Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Novel carbohydrates-based bifunctional organocatalysts for the stereoselective nucleophiles addition to nitroolefins and imines

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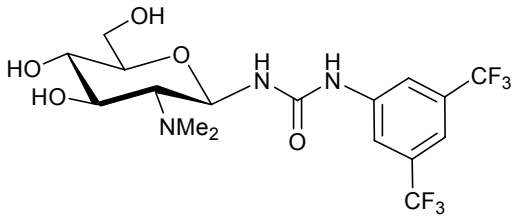
Electronic Supporting Information

Synthesis and characterization of bifunctional catalysts 13 and 16. Characterization details of bifunctional catalysts 10, 12, and 14. Copies of ^{1}H and ^{13}C NMR spectra of compounds 3, 7, 10, 11, 12, 13, 14, and 16. ^{1}H NMR and HPLC chromatograms on chiral stationary phase of products of addition of acetyl acetone to nitrostyrenes and of diethyl malonate to imines.

General. All reactions were carried out in oven-dried glassware with magnetic stirring under nitrogen atmosphere, unless otherwise stated. All commercially available reagents including dry solvents were used as received. Organic extracts were dried over sodium sulfate, filtered, and concentrated under vacuum using a rotatory evaporator. Nonvolatile materials were dried under high vacuum. Reactions were monitored by thin-layer chromatography on pre-coated Merck silica gel 60 F254 plates and visualized either by UV or by staining with a solution of cerium sulfate (1g) and ammonium heptamolybdate tetrahydrate (27 g) in water (469 mL) and concentrated sulfuric acid (31 mL). Flash chromatography was performed on Fluka silica gel 60. Proton NMR spectra were recorded at 300 K (unless otherwise stated) on spectrometers operating at 300, 400 or 500 MHz respectively. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). In ^{13}C NMR spectra, signals corresponding to aromatic carbons are omitted. Optical rotations were obtained on a polarimeter at 589 nm using a 5 mL cell with a length of 1 dm. HPLC for e.e. determination was performed under the conditions reported below. High resolution mass spectra (MS) were performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature), with Mass Spectrometer *APEX II* & *Xmass* software (Bruker Daltonics). Mass spectra (MS) were performed on a hybrid quadrupole time of flight mass spectrometer equipped with an ESI ion source.

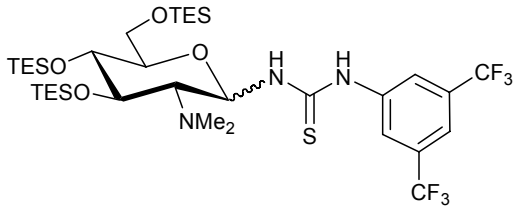
Synthesis and characterization of bifunctional catalysts 13 and 16

***N*-[2-*N*,*N*-dimethylamino-2-deoxy-β-D-glucopyranosyl], *N*'-(3,5-bis-trifluoromethyl)phenyl urea (13).**



Compound **10** (52 mg, 0.089 mmol) was dissolved in dry methanol (10 mL) under inert atmosphere, then a 1M soln of MeONa in MeOH was added at rt until basic pH. When the starting material disappeared (TLC analysis), the reaction was neutralized with IR-120 resin (H^+ form), filtered and concentrated under reduced pressure, obtaining compound **13** as a colourless glass (38 mg, qu).
^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H, NH), 8.06 (s, 2H, Ar), 7.50 (s, 2H, Ar), 5.05 (d, 1H, J = 9.6 Hz, H-1), 3.89 (dd, 1H, J = 11.7, 1.9 Hz, H-6a), 3.73-3.65 (m, 2H, H-3, H-6b), 3.38-3.30 (m, 2H, H-4, H-5), 2.54 (s, 6H, NMe_2), 2.48 (t, 1H, J = 93.9 Hz, H-2), ^{13}C NMR (100.6 MHz, CD_3OD) δ 78.7, 77.8, 73.1, 71.4, 67.5, 61.5, 40.8; Anal. Calcd for $C_{17}H_{21}F_6N_3O_5$ (461.36): C, 44.26; H, 4.59; N, 9.11; Found: C, 44.31; H, 4.50; N, 9.05.

***N*-[2-*N*,*N*-dimethylamino-2-deoxy-3,4,6-tri-*O*-triethylsilyl-β-D-glucopyanosyl], *N*'-(3,5-bis-trifluoromethyl)phenyl thiourea (16).**



Compound **15** (71 mg, 0.123 mmol), obtained from **3** as described in the general procedure reported in the Experimental Section, and 3,5-bis-trifluoromethylphenyl isothiocianate (22 μL, 0.123 mmol) were dissolved in dry THF under inert atmosphere, then a catalytic amount of Pd/C was added and the solution was stirred at rt for 2 days. The reaction was filtered over a celite pad and concentrated. Purification of the crude by flash chromatography (eluent Hexane/EtOAc 98:2 + TEA 1%) provided compound **16** (46 mg, 46%, α/β mixture), as a pale yellow oil.

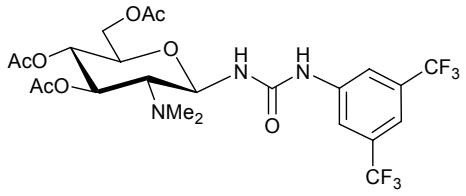
α_D = -17,63 (c 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, 300K, CD_3CN) first epimer: δ 9.10 (bs, 1H, NH), 8.20 (s, 2H, Ar), 7.75 (s, 1H, Ar), 5.90 (s, 1H, H-1), 3.89 (m, 1H, H-3), 3.85 (dd, 1H, *J* = 9.0, 11.0 Hz, H-6a), 3.80 (m, 1H, H-4), 3.78 (dd, 1H, *J* = 3.0 Hz, H-6b), 3.60 (m, 1H, H-5), 2.77 (m, 1H, H-2), 2.50 (s, 6H, NMe_2), 1.0-0.5 (m, 45H, 3 Et_3Si), ^{13}C NMR (125.75 MHz, 300K, CD_3CN) first epimer: δ 182.1, 80.3, 79.5, 75.0, 72.1, 70.2, 63.3, 42.1, 6.4, 3.1.

^{1}H NMR (500 MHz, 300K, CD_3CN) second epimer: δ 9.10 (s, 1H, NH), 8.20 (s, 2H, Ar), 7.76 (s, 1H, Ar), 5.5 (s, 1H, H-1), 3.94 (m 1H, H-3), 3.93 (dd, 1H, *J* = 9.0, 11.0 Hz, H-6a), 3.82 (dd, 1H, *J* = 3.0 Hz, H-6b), 3.41 (m, 1H, H-4), 3.37 (m, 1H, H-5), 2.60 (m, 1H, H-2), 2.60 (s, 6H, NMe_2), 1.0-0.5 (m, 45H, 3 Et_3Si); ^{13}C NMR (125.75 MHz, 300K, CD_3CN) second epimer: δ 183.2, 81.5, 77.6, 74.8, 72.8, 68.5, 63.0, 41.5, 6.7, 3.8;

ESI-MS: 820.4 g/mol; Anal. Calcd for $C_{35}H_{63}F_6N_3O_4SSi_3$ (820.20): C, 51.25; H, 7.74; N, 5.12; Found: C, 51.35; H, 7.87; N, 5.06.

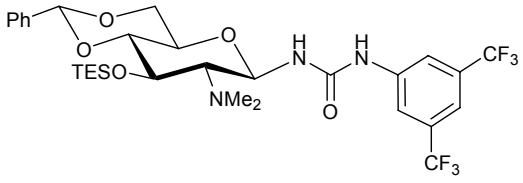
Characterization details of bifunctional catalysts 10, 12, and 14

***N*-[3,4,6-tri-*O*-acetyl-2-*N*,*N*-dimethylamino-2-deoxy-β-D-glucopyranosyl], *N*'-(3,5-bis-trifluoromethyl)phenyl urea (10).**



Flash chromatography: Hex/EtOAc 6:4 + TEA 1% (yield 52%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.97-7.88 (m, 3H, Ar, NH), 7.51 (s, 1H, Ar), 6.09 (d, 1H, *J* =5.6 Hz, NH), 5.44 (dd, 1H, *J* = 9.0, 10.3 Hz, H-3), 5.01 (dd, 1H, *J* =9.1, 10.1 Hz, H-4), 4.94 (dd, 1H, *J* = 4.7, 9.1 Hz, H-1), 4.31-4.21 (m, 2H, H-6a, H-6b), 3.84 (ddd, 1H, *J* = 2.6, 5.2, 7.9 Hz, H-5), 2.89 (t, 1H, *J* = 10.0 Hz, H-2), 2.47 (s, 6H, NMe_2), 2.11 (s, 3H, OAc), 2.09 (s, 6H, 2OAc); ^{13}C NMR (100.6 MHz, CD_3OD) δ 170.8, 170.00, 169.9, 154.5, 80.5, 73.7, 70.8, 69.9, 66.1, 62.5, 41.6, 21.1, 20.7; ESI-MS 588.2 g/mol; Anal. Calcd. for $C_{23}H_{27}F_6N_3O_8$ (587.47): C, 47.02; H, 4.63; N, 7.15; Found: C, 47.12; H, 4.63; N, 7.08.

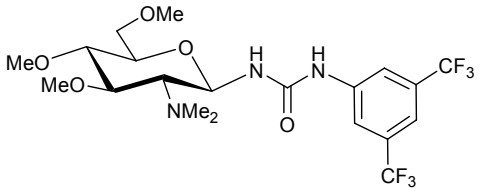
***N*-[2-*N*,*N*-dimethylamino-2-deoxy-4,6-*O*-benzylidene-3-*O*-triethylsilyl-β-D-glucopyranosyl], *N*'-(3,5-bis-trifluoromethyl)phenyl urea (12).**



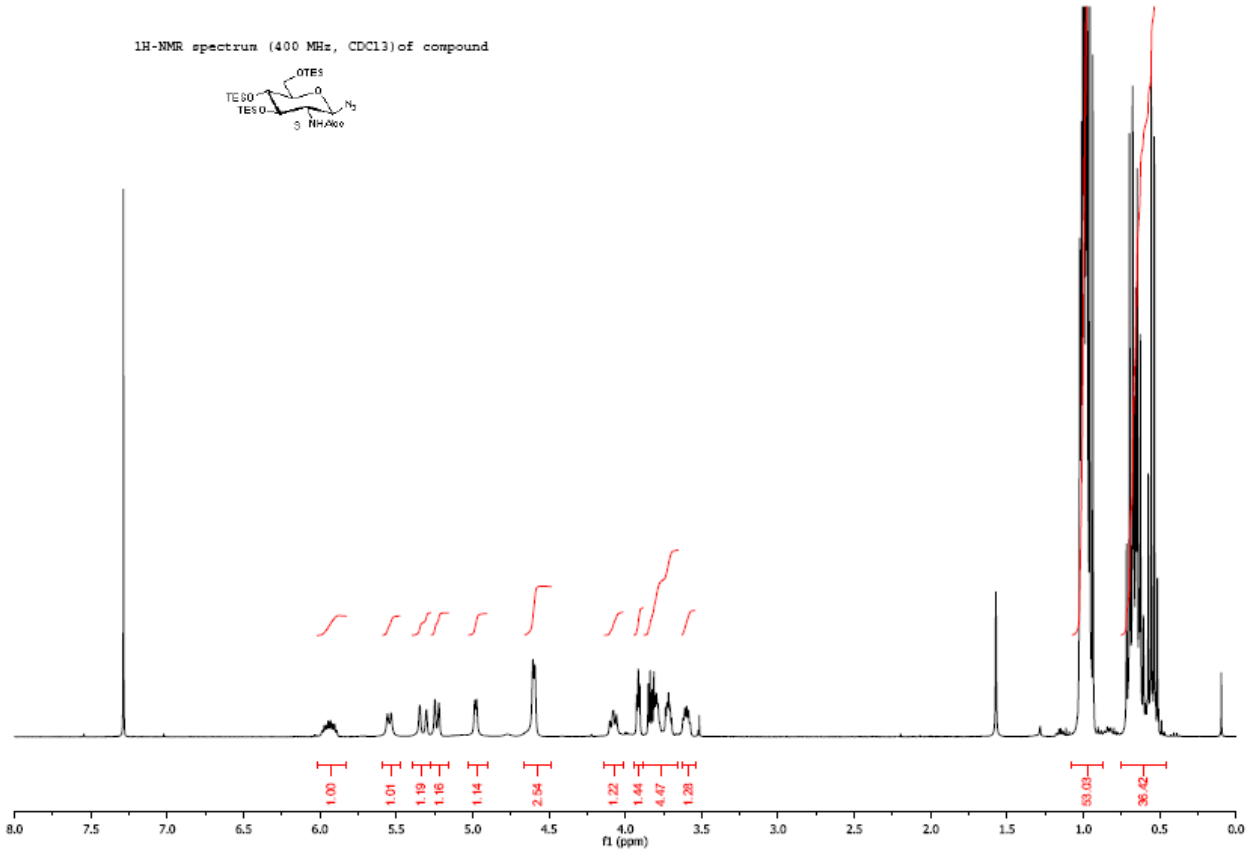
Flash chromatography: Hex/EtOAc 8:2 + TEA 1% (yield 61%); α_D = -33,2 (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (bs, 1H, NH), 7.87 (s, 2H, Ar), 7.52 (s, 1H, Ar), 7.50-7.7.38 (m, 5H, Ph), 6.13 (d, 1H, *J* = 5.3 Hz, NH), 5.48 (s, 1H, CHPh), 4.97 (dd, 1H, *J* = 9.4, 5.3 Hz, H-1), 4.37 (dd, 1H, *J* = 4.7, 10.4 Hz, H-6a), 4.17 (t, 1H, *J* = 9.0 Hz, H-3), 3.76 (t, 1H, *J* = 10.1 Hz, H-6b), 3.56 (dt, 1H, *J* = 9.6, 4.8 Hz, H-5), 3.47 (t, 1H, *J* = 8.8 Hz, H-4), 2.64 (t, 1H, *J* = 9.5 Hz, H-2), 2.58 (s, 6H, NMe_2), 0.90 (t, 9H, 3 $CH_{3\ TES}$), 0.60 (q, 6H, 3 $CH_{2\ TES}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.3, 102.7,

83.2, 81.2, 71.7, 69.9, 69.0, 68.4, 42.6, 7.3, 5.7; ESI-MS 664.4 g/mol; Anal. Calcd. for $C_{30}H_{39}F_6N_3O_5Si$ (663.72): C, 54.29; H, 5.92; N, 6.33; Found: C, 54.35; H, 6.01; N, 6.38.

