Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

A Way to Highly Enantiomerically Enriched aza-Morita-Baylis-Hillman-Type Products

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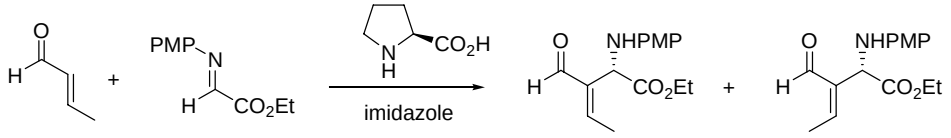
General: For thin layer chromatography (TLC), silica gel plates VWR GL60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), and conc. H_2SO_4 (60 mL) in H_2O (940 mL) followed by heating or treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), and acetic acid (10 mL) in ethanol (900 mL) followed by heating. Flash column chromatography was performed using Bodman silica gel 32-63, 60+. ^{1}H NMR and ^{13}C NMR spectra were recorded on INOVA-400, AMX-400 or DRX-500. Proton chemical shifts are given in δ value to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$. Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.00 ppm). High-resolution mass spectra were recorded on an Agilent ESI-TOF mass spectrometer. Enantiomeric excesses were determined by chiral-phase HPLC using a Hitachi instrument.

1. Evaluation of reaction conditions to afford aza-MBH-type product 3.

Table S1.[a]



1 **2** (*E*)-**3** (*Z*)-**3**

entry	aldehyde **1** (equiv)	(S)-proline (equiv)	imidazole (equiv)	solvent (0.5 M)	time (h)	temp (^oC)	yield[b] (%)	*E*:*Z*[c]	ee[d] (%)
1	5	0.3	0	DMF	6	4	35	12:1	96
2	5	0.3	0.3	DMF	6	4	47	15:1	97
3	5	0.3	1	DMF	2	4	65	15:1	98
4	5	0.3	5	DMF	2	4	49	14:1	97
5	1.2	0.3	1	DMF	5	4	50	20:1	98
6	10	0.3	1	DMF	2	4	57	10:1	98
7[e]	10	0.3	1	DMF	2	4	70	17:1	98
8[f]	15	0.3	1	DMF	2	4	71	13:1	97
9	5	1	1	DMF	2	4	66	11:1	99
10	5	0.2	1	DMF	3	4	63	14:1	97
11	5	0.1	1	DMF	3	4	58	14:1	97
12	5	0.05	1	DMF	24	4	37	14:1	97
13	5	0.3	1	DMF	1	25	58	13:1	97
14	5	0.3	1	DMF	6	-15	65	15:1	99
15	5	0.3	1	DMSO	2	4	61	17:1	99
16	5	0.3	1	CH_3CN	2	4	55	14:1	99
17	5	0.3	1	2-propanol	2	4	44	17:1	99
18	5	0.3	1	CH_2Cl_2	2	4	43	13:1	98
19	5	0.3	1	1,4-dioxane	2	4	37	14:1	97

[a] PMP = *p*-methoxyphenyl. Reactions were performed in a closed system (a vial with a cap). To a solution of *N*-PMP protected α-imino ethyl glyoxylate (**2**) (0.3 mmol, 1 equiv) in anhydrous solvent (0.6 mL), (*S*)-proline and imidazole were added followed by crotonaldehyde (**1**). The reaction mixture was stirred as indicated, worked up by addition of water, and extracted with ether (three times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography (10% AcOEt/hexane) to afford aza-MBH-type product **3** as an *E*/*Z* mixture. [b] Isolated yield containing (*E*)- and (*Z*)-**3**. [c] Determined by ^{1}H NMR of the isolated **3**. [d] Determined by chiral-phase HPLC for (*S*)-(*E*)-**3**. [e] Aldehyde **1** was added portion-wise: 5 equiv at 0 min, 5 equiv at 30 min. [f] Aldehyde **1** was added portion-wise: 5 equiv at 0 min, 5 equiv at 30 min, 5 equiv at 60 min.

Imidazole loading (entries 1-4).

With increased imidazole loading from 0 to 1 equiv, the yield of product **3** increased (entries 1-3). Overloading of imidazole (5 equiv), however, decreased the yield (entry 4).

Loading and addition method of crotonaldehyde (1) (entries 3, 5-8).

Increase of crotonaldehyde (**1**) loading from 1.2 to 5 equiv increased the yield of **3** (entries 3, 5), but further increases in the amount of **1** did not increase the yield (entries 3, 6). Portion-wise addition of **1** gave **3** in better yield than one shot addition of **1** (entries 6-8). Use of 5 equiv or 10 equiv (portion-wise addition) of **1** afforded the best results (entries 3, 7)

(*S*)-Proline loading (entries 3, 9-12).

The yield of **3** was similar with 0.2 – 1.0 equiv of (*S*)-proline (entries 3, 9, 10).

Reaction temperature (entries 3, 13, 14).

Reactions at 4 ^{o}C and -15 ^{o}C gave similar yield of **3**, but reaction at 25 ^{o}C gave slightly lower yield.

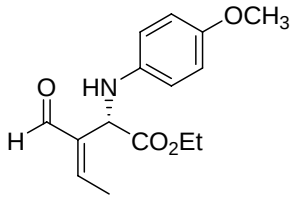
Solvents (entries 3, 15-19).

Among tested solvents, DMF gave the best yield. Ee of **3** was high in all cases.

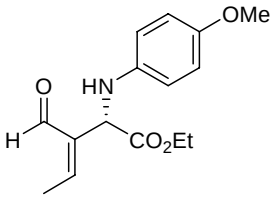
2. Formation of aza-Morita-Baylis-Hillman-type products (3-8) through Mannich-type reactions (Table 2).

General procedure: Reactions were performed in a closed system (a vial with a cap). An inert atmosphere of nitrogen or argon was not necessary for the reactions. To a solution of *N*-PMP protected α-imino ethyl glyoxylate (**2**) or *N*-PMP protected α-imino isopropyl glyoxylate (0.3 mmol, 1.0 equiv) in anhydrous DMF (0.6 mL), (*S*)-proline (0.09 mmol, 0.3 equiv) and imidazole (0.3 mmol, 1.0 equiv) was added followed by aldehyde (1.5 mmol, 5 equiv) at 4 ^{o}C. After stirring for 2-3 h at the same temperature, the reaction mixture was worked up by addition of water, and extracted with ether (three times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography (5-10% AcOEt/hexane) to afford the corresponding aza-Morita-Baylis-Hillman-type products as an *E*/*Z* mixture. Racemic standards were prepared using (±)-proline.

Ethyl (*S*)-3-formyl-2-(*p*-methoxyphenylamino)pent-3-enoate (3).



(*S*)-(*E*)-**3**

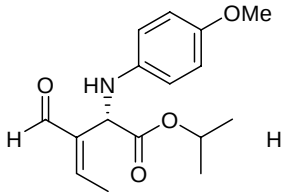


(*S*)-(*Z*)-**3**

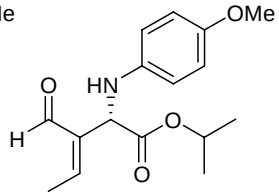
^{1}H NMR (400 MHz $CDCl_3$): (*E*)-**3**:(*Z*)-**3** = 13:1, *denotes *Z*-isomer ((*Z*)-**3**), δ 1.22 (t, *J* = 7.2 Hz, 3H x 13/14, OCH_2CH_3), 1.23 (t, *J* = 7.2 Hz, 3H* x 1/14, OCH_2CH_3), 2.13 (d, *J* = 7.2 Hz, 3H x 13/14, $C{=}CHCH_3$), 2.16 (d, *J* = 7.6 Hz, 3H* x 1/14, $C{=}CHCH_3$), 3.72 (s, 3H, OC*H3*), 4.19 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.63 (brs, 1H, N*H*PMP), 4.93 (s, 1H* x 1/14, C*H*NHPMP), 5.10 (s, 1H

x 13/14, C*H*NHPMP), 6.50-6.58 (m, 2H, Ar*H*), 6.73-6.77 (m, 2H, Ar*H*), 6.78 (q, *J* = 7.2 Hz, 1H x 13/14, C=C*H*CH_3), 6.90 (q, *J* = 7.6 Hz, 1H* x 1/14, C=C*H*CH_3), 9.36 (s, 1H x 13/14, C*H*O) 10.19 (s, 1H* x 1/14, C*H*O). ^{13}C NMR (100 MHz, $CDCl_3$): (*E*)-**3**, δ 14.0, 15.2, 53.2, 55.6, 61.7, 114.7, 115.4, 140.1, 140.8, 152.8, 153.26, 171.0, 193.3. HRMS: calcd for $C_{15}H_{19}NO_4$ (MH^+) 278.1387, found 278.1384. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm): t_R (*E* major enantiomer, (*S*)-(*E*)-**3**) = 13.7 min, t_R (*E* minor enantiomer, (*R*)-(*E*)-**3**) = 23.9 min. (*Z* major enantiomer, (*S*)-(*Z*)-**3**) = 17.6 min, t_R (*Z* minor enantiomer, (*R*)-(*Z*)-**3**) = 43.0 min. $[\alpha]^{25}_D$ +65.1 (c = 1.44, $CHCl_3$, (*S*)-(*E*)-**3** 97% ee, (*E*)-**3**:(*Z*)-**3** = 13:1).

Isopropyl (*S*)-3-formyl-2-(*p*-methoxyphenylamino)pent-3-enoate (4).



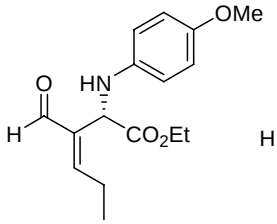
(*S*)-(*E*)-**4**



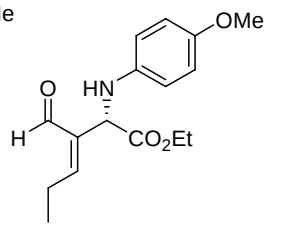
(*S*)-(*Z*)-**4**

^{1}H NMR (400 MHz $CDCl_3$): (*E*)-**4**:(*Z*)-**4** = 16:1, *denotes *Z*-isomer ((*Z*)-**4**), δ 1.16 (d, *J* = 6.4 Hz, 3H, OCHC*H*$_3$), 1.24 (d, *J* = 6.4 Hz, 3H, OCHC*H*$_3$), 2.12 (d, *J* = 7.6 Hz, 3H x 16/17, C=CHC*H*$_3$), 2.16 (d, *J* = 7.6 Hz, 3H* x 1/17, C=CHC*H*$_3$), 3.72 (s, 3H, OC*H*$_3$), 4.65 (brs, 1H, N*H*PMP), 4.89 (s, 1H* x 1/17, C*H*NHPMP), 5.01-5.10 (m, 1H, OC*H*$(CH_3)_2$), 5.07 (s, 1H x 16/17, C*H*NHPMP), 6.53-6.58 (m, 2H, Ar*H*), 6.72-6.77 (m, 2H, Ar*H*), 6.76 (q, *J* = 7.6 Hz, 1H x 16/17, C=C*H*CH_3), 6.89 (q, *J* = 7.6 Hz, 1H* x 1/17, C=C*H*CH_3), 9.36 (s, 1H x 16/17, C*H*O), 10.18 (s, 1H* x 1/17, C*H*O). ^{13}C NMR (125 MHz, $CDCl_3$): (*E*)-**4**, δ 15.1, 21.4, 21.6, 53.3, 55.6, 69.4, 114.7, 115.4, 140.2, 141.0, 152.7, 153.0, 170.5, 193.2. HRMS: calcd for $C_{16}H_{21}NO_4$ (MH^+) 292.1543, found 292.1545. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm): t_R (*E* major enantiomer, (*S*)-(*E*)-**4**) = 9.7 min, t_R (*E* minor enantiomer, (*R*)-(*E*)-**4**) = 26.2 min. t_R (*Z* major enantiomer, (*S*)-(*Z*)-**4**) = 11.3 min, t_R (*Z* minor enantiomer, (*R*)-(*Z*)-**4**) = 40.0 min.

Ethyl (*S*)-3-formyl-2-(*p*-methoxyphenylamino)hex-3-enoate (5).



(*S*)-(*E*)-**5**

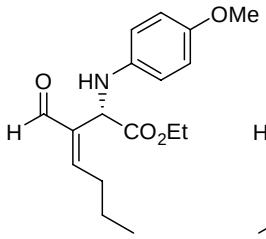


(*S*)-(*Z*)-**5**

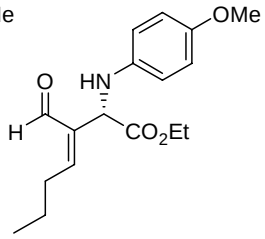
^{1}H NMR (400 MHz $CDCl_3$): (*E*)-**5**:(*Z*)-**5** = 10:1, *denotes *Z*-isomer ((*Z*)-**5**), δ 1.08 (t, *J* = 7.5 Hz, 3H* x 1/11, $CHCH_2CH_3$), 1.12 (t, *J* = 7.5 Hz, 3H x 10/11, $CHCH_2CH_3$), 1.22 (t, *J* = 7.1 Hz, 3H x 10/11, OCH_2CH_3), 1.23 (t, *J* = 7.1 Hz, 3H* x 1/11, OCH_2CH_3) 2.45-2.66 (m, 2H, $CHCH_2CH_3$), 3.72 (s, 3H, OC*H*$_3$), 4.18 (q, *J* = 7.1 Hz, 2H* x 1/11, OCH_2CH_3), 4.19 (q, *J* = 7.1 Hz, 2H x 10/11, OCH_2CH_3), 4.45 (brd, *J* = 7.0 Hz, 1H* x 1/11, N*H*PMP), 4.61 (brd, *J* = 8.2 Hz, 1H x 10/11, N*H*PMP), 4.92 (d, *J* = 7.0 Hz, 1H* x 1/11, C*H*NHPMP), 5.08 (d, *J* = 8.2 Hz, 1H x 10/11, C*H*NHPMP), 6.52-6.57 (m, 2H, Ar*H*), 6.63 (t, *J* = 7.5 Hz, 1H x 10/11, C=C*H*CH_2), 6.73-6.76 (m, 2H, Ar*H*), 6.78 (t, *J* = 8.2 Hz, 1H* x 1/10, C=C*H*CH_2), 9.36 (s, 1H x 10/11, C*H*O), 10.14 (s, 1H* x 1/11, C*H*O). ^{13}C

NMR (125 MHz, $CDCl_3$): (*E*)-**5**, δ 12.8, 14.0, 22.7, 53.5, 55.6, 61.8, 114.8, 115.57, 139.2, 140.2, 152.9, 159.6, 171.1, 193.6. HRMS: calcd for $C_{16}H_{21}NO_4$ (MH^+) 292.1543, found 292.1539. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm): t_R (*E* major enantiomer, (*S*)-(*E*)-**5**) = 37.2 min, t_R (*E* minor enantiomer, (*R*)-(*E*)-**5**) = 23.9 min. t_R (*Z* major enantiomer, (*S*)-(*Z*)-**5**) = 29.2 min, t_R (*Z* minor enantiomer, (*R*)-(*Z*)-**5**) = 25.8 min.

