Eur. J. Org. Chem. **2008** · © WILEY-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, 2008 · ISSN 1434–193X

SUPPORTING INFORMATION

Title: 2,6-Disubstituted Tetrahydropyrans by Tandem Cross-Metathesis/Iodocyclisation
Author(s): Marie-Aude Hiebel, Béatrice Pelotier, Peter Goekjian, Olivier Piva*
Ref. No.: O200700902

^{1}H and ^{13}C NMR spectra were recorded on a Brüker AM 300 MHz NMR spectrometer, which provided all necessary data for the full assignment of each compound. Chemicals shifts were reported in ppm**.** High resolution mass spectrometry (HRMS) analyses were conducted using a ThermoFinigan-MAT 95 XL instrument. IR spectra were measured on a Perkin-Elmer Spectrum One FT-IR spectrometer. Melting points were measured on a B-540 Büchi apparatus. TLC analyses were performed on plates (layer thickness 0.25mm) and were visualized with UV light, phosphomolybdic acid or *p*-anisaldehyde solution. Column chromatography was performed on silica gel (40-63 μm) using ethyl acetate (EtOAc) and hexanes as eluents. When appropriate, solvents and reagents were dried by distillation over appropriate drying agent prior to use. Diethyl ether and tetrahydrofuran were distilled from Na/benzophenone and used fresh. Dichloromethane was distilled from CaH_2.

General procedure for the γ-alkylation of methylacetoacetate

To a suspension of sodium hydride (60% in oil, 33 mmol, 1.33 g) in tetrahydrofuran (50 mL) at 0°C under nitrogen was added methyl acetoacetate (30 mmol, 3.32 mL). After 30 min stirring at 0°C, n-butyl lithium (31.5 mmol, 24.3 mL) was added and after a further 30 min, the bromoalkene (33 mmol, 1.1 eq) was added. The mixture was allowed to warm up to rt and stirred for 36h. The solution was acidified with dilute hydrochloric acid (1N, 40 mL) and the aqueous phase was extracted with diethyl ether (5x20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography with EtOAc/hexanes, 10/90.

Methyl 3-oxo-hept-6-enoate 1[1]

Pale orange oil (50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (q, J = 7.0 Hz, 2 H, CH_2CH=), 2.64 (t, J = 7.0 Hz, 2 H, CH_2CO), 3.45 (s, 2 H, CO-CH_2-CO), 3.73 (s, 3 H, OCH_3), 4.97-5.06 (m, 2 H, CH_2=),

5.79 (ddt, J =17.2, 10.4, 6.4 Hz, 1 H, CH=); ^{13}C NMR (300 MHz, $CDCl_3$) δ 27.6, 42.2, 49.2, 52.5, 115.8, 136.8, 167.8, 202.1.

Methyl 3-oxo-oct-7-enoate 2[2]

Pale orange oil (56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (quint, J = 7.3 Hz, 2 H, CH_2CH$_2$CH=), 2.02-2.09 (m, 2 H, CH_2CH=), 2.53 (t, J = 7.3 Hz, 2 H, CH$_2$CO), 3.43 (s, 2 H, CO-CH$_2$-CO), 3.72 (s, 3 H, OCH$_3$), 4.95-5.04 (m, 2 H, CH$_2$=), 5.74 (ddt, J =16.9, 10.1, 6.8 Hz, 1 H, CH=); ^{13}C NMR (300 MHz, $CDCl_3$) δ 22.6, 33.0, 42.3, 49.2, 52.4, 115.6, 137.9, 167.8, 202.7; IR ν_{max}(film)/cm^{-1} 3079, 2954, 1749, 1716, 1641, 1437, 1410, 1370, 1322, 1262, 1156, 1001, 915.

General procedure for the reduction of β-ketoesters 1 and 2

Sodium borohydride (1.3 eq) was added to a solution of methyl ester **1** or **2** (1 eq) in methanol at 0°C. The mixture was warmed up to rt and stirred for 2h. After evaporation of the solvent, the residue was diluted in dichloromethane and water. After further extraction with dichloromethane, the organic phase was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure.

Methyl 3-hydroxy-hept-6-enoate 3[1]

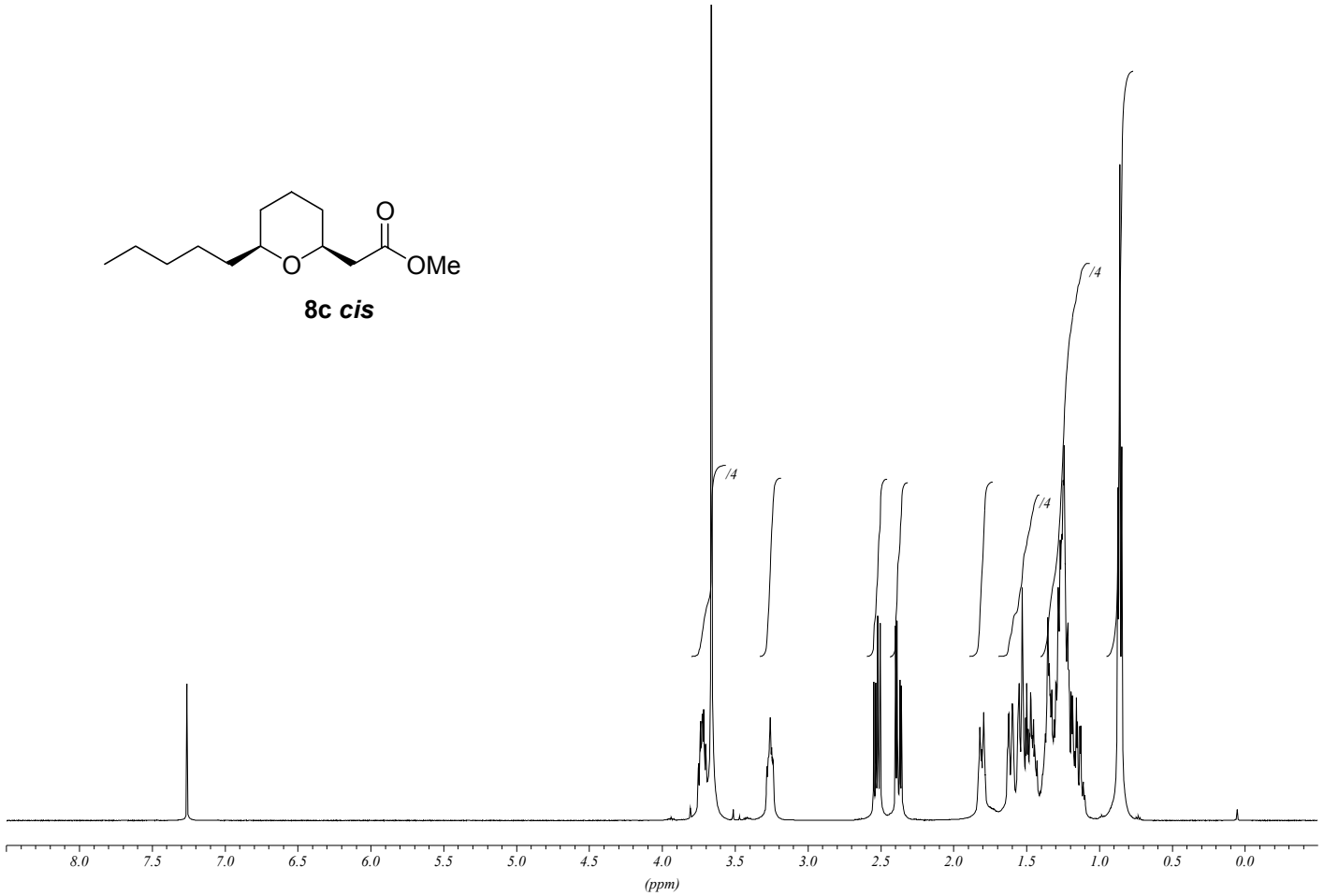
Pale orange oil (92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51-1.67 (m, 2 H, CH_2CHOH), 2.08-2.26 (m, 2 H, CH_2CH=), 2.42 (dd, J_{AB} = 16.4 Hz, J = 8.7 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.51 (dd, J_{AB} = 16.4 Hz, J = 3.6 Hz, 1 H, CH$_A$$H_BCO_2$Me), 2.93 (bs, 1 H, OH), 3.71 (s, 3 H, OCH$_3$), 3.99-4.05 (m, 1 H, CHOH), 4.97 (bd, J = 10.3 Hz, 1 H, CH_1H$_2$=), 5.04 (dd, J = 17.0, 1.1 Hz, 1 H, CH$_1$$H_2$=), 5.81 (ddt, J = 17.0, 10.3, 6.6 Hz, 1 H, CH=); ^{13}C NMR (300 MHz, $CDCl_3$) δ 29.8, 35.8, 41.5, 51.8, 67.5, 115.1, 138.2, 173.3.

Methyl 3-hydroxy-oct-7-enoate 4[3]