_N_-[2-_N_,_N_-dimethylamino-2-deoxy-3,4,6-tri-_O_-methyl-β-D-glucopyranosyl],_N_'-(3,5-bis-trifluoromethyl)phenyl urea (14).



Flash chromatography: Hex/EtOAc 65:35 + 1% TEA (yield 71%); α_D = 5.40 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 2H, Ar), 7.55 (s, 1H, Ar), 4.74 (d, 1H, J = 8.7 Hz, H-1), 3.60, 3.49, 3.38 (3s, 9H, 3 OMe), 3.68-3.29 (m, 5H, H-3, H-4, H-5, H-6a, H-6b), 2.60-2.47 (m, 7H, H-2, NMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 114.6, 88.6, 82.2, 77.4, 71.0, 70.5, 60.8, 60.0, 59.6, 43.9; ESI-MS 503.2 g/mol; Anal. Calcd. for $C_{20}H_{27}F_6N_3O_5$ (503.44): C, 47.71; H, 5.41; N, 8.35; Found: C, 47.65; H, 5.48; N, 8.35.


1H-NMR spectrum (400 MHz, CDCl3)of compound
OTES
TESO
TESO
O
N3
NHAloc
1.00
1.01
1.19
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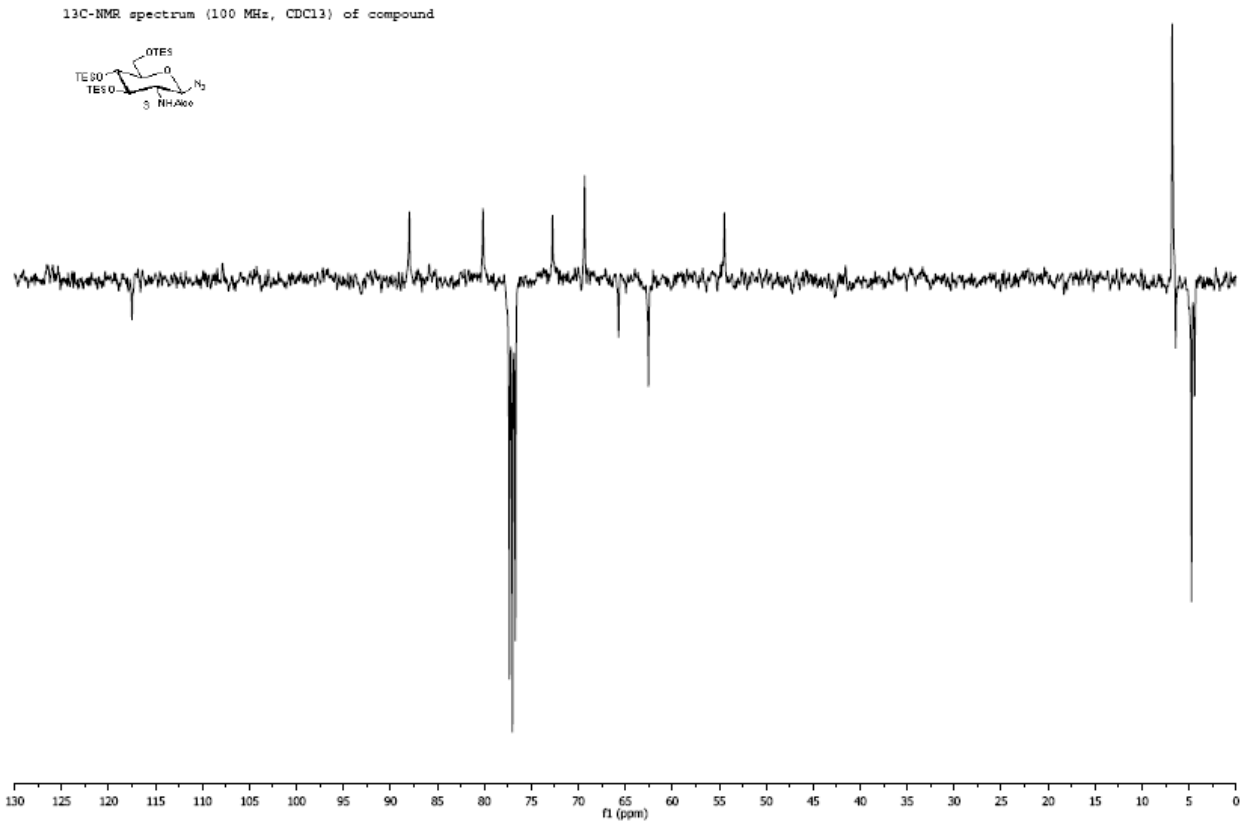
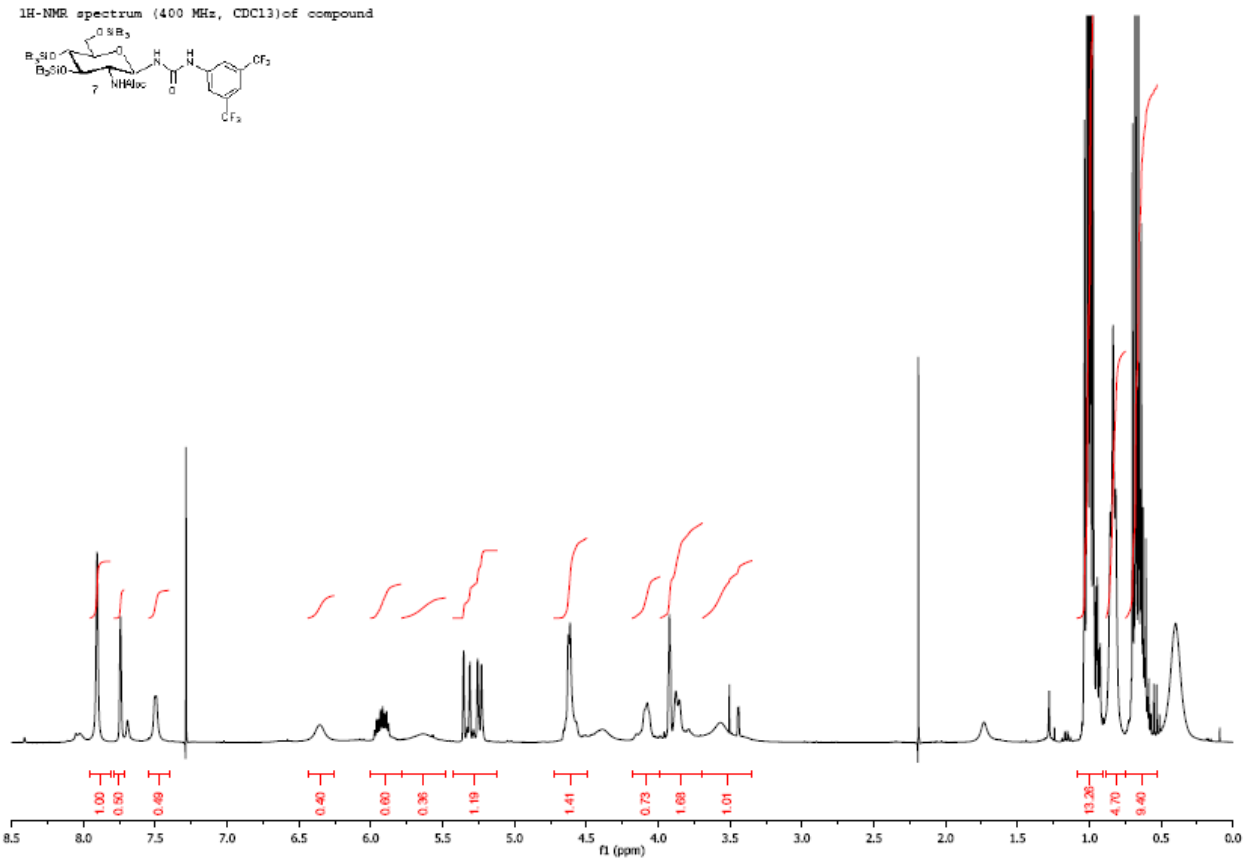
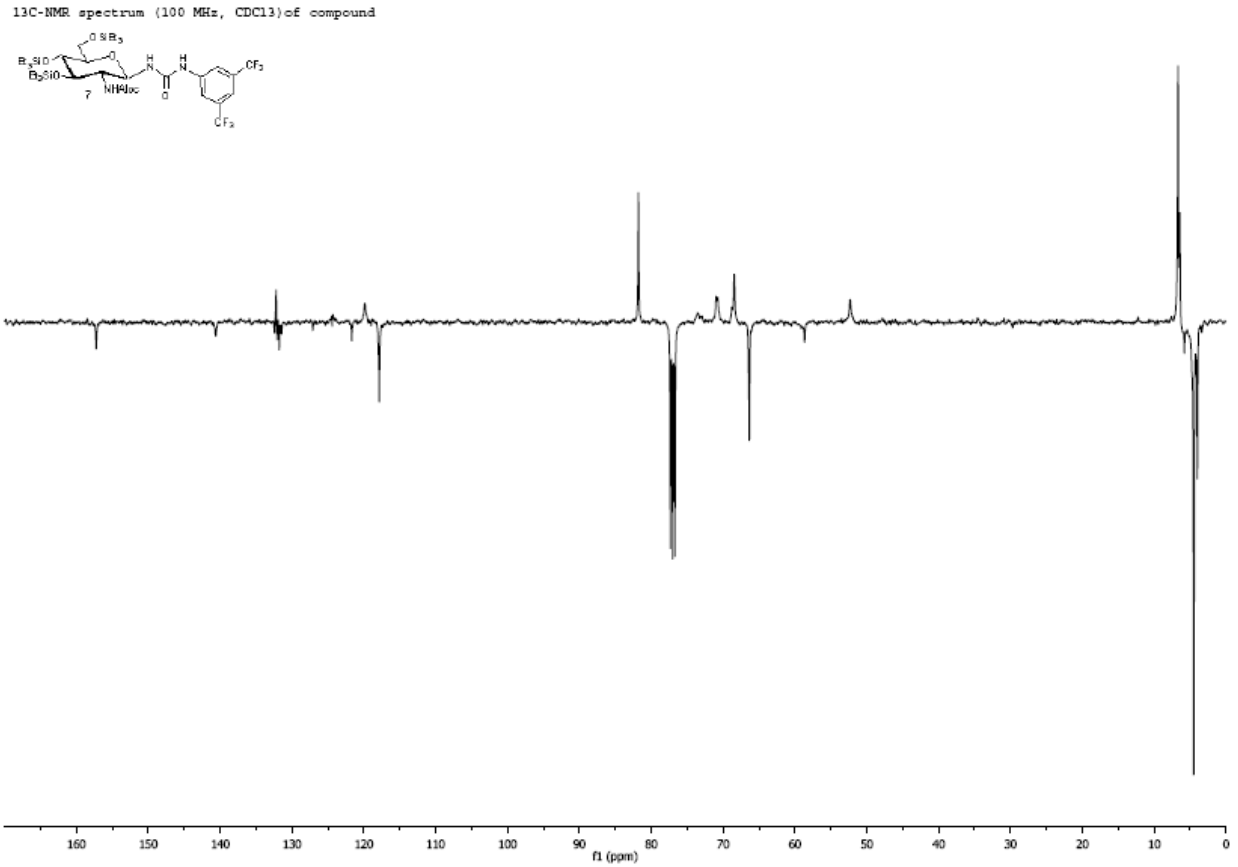
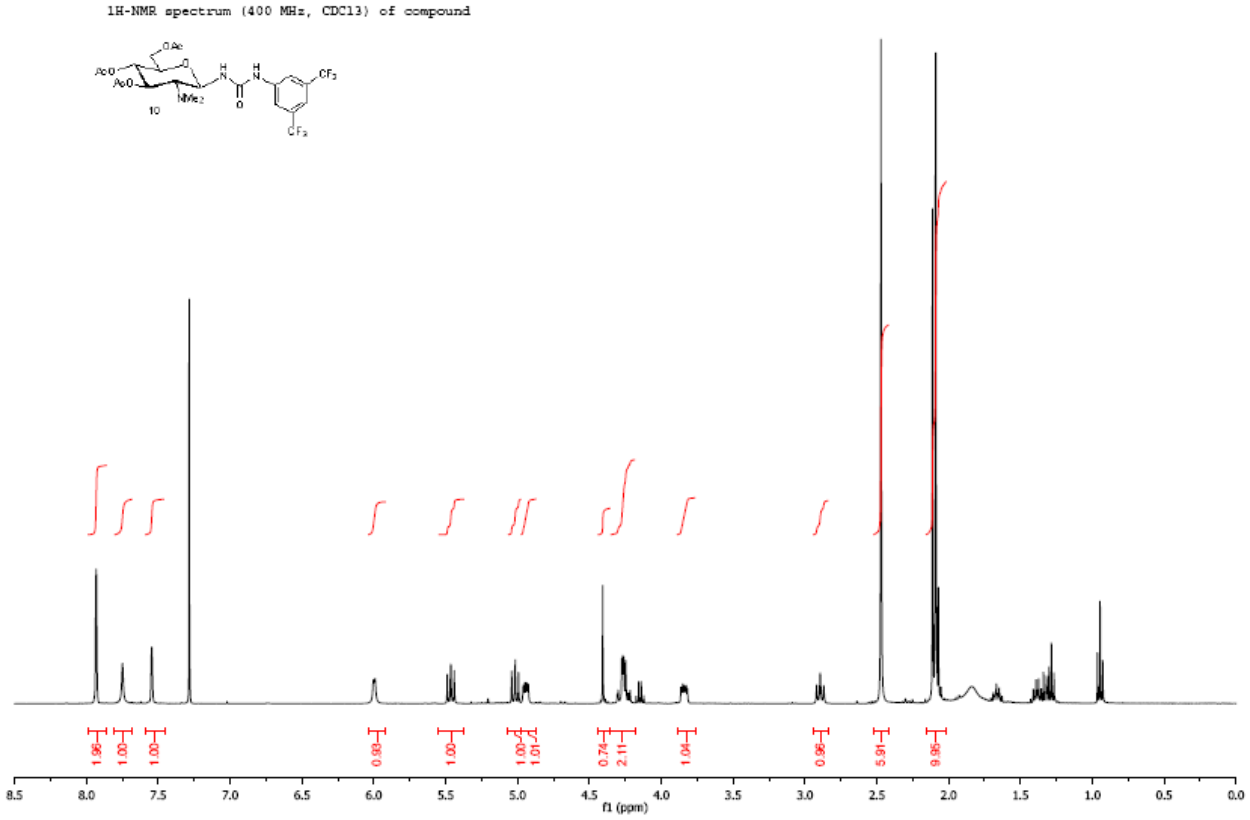
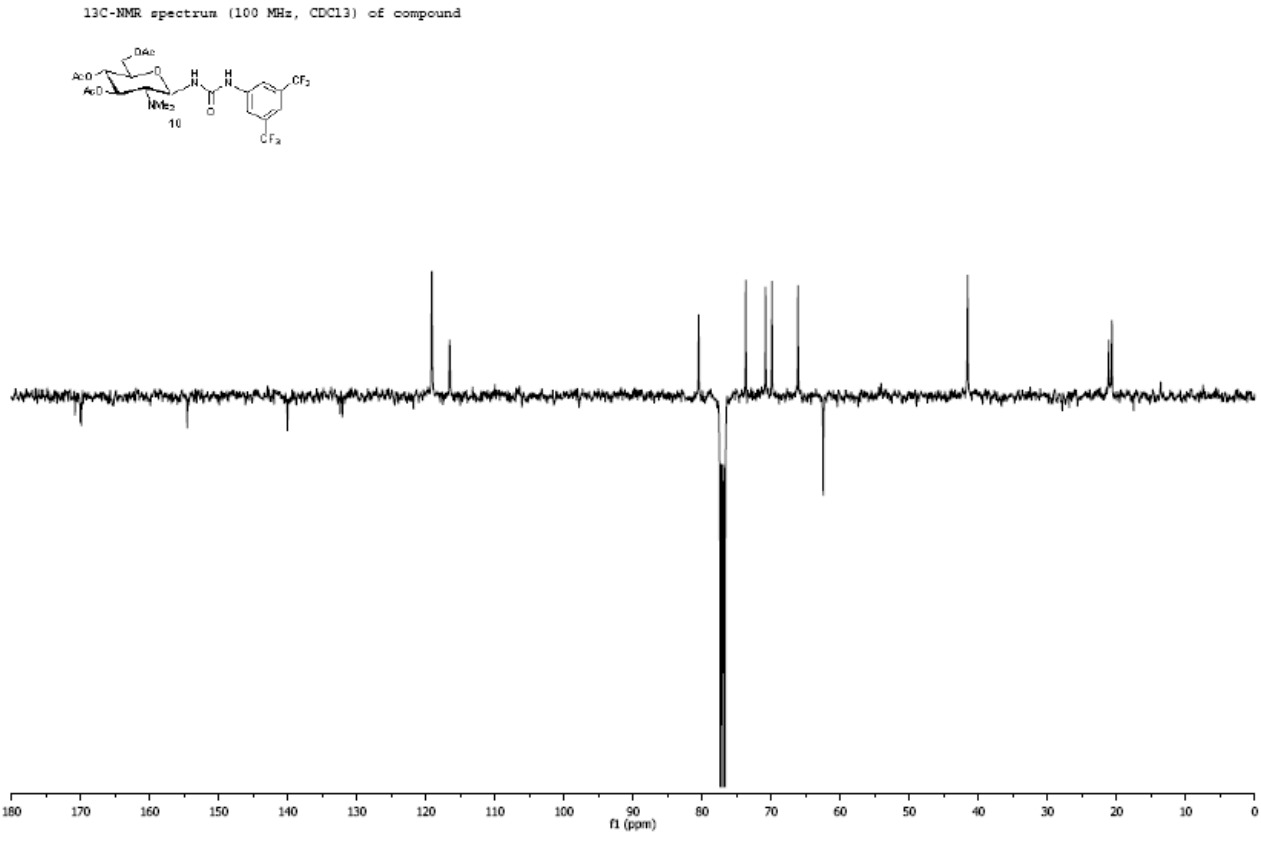
1.14
2.54
1.22
1.44
4.47
1.28
53.03
36.42
f1 (ppm)

