cis- and *trans*-Stereoselective Epoxidation of *N*-Protected 2-Cyclohexen-1-yl Amines

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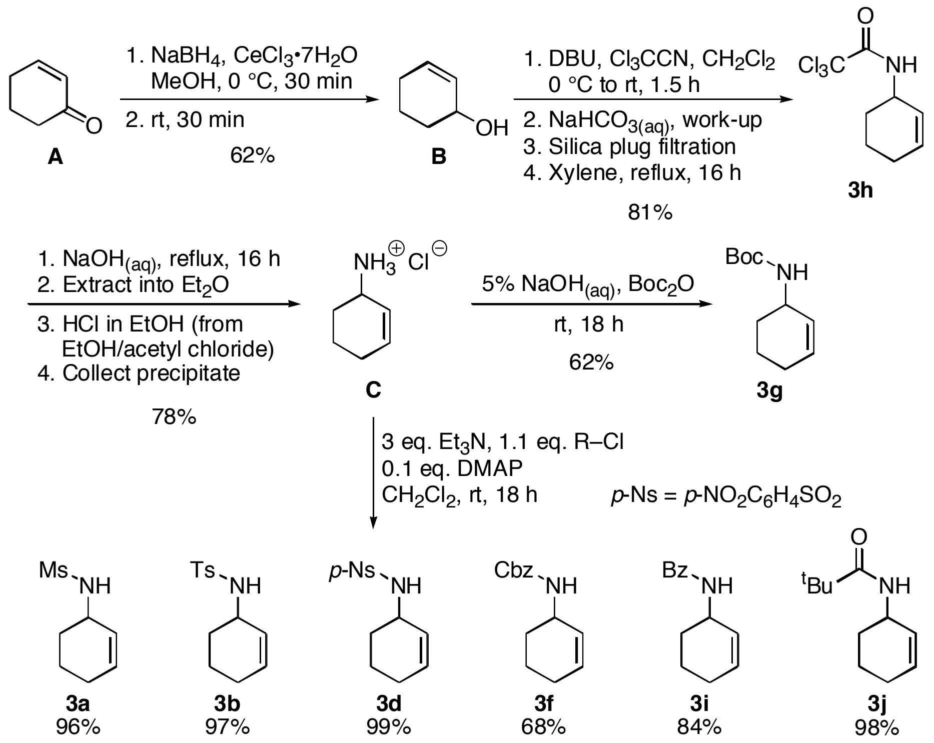
<u>Supporting information:</u> Outline details of the routes used to synthesise compounds **3a**-**b** and **5a**-**e**, general epoxidation procedure, key ^{1}H NMR spectroscopy data for all epoxides **4a**-**j** and **6a**-**d**, characterisation data for oxazolidinones **7a**-**c** and copies of ^{1}H NMR spectra of all epoxides and oxazolidinones.

Synthesis of alkenes (epoxidation substrates):

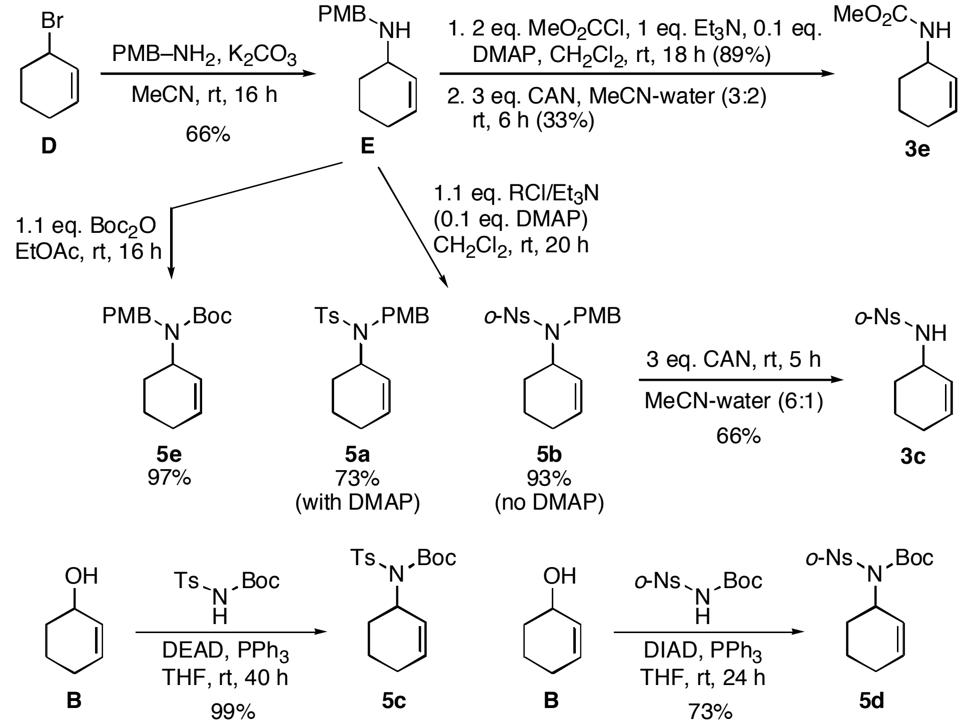
The synthesis of most of the monoprotected allylic amines **5a**-**j** proceeded *via* the hydrochloride salt **C** as outlined in Scheme 1.



Scheme 1

The sequence used to prepare hydrocloride salt **C** is also summarised in Scheme 1. Thus, Luche reduction[1] of cyclohexenone **A** gave allylic alcohol **B** which was subjected to the Isobe modification[2] of the Overman rearrangement[3] to give trichloroacetamide **3h**. Hydrolysis of trichloroacetamide **3h** was accomplished by heating in aqueous sodium hydroxide[4] for 16 hours. After extraction into diethyl ether, the hydrochloride salt **C**[5] was precipitated by addition of hydrochloric acid in ethanol. Boc protection gave **3g** and the other monoprotected systems were prepared using similar conditions to each other (as indicated in Scheme 1).

The remaining two monoprotected alkenes (**3e** and **3c**) were prepared by CAN deprotection of the corresponding diprotected alkenes (Scheme 2). Known[6] *N*-(cyclohex-2-enyl)-4-methoxybenzylamine **E** was prepared from commercially available bromide **D** using a modification of a literature method.[7] Methyl carbamate protection followed by CAN deprotection gave **3e** whereas *o*-Ns protection and then CAn deprotection gave **3c** (*via* diprotected **5b**).



Scheme 2

Routes to the remaining diprotected alkenes are also summarised in Scheme 2. Boc protection[8] of **E** gave alkene **5e** and tosylation of **E** gave **5a**. Finally, a Mitsunobu approach was used to prepare **5c** and **5d**.[9]

Epoxidation of alkenes:

General method for epoxidation:

m-CPBA (247 mg of approx. 70% pure material, 1.0 mmol) was added in one portion to a stirred suspension of alkene (0.5 mmol) and $NaHCO_3$ (84 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) at rt under N_2. The resulting suspension was stirred at rt for 19 h. Then, 20% $Na_2SO_{3(aq)}$ (10 mL) was added and the resulting two-phase mixture was stirred vigorously for 15 min. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined CH_2Cl_2 layers were washed with 20% $Na_2SO_{3(aq)}$ (10 mL) and 5% $NaHCO_{3(aq)}$ (2 × 20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product in essentially quantitative yield. The ratio of epoxide diastereoisomers was determined from the ^{1}H NMR spectrum of the crude product.

Monoprotected alkenes (Table 1):

Epoxides *cis*- and *trans*-**4a** (90:10); R = Ms
Characteristic signals for CHO signals in ^{1}H NMR spectrum:
δ_H(400 MHz, $CDCl_3$) *cis*-**4a**: 3.35-3.12 (m, 2H); *trans*-**4a**: 3.21 (m, 1H), 3.18 (m, 1H).

Epoxides *cis*- and *trans*-**4b** (90:10); R = Ts
Characteristic signals for CHO signals in ^{1}H NMR spectrum:
δ_H(400 MHz, $CDCl_3$) *cis*-**4b**: 3.21 (dt, 1H, *J* = 1.0, 3.5), 2.95 (br t, 1H, *J* = 3.5); *trans*-**4b**: 3.13 (br m, 1H), 2.99 (br d, 1H, *J* = 3.0).
^{1}H NMR spectroscopic data for *cis*-**4b** consistent with that reported in the literature.[10]

Epoxides *cis*- and *trans*-**4c** (90:10); R = *o*-$NO_2C_6H_4SO_2$
Characteristic signals for CHO signals in ^{1}H NMR spectrum:
δ_H(270 MHz, $CDCl_3$) *cis*-**4c**: 3.22 (dt, 1H, *J* = 1.0, 3.5), 3.07 (br t, 1H, *J* = 3.5); *trans*-**4c**: 3.18 (br m, 1H), other CHO hidden.

Epoxides *cis*- and *trans*-**4d** (>95:5); R = *p*-$NO_2C_6H_4SO_2$

Characteristic signals for CHO signals in ^{1}H NMR spectrum:

δ_H(400 MHz, $CDCl_3$) *cis*-**4d**: 3.26 (dt, 1H, *J* = 1.0, 3.5), 3.01 (br t, 1H, *J* = 3.5); *trans*-**4d**: 3.16 (br m, 1H), 2.98 (br m, 1H).

Epoxides *cis*- and *trans*-**4e** (90:10); R = CO_2Me

Characteristic signals for CHO signals in ^{1}H NMR spectrum:

δ_H(270 MHz, $CDCl_3$) *cis*-**4e**: 3.27-3.23 (m, 2H); *trans*-**4e**: 3.16 (br s, 1H), 3.04 (d, 1H, *J* = 3.5).

Epoxides *cis*- and *trans*-**4f** (90:10); R = Cbz

Characteristic signals for CHO signals in ^{1}H NMR spectrum:

δ_H(400 MHz, $CDCl_3$) *cis*-**4f**: 3.31-3.26 (m, 2H); *trans*-**4f**: 3.19 (br s, 1H), 3.09 (br d, 1H, *J* = 3.5).