Ethyl (*S*)-3-formyl-2-(*p*-methoxyphenylamino)hept-3-enoate (6).



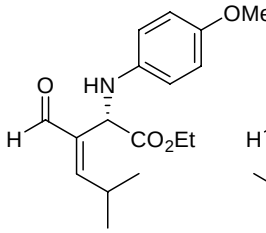
(*S*)-(*E*)-**6**



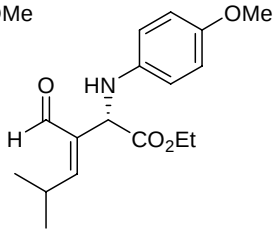
(*S*)-(*Z*)-**6**

^{1}H NMR (400 MHz $CDCl_3$): (*E*)-**6**:(*Z*)-**6** = 8:1, *denotes *Z*-isomer ((*Z*)-**6**), δ 0.88 (t, *J* = 7.4 Hz, 3H* x 1/9, $CH_2CH_2CH_3$), 0.98 (t, *J* = 7.4 Hz, 3H x 8/9, $CH_2CH_2CH_3$), 1.216 (t, *J* = 7.1 Hz, 3H x 8/9, OCH_2CH_3), 1.222 (t, *J* = 6.9 Hz, 3H* x 1/9, OCH_2CH_3), 1.46-1.64 (m, 2H, $CH_2CH_2CH_3$), 2.40-2.62 (m, 2H, $CH_2CH_2CH_3$), 3.72 (s, 3H, OCH_3), 4.18 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.62 (brs, 1H, NHPMP), 4.94 (s, 1H* x 1/9, CHNHPMP), 5.08 (s, 1H x 8/9, CHNHPMP), 6.53-6.58 (m, 2H, ArH), 6.65 (t, *J* = 7.6 Hz, 1H x 8/9, $C=CHCH_2$), 6.72-6.76 (m, 2H, ArH), 6.78 (t, *J* = 8.4 Hz, 1H* x 1/9, $C=CHCH_2$), 9.37 (d, *J* = 0.8 Hz, 1H x 8/9, CHO). 10.13 (s, 1H* x 1/9, CHO). ^{13}C NMR (100 MHz, $CDCl_3$): (*E*)-**6**, δ 13.8, 14.0, 21.7, 31.2, 53.5, 55.6, 61.7, 114.7, 115.5, 139.8, 140.2, 152.8, 158.4, 171.1, 193.6. HRMS: calcd for $C_{17}H_{23}NO_4$ (MH^+) 306.1700, found 306.1698. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm): t_R (*E* major enantiomer, (*S*)-(*E*)-**6**) = 16.3 min, t_R (*E* minor enantiomer, (*R*)-(*E*)-**6**) = 11.4 min. t_R (*Z* major enantiomer, (*S*)-(*Z*)-**6**) = 14.0 min, t_R (*Z* minor enantiomer, (*R*)-(*Z*)-**6**) = 13.0 min.

Ethyl (*S*)-3-formyl-2-(*p*-methoxyphenylamino)-5-methylhex-3-enoate (7).



(*S*)-(*E*)-**7**

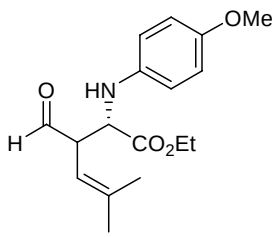


(*S*)-(*Z*)-**7**

(*E*)-**7**: ^{1}H NMR (500 MHz $CDCl_3$): δ 1.069 (d, *J* = 6.5 Hz, 3H, $CHCH_3$), 1.09 (d, *J* = 6.5 Hz, 3H, $CHCH_3$), 1.223 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 3.01-3.12 (m, 1H, $CH(CH_3)_2$), 3.72 (s, 3H, OCH_3), 4.19 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 4.62 (brs, 1H, NHPMP), 5.07 (s, 1H, CHNHPMP), 6.40 (d, *J* = 10.7 Hz 1H, $C=CHCH$), 6.52-6.56 (m, 2H, ArH), 6.72-6.75 (m, 2H, ArH), 9.34 (d, *J* = 1.0 Hz, 1H, CHO). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 21.7, 21.7, 28.8, 53.7, 55.6, 61.7, 114.7, 115.7, 137.3, 140.2, 152.9, 164.1, 171.1, 193.9. HRMS: calcd for $C_{17}H_{23}NO_4$ (MH^+) 306.1700, found 306.1688. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm): t_R (*E* major enantiomer, (*S*)-(*E*)-**7**) = 12.4 min, t_R (*E* minor enantiomer, (*R*)-(*E*)-**7**) = 22.6 min. $[\alpha]^{25}_D$ +54.5 (c = 1.03, $CHCl_3$, (*S*)-(*E*)-**7** 98% ee, (*E*)-**7**:(*Z*)-**7** = 17:1).

(*Z*)-**7**, ^{1}H NMR (500 MHz $CDCl_3$): δ 1.04 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$), 1.067 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$), 1.219 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$), 3.30-3.39 (m, 1H, C*H*(CH$_3$)$_2$), 3.72 (s, 3H, OC*H*$_3$), 4.18 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 4.42 (brs, 1H, N*H*PMP), 4.90 (s, 1H, C*H*NHPMP), 6.53 (d, *J* = 9.0 Hz 1H, C=C*H*CH), 6.52-6.56 (m, 2H, Ar*H*), 6.72-6.75 (m, 2H, Ar*H*), 10.13 (s, 1H, C*H*O). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.7, 22.8, 26.2, 55.7, 56.5, 61.6, 114.7, 115.4, 134.6, 140.0, 152.8, 158.0, 171.6, 189.2. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm): t_R (*Z* major enantiomer, (*S*)-(*Z*)-**7**) = 16.6 min, t_R (*Z* minor enantiomer, (*R*)-(*Z*)-**7**) = 34.9 min.

Ethyl 3-formyl-2-(*p*-methoxyphenylamino)-5-methylhex-4-enoate (9).



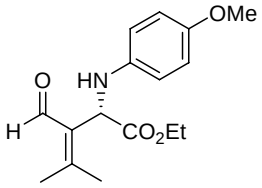
9

Obtained as a mixture of (*E*)-**7**:(*Z*)-**7**:major isomer of **9**:minor isomer of **9** = 10:10:2:1 (determined by ^{1}H NMR). ^{1}H NMR (500 MHz $CDCl_3$):

Major isomer of **9**: δ 1.67 (d, *J* = 1.0 Hz, 3H, C=CC*H*$_3$), 1.87 (d, *J* = 1.5 Hz, 3H, C=CC*H*$_3$), 3.65-3.70 (m, 1H, C*H*CHO), 3.74 (s, 3H, OC*H*$_3$), 5.24-5.26 (m, 1H, C*H*=C(CH$_3$)$_2$), 9.59 (d, *J* = 1.5 Hz, 1H, C*H*O).

Minor isomer of **9**: δ 1.64 (d, *J* = 1.0 Hz, 3H, C=CC*H*$_3$), 1.80 (d, *J* = 1.5 Hz, 3H, C=CC*H*$_3$), 3.63-3.68 (m, 1H, C*H*CHO), 3.74 (s, 3H, OC*H*$_3$), 5.12-5.16 (m, 1H, C*H*=C(CH$_3$)$_2$), 9.55 (d, *J* = 2.5 Hz, 1H, C*H*O).

Ethyl (*S*)-3-formyl-2-(*p*-methoxyphenylamino)-4-methylpent-3-enoate (8).

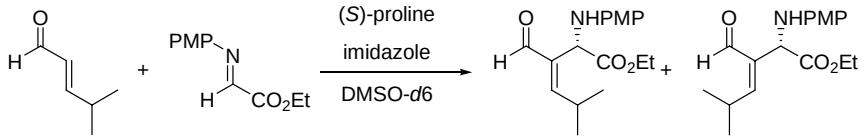


8

^{1}H NMR (400 MHz $CDCl_3$): δ 1.22 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 2.14 (s, 3H, C=CC*H*$_3$), 2.24 (s, 3H, C=CC*H*$_3$), 3.73 (s, 3H, OC*H*$_3$), 4.18 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.59 (brs, 1H, N*H*PMP), 5.11 (s, 1H, C*H*NHPMP), 6.55-6.60 (m, 2H, Ar*H*), 6.72-6.77 (m, 2H, Ar*H*), 10.1 (s, 1H, C*H*O). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 20.3, 23.6, 54.9, 55.6, 61.5, 114.7, 115.6, 134.8, 140.7, 152.7, 159.0, 172.0, 190.0. HRMS: calcd for $C_{16}H_{21}NO_4$ (MH^+) 292.1543, found 292.1540. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm): t_R (major enantiomer, (*S*)-**8**) = 16.0 min, t_R (minor enantiomer, (*R*)-**8**) = 22.3 min. $[\alpha]^{25}_D$ +66.3 (c = 1.00, $CHCl_3$, 92% ee).

3. ^{1}H NMR analysis of the reaction.

Table S2. ^{1}H NMR Analysis of the reaction affording 7.[a]

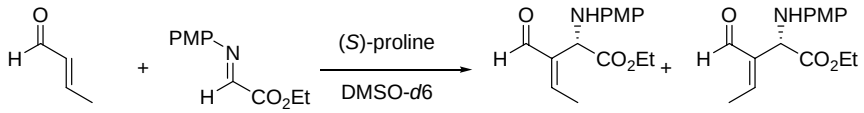


2 (*E*)-**7** (*Z*)-**7**

time	relative amount of **7**[b,c]	(*E*)-**7**:(*Z*)-**7**[b]
10 min	1	0:100
20 min	31	33:67
80 min	97	46:54
24 h	100	84:16

[a] A mixture of imine **2** (62.2 mg, 0.3 mmol), DMSO-*d*6 (0.6 mL), (*S*)-proline (10.4 mg, 0.09 mmol), imidazole (20.6 mg, 0.3 mmol), and 4-methy-2-pentenal (147 mg, 1.5 mmol) in a NMR tube was continuously shaken at room temperature and analyzed by ^{1}H NMR. Formation of **9** was not able to be monitored because signals of **9** were not well separated from signals of other compounds including 4-methyl-2-pentenal and byproducts. [b] Determined based on the integration of the aldehyde protons: (*E*)-**7** (s, 9.43 ppm) and (*Z*)-**7** (s, 10.17 ppm). [c] Relative amount of **7** was determined by comparing the amount of **7** at 24 h. The residual proton of the solvent signal was used as internal standard.

Table S3. ^{1}H NMR analysis of the reaction affording 3.[a]



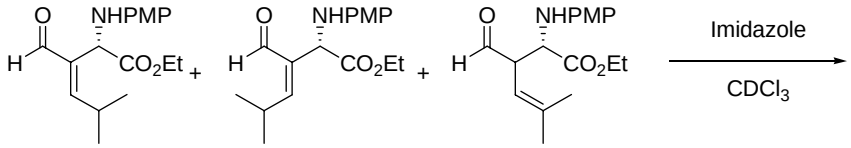
1 **2** (*E*)-**3** (*Z*)-**3**

time	relative amount of **3**[b,c]	(*E*)-**3**:(*Z*)-**3**[b]
10 min	29	85:15
30 min	92	86:14
2 h	100	88:12
16 h	93	90:10

[a] A mixture of imine **2** (56.5 mg, 0.27 mmol), DMSO-*d*6 (0.6 mL), (*S*)-proline (10.4 mg, 0.09 mmol), and crotonaldehyde **1** (21.0 mg, 0.3 mmol) in NMR tube was continuously shaken at room temperature and analyzed by ^{1}H NMR. [b] Determined based on the integration of the aldehyde protons: (*E*)-**3** (s, 9.40 ppm) and (*Z*)-**3** (s, 10.17 ppm). [c] Relative amount of **3** was determined by comparing the amount of **3** at 2 h. The residual proton of the solvent signal was used as internal standard.

4. Isomerization of 7 and 9 with imidazole.

Table S4.



(*E*)-**7** (*Z*)-**7** **9** (*anti*-*syn* mixture)

time (min)	**7**:**9**[b,c]	(*E*)-**7**:(*Z*)-**7**[b]
0[d]	87:13	51:49
10	93:7[e]	60:40
30	-[e f]	82:18
40	-[e f]	85:15
90	-[e f]	95:5

[a] In a NMR tube, to a solution of a 44:43:13 mixture of (*E*)-**7**, (*Z*)-**7**, and **9** (5.8 mg, 0.019 mmol as combined) in $CDCl_3$ (0.6 mL) was added imidazole (20 mg, 0.294 mmol, 15 equiv) at room temperature. The mixture was continuously shaken at the same temperature and analyzed by ^{1}H NMR. [b] Determined based on the integration of aldehyde protons of **7** and **9**. [c] For **7**, (*E*)- and (*Z*)-isomers were combined. For **9**, *anti*- and *syn*-isomers were combined. [d] Before addition of imidazole. [e] Signals of **9** were broaden by imidazole. No broadening of signals of **7** was observed. [f] Not determined. Chemical shifts of **9** overlapped with those of decomposed products.

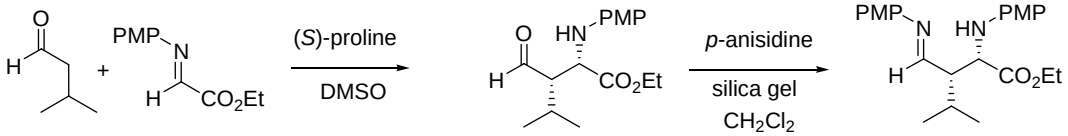
5. Determination of absolute stereochemistry.

Transformation of 8 to 10.

8 (2*S*,3*S*)-**10** **13** (*anti*)

Compound **8** obtained from the (*S*)-proline-catalyzed reaction between crotonaldehyde (**1**) and imine **2** was transformed to **10**. To a solution of **8** (17.2 mg, 0.059 mmol) in AcOEt (1 mL), was added *p*-anisidine (8.7 mg, 0.071 mmol) and MS 4A (35 mg) at room temperature. After stirring for 2 h at room temperature, the resulting mixture was filtered and washed with AcOEt (4 mL). To the filtrate, 10 wt% Pd/C (5.1 mg) was added at room temperature and purged by hydrogen. After stirring for 4 h at the same temperature under hydrogen (1 atm), the reaction mixture was filtered, concentrated in vacuo, purified by flash column chromatography (10% AcOEt/hexane) to afford a mixture of (2*S*,3*S*)-**10** and **13** (4.0 mg, 17%, **10**:**13** = 2.6:1). (2*S*,3*S*)-**10**: 98% ee, determined by HPLC analysis. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R (*syn* major enantiomer, (2*S*,3*S*)-**10**) = 23.5 min, t_R (*syn* minor enantiomer, (2*R*,3*R*)-**10**) = 20.2 min. Based on the retention time of **10** in HPLC analysis, the absolute stereochemistry of **10** obtained from **8** was determined to be 2*S*,3*S*. Thus, the absolute stereochemistry of **8** was determined to be *S*. Synthesis of the standards (2*S*,3*S*)-**10**, (±)-**10**, and **13** (*anti*) are described below.