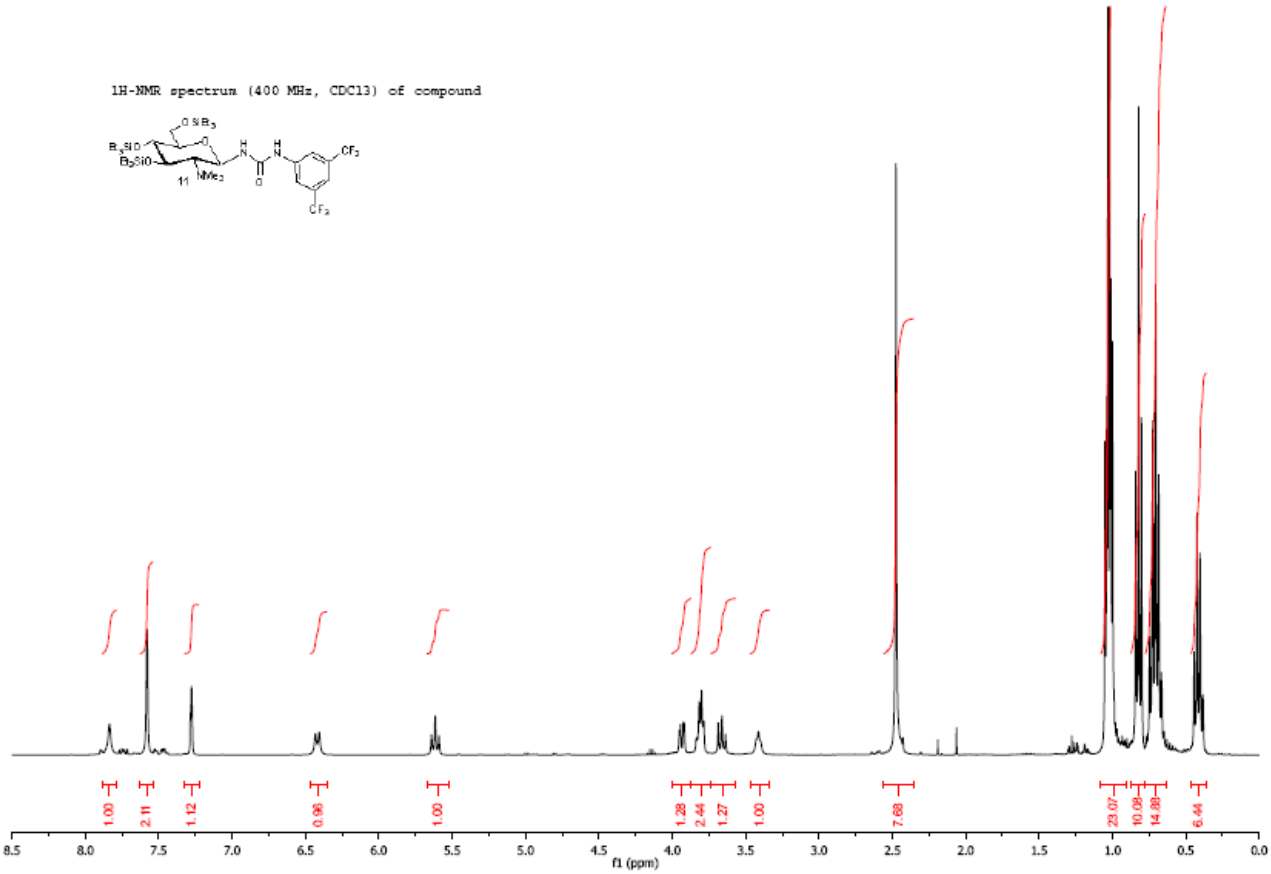

13C-NMR spectrum (100 MHz, CDCl3) of compound
OTES
TESO
TESO
O
N3
NHAloc
f1 (ppm)

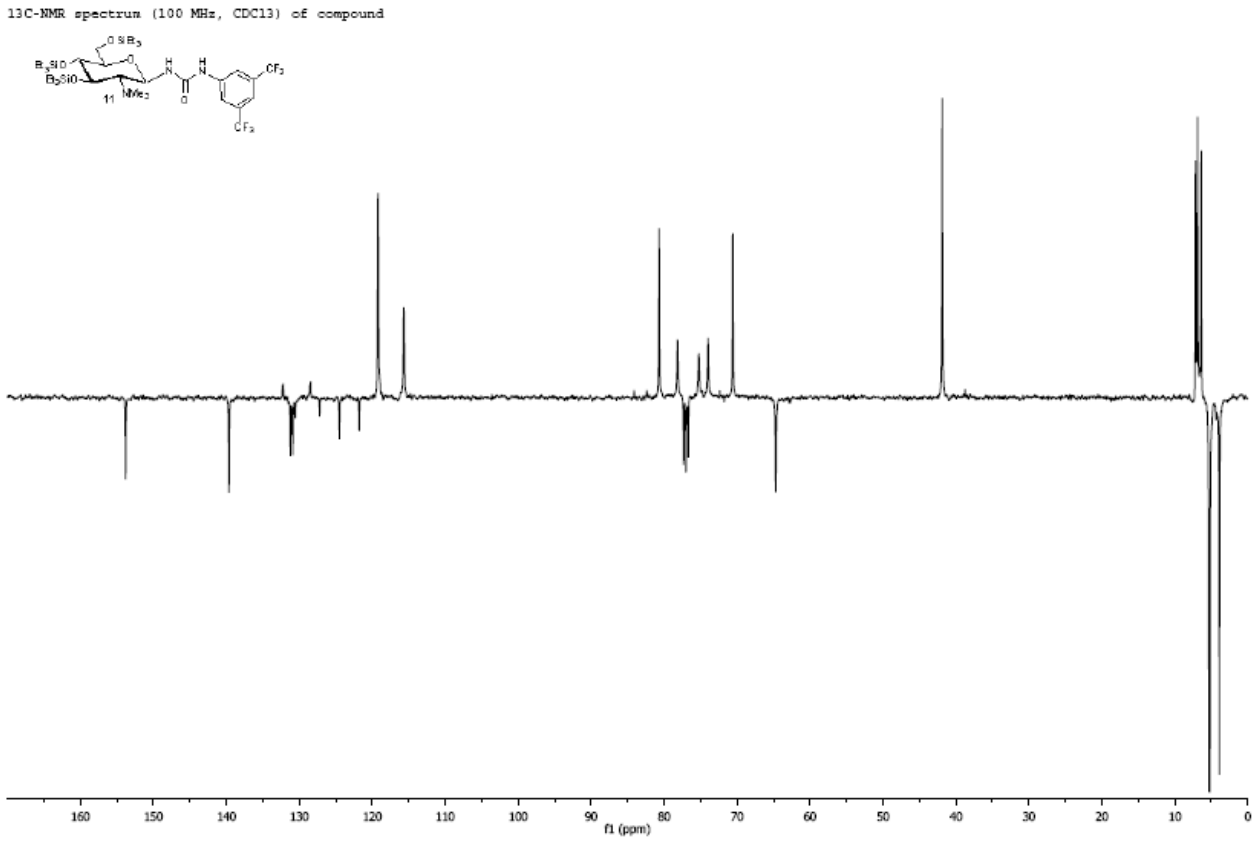

1H-NMR spectrum (400 MHz, CDCl3)of compound
1.00
0.50
0.49
0.40
0.60
0.36
1.19
1.41
0.73
1.68
1.01
13.26
4.70
9.40
f1 (ppm)