^{1}H NMR spectroscopic data for *cis*-**4f** consistent with that reported in the literature.[11]

Epoxides *cis*- and *trans*-**4g** (85:15); R = Boc

Characteristic signals for CHO signals in ^{1}H NMR spectrum:

δ_H(400 MHz, $CDCl_3$) *cis*-**4g**: 3.29-3.25 (m, 2H); *trans*-**4g**: 3.18 (br m, 1H), 3.07 (br d, 1H, *J* = 3.5).

Epoxides *cis*- and *trans*-**4h** (95:5); R = $Cl_3CC(O)$

Characteristic signals for CHO signals in ^{1}H NMR spectrum:

δ_H(400 MHz, $CDCl_3$) *cis*-**4h**: 3.29-3.25 (m, 2H); *trans*-**4h**: 3.18 (br m, 1H), 3.07 (br d, 1H, *J* = 3.5). NMR signals needs changing.

Epoxides *cis*- and *trans*-**4i** (>98:2); R = Bz

Characteristic signals for CHO signals in ^{1}H NMR spectrum:

δ_H(400 MHz, $CDCl_3$) *cis*-**4i**: 3.37-3.34 (m, 2H).

There was no evidence for epoxide *trans*-**4i** in the ^{1}H NMR spectrum of the crude product.

^{1}H NMR spectroscopic data for *cis*-**4i** consistent with that reported in the literature.[12]

Epoxides *cis*- and *trans*-**4j** (>98:2); R = ^{t}BuC(O)

Characteristic signals for CHO signals in ^{1}H NMR spectrum:

δ_H(400 MHz, $CDCl_3$) *cis*-**4j**: 3.31-3.29 (m, 1H), 3.23 (t, 1H, *J* = 3.5).

There was no evidence for epoxide *trans*-**4j** in the ^{1}H NMR spectrum of the crude product.

Diprotected alkenes (Table 2):

Epoxides *trans*- and *cis*-**6a** (85:15)

Characteristic signals for CHO signals in ^{1}H NMR spectrum:

δ_H(400 MHz, $CDCl_3$) *trans*-**6a**: 2.98 (br s, 1H), 2.76 (d, 1H, *J* = 2.5); *cis*-**6a**: 3.02 (t, 1H, *J* = 4.0), 2.79 (br d, 1H, *J* = 4.0).

Epoxides *trans*- and *cis*-**6b** (90:10)

Characteristic signals for CHO signals in ^{1}H NMR spectrum:

δ_H(270 MHz, $CDCl_3$) *trans*-**6b**: 2.95 (br m, 1H), 2.88 (dd, 1H, *J* = 1.0, 4.0); *cis*-**6b**: 3.30 (br d, 1H, *J* = 4.0), 3.18 (br t, 1H, *J* = 4.0).

Epoxides *trans*- and *cis*-**6c** (>98:2)

Characteristic signals for CHO signals in ^{1}H NMR spectrum:

δ_H(400 MHz, $CDCl_3$) *trans*-**6c**: 3.32 (br m, 1H), 3.19 (dd, 1H, *J* = 1.0, 4.0).

There was no evidence for epoxide *cis*-**6c** in the ^{1}H NMR spectrum of the crude product.

Epoxide *cis*-**6c** was prepared by Boc protection of a 90:10 mixture of *cis*- and *trans*-**4b** and showed characteristic signals for CHO signals in the ^{1}H NMR spectrum:

δ_H(400 MHz, $CDCl_3$) *cis*-**6c**: 3.25 (br d, 1H, *J* = 4.0), 3.19 (br t, 1H, *J* = 4.0).

Epoxides *trans*- and *cis*-**6d** (>98:2)

Characteristic signals for CHO signals in ^{1}H NMR spectrum:

δ_H(270 MHz, $CDCl_3$) *trans*-**6d**: 3.30-3.27 (br m, 2H).

There was no evidence for epoxide *cis*-**6d** in the ^{1}H NMR spectrum of the crude product.

Epoxide *cis*-**6d** was prepared by Boc protection of a 90:10 mixture of *cis*- and *trans*-**4c** and showed characteristic signals for CHO signals in the ^{1}H NMR spectrum: δ_H(270 MHz, $CDCl_3$) *cis*-**6d**: 3.42 (br d, 1H, *J* = 4.0), 3.22 (br m, 1H).

Epoxides *trans*- or *cis*-**6e** were never observed by ^{1}H NMR spectroscopy of the crude product mixture.

Spectroscopic characterisation data for oxazolidinones **7a**, **7b** and **7c**:
Key identifying data included OH stretch in the IR spectrum; no ^{t}Bu resonances in the ^{1}H and ^{13}C NMR spectra; no epoxide resonances in the ^{1}H NMR spectra (epoxide signals in the ^{1}H NMR spectra of **4a-j** and **6a-d** range from 3.42-2.76 ppm).

Oxazolidinone **7a**:
IR ($CHCl_3$) 3600, 2940, 1786, 1545, 1373, 1175 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 7.95 (d, 2H, *J* = 8.5), 7.36 (d, 2H, *J* = 8.5), 4.49 (td, 1H, *J* = 6.0, 8.5), 4.35 (dd, 1H, *J* = 4.5, 6.0), 4.13-4.08 (m, 1H), 2.46 (s, 3H), 2.21-2.12 (m, 1H), 1.97 (br s, 1H), 1.84-1.50 (m, 5H); δ_C(100.6 MHz, $CDCl_3$) 151.9, 145.6, 134.8, 129.8, 128.5, 77.8, 67.2, 57.0, 27.7, 27.1, 21.7, 15.6; MS (CI; NH_3) *m/z* 329 [100%, $(M + NH_4)^+$]; HRMS (CI; NH_3) *m/z* calcd for $C_{14}H_{17}NO_5S$ $(M + NH_4)^+$ 329.1171, found 329.1172.

Oxazolidinone **7b**:
IR ($CHCl_3$) 3607, 2954, 1784, 1545, 1370, 1180 cm^{-1}; δ_H(270 MHz, $CDCl_3$) 8.42 (d, 1H, *J* = 8.0), 7.87-7.76 (m, 3H), 4.76-4.68 (m, 1H), 4.55-4.51 (m, 1H), 4.18 (dd, 1H, *J* = 5.0, 10.0), 2.34-2.02 (m, 2H), 1.99-1.78 (m, 2H), 1.74-1.67 (m, 2H); δ_C(67.9 MHz, $CDCl_3$) 151.5, 147.8, 135.4, 134.3, 132.1, 130.4, 124.5, 78.4, 66.5, 57.6, 27.9, 27.4, 15.5; MS (CI; NH_3) *m/z* 360 [1%, $(M + NH_4)^+$], 229 (100); HRMS (CI; NH_3) *m/z* calcd for $C_{13}H_{14}N_2O_7S$ $(M + NH_4)^+$ 360.0865, found 360.0866.

Oxazolidinone **7c**:
IR ($CHCl_3$) 3600, 1751, 1612, 1514 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 7.21 (d, 2H, *J* = 8.5), 6.86 (d, 2H, *J* = 8.5), 4.66 (d, 1H, *J* = 15.25), 4.19 (t, 1H, *J* = 7.0), 3.87-3.81 (m, 1H), 3.81 (s, 3H), 3.77-3.72 (m, 1H), 2.37 (br s, 1H), 1.96-1.84 (m, 2H), 1.71-1.48 (m, 4H); δ_C(100.6 MHz, $CDCl_3$) 159.3, 158.9, 129.6, 127.6, 114.3, 79.5, 71.1, 55.3, 54.5,

45.4, 29.1, 24.3, 17.5; MS (CI; NH_3) *m/z* 295 [10%, $(M + NH_4)^+$], 278 [100, $(M + H)^+$], 136 (10), 121 (10); HRMS (CI; NH_3) *m/z* calcd for $C_{15}H_{19}NO_4$ $(M + H)^+$ 278.1392, found 278.1396.

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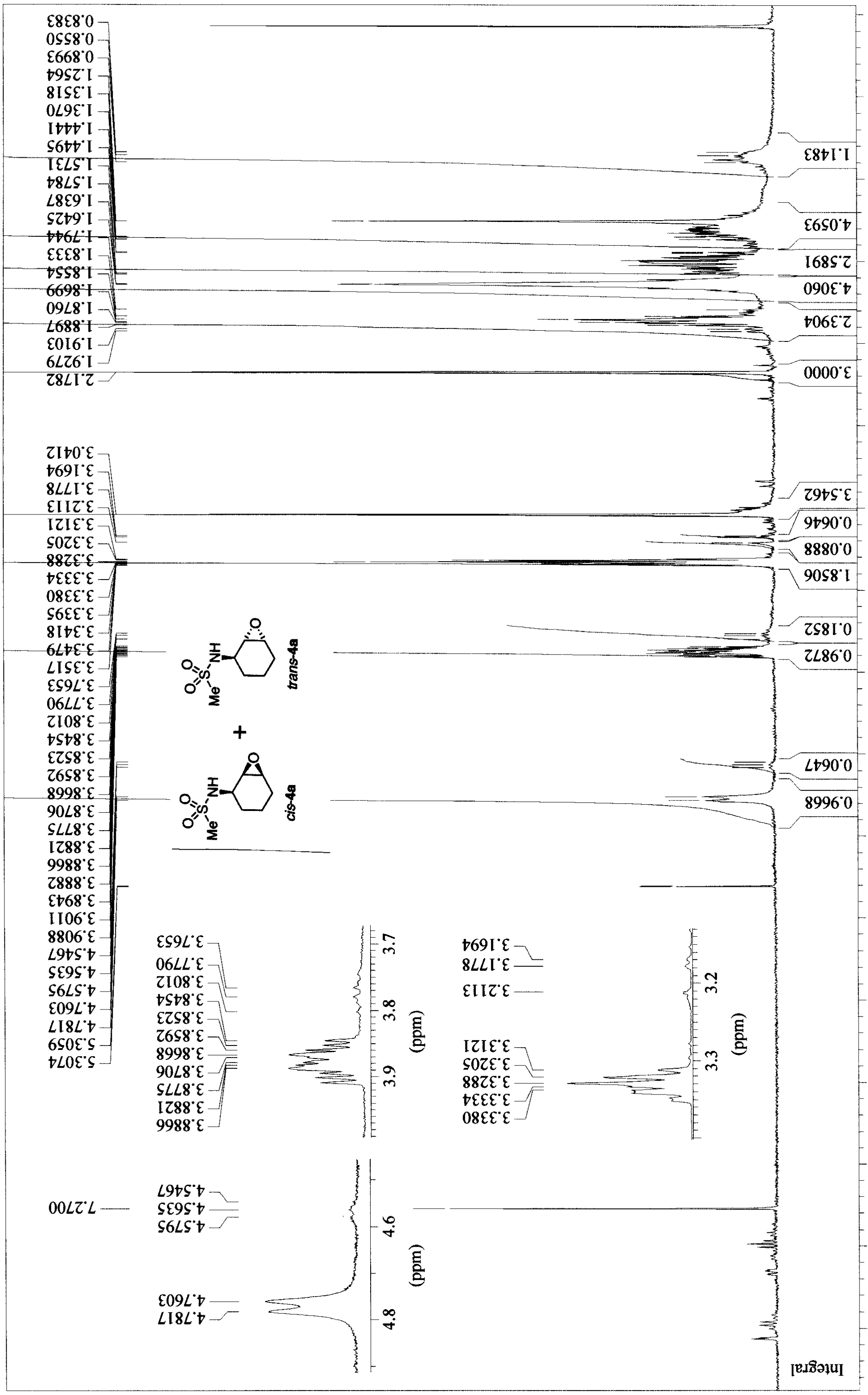