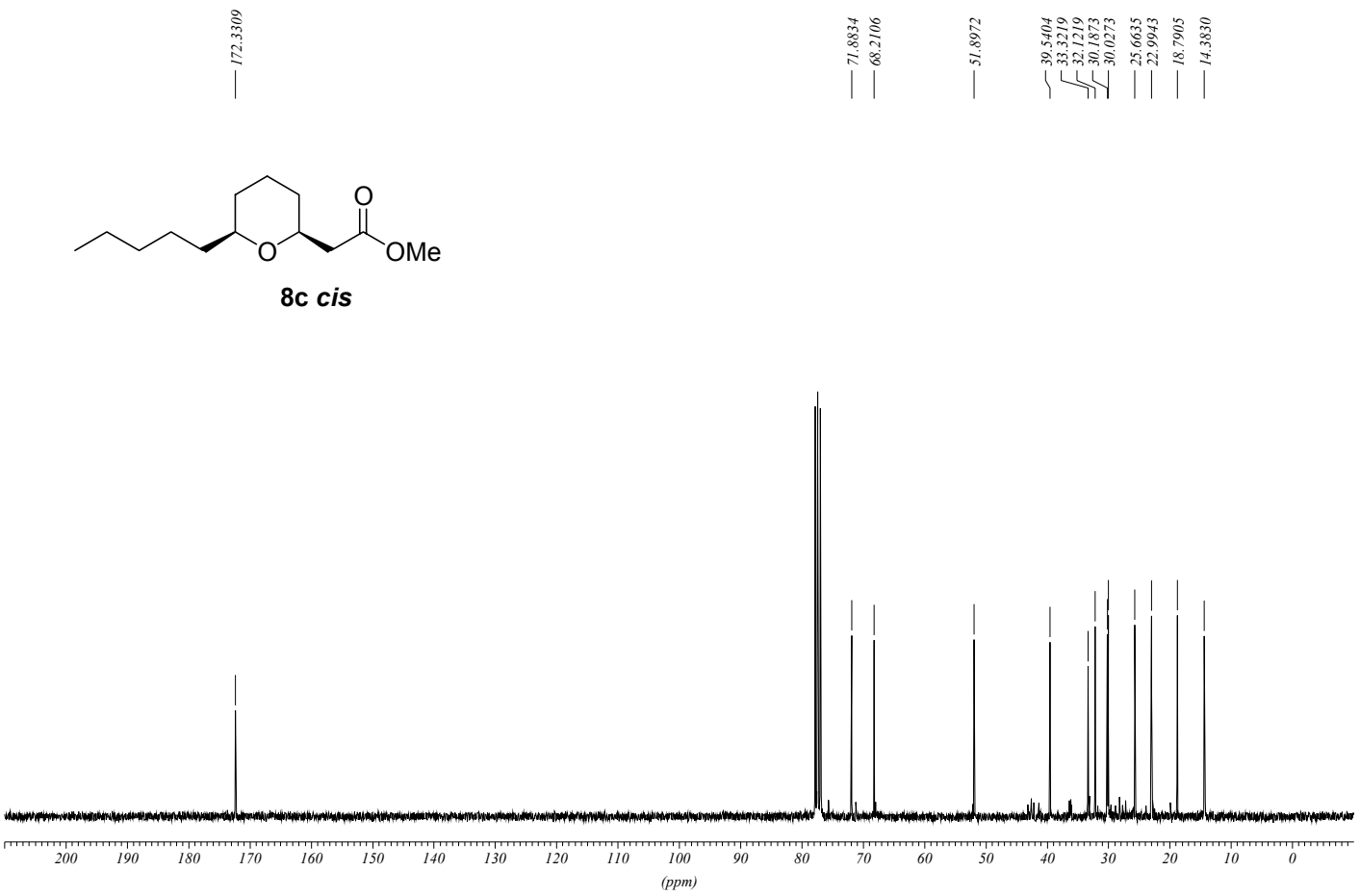
Pale yellow oil (89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38-1.56 (m, 4 H, CH_2CH_2CHOH), 2.03 (q, J = 6.0 Hz, 2 H, CH_2CH=), 2.37 (dd, J_{AB} = 16.3 Hz, J = 8.7 Hz, 1 H, CH_AH$_B$CO$_2$Me), 2.47 (dd, J_{AB} = 16.3 Hz, J = 3.6 Hz, 1 H, CH$_A$$H_BCO_2$Me), 3.07 (bs, 1 H, OH), 3.66 (s, 3 H, OCH$_3$), 3.97-3.99 (m, 1 H, CHOH), 4.89-4.99 (m, 2 H, CH$_2$=), 5.75 (ddt, J = 17.1, 10.4, 6.6 Hz, 1 H, CH=); ^{13}C NMR (300 MHz, $CDCl_3$) δ 24.9, 33.7, 36.2, 41.5, 52.0, 68.1, 114.9, 138.7, 173.6; IR ν_{max}(film)/cm^{-1} 3700-3100**,** 3060, 2933, 1737, 1641, 1438, 1373, 1162, 1073, 913.

[1] A. S. Kende, J. I. Martin Hernando, J. B. J. Milbank, *Tetrahedron* **2002**, *58*, 61-74.
[2] J.-M. Poirier, L. Hennequin, *Tetrahedron* **1989**, *45*, 4191-4202.
[3] T. Beuerle, S. Engelhard, C. Bicchi, W. Schwab, *J. Nat. Prod.* **1999**, *62*, 35-40.

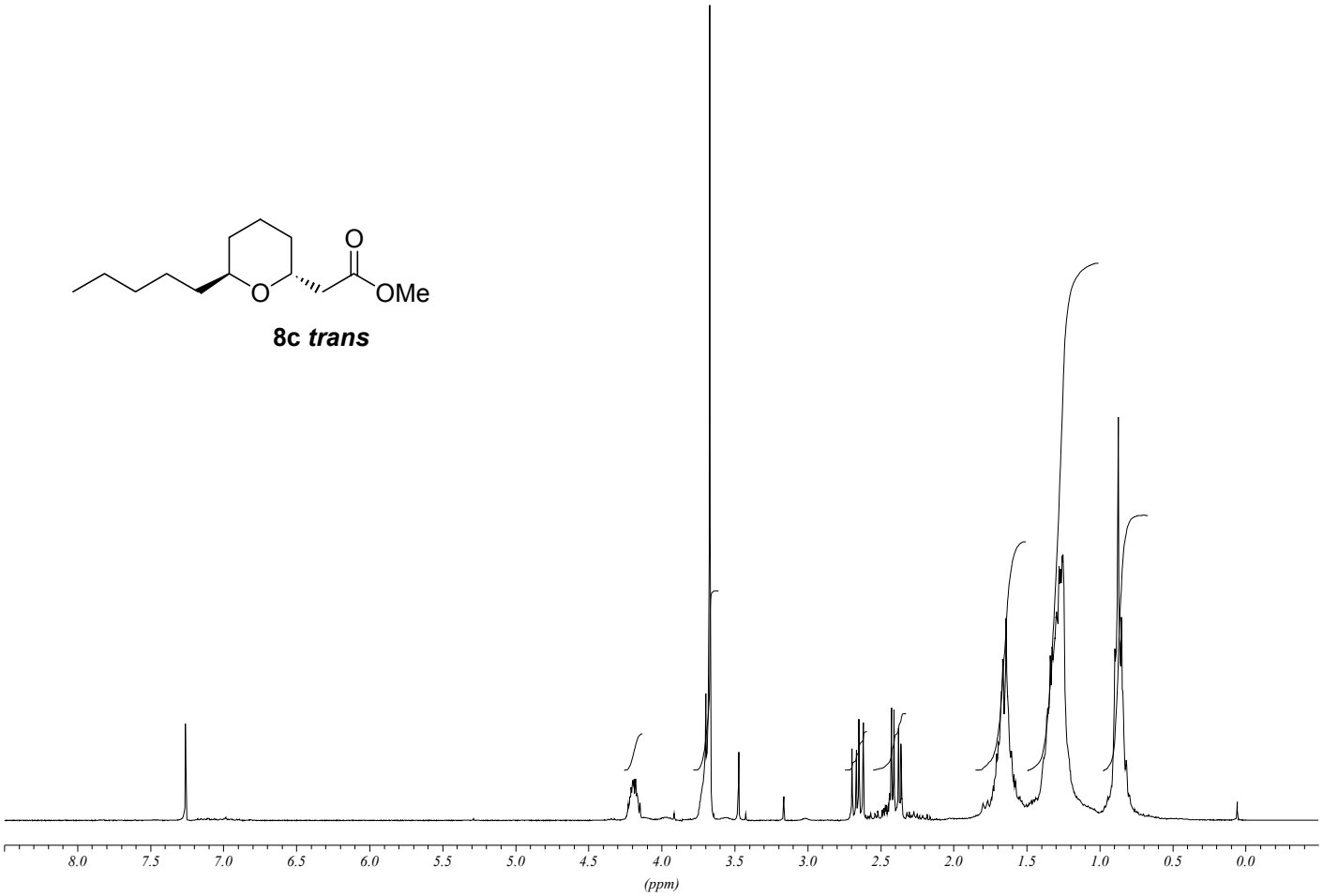
^{1}H-NMR spectrum of compound **8c *cis***