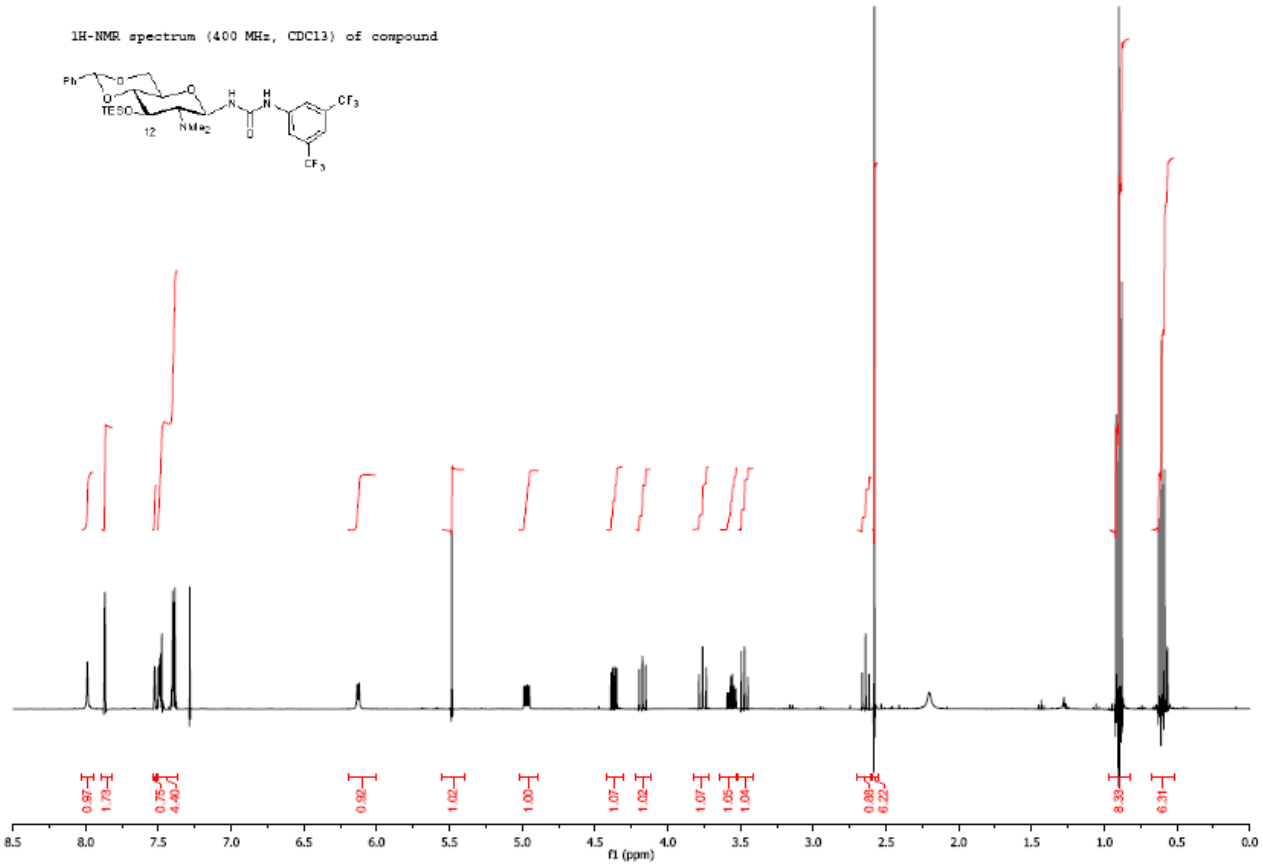

13C-NMR spectrum (100 MHz, CDCl3)of compound
f1 (ppm)

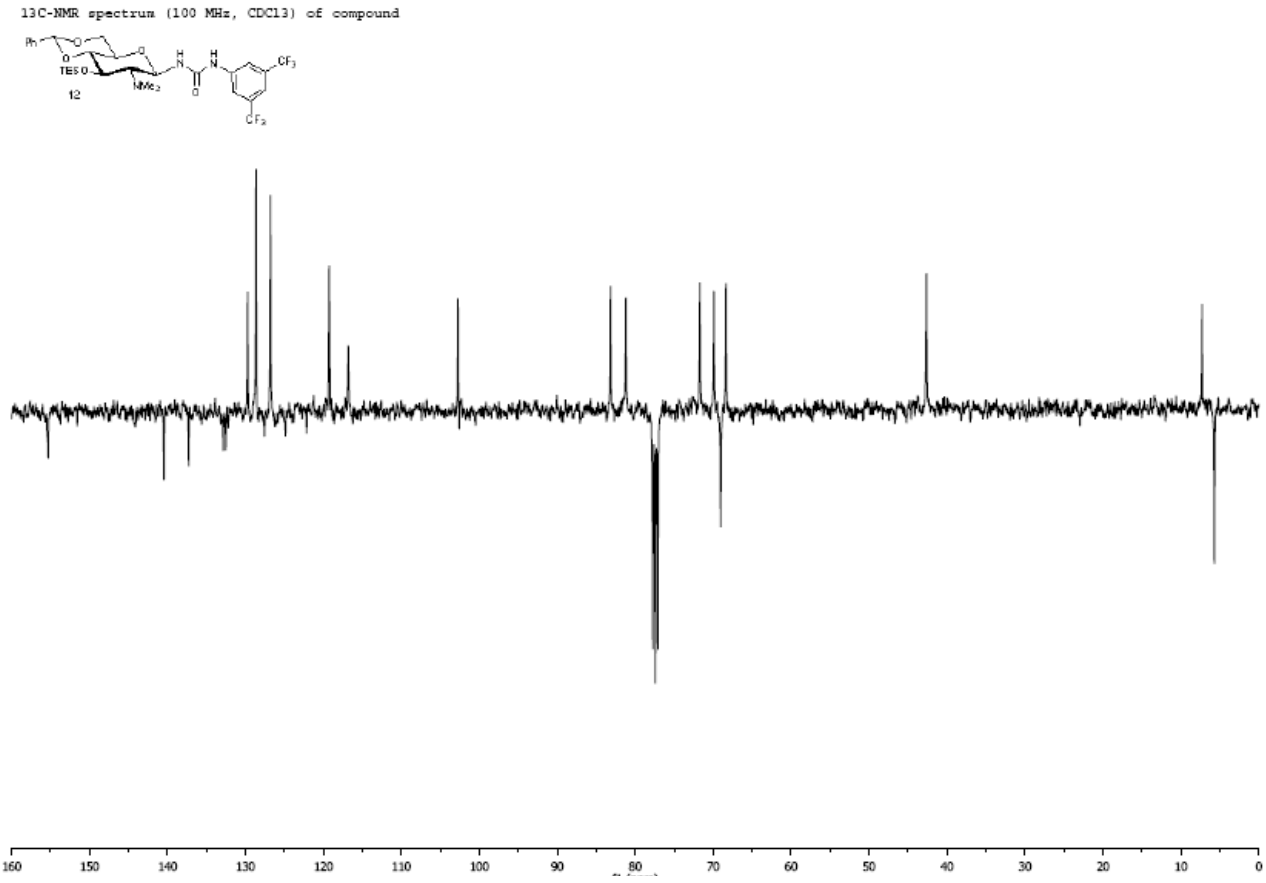

1H-NMR spectrum (400 MHz, CDCl3) of compound
f1 (ppm)

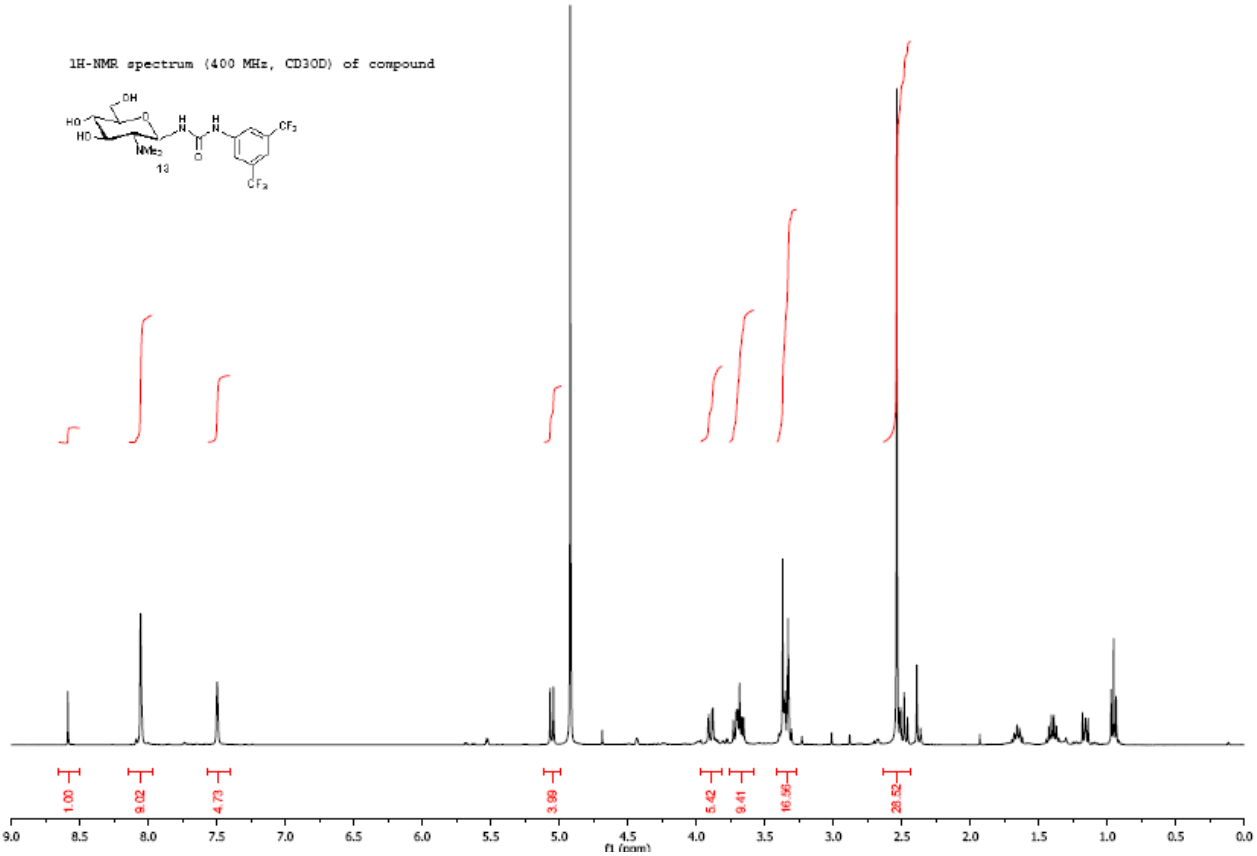

13C-NMR spectrum (100 MHz, CDCl3) of compound
f1 (ppm)

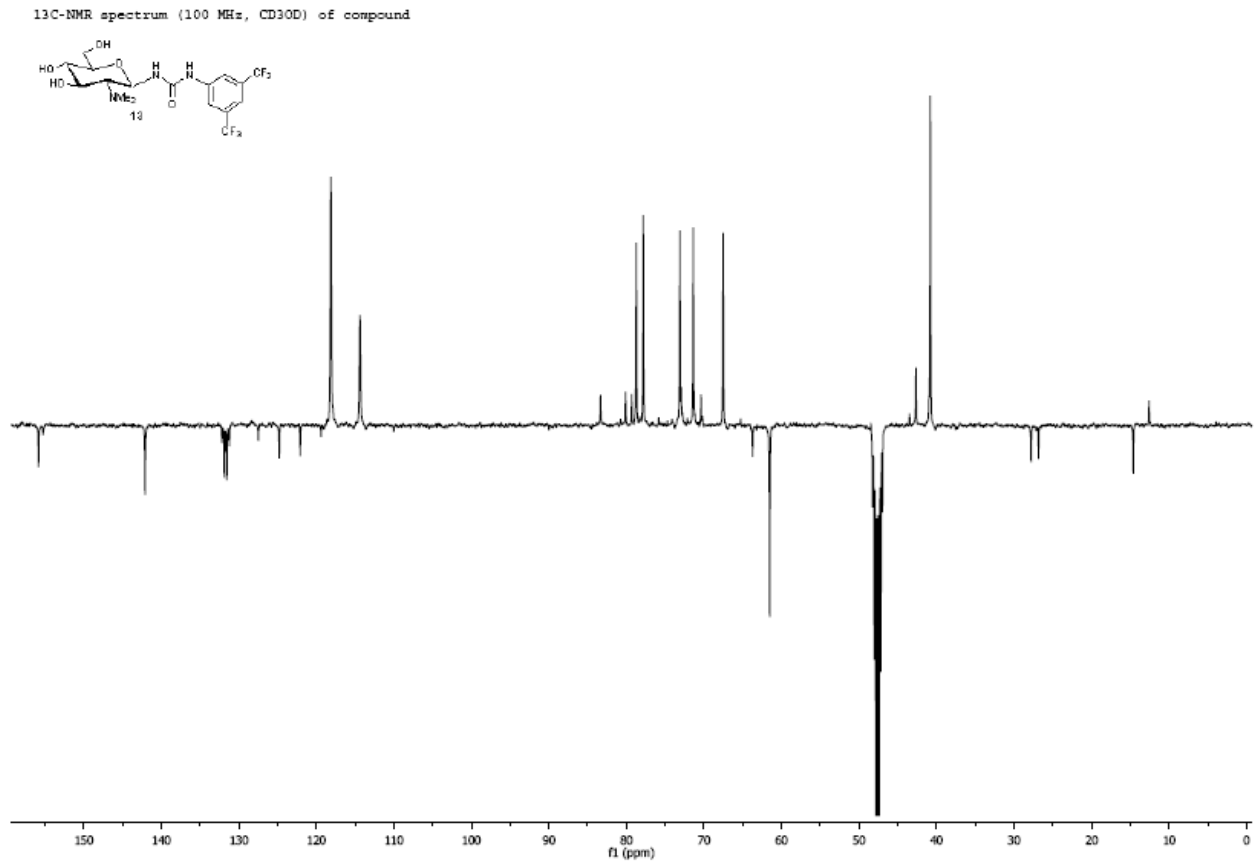

1H-NMR spectrum (400 MHz, CDCl3) of compound
1.00
2.11
1.12
0.98
1.00
1.28
2.44
1.27
1.00
7.68
23.07
10.08
14.88
6.44
f1 (ppm)

