Supporting information

Enantioselective synthesis of 2-methyl indoline by palladium catalysed asymmetric C(sp^3)-H activation/cyclisation

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Contents

Experimental section

General: All reactions were carried out in oven dried glasswares. Progress of the reaction was monitored by Thin Layer Chromatography, which was performed on Merck precoated plates (silica gel. 60 F_{254}, 0.25 mm) and was visualized by fluorescence quenching under UV light. Column chromatography was done using 60-120 mesh silica gel and appropriate mixture of pentane and ethyl acetate for elution. The IR spectra were recorded on Perkin-Elmer Spectrum 100 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker FT-NMR spectrometers (360 and 250 MHz respectively) using $CDCl_3$ as solvent. TMS was used as internal standard and chemical shifts are in δ-scale. High resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) using mass spectrometer. Enantiomeric excesses were determined by HPLC analysis with a Chiralcel OD-H column (*n*-hexane/^{i}PrOH 99:1, 1 mL/min, 254 nm, rt) unless specified.

1. Representative procedures for the preparation of *N*-alkyl-2-bromoaniline:

1a) Preparation of *N*-isopropyl-2-bromoaniline: Method A[1]

To a solution of 2-bromo aniline (5.8 mmol, 1 g)) in dichloroethane (10 mL) were added 2-methoxy propane (11.6 mmol), acetic acid (5.8 mmol) and $NaBH_4$ (5.8 mmol) under inert atmosphere at room temperature for 16 h. After the reaction, the mixture was neutralized with 1N NaOH. The mixture was extracted with dichloromethane and dried over $MgSO_4$ and concentrated in *vacuo*. The crude material was purified by column chromatography with pentane to afford the 2-bromo-*N*-isopropylaniline (53% yield).

1b) Preparation of *N*-alkyl-2-bromoaniline: Method B[2]

To a solution of 2-bromo-1-iodobenzene (1 eq.) in DMF were added CuI (20 mol%), *rac*-BINOL (20 mol%), K_3PO_4 (3 eq.) and corresponding amine (1.5 eq.) under argon. The mixture was stirred at 50 ^{o}C for 1 day. The mixture was filtered and diluted with diethylether, dried over $MgSO_4$ and concentrated in *vacuo*. The crude material was purified by silicagel column chromatography with pentane/ethyl acetate (50:1) to afford the products in 50-60% yield.

2) Preparation of Methyl 2-Bromophenyl(isopropyl)carbamate 1a[3]

A mixture of 2-bromo-*N*-isopropylaniline (1.0 g, 4.5 mmol) in methyl chloroformate (20 mL) was heated under reflux for 6 h. The mixture was poured into water and extracted with chloroform. The organic layer was, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by silicagel column chromatography with pentane/ethyl acetate (30:1) to afford the methyl 2-bromo phenyl*(*isopropyl) carbamate **1a** in quantitative yield.

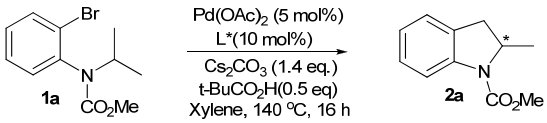
1. T. J. Reddy, M. Leclair, M. Proulx, *Synlett* **2005**, 583
2. D. Jiang, H. Fu, Y. Jiang, Y. Zhao *J. Org. Chem.,* **2007**, *72*, 672
3. T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* 2008, **10**, 1759

Optimization reactions

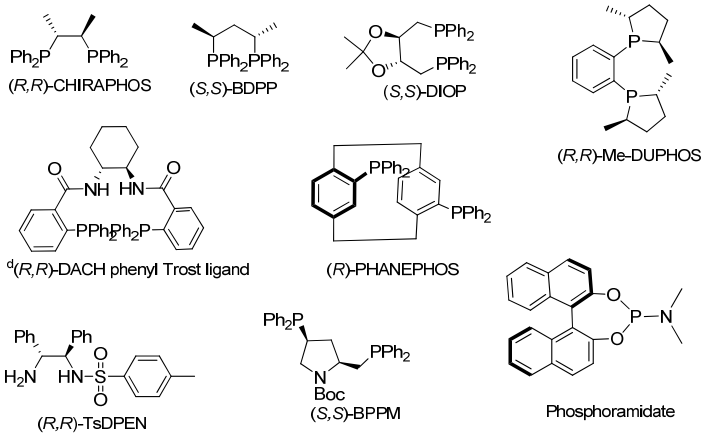
1) Initial Ligand screening studies

These reactions were performed with 0.2 mmol of the substrate **1a** in presence of 5 mol% $Pd(OAc)_2$, 10 mol% chiral ligand, 1.4 eq. Cs_2CO_3 and 0.5 eq. pivalic acid in 2 mL xylene at 140 ^oC under argon atmosphere. Better results in terms of yields as well as *ee*'s were obtained with (*S*,*S*)-DIOP and (*R*,*R*)-Me-DUPHOS as ligands. The results are presented in table 4.

Table 3



Entry	Ligand (L*)	Yield%[b]	ee%[b]
1	$PCy_3.HBF_4$	100(80[c])	-
2	(*R*)-BINAP	26	0
3	(*2S,5S*)-BDPP	70	5
4	Trost ligand[d]	5	8
5	JOSIPHOS	23	4
6	(*S,S*)-DIOP	100(92[c])	43
7	(*R,R*)-Me-DUPHOS	100(98[c])	90
8	(*R,R*)-iPr-DUPHOS	16	2
9	(*R*)-PHANEPHOS	78	4
10	(R,R)-CHIRAPHOS	77	27
11	(*S,S*)-BPPM	100	2
12	Phosphoramidate[e]	23	3
13	(-)-Sparteine	8	0
14	(*R,R*)-TsDPEN	No reaction	-



[a] Procedure: 0.2 mmol of **1a** is mixed with the reagents in xylene at 140 °C and keep stirring for 16 h.
[b] Determined by HPLC analysis.
[c] Isolated yield

2) Optimization reaction for a suitable catalyst/ligand ratio

These reactions were performed with 0.2 mmol of the substrate **1a** in presence of 5 mol% $Pd(OAc)_2$, 2.5-10 mol% (*R*,*R*)-Me-DUPHOS, 1.4 eq. Cs_2CO_3 and 0.5 eq. pivalic acid in 2 mL xylene at 140 ^oC under argon atmosphere and keep stirring for 16 h. The results are presented in table 4.

Table 4

Entry	Catalyst (mol%)	Ligand (mol%)	Trial 1[a]		Trial 2[a]	
			Yield%	*ee*%	Yield%	*ee*%
1	5	5	77	17	trace	
2	5	7.5	25	44	15	64
3	5	10	55	82	40	63
4	5	2.5	87	19	72	21

[a] Yield and *ee* calculated by HPLC analysis

3) Optimization studies with different modes of addition of the reagents

These reactions were performed with 0.2 mmol of the substrate **1a** in presence of 5 mol% $Pd(OAc)_2$, 10 mol% (*S*,*S*)-DIOP and/or (*R*,*R*)-Me-DUPHOS, 1.4 eq. Cs_2CO_3 and 0.5 eq. pivalic acid in 2 mL xylene at 140 ^oC in the absence of argon and keep stirring for 16 h. We monitored the progress of the reaction by means of HPLC analysis with time. The results are presented in table 5.