^{13}C-NMR spectrum of compound **8c *cis***

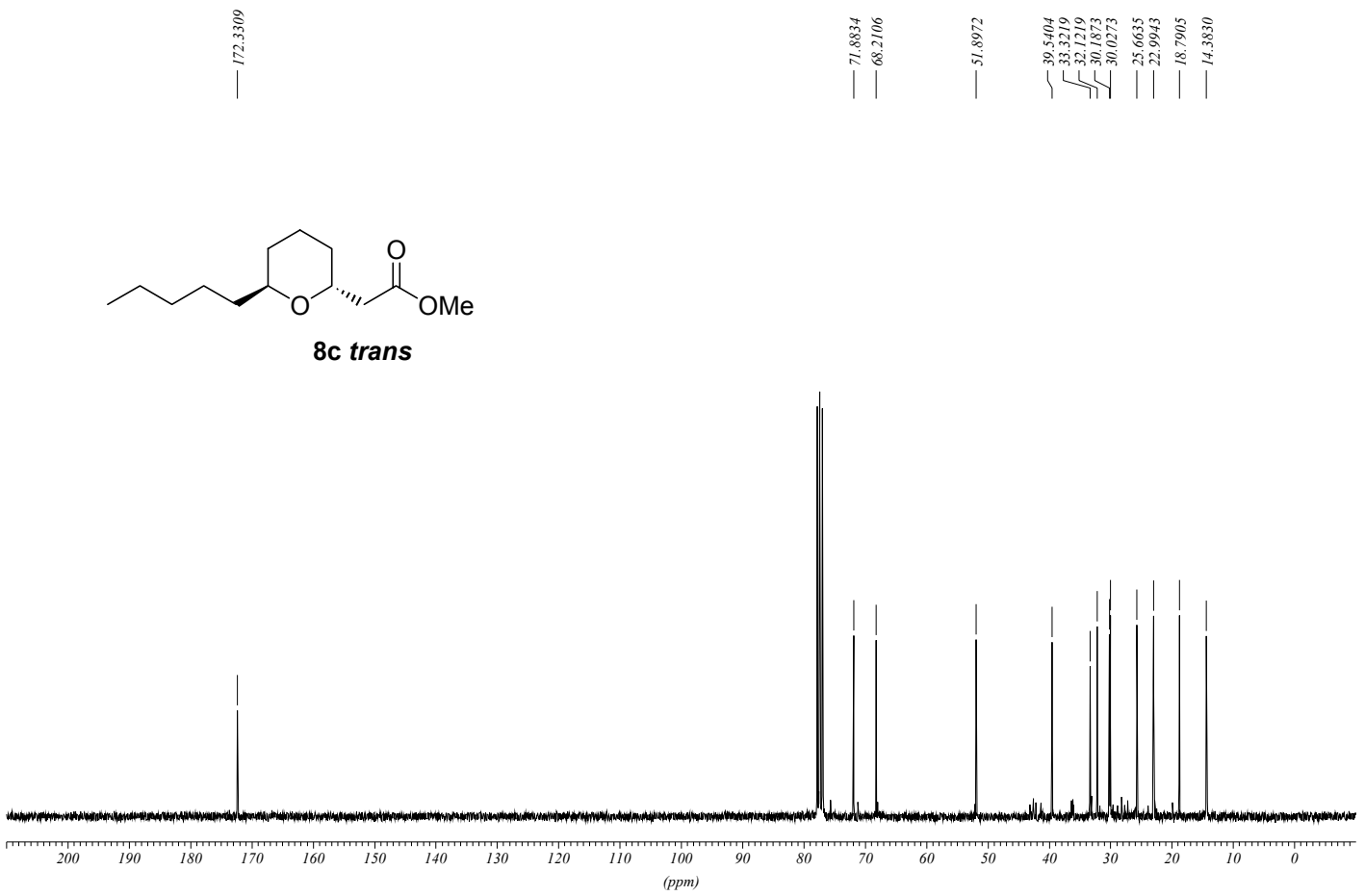


^{1}H-NMR spectrum of compound **8c *trans***



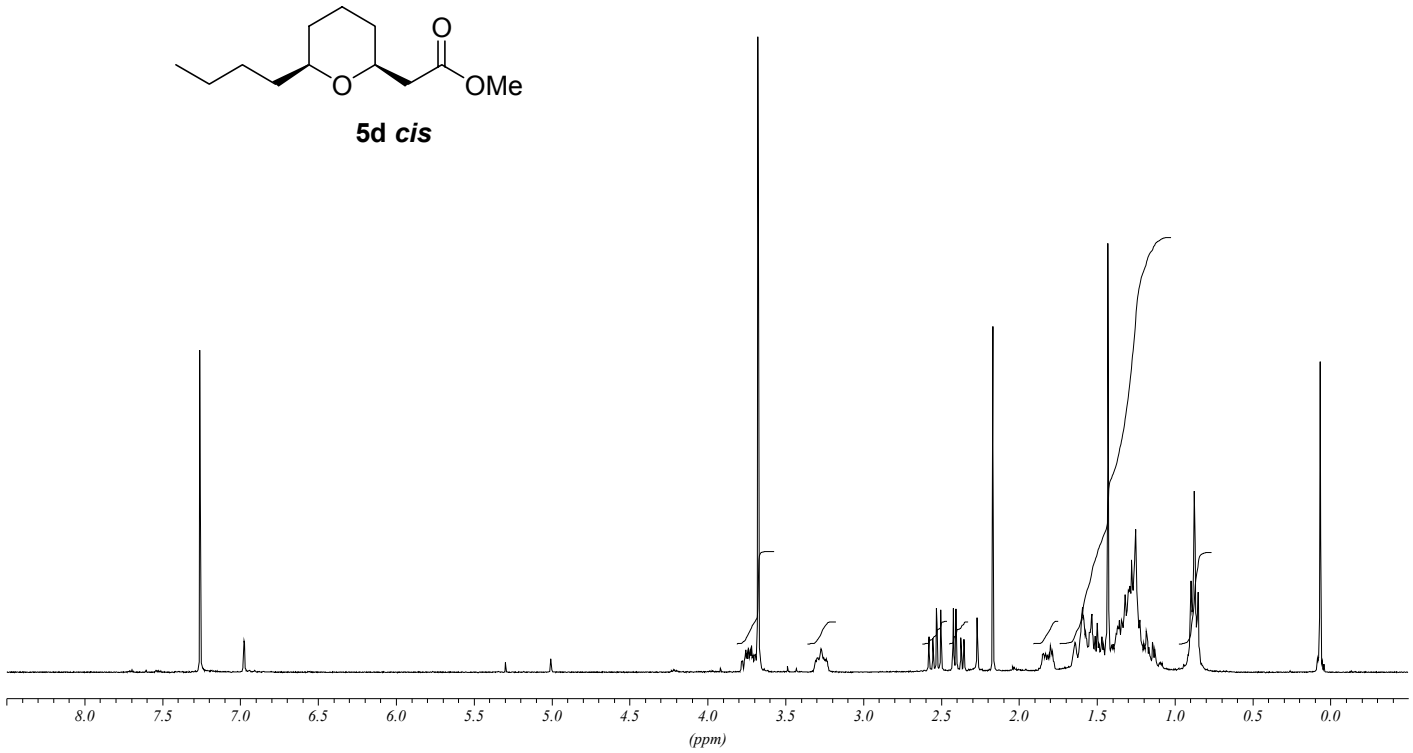
8c *trans*

^{13}C-NMR spectrum of compound **8c *trans***



