 7.72 (m, 3H), 7.54 – 7.35 (m, 9H), 7.32 – 7.15 (m, 4H), 6.67 (s, 1H), 5.28 (s, 1H), 4.94 (d, *J* = 6.4 Hz, 1H), 4.81 (d, *J* = 6.5 Hz, 1H), 3.83 (s, 3H), 3.36 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 171.9, 167.7, 137.3, 135.3, 134.5, 133.2, 132.6, 131.4, 128.7, 128.6, 128.3, 128.0, 127.9, 127.8, 127.5, 127.0, 126.5, 126.4, 126.0, 125.9, 73.7, 69.2, 65.1, 57.6, 52.5, 52.5.

MS (ESI+): 509.21 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{31}H_{29}N_2O_5$, 509.2070; found, 509.2089.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(1,3-benzodioxol-5-yl)-5-phenylpyrrolidine-2,4-dicarboxylate (4t)



4t

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (60.3 mg, 0.34 mmol) with (Z)-2-phenyl-4-piperonylidene2-oxazoline-5(4H)-one (**2t**) (50.0 mg, 0.17 mmol) in the presence of (*R*)-DTBM-Segphos (11.1 mg, 9.4 10^{-3} mmol), and AgOAc (1.4 mg, 8.50 10^{-3} mmol) for 17 h afforded, after chromatography (hexane-EtOAc 9:1-1:1), a mixture (97:3) of cycloadducts **4t** and **5t** (54.9 mg, 64%, colorless solid).

M.p.: 96-99ºC.

$[\alpha]_D^{20}$: +69.7 (c=0.9, $CHCl_3$), 93% *ee*.

HPLC: Daicel Chiralpak IA, etanol-hexane 20-80, flow rate 0.7 mL/min (λ = 254 nm), t_R: 20.4 min (2*R*, 3*S*, 4*S*, 5*R*)-**4t** and 31.6 min (2*S*, 3*R*, 4*R*, 5*S*)-**4t**.

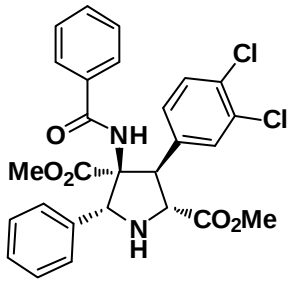
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.32 (m, 3H), 7.30 – 7.20 (m, 7H), 6.76 (s, 1H), 6.74 – 6.68 (m, 1H), 6.61 – 6.56 (m, 1H), 6.54 (s, 1H), 5.77 – 5.74 (m, 2H), 5.06 (s, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.40 (d, *J* = 6.7 Hz, 1H), 3.74 (s, 3H), 3.19 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): 173.8, 171.9, 167.6, 147.5, 146.6, 137.3, 134.7, 131.5, 131.3, 128.5, 128.5, 128.2, 126.7, 126.4, 122.4, 109.4, 108.0, 100.9, 73.6, 69.0, 65.1, 57.3, 52.5, 52.4.

MS (ESI+): 503.18 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{28}H_{27}N_2O7$, 503.1812; found, 503.1811.

(2*R*, 3*R*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(3,4-dichlorophenyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4u)

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (55.6 mg, 0.31 mmol) with (*E*)-4-(3,4-dichlorobenzylidene)-2-phenyloxazol-5(4H)-one (**2u**) (50.0 mg, 0.16 mmol) in the presence of (*R*)-DTBM-Segphos (10.2 mg, 8.6 10^{-3} mmol) and AgOAc (1.3 mg, 7.9 10^{-3} mmol) for 72 h afforded, after chromatography (hexane-EtOAc 9:1-7:3), a mixture (95:5) of the cycloadduct **4u** and **5u** (37.0 mg, 45%, colorless-pink solid).



4u

M.p.: 163-166ºC.

[α]$_D^{20}$: +41.8 (c=0.1, $CHCl_3$), >99% *ee*.

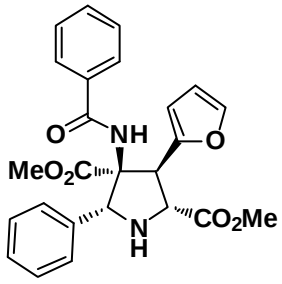
HPLC: Daicel Chiralpak IB, etanol-hexane 5-95, flow rate 0.7 mL/min (λ = 210 nm), t_R: 21.9 min (2*R*, 3*R*, 4*S*, 5*R*)-**4u** and 34.9 min (2*S*, 3*S*, 4*R*, 5*S*)-**4u**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 – 7.06 (m, 13H), 6.63 (s, 1H), 5.01 (s, 1H), 4.64 (d, *J* = 7.1 Hz, 1H), 4.42 (d, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 3.22 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 171.6, 167.5, 137.9, 136.9, 134.1, 132.1, 131.8, 131.3, 130.9, 130.0, 128.7, 128.6, 128.5, 128.5, 126.6, 126.3, 73.4, 69.2, 64.7, 56.5, 52.6, 52.6.

MS (ESI+): 527.1125 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{27}H_{25}N_2O_5Cl_2$, 527.1135; found, 527.1125.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(2-furyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4v)



4v

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (148.0 mg, 0.84 mmol) with (*Z*)-4-(furan-2-ylmethylene)-2-phenyloxazol-5(4H)-one (**2r**) (100.0 mg, 0.42 mmol) in the presence of (*R*)-DTBM-Segphos (27.1 mg, 23.0 10^{-3} mmol), and AgOAc (3.5 mg, 21.0 10^{-3} mmol) for 6.5 h afforded, after chromatography (hexane-EtOAc 9:1-8:2), the cycloadduct **4v** (75.5 mg, 40%, pale yellow solid).

M.p.: 73-76ºC.

[α]$_D^{20}$: +118.0 (c=0.2, $CHCl_3$), >99% *ee*.

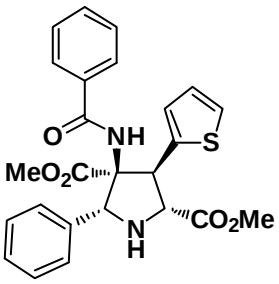
HPLC: Daicel Chiralpak IB, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 254 nm), t_R: 19.8 min (2*S*, 3*R*, 4*R*, 5*S*)-**4v** and 43.3 min (2*R*, 3*S*, 4*S*, 5*R*)-**4v**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 – 7.45 (m, 3H), 7.43 – 7.27 (m, 8H), 6.58 (s, 1H), 6.31 (s, 1H), 6.24 (s, 1H), 5.13 (s, 1H), 4.75 (d, *J* = 6.3 Hz, 1H), 4.66 (d, *J* = 6.3 Hz, 1H), 3.87 (s, 3H), 3.35 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 171.0, 167.7, 151.8, 142.1, 136.5, 134.3, 131.6, 128.6, 128.5, 126.8, 126.4, 110.5, 109.6, 72.6, 69.3, 63.4, 52.5, 52.4, 50.8.

MS (ESI+): 449.17 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{25}H_{26}N_2O_6$, 449.1707; found, 449.1701.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(2-thiophenyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4w)



4w

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (138.7 mg, 0.78 mmol) with (Z)-4-(thiophen-2-ylmethylene)-2-phenyloxazol-5(4H)-one (**2w**) (100.0 mg, 0.39 mmol) in the presence of (*R*)-DTBM-Segphos (25.4 mg, 21.0 10^{-3} mmol) and AgOAc (3.3 mg, 20.0 10^{-3} mmol) for 16 h afforded, after chromatography (hexane-EtOAc 9:1-7:3), the cycloadduct **4w** (111.9 mg, 62%, colorless solid).

M.p.: 87-90ºC.

$[\alpha]_D^{20}$: +80.4 (c=1.6, $CHCl_3$), >99% *ee*.

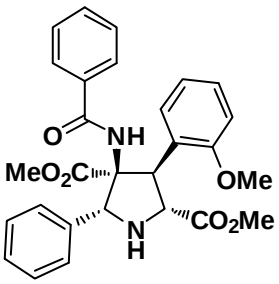
HPLC: Daicel Chiralpak IB, isopropanol-hexane 15-85, flow rate 0.7 mL/min (λ = 254 nm), t_R: 22.2 min (2*R*, 3*S*, 4*S*, 5*R*)-**4w** and 25.4 min (2*S*, 3*R*, 4*R*, 5*S*)-**4w**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 – 7.32 (m, 3H), 7.31 – 7.16 (m, 7H), 7.06 (d, *J* = 5.1 Hz, 1H), 6.94 (d, *J* = 3.6 Hz, 1H), 6.76 (t, *J* = 4.0 Hz, 1H), 6.56 (s, 1H), 5.10 (s, 1H), 4.79 (d, *J* = 6.7 Hz, 1H), 4.60 (d, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 3.21 (s, 3H), 2.80 (bs, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 171.2, 167.8, 140.1, 137.1, 134.5, 131.6, 128.5, 128.4, 127.7, 126.8, 126.7, 126.5, 124.8, 73.3, 68.8, 66.5, 52.6, 52.5, 52.4.

MS (ESI+): 465.15 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{25}H_{25}N_2O_5S$, 465.1478; found, 465.1485.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-(2-methoxyphenyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4x)



4x

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (126.8 mg, 0.72 mmol) with (Z)-4-(2-methoxybenzylidene)-2-phenyloxazol-5(4H)-one (**2x**) (100.0 mg, 0.36 mmol) in the presence of (*R*)-DTBM-Segphos (23.2 mg, 19.7 10^{-3} mmol) and AgOAc (3.0 mg, 17.9 10^{-3} mmol) for 51 h afforded, after chromatography (hexane-EtOAc 9:1), the cycloadduct **4x** (44.3 mg, 25%, colorless solid).

M.p.: 178-181ºC.

$[\alpha]_D^{20}$: -56.7 (c=0.4, $CHCl_3$), 74% *ee*.

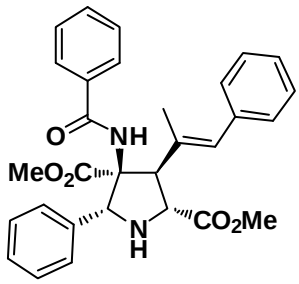
HPLC: Daicel Chiralpak IB, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 254 nm), t_R: 14.4 min (2*S*, 3*R*, 4*R*, 5*S*)-**4x** and 27.4 min (2*R*, 3*S*, 4*S*, 5*R*)-**4x**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.3 Hz, 1H), 7.38 – 7.12 (m, 11H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 5.63 (s, 1H), 5.20 (d, *J* = 10.6 Hz, 1H), 4.24 (d, *J* = 10.6 Hz, 1H), 3.68 (s, 3H), 3.55 (s, 3H), 3.30 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 173.2, 166.8, 156.8, 137.2, 135.3, 131.1, 129.9, 128.4, 128.1, 127.9, 127.4, 126.3, 125.9, 123.9, 120.1, 109.0, 73.9, 65.6, 62.2, 55.0, 54.7, 52.4, 52.3.

MS (ESI+): 489.20 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{28}H_{29}N_2O_6$, 489.2020; found, 489.2036.

(2*R*, 3*S*, 4*S*, 5*R*)-Dimethyl-4-benzamido-3-((*E*)-1-methylcinnamyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4y)



4y

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (**1a**) (61.2 mg, 0.35 mmol) with (Z)-4-(β-methylcinnamylidene)-2-phenyloxazol-5(4H)-one (**2y**) (50.0 mg, 0.17 mmol) in the presence of (*R*)-DTBM-Segphos (11.2 mg, 9.5 10^{-3} mmol) and AgOAc (1.4 mg, 8.6 10^{-3} mmol) for 17 h afforded, after chromatography (hexane-EtOAc 9:1-7:3), a mixture (90:10) of cycloadducts **4y** and **5y** (46.1 mg, 54%, pale yellow solid).

M.p.: 82-85ºC.

$[\alpha]_D^{20}$: +21.5 (c=0.7, $CHCl_3$), 97% *ee*.

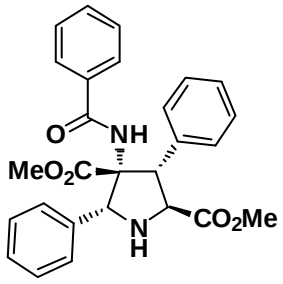
HPLC: Daicel Chiralpak IA, isopropanol-hexane 30-70, flow rate 0.7 mL/min (λ = 254 nm), t_R: 15.4 min (2*R*, 3*S*, 4*S*, 5*R*)-**4y** and 29.2 min (2*S*, 3*R*, 4*R*, 5*S*)-**4y**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.48 – 7.39 (m, 1H), 7.38 – 7.30 (m, 2H), 7.26 – 7.25 (m, 4H), 7.23 – 7.16 (m, 2H), 7.16 – 7.09 (m, 2H), 7.09 – 7.01 (m, 1H), 6.96 (d, *J* = 7.6 Hz, 2H), 6.53 (s, 1H), 5.35 (s, 1H), 4.80 (d, *J* = 8.9 Hz, 1H), 3.78 (s, 3H), 3.77– 3.75 (m, 1H), 3.20 (s, 3H), 1.72 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 172.9, 167.0, 137.7, 137.6, 134.8, 132.2, 131.7, 130.1, 128.9, 128.7, 128.3, 127.9, 126.9, 126.3, 126.1, 73.6, 68.1, 63.1, 61.9, 52.6, 52.4, 18.3.

MS (ESI+): 499.22 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{30}H_{31}N_2O_5$, 499.2227; found, 499.2237.

(2*S, 3*R**, 4*R**, 5*S**)-Dimethyl-4-benzamido-3-phenyl-5-phenylpyrrolidine-2,4-dicarboxylate (6a)**



6a

To a solution of (*R*)-Tol-Binap (6.0 mg, 9.0 10^{-3} mmol), AgOAc (1.4 mg, 8.0 10^{-3} mmol) and (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (20.0 mg, 0.08 mmol), in tetrahydrofuran (0.5 mL), under nitrogen atmosphere, at room temperature, a solution of (*E*)-*N*-[phenylmethylene]glycinate (**1a**) (22.7 mg, 0.13 mmol) in tetrahydrofuran (0.5 mL) was added. The mixture was stirred for 12 h. The reaction was quenched with HCl 3M in methanol (0.7 mL) at room temperature afforded, after work-up and purification by silica gel flash chromatography (hexane-EtOAc 9:1-8:2), the cycloadduct **6a** (20.0 mg, 55%, colorless solid).

M.p.: 143-146 ºC.

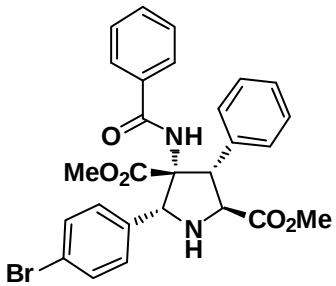
HPLC: Daicel Chiralpak IC, isopropanol-hexane 20-80, flow rate 0.7 mL/min (λ = 210 nm), t_R: 33.8 min (2*S**, 3*R**, 4*R**, 5*S**)-**6a** and 52.3 min (2*R**, 3*S**, 4*S**, 5*R**)-**6a**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 – 7.40 (m, 4H), 7.40 – 7.20 (m, 4H), 7.18 – 7.01 (m, 5H), 6.86 (d, *J* = 7.2 Hz, 2H), 5.91 (s, 1H), 4.91 (s, 1H), 4.78 (d, *J* = 3.5 Hz, 1H), 4.25 (d, *J* = 3.5 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.09 (bs, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 172.6, 166.0, 139.1, 137.1, 134.1, 131.1, 129.4, 128.7, 128.6, 128.2, 128.0, 127.1, 126.3, 69.9, 68.5, 65.0, 55.3, 52.8, 52.5.

MS (ESI+): 459.1915 ([M+H], 90). **HRMS** (ESI+): Calculated for $C_{27}H_{27}N_2O_5$, 459.1914; found, 459.1915.

(2*S, 3*R**, 4*R**, 5*S**)-Dimethyl-4-benzamido-3-phenyl-5-(4-bromophenyl)pyrrolidine-2,4-dicarboxylate (6c)**



6c

Following the general procedure above, the reaction of (*E*)-*N*-[(4-bromophenyl)methylene]glycinate (**1c**) (205.5 mg, 0.80 mmol) with (4*Z*)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one (**2a**) (100.0 mg, 0.40 mmol) using (*R*)-Tol-Binap (30.0 mg, 44.00 10^{-3} mmol) and AgOAc (6.7 mg, 40.00 10^{-3} mmol) for 12 h afforded, after chromatography (hexane-EtOAc 9:1-8:2) the cycloadduct **6c** (84.4 mg, 39%, colorless solid).

M.p.: 225-227ºC.

HPLC: Daicel Chiralpak AD, etanol-hexane 20-80, flow rate 0.7 mL/min (λ = 254 nm), t_R: 5.3 min (2*S**, 3*R**, 4*R**, 5*R**)-**6c** and 6.8 min (2*R**, 3*S**, 4*S**, 5*S**)-**6c**.

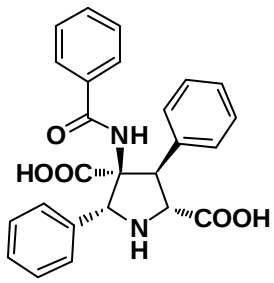
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 – 7.38 (m, 4H), 7.37 – 7.32 (m, 2H), 7.30 – 7.21 (m, 1H), 7.19 (s, 1H), 7.18 – 7.13 (m, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.89 (d, *J* = 7.0 Hz, 2H), 5.88 (s, 1H), 4.92 (s, 1H), 4.67 (d, *J* = 3.9 Hz, 1H), 4.25 (d, *J* = 3.8 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.09 (bs, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 172.2, 166.1, 138.4, 136.2, 133.9, 131.6, 131.3, 129.9, 129.2, 128.3, 128.3, 127.4, 126.3, 122.4, 69.9, 67.8, 64.5, 55.5, 52.9, 52.6.

MS (ESI+): 537.1 ([M+H], 90). **HRMS** (ESI+): Calculated for $C_{27}H_{26}N_2O_5Br$, 537.1019; found, 537.1018.

6. General procedure for hydrolysis of the methylcarboxylates.

(2*R*, 3*S*, 4*S*, 5*R*)- 4-Benzamido-3,5-diphenylpyrrolidine-2,4-dicarboxylic acid (7a)[3]



7a

Cycloadduct **4a** (20.0 mg, 43.6 10^{-3} mmol) was diluted in ethanol (0.3 mL) and a solution of NaOH (10%, 0.3 mL) was added. The solution was stirred at room temperature for 24 h. After solvent evaporation, the residue was taken up with an aqueous solution of HCl (10%, 0.3 mL) and the mixture was extracted for three times with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford compound **7a** (15.9 mg, 85%, colorless solid).

M.p.: 240-243ºC.

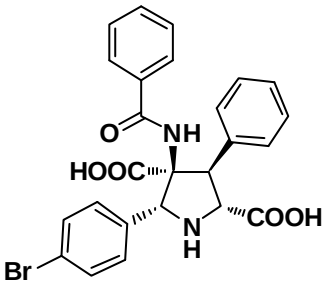
[α]$_D^{20}$: +10.9 (c=0.1, H_2O-Acetone 1:1)

^{1}H NMR (500 MHz, D_2O) δ 7.55 – 7.20 (m, 15H), 5.96 (s, 1H), 5.05 (d, *J* = 9.3 Hz, 1H), 4.59 (d, *J* = 9.3 Hz, 1H).

^{13}C NMR (125 MHz, D_2O): δ 173.8, 172.4, 170.2, 136.0, 133.6, 132.1, 130.8, 129.5, 129.4, 129.0, 128.5, 128.2, 127.8, 126.6, 126.4, 71.9, 64.3, 63.2, 55.2.

MS (ESI+): 431.16 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{25}H_{23}N_2O_5$, 431.1601; found, 431.1599.

(2*R*, 3*S*, 4*S*, 5*R*)-4-Benzamido-3-phenyl-5-(4-bromophenyl)pyrrolidine-2,4-dicarboxylic acid (7c)



7c

Following the general procedure, the reaction of cycloadduct **4c** (80 mg, 0.15 mmol) with NaOH (10%, 0.9 mL) in ethanol (0.9 mL) at room temperature for 24 h, afforded after work-up the compound **8c** (61 mg, 80%, colorless solid).

M.p.: 195-200ºC (descomposition)

[α]$_D^{20}$: +72.6 (c=0.2, MeOH)

^{1}H NMR (300 MHz, , methanol-d4) δ 7.66 – 7.59 (m, 2H), 7.57 – 7.48 (m, 2H), 7.48 – 7.15 (m, 10H), 5.79 (s, 1H), 5.21 (d, *J* = 9.3 Hz, 1H), 4.82 (d, *J* = 9.3 Hz, 1H).

^{13}C NMR (75 MHz, methanol-d4) δ 172.6, 170.6, 170.4, 137.0, 135.3, 133.1, 132.9, 132.3, 130.6, 130.3, 129.4, 129.3, 128.9, 128.0, 124.7, 73.1, 66.2, 65.0, 55.8.

MS (ESI+): 509.07 ([M+H], 100). **HRMS** (ESI+): Calculated for $C_{25}H_{22}N_2O_5Br$, 509.0706; found, 509.0719.

7. Preparation of racemic products for HPLC analysis

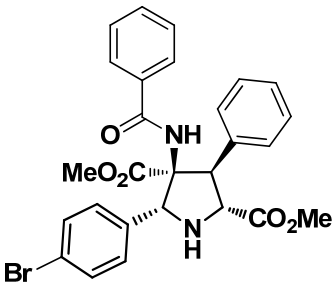
The racemic pyrrolidines were prepared according to the general procedure, but using (±)–DTBM–Segphos or (±)–Tol–Binap as ligand.

The samples for HPLC analysis were dissolved in isopropyl alcohol and used as quickly as possible to minimize the formation of decomposition products

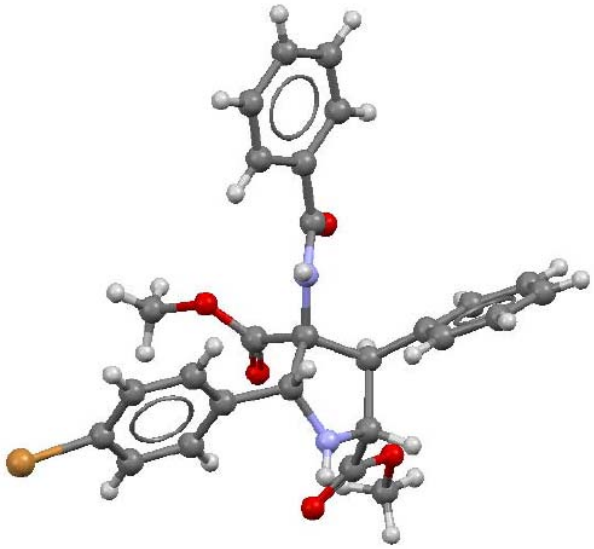
8. Stereochemical assignment

X Ray Structure of 4c

The absolute and relative configuration of (+)-**4c** were unequivocally established by X-ray crystal structure analysis.

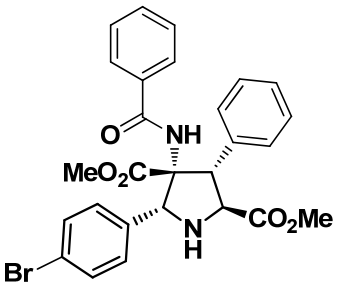


(+)–4c

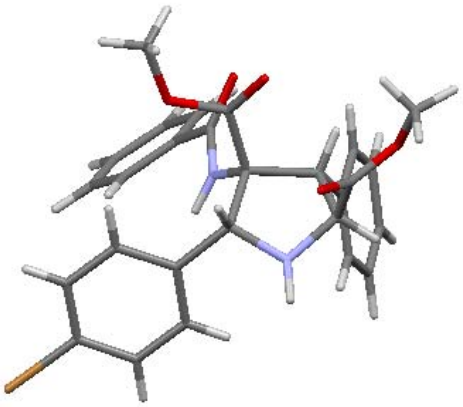


X Ray Structure of 6c

The relative configuration of compound (±)–**6c** was established by X-ray crystal structure analysis.



(±)–6c

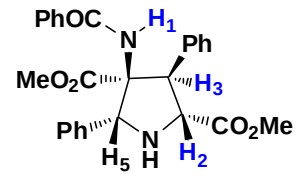


^{1}H NMR comparative study between compound 4a (2,5–*cis*) and compound 6a (2,5–*trans*)

The analysis of the ^{1}H NMR spectra (in $CDCl_3$) of **4a** (H2/H5 in *cis* arrangement) and **6a** (H2/H5 in *trans* arrangement) revealed two significant characteristic signal patterns (Figure 1):

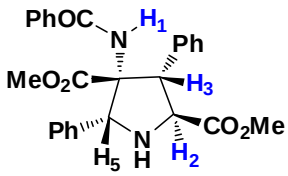
a) The chemical shift of amide proton (H1) in the isomer **4a** (δ = 6.60 ppm) is always higher than in the isomer **6a** (δ = 5.91 ppm).

b) The coupling constant between H2 and H3 is much lower in the case of isomer **6a** ($J_{2,3}$ = 3.5 Hz) that in the isomer **4a** ($J_{2,3}$ = 6.8 Hz)



4a

δ $_{H1}$ = 6.60 ppm, $J_{2,3}$ = 6.8 Hz

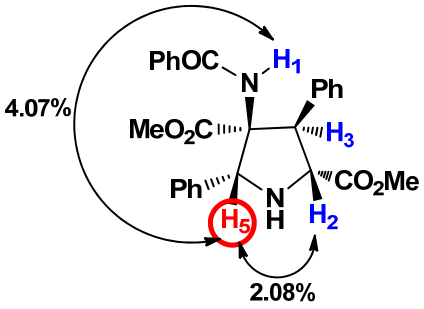


6a

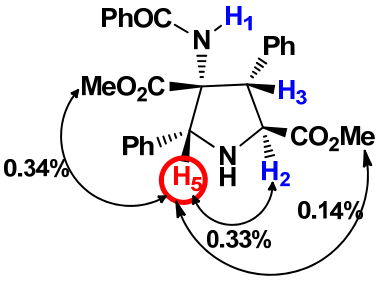
δ $_{H1}$ = 5.91 ppm, $J_{2,3}$ = 3.5 Hz

Figure 1

The NOE spectrum of adduct **4a** (2,5-*cis* arrangement) shows an important correlation (2.08%) between H5 and H2. As expected, the NOE observed between H5 and H2 in pyrrolicine **6a** (2,5-*trans* arrangement) is significantly lower (0.33%) (Figure 2). In addition, an important correlation between H1 and H5 (4.07%) was detected in **4a** but was not observed in compound **6a**. On the other hand, a correlation between the proton H5 and the protons of esters groups (0.34% and 0.14%) was observed in adduct **6a**. (Figure 2).



4a

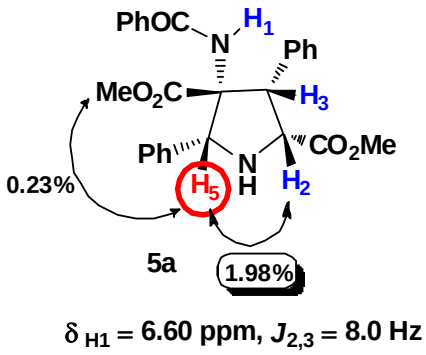


6a

Figure 2

On the basis of these results, the relative configuration of compound **5a** was stablished by NMR experiments. As shown in Figure 3, in the NOE spectrum of compound **5a** a strong cross-peak between H5/H2 (1.98%) was observed. This value indicates a *cis* arrangement of H5 and H2 protons. Furthemore, a NOE correlation (0.23%) between H5 and the ester group at C4 was

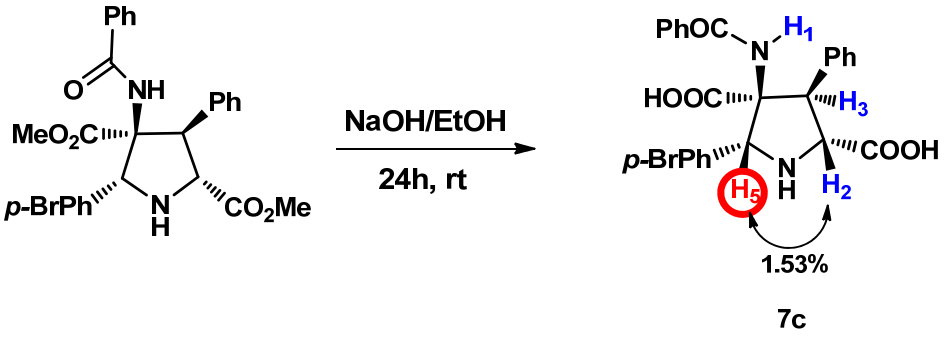
detected. Finally, the δ_{H1} and $J_{2,3}$ parameters observed in compound **5a** fit perfectly well with those found on the adduct **4a**. (compare Figures 1 and 3)



δ_{H1} = 6.60 ppm, $J_{2,3}$ = 8.0 Hz

Figure 3

The NOE spectrum of compound **7c** shows a NOE correlation (1.5%) between H5/H2 which matches with the configuration *cis* of these protons. This result indicates that no epimerization occurs at C2 in the hydrolysis of the methyl esters under basic conditions.



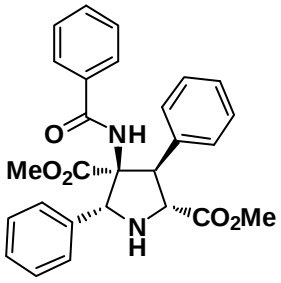
References

1.a) S. Cabrera, R. Gómez Arrayás, J. C. Carretero *J. Am. Chem. Soc.* 2005**, 127**, 16394. b) C. Nájera, M. de Garcia Retamosa, J. M. Sansano *Org. Lett.*, 2007**, 9**, 4025.

2. a) B. M. Trost, P. J. Morris, S. J. Sprague *J. Am. Chem. Soc.* 2012**, 134**, 17823. b) M. B. M. Reddy, M. A. Pasha *Synthetic Communications* 2010, **40**, 1895. c) P. A. Conway, K. Devine, F. Paradisi *Tetrahedron* 2009, **65**, 2935. d) B. S. Jursic, S. Sagiraju, D. K. Ancalade, T. Clark, E. D. Stevens *Synthetic Communications* 2007, **37**, 1709 e) S. Paul, P. Nanda, R. Gupta, A. Loupy *Tetrahedron Letters* 2004, **45**, 425. f) H. N. C. Wong, Z. L. Xu, H. M. Chang, C. M. Lee *Synthesis*, 1992, 793.