Synthesis of standard (2*S*, 3*S*)-10.



11 **10**

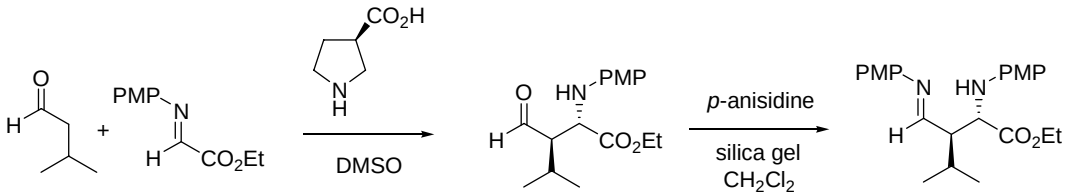
Ethyl (2*S*,3*S*)-2-(*p*-methoxyphenylamino)-3-[(*E*)-(*p*-methoxyphenylimino)methyl] -4-methylpentanoate [(2*S*,3*S*)-10].

Compound (2*S*,3*S*)-**11** was synthesized by the Mannich-type reaction between isovaleraldehyde and imine **2** with (*S*)-proline by the reported procedure.[S1] To a solution of (2*S*,3*S*)-**11** (15 mg, 0.051 mmol) in CH_2Cl_2 (0.5 mL), were added *p*-anisidine (6.9 mg, 0.056 mmol) and silica gel (15 mg) at room temperature. After stirring for 2 h, the reaction mixture was purified by flash column chromatography (10% AcOEt/hexane) to afford a 2:1 mixture of (2*S*,3*S*)-**10** and *p*-anisidine (12.7 mg, 52%). Racemic standard (±)-**10** was synthesized in the same manner from (±)-**11**, prepared with (±)-proline. ^{1}H NMR (400 MHz $CDCl_3$): δ 1.01 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.15 (d, *J* = 6.9 Hz, 3H CHC*H*$_3$), 1.18 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$),

[S1] Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866-1867.

2.12-2.27 (m, 1H, CHC*H*$(CH_3)_2$), 2.62 (q, 1H, *J* = 7.1 Hz, C*H*CH$(CH_3)_2$), 3.74 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.02-4.10 (m, 1H, N*H*PMP), 4.10-4.18 (m, 2H, OCH_2CH$_3$), 4.30-4.36 (m, 1H, C*H*NHPMP), 6.62-6.67 (m, 2H, Ar*H*), 6.72-6.79 (m, 2H, Ar*H*), 6.86-6.91 (m, 2H, Ar*H*), 7.05-7.10 (m, 2H, Ar*H*), 7.80 (d, *J* = 7.1 Hz, 1H, C*H*=NPMP). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 19.8, 21.1, 27.6, 54.3, 55.5, 55.7, 58.5, 61.0, 114.3, 114.8, 115.5, 122.0, 140.6, 144.8, 152.9, 158.1, 163.7, 173.1. HRMS: calcd for $C_{23}H_{30}N_2O_4$ (MH^+) 399.2278, found 399.2284. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R (*syn* major enantiomer, (2*S*,3*S*)-**10**) = 23.5 min, t_R (*syn* minor enantiomer, (2*R*,3*R*)-**10**) = 20.2 min, t_R (*p*-anisidine) > 90 min.

Synthesis of standard (2*S*,3*R*)-13.



12 **13**

Ethyl (2*S*,3*R*)-2-(*p*-methoxyphenylamino)-3-[(*E*)-(*p*-methoxyphenylimino)methyl] -4-methylpentanoate [(2*S*,3*R*)-13]

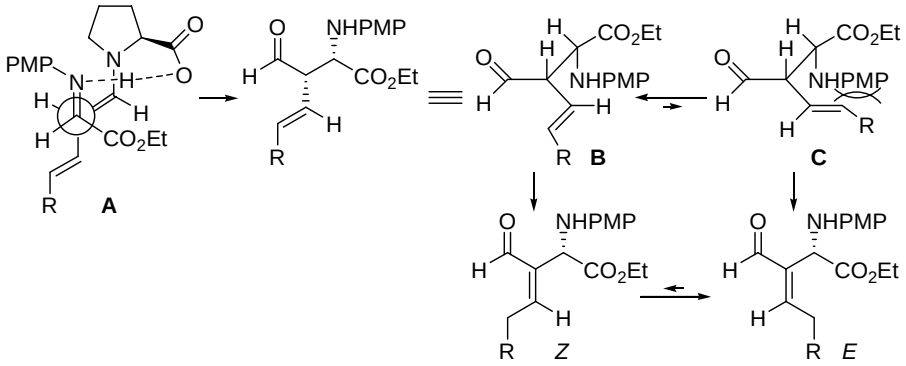
Compound (2*S*,3*R*)-**12** was synthesized by the Mannich-type reaction using (*R*)-pyrrolidine-3-carboxylic acid by the reported procedure.[S2,S3] To a solution of (2*S*,3*R*)-**12** (6.2 mg, 0.021 mmol) in CH_2Cl_2 (0.2 mL), were added *p*-anisidine (3.9 mg, 0.032 mmol) and silica gel (6.2 mg) at room temperature. After stirring for 2 h, the reaction mixture was purified by flash column chromatography (10% AcOEt/hexane) to afford a 1.8:1 mixture of (2*S*,3*R*)-**13** and *p*-anisidine (4.2 mg, 43%). Racemic standard (±)-**13** was synthesized in the same manner from (±)-**12**, prepared with (±)-pyrroridine-3-carboxylic acid. ^{1}H NMR (500 MHz $CDCl_3$): δ 1.09 (d, *J* = 6.8 Hz, 3H, CHCH_3), 1.09 (d, *J* = 6.8 Hz, 3H, CHCH_3), 1.20 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 2.10-2.18 (m, 1H, CHC*H*$(CH_3)_2$), 2.74 (q, *J* = 6.8 Hz, 1H, C*H*CH$(CH_3)_2$), 3.73 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.15 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 4.15-4.35 (br, 1H, N*H*PMP), 4.30 (d, *J* = 6.8 Hz, 1H, C*H*NHPMP), 6.62-6.68 (m, 2H, ArH), 6.72-6.78 (m, 2H, Ar*H*), 6.84-6.88 (m, 2H, Ar*H*), 6.98-7.03 (m, 2H, Ar*H*), 7.84 (d, *J* = 6.8 Hz, 1H, C*H*=NPMP). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 19.5, 21.4, 28.5, 54.0, 55.5, 55.7, 58.8, 61.1, 114.3, 114.8, 115.3, 121.9, 141.2, 144.9, 152.8, 158.0, 163.5, 173.5. HRMS: calcd for $C_{23}H_{30}N_2O_4$ (MNa^+) 421.2098, found 421.2103. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R (2*S*,3*R*)-**13** and (2*R*,3*S*)-**13**) = 16.8 min. Enantiomers of **13** were not separated under the HPLC conditions for the separation of (2*S*,3*S*)-**10** and (2*R*,3*R*)-**10**.

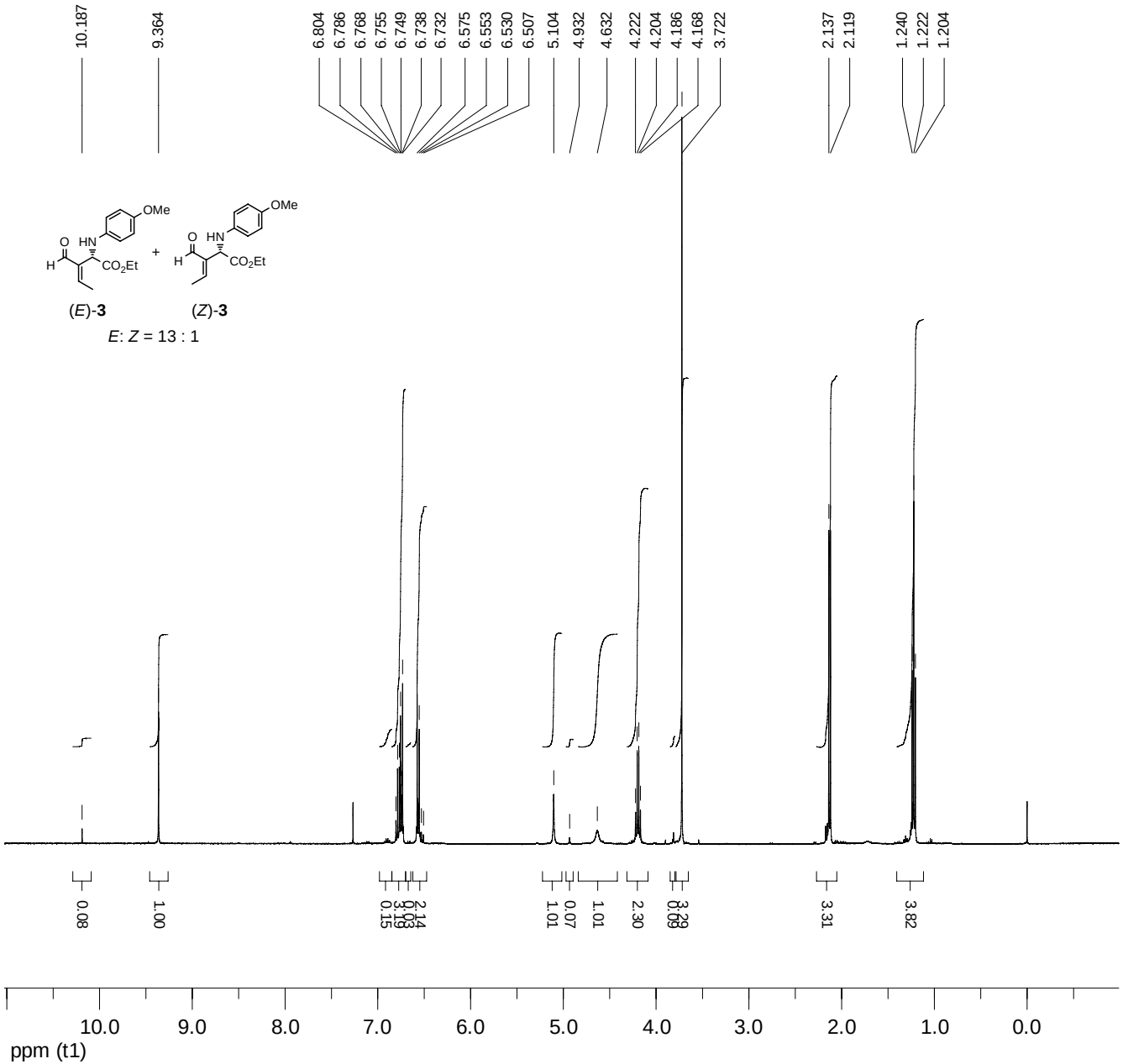
[S2] Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K.N.; Tanaka, F.; Barbas, C.F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040-1041.
[S3] Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 9630-9631.

6. Plausible mechanism leading the product stereochemistry (Scheme S1).

The C-C bond-forming reaction should proceed through transition state **A**, like the (*S*)-proline-catalyzed Mannich-type reactions of alkyl aldehydes. For the resulting Mannich product intermediate or its iminium with proline, conformation **B** should be favorably present over conformation **C** because of steric interactions in **C**. Isomerization of the double bond position should occur from conformation **B** and as a result the (*Z*)-aza-MBH-product forms initially. The *E*-isomer should eventually predominate through *E*-*Z* isomerization via the enol form because *E*-enals are thermodynamically more stable than *Z*-enals.

Scheme S1





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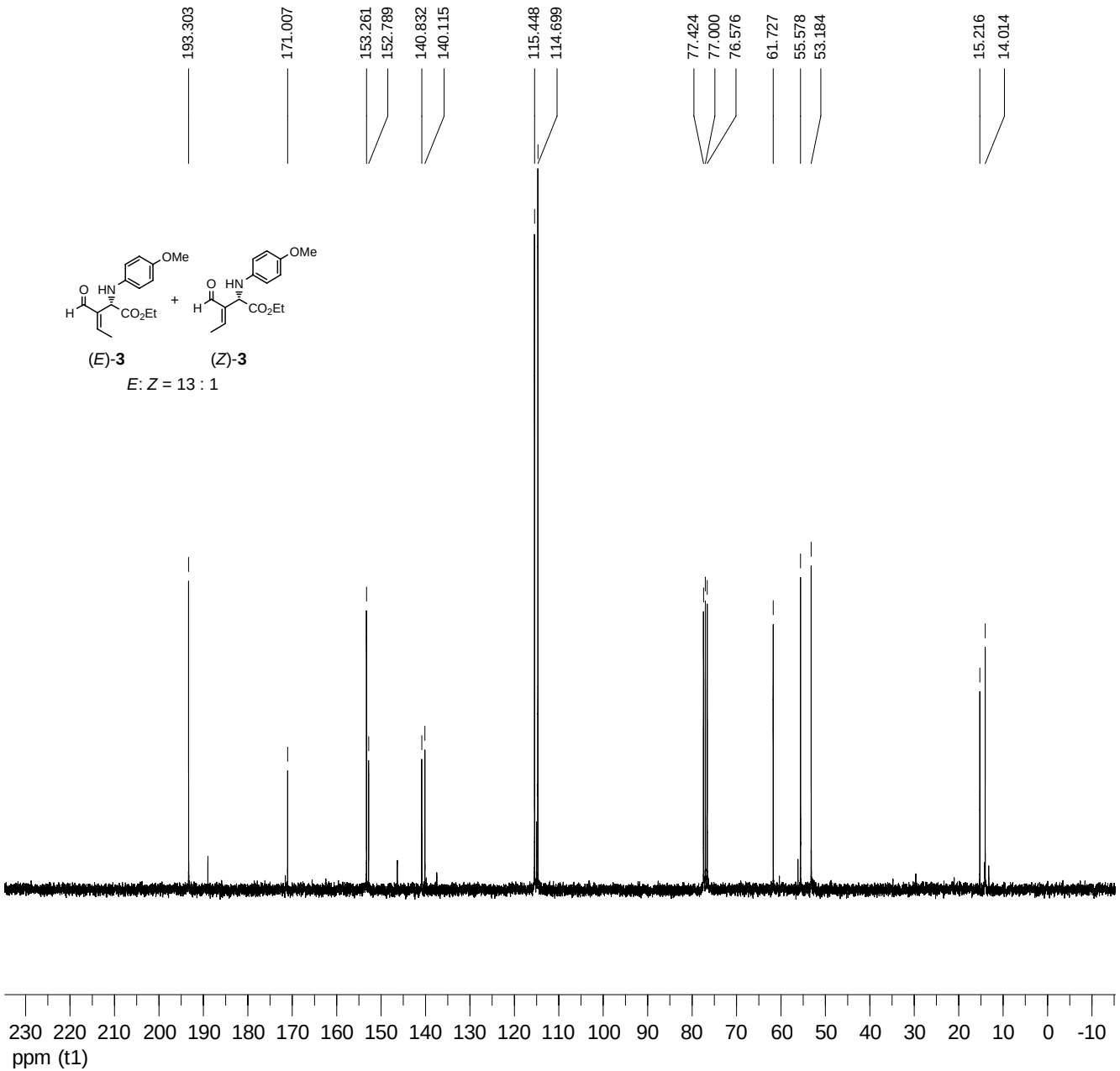