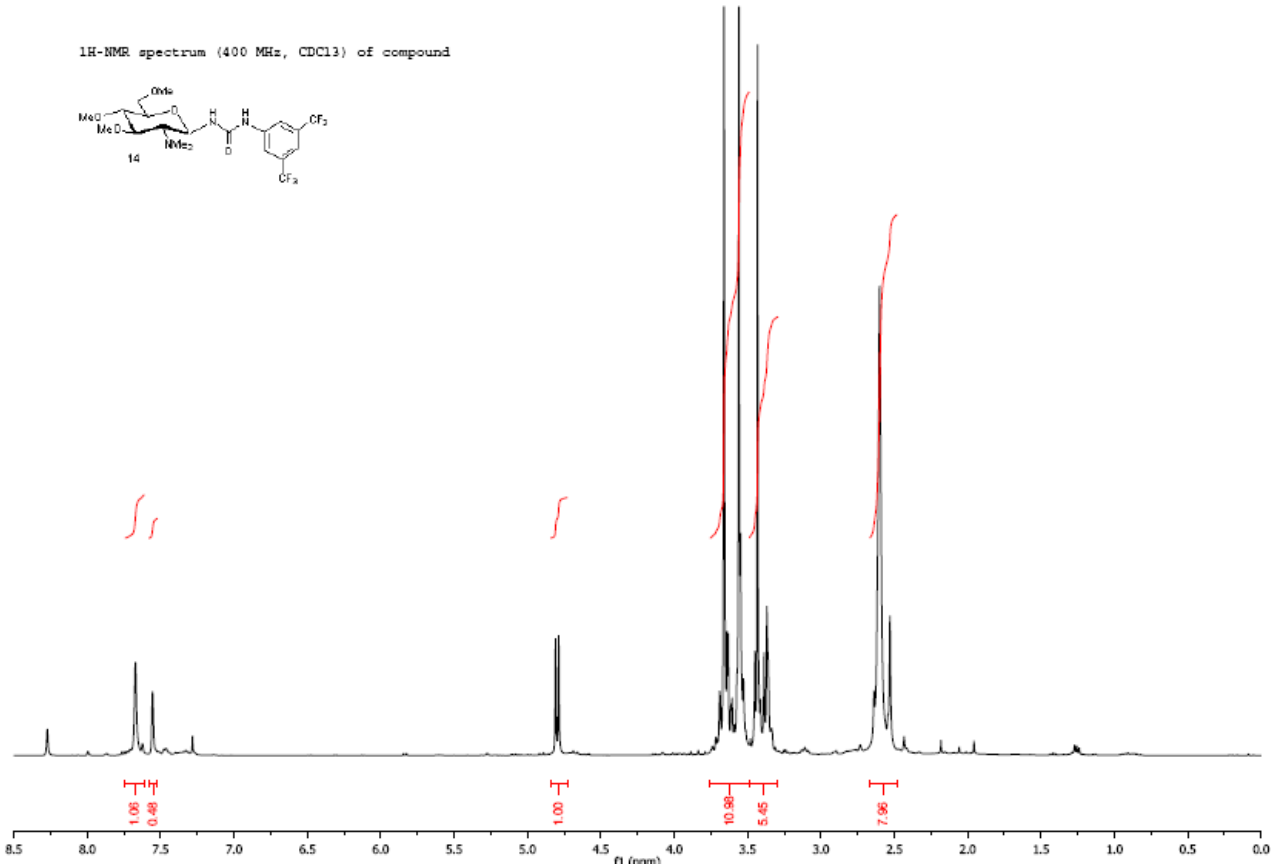

13C-NMR spectrum (100 MHz, CDCl3) of compound
f1 (ppm)

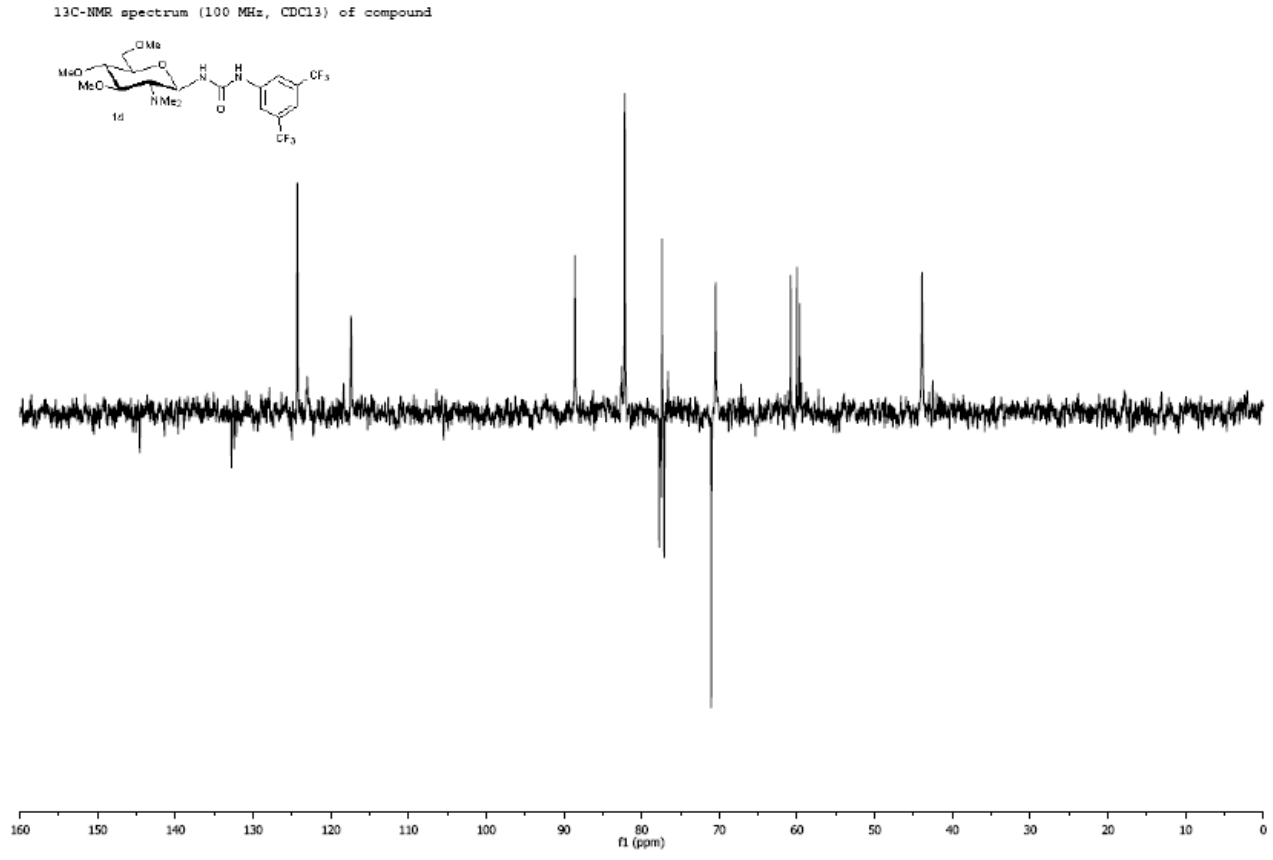

1H-NMR spectrum (400 MHz, CDCl3) of compound
f1 (ppm)


13C-NMR spectrum (100 MHz, CDCl3) of compound


1H-NMR spectrum (400 MHz, CD3OD) of compound
13
1.00
9.02
4.73
3.99
5.42
9.41
16.56
28.52
f1 (ppm)


13C-NMR spectrum (100 MHz, CD3OD) of compound
13
f1 (ppm)


1H-NMR spectrum (400 MHz, CDCl3) of compound
14
1.06
0.49
1.00
10.98
5.45
7.96
f1 (ppm)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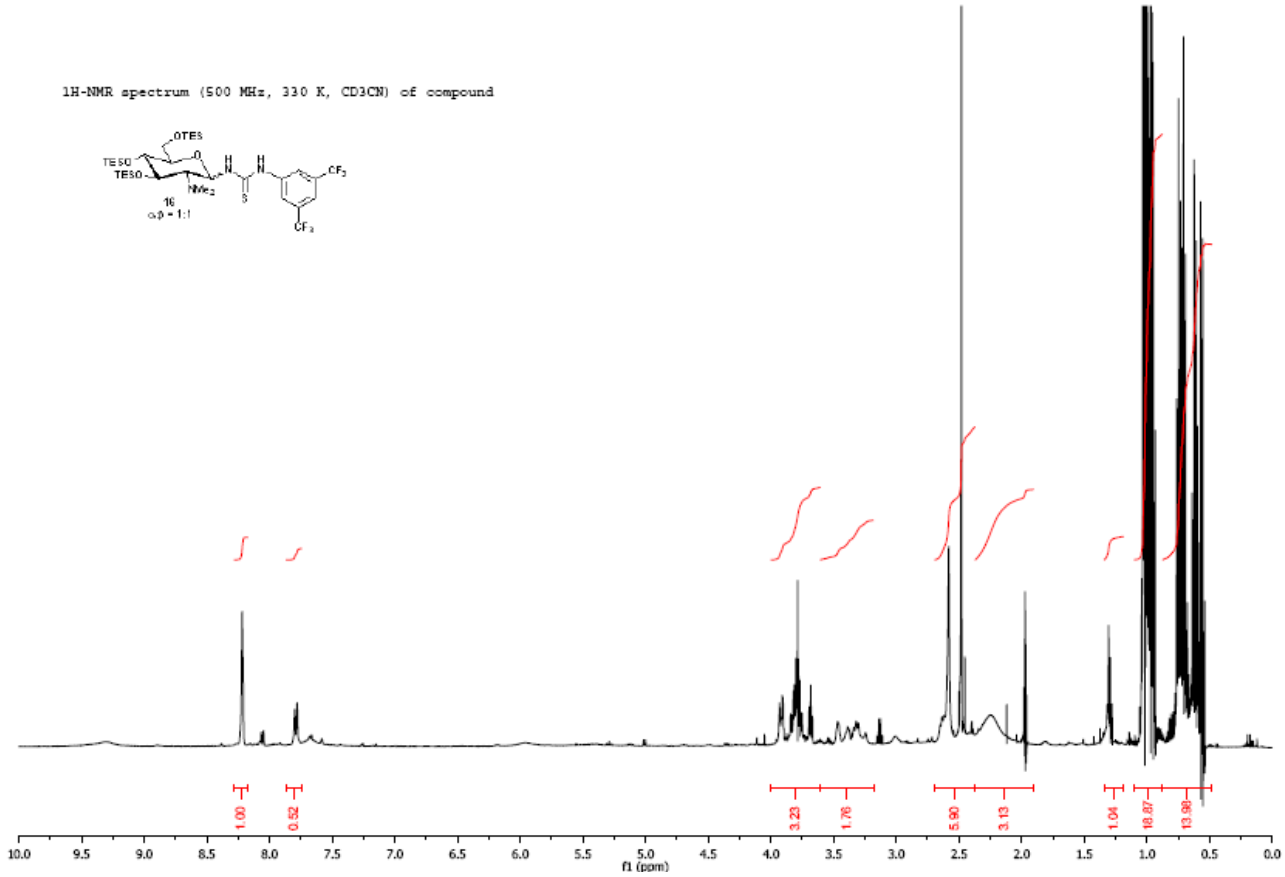
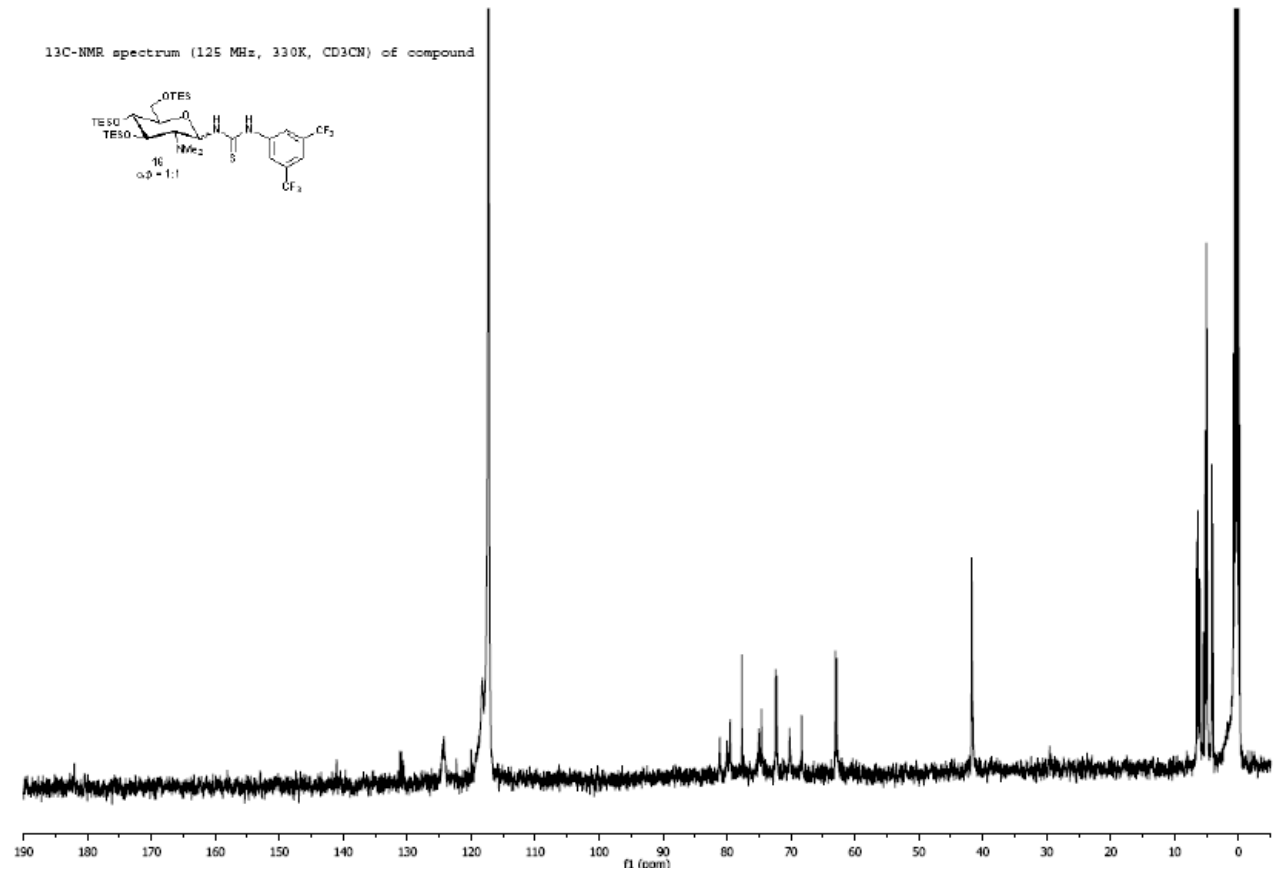
1d
f1 (ppm)