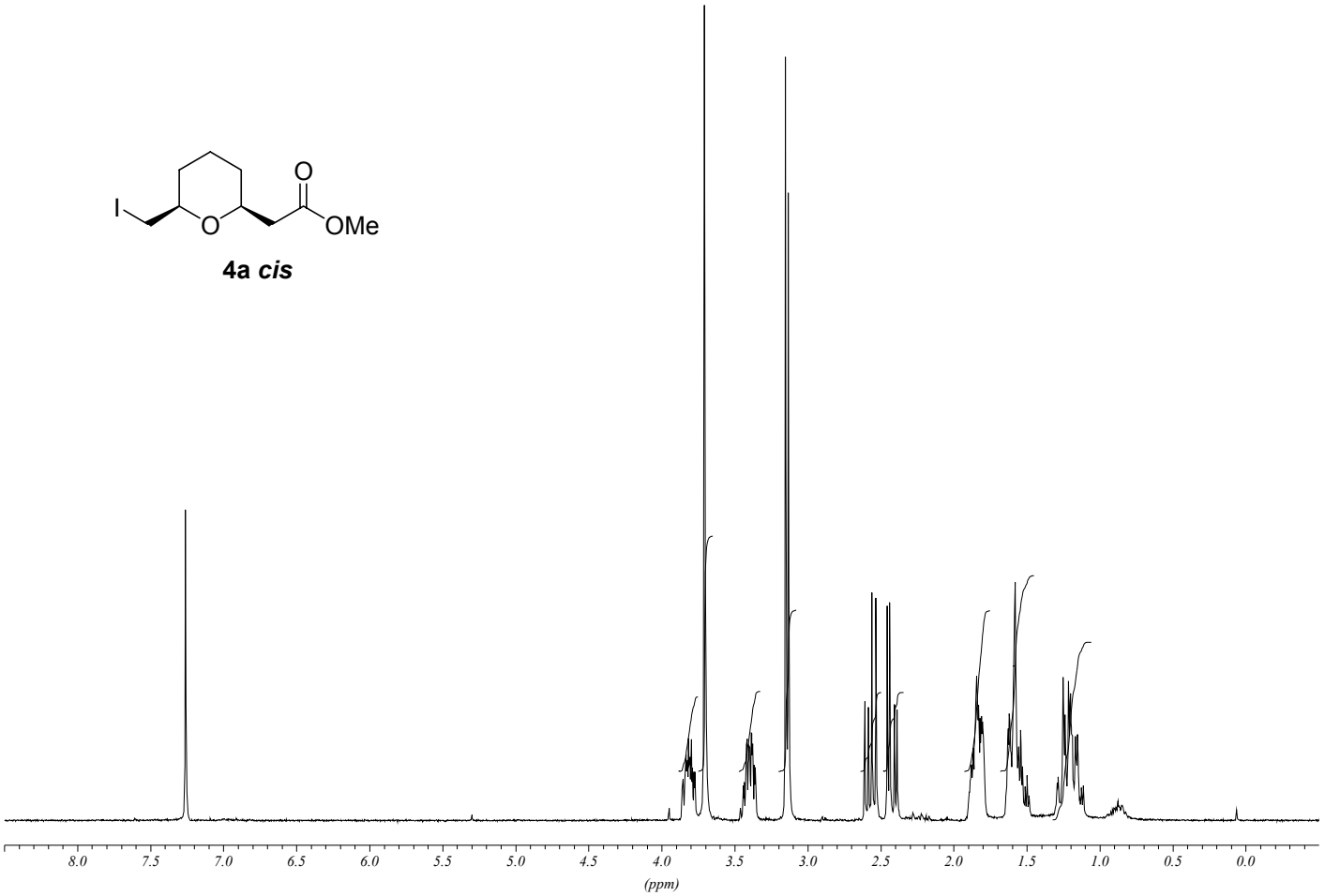
8c *trans*

^{1}H-NMR spectrum of compound **5d *cis***

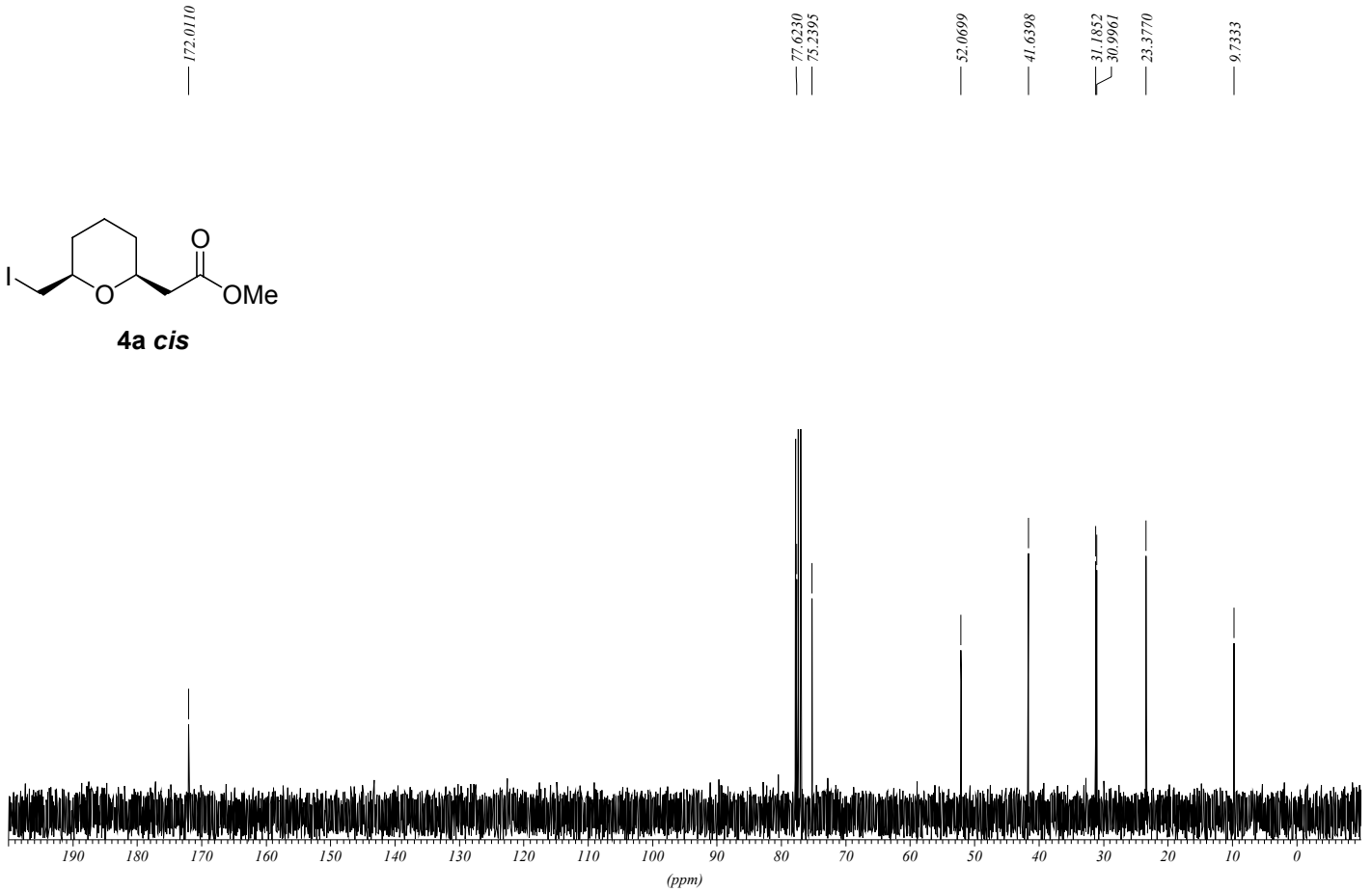


5d *cis*

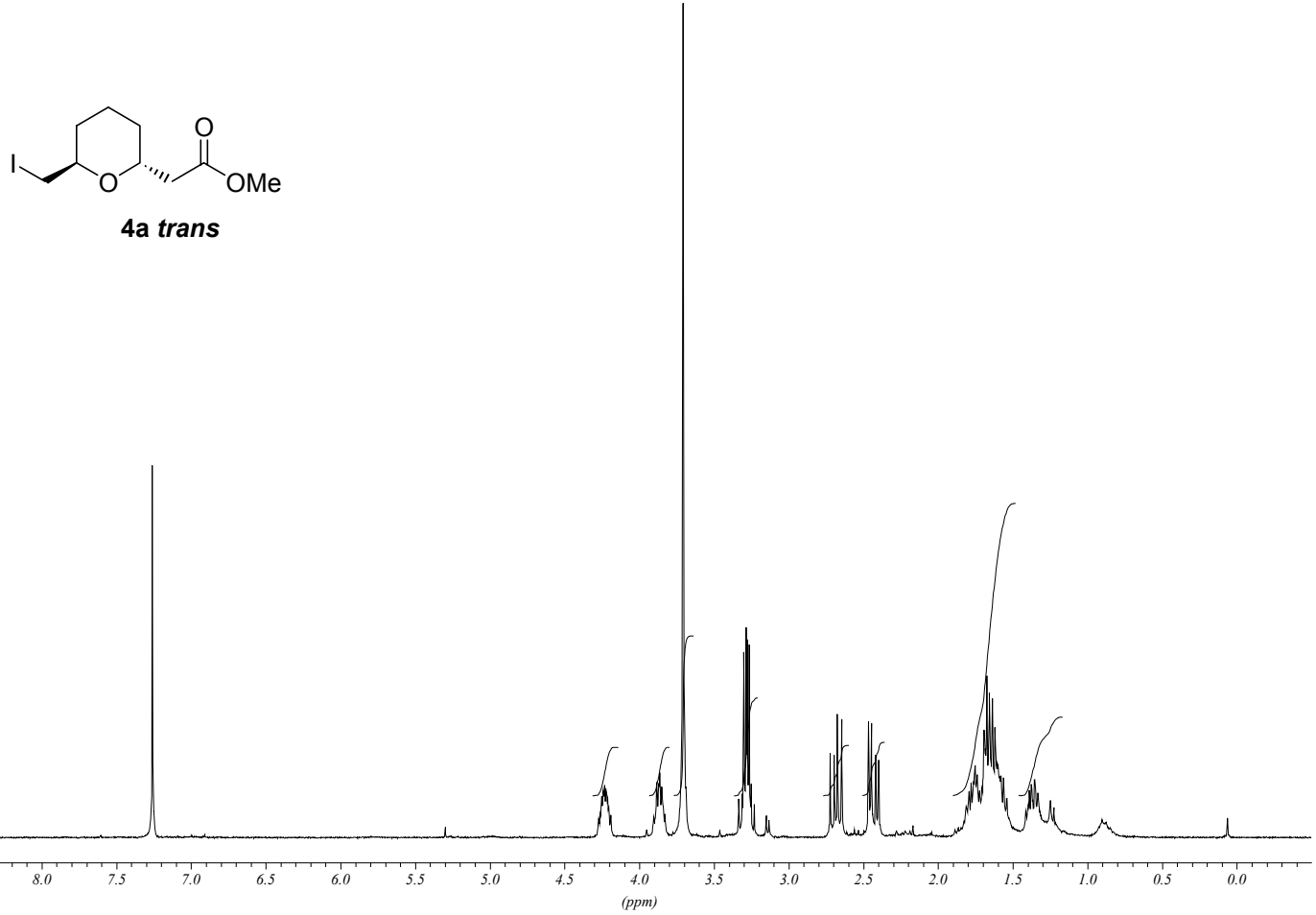
^{1}H-NMR spectrum of compound **4a *cis***