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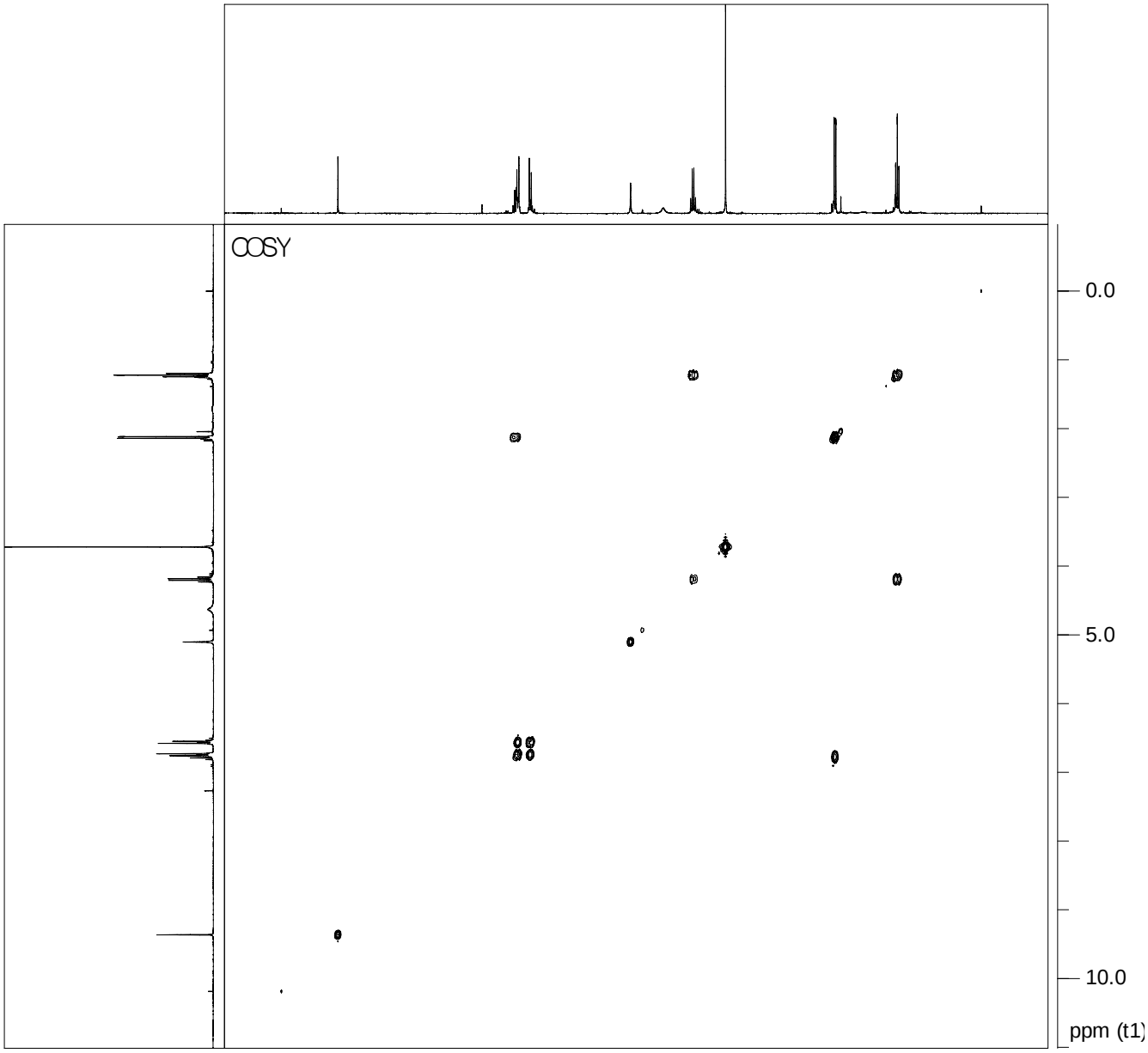

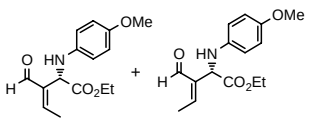

(*E*)-**3** (*Z*)-**3**

E: *Z* = 13 : 1

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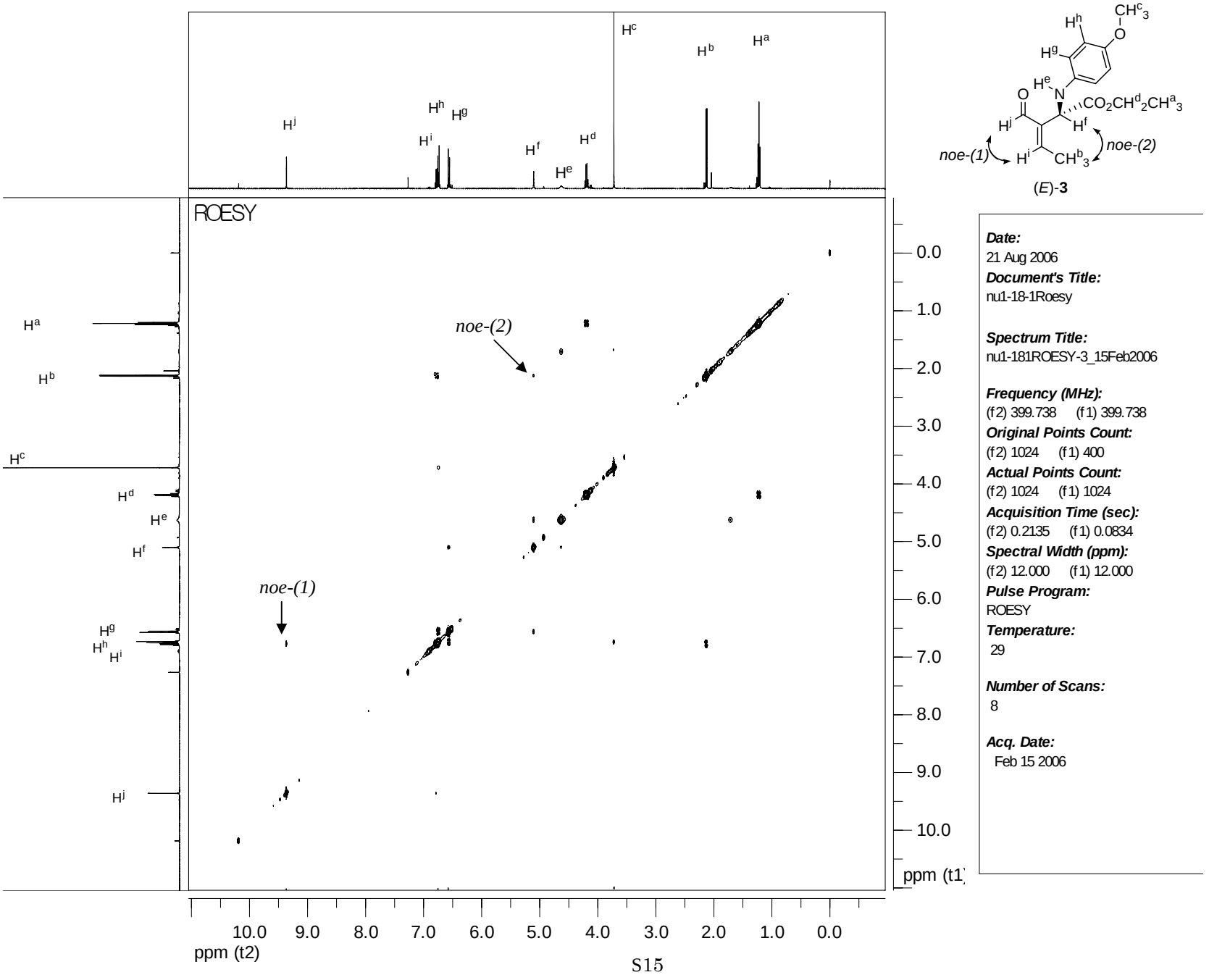

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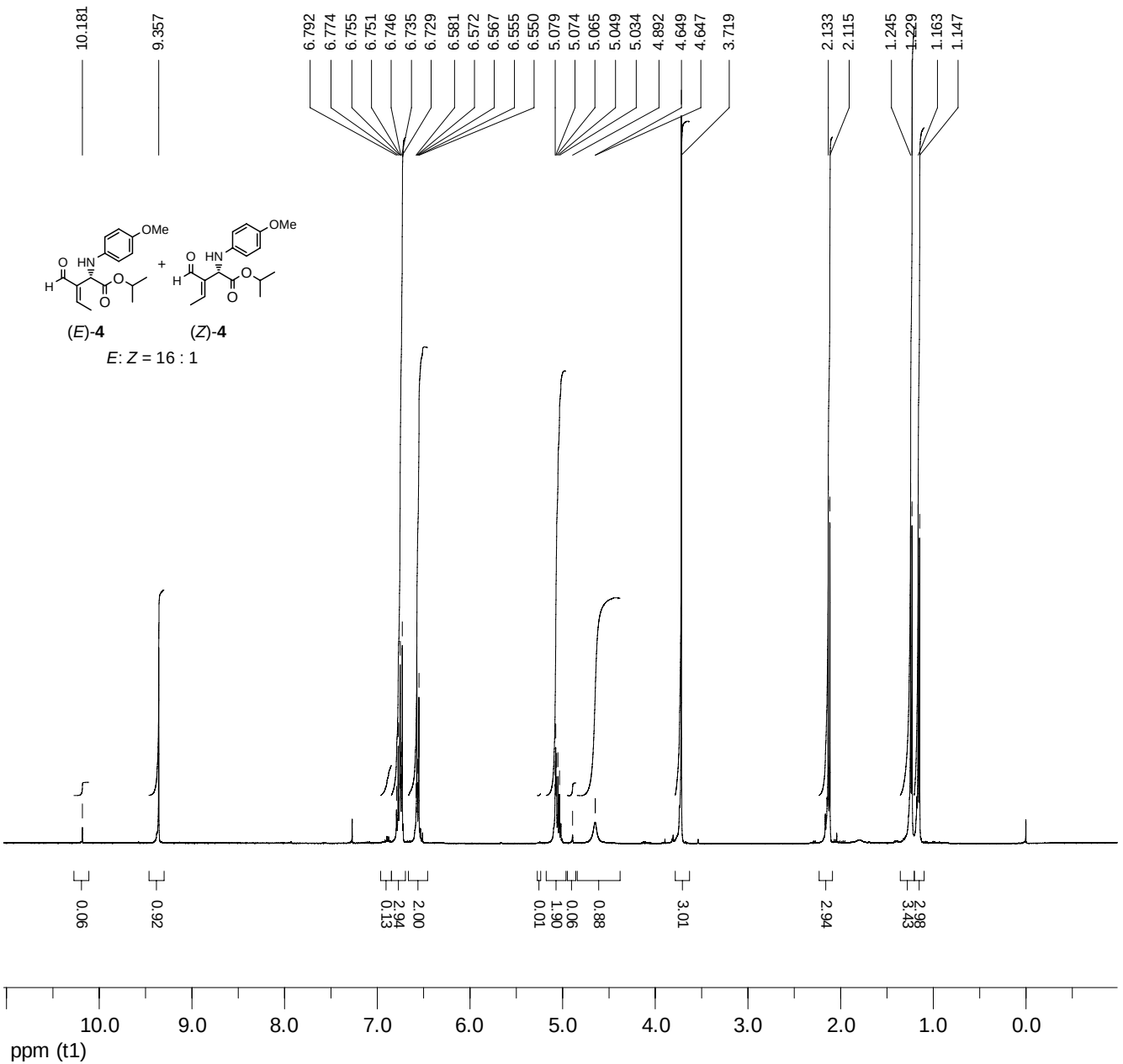

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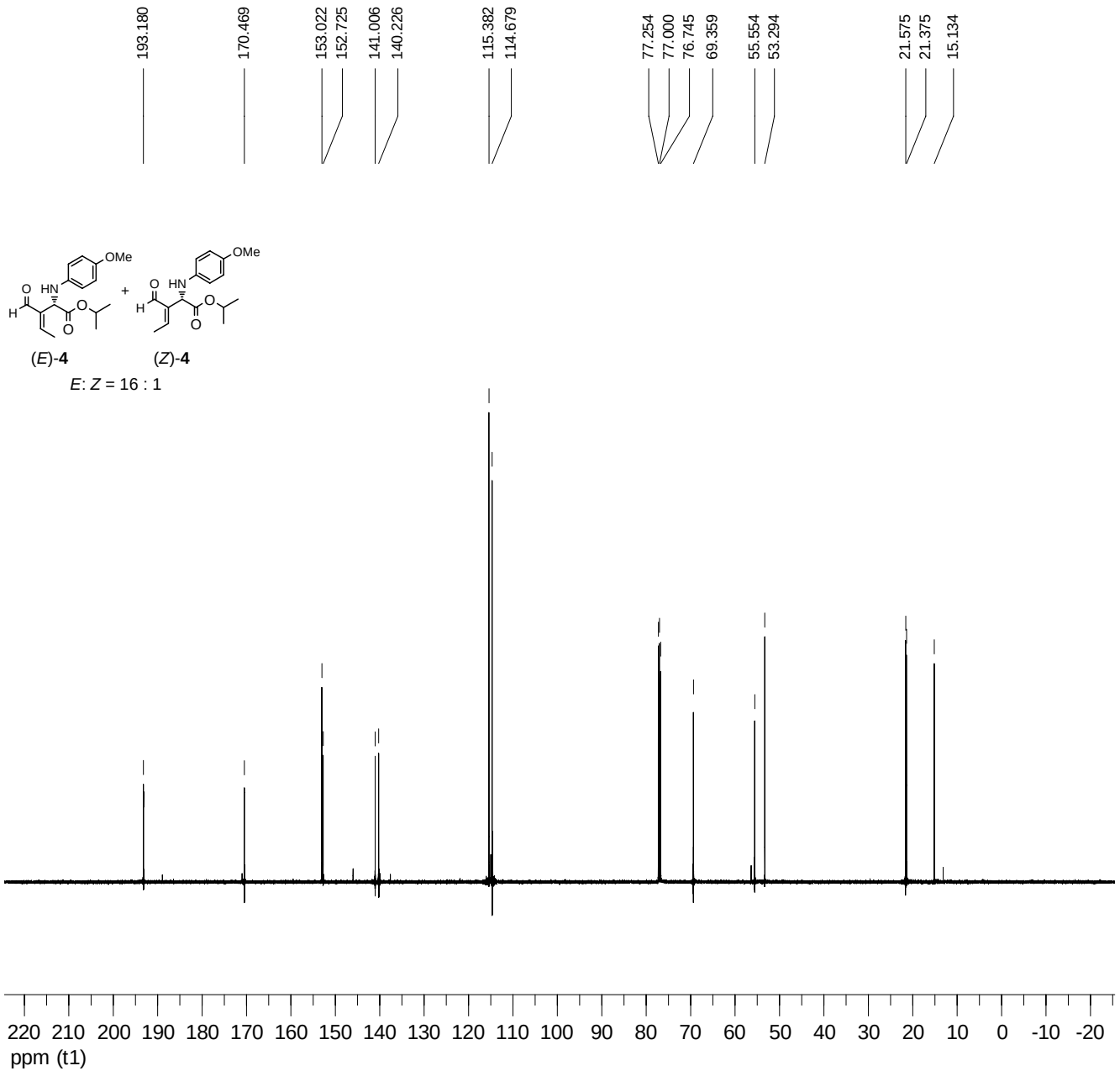