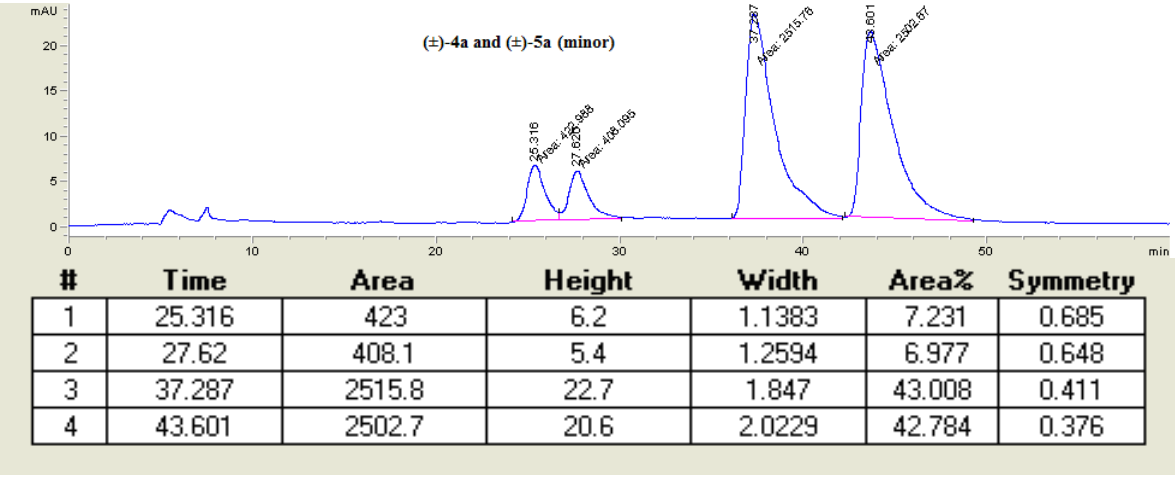
3. F. Clerici, M. L. Gelmi, A. Gambini, D. Nava *Tetrahedron* 2001, **57**, 6429.

9. HPLC charts.



4a

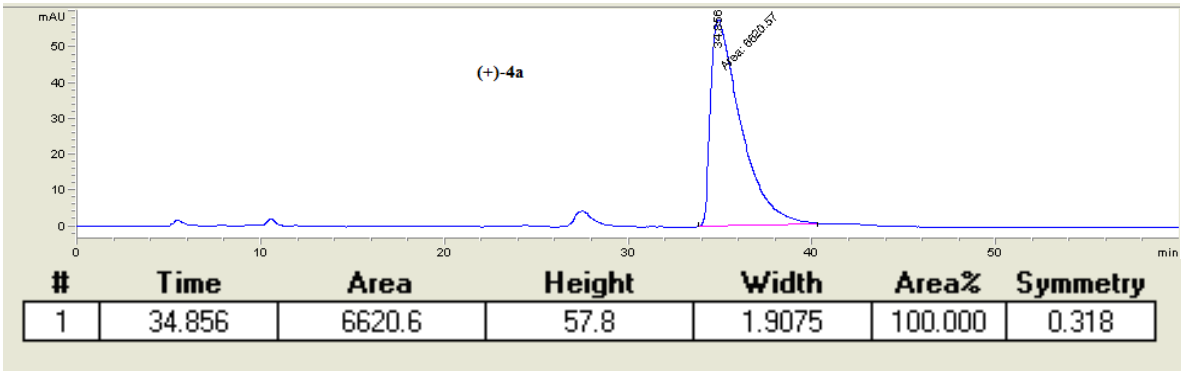
Racemic **4a**



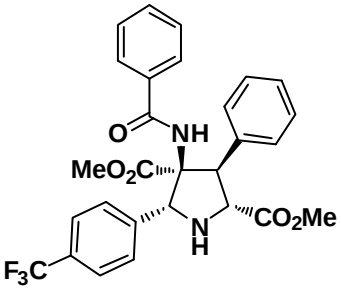
#	Time	Area	Height	Width	Area%	Symmetry
1	25.316	423	6.2	1.1383	7.231	0.685
2	27.62	408.1	5.4	1.2594	6.977	0.648
3	37.287	2515.8	22.7	1.847	43.008	0.411
4	43.601	2502.7	20.6	2.0229	42.784	0.376

Table 1, entry 6.

(+)-4a; ≥ 99% *ee*

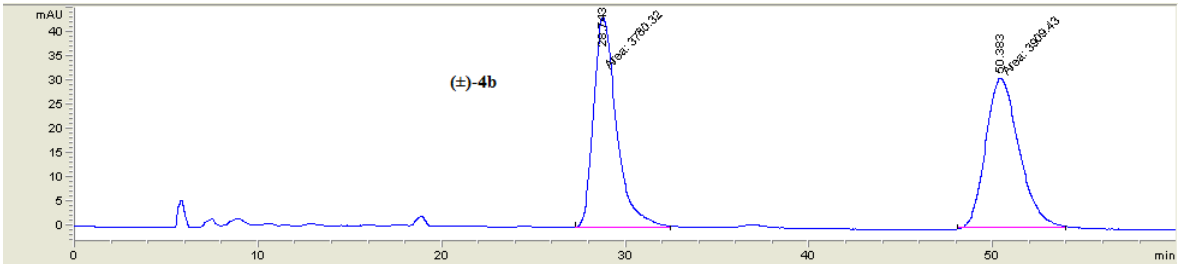


#	Time	Area	Height	Width	Area%	Symmetry
1	34.856	6620.6	57.8	1.9075	100.000	0.318



4b

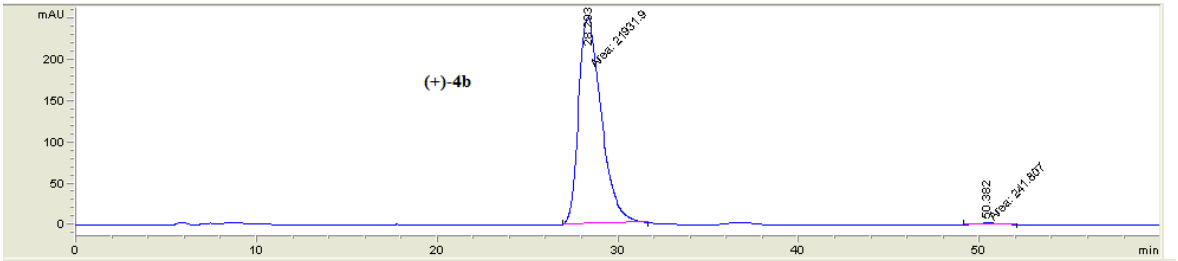
Racemic **4b**



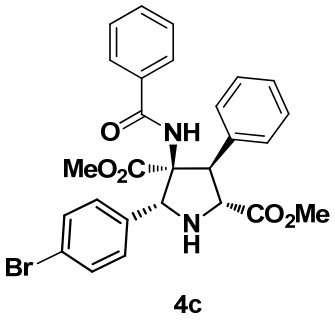
#	Time	Area	Height	Width	Area%	Symmetry
1	28.743	3780.3	43.4	1.4528	49.161	0.676
2	50.383	3909.4	31.1	2.0983	50.839	0.776

Table 2, entry 1.

(+)-4b; 98% *ee*

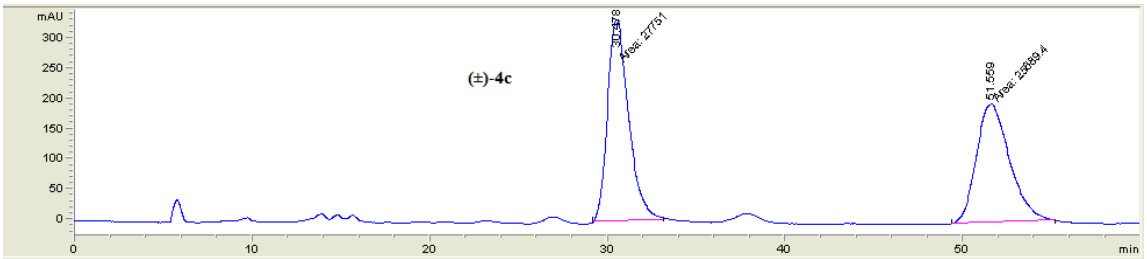


#	Time	Area	Height	Width	Area%	Symmetry
1	28.293	21931.9	250.5	1.4591	98.909	0.637
2	50.382	241.8	2.2	1.8598	1.091	0.741



4c

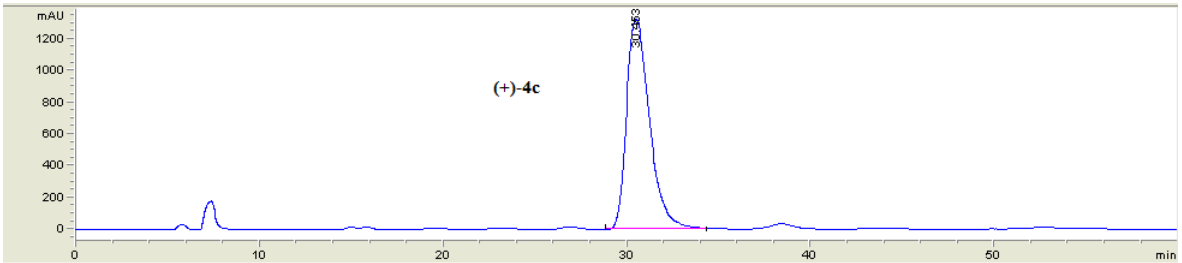
Racemic **4c**



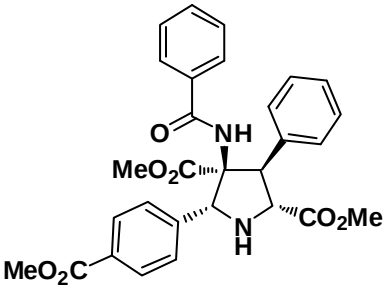
#	Time	Area	Height	Width	Area%	Symmetry
1	30.478	27751	334.3	1.3837	51.929	0.699
2	51.559	25689.4	196.6	2.1778	48.071	0.752

Table 2, entry 2.

(+)-4c; ≥ 99% *ee*

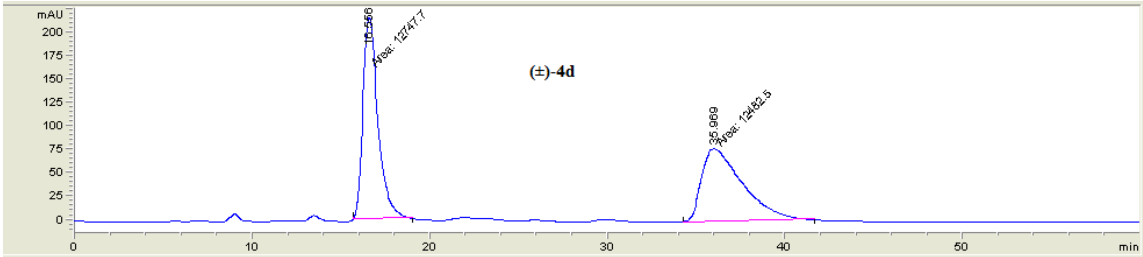


#	Time	Area	Height	Width	Area%	Symmetry
1	30.453	115318	1324	1.0381	100.000	0.622



4d

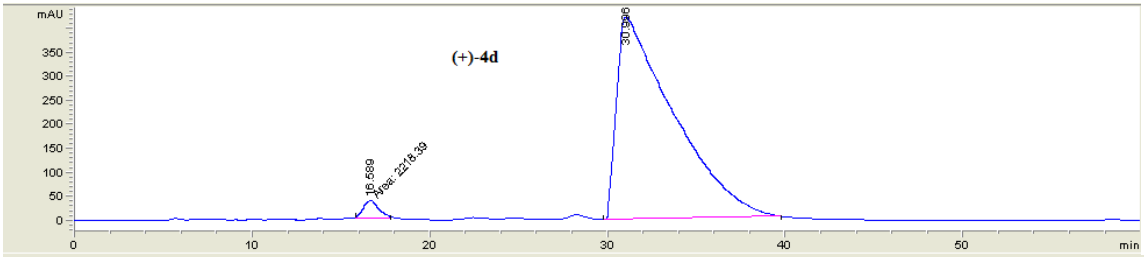
Racemic **4d**



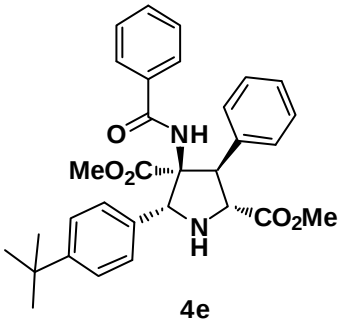
#	Time	Area	Height	Width	Area%	Symmetry
1	16.556	12747.7	215.6	0.9852	50.525	0.682
2	35.969	12482.5	77.5	2.6831	49.475	0.422

Table 2, entry 3.

(+)-4d; 95% *ee*

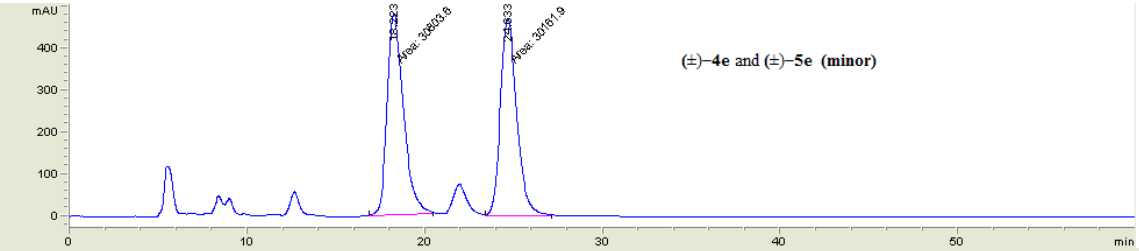


#	Time	Area	Height	Width	Area%	Symmetry
1	16.589	2218.4	35.9	1.0305	2.299	0.757
2	30.996	94286.9	421.3	2.8352	97.701	0.186



4e

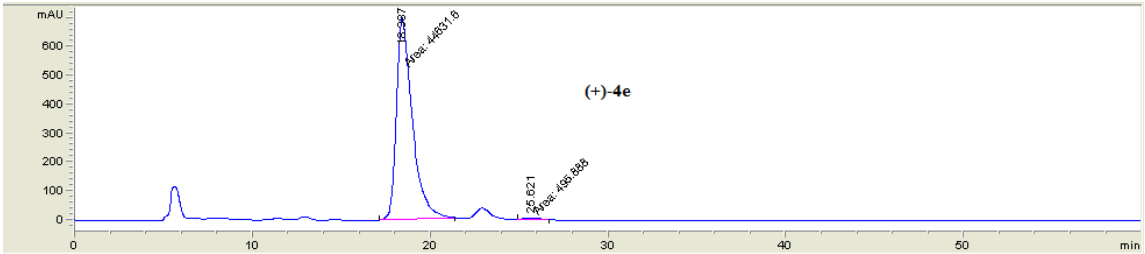
Racemic **4e**



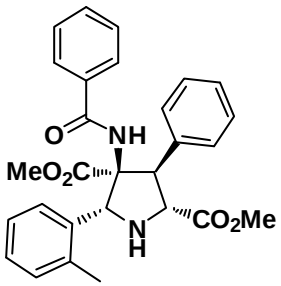
#	Time	Area	Height	Width	Area%	Symmetry
1	18.223	30803.6	479.8	1.0699	50.526	0.649
2	24.633	30161.9	468.1	1.0738	49.474	0.762

Table 2, entry 4.

(+)-4e; 98% *ee*

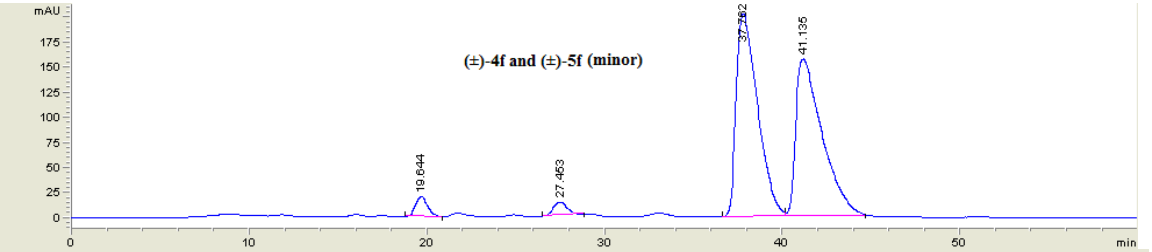


#	Time	Area	Height	Width	Area%	Symmetry
1	18.387	44631.6	704.3	1.0562	98.901	0.54
2	25.621	495.9	7	1.1754	1.099	0.712



4f

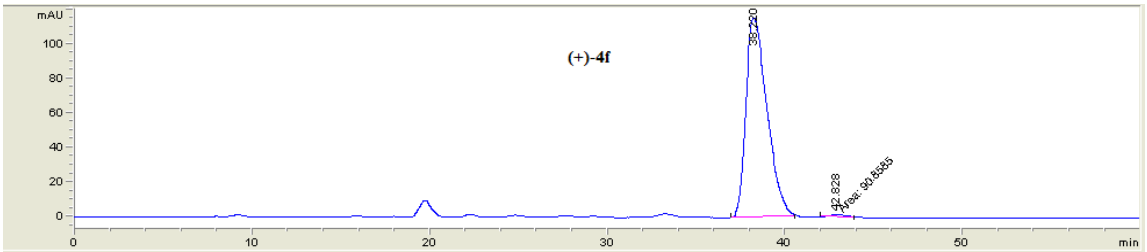
Racemic **4f**



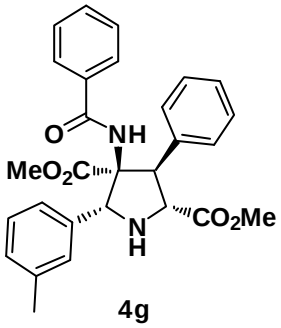
#	Time	Area	Height	Width	Area%	Symmetry
1	19.644	911.5	19.4	0.6709	2.623	0.851
2	27.453	700.2	13	0.6408	2.015	0.934
3	37.762	16925.4	202.3	1.1962	48.703	0.452
4	41.135	16215.1	156.7	1.4374	46.659	0.356

Table 2, entry 5.

(+)-4f; 98% *ee*

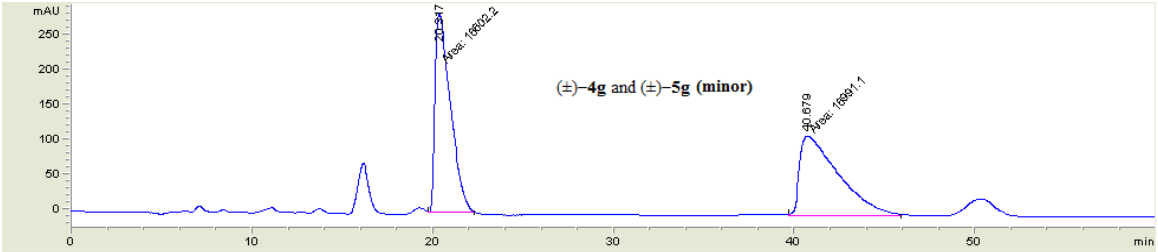


#	Time	Area	Height	Width	Area%	Symmetry
1	38.22	9510.4	115.1	1.1903	99.054	0.571
2	42.828	90.9	1.3	1.1825	0.946	0.62



4g

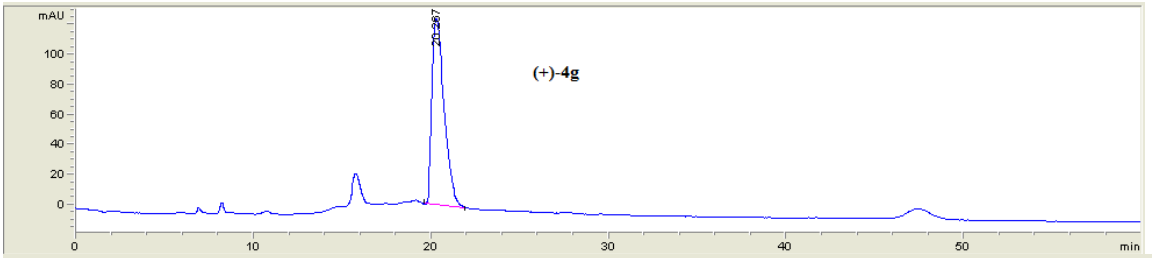
Racemic **4g**



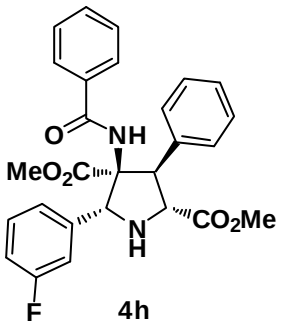
#	Time	Area	Height	Width	Area%	Symmetry
1	20.317	16602.2	283.6	0.9758	49.421	0.337
2	40.679	16991.1	113.7	2.49	50.579	0.232

Table 2, entry 6.

(+)-4g; ≥ 99% *ee*

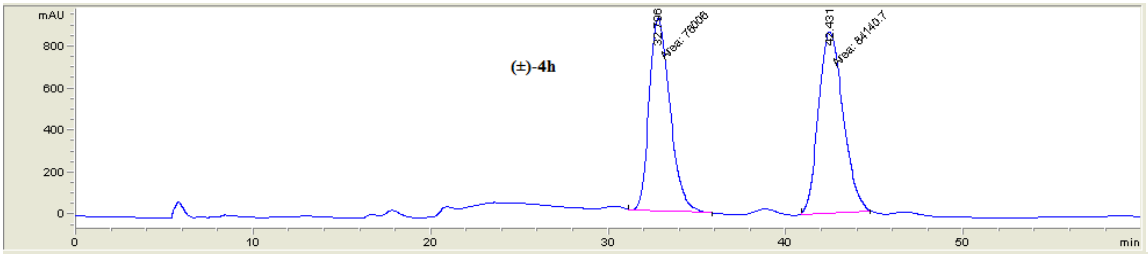


#	Time	Area	Height	Width	Area%	Symmetry
1	20.267	5921.4	124.4	0.6893	100.000	0.493



4h

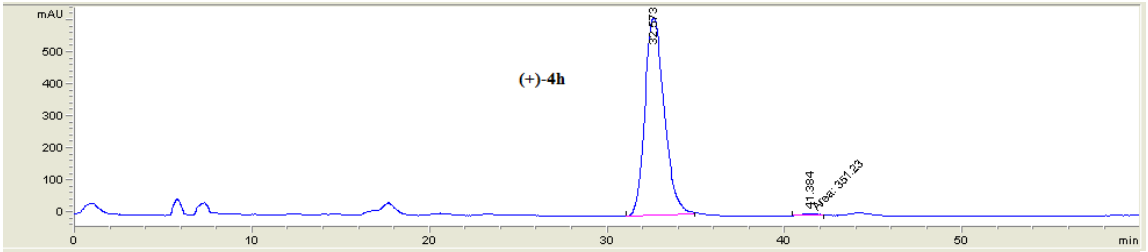
Racemic **4h**



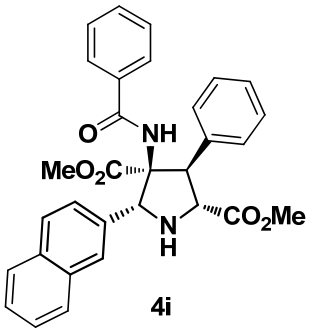
#	Time	Area	Height	Width	Area%	Symmetry
1	32.796	76006	922.2	1.3737	47.460	0.779
2	42.431	84140.7	864.7	1.6217	52.540	0.797

Table 2, entry 7.

(+)-4h; 99% *ee*

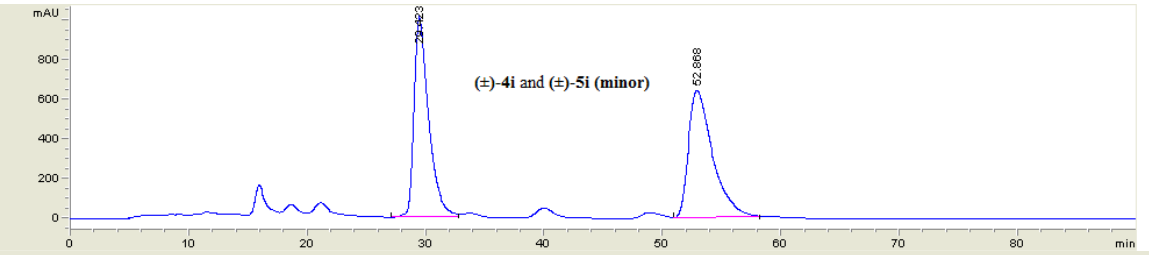


#	Time	Area	Height	Width	Area%	Symmetry
1	32.573	47243.8	620.1	0.8968	99.262	0.76
2	41.384	351.2	5.7	1.0318	0.738	0.965



4i

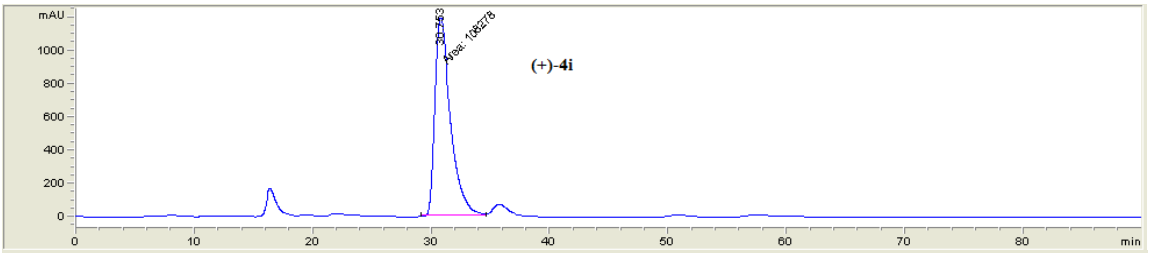
Racemic **4i**



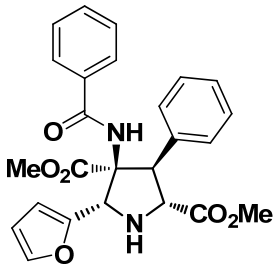
#	Time	Area	Height	Width	Area%	Symmetry
1	29.423	89258.4	1015.6	1.1774	49.689	0.538
2	52.868	90376.8	639.5	1.6627	50.311	0.519

Table 2, entry 8.

(+)-4i; ≥ 99% *ee*

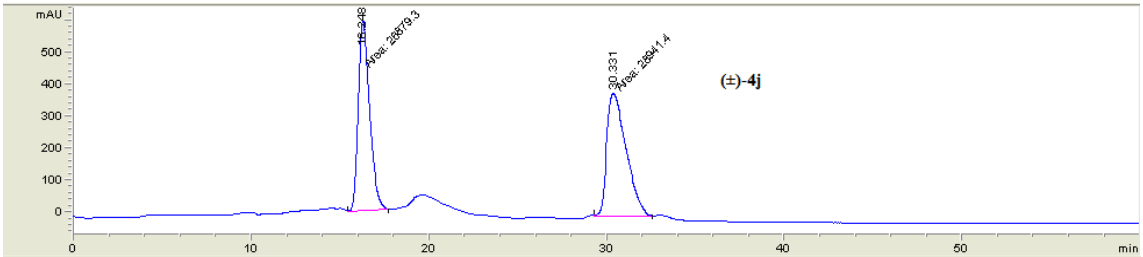


#	Time	Area	Height	Width	Area%	Symmetry
1	30.753	108277.6	1187.7	1.5194	100.000	0.528



4j

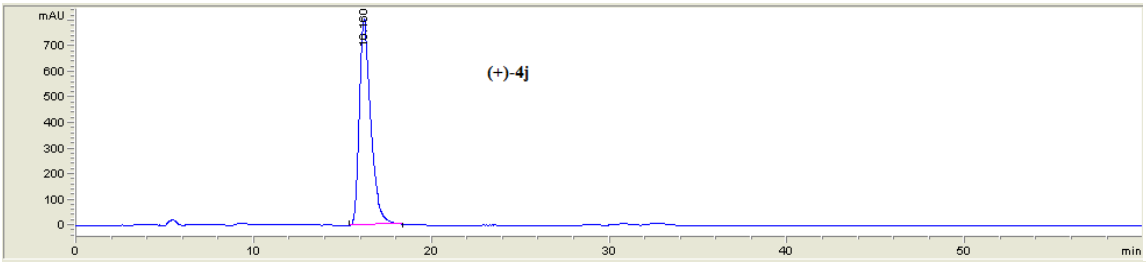
Racemic **4j**



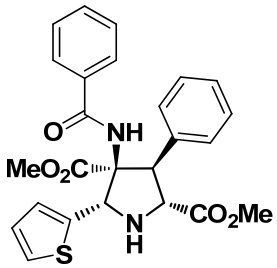
#	Time	Area	Height	Width	Area%	Symmetry
1	16.248	26879.3	605	0.7405	48.153	0.67
2	30.331	28941.4	382.2	1.262	51.847	0.473

Table 2, entry 9.

(+)-4j; ≥ 99% *ee*

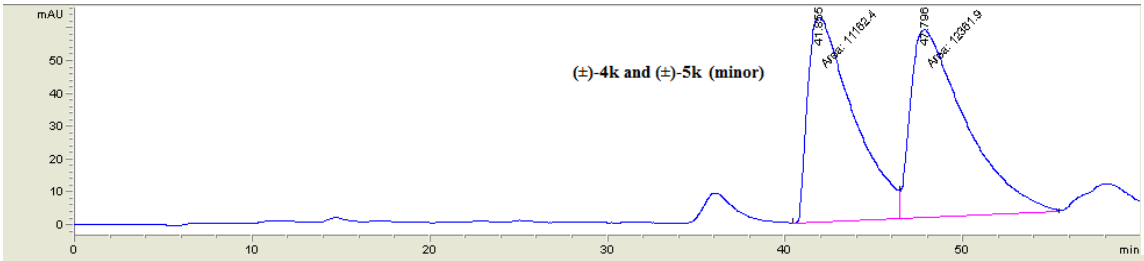


#	Time	Area	Height	Width	Area%	Symmetry
1	16.16	36369.5	807.1	0.6777	100.000	0.609



4k

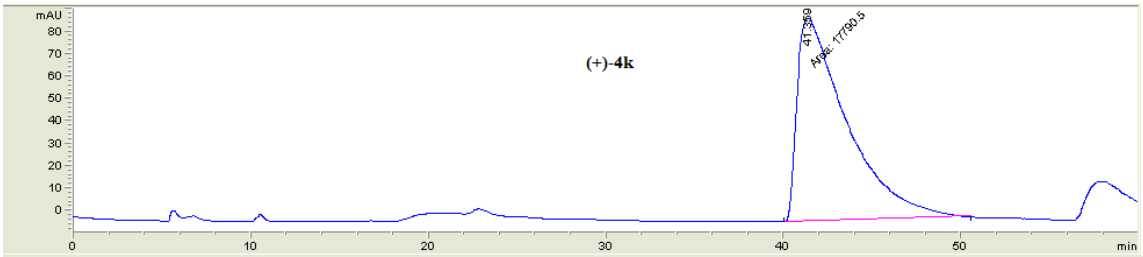
Racemic **4k**



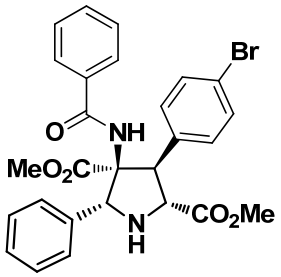
#	Time	Area	Height	Width	Area%	Symmetry
1	41.855	11162.4	62.4	2.9798	47.451	0
2	47.796	12361.9	57.2	3.6039	52.549	0.328

Table 2, entry 10.