^{13}C-NMR spectrum of compound **4a *cis***

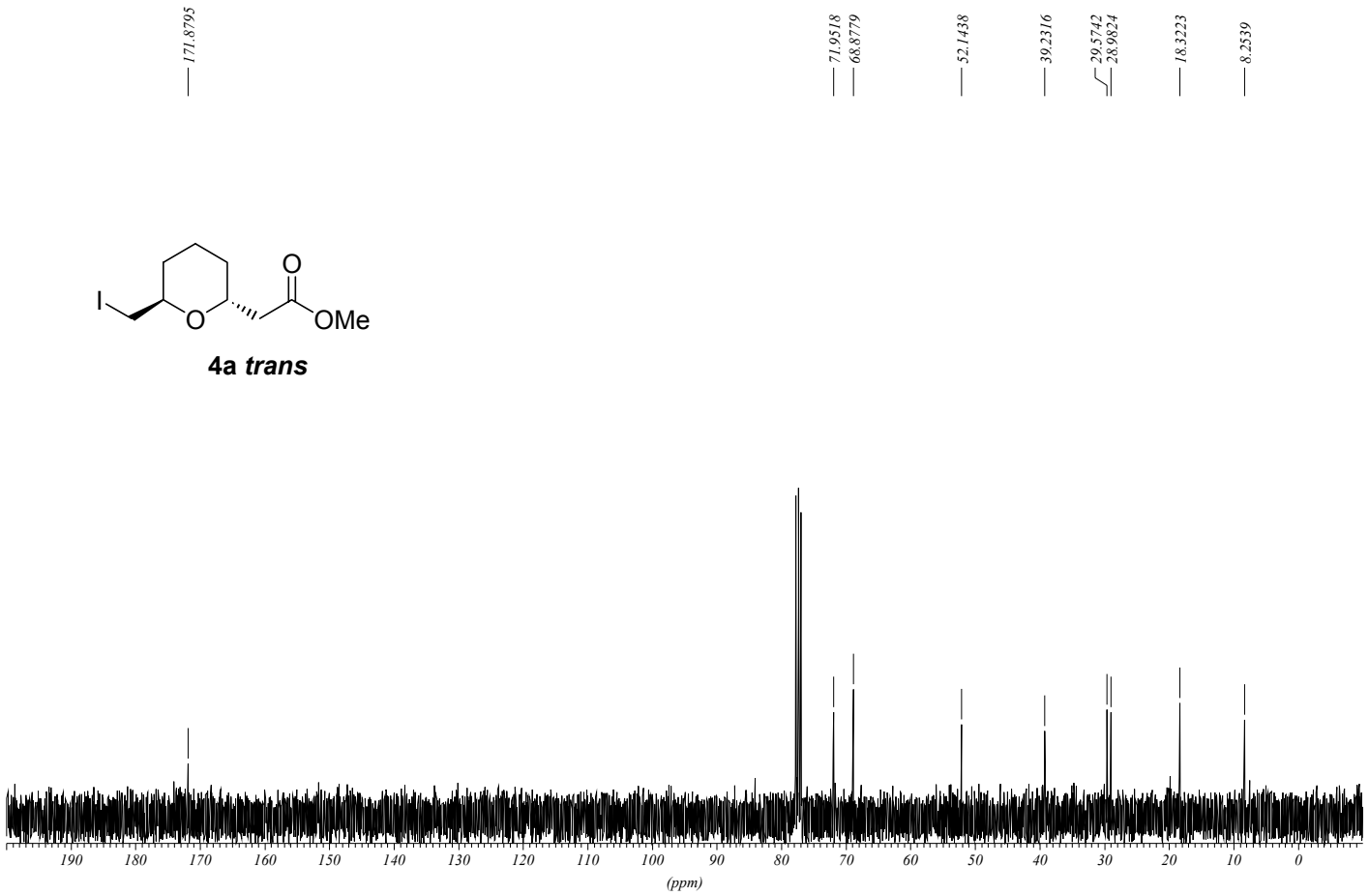


^{1}H-NMR spectrum of compound **4a *trans***



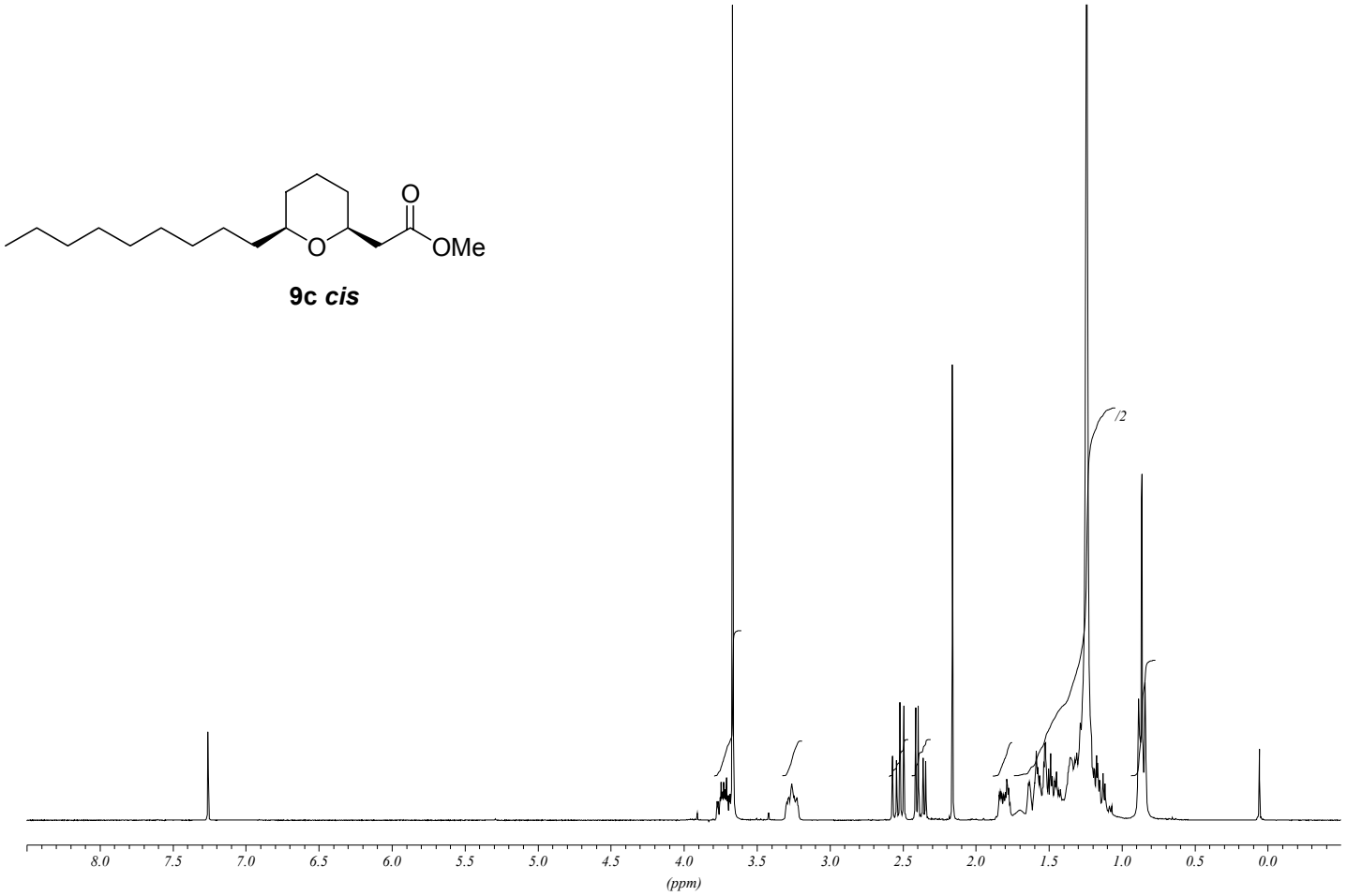
4a *trans*

^{13}C-NMR spectrum of compound **4a *trans***



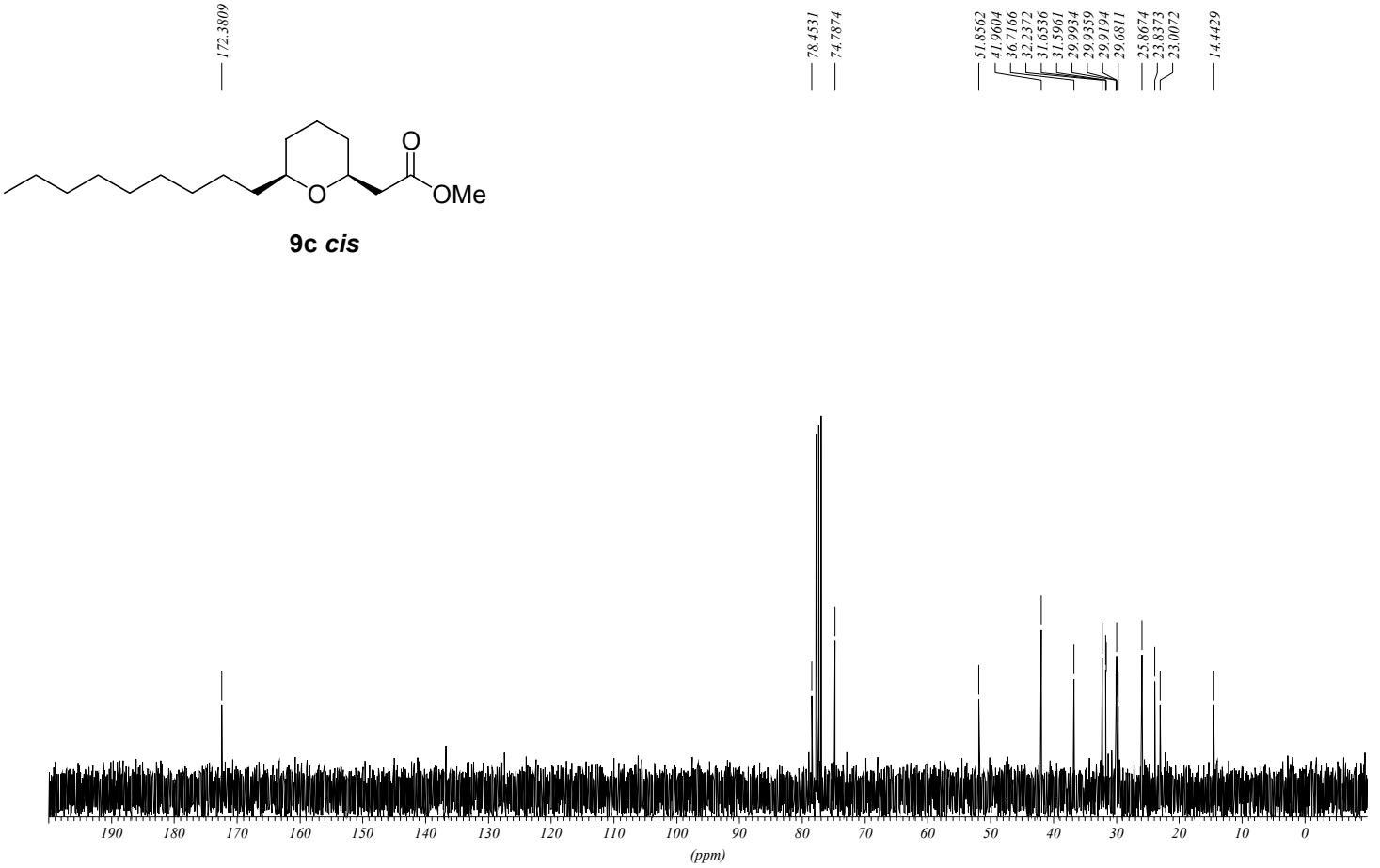
4a *trans*

^{1}H-NMR spectrum of compound **9c *cis***