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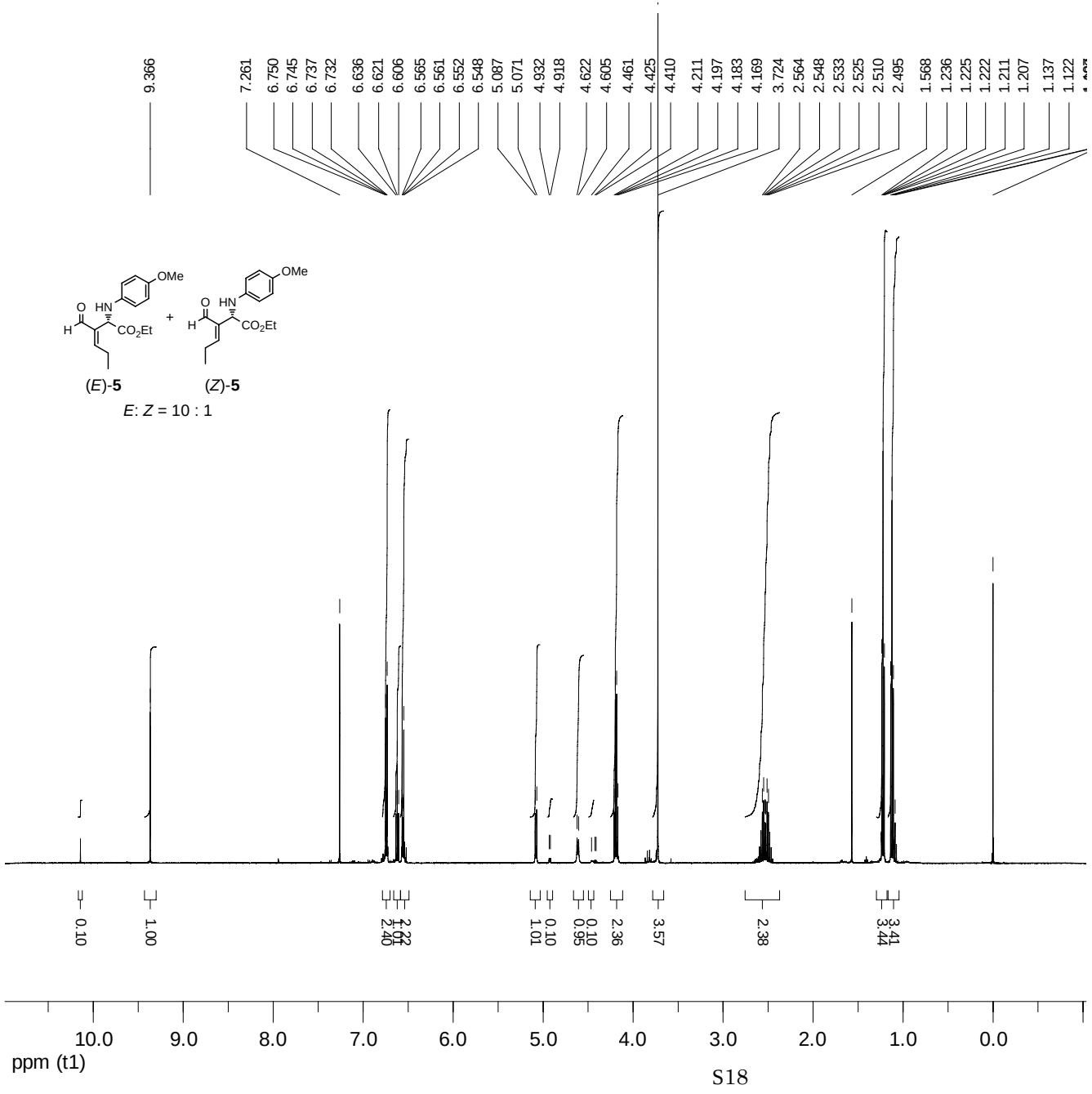

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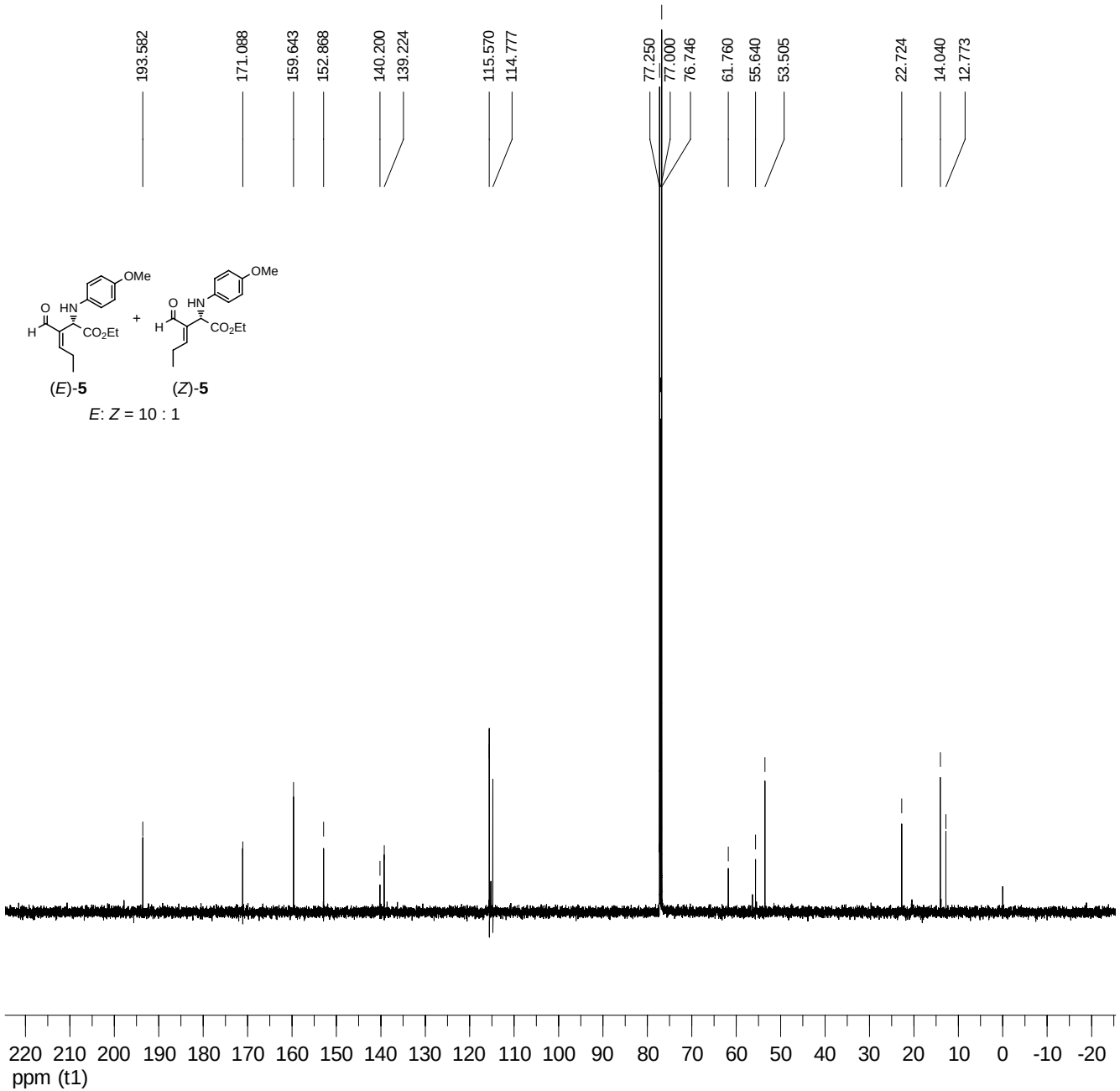

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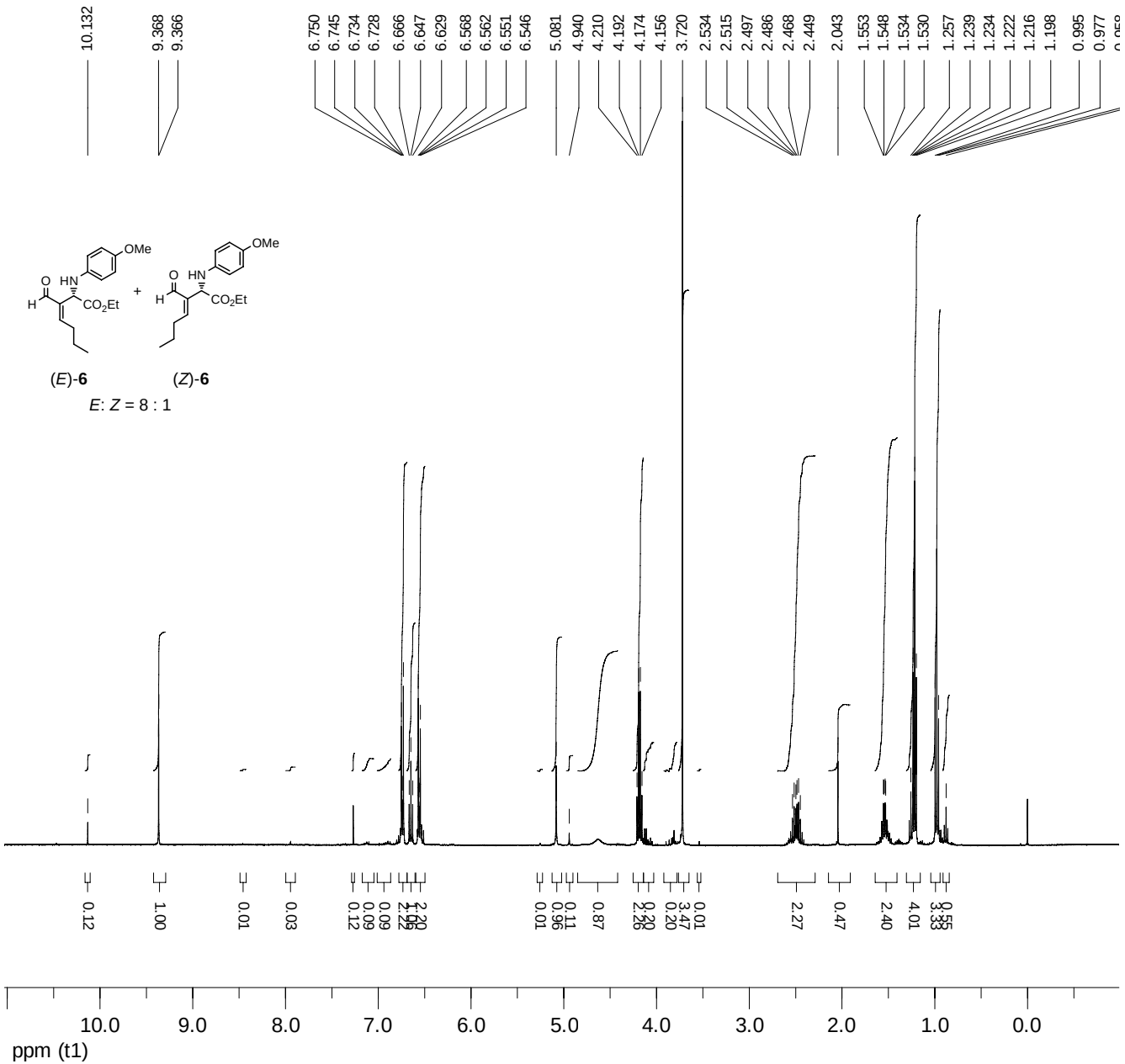