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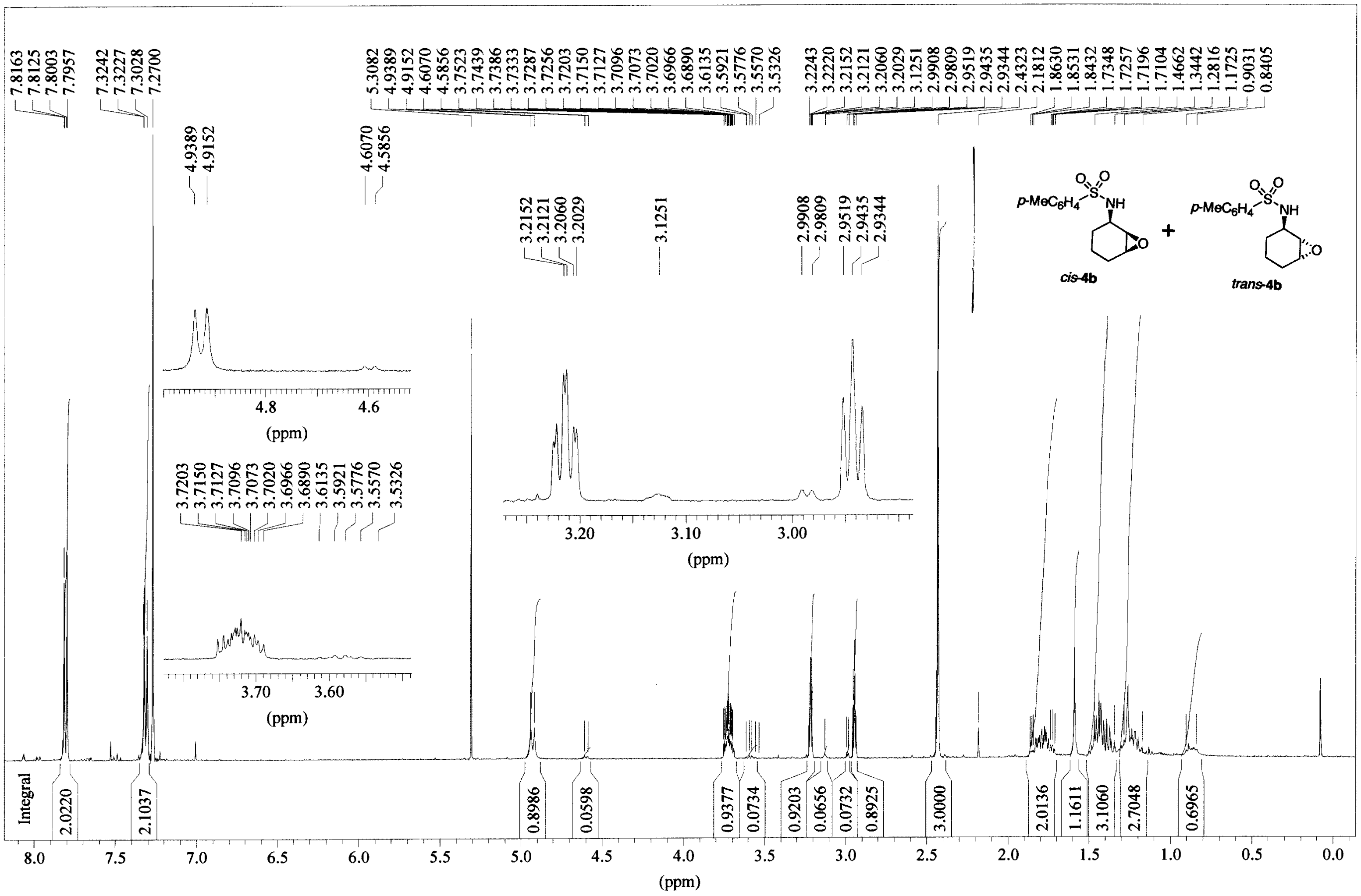

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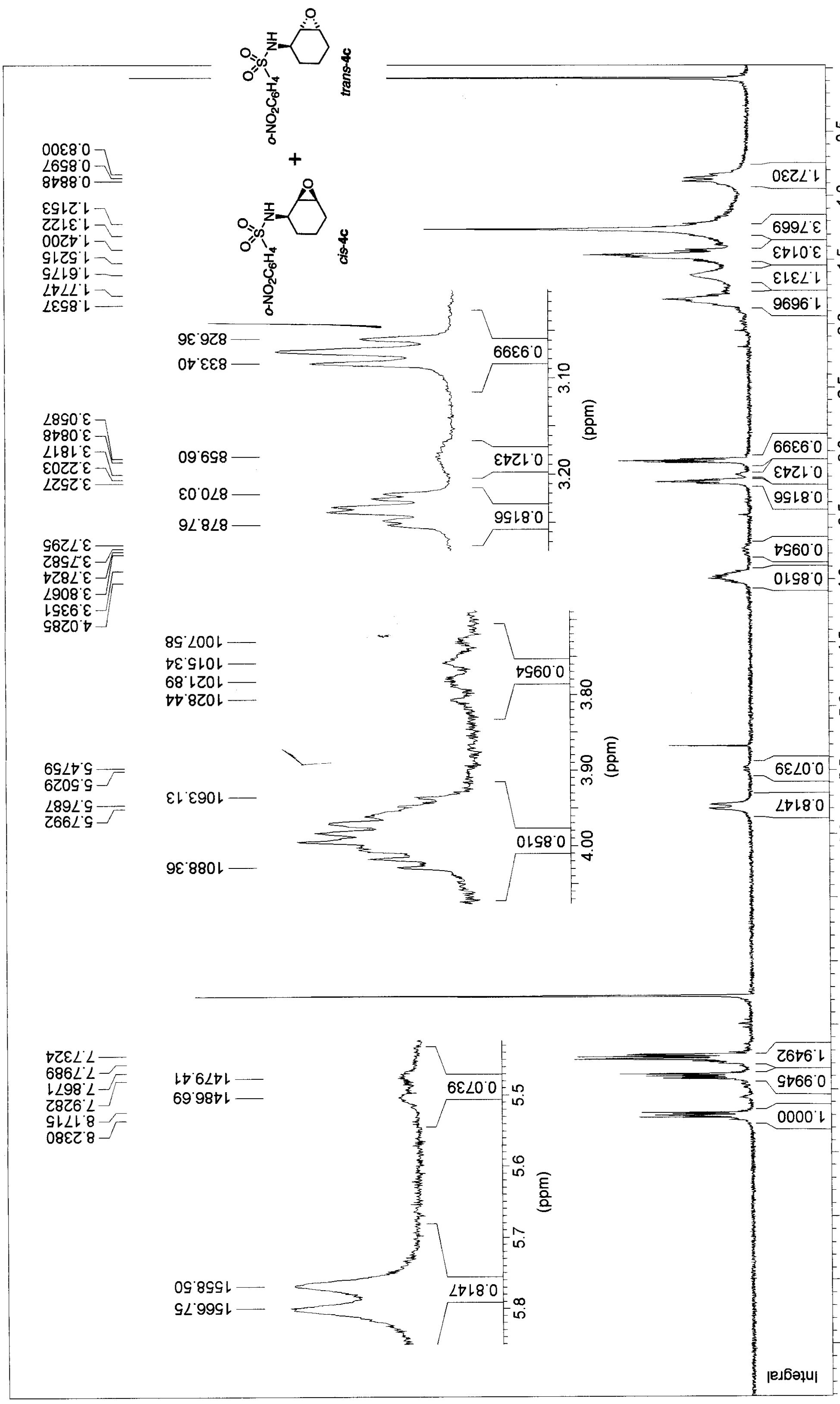