Table 5

Entry	Mode of addition of substrates	Time (hour)	(*S,S*)-DIOP Yield(*ee*)% trial 1	(*S,S*)-DIOP Yield(*ee*)% trial 2	(*R,R*) MeDuphos Yield(*ee*)%
1	**Substrate** was dissolved in xylene **at 140 °C**. After 5 min catalyst & ligand were added together.Then additive & base were added	0.1 1 16	4(89) 98(45) 99(45)	5(87) 25(42) 50(41)	8(63) 17(47) 22(45)
2	Catalyst & ligand were premixed in xylene **at rt** and kept at 140 °C. Followed by addition of the substrate, additive and base	0.1 1 16	3(72) 16(41) 25(35)		
3	Catalyst & ligand were premixed in xylene **at rt** and kept at 140 °C. Followed by added the additive, base and **finally** the substrate	0.1 1 16	3(99) 4(93) 4(90)		
4	Substrate and ligand were premixed in xylene at 140 °C. After 5 min additive and base were added then **finally the catalyst**	0.1 1 16	3(98) 70(49) 97(44)	3(94) 70(48) >99(47)	5(93) 11(93) 24(75)
5	Catalyst & ligand were premixed in xylene **at rt** . Followed by added the additive, base and finally the substrate. **gradually increased** the temp to 140 °C	0.1 1 16	no reaction trace 5(65)		
6	All reagents were premixed with xylene at rt and **stirred for 1 min at rt.** Then suddenly put the reaction mixture at 140 °C.	0.1 **1** **2**	5(53) **93(48)** **100(47)**	4(50) **90(44)** **100(43)**	4(96) **95(94)** **100(93)**

Note*: We initially carried out the reactions with the cheaper ligand (S,S)-DIOP and the better results were re-checked again for reproducibility of the result which we obtained earlier with (R,R)-Me-DUPHOS. The condition which gave the consistent result with both (S,S)-DIOP and (R,R)-Me-DUPHOS (entry 6,) was selected as the optimized procedure. (ref 14 in the article)*

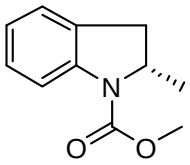
Representative procedure for the synthesis of 2a from 1a: 2-bromo-*N*-isopropylaniline derivative **1a** (55 mg, 0.20 mmol), $Pd(OAc)_2$ (2.3 mg, 5 mol %), (*R,R*)-Me-DUPHOS (6.8 mg, 10 mol %), Cs_2CO_3 (84 mg, 0.28 mmol) and *t*-$BuCO_2H$ (9 mg, 0.10 mmol) were taken in a 10 mL RB flask equipped with a reflux condenser. To this, xylene (2.0 mL) was added in an open atmosphere and mixed well under stirring at room temperature. The reaction mixture was stirred further for 2 h at 140 °C. After cooling, the reaction mixture was concentrated in *vacuo*. The crude material was purified by silicagel chromatography with pentane/ethyl acetate (30:1) to afford the indoline **2a** (40 mg, 97%, 93% *ee*).

Scale-up reaction with (*S,S*)-DIOP

The scale up reaction using substrate **1a** and (*S,S*)-DIOP as ligand also gave substantially good results. When the reaction was carried out under optimized procedure with 1 g of the substrate

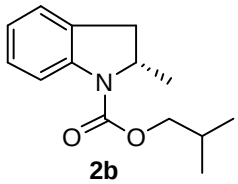
1a in presence of 5 mol% $Pd(OAc)_2$, 10 mol% (*S,S*)-DIOP,1.4 eq. Cs_2CO_3 and 0.5 eq. pivalic acid at 140 ^oC for 2 h, the product **2a** was isolated in 95% yield and 34% *ee*.

Characterization data for compounds 2a-2d, 2f and 2g



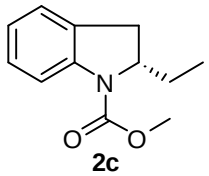
2a

Following the general procedure, **2a** was isolated as a light yellow oil: $[\alpha]_D^{20}$ +48.3 (*c* 0.8, CH_2Cl_2); IR(neat) cm^{-1}: 3422, 3019, 2957, 1698, 1603, 1486, 1445, 1393, 1288, 1265, 1216, 1140, 1062, 754, 668. ^{1}HNMR (360 MHz, $CDCl_3$): 7.82(brs, 1H), 7.25-7.17(m, 2H), 7.0(t, 1H), 4.58(brs, 1H), 3.88(s, 3H), 3.40 (dd, 1H), 2.66(d, 1H), 1.32(d, 3H). ^{13}CNMR (250 MHz, $CDCl_3$):153.6, 141.3, 130.1, 127.8, 125.1, 122.7, 115.3, 55.5, 52.6, 36.1, 21.3. HRMS (EI) exact mass calculated for $C_{11}H_{13}NO_2$ $[M+Na]^+$ 214.0845, found 214.0844. The enantiomers were separated on Chiralcel OJ-H column (1% IPA/hexane, 1mL/min): 254 nm, rt = 9.3 (3.5%), 10.3 (96.5%).



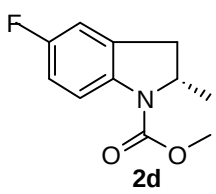
2b

Following the general procedure, **2b** was isolated as a viscous oil; IR(neat) cm^{-1}: 3457, 3019, 2963, 2400, 1643, 1486, 1261, 1215, 1110, 929, 755, 669. ^{1}HNMR (360 MHz, $CDCl_3$): 7.74(d, 1H), 7.57-7.54(m, 1H), 7.24-7.17(m, 1H), 6.99(t, 1H), 4.60(brs, 1H), 4.05(d, 2H), 3.40(dd, 1H), 2.66(d, 1H), 2.10-2.04(m, 1H), 1.35-1.28(m, 6H), 1.03(d, 3H) ^{13}CNMR (250 MHz, $CDCl_3$): 154.7, 141.6, 131.0, 128.1, 124.7, 122.0, 115.6, 56.0, 52.8, 35.4,, 23.0, 20.1, 13.2, 13.0. HRMS (EI) exact mass calculated for $C_{14}H_{19}NO_2$ $[M+Na]^+$ 256.1306, found 256.1313. The enantiomers were separated on the Chiralcel OJ-H column (1% IPA/hexane, 1 mL/min): 254 nm, rt = 7.3 (22.5%), 7.6 (77.5%).



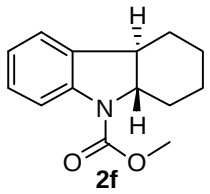
2c

Following the general procedure, **2c** was isolated as a colourless oil: $[\alpha]_D^{20}$ –27.7 (*c* 0.065, $CHCl_3$); IR(neat) cm^{-1}: 3433, 3019, 2967, 1694, 1645, 1486, 1445, 1395, 1289, 1265, 1216, 1137, 1062, 757, 668. ^{1}HNMR (360 MHz, $CDCl_3$): 7.75(brs, 1H), 7.23-7.01(m, 2H), 6.99(t, 1H), 4.42(m, 1H), 3.88(s, 3H), 3.32(dd, 1H), 2.80(d, 1H), 1.81(m, 1H), 1.64-1.57(m, 1H), 0.92(t, 3H) ^{13}CNMR (250 MHz, $CDCl_3$): 154.1, 141.7, 130.3, 127.9, 124.6, 123.0, 115.5, 59.8, 52.4, 33.6, 27.8, 10.1. LRMS (FAB) exact mass calculated for $C_{12}H_{15}NO_2$ $[M]^+$ 205.1503, found 205.16. The enantiomers were separated on the Chiralcel OJ-H column (1% IPA/hexane, 1 mL/min): 254 nm, rt = 7.7 (61.5%), 8.8 (38.5%).