(+)-4k; ≥ 99% *ee*

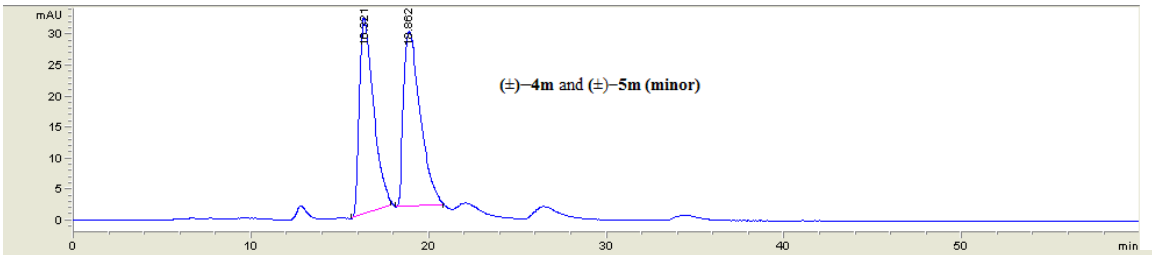


#	Time	Area	Height	Width	Area%	Symmetry
1	41.359	17790.5	90.9	3.2622	100.000	0.272



4m

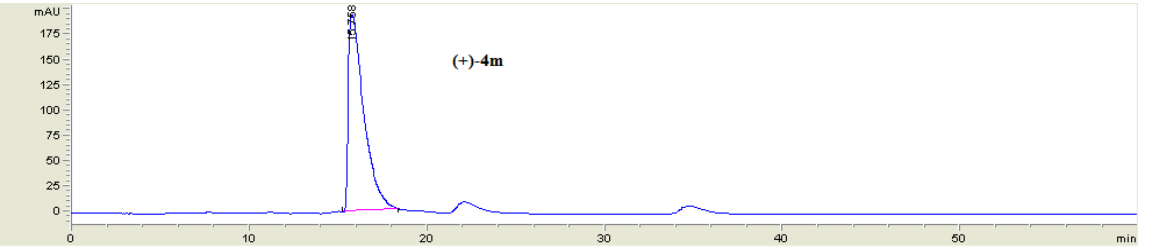
Racemic **4m**



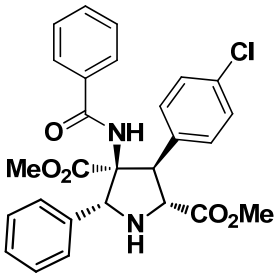
#	Time	Area	Height	Width	Area%	Symmetry
1	16.321	1787	31.7	0.8114	49.052	0.485
2	18.862	1856.1	28.3	0.922	50.948	0.463

Table 3, entry 1.

(+)-4m; ≥ 99% *ee*

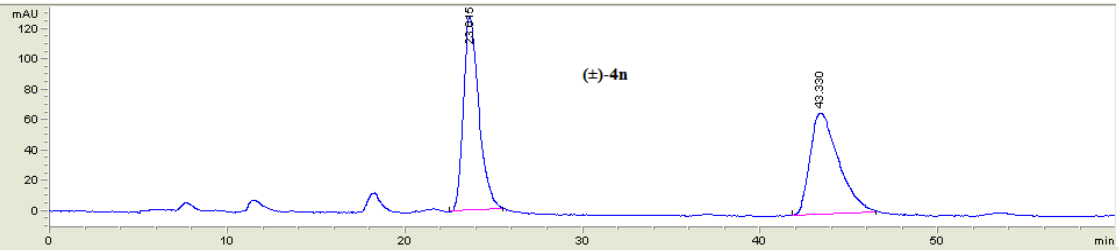


#	Time	Area	Height	Width	Area%	Symmetry
1	15.758	11921.2	194.3	0.8798	100.000	0.316



4n

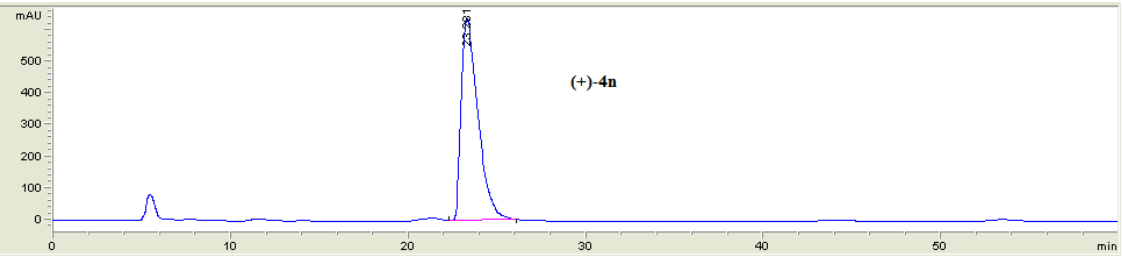
Racemic **4n**



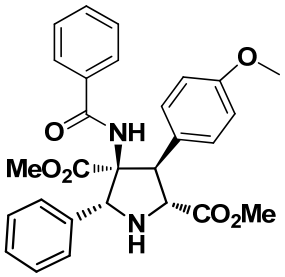
#	Time	Area	Height	Width	Area%	Symmetry
1	23.615	7795	127.7	0.7639	51.025	0.673
2	43.33	7481.9	66.8	1.322	48.975	0.529

Table 3, entry 2.

(+)-4n; ≥ 99% *ee*

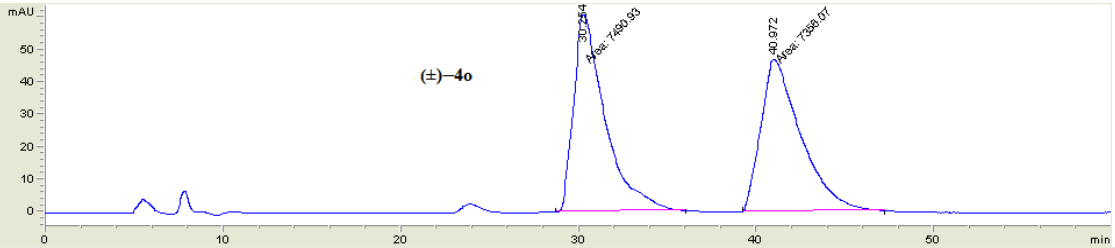


#	Time	Area	Height	Width	Area%	Symmetry
1	23.281	41974.9	638.2	0.8853	100.000	0.477



4o

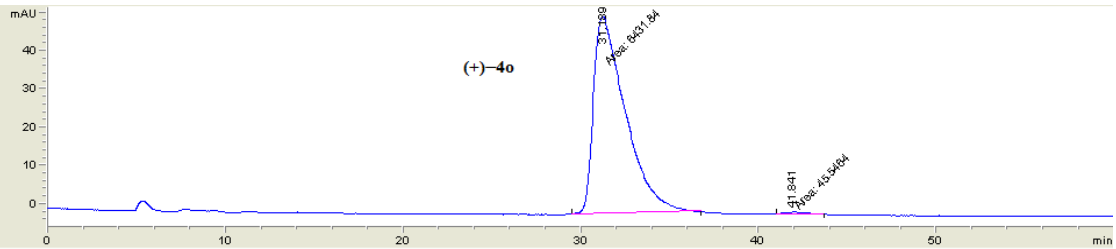
Racemic **4o**



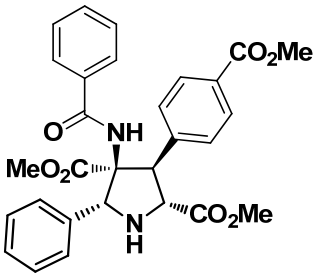
#	Time	Area	Height	Width	Area%	Symmetry
1	30.254	7490.9	60.7	2.0573	50.454	0.449
2	40.972	7356.1	46.9	2.6142	49.546	0.482

Table 3, entry 3.

(+)-4o; 99% *ee*

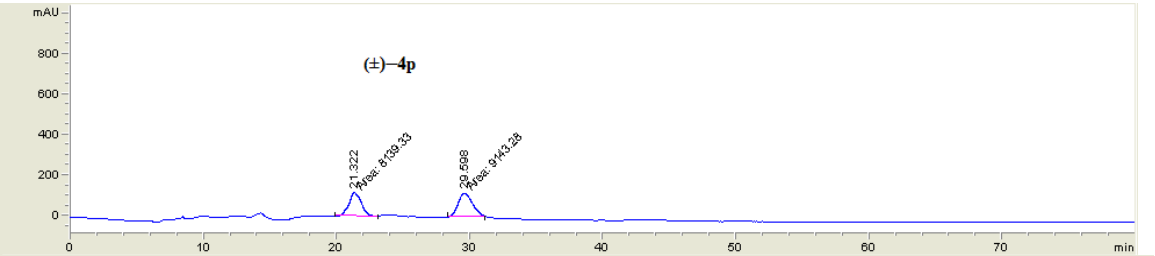


#	Time	Area	Height	Width	Area%	Symmetry
1	31.189	6431.8	51.4	2.0843	99.297	0.387
2	41.841	45.5	5.4E-1	1.4097	0.703	0.527



4p

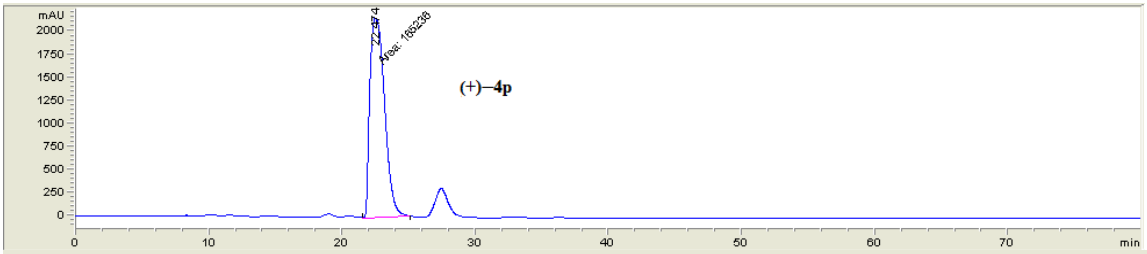
Racemic **4p**



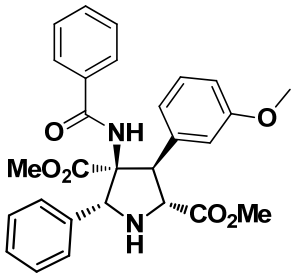
#	Time	Area	Height	Width	Area%	Symmetry
1	21.322	8139.3	117.3	1.1563	47.096	0.711
2	29.598	9143.3	118.3	1.288	52.904	0.874

Table 3, entry 4.

(+)-4p; ≥ 99% *ee*

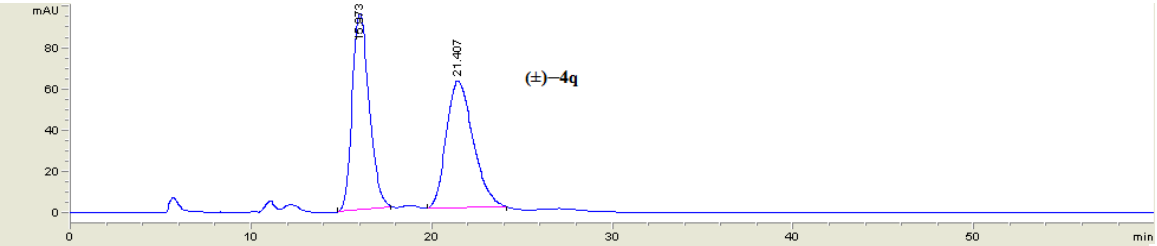


#	Time	Area	Height	Width	Area%	Symmetry
1	22.474	165236.5	2163.8	1.2727	100.000	0.547



4q

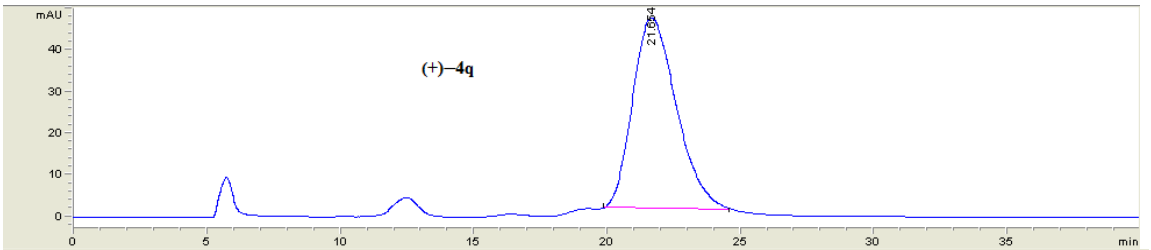
Racemic **4q**



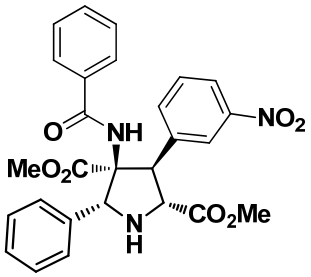
#	Time	Area	Height	Width	Area%	Symmetry
1	15.973	6251.5	95.4	1.0147	49.443	0.756
2	21.407	6392.4	61.6	1.467	50.557	0.724

Table 3, entry 5.

(+)-4q; ≥ 99% *ee*

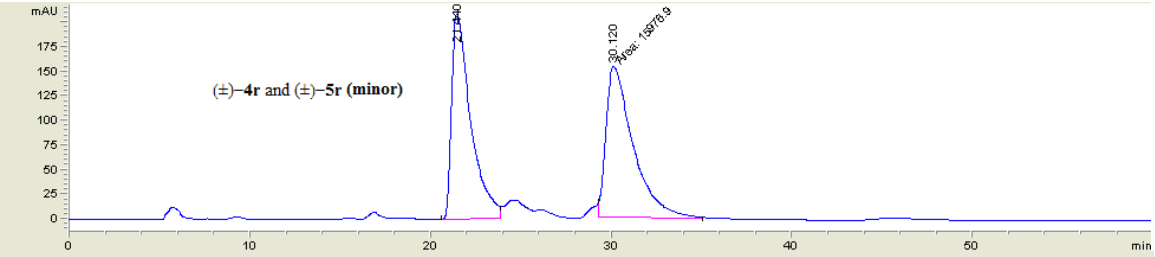


#	Time	Area	Height	Width	Area%	Symmetry
1	21.654	5229.8	45.8	1.5515	100.000	0.732



4r

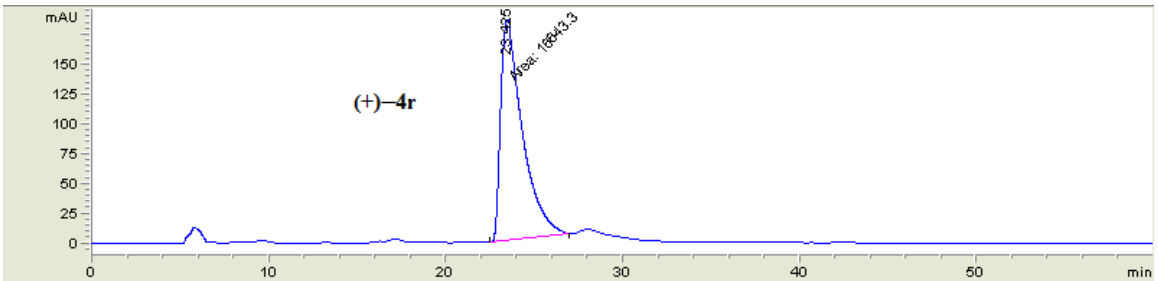
Racemic **4r**



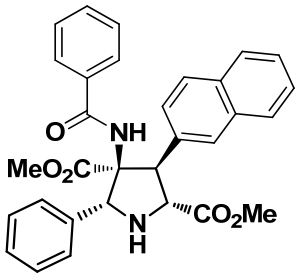
#	Time	Area	Height	Width	Area%	Symmetry
1	21.44	15512	208.8	1.0688	49.262	0.385
2	30.12	15976.9	152.9	1.741	50.738	0.396

Table 3, entry 6.

(+)-4r; ≥ 99% *ee*

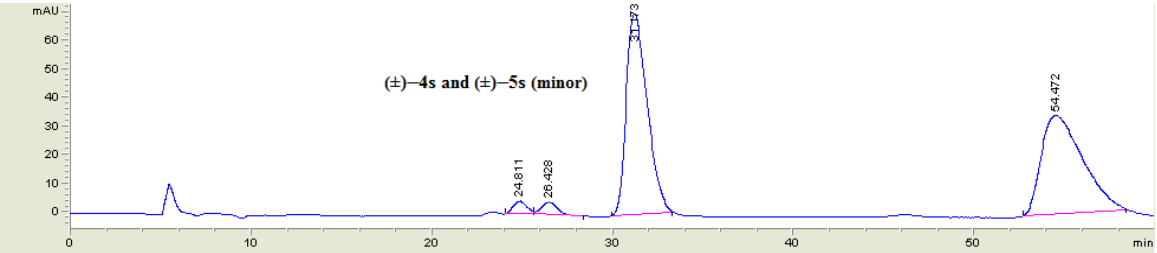


#	Time	Area	Height	Width	Area%	Symmetry
1	23.425	16643.3	186.2	1.4894	100.000	0.402



4s

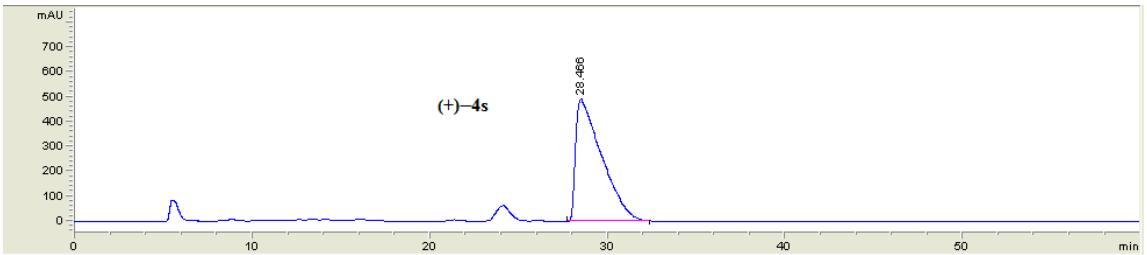
Racemic **4s**



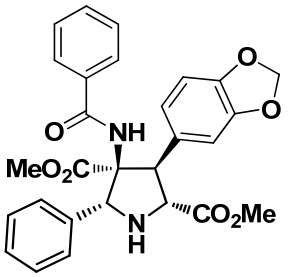
#	Time	Area	Height	Width	Area%	Symmetry
1	24.811	235.5	4.5	0.6161	2.014	0.768
2	26.428	272.8	4.5	0.7182	2.333	0.846
3	31.173	5692.3	70.3	1.151	48.675	0.604
4	54.472	5493.8	34.5	1.875	46.978	0.504

Table 3, entry 7.

(+)-4s; ≥ 99% *ee*

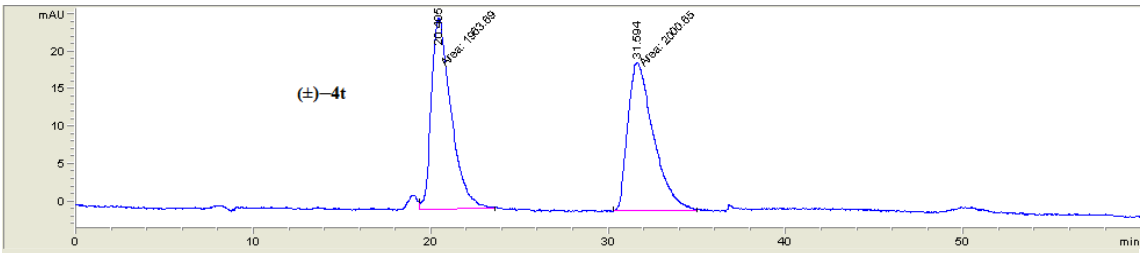


#	Time	Area	Height	Width	Area%	Symmetry
1	28.466	50043.3	492.8	1.4026	100.000	0.226



4t

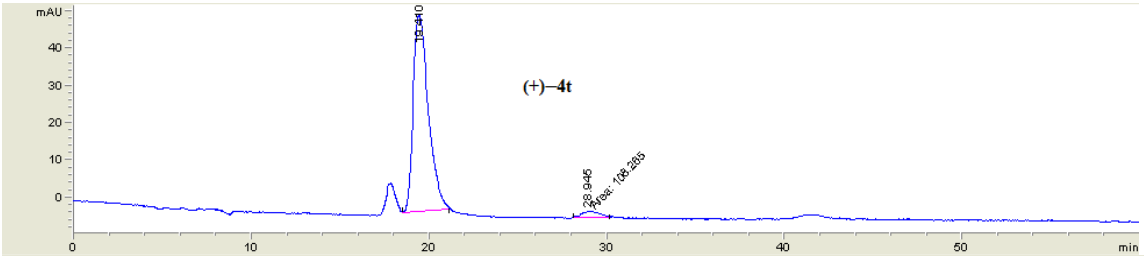
Racemic **4t**



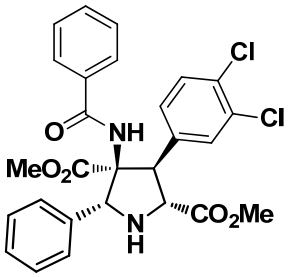
#	Time	Area	Height	Width	Area%	Symmetry
1	20.405	1963.7	25.5	1.2821	49.534	0.562
2	31.594	2000.6	19.8	1.6854	50.466	0.564

Table 3, entry 8.

(+)-4t; 93% *ee*

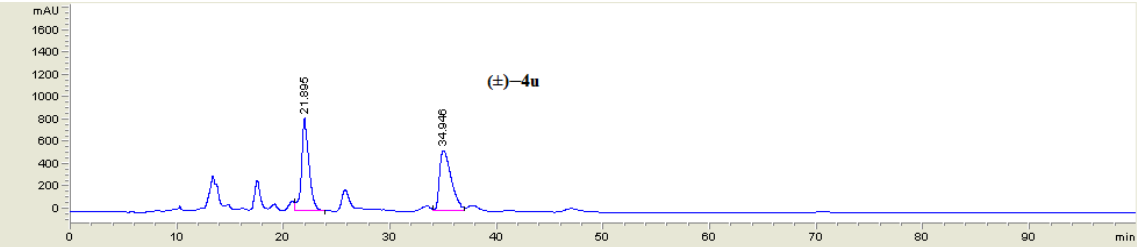


#	Time	Area	Height	Width	Area%	Symmetry
1	19.41	3159.6	52.8	0.7299	96.687	0.596
2	28.945	108.3	1.6	1.1466	3.313	0.613



4u

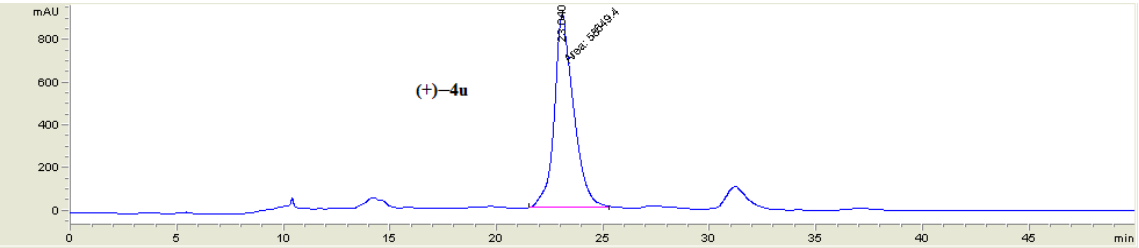
Racemic **4u**



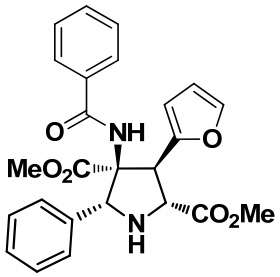
#	Time	Area	Height	Width	Area%	Symmetry
1	21.895	43686.2	829	0.8088	50.891	0.605
2	34.946	42156.8	549.2	1.1536	49.109	0.469

Table 3, entry 9.

(+)-4u; ≥99% *ee*

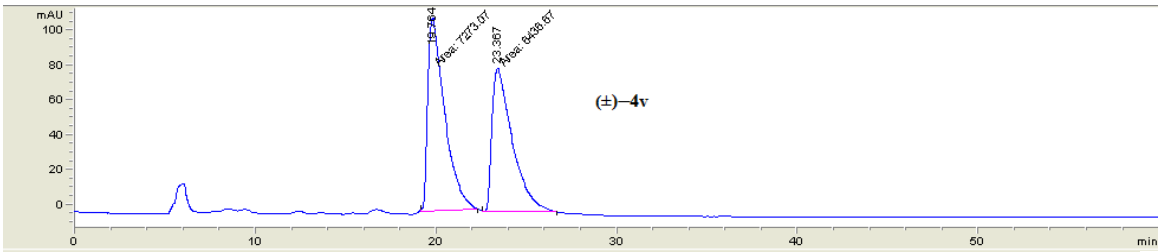


#	Time	Area	Height	Width	Area%	Symmetry
1	23.04	58649.4	904.3	1.0809	100.000	0.65



4v

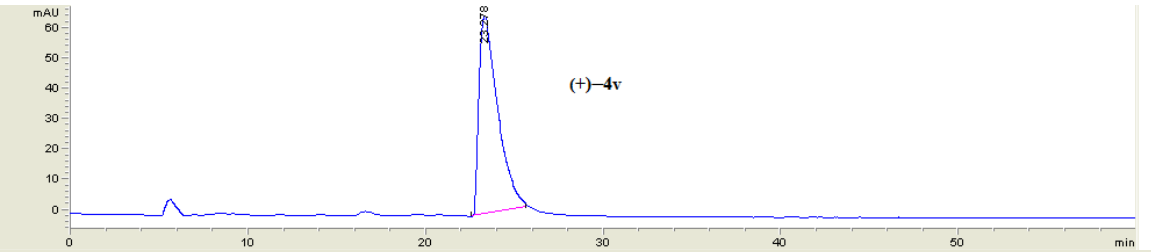
Racemic **4v**



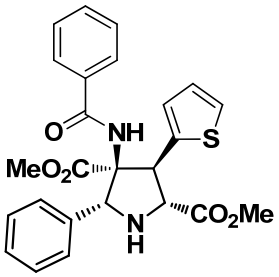
#	Time	Area	Height	Width	Area%	Symmetry
1	19.764	7273.1	110.9	1.0931	53.050	0.365
2	23.367	6436.7	82.3	1.304	46.950	0.353

Table 3, entry 10.

(+)-4v; ≥ 99% *ee*

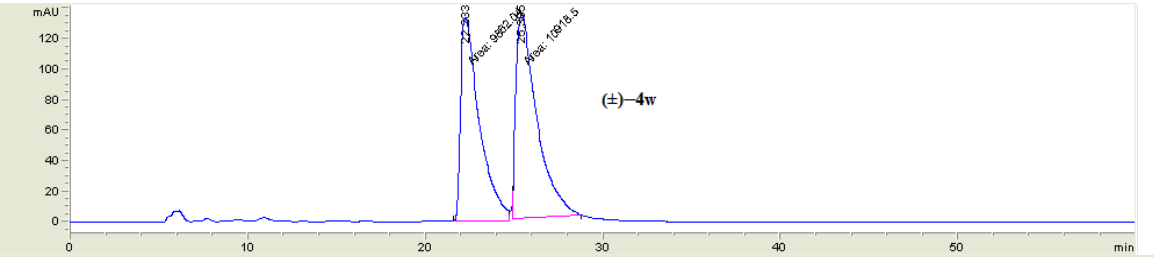


#	Time	Area	Height	Width	Area%	Symmetry
1	23.278	4775.3	65.4	1.042	100.000	0.373



4w

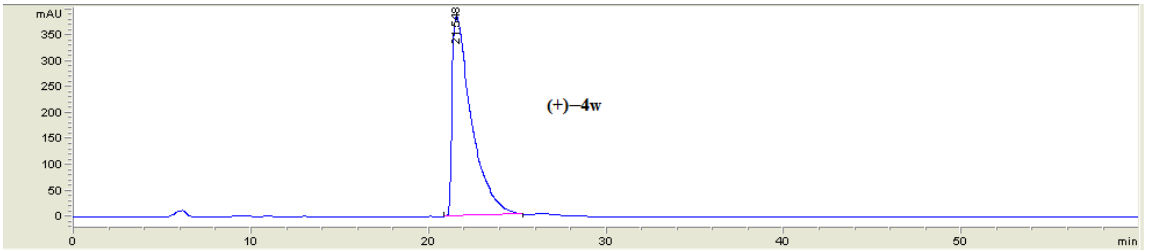
Racemic **4w**



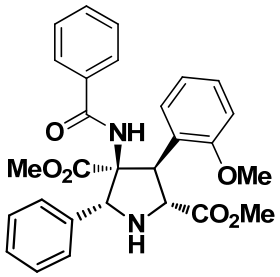
#	Time	Area	Height	Width	Area%	Symmetry
1	22.233	9862	133.3	1.2329	47.458	0.349
2	25.385	10918.5	133.1	1.3672	52.542	0.337

Table 3, entry 11.

(+)-4w; ≥ 99% *ee*

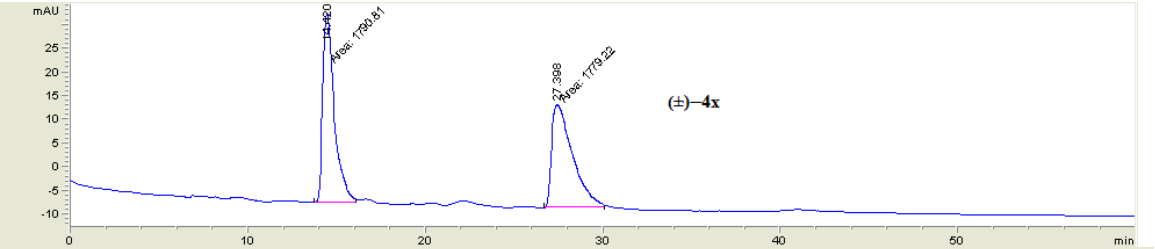


#	Time	Area	Height	Width	Area%	Symmetry
1	21.548	29293.5	384.4	1.095	100.000	0.279



4x

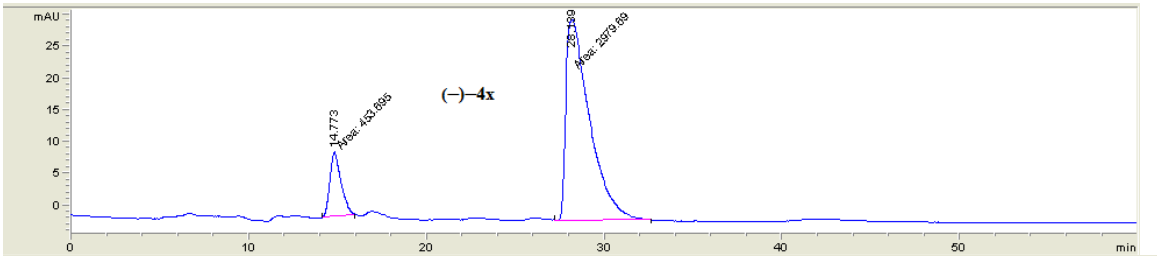
Racemic **4x**



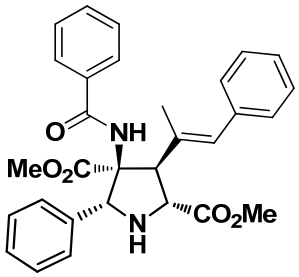
#	Time	Area	Height	Width	Area%	Symmetry
1	14.42	1790.8	39.7	0.7521	50.162	0.546
2	27.398	1779.2	21.7	1.3687	49.838	0.369

Table 3, entry 12.