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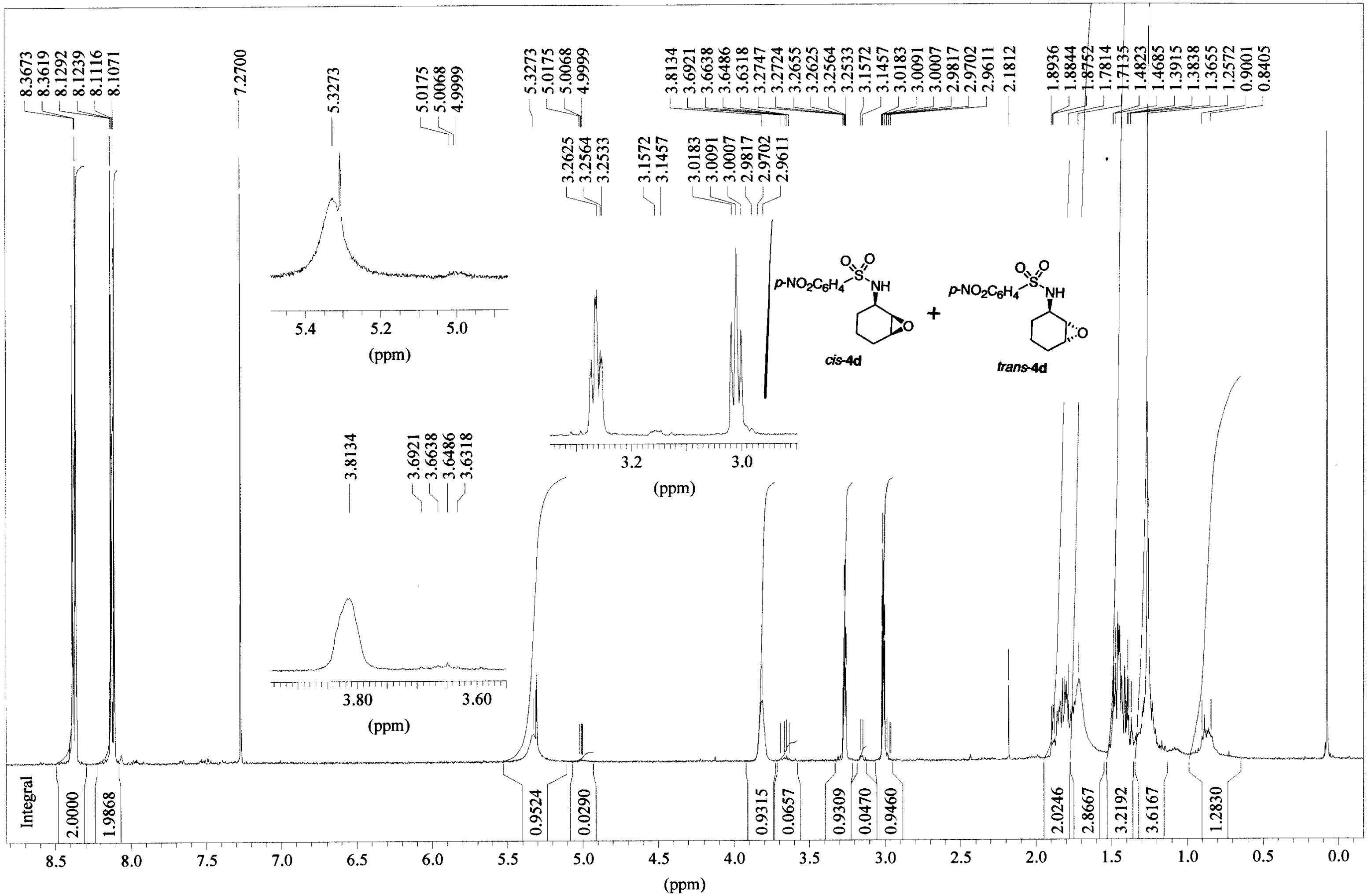

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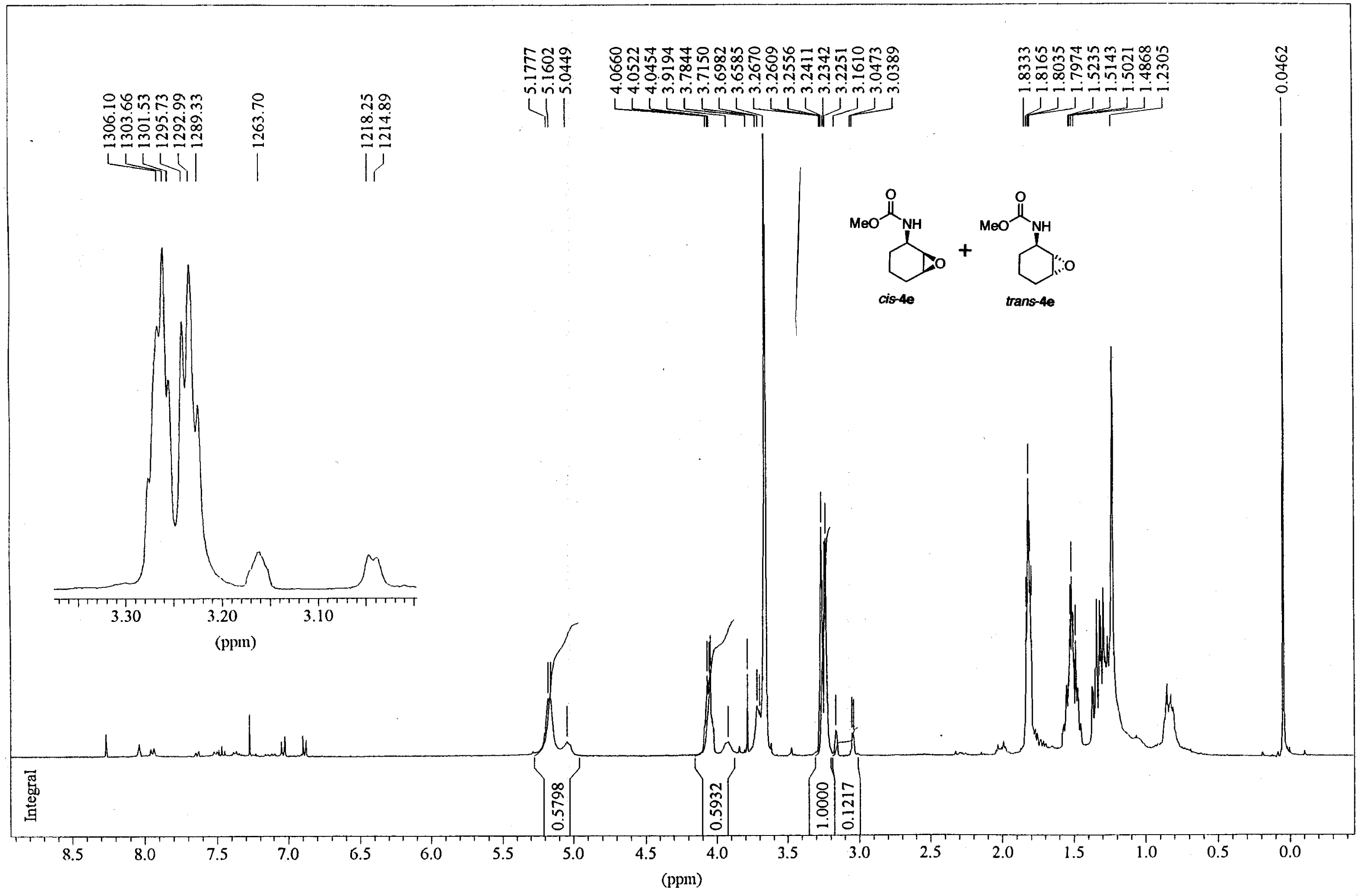