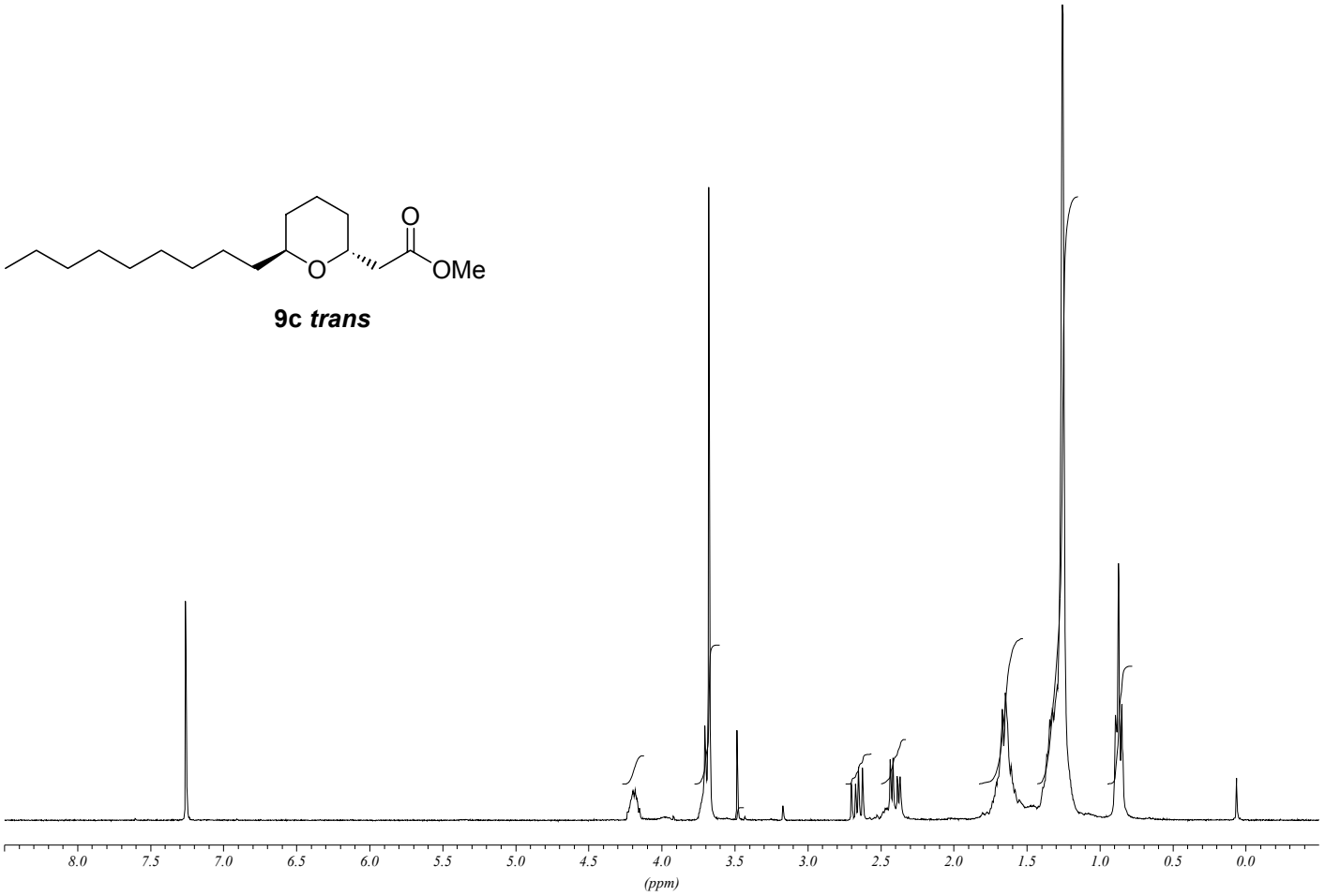
9c *cis*

^{13}C-NMR spectrum of compound **9c *cis***



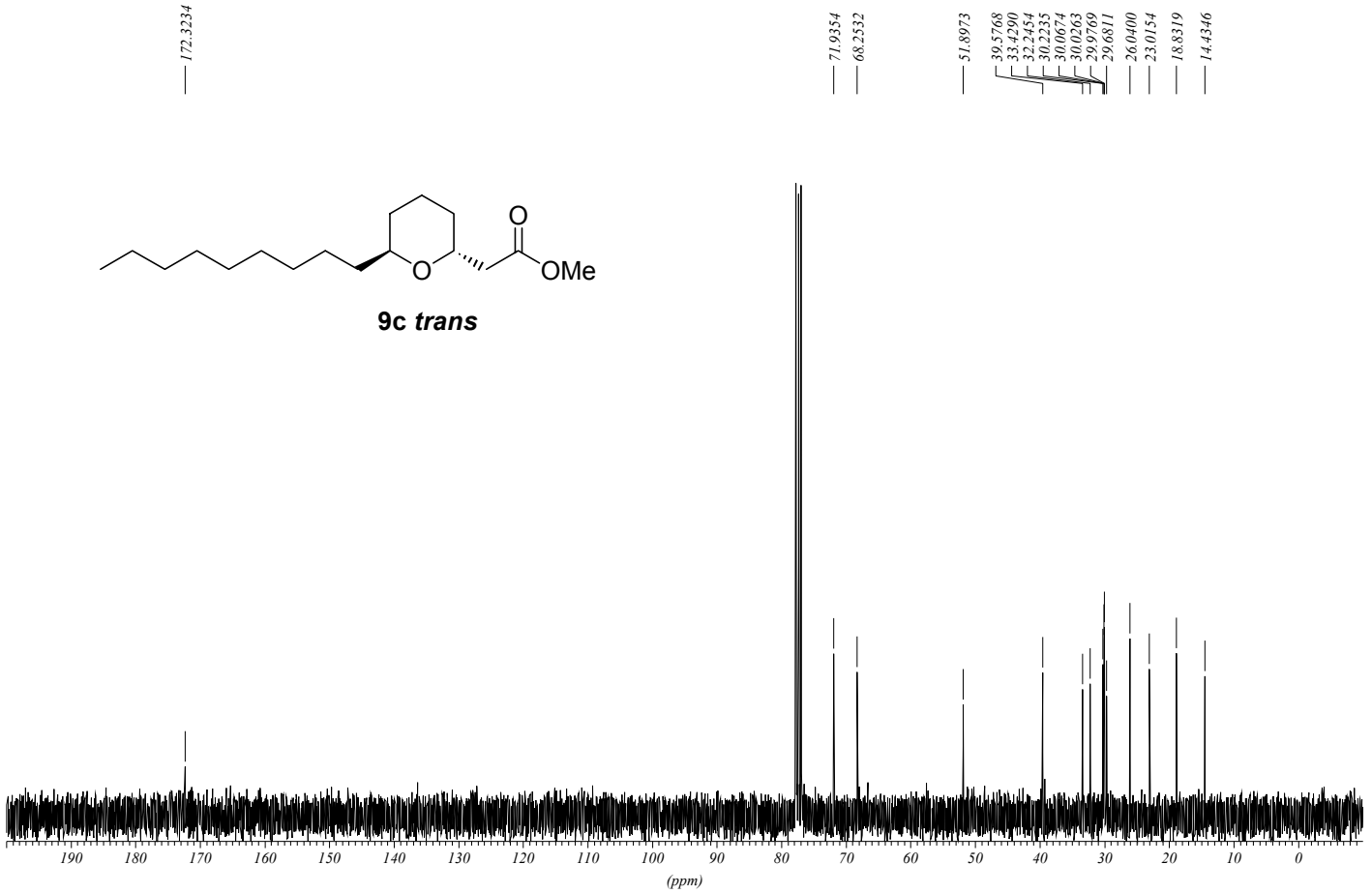
9c *cis*

^{1}H-NMR spectrum of compound **9c *trans***

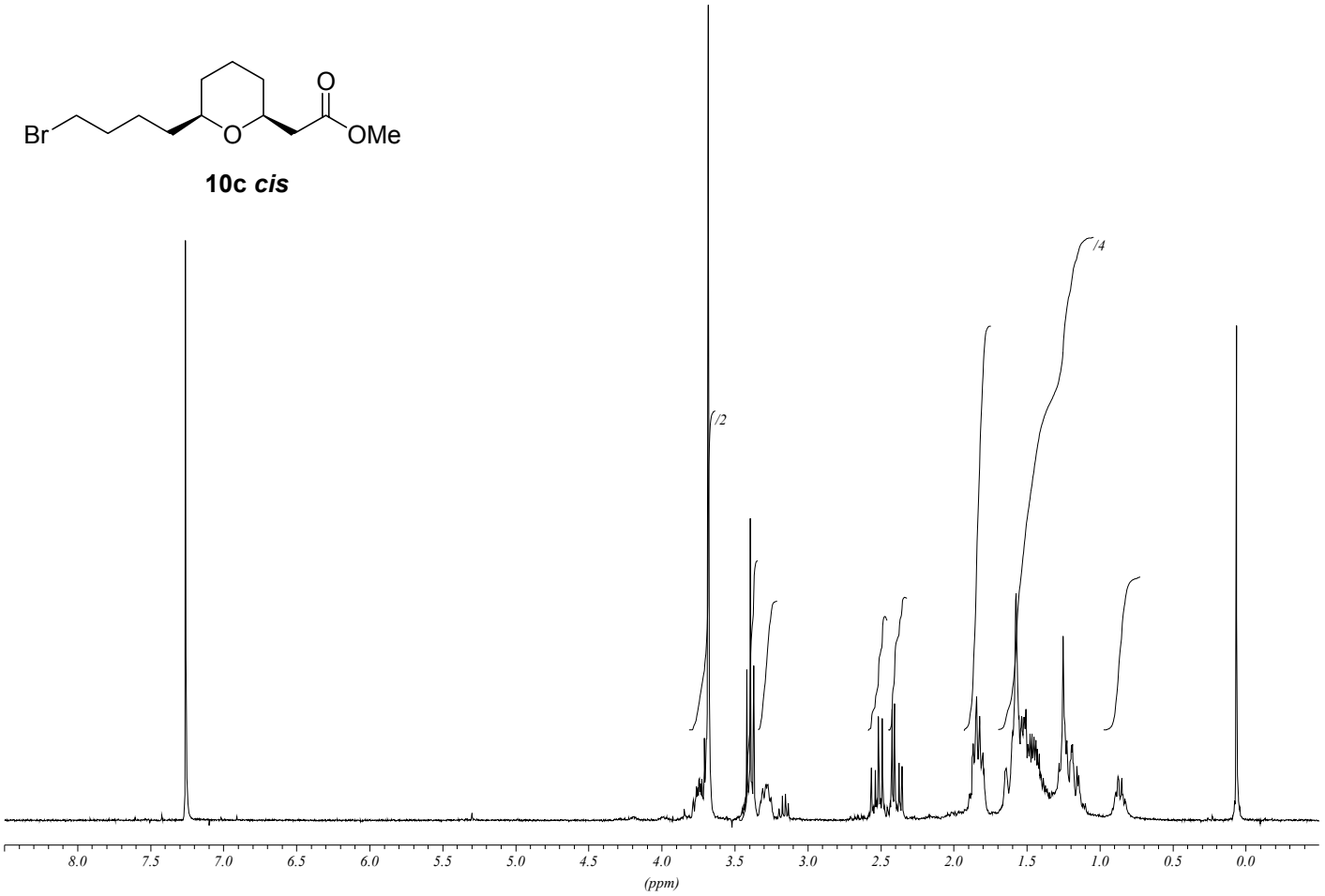


9c *trans*

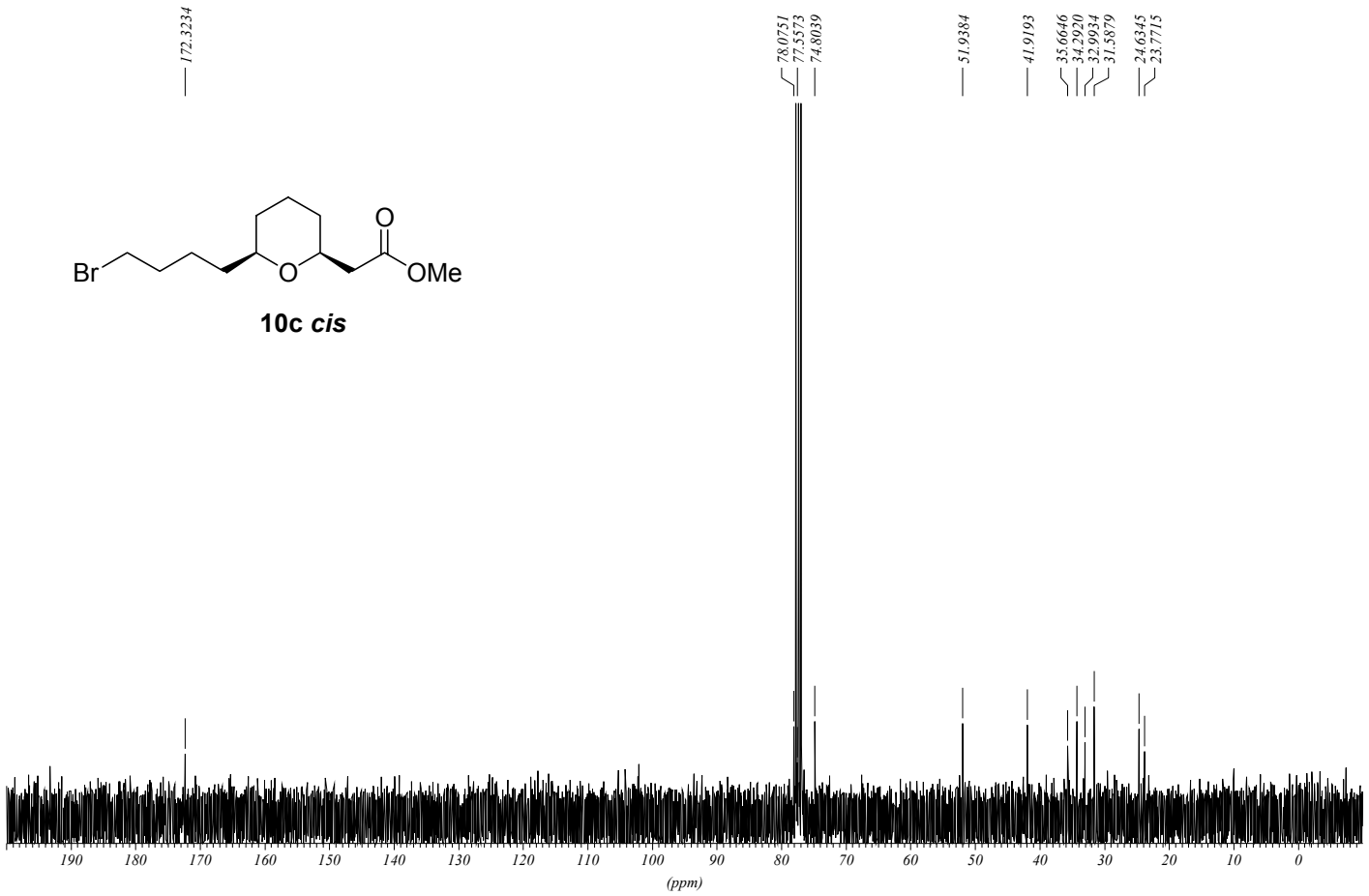
^{13}C-NMR spectrum of compound **9c *trans***