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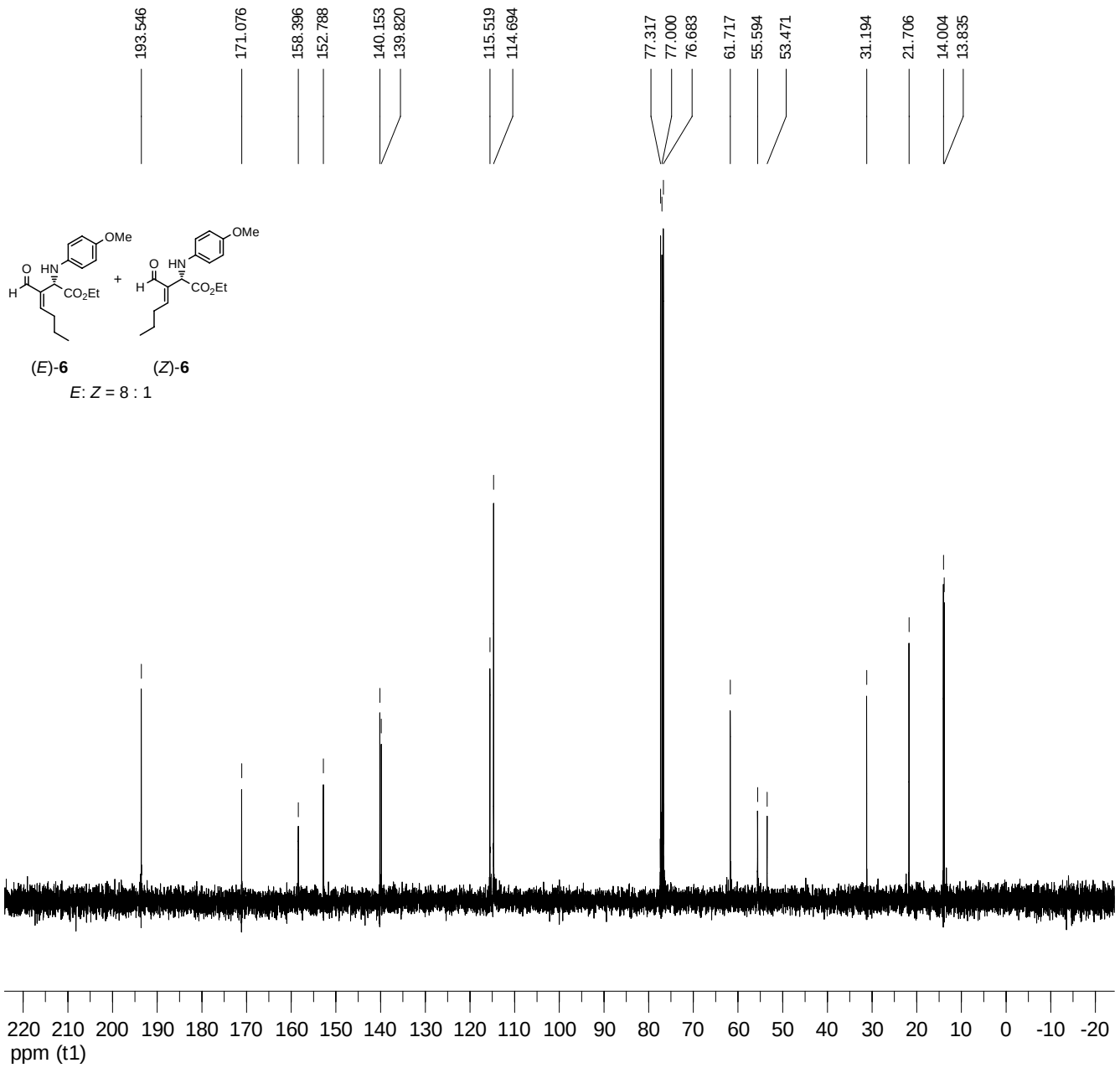
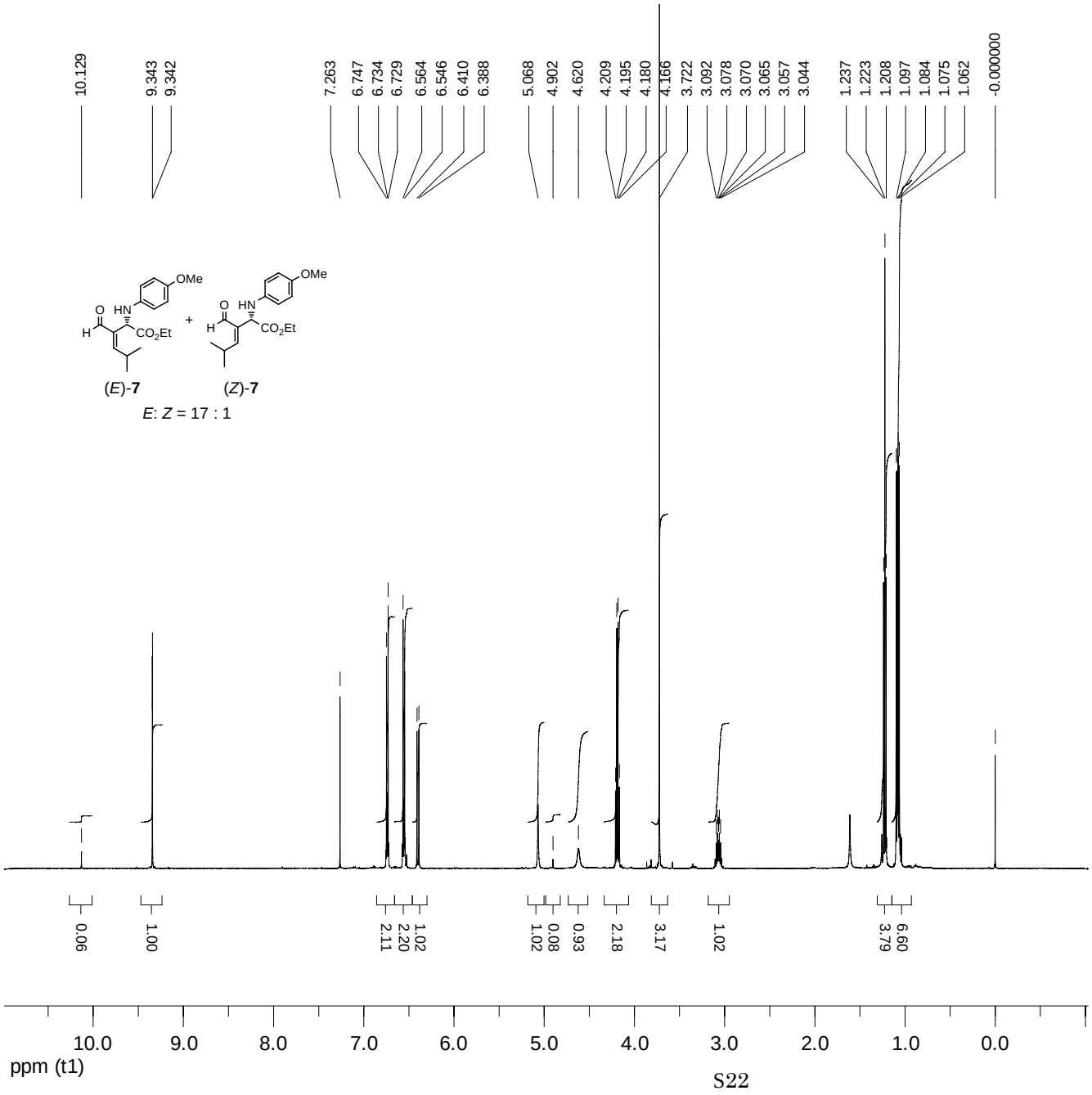
Acq. Date:
Fri May 05 05:29:39 PM



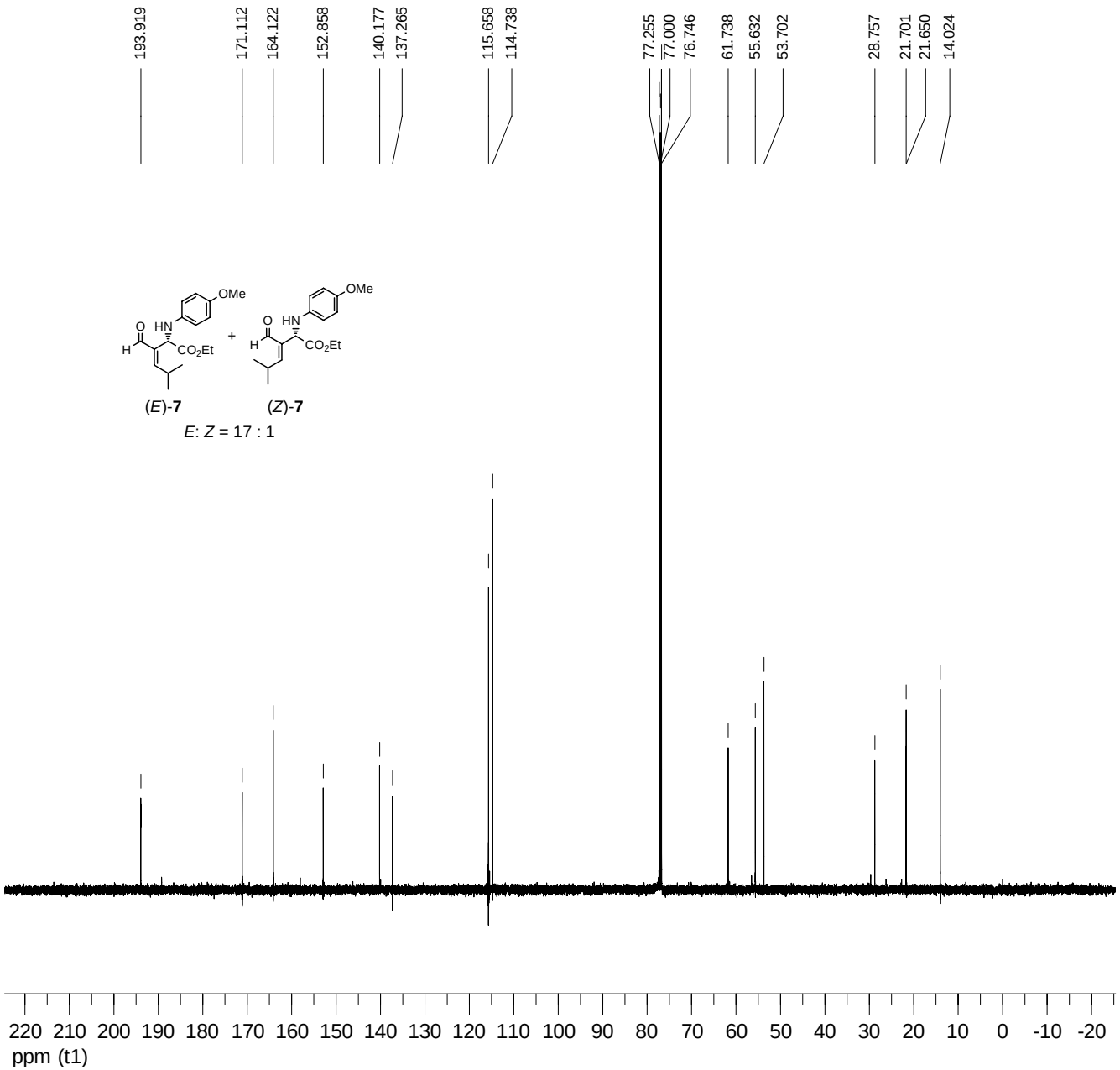
Date:
15 Aug 2006
Document's Title:
nu1-227-1

Spectrum Title:
None
Frequency (MHz):
(f1) 100.624
Original Points Count:
(f1) 8192
Actual Points Count:
(f1) 16384
Acquisition Time (sec):
(f1) 0.3277
Spectral Width (ppm):
(f1) 248.450
Pulse Program:
ZGPG60
Temperature:
300
Number of Scans:
365
Acq. Date:
Wed Mar 29 05:19:49 PM



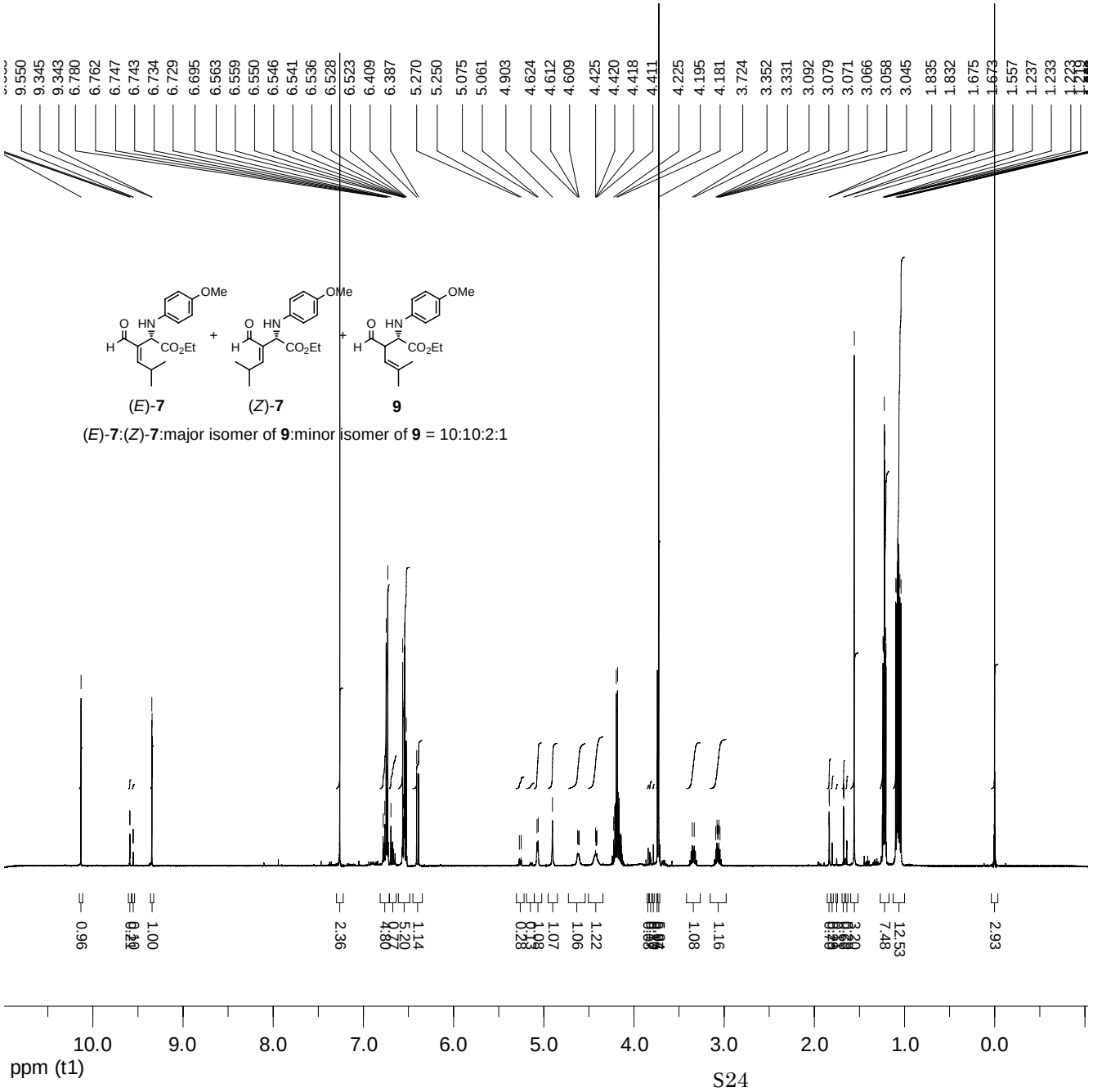
Date:
15 Aug 2006
Document's Title:
nu2-24-1

Spectrum Title:
None
Frequency (MHz):
(f1) 500.133
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 2.7263
Spectral Width (ppm):
(f1) 12.016
Pulse Program:
ZG30
Temperature:
298.16
Number of Scans:
32
Acq. Date:
Wed Jul 19 10:04:52 PM