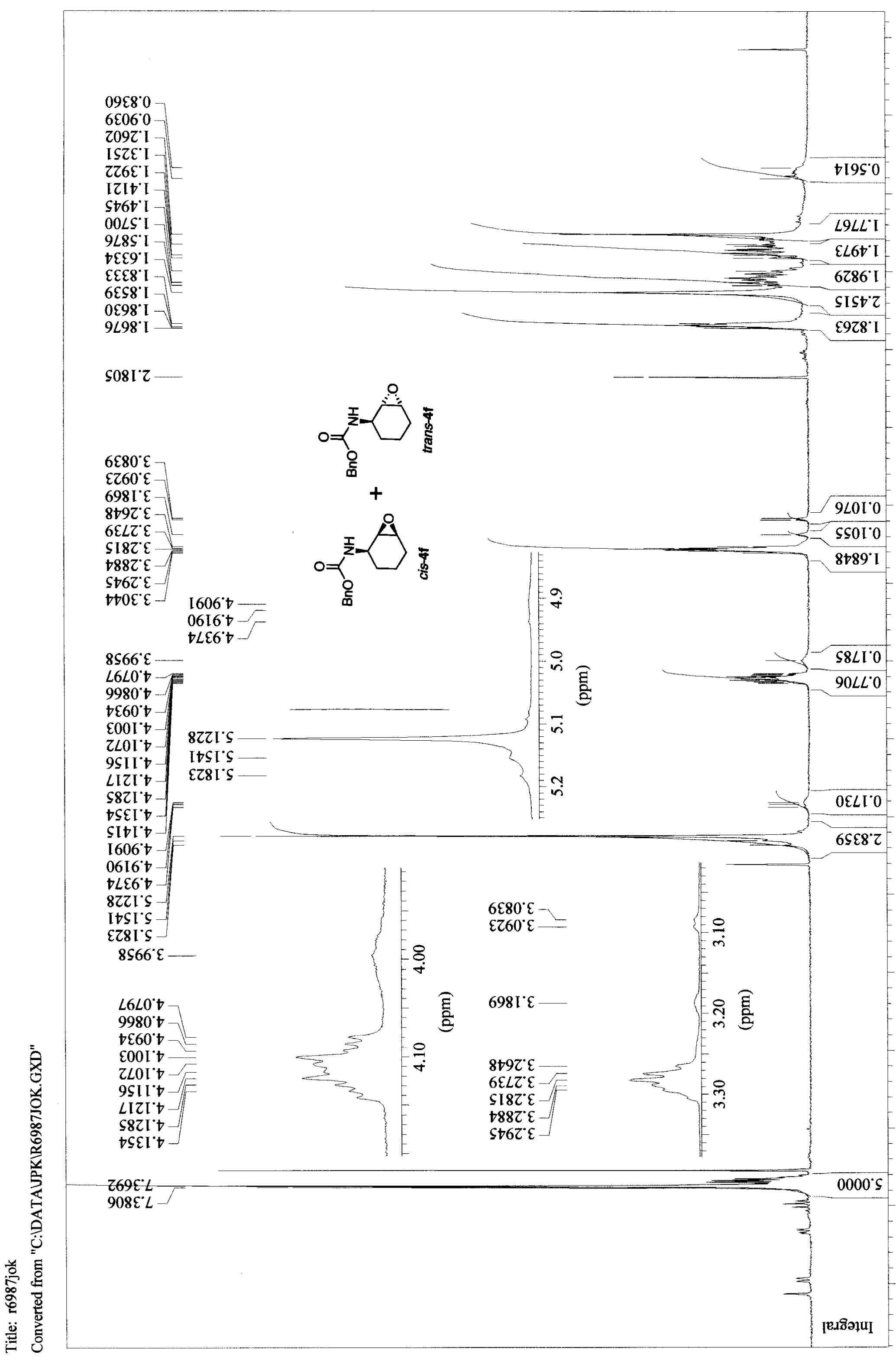
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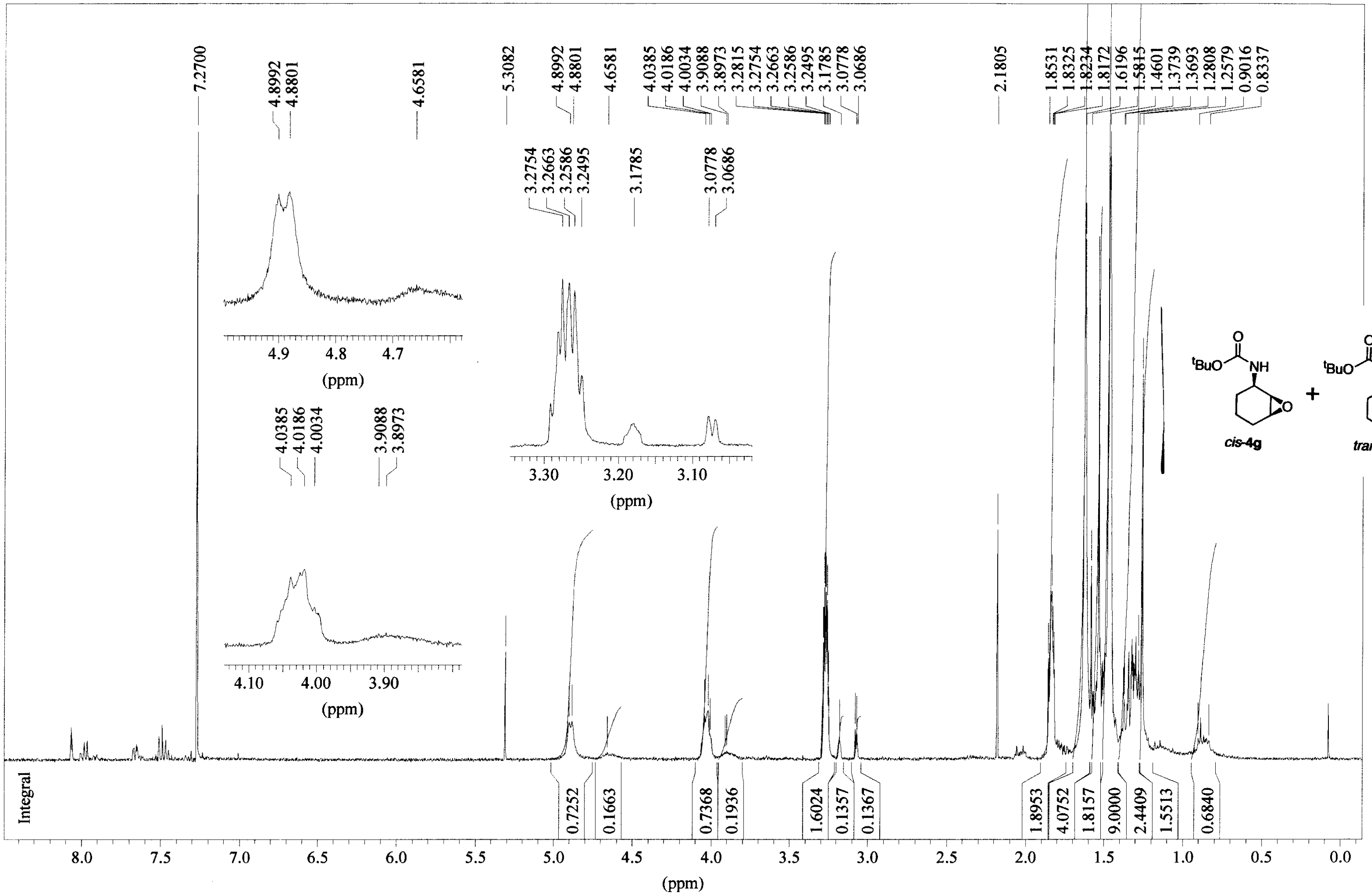

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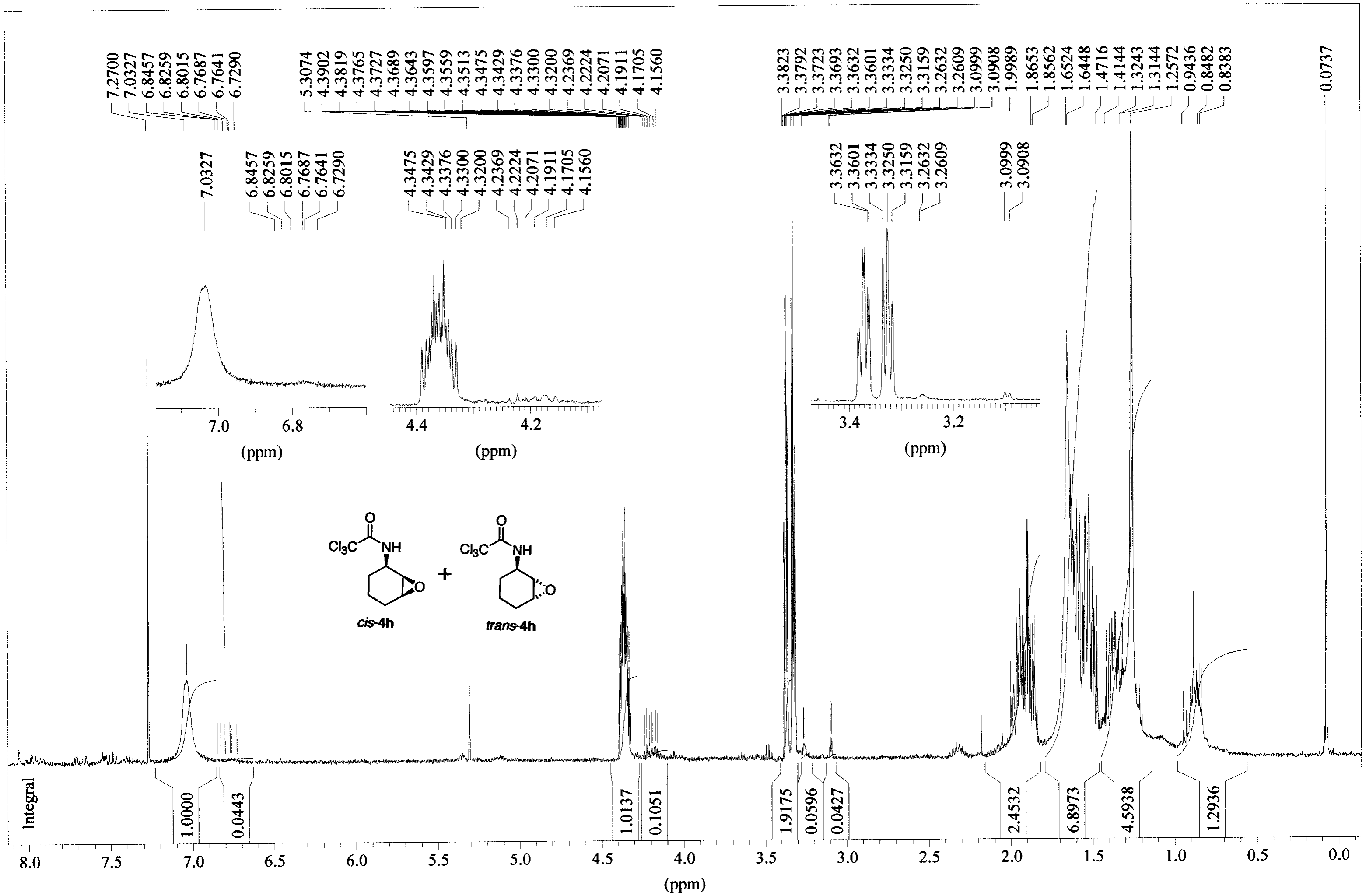