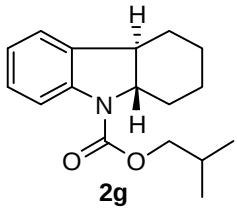
2d

Following the general procedure, **2d** was isolated as a pale yellow oil: $[\alpha]_D^{20}$ -21.5 (*c* 0.2, $CHCl_3$); IR(neat) cm^{-1}: 3017, 2950, 1696, 1612, 1487, 1389, 1258, 1215, 1126, 1098, 1064, 815, 753, 665. ^{1}HNMR (360 MHz, $CDCl_3$): 7.76 (br, 1H), 6.91-6.86(m,2H), 4.58 (brs, 1H), 3.85(s, 3H), 3.36(ddd, 1H), 2.63(d, 1H), 1.30(d, 3H). ^{13}CNMR (250 MHz, $CDCl_3$): 157.8, 153.6, 138.1, 130.7, 126.2, 119.6, 113.8, 62.7, 52.5, 44.9, 25.9. LRMS (FAB) exact mass calculated for $C_{12}H_{15}FNO_2$ $[M]^+$ 224.1087, found 224.19. The enantiomers were separated on the Chiralcel OJ-H column (1% IPA/hexane, 1 mL/min): 254 nm, rt = 11.5 (7.5%), 13.1 (92.5%).



2f

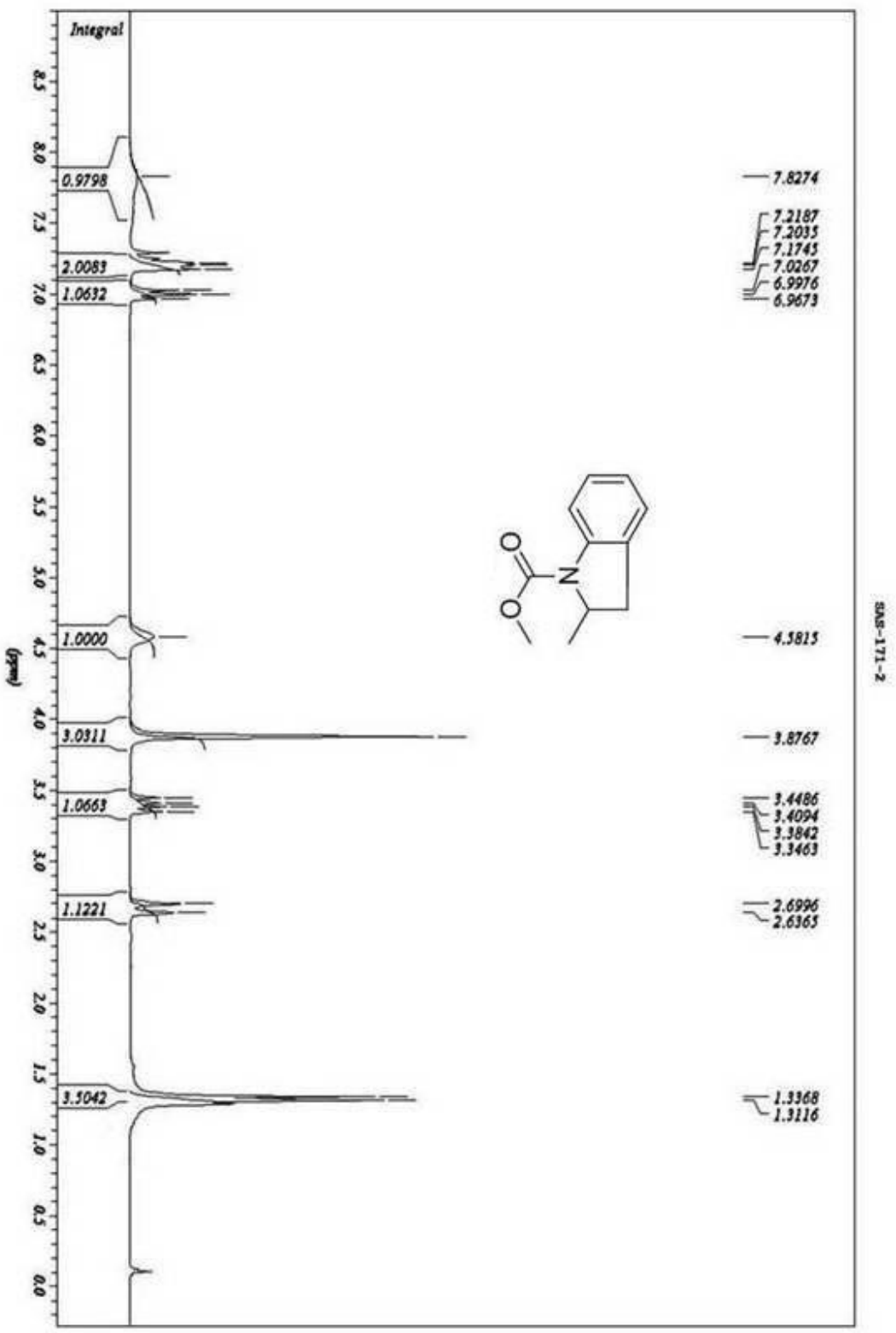
Following the general procedure, **2f** was isolated as a pale yellow oil; IR (neat) cm^{-1}: 3435, 3020, 2686, 2401, 1643, 1524, 1422, 1265, 1216, 928, 896, 763, 669. ^{1}HNMR (360 MHz, $CDCl_3$): 7.75(d, 1H), 7.22(t, 1H), 7.13(d, 1H), 6.99(t, 1H), 3.86(s, 3H), 3.44 (ddd, 1H), 2.90(dd, 1H), 2.74(m, 1H), 2.36(m, 1H),1.95-1.91(m, 2H), 1.49-1.43(m, 2H), 1.22-1.10(m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$):155.5, 142.7, 133.4, 127.5, 122.6, 120.8, 115.1, 70.1, 52.8, 48.5, 31.9, 28.3, 26.1, 25.2. LRMS (FAB) exact mass calculated for $C_{14}H_{17}NO_2$ $[M+1]^+$ 232.1259, found 232.13. The enantiomers were separated on the IB column (1% IPA/hexane, 1 mL/min): 254 nm, rt = 12.5 (27 %), 13.3 (73%).