(-)-4x; 74% *ee*

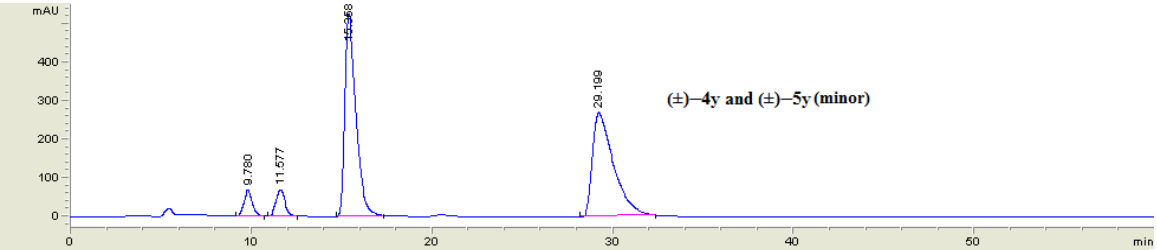


#	Time	Area	Height	Width	Area%	Symmetry
1	14.773	453.7	10.2	0.7431	13.214	0.624
2	28.139	2979.7	31.8	1.564	86.786	0.323



4y

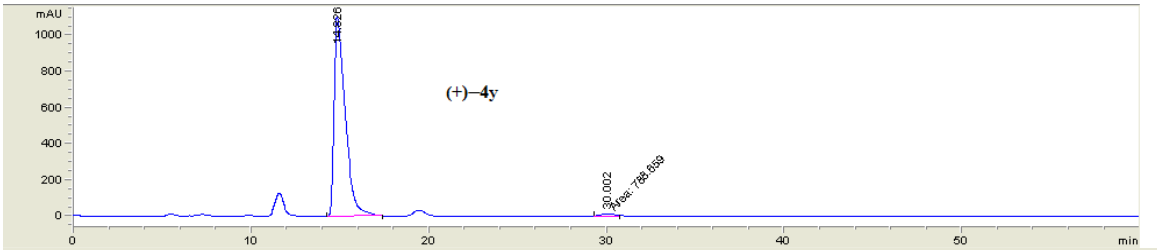
Racemic **4y**



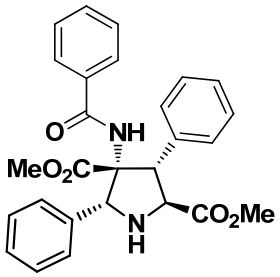
#	Time	Area	Height	Width	Area%	Symmetry
1	9.78	2216.7	68.4	0.4818	4.538	0.889
2	11.577	2328.8	68.5	0.5169	4.767	0.882
3	15.358	22428.2	526.3	0.6492	45.911	0.499
4	29.199	21877.7	270.5	1.1717	44.784	0.403

Table 3, entry 13.

(+)-4y; 97% *ee*

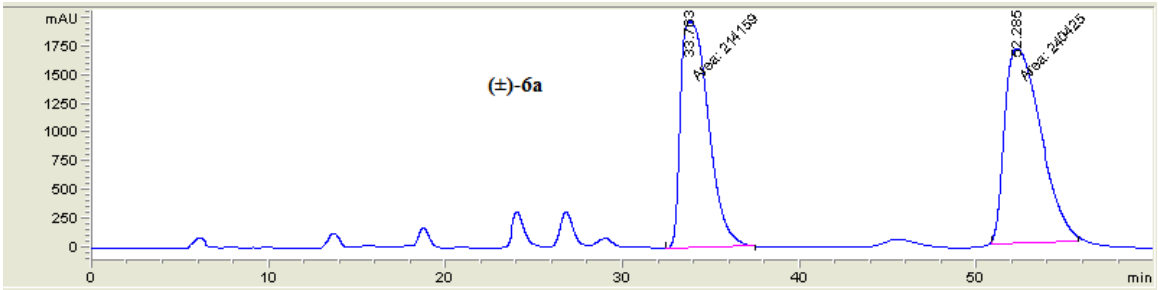


#	Time	Area	Height	Width	Area%	Symmetry
1	14.826	48829	1102.4	0.6427	98.411	0.42
2	30.002	788.7	12.9	1.0196	1.589	0.854



6a

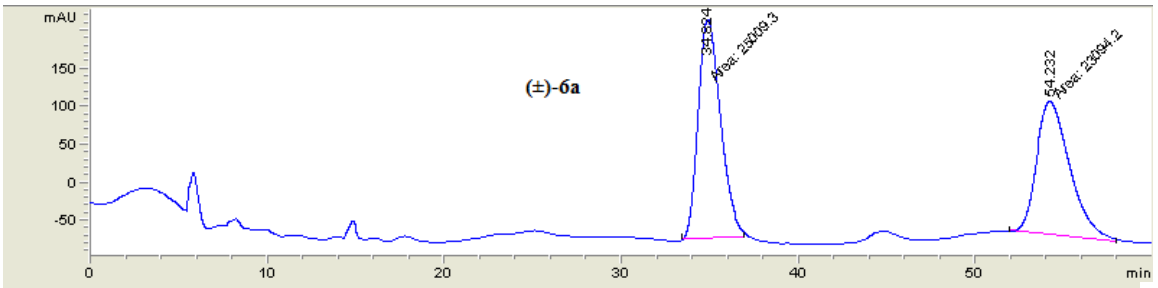
Racemic **6a**



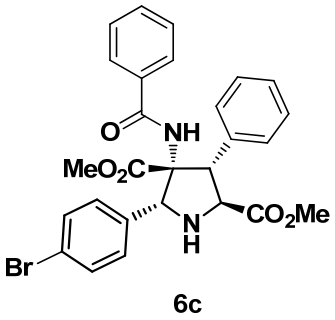
#	Time	Area	Height	Width	Area%	Symmetry
1	33.763	214159.1	1978.2	1.8043	47.111	0.47
2	52.285	240425.2	1693.6	2.366	52.889	0.533

(*R*)–Tol–Binap as ligand

(±)-6a; 0% *ee*

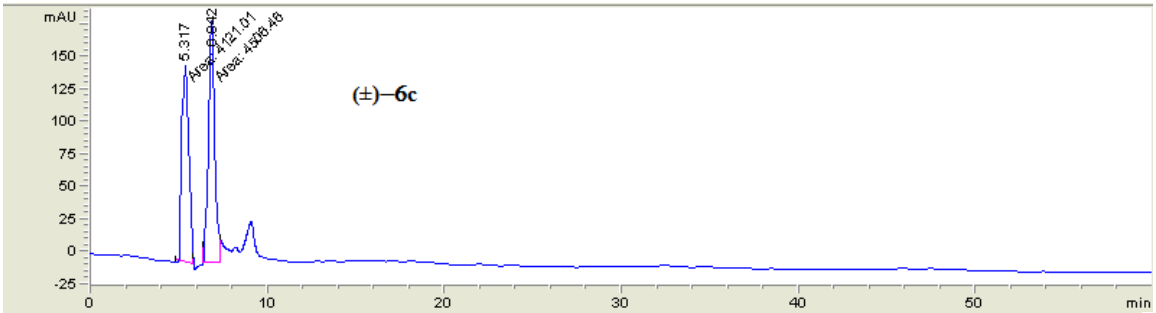


#	Time	Area	Height	Width	Area%	Symmetry
1	34.824	25009.3	287.1	1.4517	51.991	0.695
2	54.232	23094.2	175.9	2.1886	48.009	0.721



6c

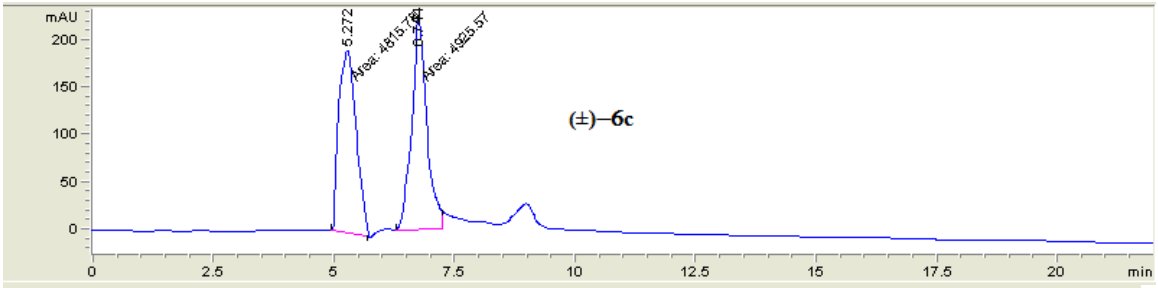
Racemic **6c**



#	Time	Area	Height	Width	Area%	Symmetry
1	5.317	4121	151	0.4548	47.766	1.035
2	6.842	4506.5	186.5	0.4028	52.234	0.982

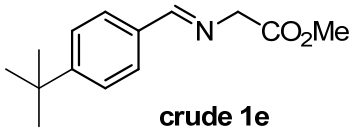
(*R*)–Tol–Binap as ligand

(±)-6c; 0% *ee*

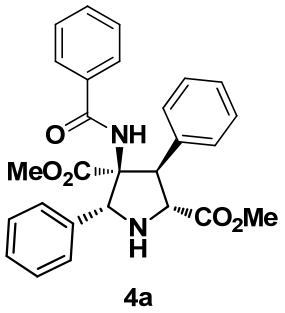


#	Time	Area	Height	Width	Area%	Symmetry
1	5.272	4815.8	192.7	0.4164	49.437	1.018
2	6.744	4925.6	222.7	0.3686	50.563	0.889

10. NMR Spectra collection

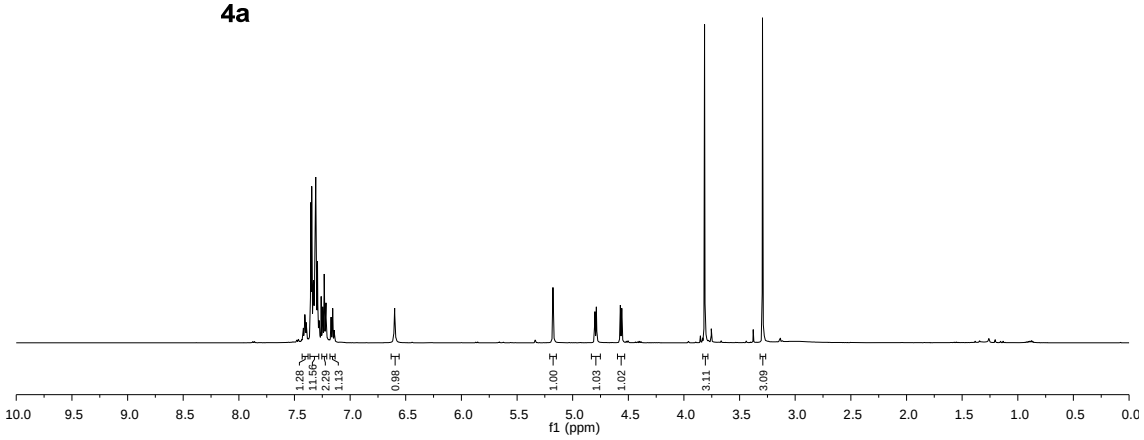


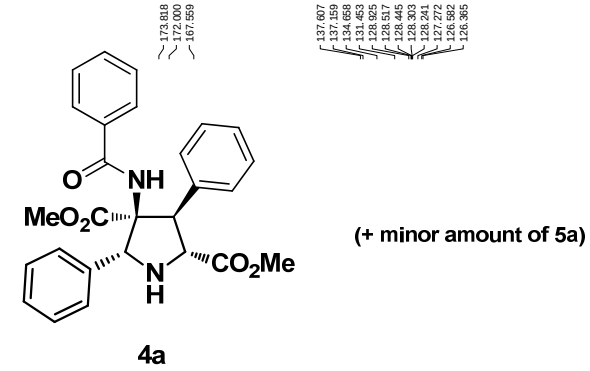
crude 1e



4a

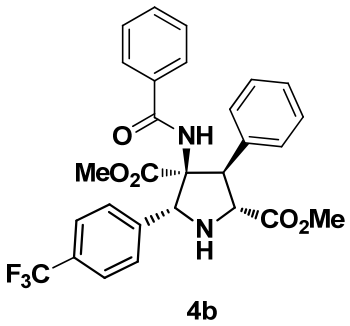
(+ minor amount of 5a)



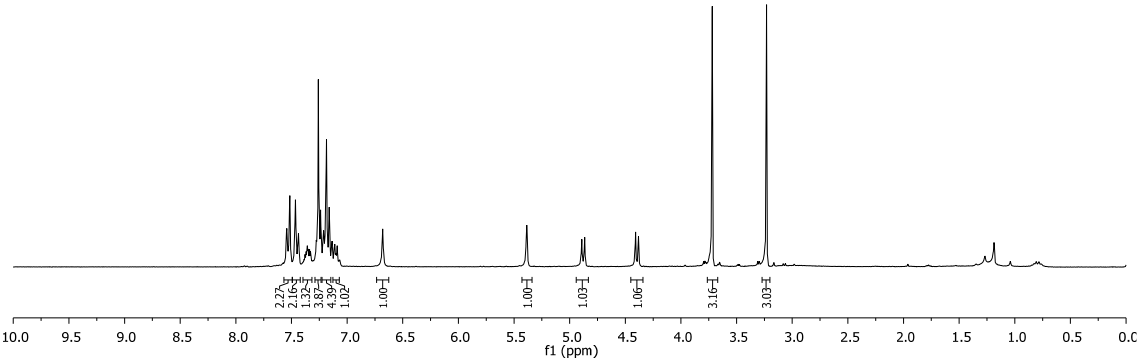


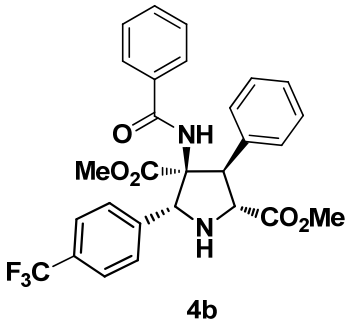
4a

(+ minor amount of 5a)



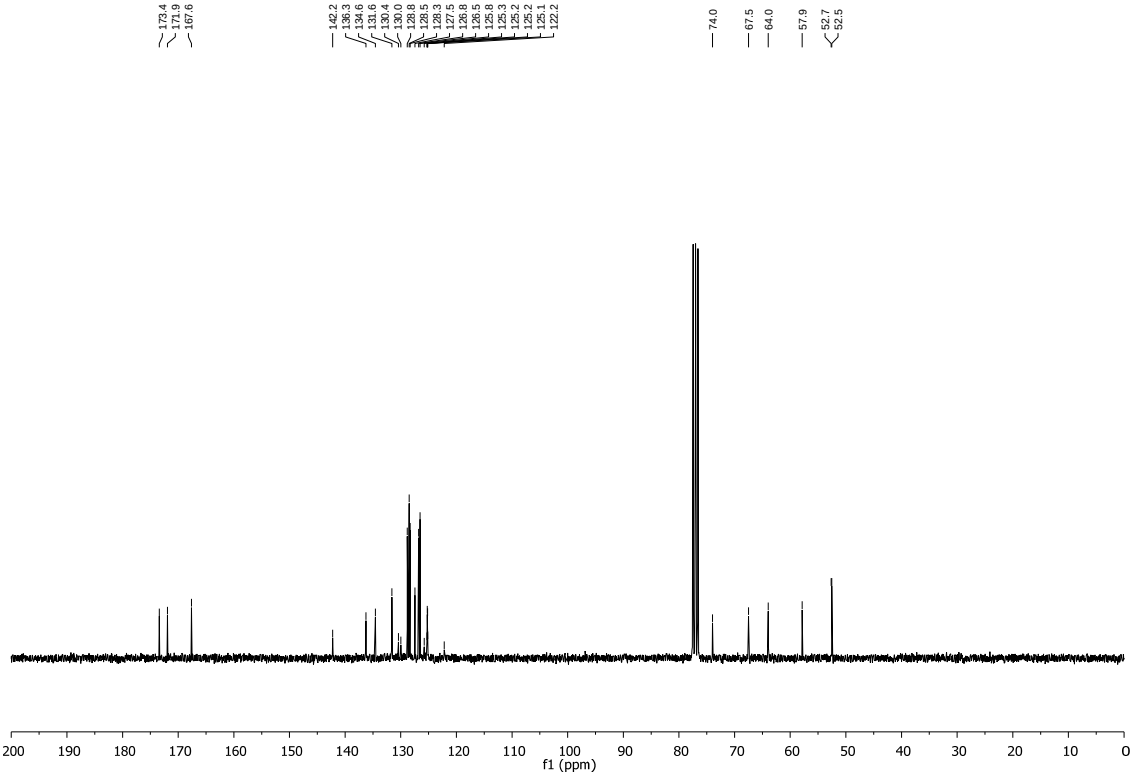
4b

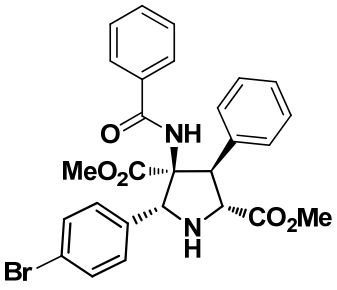



O
NH
MeO2C
CO2Me
N
H
F3C

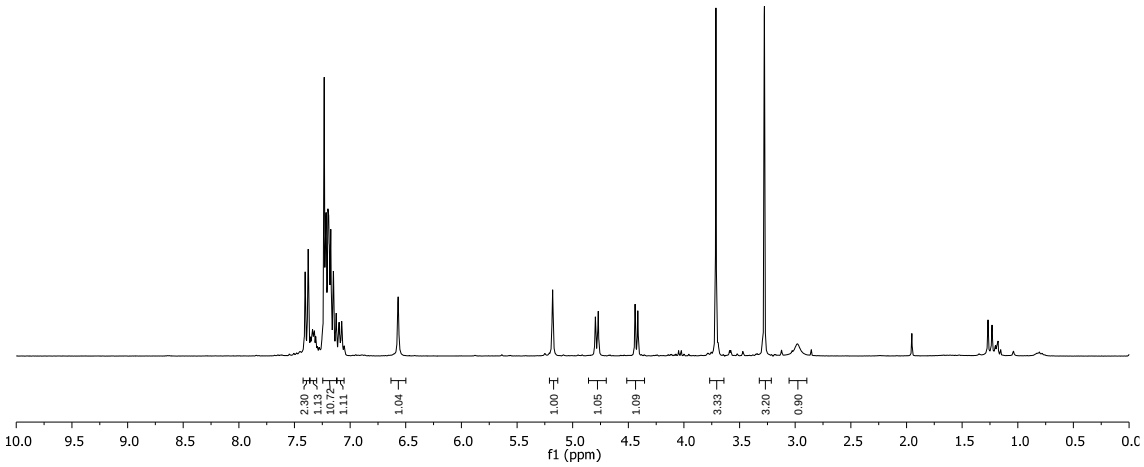
4b

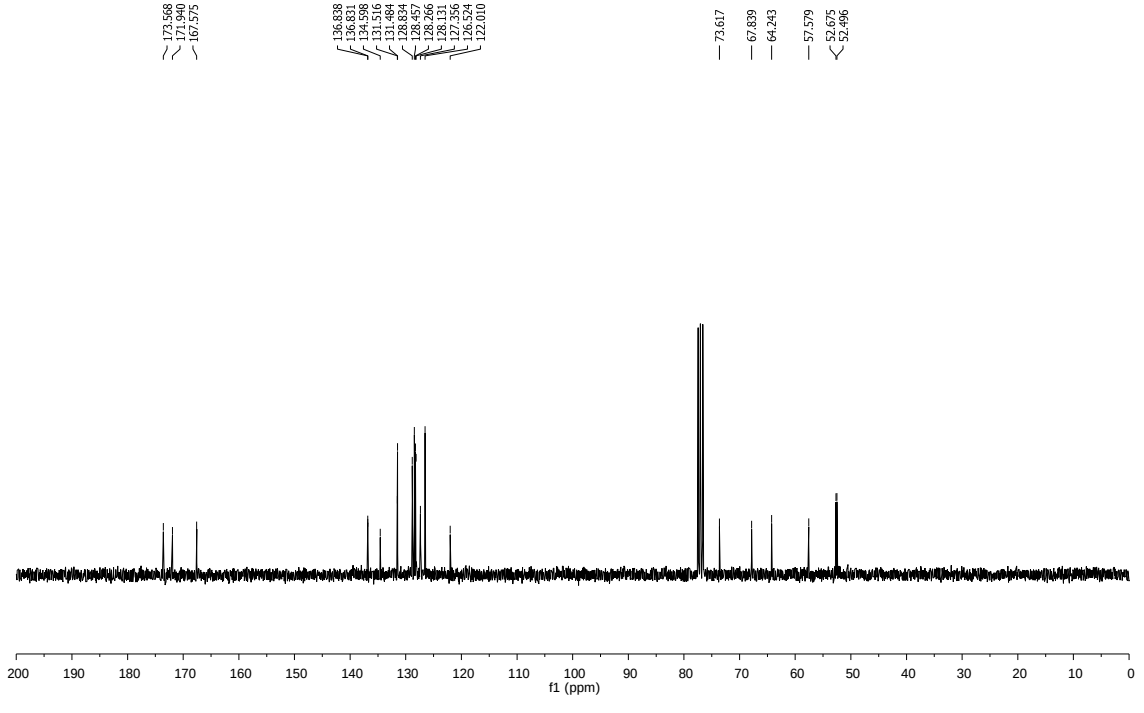
-62.585
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
f1 (ppm)

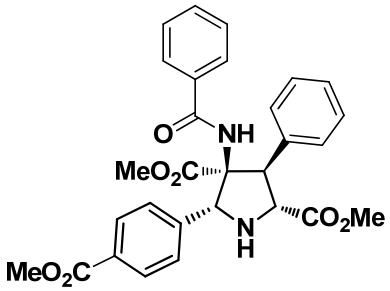

173.4
172.9
167.6
142.2
136.3
134.6
131.6
131.4
130.0
128.8
128.5
128.3
127.5
126.8
126.5
125.8
125.3
125.2
125.2
125.1
122.2
74.0
67.5
64.0
57.9
52.7
52.5
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
NH
MeO2C
CO2Me
N
H
Br

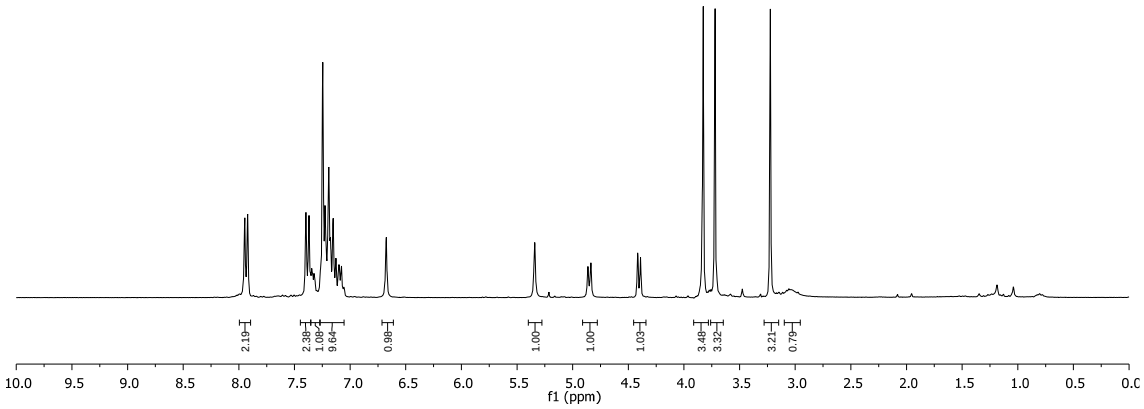
4c

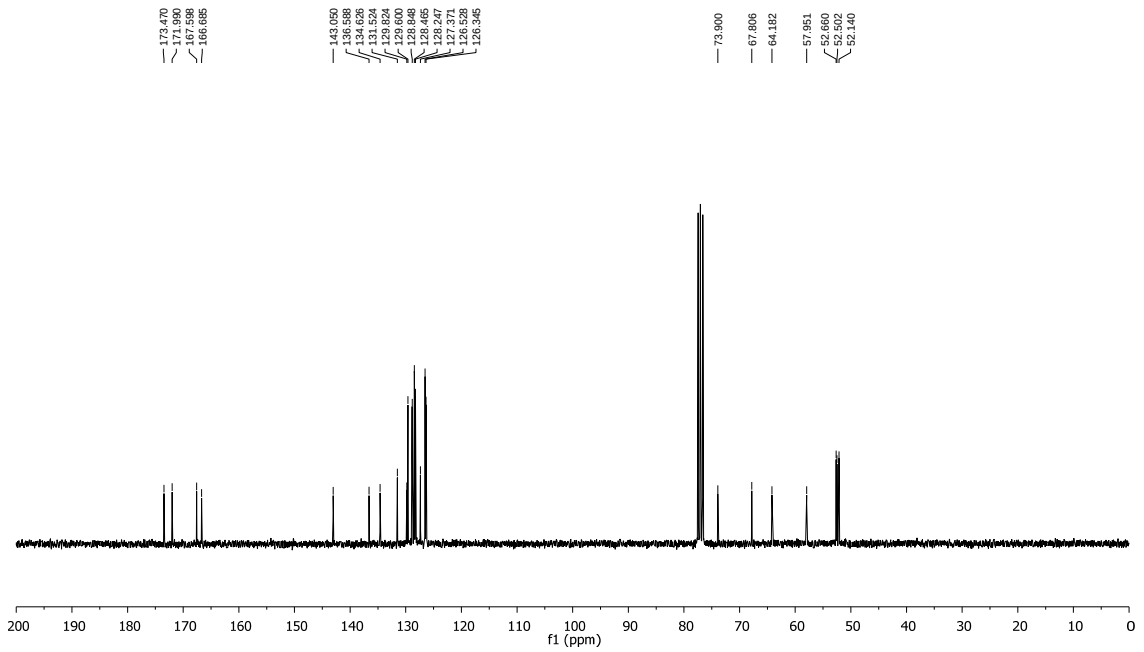

2.30
1.13
10.72
1.11
1.04
1.00
1.05
1.09
3.33
3.20
0.90
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

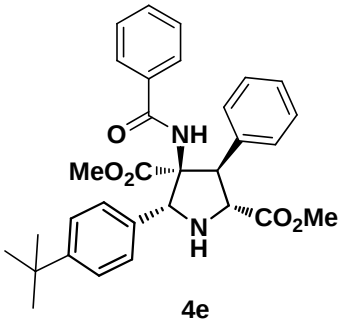

173.568
171.940
167.575
136.838
136.831
134.598
131.556
131.484
128.834
128.457
128.266
128.131
127.356
126.524
122.010
73.617
67.839
64.243
57.579
52.675
52.496
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
NH
MeO2C
N
H
CO2Me
MeO2C

4d

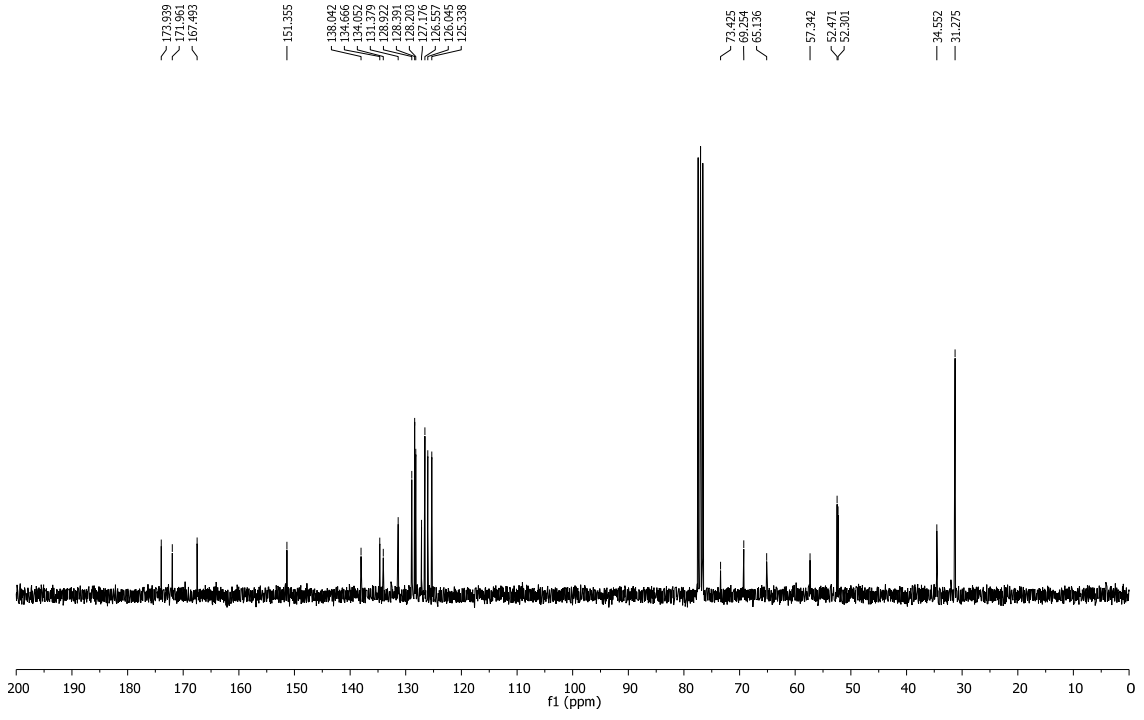

2.19
2.39
1.09
9.64
0.98
1.00
1.00
1.03
3.48
3.32
3.21
0.79
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

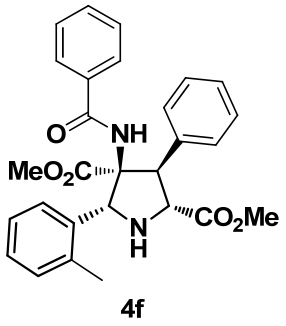

173.470
171.990
167.598
166.685
143.050
136.588
134.626
131.524
129.824
129.600
128.848
128.465
128.247
127.371
126.528
126.345
73.900
67.806
64.182
57.951
52.660
52.502
52.140
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



4e

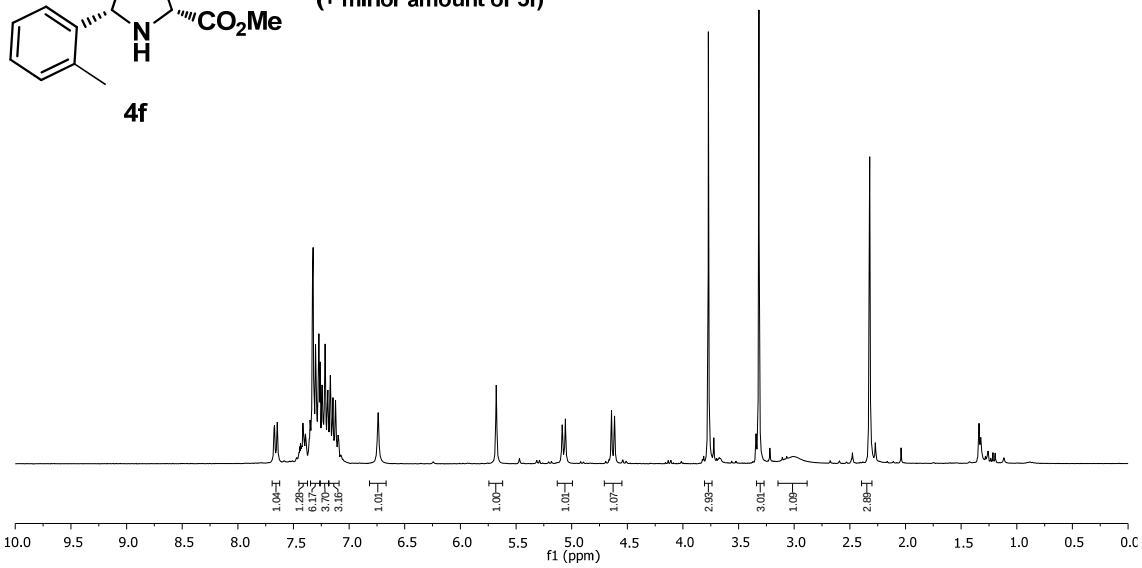
(+ minor amount of 5e)