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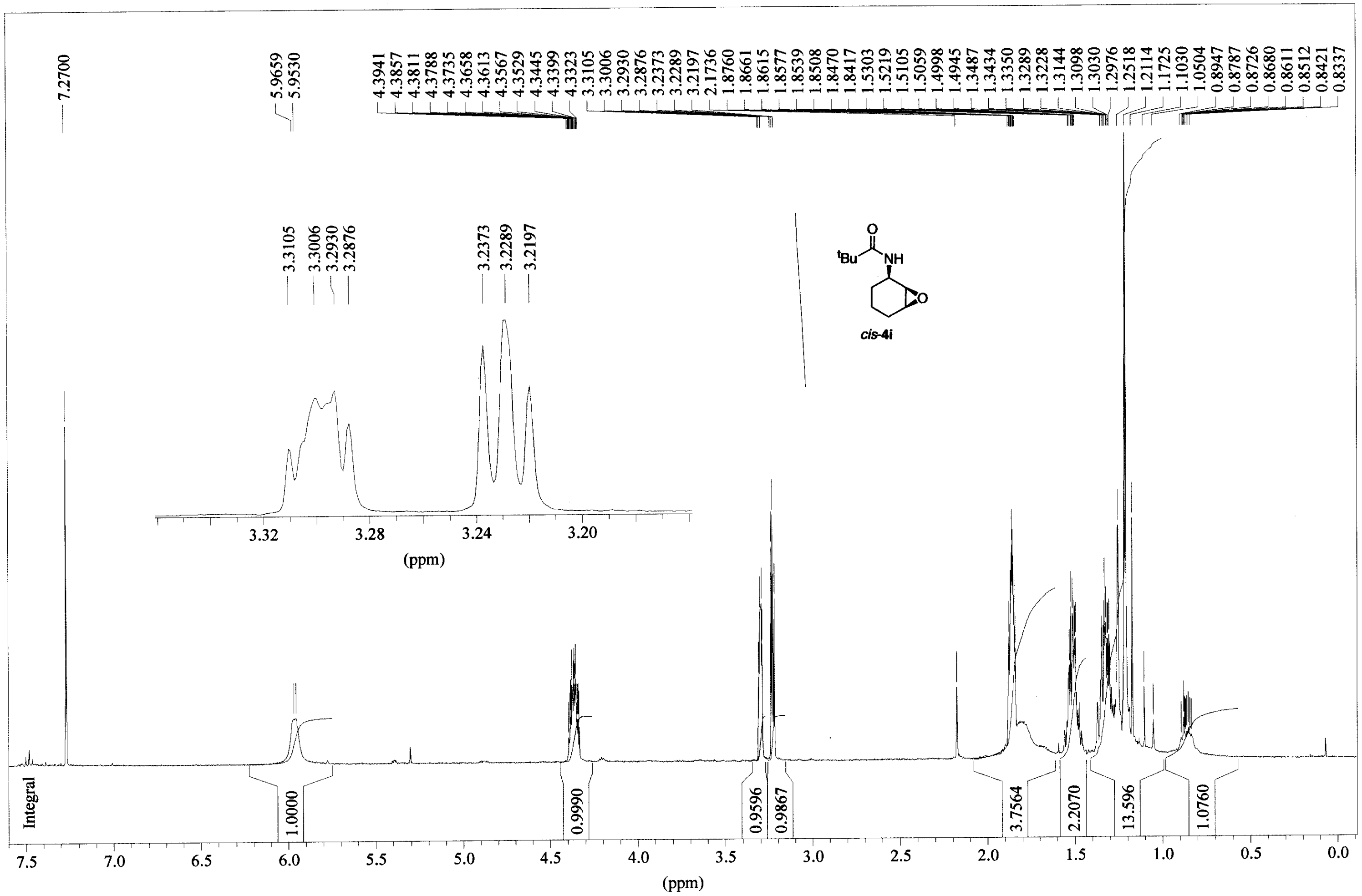

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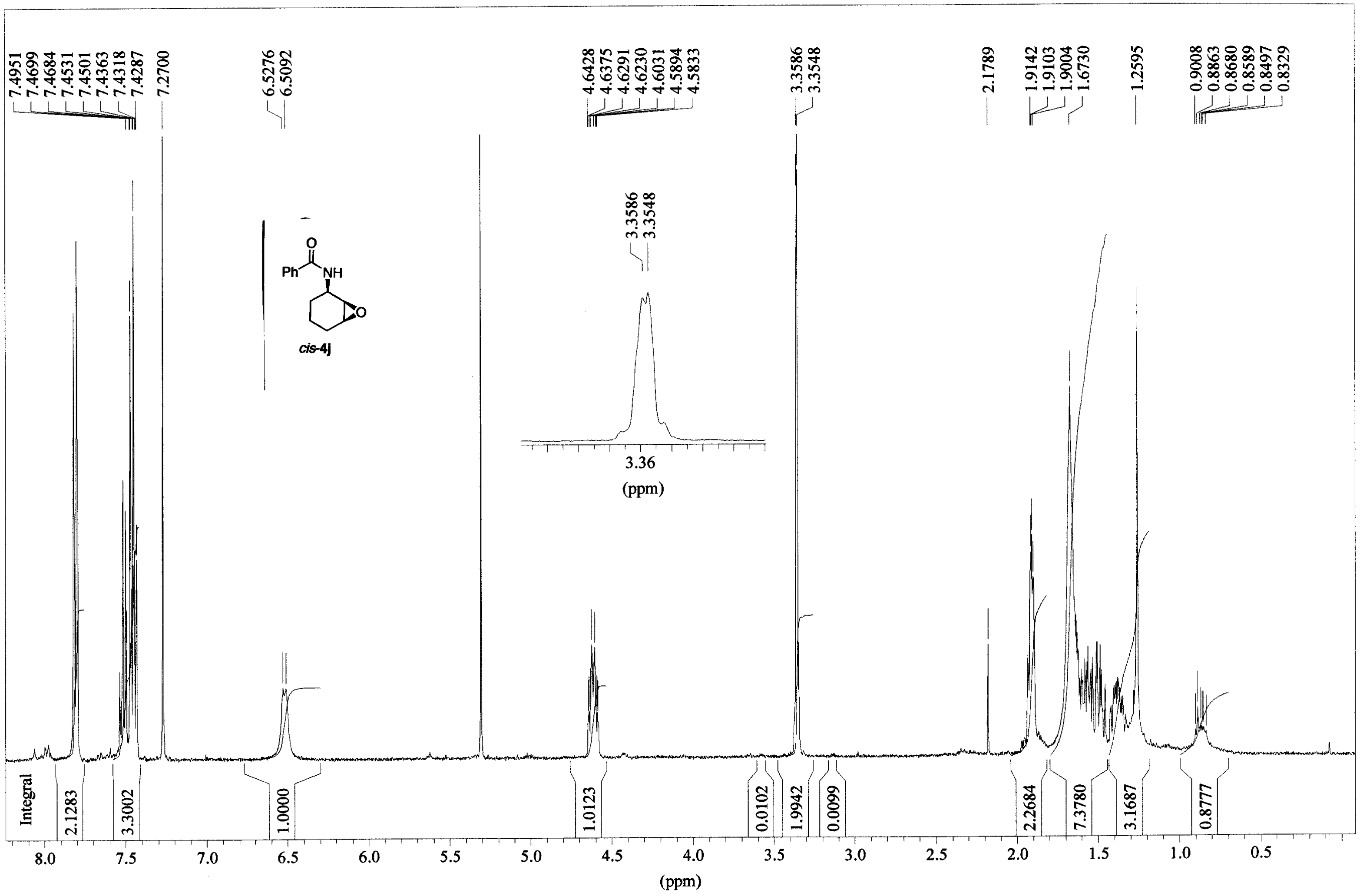

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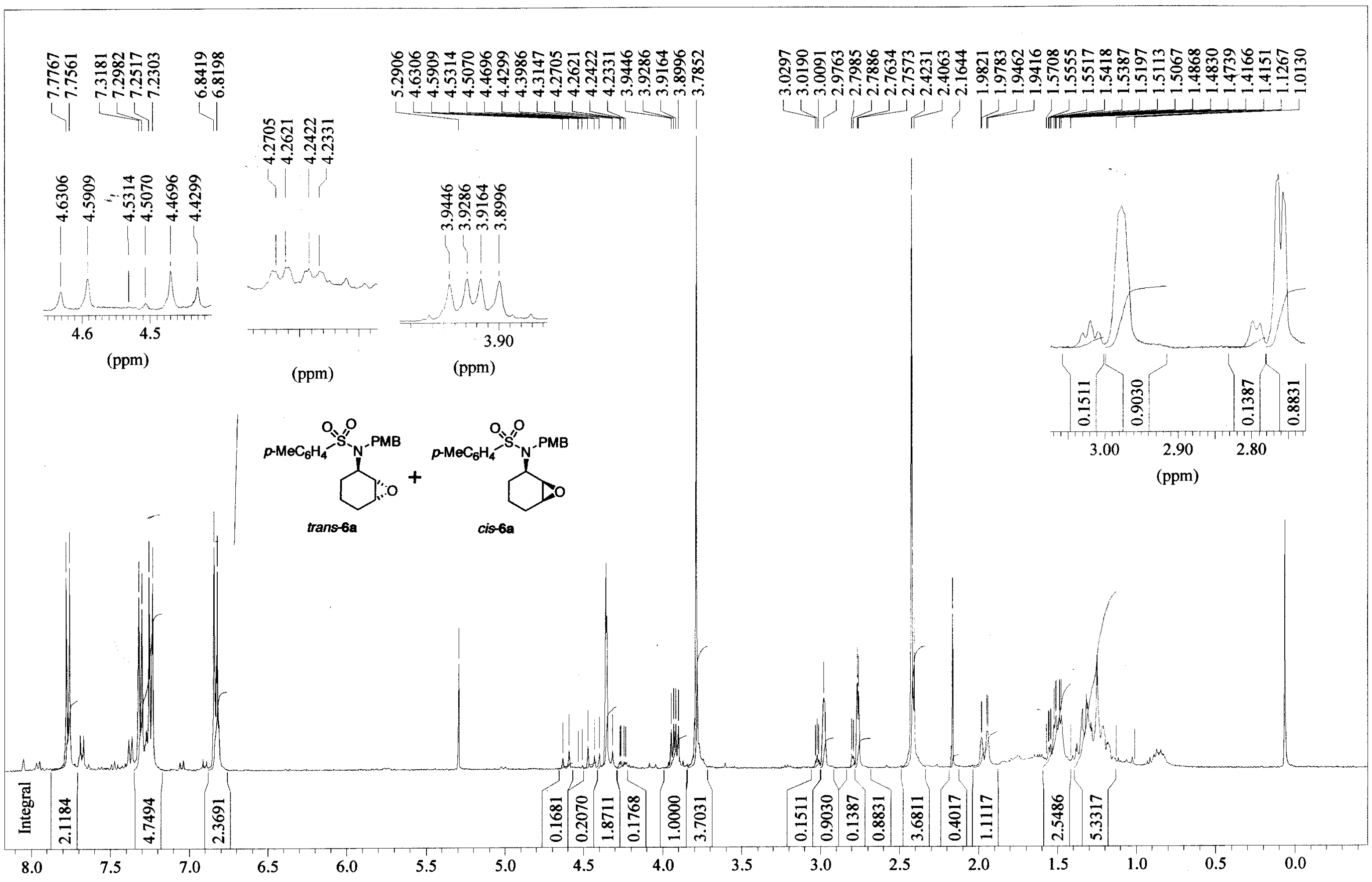