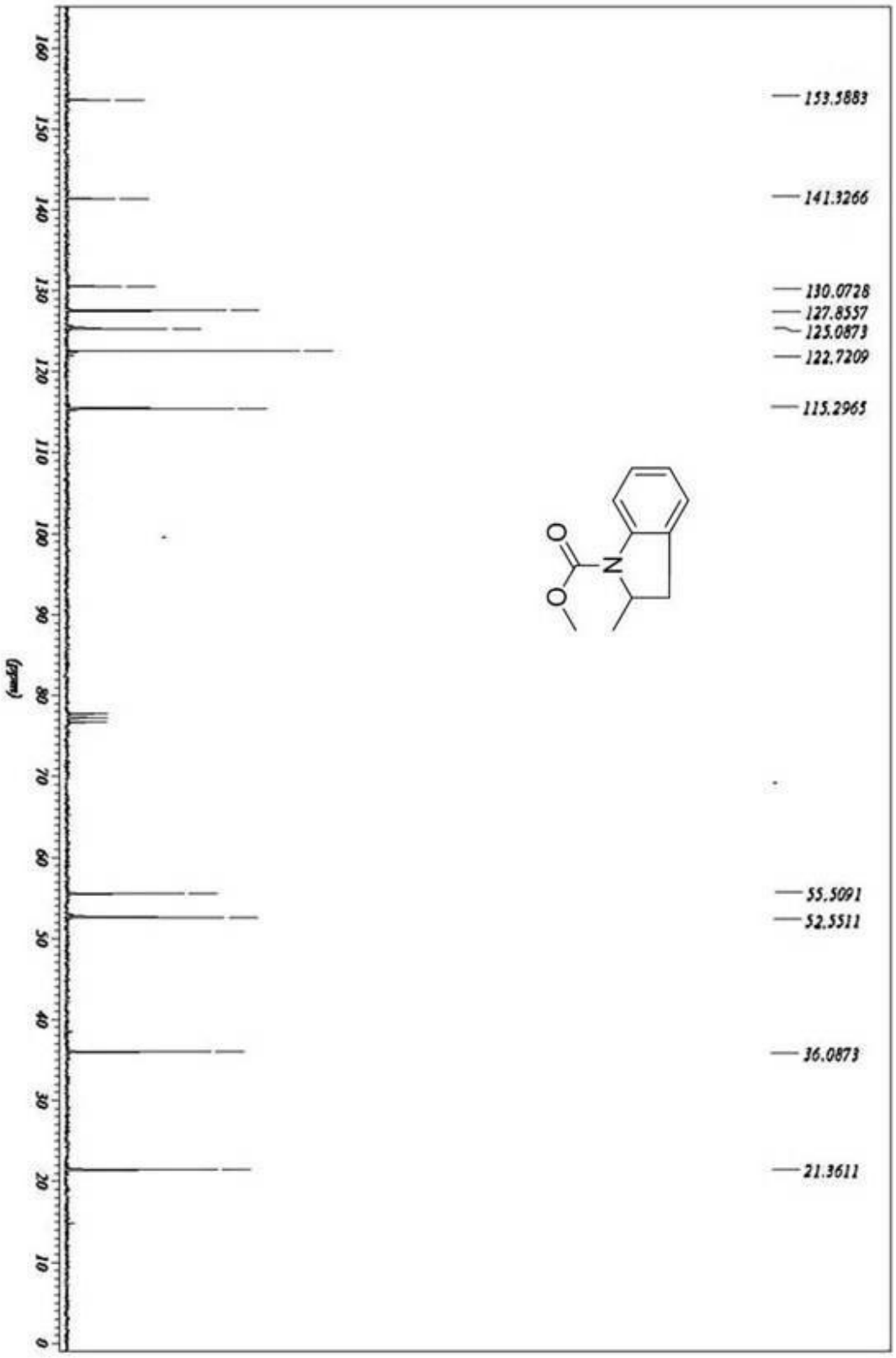


2g

Following the general procedure, **2g** was isolated as a colorless oil: $[\alpha]_D^{20}$ +3.7 (*c* 0.16, $CHCl_3$); IR(neat) cm^{-1}: 3435, 3019, 2932, 2962, 1777, 1694, 1477, 1460, 1412, 1332, 1263, 1216, 1115,1040,757, 669. ^{1}HNMR (360 MHz, $CDCl_3$): 7.79 (d, 1H), 7.24-7.12(m, 2H), 7.01(t, 1H), 4.14-3.93(m, 2H), 3.45(ddd, 1H), 2.98-2.93(m, 1H), 2.75-2.71(m, 1H), 2.37(m, 1H), 2.14-2.01(m, 2H), 1.32-1.20(m, 4H), 0.99-0.88 (m, 7H). ^{13}CNMR (250 MHz, $CDCl_3$): 154.7, 141.7, 131.9, 