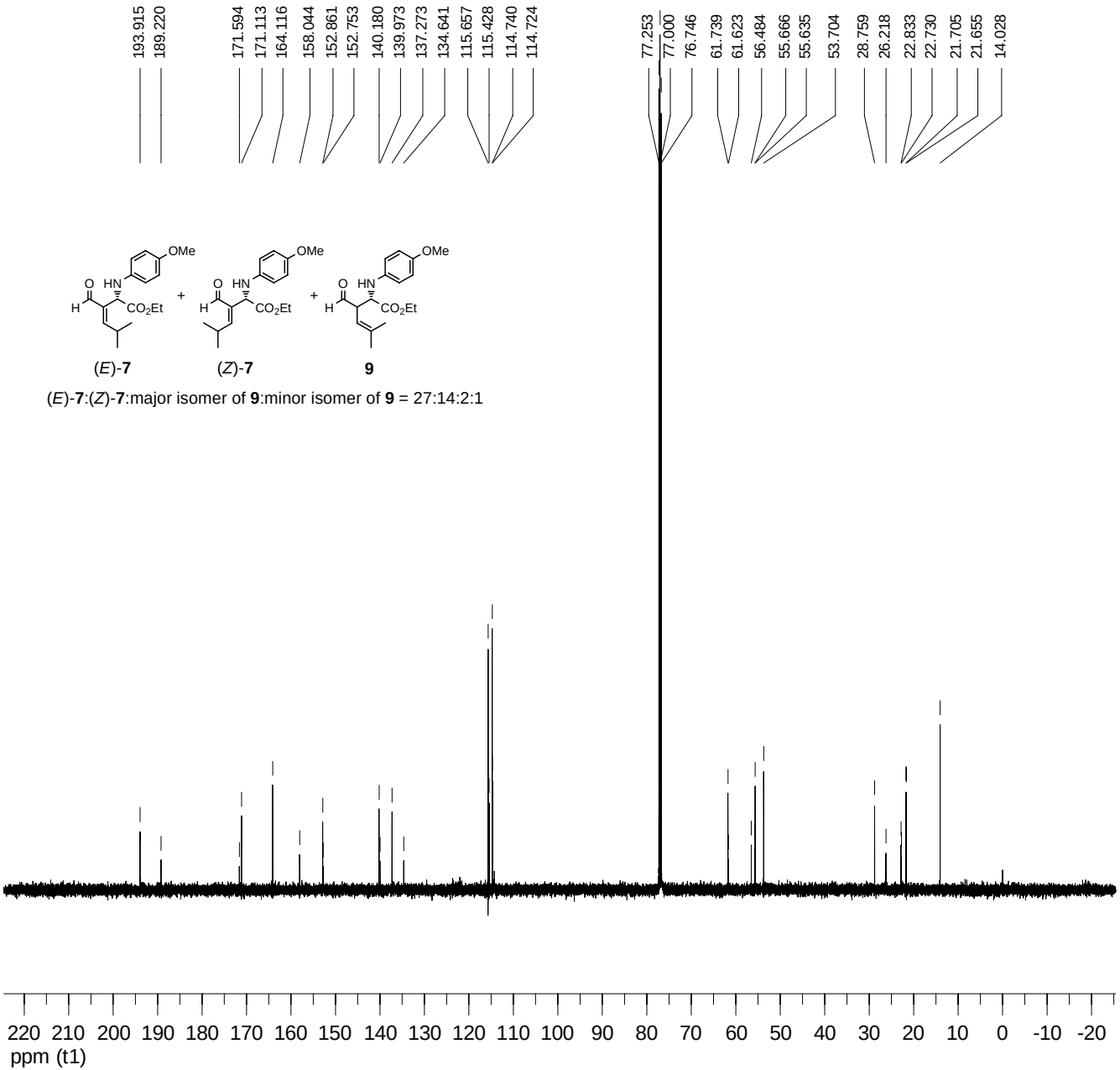
Date:
15 Aug 2006
Document's Title:
nu2-24-1

Spectrum Title:
None
Frequency (MHz):
(f1) 125.770
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 0.5210
Spectral Width (ppm):
(f1) 250.031
Pulse Program:
ZGPG45
Temperature:
298.16
Number of Scans:
733
Acq. Date:
Wed Jul 19 10:08:45 PM



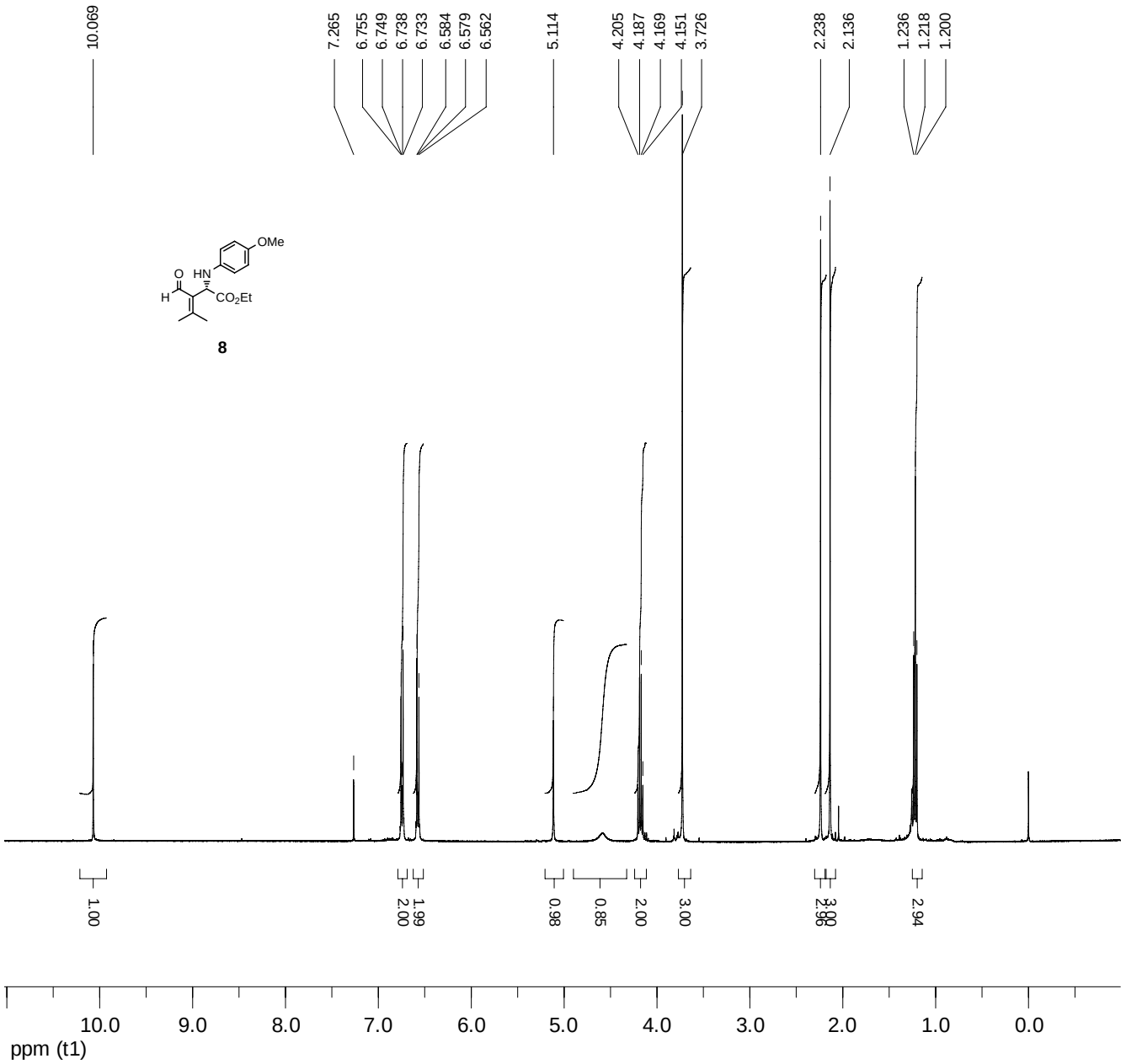
Date:
15 Aug 2006
Document's Title:
nu1-239-1

Spectrum Title:
None
Frequency (MHz):
(f1) 500.133
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 2.7263
Spectral Width (ppm):
(f1) 12.016
Pulse Program:
ZG30
Temperature:
298.16
Number of Scans:
32
Acq. Date:
Tue Apr 11 02:19:20 PM



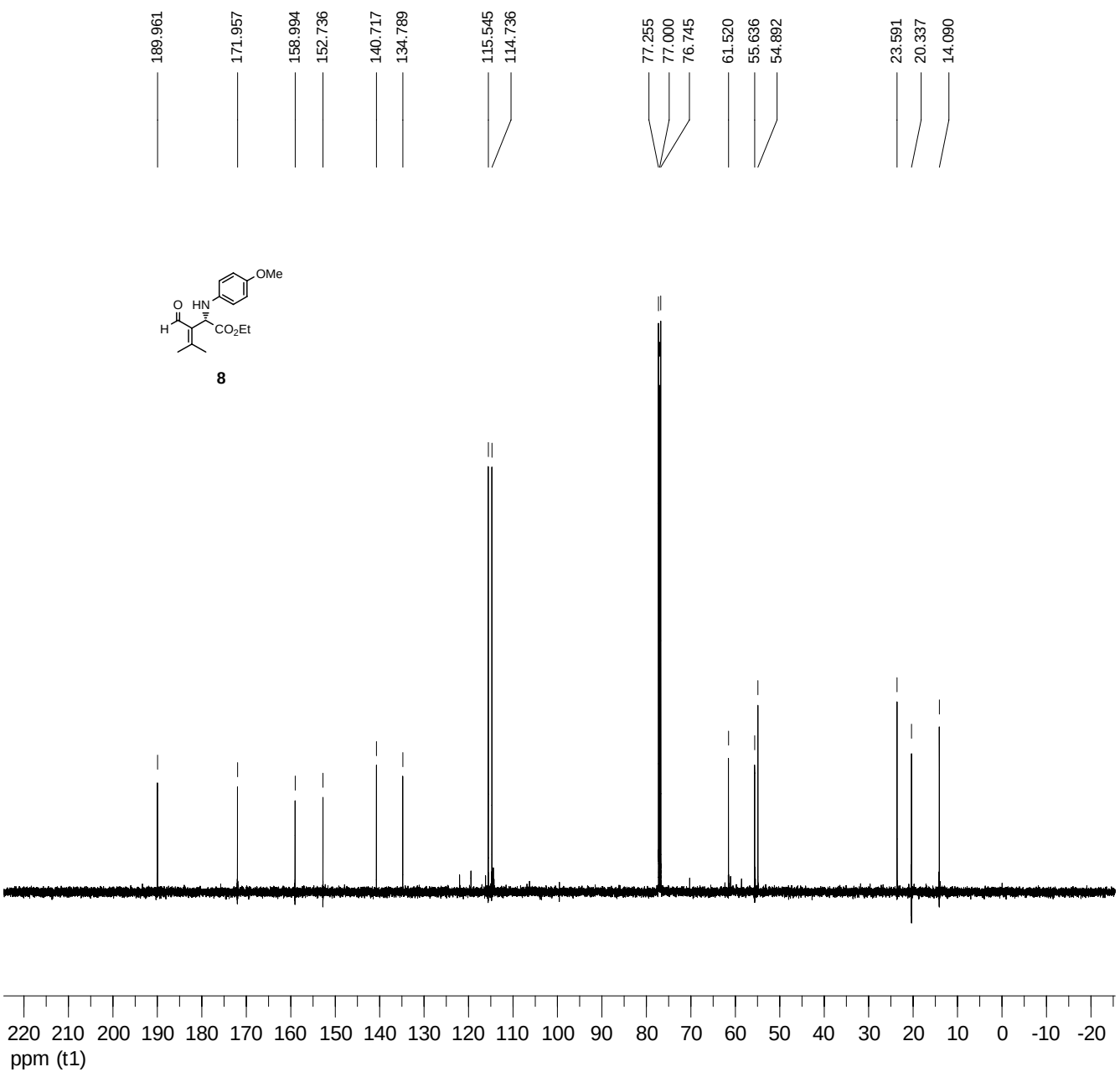
Date:
15 Aug 2006
Document's Title:
nu1-250-2

Spectrum Title:
None
Frequency (MHz):
(f1) 125.770
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 0.5210
Spectral Width (ppm):
(f1) 250.031
Pulse Program:
ZGPG45
Temperature:
298.16
Number of Scans:
512
Acq. Date:
Wed May 24 11:30:12 AM



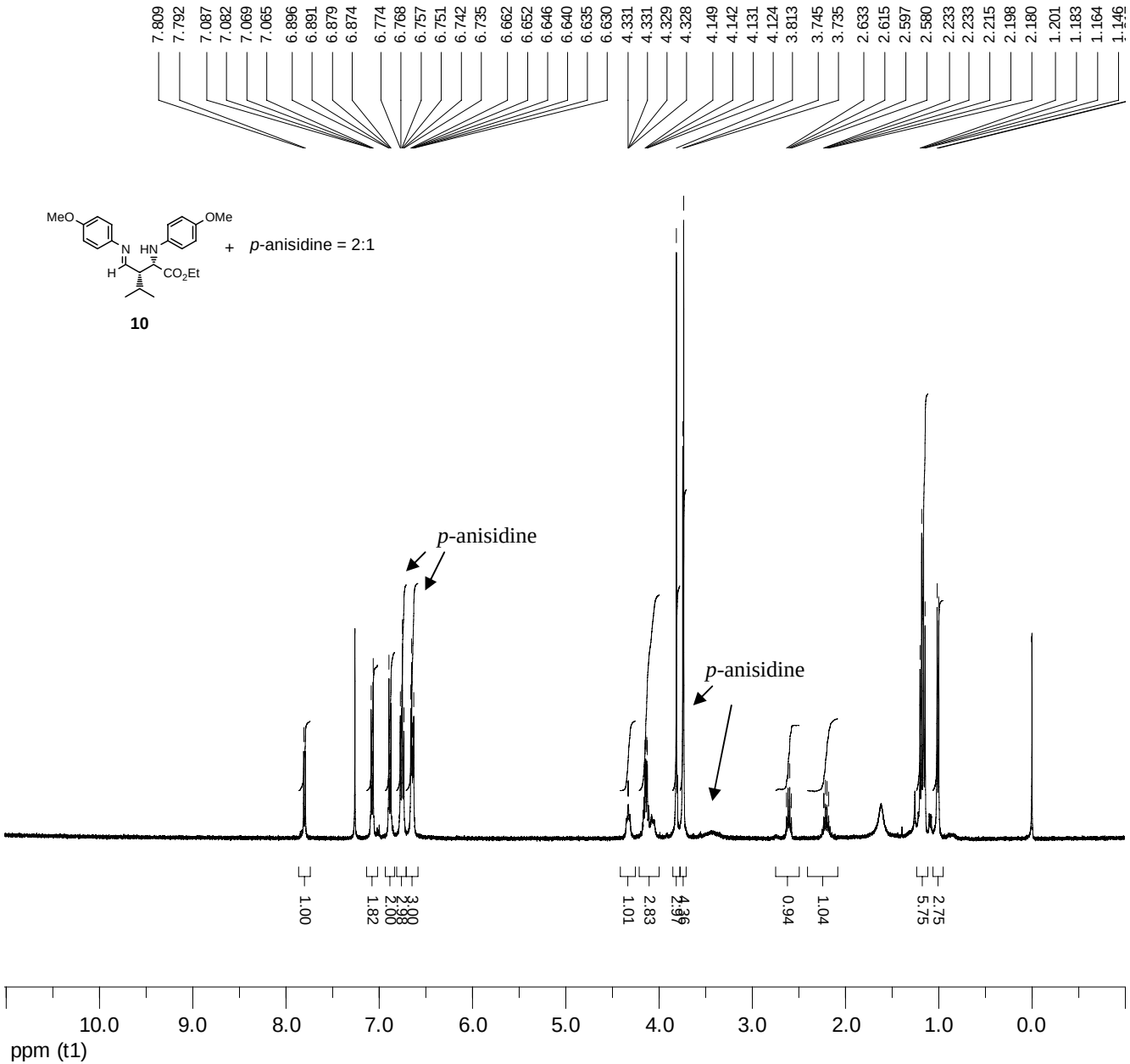
Date:
15 Aug 2006
Document's Title:
nu1-286-1