1H-NMR spectrum (500 MHz, 330 K, CD3CN) of compound
OTES
TESO
TESO
NMe2
16
α:β = 1:1
CF3
CF3
1.00
0.52
3.23
1.76
5.90
3.13
1.04
18.87
13.98
f1 (ppm)


13C-NMR spectrum (125 MHz, 330K, CD3CN) of compound
OTES
TESO
TESO
NMe2
16
α:β = 1:1
CF3
CF3
f1 (ppm)

Products of catalytic addition of acetyl acetone to different nitrostyrenes are known (Jian Wang, Hao Li, Wenhu Duan, Liansuo Zu, and Wei Wang, *Org. Lett.*, **2005**, *7* (21), pp 4713–4716
the product of addition of diethyl malonate to imine is known (A. Puglisi , M. Benaglia, R. Annunziata, D. Rossi, *Tetrahedron Asymm.,* **2008,** *19*, 2258 and references cited)

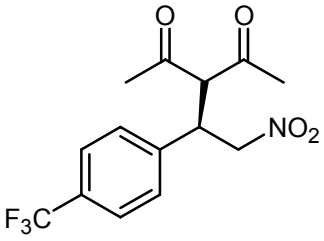
3-(-2-nitro-1-(4-methylphenyl)-ethyl)pentane-2,4-dione (**20).**
^{1}H NMR (300 MHz, CDCl3): δ 7.05-7.14(dd, *J* = 7.8 Hz, 20.4 Hz, 4 H),4.59-4.62(t, *J* = 3.0 Hz, 2 H), 4.34–4.37(d, *J* = 10.8 Hz, 1 H), 4.16–4.24(m,1 H), 2.29–2.30(d, *J* = 3.3 Hz, 6 H), 1.94(s, 3 H); ^{13}C NMR (75 MHz, CDCl3): δ 201.9, 201.1, 138.4, 132.8, 130.0, 127.8, 78.4, 70.8, 42.4, 30.4, 29.4, 21.1.
ee was determined by HPLC analysis (Chiralcel OD-H, i-PrOH/ Hexane = 10/90, 0.8 mL/min, 210 nm.) Retention time: tminor =23.7 min, tmajor =29.7 min,

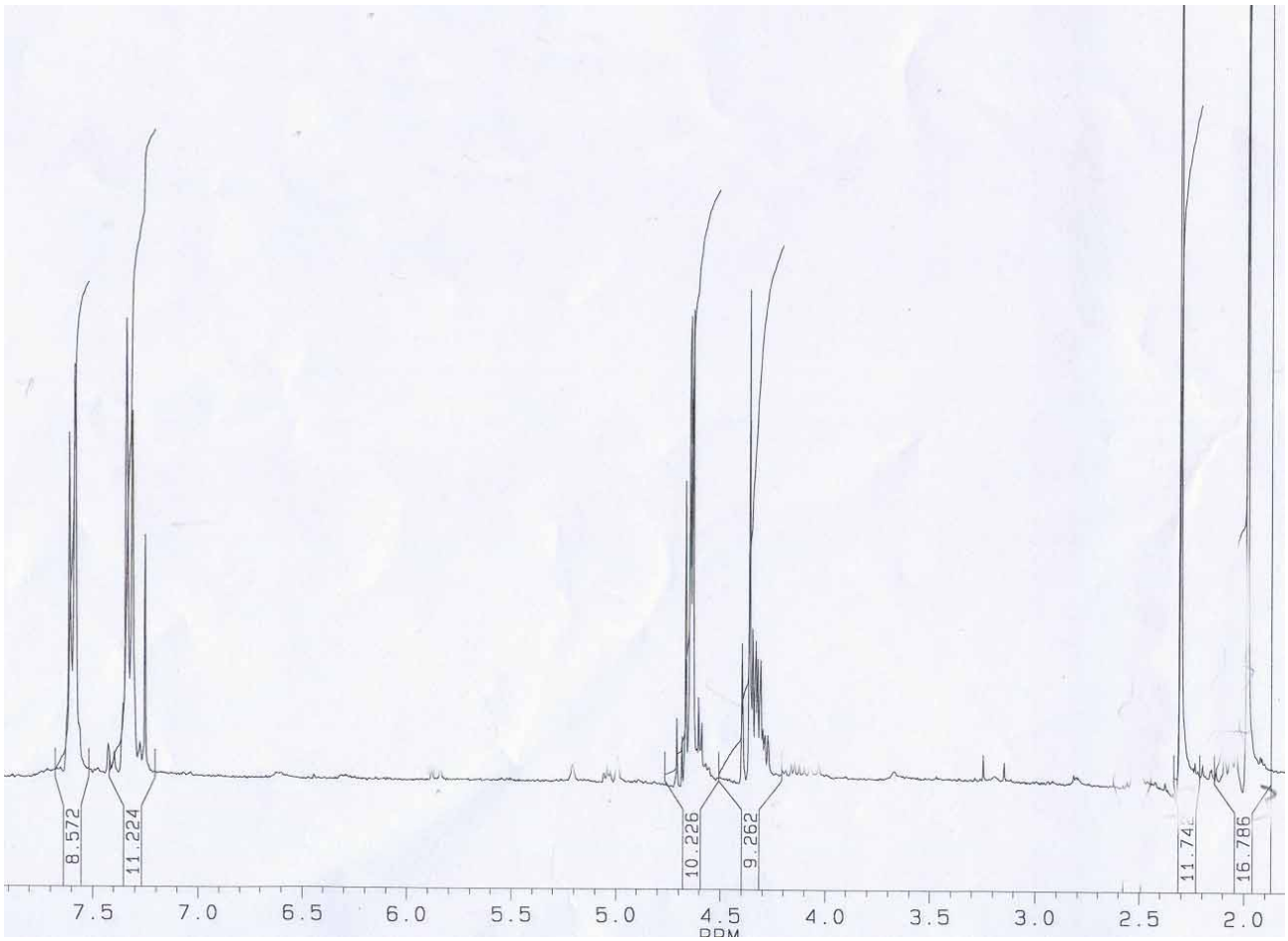
3-(-2-nitro-1-(4-methoxylphenyl)-ethyl)pentane-2,4-dione (**22).**
^{1}H NMR (300 MHz, CDCl3): δ = 7.10 (d, *J* = 8.5 Hz, 2H; Ph), 6.82 (d, *J* = 8.5 Hz, 2H; Ph), 4.61-4.55 (m, 2H; CH_2), 4.35 (d, *J* = 11.0 Hz, 1H; CH), 4.24-4.20 (m, 1H;CH), 3.76 (s, 3H; OCH_3), 2.30 (s, 3H; CH_3), 1.95 (s, 3H; CH_3); ^{13}C NMR (75 MHz, CDCl3): δ = 201.8, 201.1, 159.4, 129.0, 127.5, 114.6, 78.4, 70.8, 55.1, 42.0, 30.3, 29.4; HPLC
ee was determined by HPLC analysis (Chiralcel OD-H, i-PrOH/ Hexane = 10/90, 0.8 mL/min, 210 nm.) Retention time: tminor =44.9 min, tmajor =47.13 min,

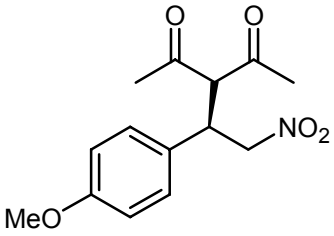
3-(-2-nitro-1-(4-chlorophenyl)-ethyl)pentane-2,4-dione (**24).**
^{1}H NMR (300 MHz, CDCl3): δ 7.20-7.30(m, 2 H), 7.0-7.16(m, 2 H), 4.60-4.62(t, *J* = 1.8 Hz, 2 H), 4.30-4.32 (d, *J* = 10.8 Hz, 1 H), 4.11–4.3(m, 1H), 2.30(s, 3 H), 1.95 (s, 3 H); ^{13}C NMR (75 MHz, CDCl3): δ 201.4, 200.6, 134.6., 134.5, 129.6,129.3, 77.9, 70.5, 42.1, 30.5, 29.7.
ee was determined by HPLC analysis (Chiralcel OD-H, i-PrOH/ Hexane = 10/90, 0.8 mL/min, 210 nm.) Retention time: tminor =38.78 min, tmajor =43.3 min,