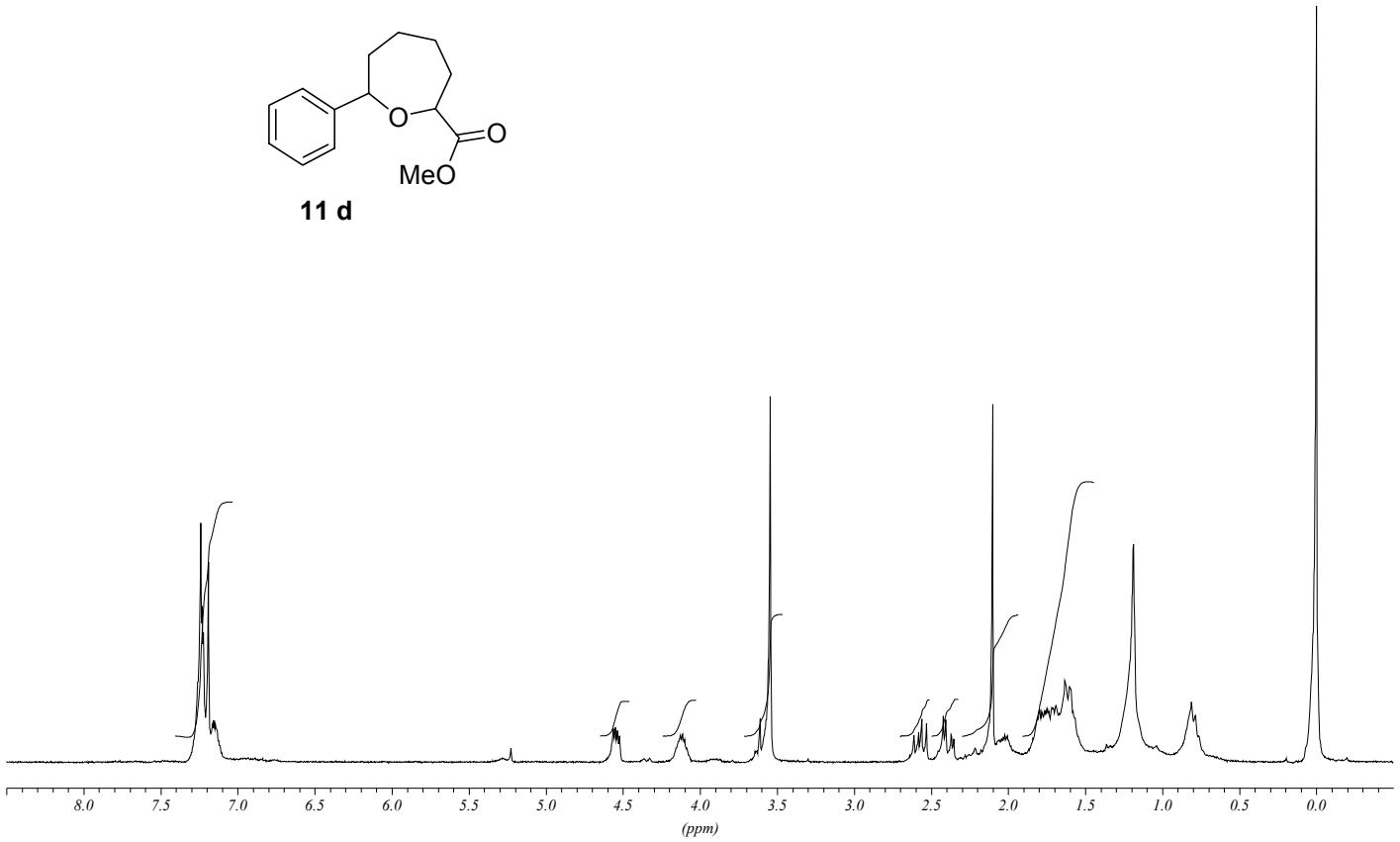
^{1}H-NMR spectrum of compound **10c *cis***



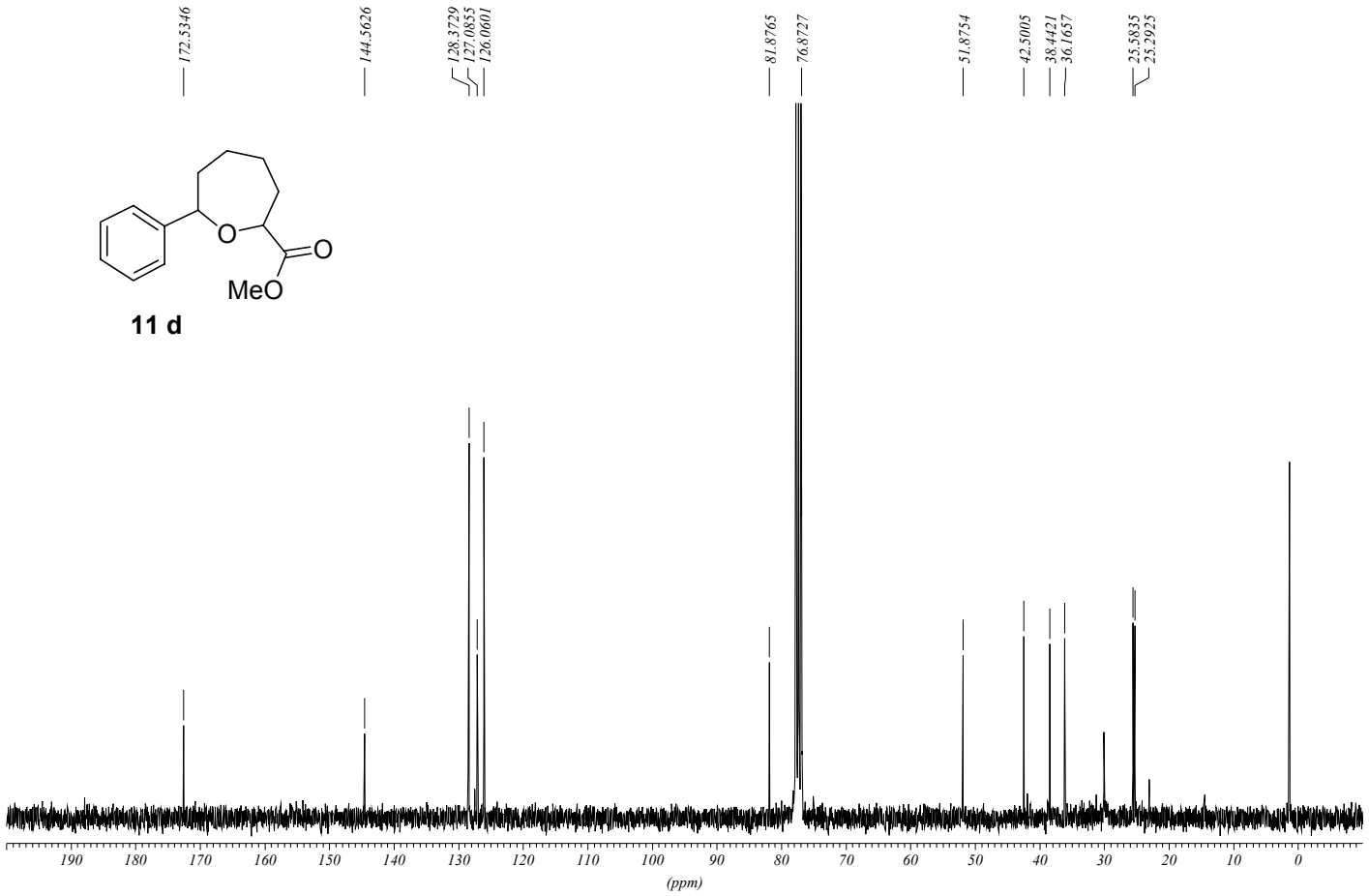
^{13}C-NMR spectrum of compound **10c *cis***