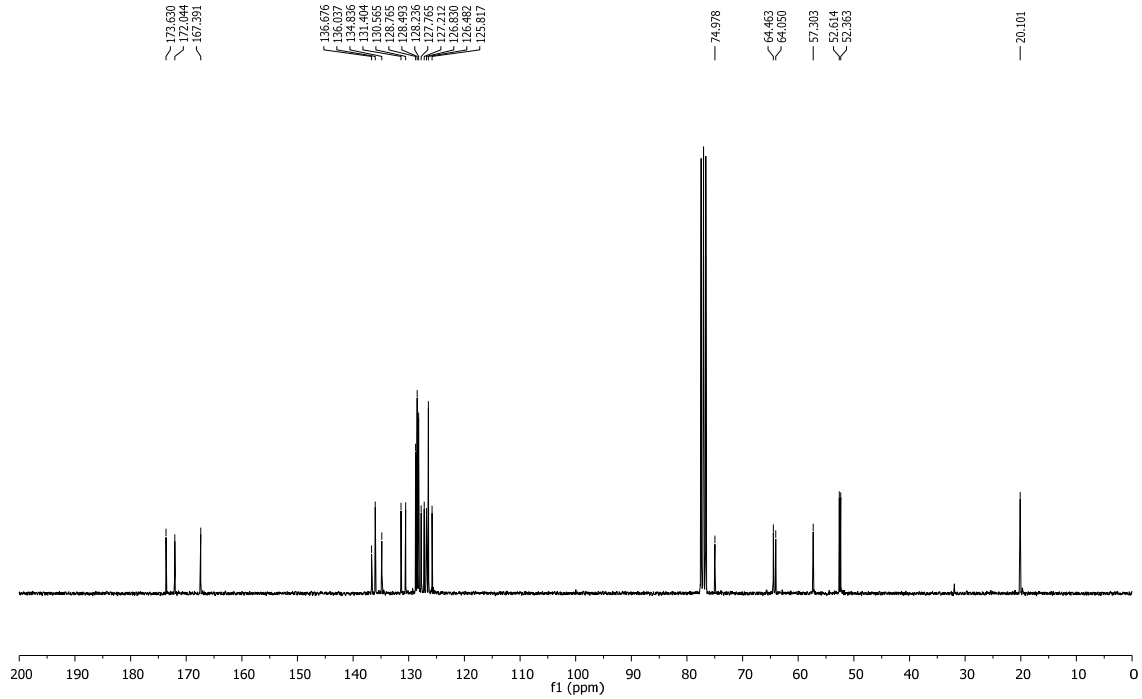


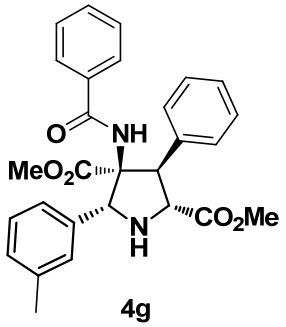


4f

(+ minor amount of 5f)

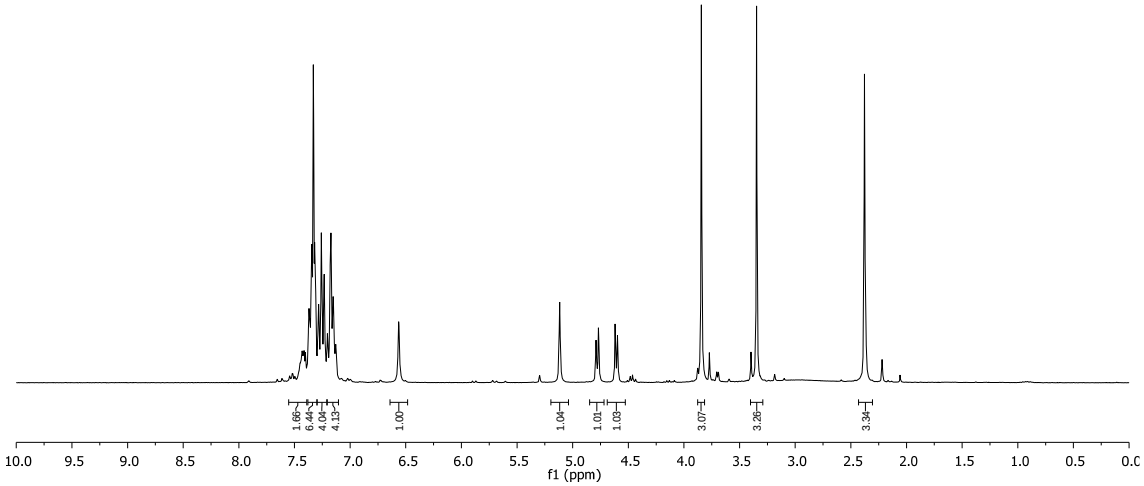


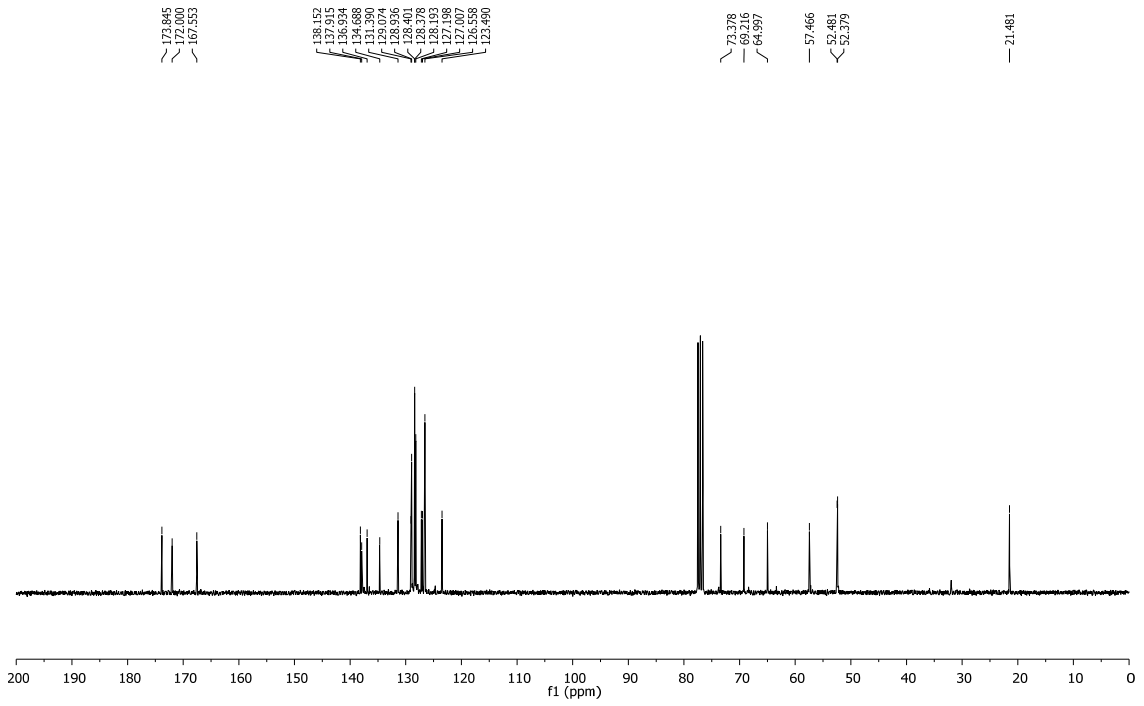


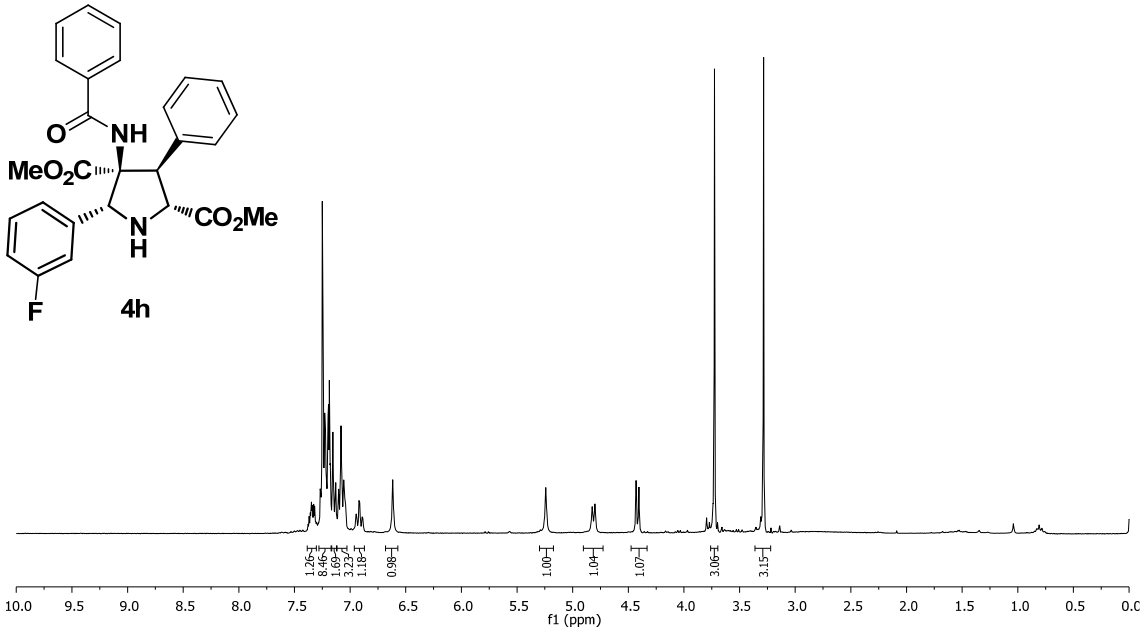


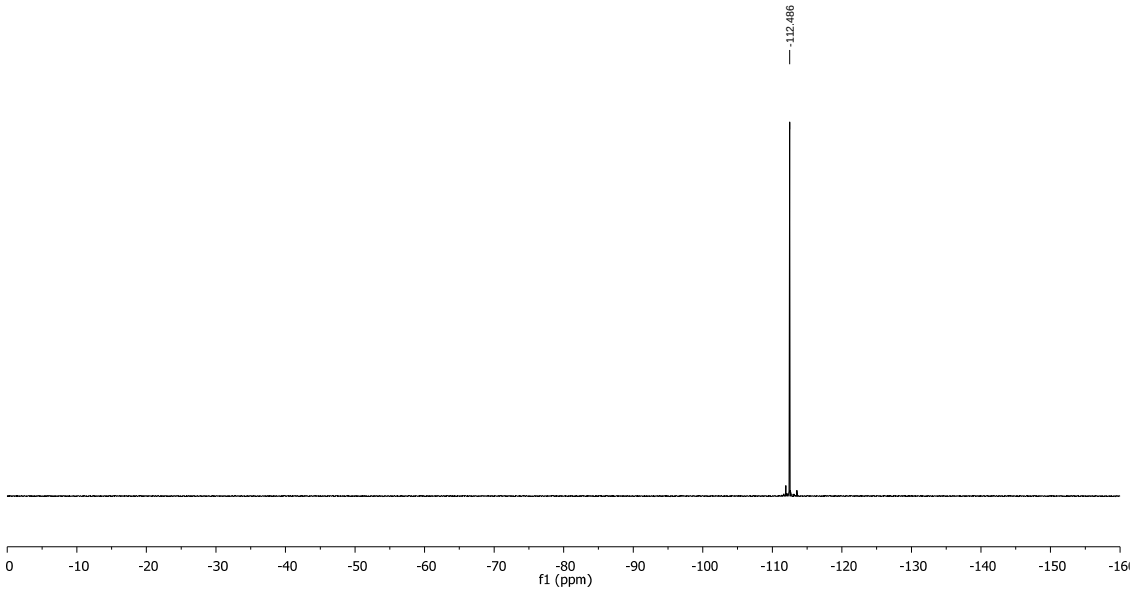
4g

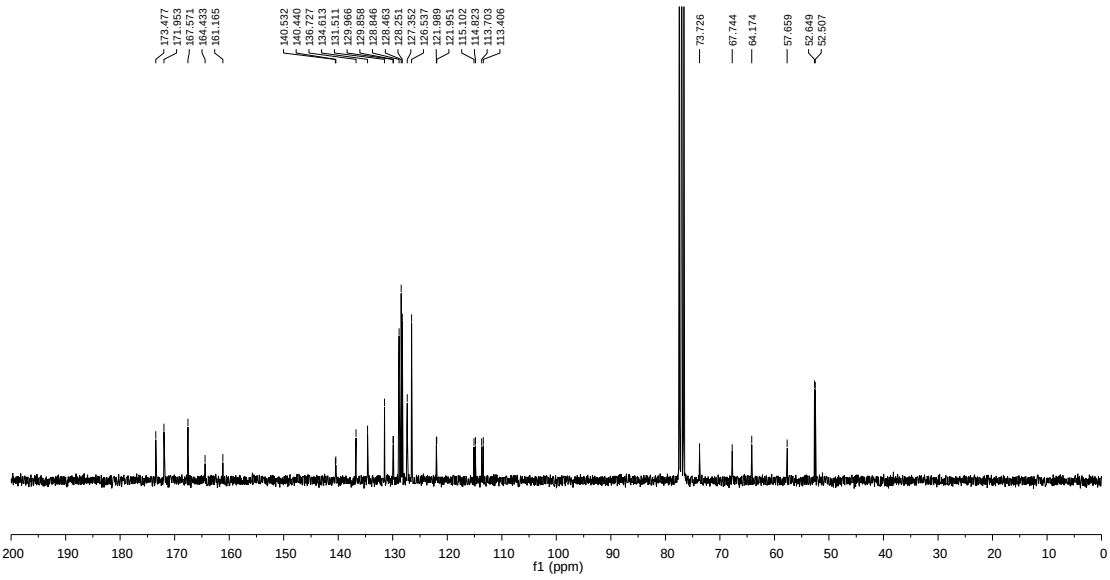
(+ minor amount of 5g)

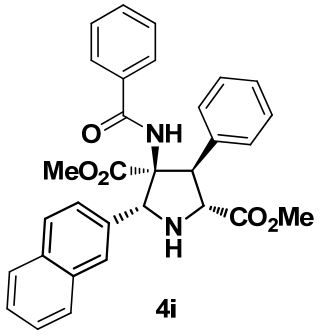





O
NH
MeO2C
CO2Me
N
H
F
4h
1.26
8.46
1.09
3.22
1.18
0.98
1.00
1.04
1.07
3.06
3.15
f1 (ppm)

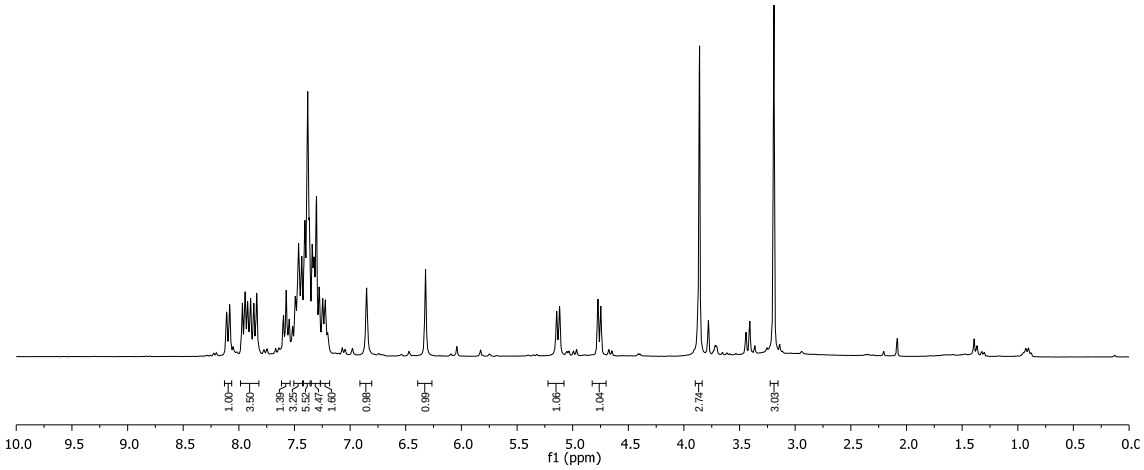

-112.486
f1 (ppm)

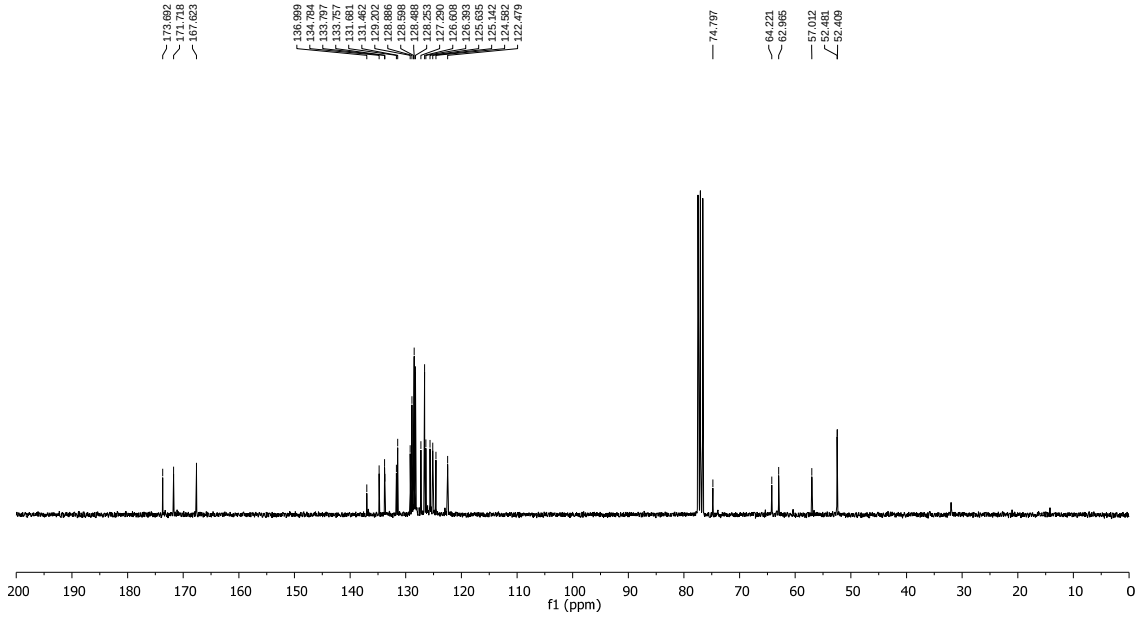

173.477
171.953
167.571
164.433
161.165
140.532
140.440
136.727
134.613
131.511
129.966
129.858
128.846
128.463
128.251
127.352
126.537
121.989
121.951
115.102
114.823
113.703
113.406
73.726
67.744
64.174
57.659
52.649
52.507
f1 (ppm)

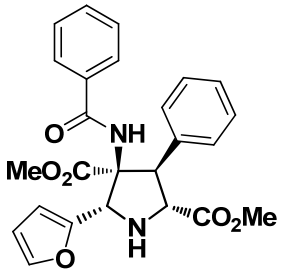


4i

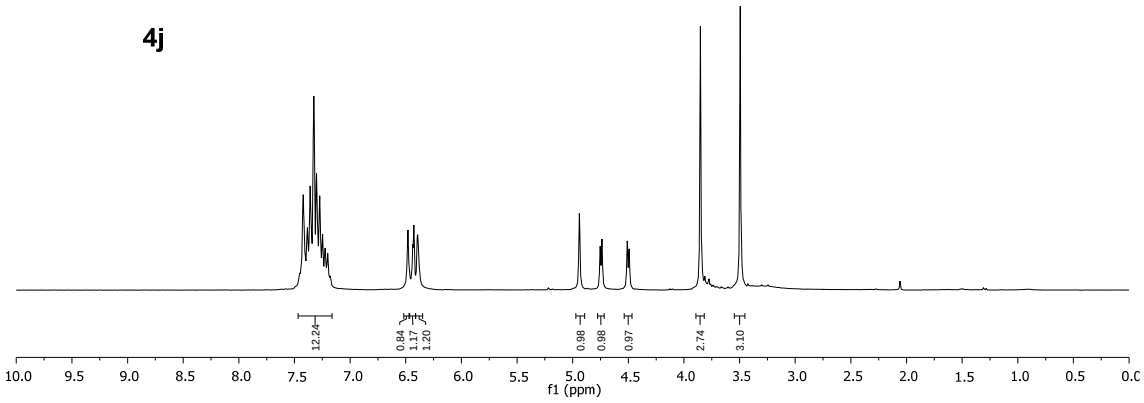
(+ minor amount of 5i)

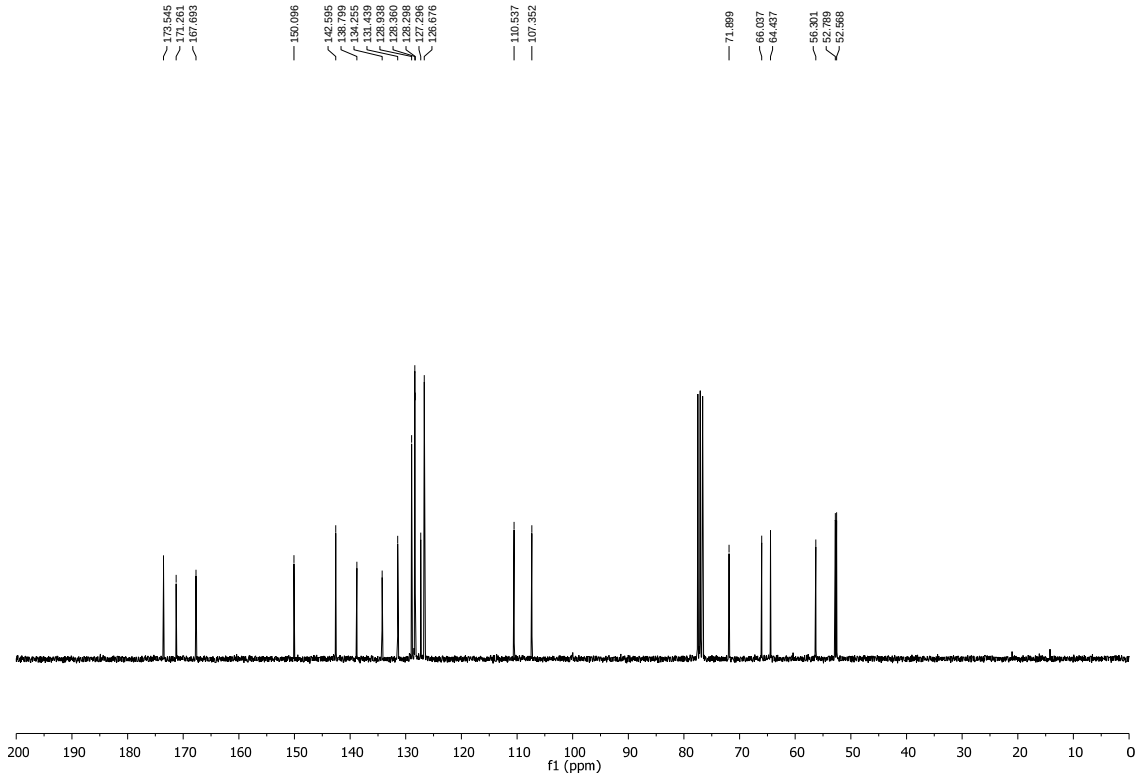


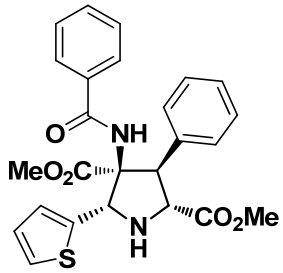



O
NH
MeO2C
CO2Me
N
H
O

4j

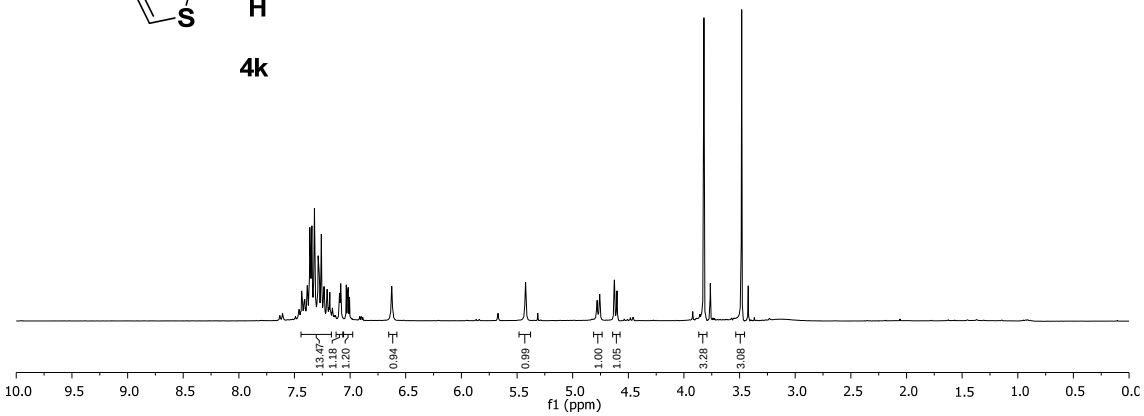

12.24
0.84
1.17
1.20
0.98
0.98
0.97
2.74
3.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

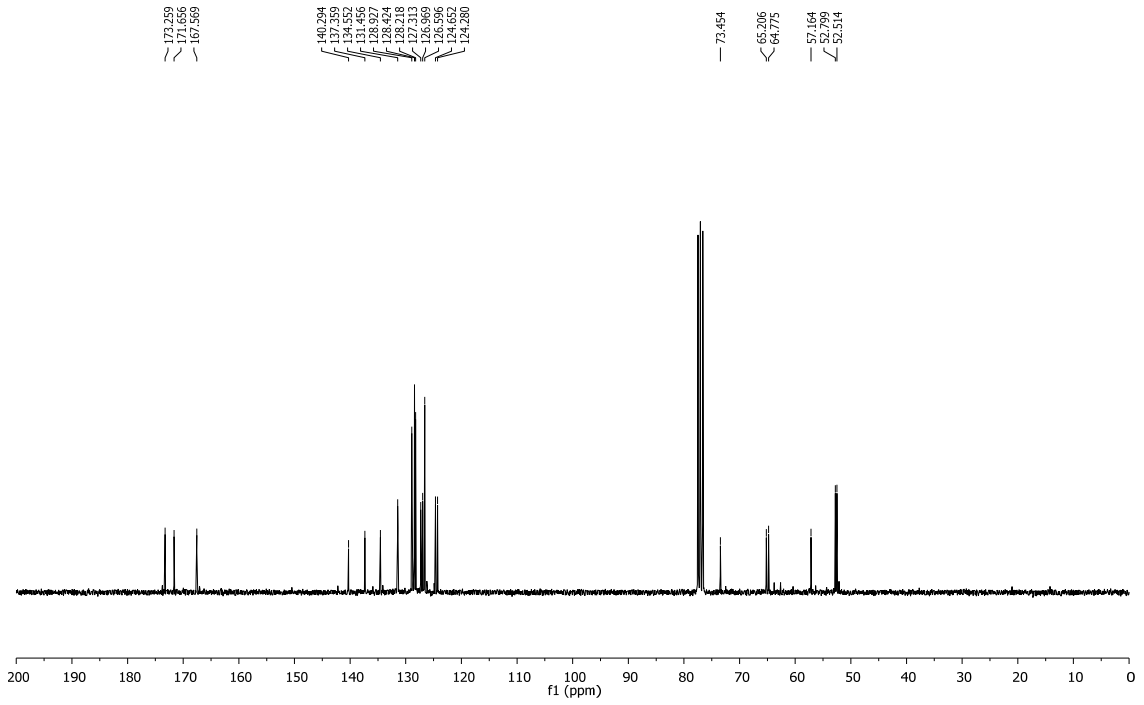

173.545
172.261
167.693
150.096
142.595
138.799
134.255
131.439
128.938
128.360
128.298
127.296
126.676
110.537
107.352
71.899
66.037
64.437
56.301
52.789
52.568
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

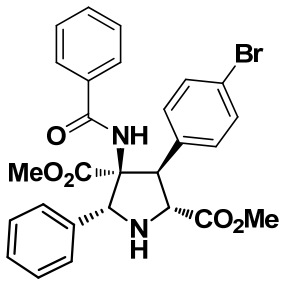


4k

(+ minor amount of 5k)