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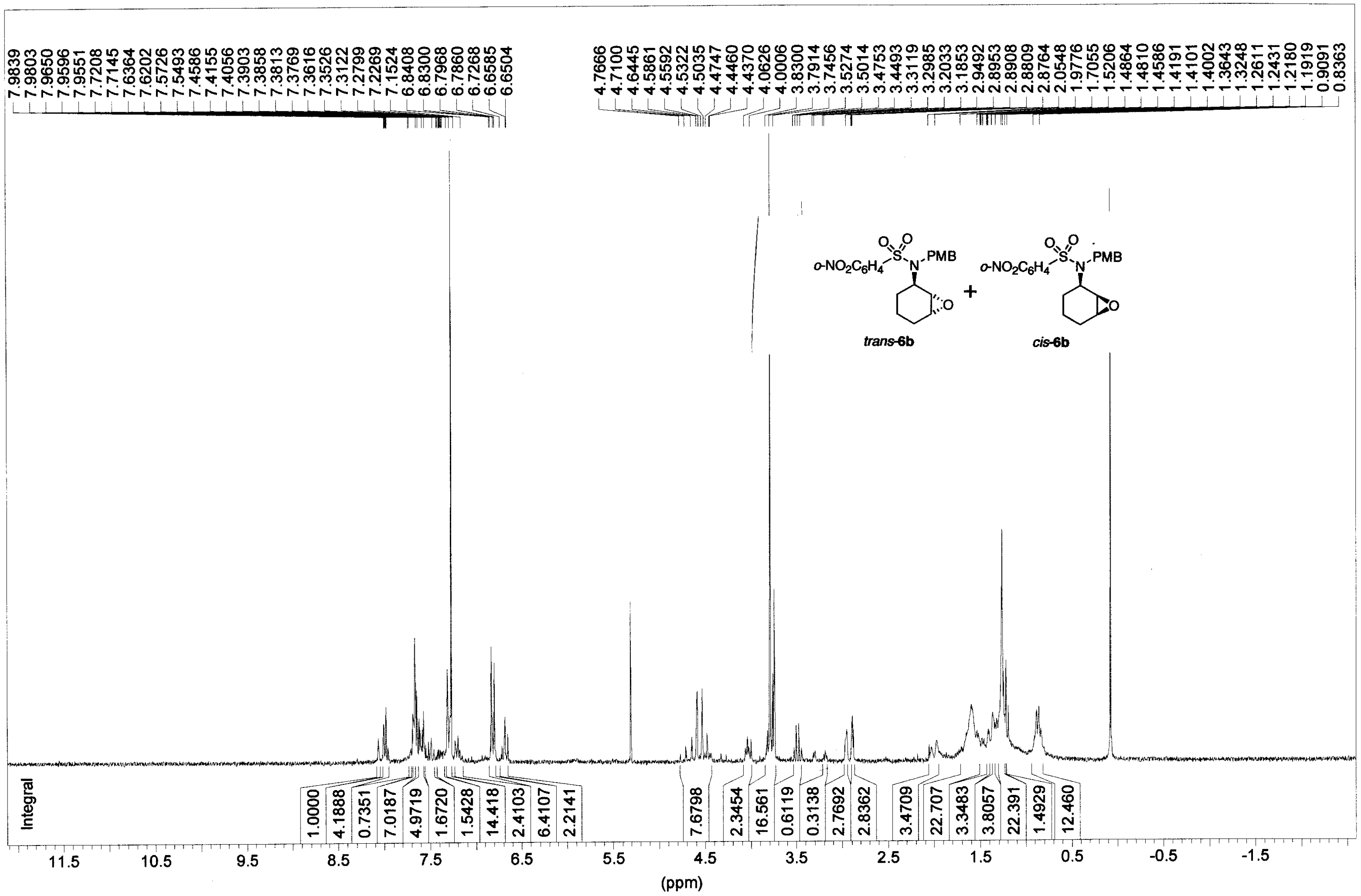

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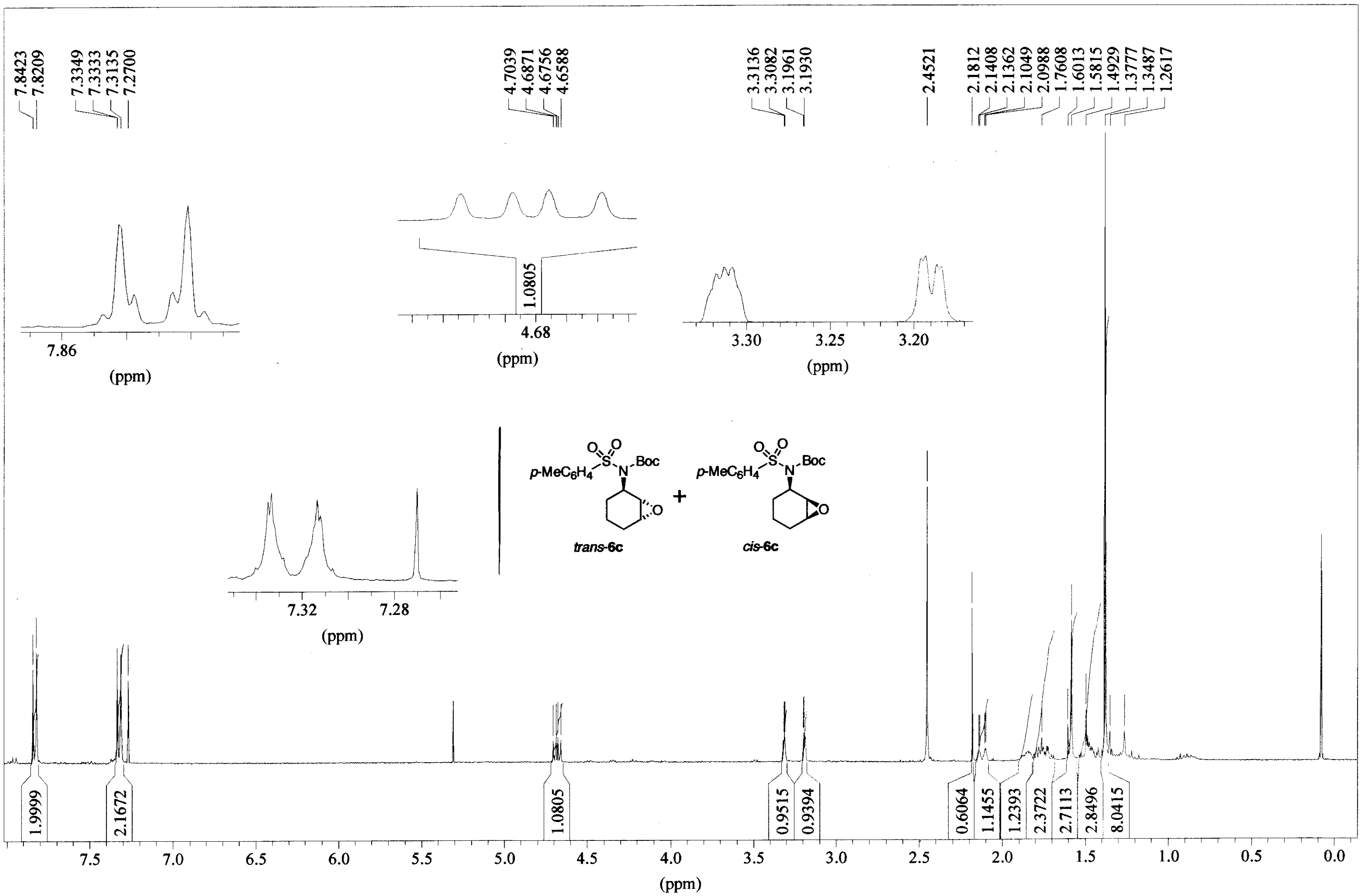