127.8, 123.1, 120.5, 114.6, 68.3, 54.9, 47.4, 33.0, 28.7, 25.2, 24.4, 20.7, 14.1, 13.2, HRMS (EI) exact mass calculated for $C_{17}H_{23}NO_2$ $[M+1]^+$ 274.1801, found 274.1807. The enantiomers were separated on the Chiralcel OD-H column (1% IPA/hexane, 0.3 mL/min): 254 nm, rt = 18.1 (21%), 19.4 (79%).

^{1}H & ^{13}C NMR Spectra of compounds 2a-f

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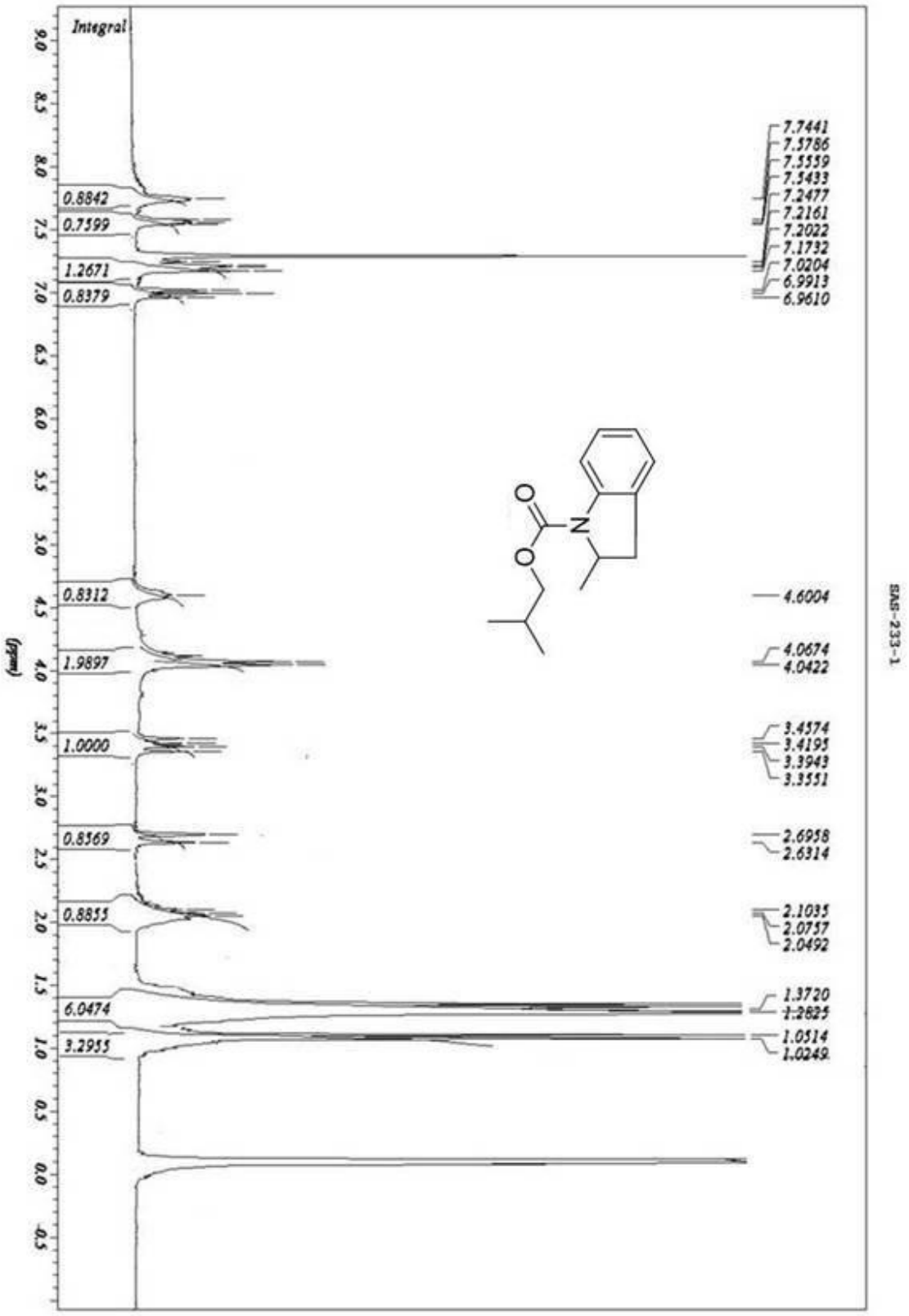
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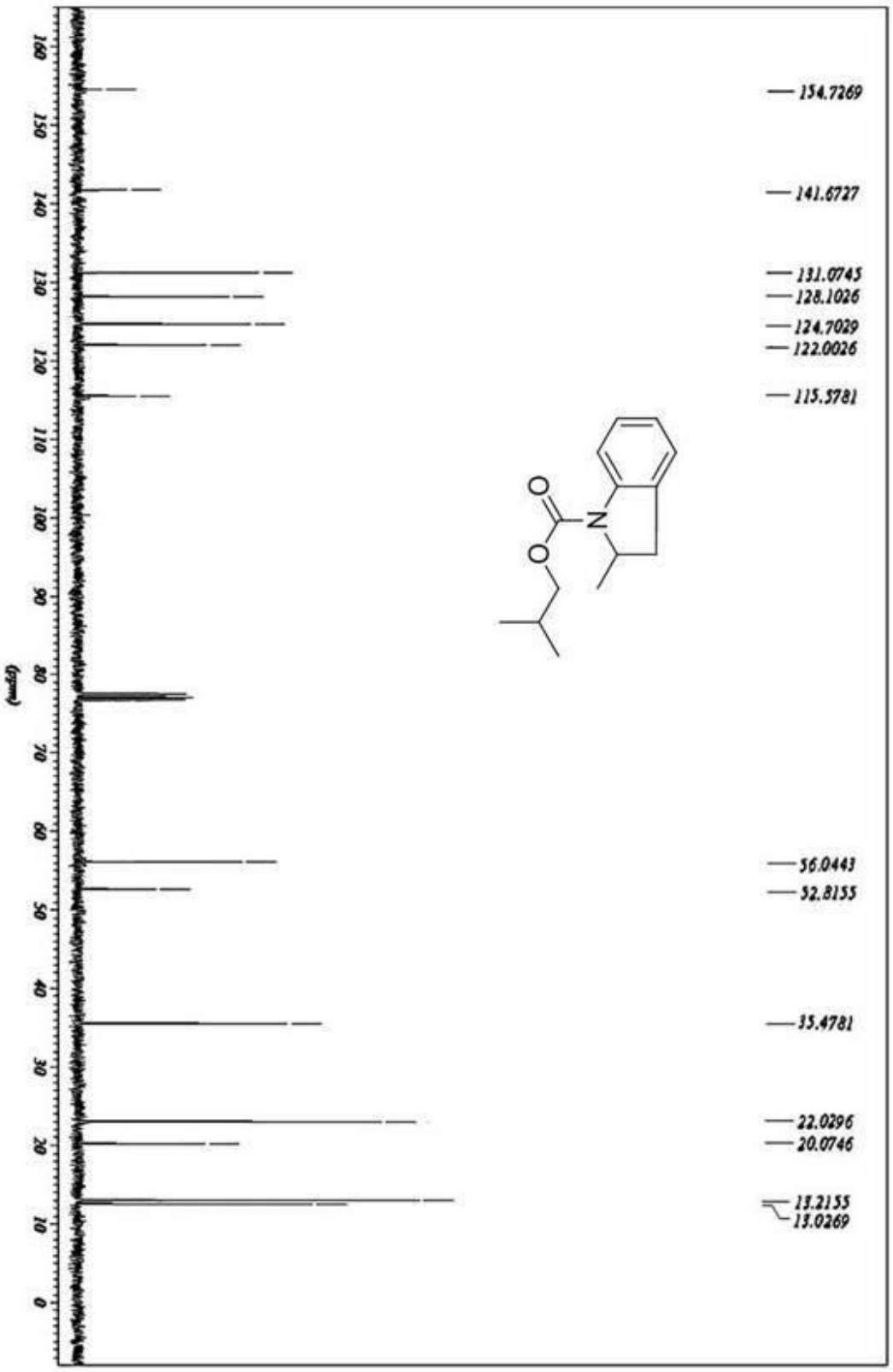