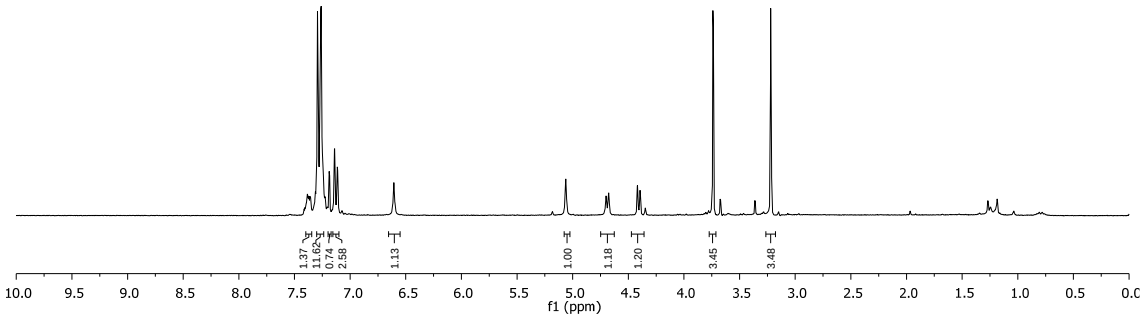


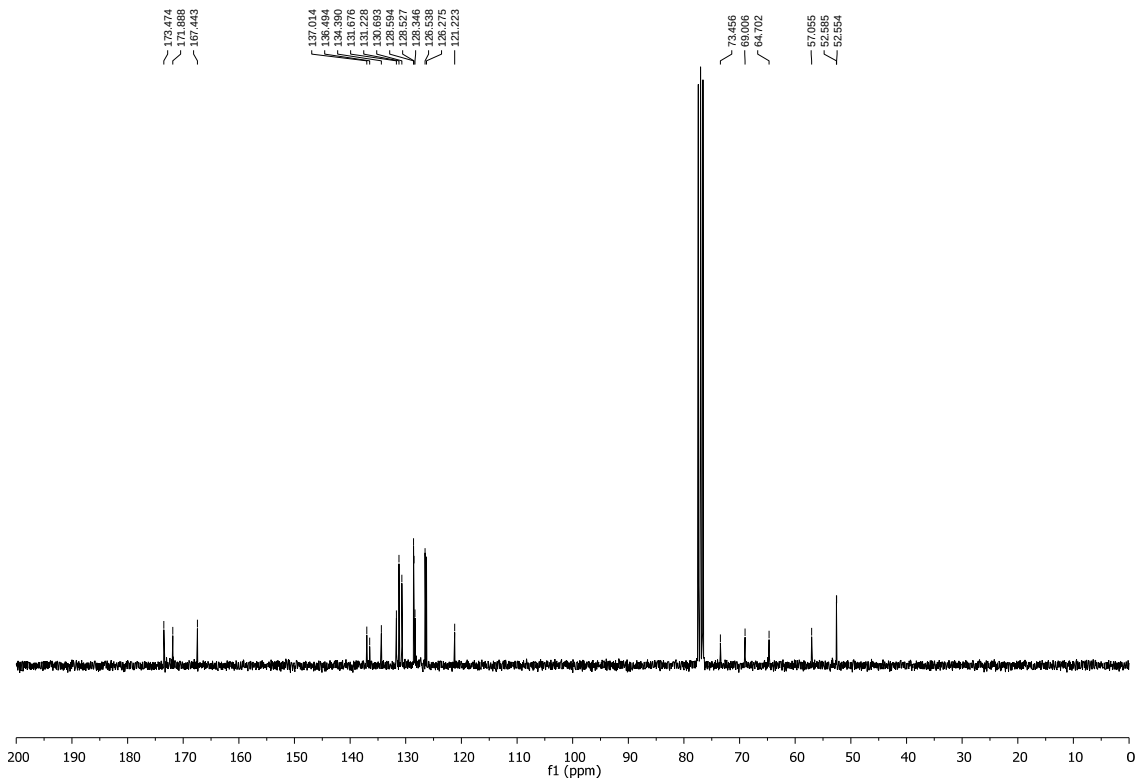


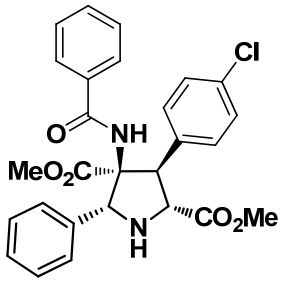


4m

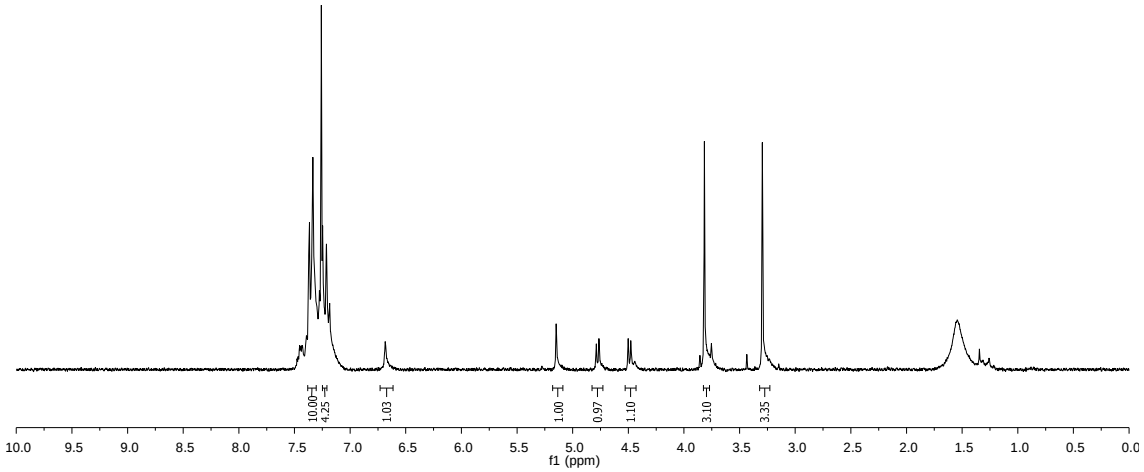
(+ minor amount of 5m)

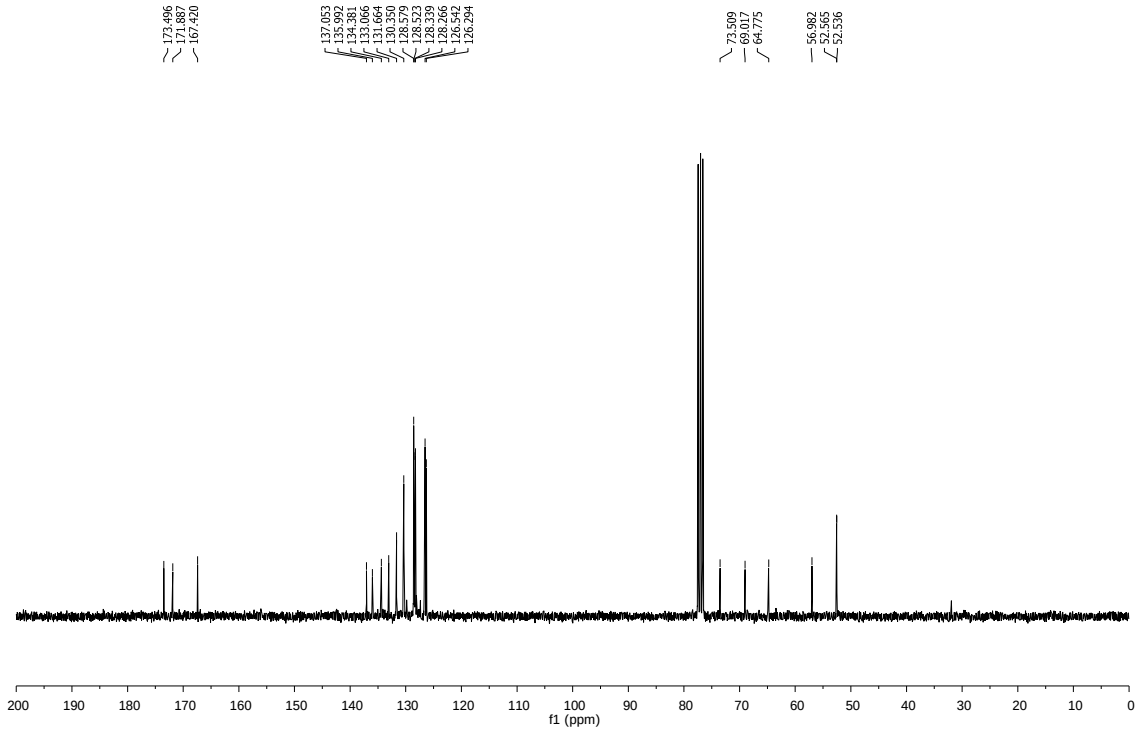


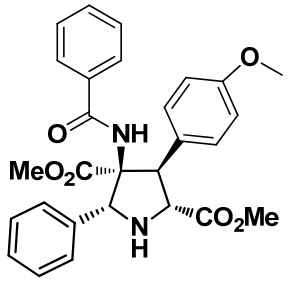



Cl
O
NH
MeO2C
CO2Me
N
H

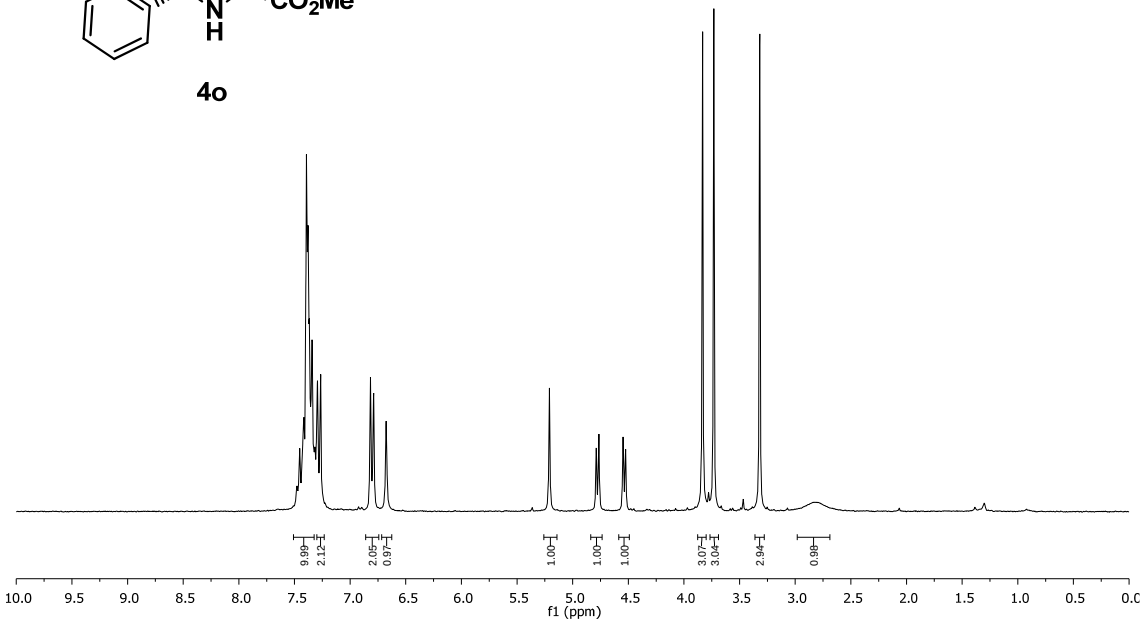
4n


10.00
4.25
1.03
1.00
0.97
1.10
3.10
3.35
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

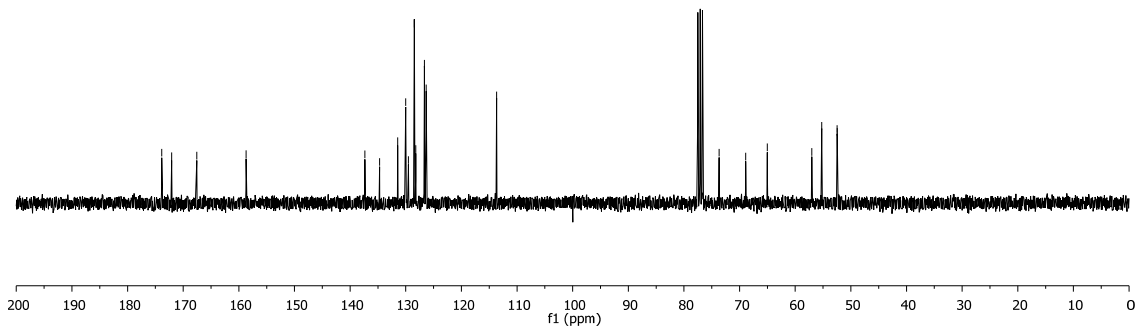

173.496
171.897
167.420
137.053
135.992
134.381
133.066
131.664
130.350
128.579
128.523
128.339
128.266
126.542
126.294
73.509
69.017
64.775
56.982
52.565
52.536
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

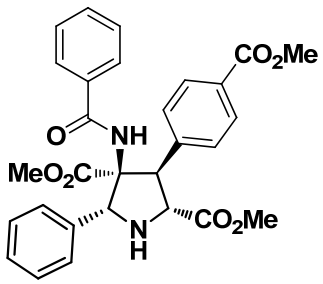

O
NH
MeO2C
CO2Me
N
H

4o

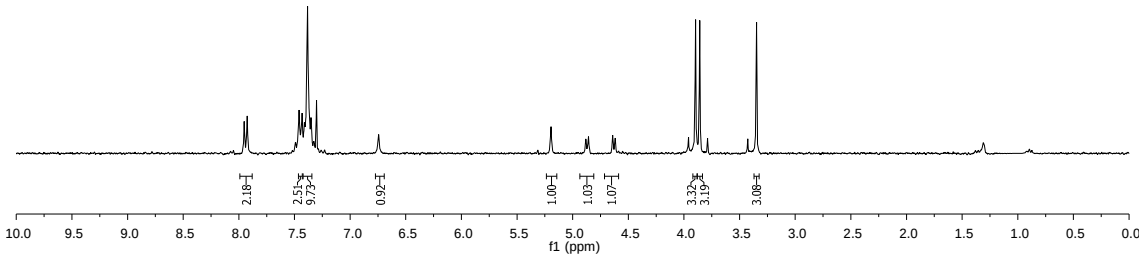

9.99
2.12
2.05
0.97
1.00
1.00
1.00
3.07
3.04
2.94
0.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

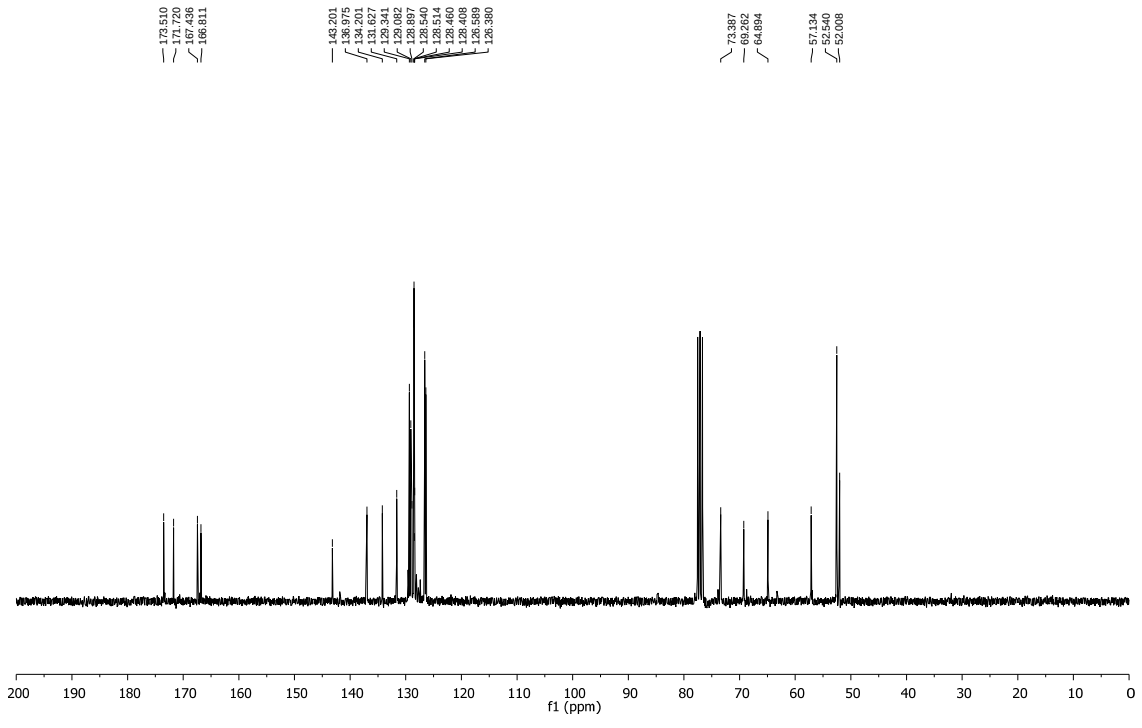

173.856
172.067
167.571
158.702
137.363
134.715
131.464
130.007
129.528
128.464
128.209
126.634
126.343
113.661
73.669
68.899
65.008
57.033
55.227
52.481
52.444

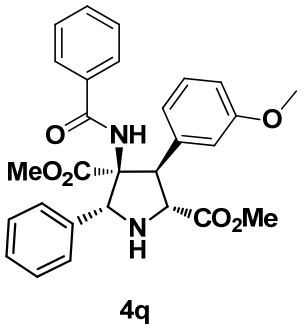

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CO2Me
O
NH
MeO2C
CO2Me
N
H

4p

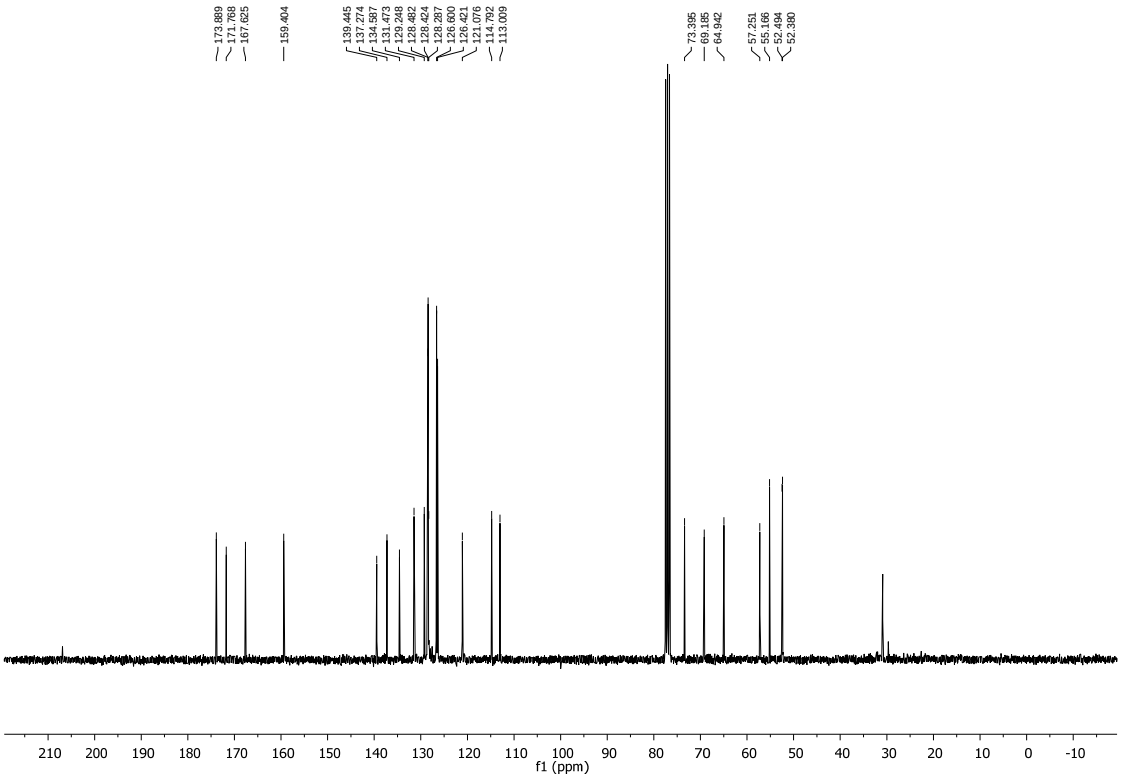

2.18
2.51
9.73
0.92
1.00
1.03
1.07
3.32
3.19
3.08
f1 (ppm)

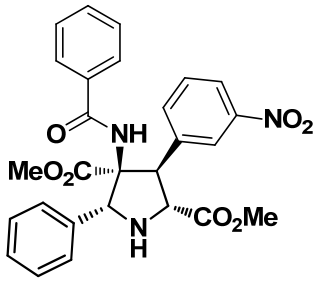

173.510
171.720
167.436
166.811
143.201
136.975
134.201
131.627
129.341
129.082
128.897
128.540
128.514
128.460
128.408
126.589
126.380
73.387
69.262
64.894
57.134
52.540
52.008
f1 (ppm)


O
NH
MeO2C
O
CO2Me
N
H

4q

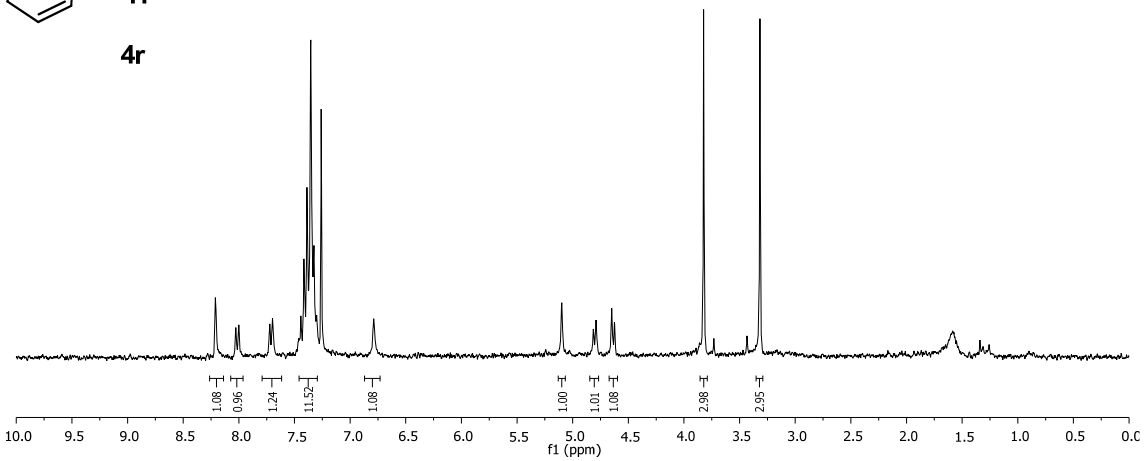
10.80
1.34
2.12
1.19
0.98
1.00
1.01
0.98
3.28
3.38
3.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

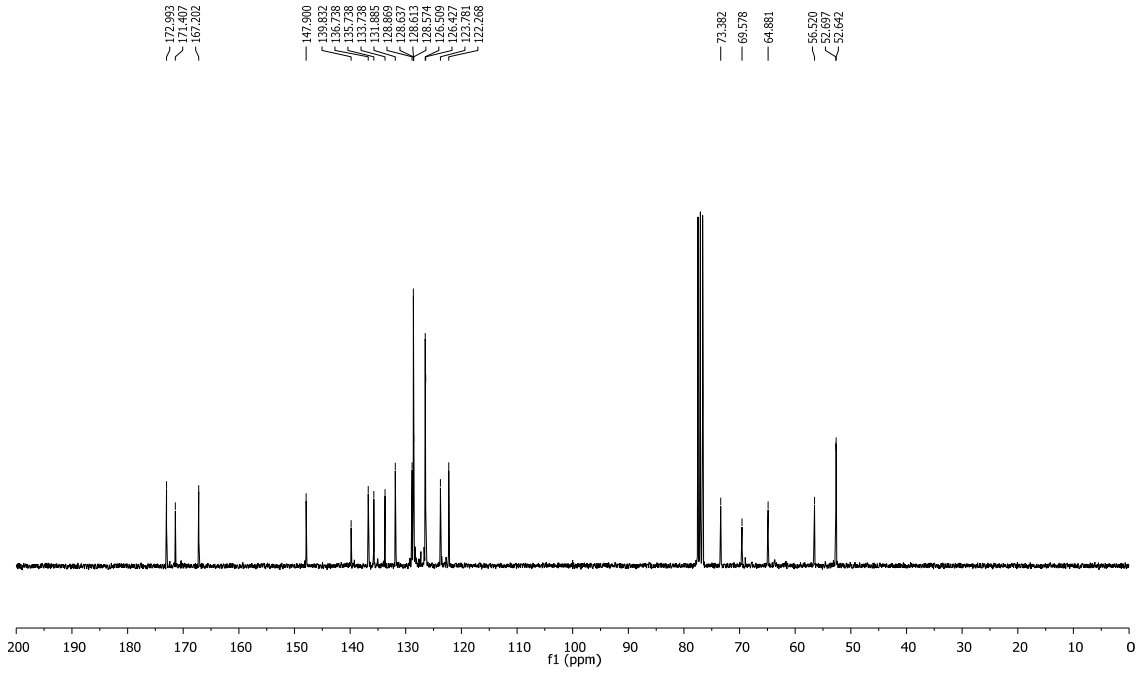

173.889
171.768
167.625
159.404
139.445
137.274
134.587
131.473
129.248
128.482
128.424
128.267
126.600
126.421
121.076
114.792
113.009
73.396
69.185
64.942
57.251
55.166
52.494
52.380
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

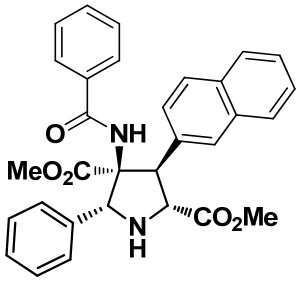


4r

(+ minor amount of 5r)

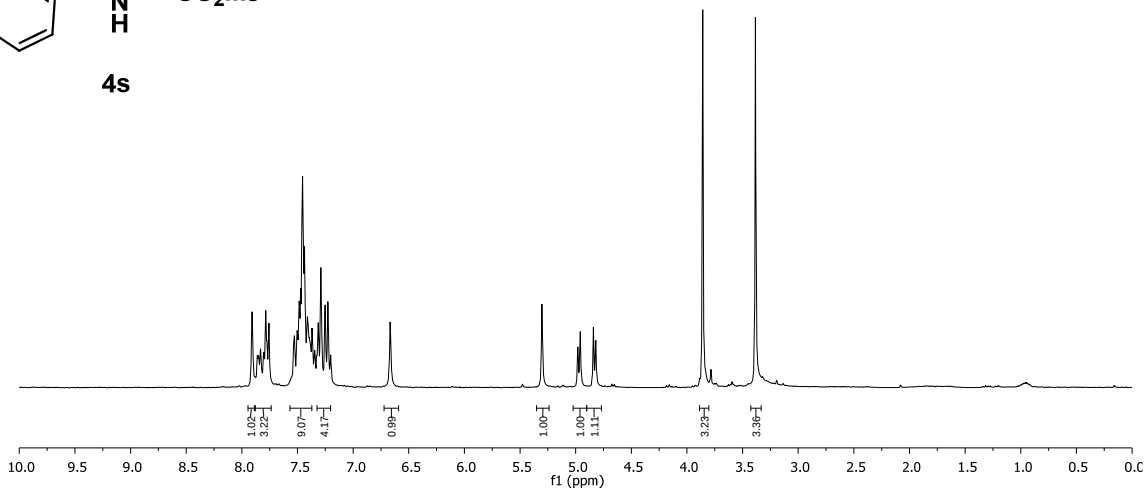


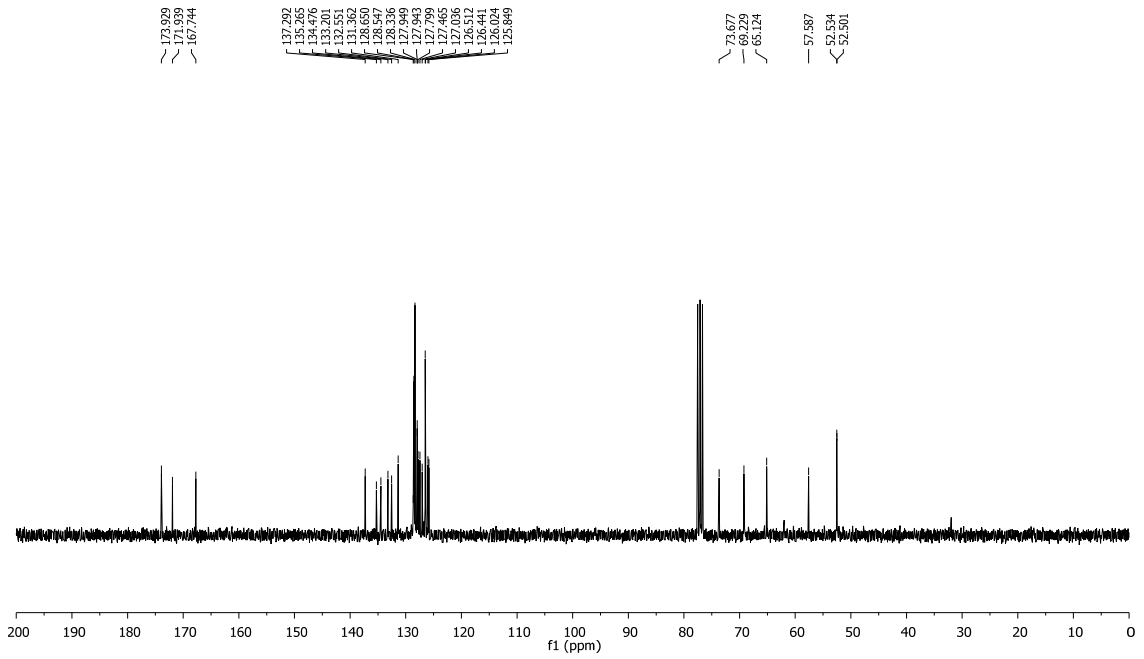


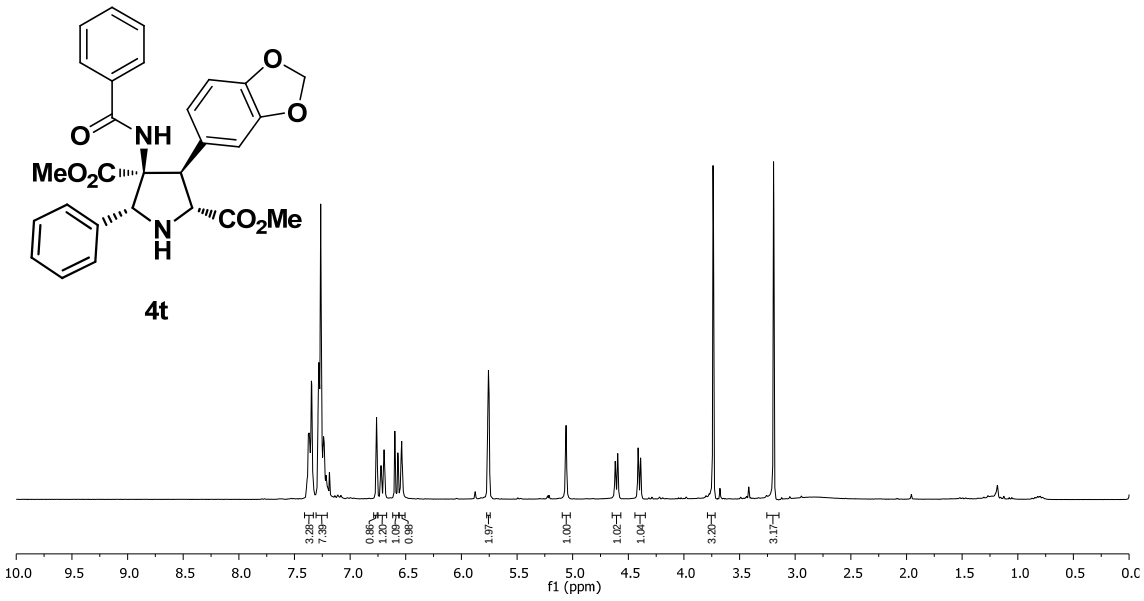


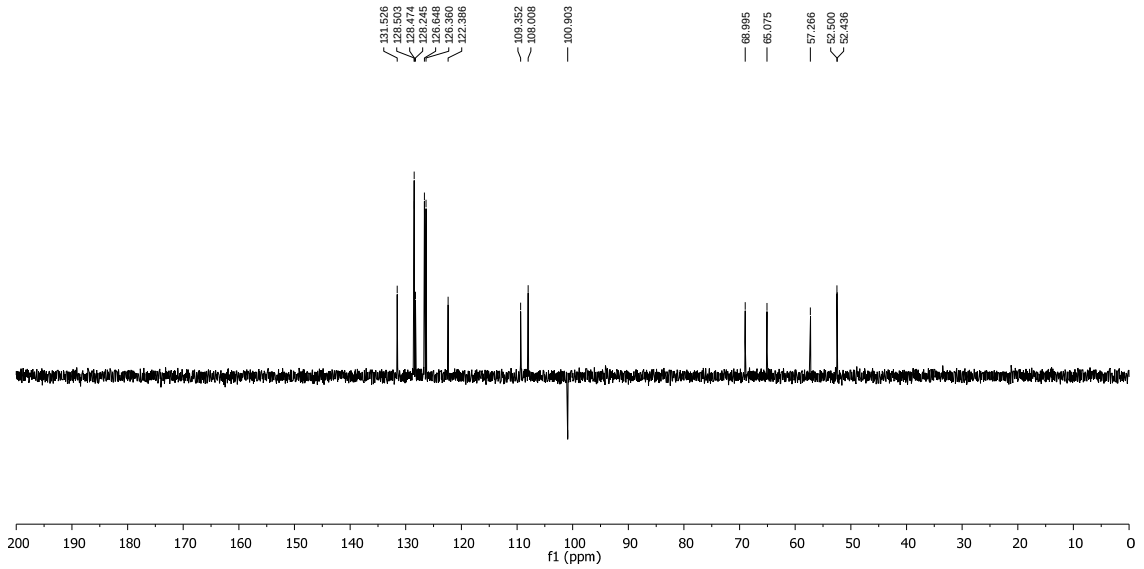
4s

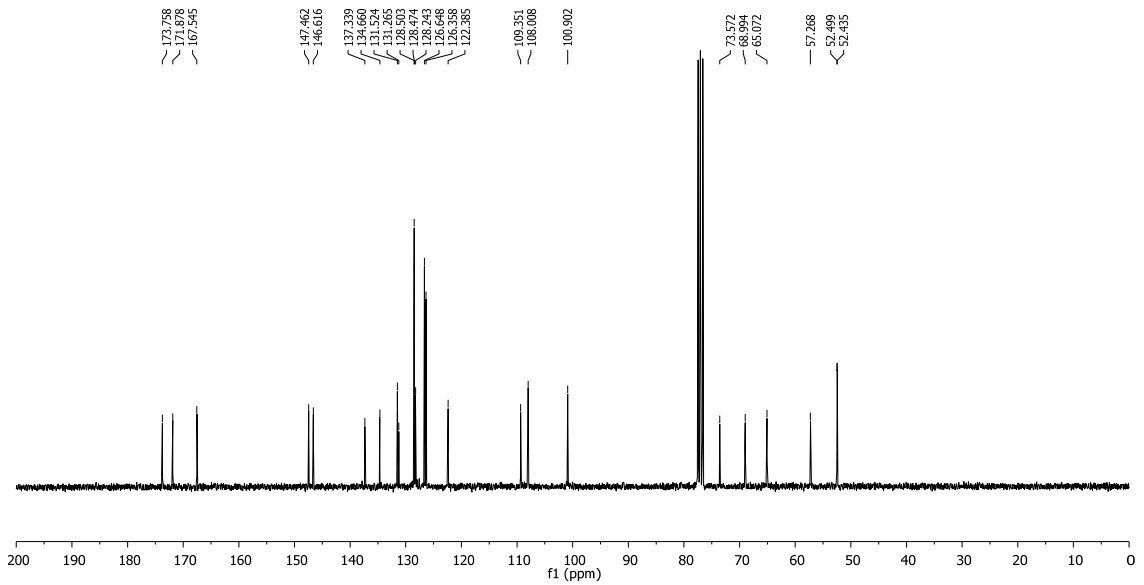
(+ minor amount of 5s)