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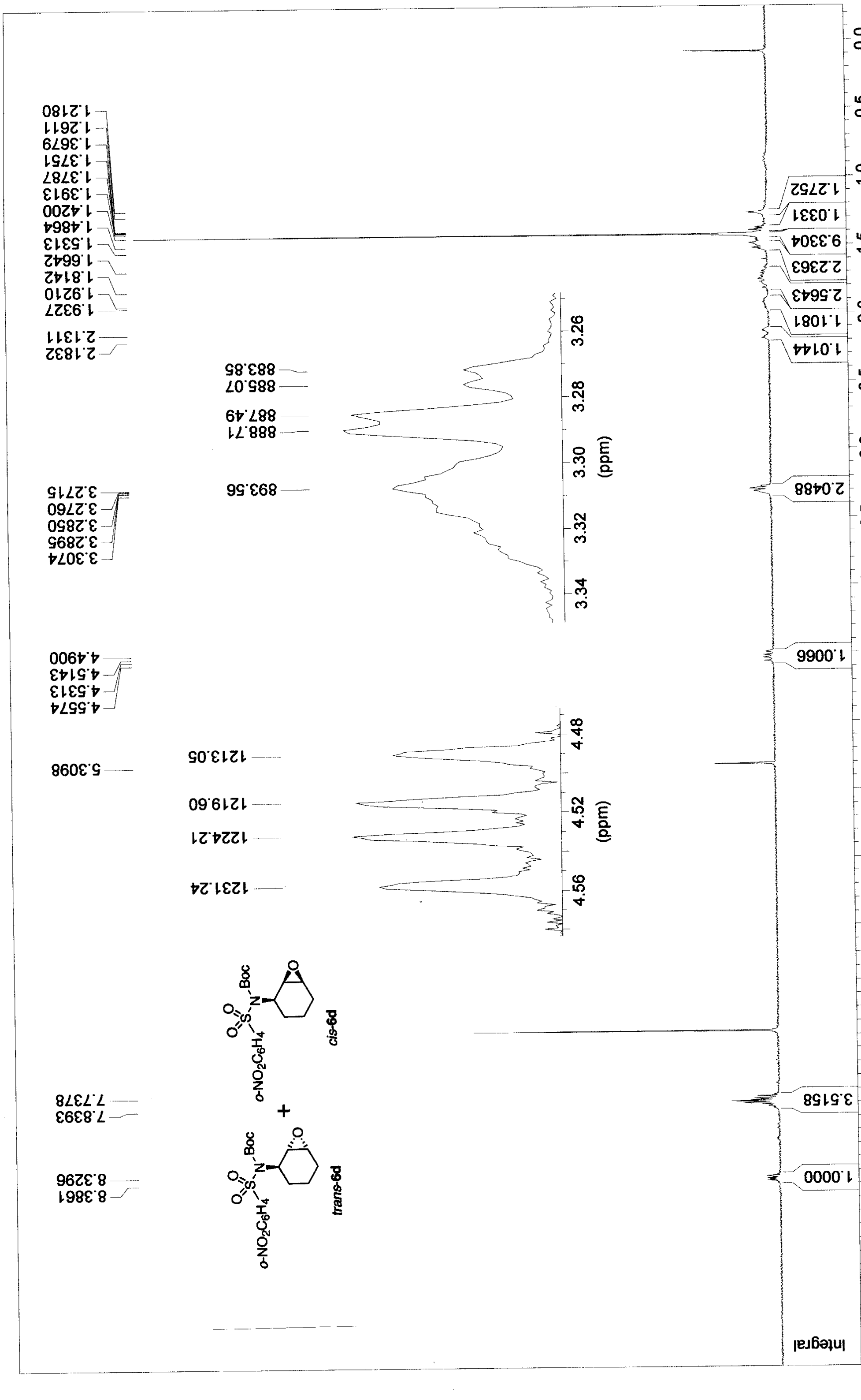

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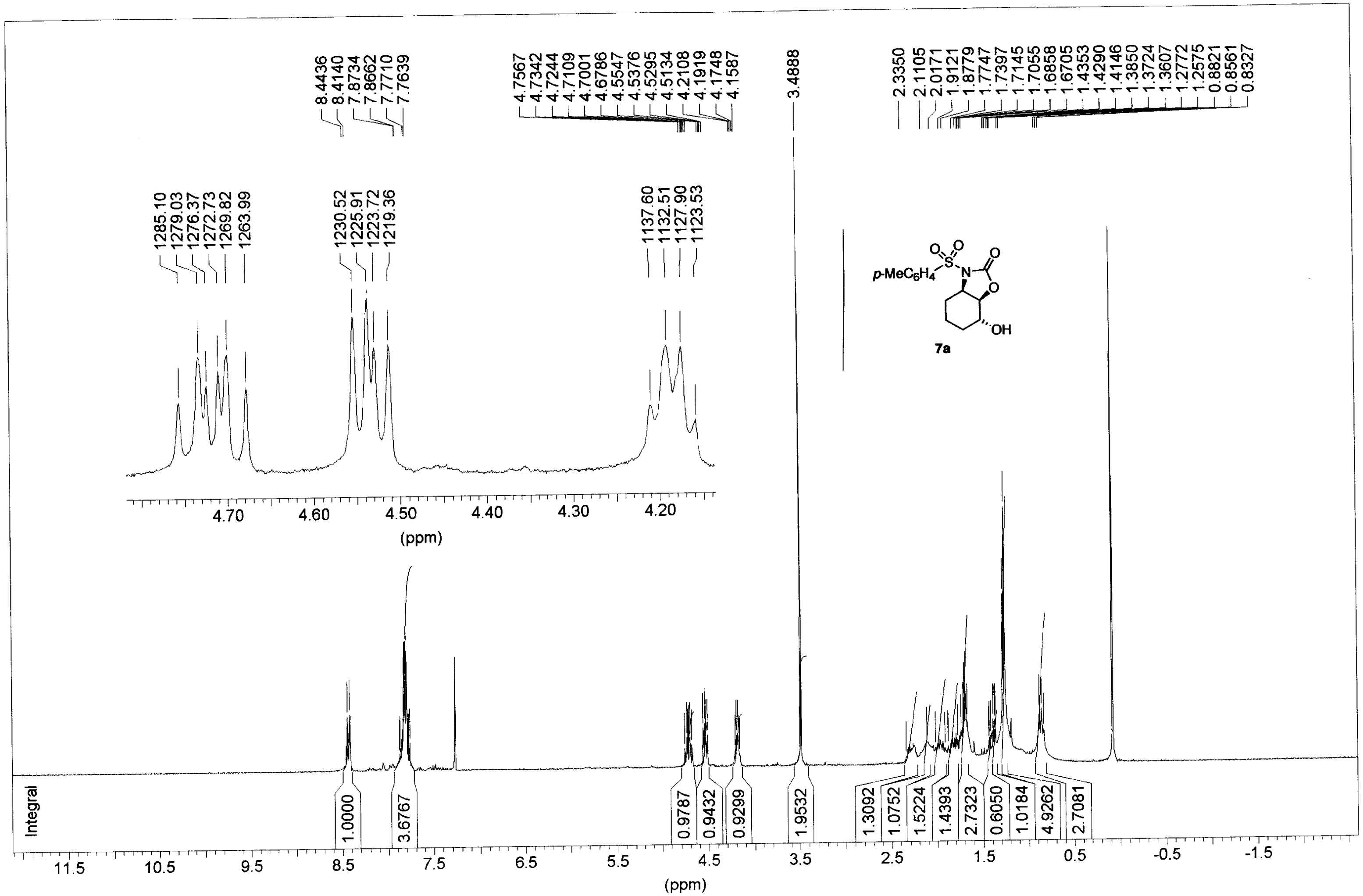

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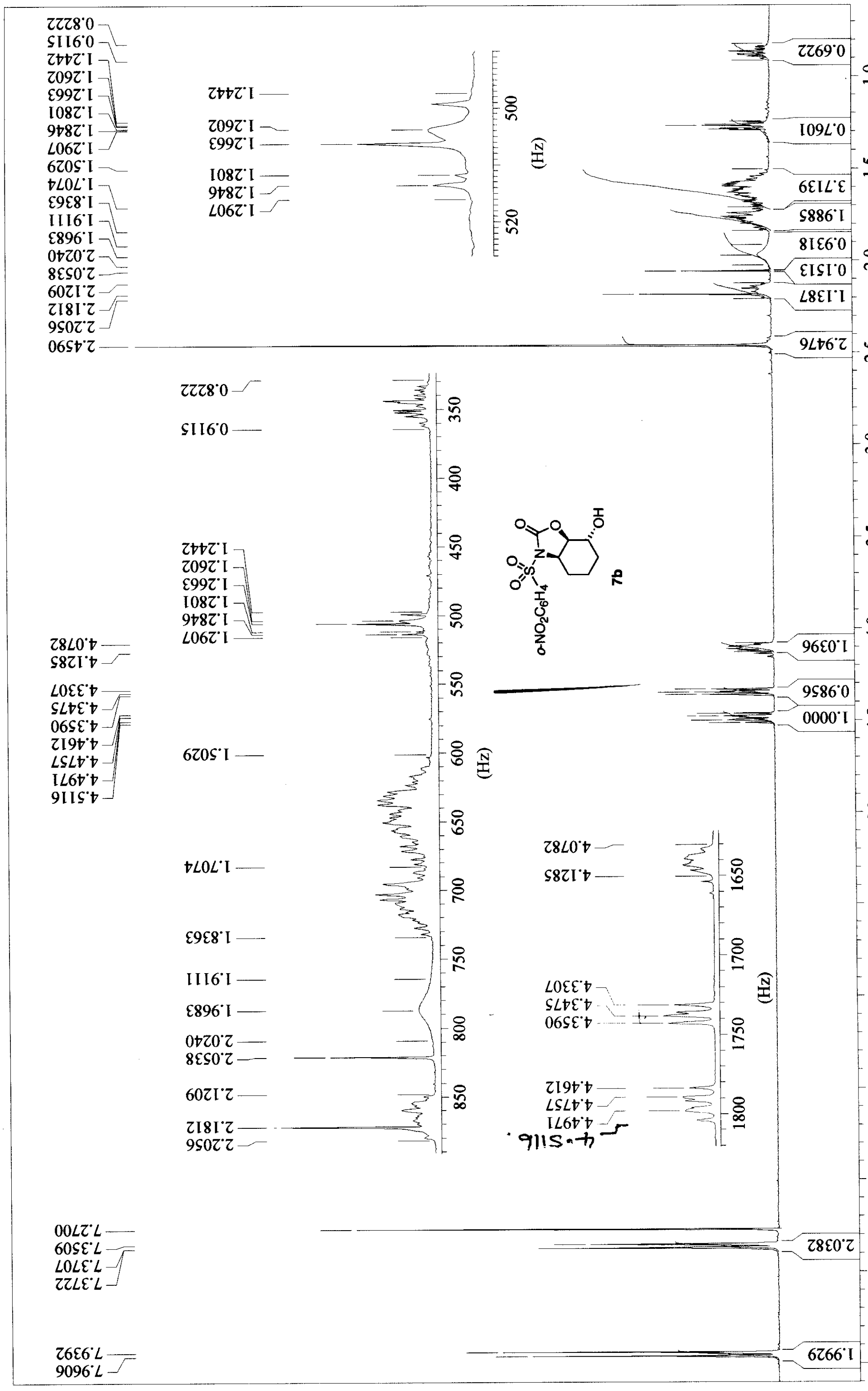

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