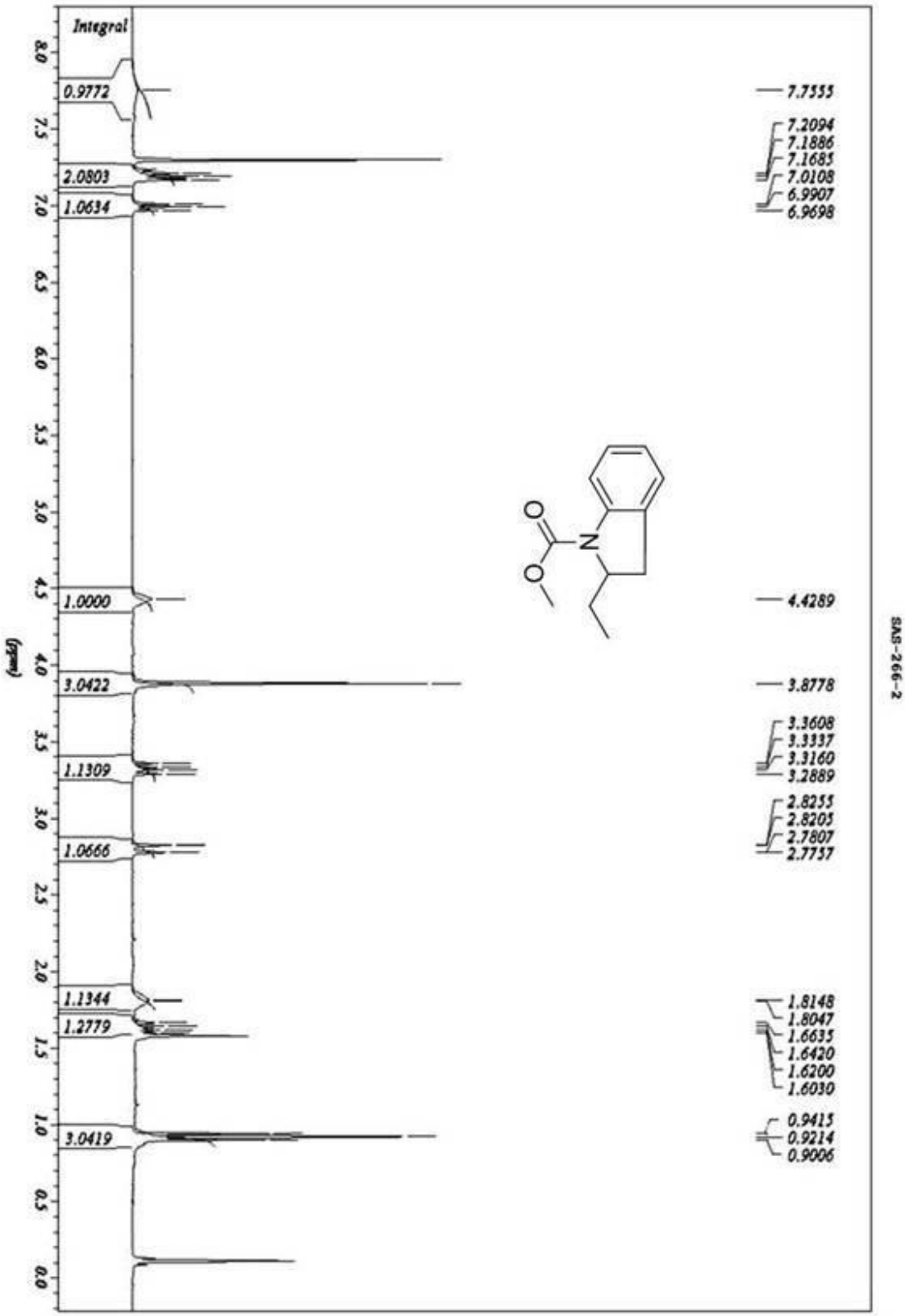
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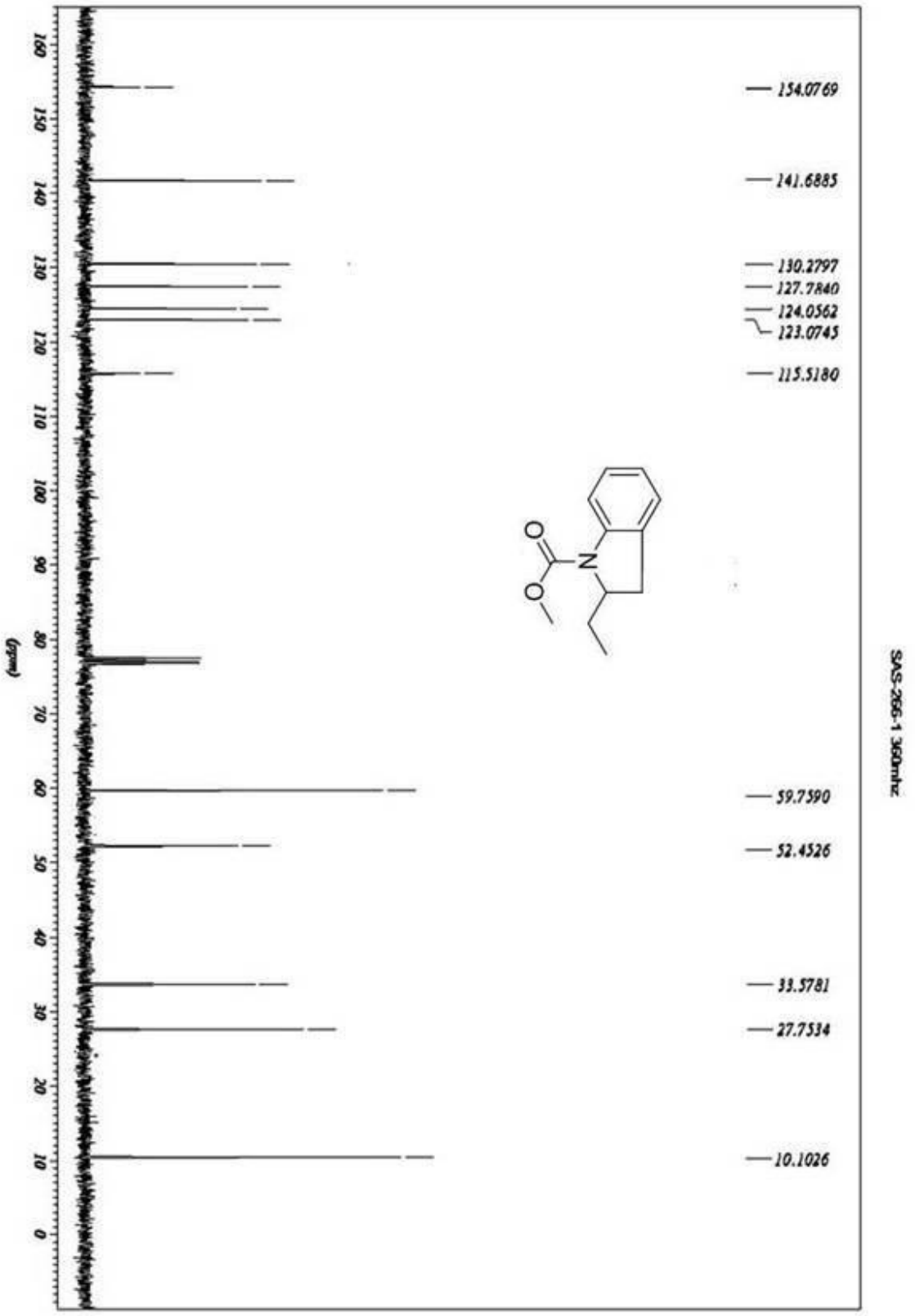
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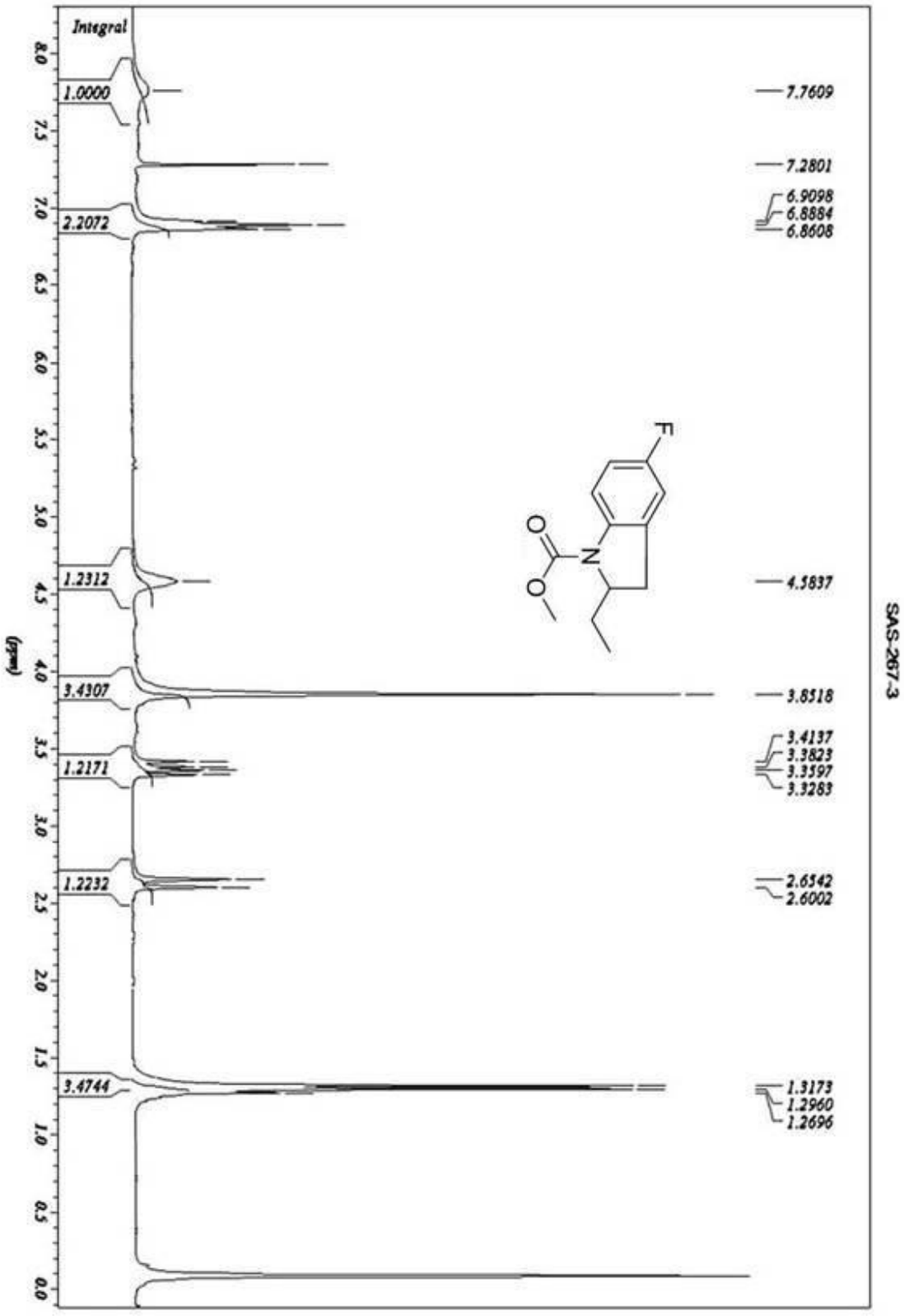
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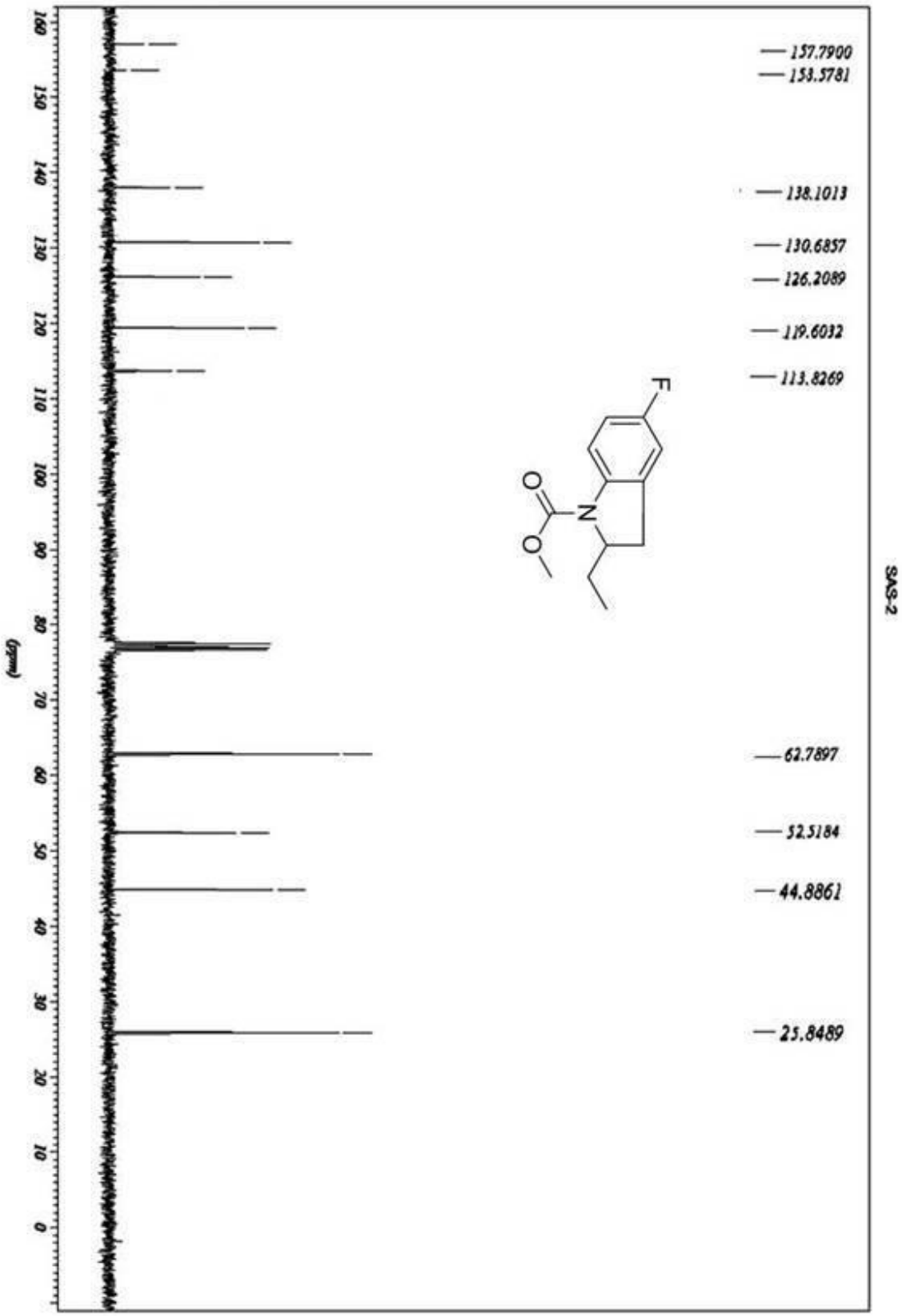
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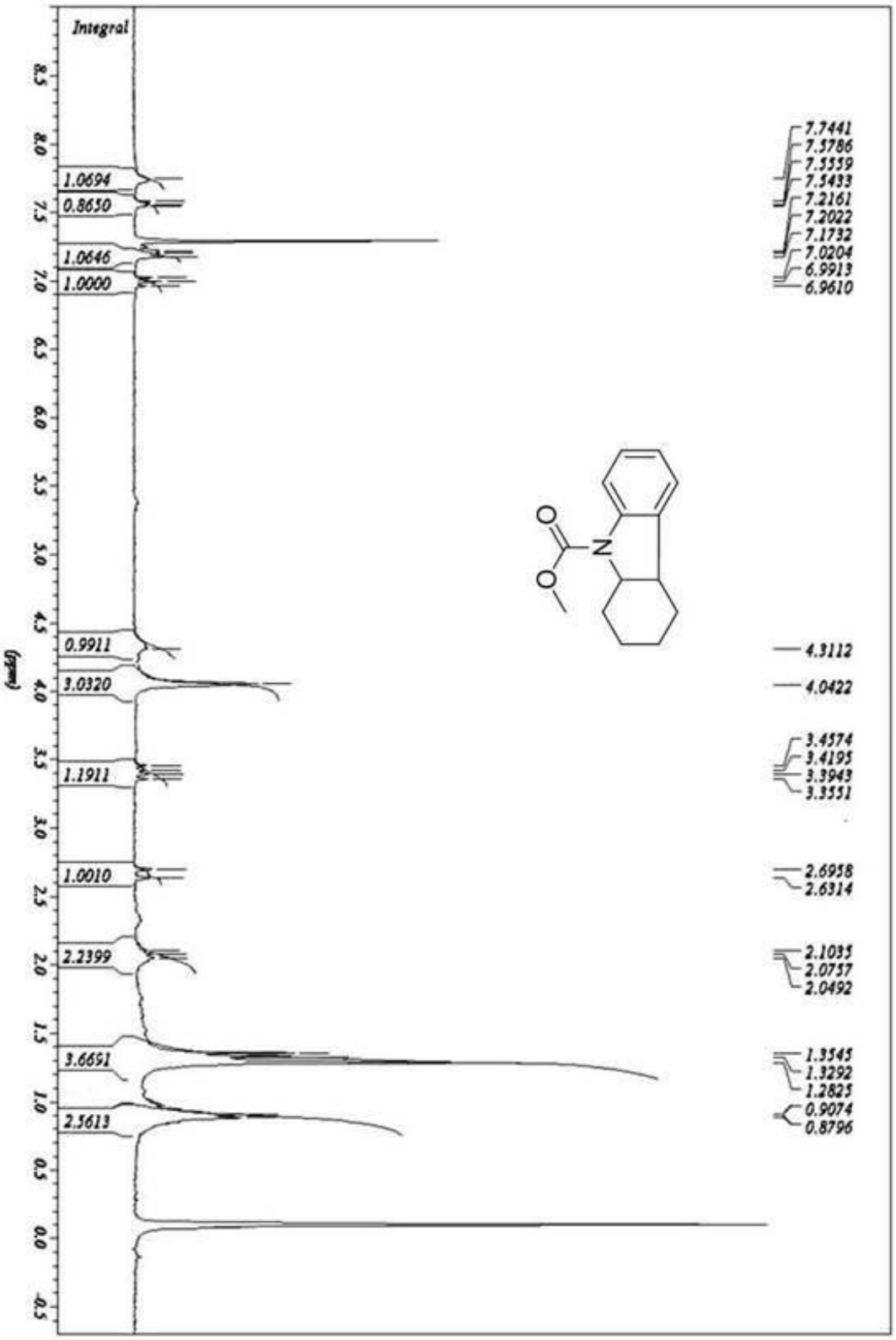
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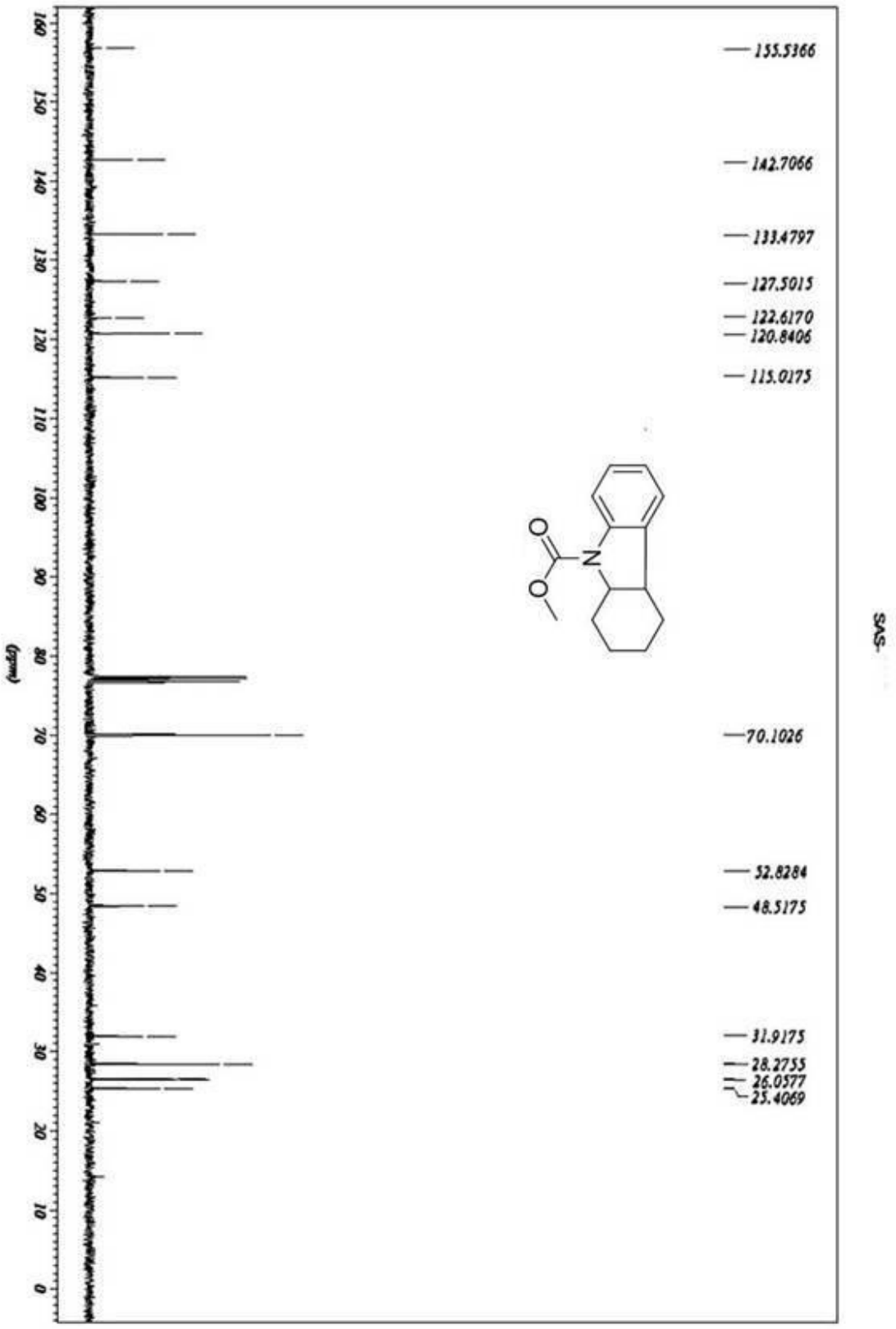