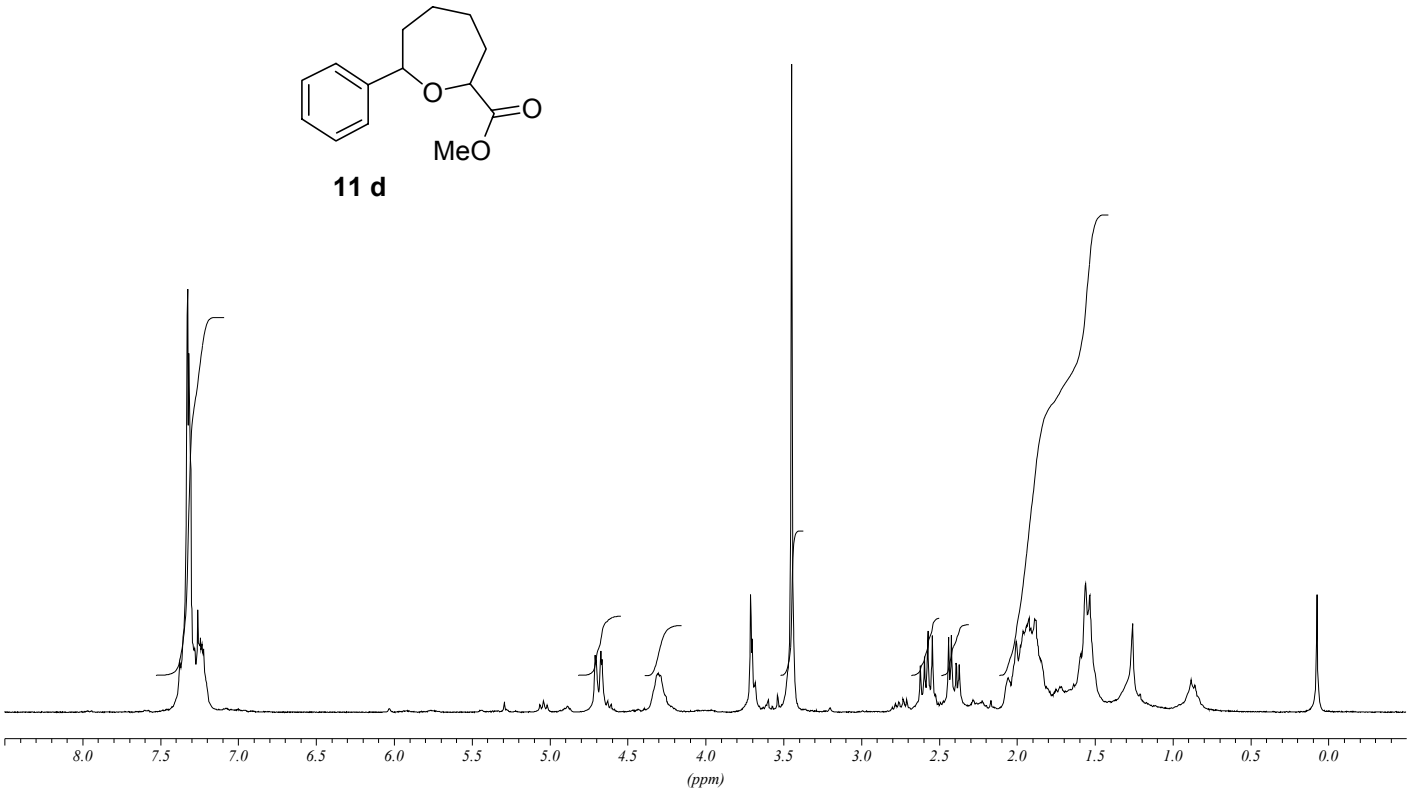
^{1}H-NMR spectrum of compound **11d less polar isomer**



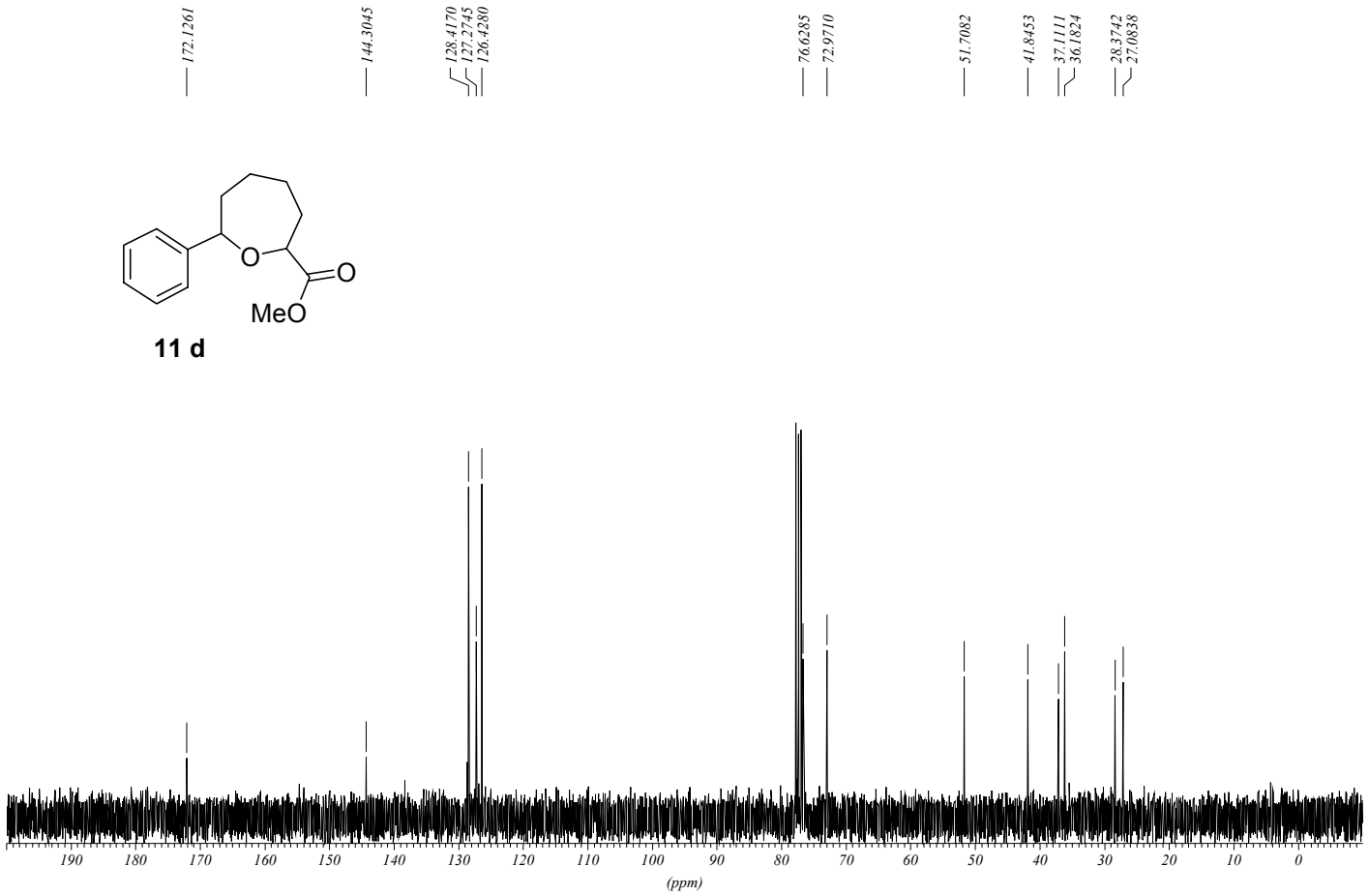
^{13}C-NMR spectrum of compound **11d less polar isomer**



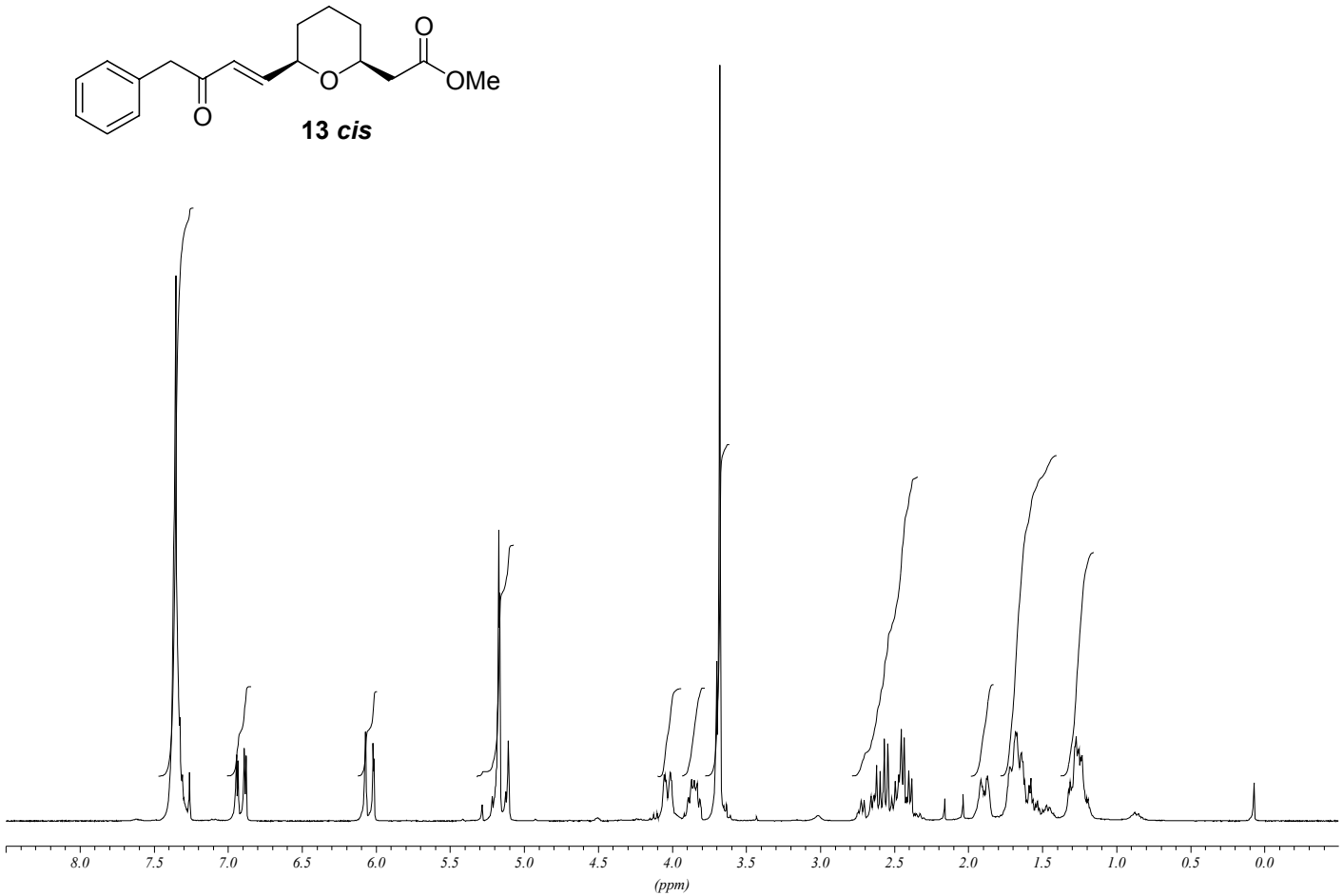
^{1}H-NMR spectrum of compound **11d more polar isomer**



^{13}C-NMR spectrum of compound **11d more polar isomer**



^{1}H-NMR spectrum of compound **13 *cis***



^{13}C-NMR spectrum of compound **13 *cis***