Spectrum Title:
None
Frequency (MHz):
(f1) 400.136
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 3.4079
Spectral Width (ppm):
(f1) 12.015
Pulse Program:
ZG30
Temperature:
300
Number of Scans:
16
Acq. Date:
Wed Jun 14 11:49:15 AM



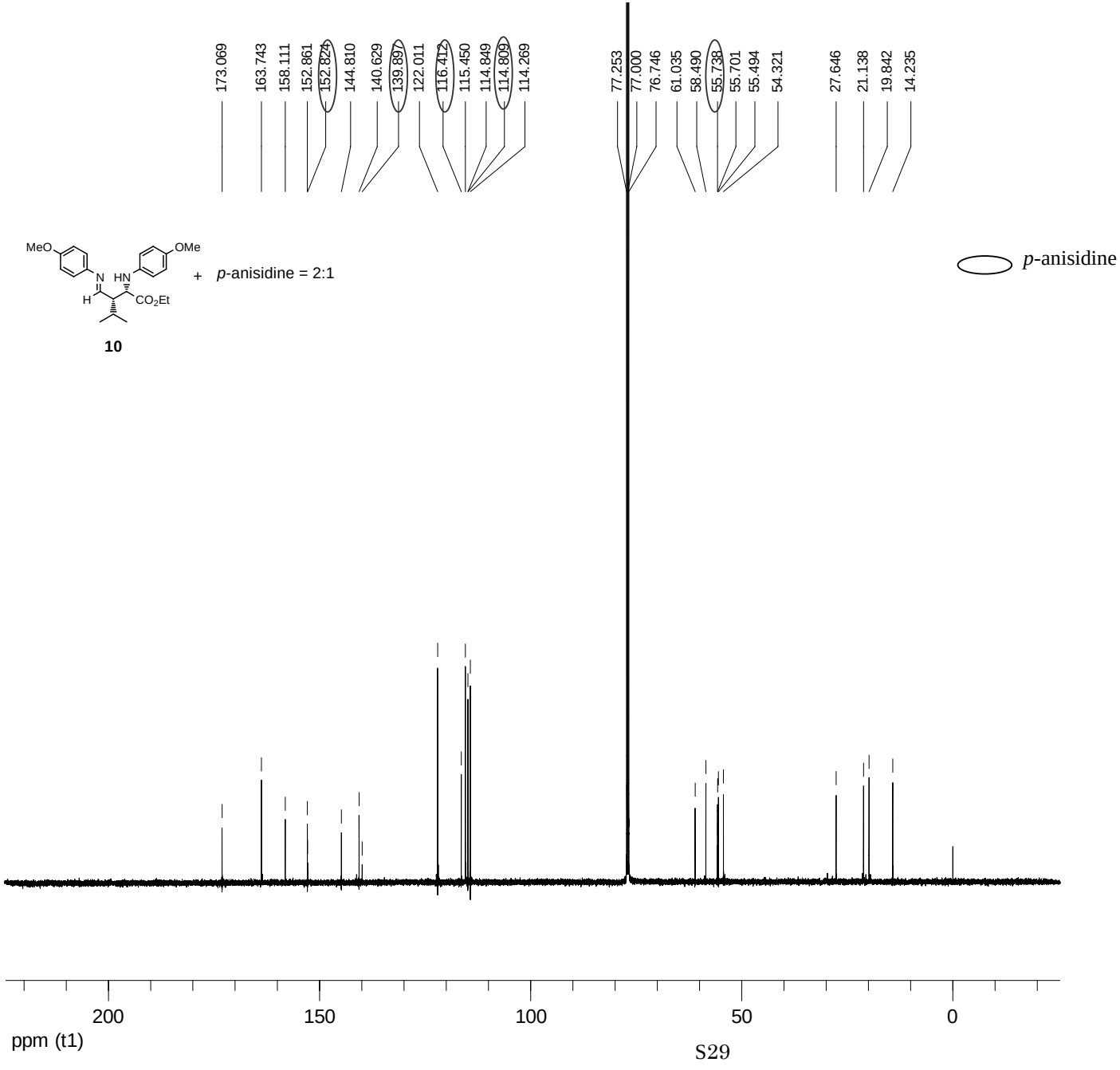
Date:
15 Aug 2006
Document's Title:
nu1-244-1

Spectrum Title:
None
Frequency (MHz):
(f1) 125.770
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 0.5210
Spectral Width (ppm):
(f1) 250.031
Pulse Program:
ZGPG45
Temperature:
298.16
Number of Scans:
406
Acq. Date:
Tue May 23 05:11:54 PM



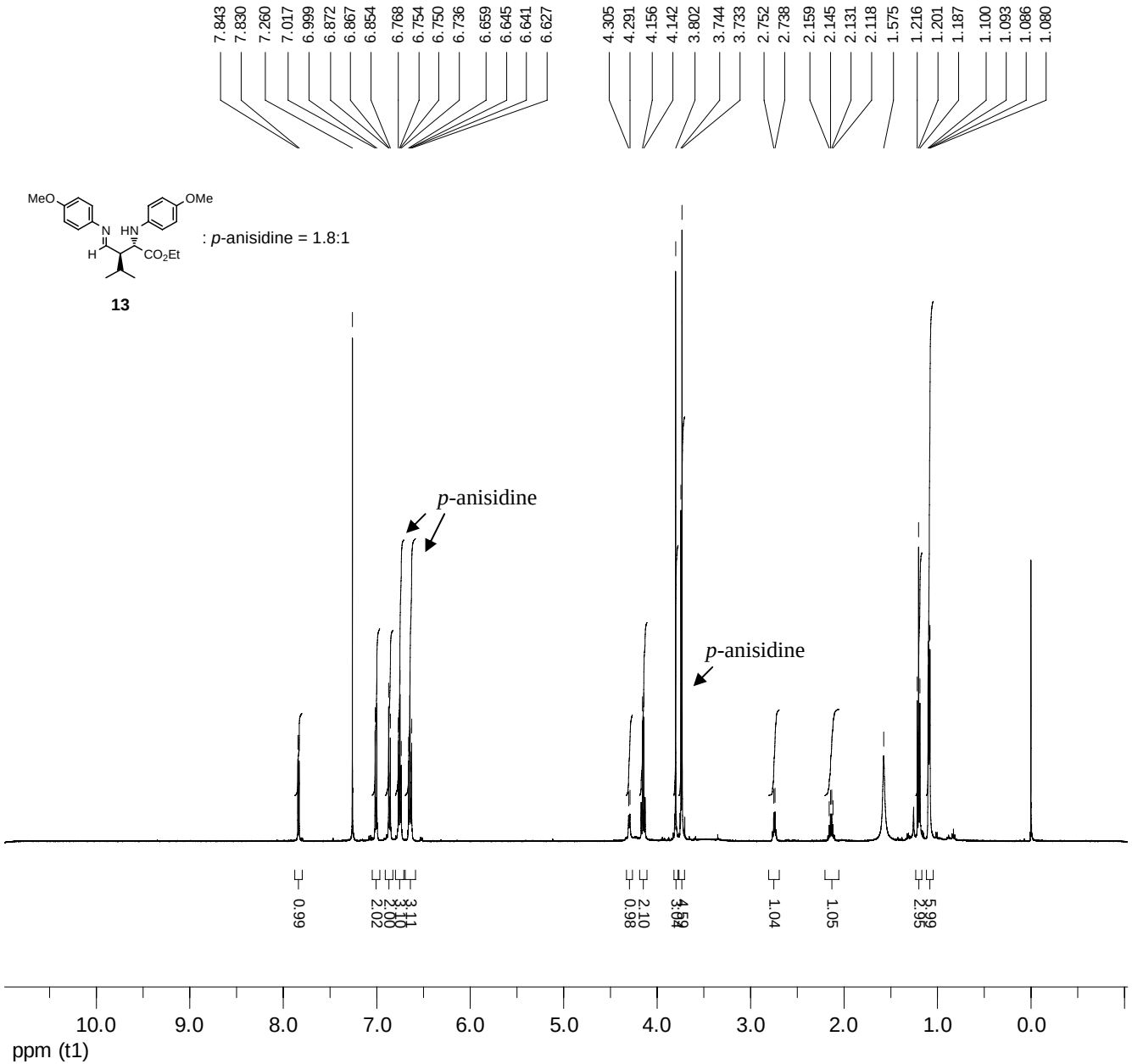
Date:
15 Aug 2006
Document's Title:
nu2-5-1

Spectrum Title:
None
Frequency (MHz):
(f1) 400.136
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 3.4079
Spectral Width (ppm):
(f1) 12.015
Pulse Program:
ZG30
Temperature:
300
Number of Scans:
16
Acq. Date:
Fri Jul 07 04:47:09 PM



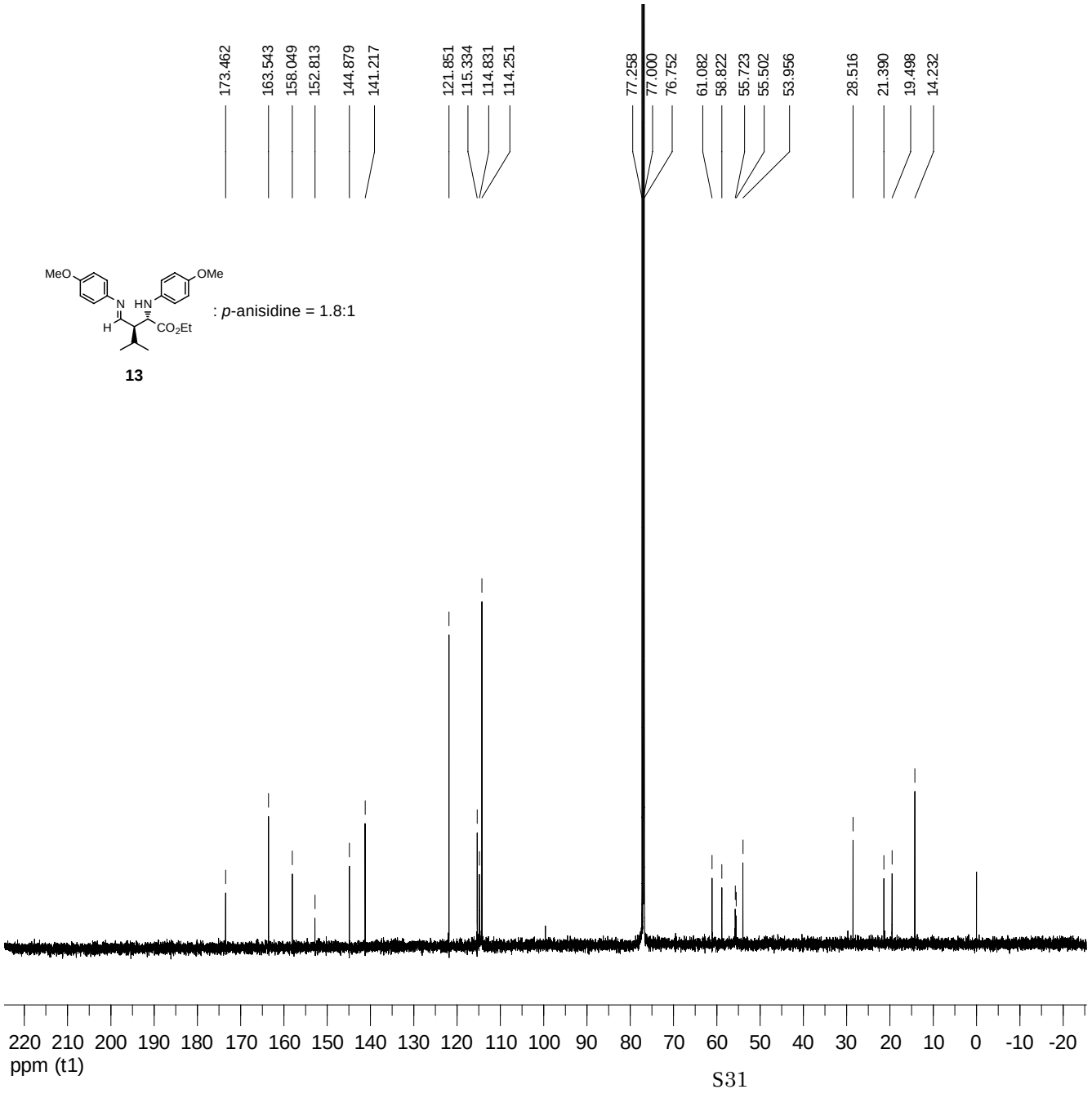
Date:
15 Aug 2006
Document's Title:
nu2-5-1

Spectrum Title:
None
Frequency (MHz):
(f1) 125.770
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 0.5210
Spectral Width (ppm):
(f1) 250.031
Pulse Program:
ZGPG45
Temperature:
298.16
Number of Scans:
8319
Acq. Date:
Fri Jul 21 12:20:16 AM



Date:
15 Aug 2006
Document's Title:
nu1-303-1

Spectrum Title:
None
Frequency (MHz):
(f1) 500.133
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 2.7263
Spectral Width (ppm):
(f1) 12.016
Pulse Program:
ZG30
Temperature:
298.16
Number of Scans:
32
Acq. Date:
Wed Jun 21 04:13:19 PM



Date:
15 Aug 2006
Document's Title:
nu1-303-1

Spectrum Title:
None
Frequency (MHz):
(f1) 125.770
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 16384
Acquisition Time (sec):
(f1) 0.5210
Spectral Width (ppm):
(f1) 250.031
Pulse Program:
ZGPG45
Temperature:
298.16
Number of Scans:
8868
Acq. Date:
Mon Jul 24 11:37:25 PM