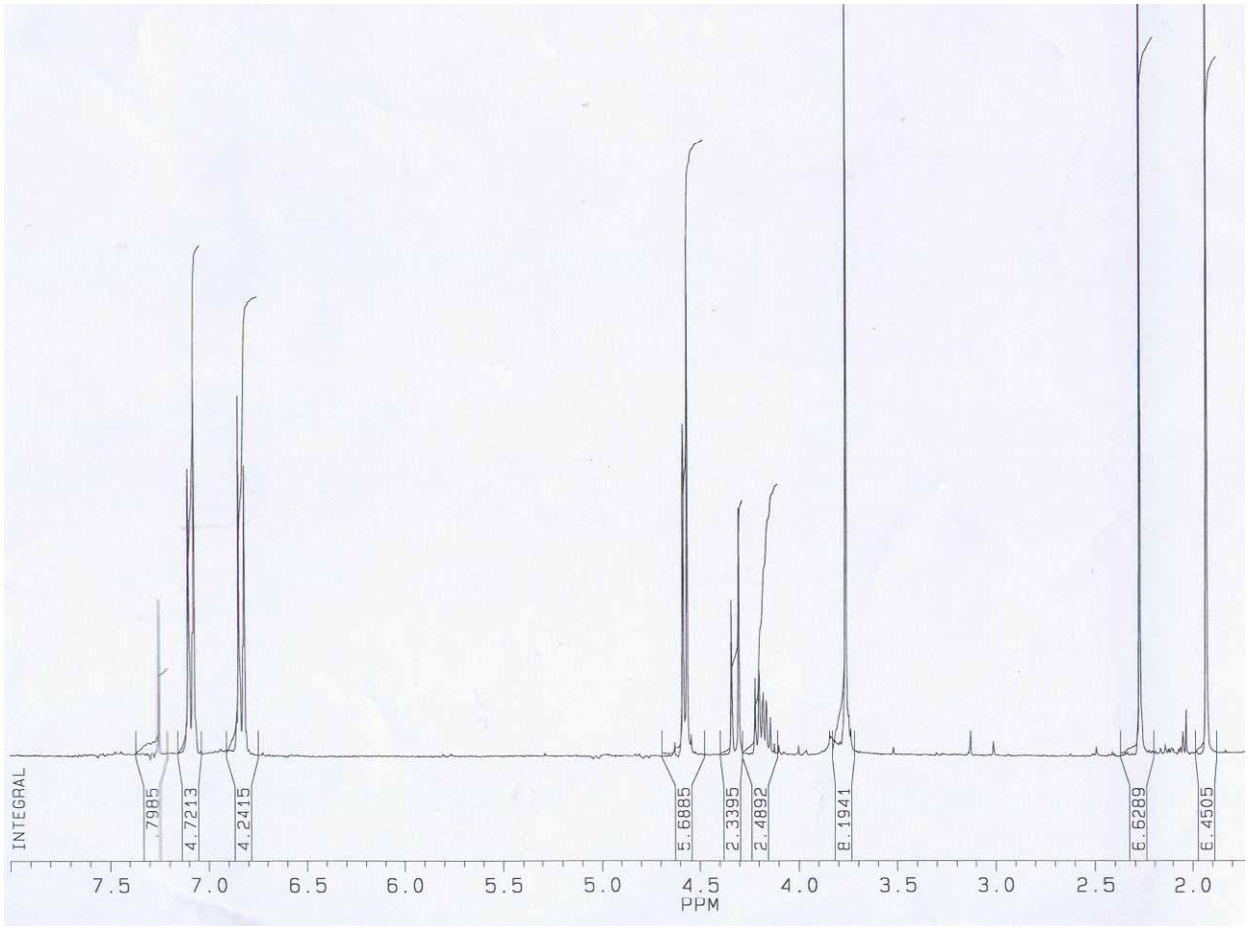
3-(-2-nitro-1-(4-trifluoromethylphenyl)-ethyl)pentane-2,4-dione (**26).**
^{1}H NMR (300 MHz, CDCl3): δ = 7.60 (d, *J* = 7.5 Hz, 2H; Ph), 7.30 (d, *J*(H,H) = 7.5 Hz, 2H; Ph), 4.65-4.57 (m 2H), 4.38-4.30 (m, 2H), 2.25 (s, 3H; CH_3), 1.98 (s, 3H; CH_3);. ^{13}C NMR (75 MHz, CDCl3): δ 201.2, 200.3, 140.1., 128.5, 126.5, 126.3, 77.6, 70.1, 42.1, 30.5, 29.7.
ee was determined by HPLC analysis (Chiralcel OD-H, i-PrOH/ Hexane = 10/90, 0.8 mL/min, 210 nm.) Retention time: tminor =40.52 min, tmajor =46.35 min,

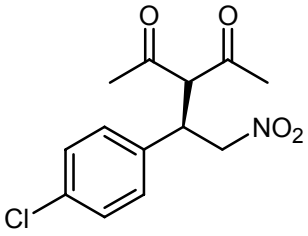
***N*-Boc derivative 27**
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.3 (m, 5H), 6.25 (brs, 1H), 5.4 (brs, 1H), 4.35-4.25 (m, 4H), 4.1 (d, 1H), 3.7 (s, 3H), 1.5 (t, 3H), 1.25 (t, 9H), 1.15 (t, 3H). $[\alpha]^{20}_{D}$= -5.7 (c = 0.1, $CHCl_3$) (*R*) enantiomer.
.HPLC (Daicel Chiralpak AD, hexane:*i*-propanol 90:10, flow rate = 0.8 ml/min, P = 15 bar, λ= 225 nm) t_{magg} = 18.63 min, t_{minor} = 23.36 min.

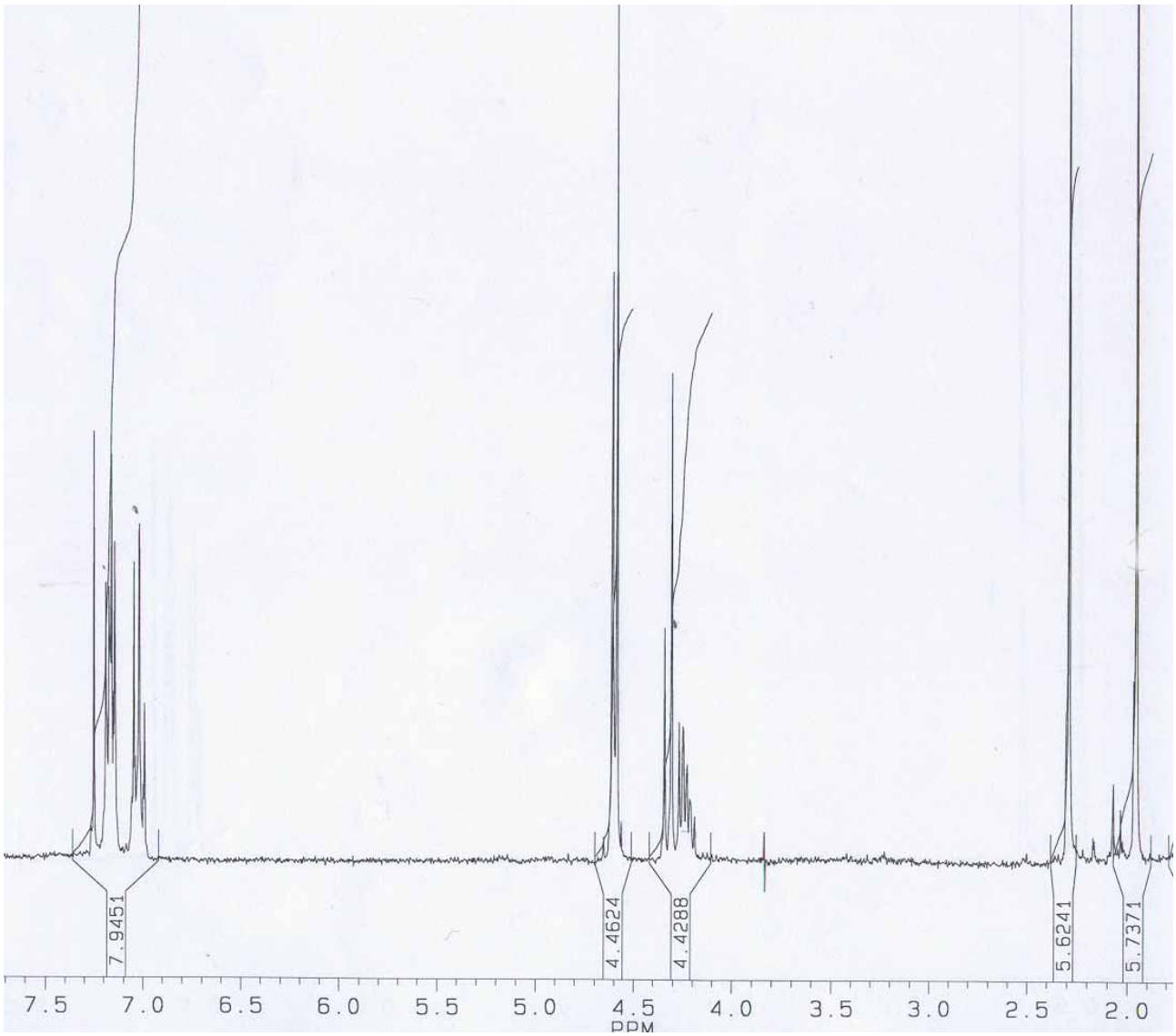

O
O
NO2
F3C

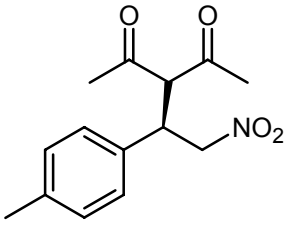

8.572
11.224
10.226
9.262
11.74
16.786
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
PPM

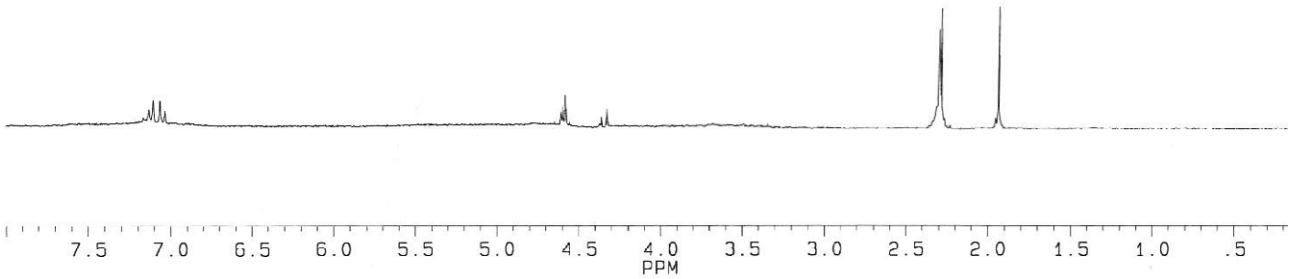

O
O
NO2
MeO

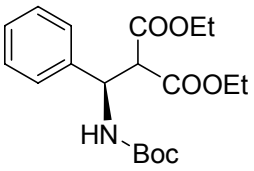

INTEGRAL
.7985
4.7213
4.2415
5.6885
2.3395
2.4892
8.1941
6.6289
6.4505
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
PPM

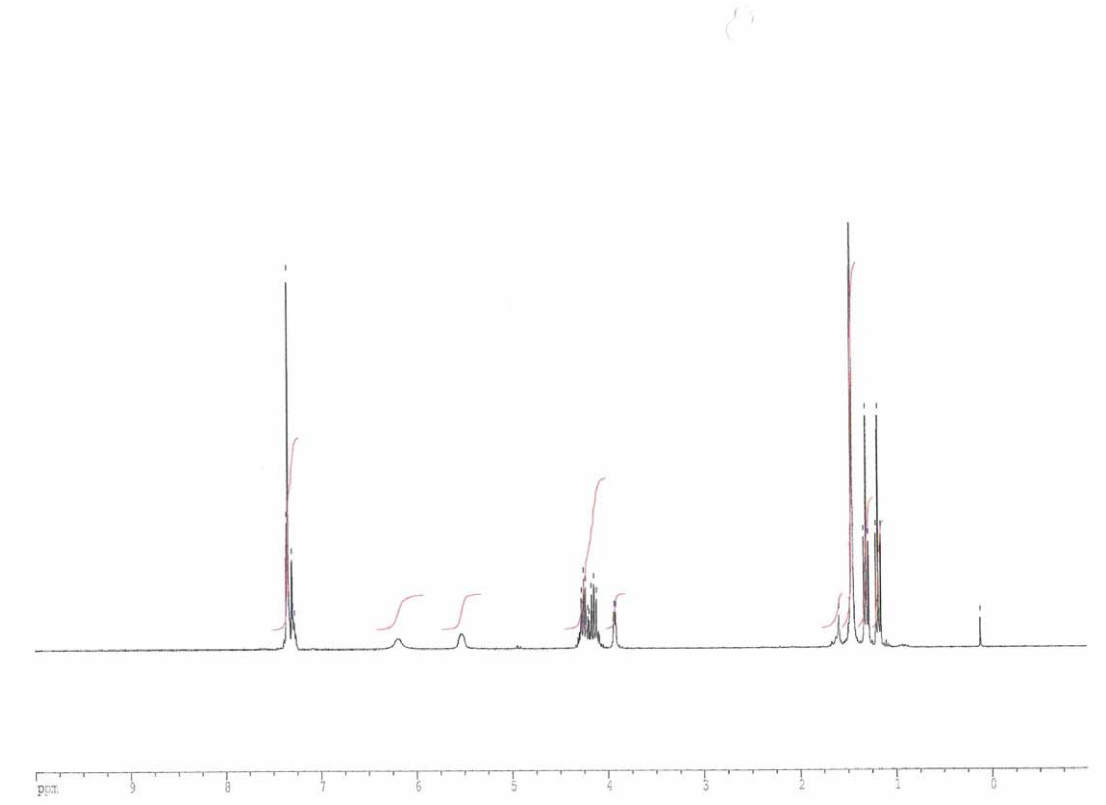

O
O
NO2
Cl


7.9451
4.4624
4.4288
5.6241
5.7371
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
PPM