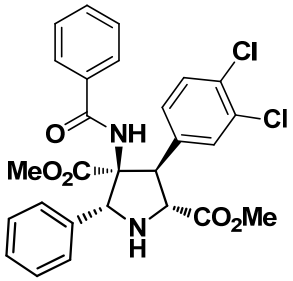




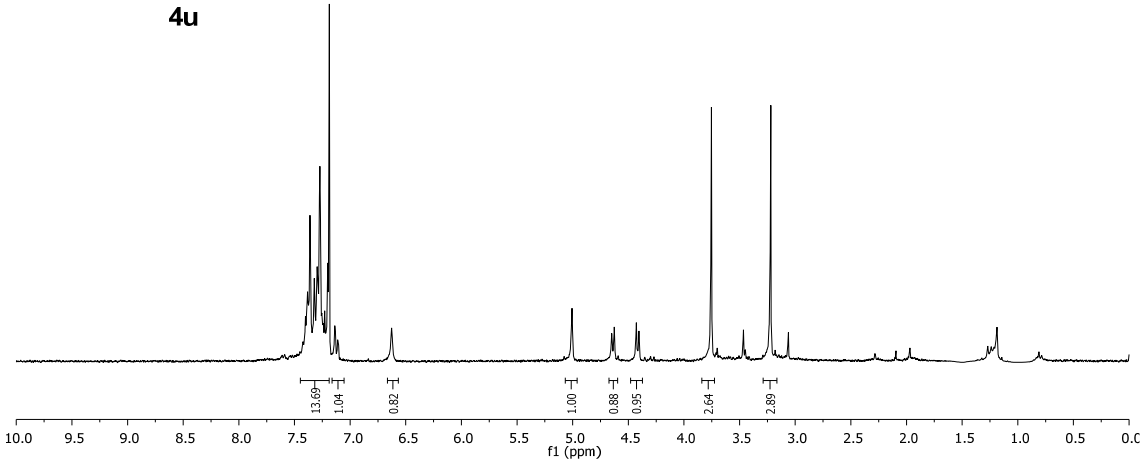

O
NH
MeO2C
CO2Me
N
H
O
O
4t
3.28
7.39
0.86
1.20
1.09
0.98
1.97
1.00
1.02
1.04
3.20
3.17
f1 (ppm)

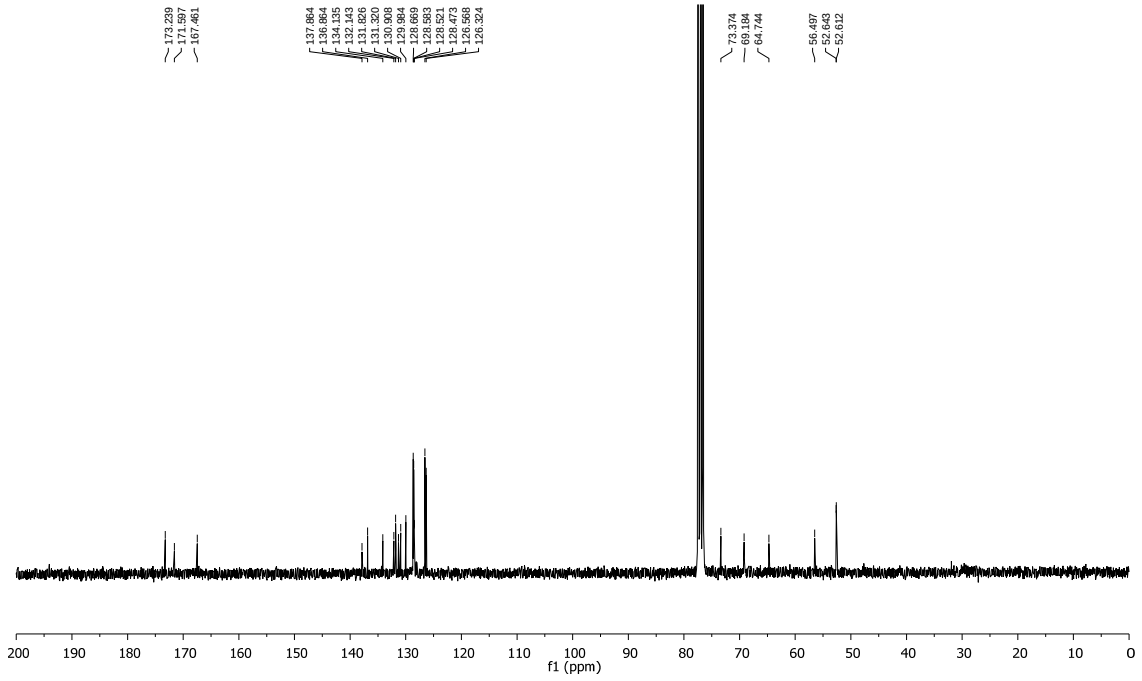

131.526
128.503
128.474
128.245
126.648
126.360
122.386
109.352
108.008
100.903
68.995
65.075
57.266
52.500
52.436
f1 (ppm)

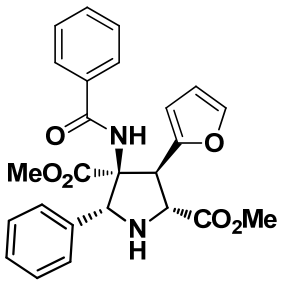

173.758
171.878
167.545
147.462
146.616
137.339
134.660
131.524
131.265
128.503
128.474
128.243
126.648
126.358
122.385
109.351
108.008
100.902
73.572
68.994
65.072
57.268
52.499
52.435
f1 (ppm)


Cl
Cl
O
NH
MeO2C
CO2Me
N
H

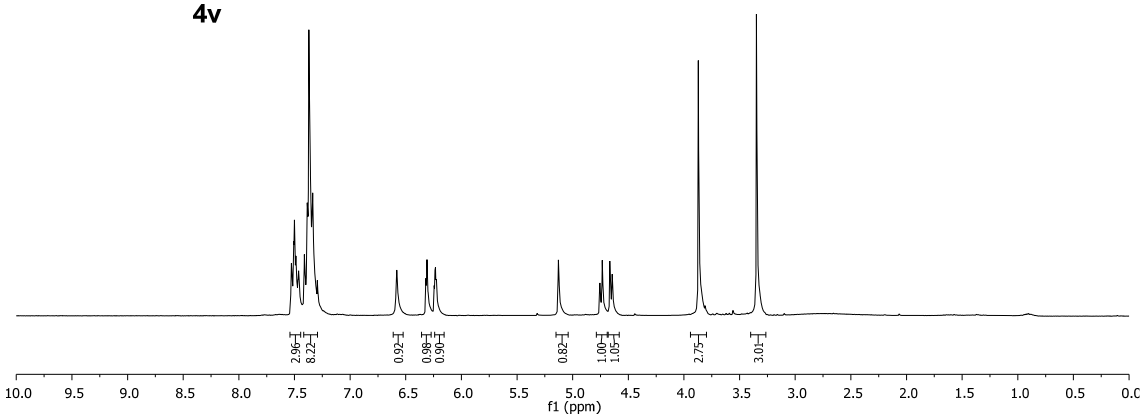
4u

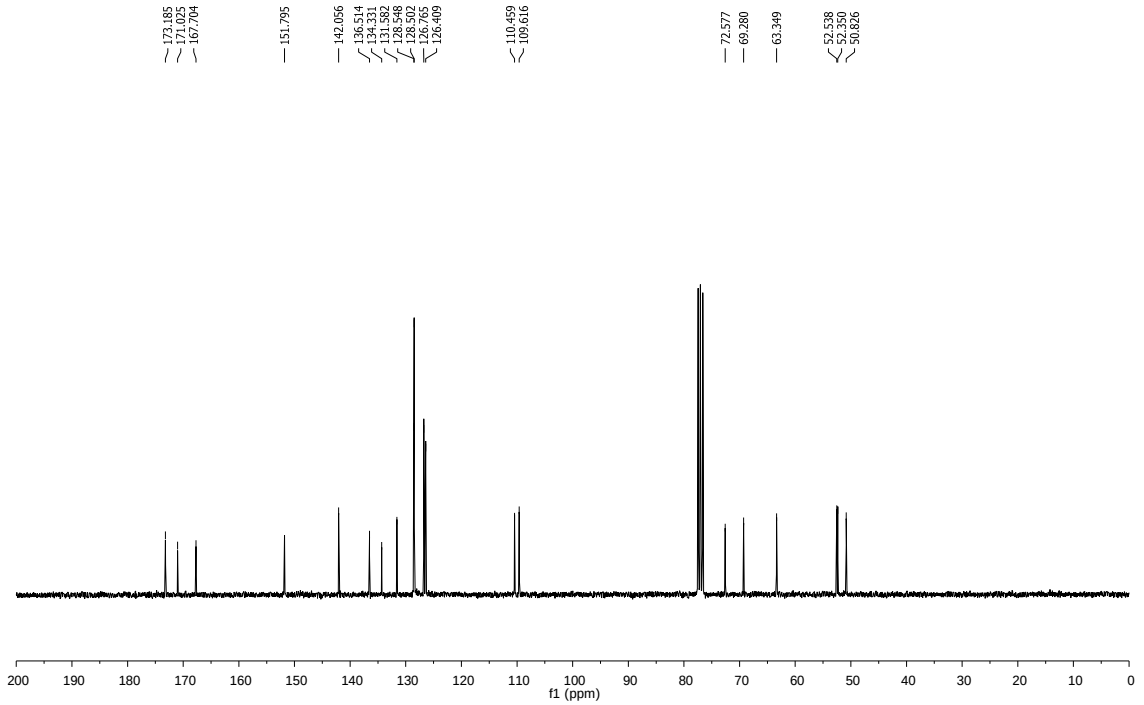

13.69
1.04
0.82
1.00
0.88
0.95
2.64
2.89
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

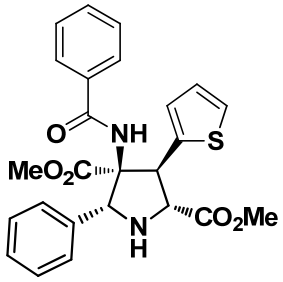

173.239
171.597
167.461
137.864
136.864
134.155
132.243
131.826
131.320
130.908
129.984
128.669
128.593
128.521
128.473
126.568
126.324
73.374
69.184
64.744
56.497
52.643
52.612
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
NH
O
MeO2C
N
H
CO2Me

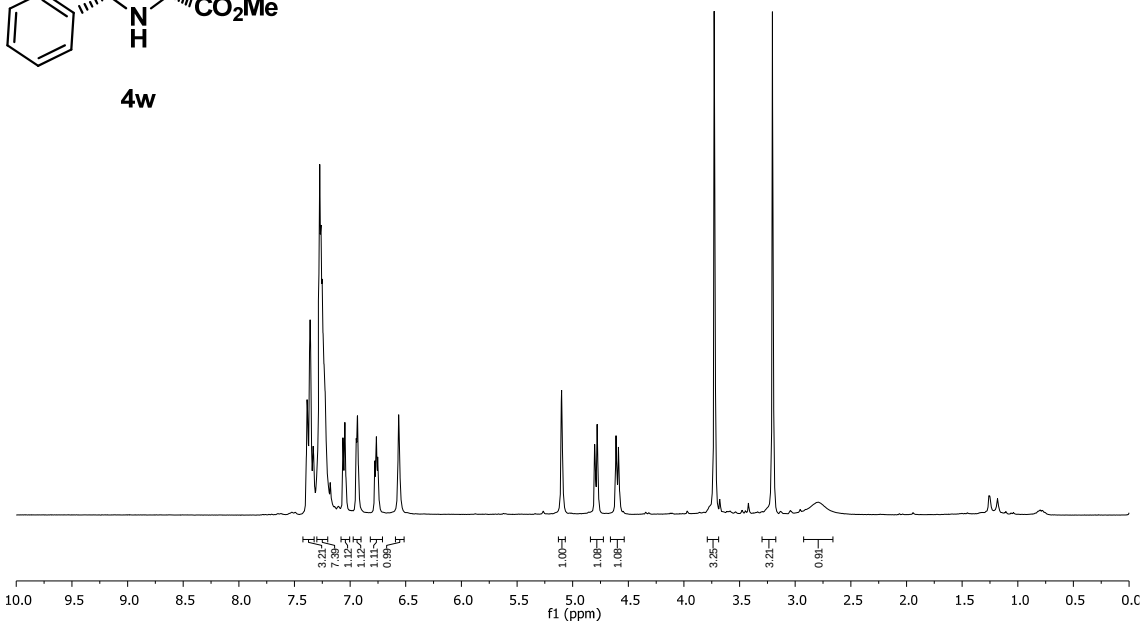
4v

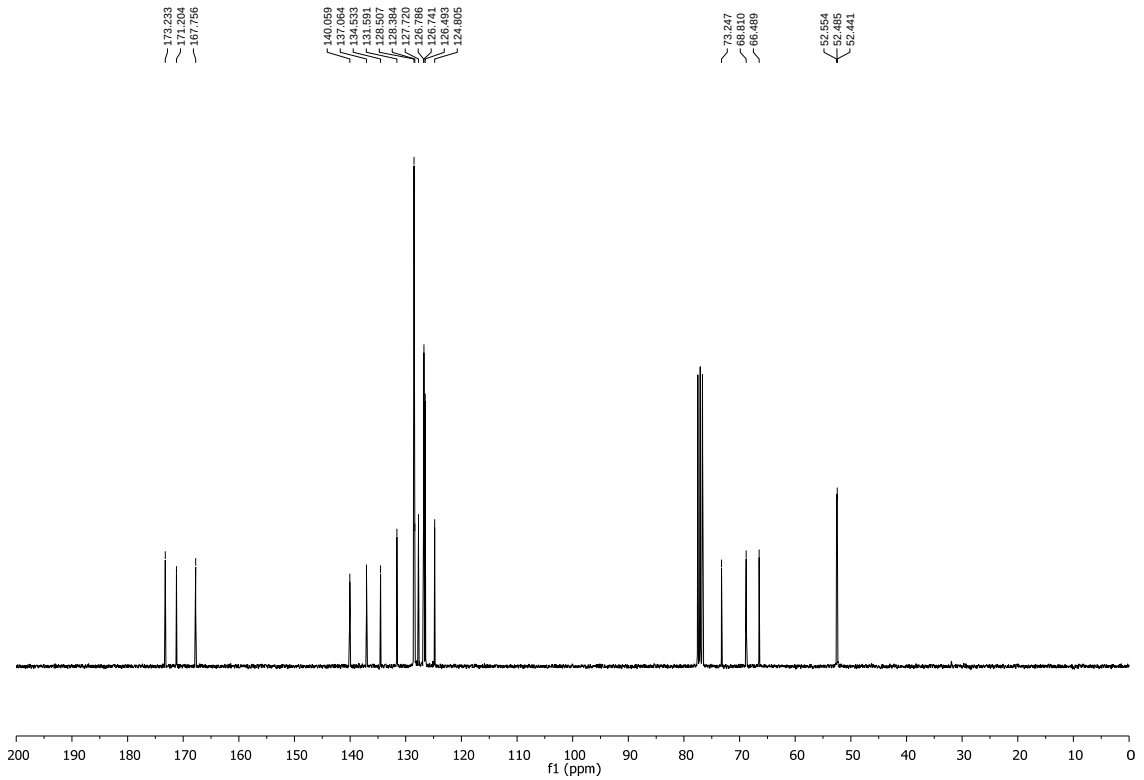

2.96
8.22
0.92
0.98
0.90
0.82
1.00
1.05
2.75
3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

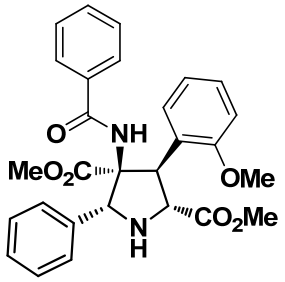

173.185
171.025
167.704
151.795
142.056
136.514
134.331
131.582
128.548
128.502
126.765
126.409
110.459
109.616
72.577
69.280
63.349
52.538
52.350
50.826
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
NH
S
MeO2C
CO2Me
N
H

4w

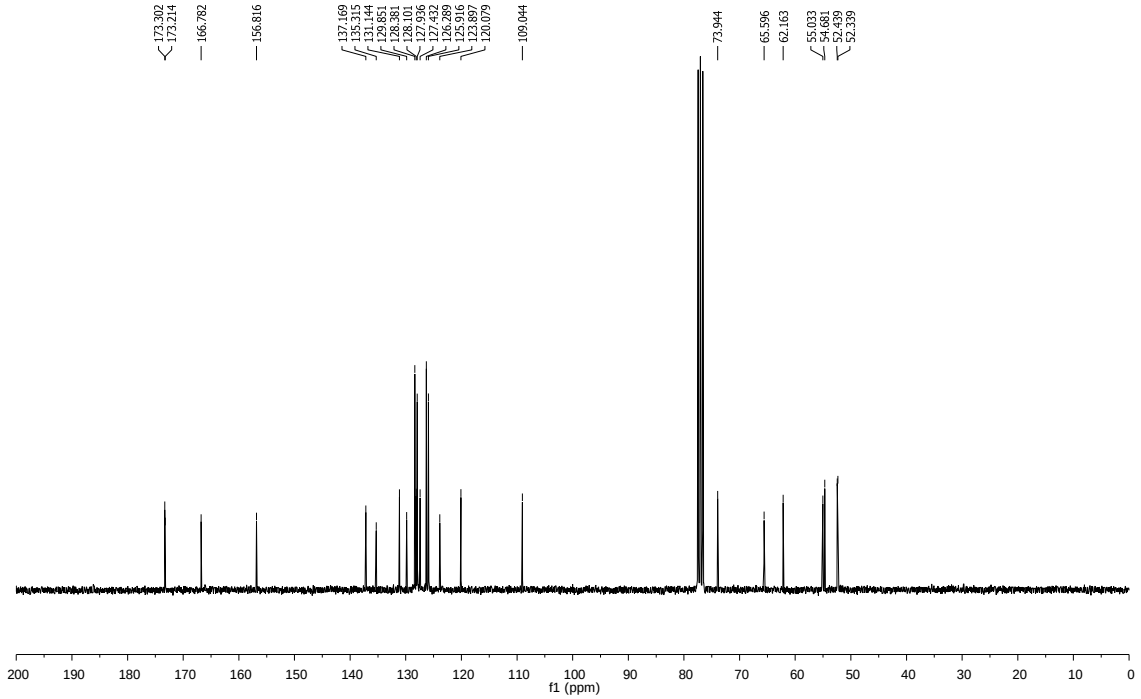

3.21
2.38
1.12
1.11
0.99
1.00
1.00
1.00
3.25
3.21
0.91
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

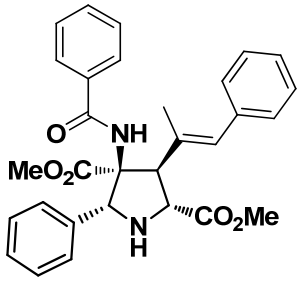

173.233
171.204
167.756
140.059
137.064
134.533
131.591
128.507
128.384
127.720
126.786
126.741
126.493
124.805
73.247
68.410
66.489
52.554
52.485
52.441
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
NH
MeO2C
OMe
N
H
CO2Me

4x

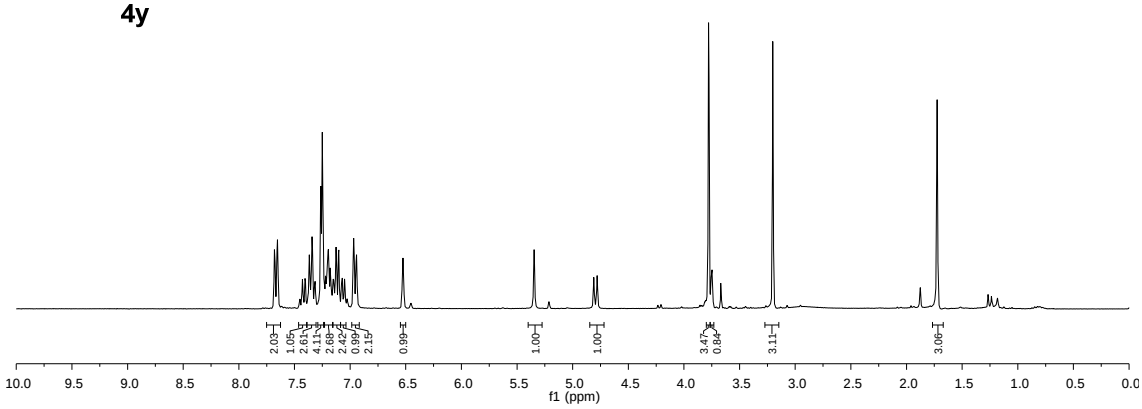
1.08
1.21
10.82
1.18
1.10
1.04
1.00
1.16
1.04
3.31
3.02
3.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

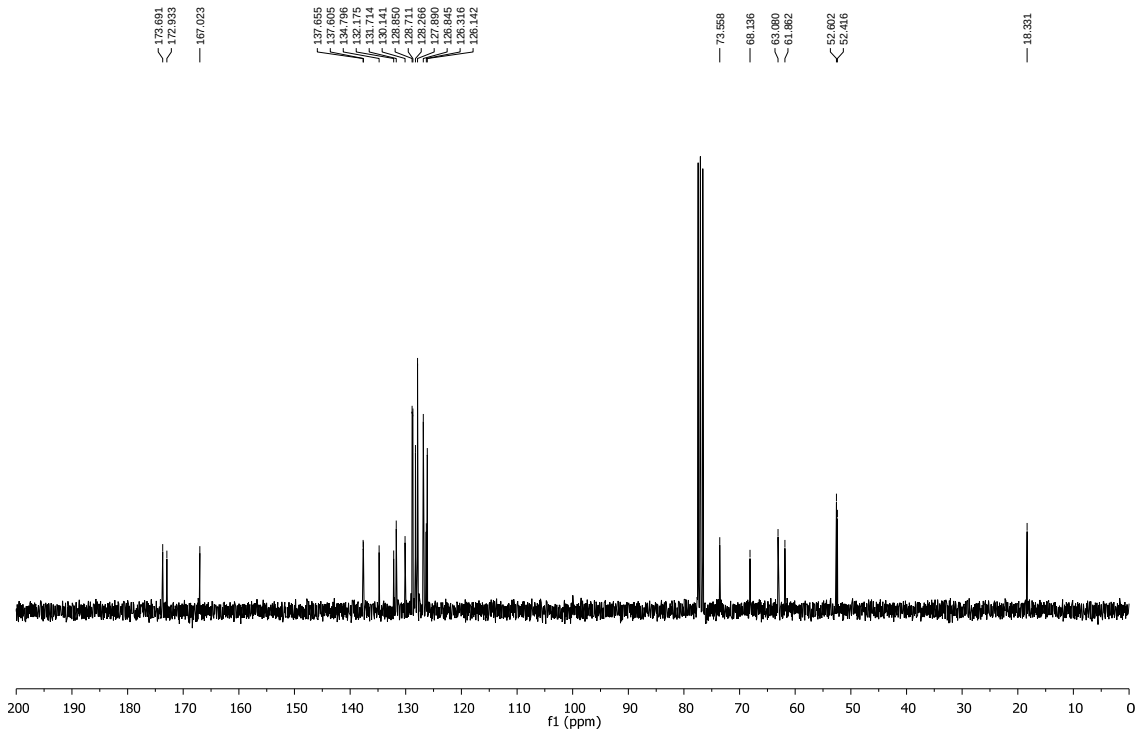

173.302
173.214
166.782
156.816
137.169
135.315
131.144
129.851
128.381
128.101
127.936
127.432
126.289
125.916
123.897
120.079
109.044
73.944
65.596
62.163
55.033
54.681
52.439
52.339
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

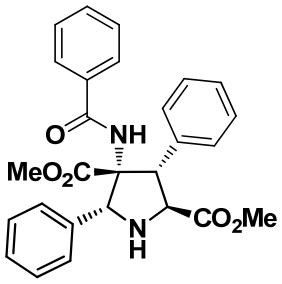


(+ minor amount of 5y)

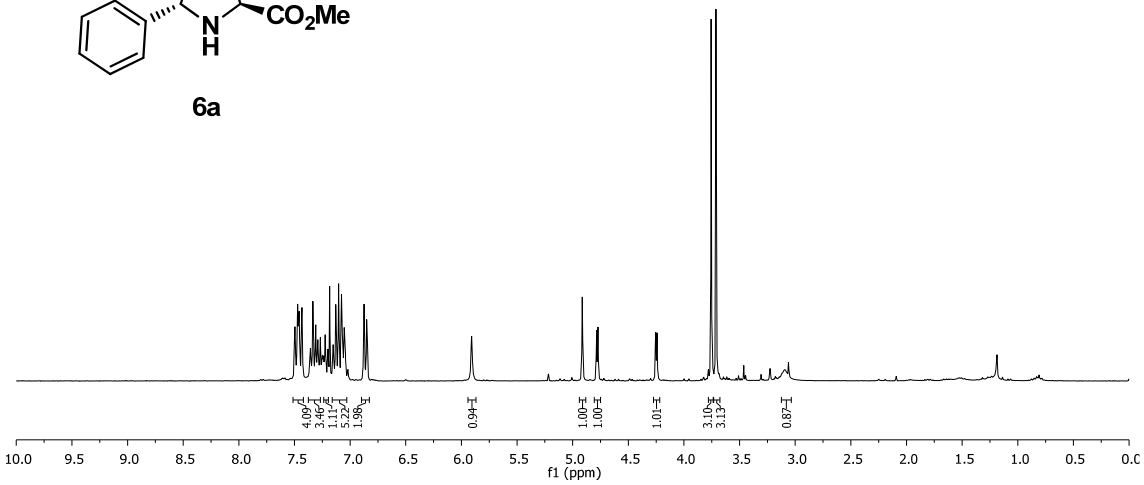
4y

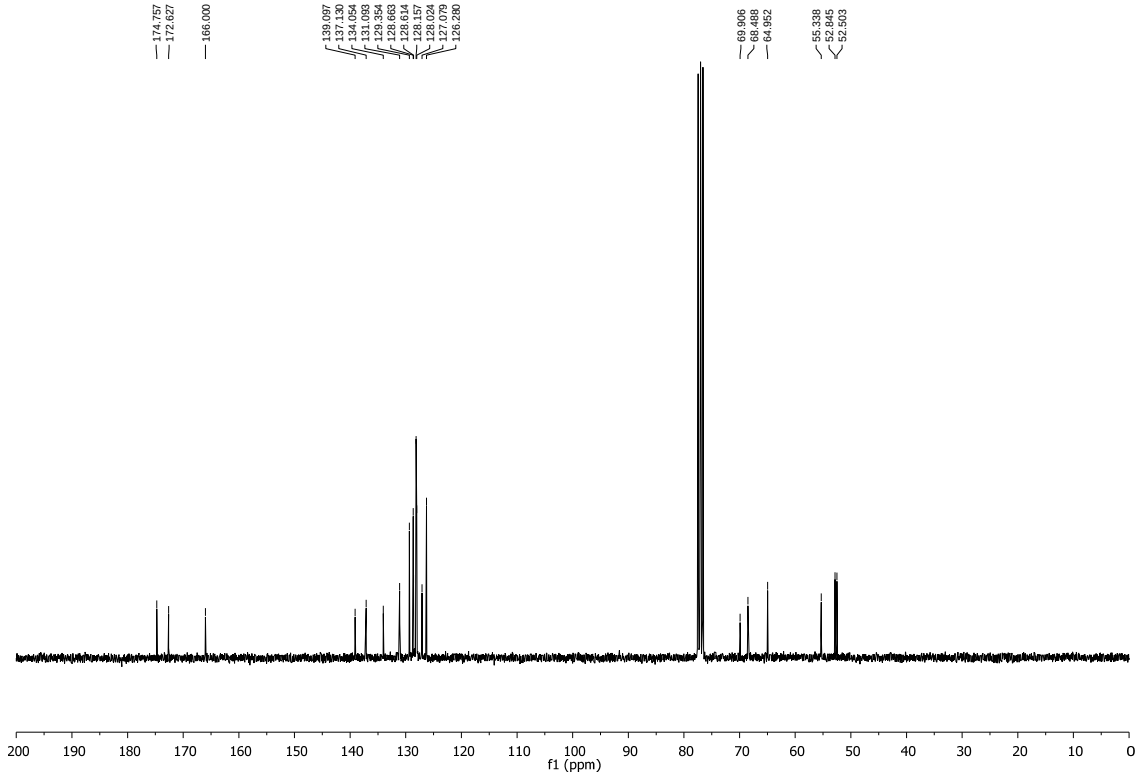


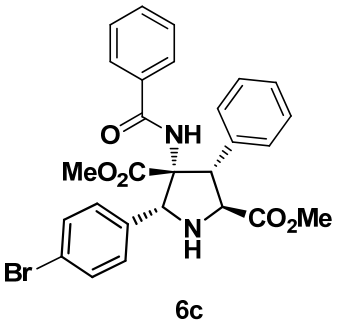



O
NH
MeO2C
CO2Me
N
H

6a

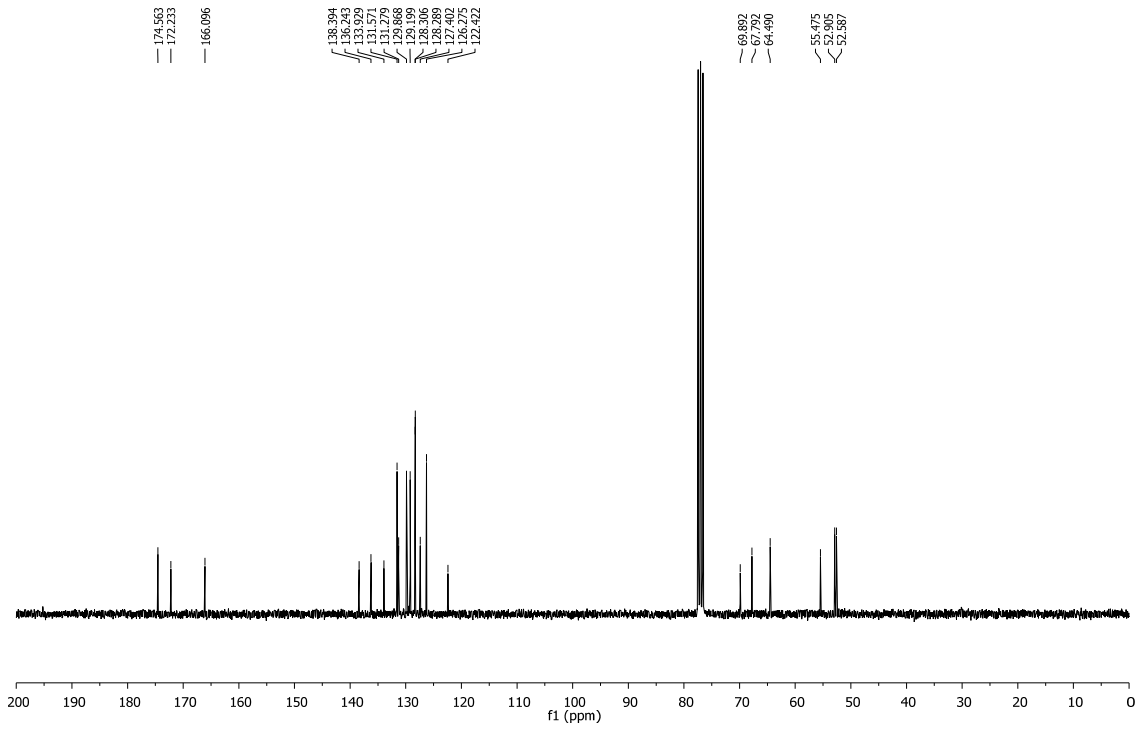

4.09
3.46
1.11
5.22
1.98
0.94
1.00
1.00
1.01
3.10
3.13
0.87
f1 (ppm)