O
O
NO2

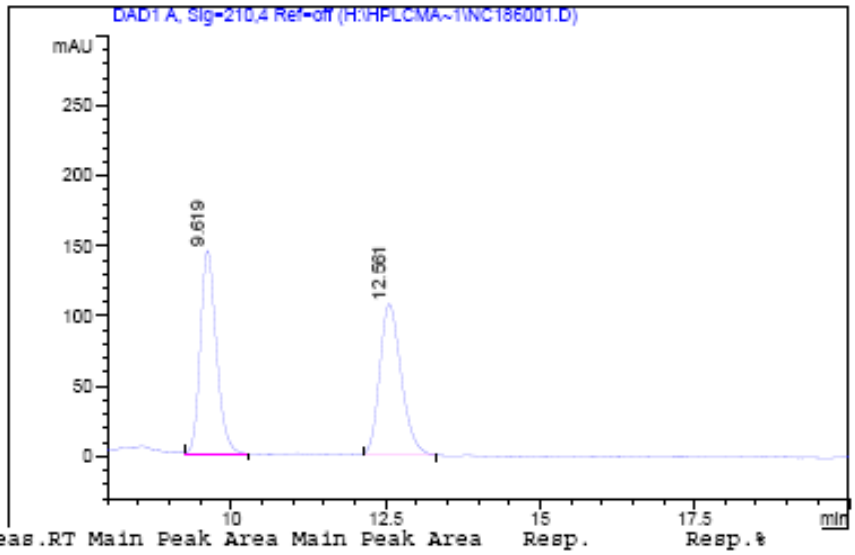

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM


COOEt
COOEt
HN
Boc


ppm
9
8
7
6
5
4
3
2
1
0

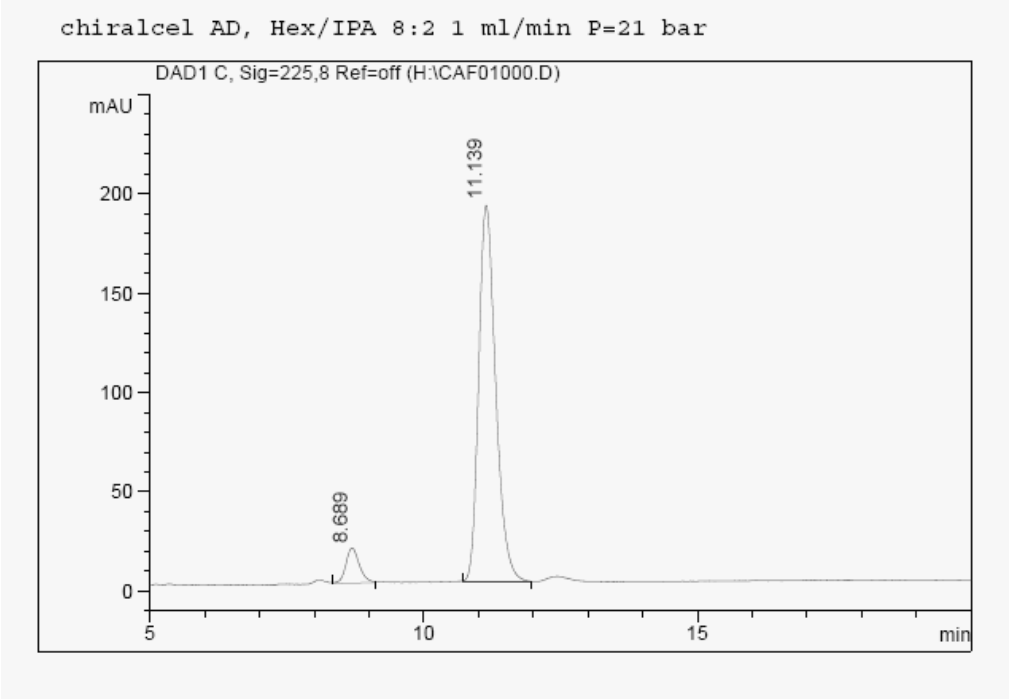
HPLC chromatograms on chiral stationary phase of products of catalytic addition of acetyl acetone to different nitrostyrenes and of diethyl malonate to imines.

Racemic 3-(-2-nitro-1-phenylethyl)pentane-2,4-dione (**18).**



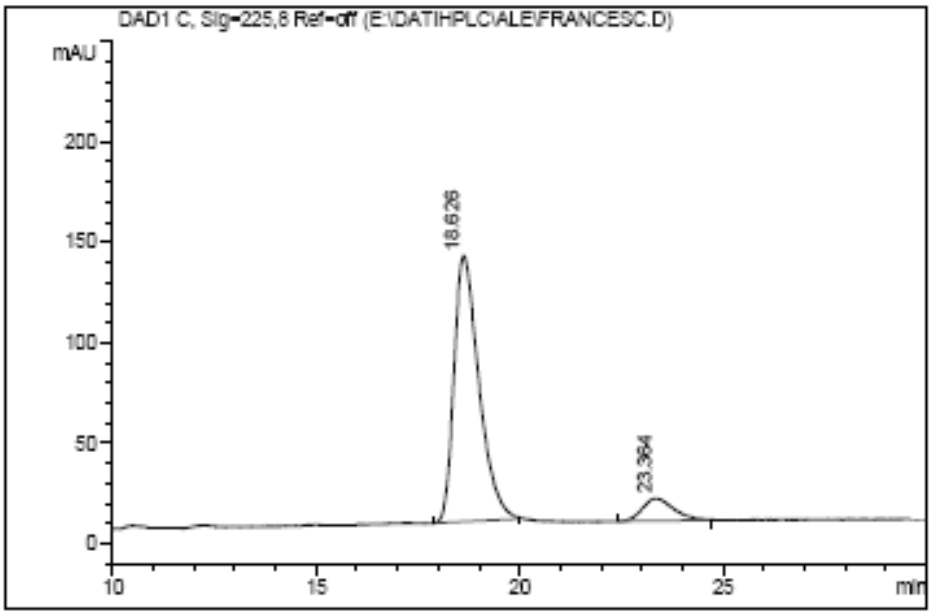
Meas.RT	Main Peak Area	Main Peak Area	Resp.	Resp.%
9.619	2649.777	50.286	2649.777	50.286
12.561	2619.656	49.714	2619.656	49.714

Enantiomerically enriched 3-(-2-nitro-1-phenylethyl)pentane-2,4-dione (**18).**

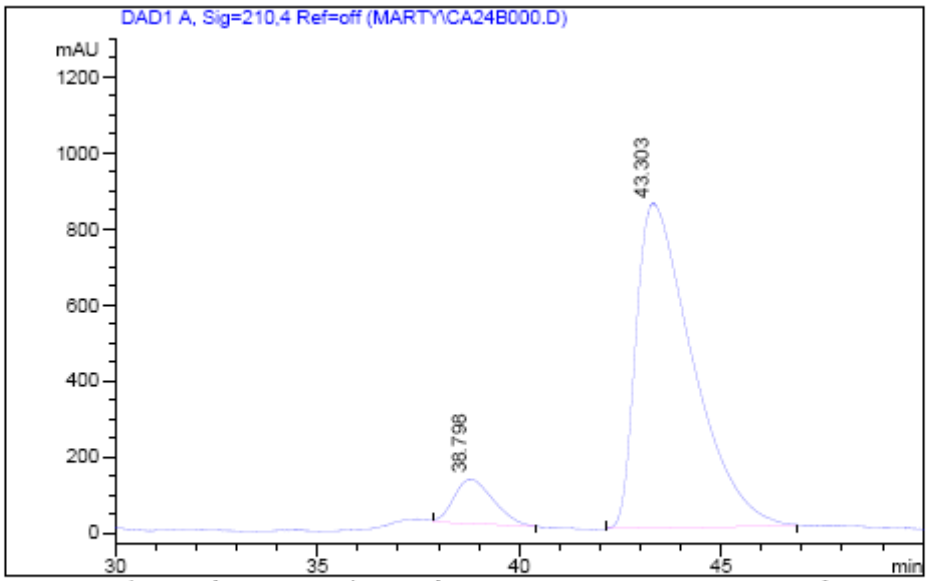


Compound **(27)**

CHIRALPAK AD Hex/IPA 9:1 0.8 ml/min P=15 bar

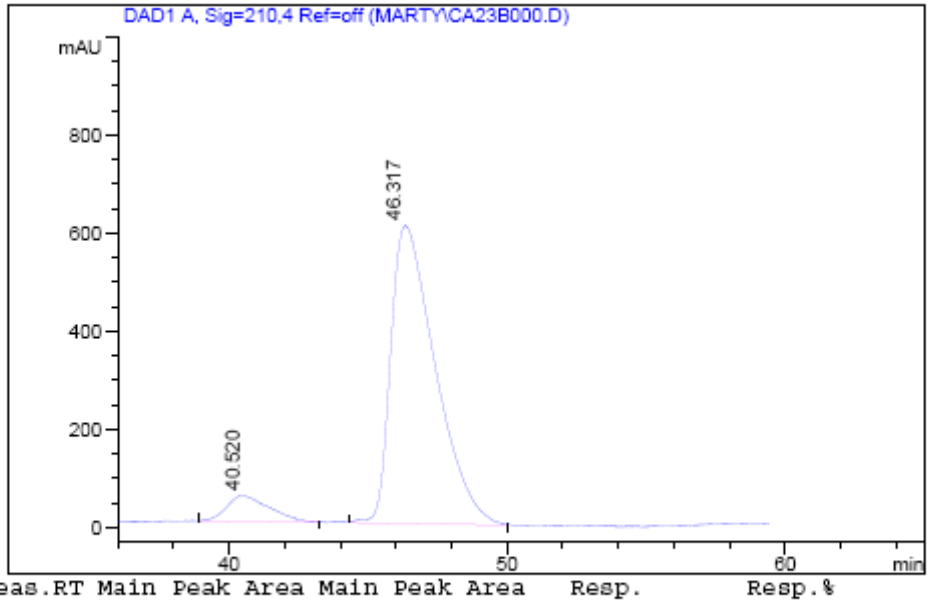


Adduct **(24)**



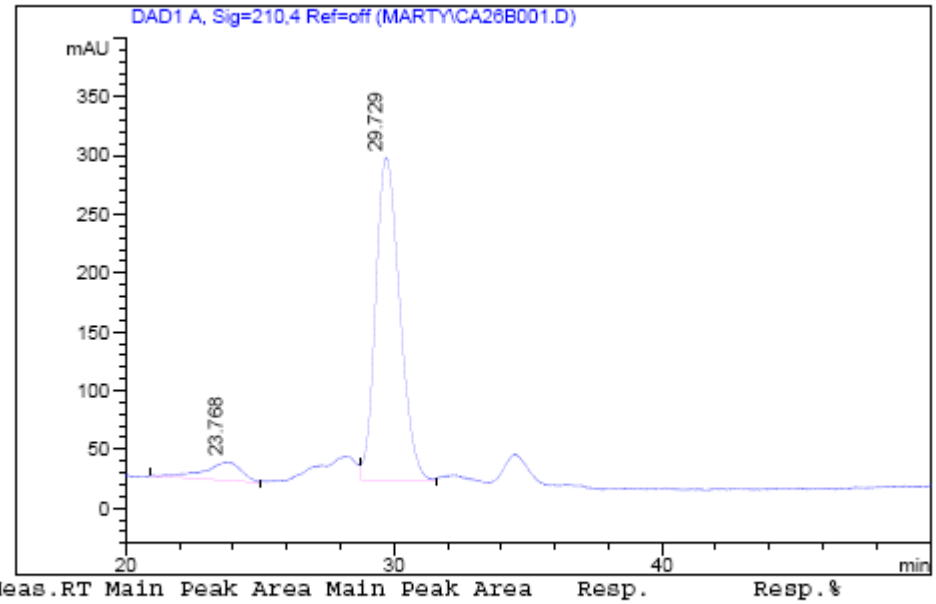
Meas.RT	Main Peak Area	Main Peak Area	Resp.	Resp.%
38.798	7894.036	8.678	7894.036	8.678
43.303	83067.367	91.322	83067.367	91.322

Adduct **(26)**



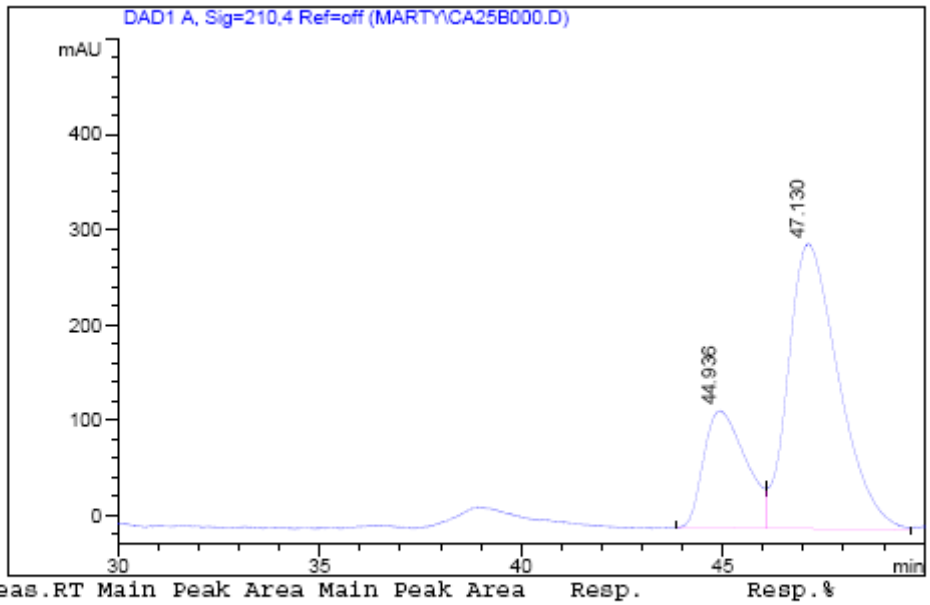
Meas.RT	Main Peak Area	Main Peak Area	Resp.	Resp.%
40.520	5585.760	7.636	5585.760	7.636
46.317	67567.750	92.364	67567.750	92.364

Adduct **(20)**



Meas.RT	Main Peak Area	Main Peak Area	Resp.	Resp.%
23.768	1504.790	8.091	1504.790	8.091
29.729	17094.564	91.909	17094.564	91.909

Adduct **(22)**



Meas.RT	Main Peak Area	Main Peak Area	Resp.	Resp.%
44.936	9008.229	25.740	9008.229	25.740
47.130	25988.617	74.260	25988.617	74.260