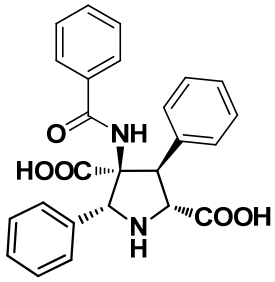

174.757
172.627
166.000
139.097
137.130
134.054
131.093
129.954
128.668
128.614
128.157
128.024
127.079
126.280
69.906
68.468
64.952
55.338
52.845
52.503
f1 (ppm)


O
NH
MeO2C
CO2Me
N
H
Br

6c

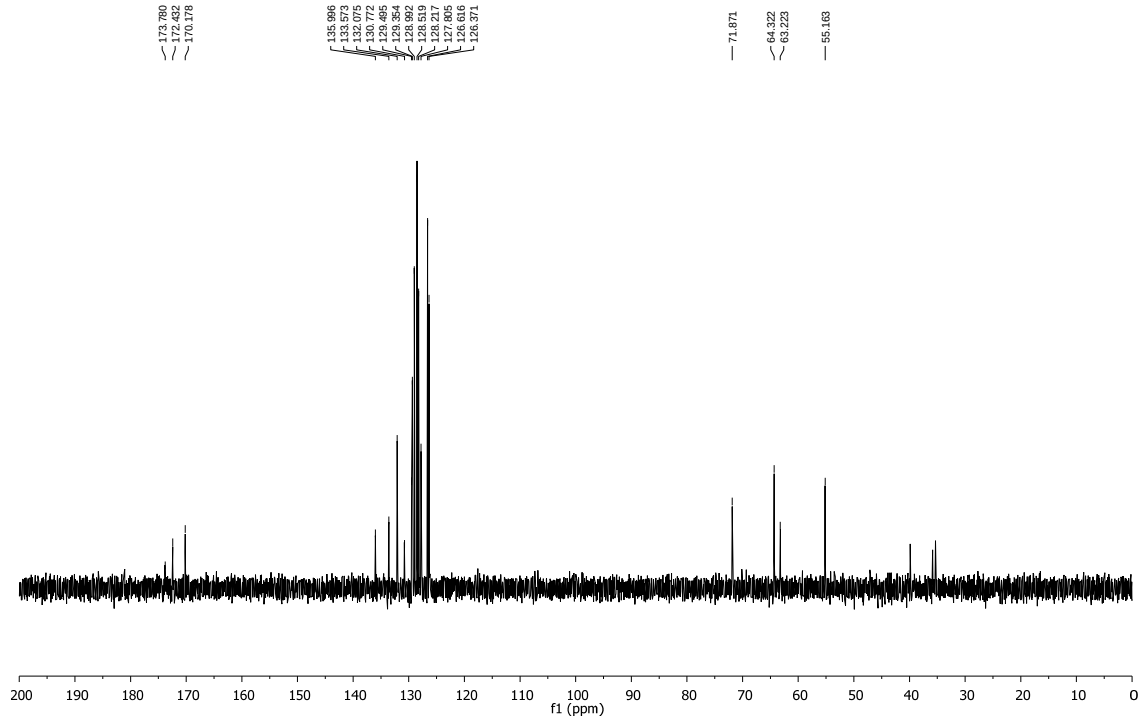
4.07
2.07
1.10
1.96
2.25
2.39
2.07
1.00
1.03
1.03
1.02
2.91
3.14
0.85
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

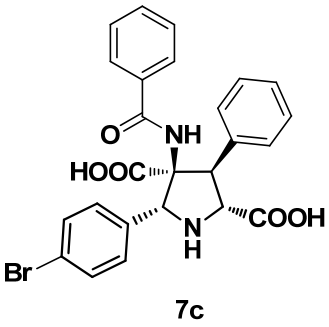

174.563
172.233
166.096
138.394
136.243
133.929
131.571
131.279
129.868
129.199
128.306
128.289
127.402
126.275
122.422
69.892
67.792
64.490
55.475
52.905
52.587
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
NH
HOOC
COOH
N
H

7a

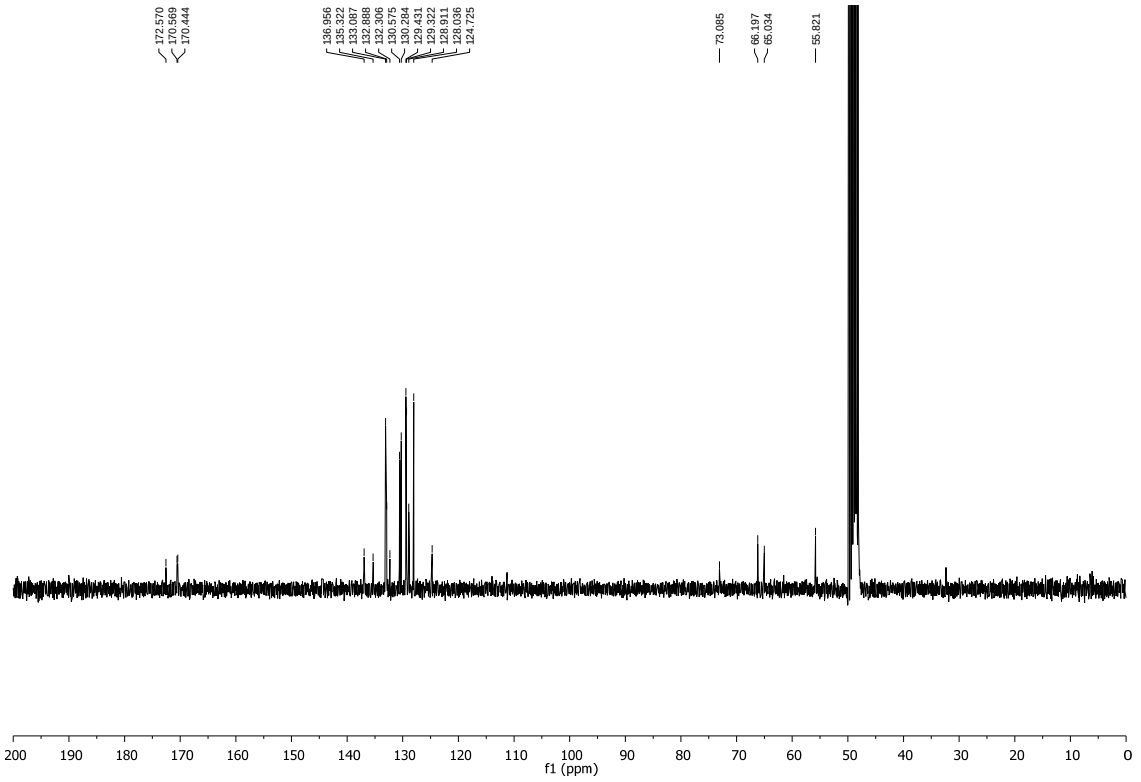
6.09
8.19
1.07
1.00
1.07
1.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

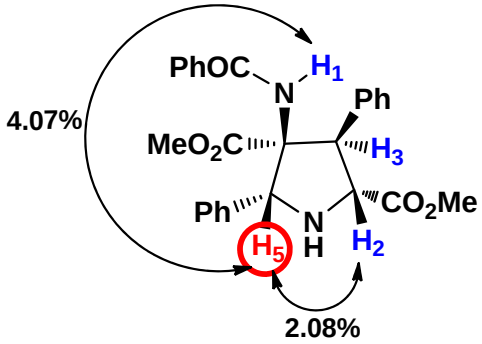

173.780
172.432
170.178
135.996
133.573
132.075
130.772
129.495
129.354
128.992
128.519
128.217
127.805
126.616
126.371
71.871
64.322
63.223
55.163
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
NH
HOOC
COOH
N
H
Br

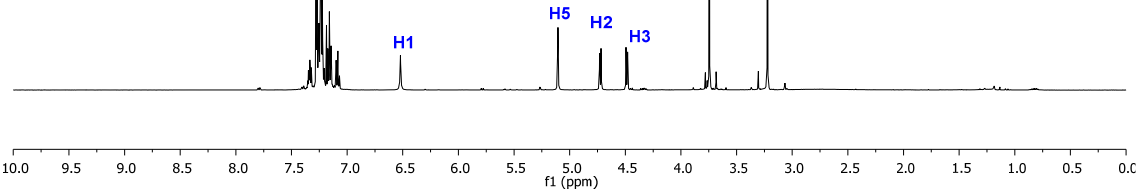
7c

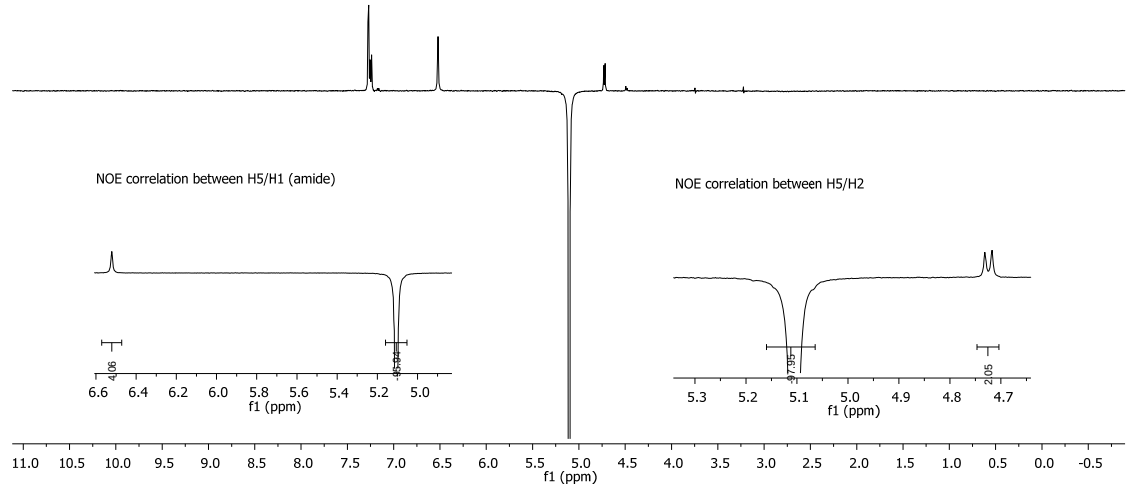
2.47
2.63
10.58
1.00
1.01
0.81
f1 (ppm)

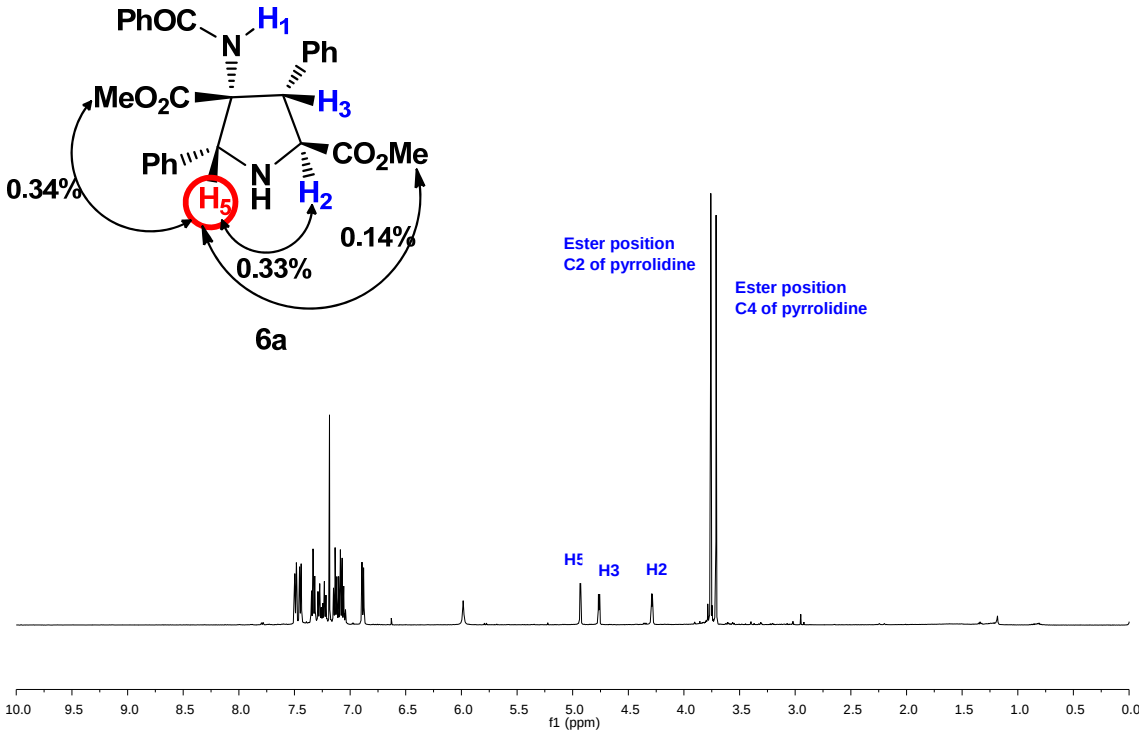

172.570
170.569
170.444
136.956
135.322
133.087
132.888
132.306
130.575
130.284
129.431
129.322
129.011
128.036
124.725
73.085
66.197
65.034
55.821
f1 (ppm)

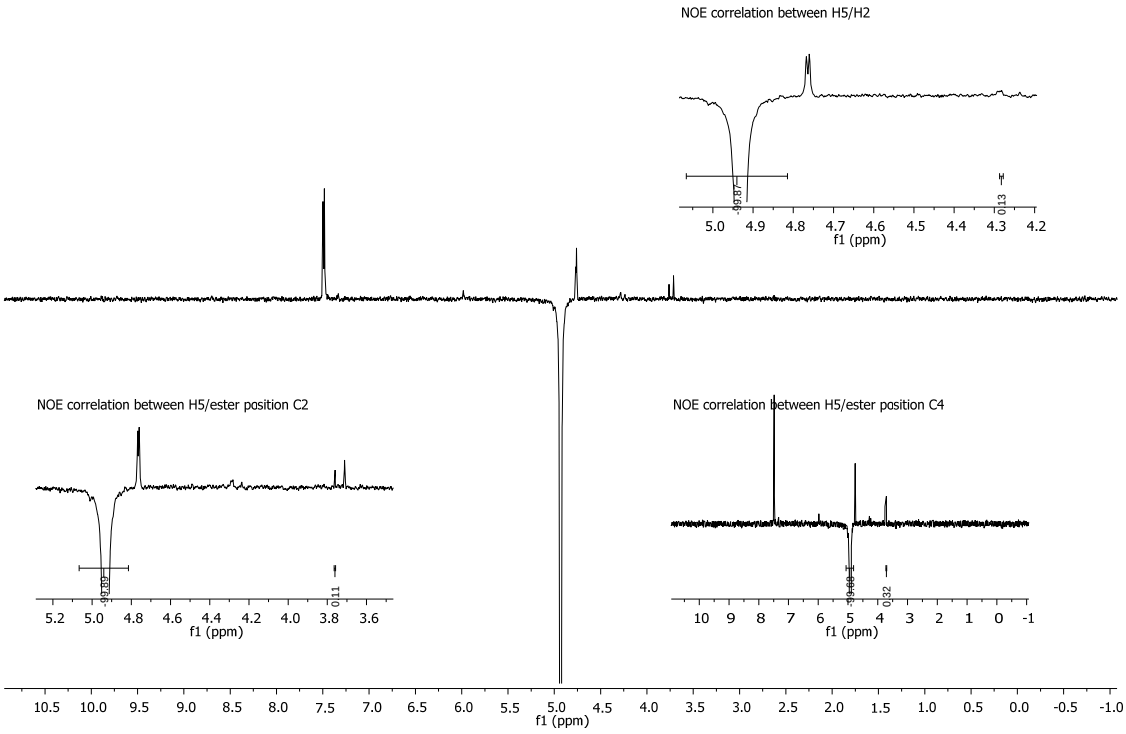

PhOC
N
H1
Ph
4.07%
MeO2C
H3
Ph
CO2Me
N
H
H5
H2
2.08%

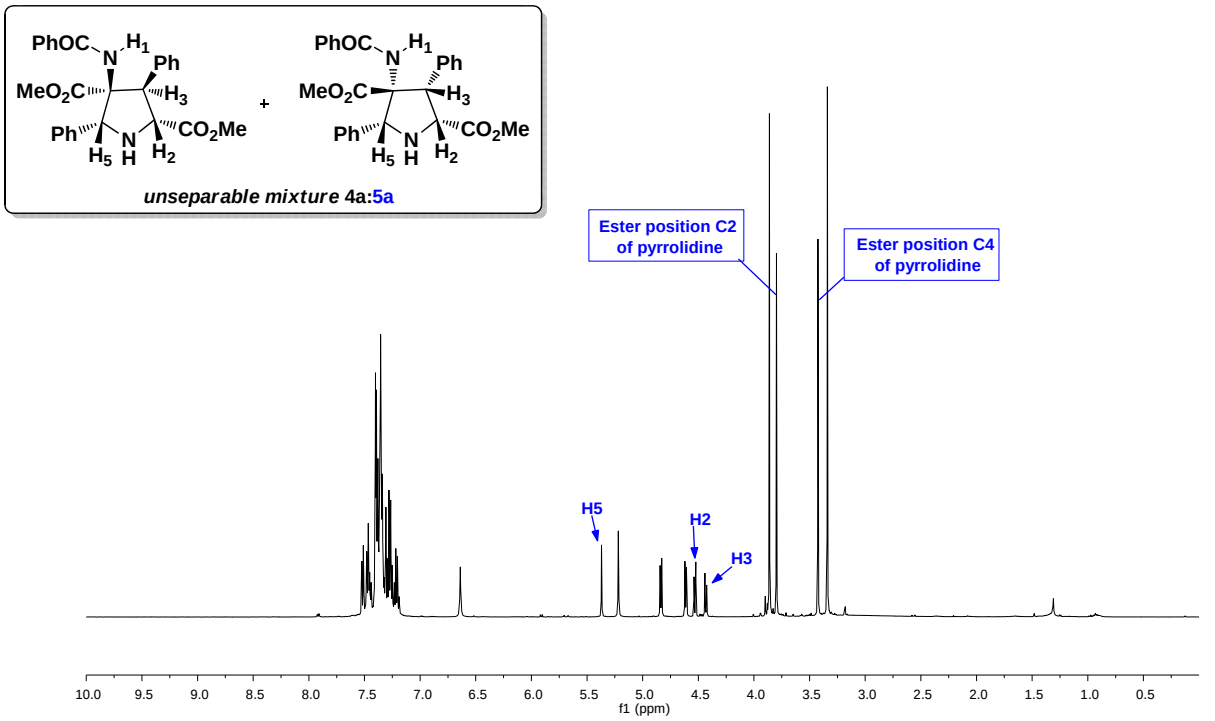
4a

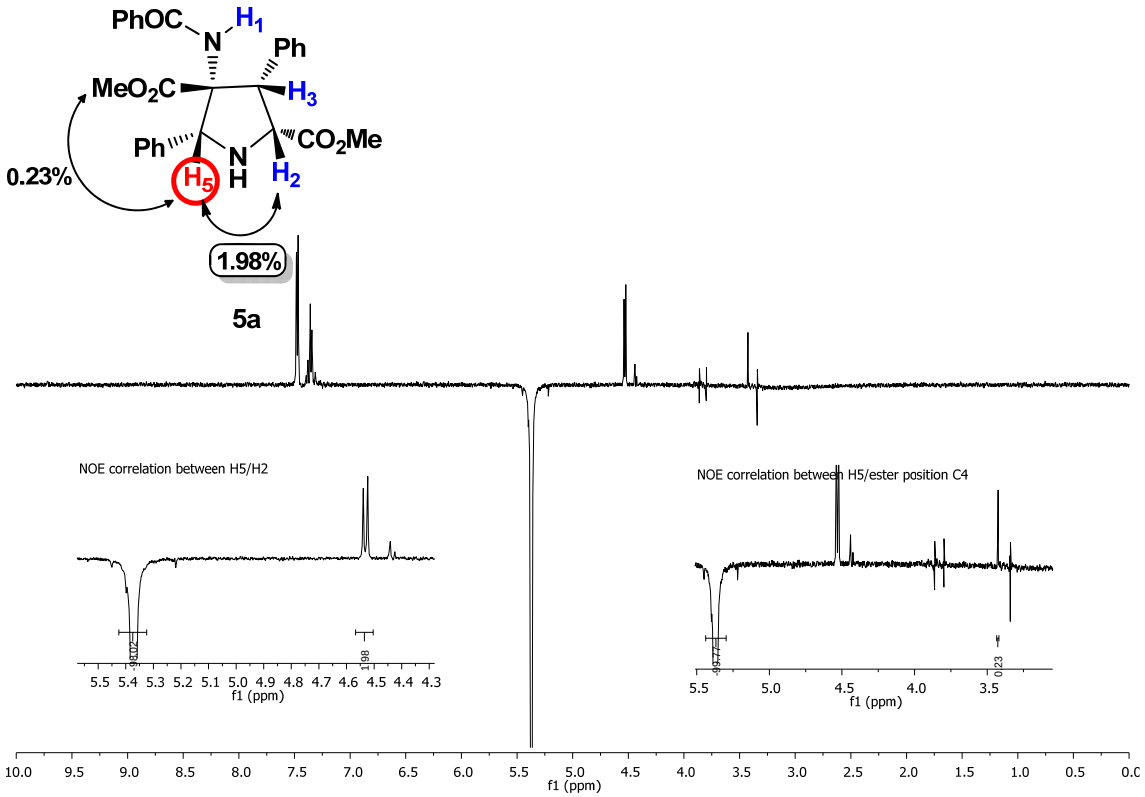

H5
H2
H3
H1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

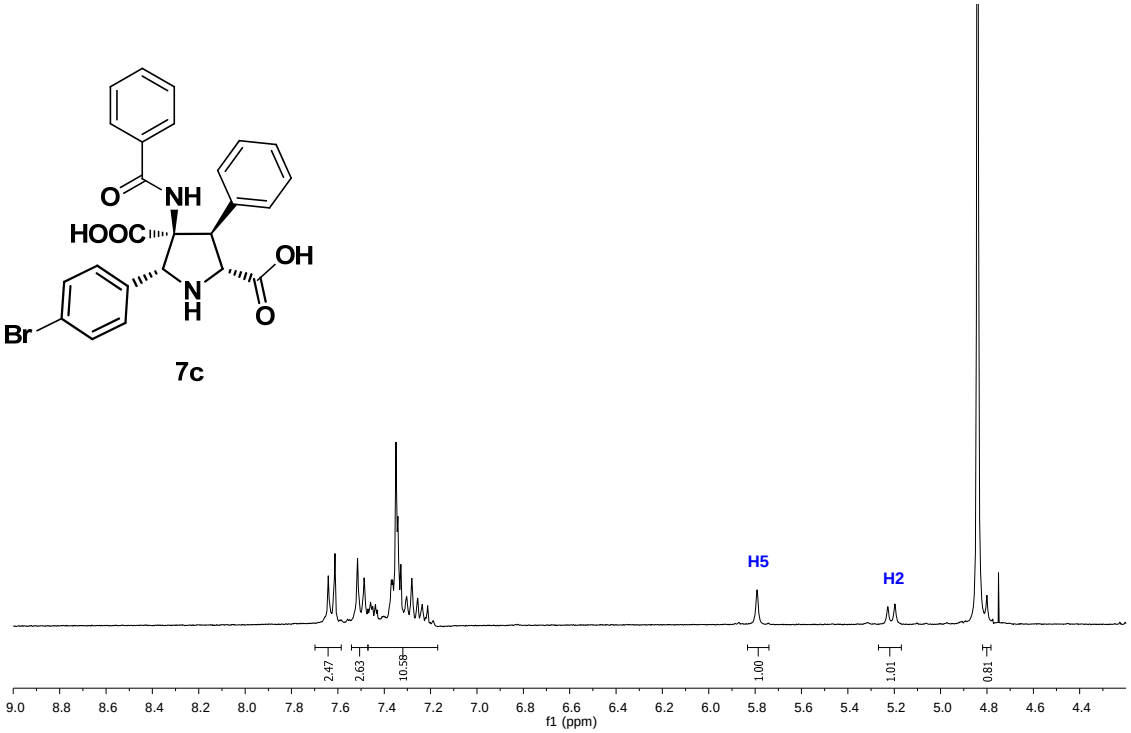

NOE correlation between H5/H1 (amide)
4.06
45.34
6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0
f1 (ppm)
NOE correlation between H5/H2
37.95
2.05
5.3 5.2 5.1 5.0 4.9 4.8 4.7
f1 (ppm)
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

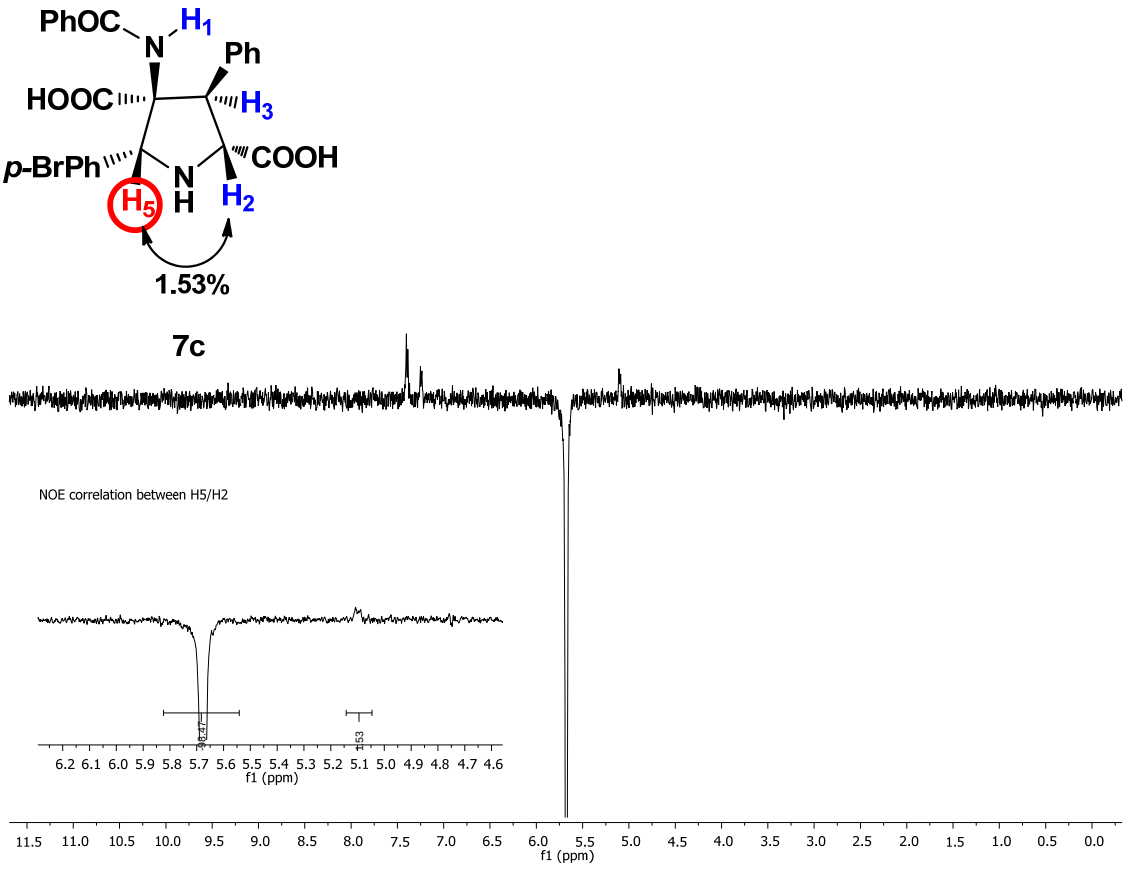

PhOC
N
H1
Ph
MeO2C
H3
Ph
N
H
CO2Me
H5
H2
0.34%
0.14%
0.33%
6a
Ester position
C2 of pyrrolidine
Ester position
C4 of pyrrolidine
H5
H3
H2
f1 (ppm)


NOE correlation between H5/H2
NOE correlation between H5/ester position C2
NOE correlation between H5/ester position C4
f1 (ppm)


PhOC
N
H1
Ph
MeO2C
H3
Ph
N
H
H5
CO2Me
H2
+
unseparable mixture 4a:5a
Ester position C2 of pyrrolidine
Ester position C4 of pyrrolidine
H5
H2
H3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


PhOC
N
H1
Ph
MeO2C
H3
Ph
N
H
H5
CO2Me
H2
0.23%
1.98%
5a
NOE correlation between H5/H2
5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3
f1 (ppm)
NOE correlation between H5/ester position C4
5.5 5.0 4.5 4.0 3.5
f1 (ppm)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


O
NH
HOOC
OH
N
H
O
Br
7c
H5
H2
2.47
2.63
10.58
1.00
1.01
0.81
9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4
f1 (ppm)


PhOC
N
H1
Ph
HOOC
H3
p-BrPh
COOH
N
H
H5
H2
1.53%
7c
NOE correlation between H5/H2
38.47
1.53
6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6
f1 (ppm)
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)