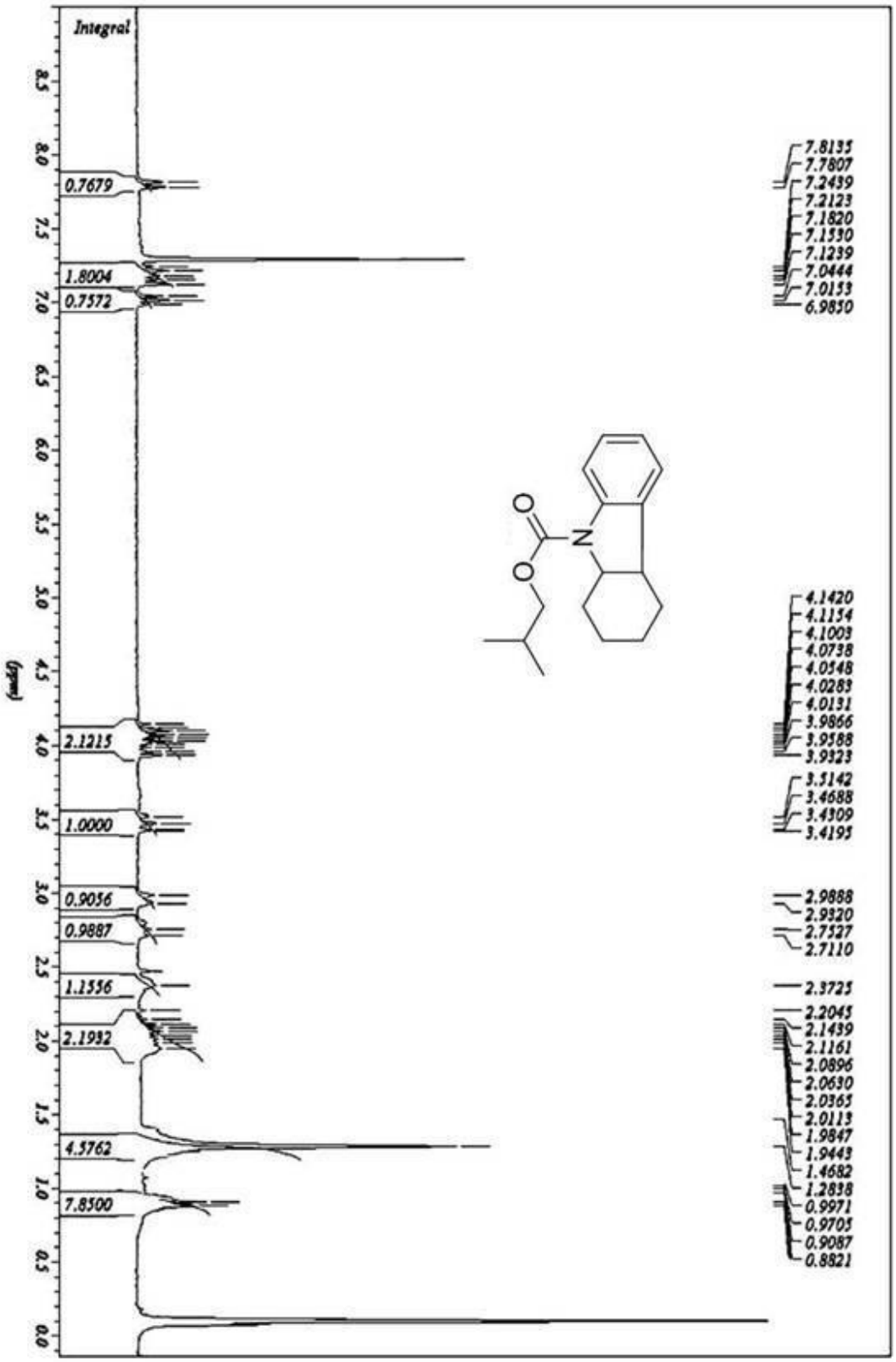
1.0010
2.2399
3.6691
2.5613
7.7441
7.5786
7.5559
7.5433
7.2161
7.2022
7.1732
7.0204
6.9913
6.9610
4.3112
4.0422
3.4574
3.4195
3.3943
3.3551
2.6958
2.6314
2.1035
2.0757
2.0492
1.3545
1.3292
1.2825
0.9074
0.8796
SAS-193-1


155.5366
142.7066
133.4797
127.5015
122.6170
120.8406
115.0175
70.1026
52.8284
48.5175
31.9175
28.2755
26.0577
25.4069
(ppm)
SAS


Integral
0.7679
1.8004
0.7572
2.1215
1.0000
0.9056
0.9887
1.1556
2.1932
4.5762
7.8500
7.8135
7.7807
7.2439
7.2123
7.1820
7.1530
7.1239
7.0444
7.0153
6.9850
4.1420
4.1154
4.1003
4.0738
4.0548
4.0283
4.0131
3.9866
3.9588
3.9323
3.5142
3.4688
3.4309
3.4195
2.9888
2.9320
2.7527
2.7110
2.3725
2.2045
2.1439
2.1161
2.0896
2.0630
2.0365
2.0113
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1.9443
1.4682
1.2838
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0.9705
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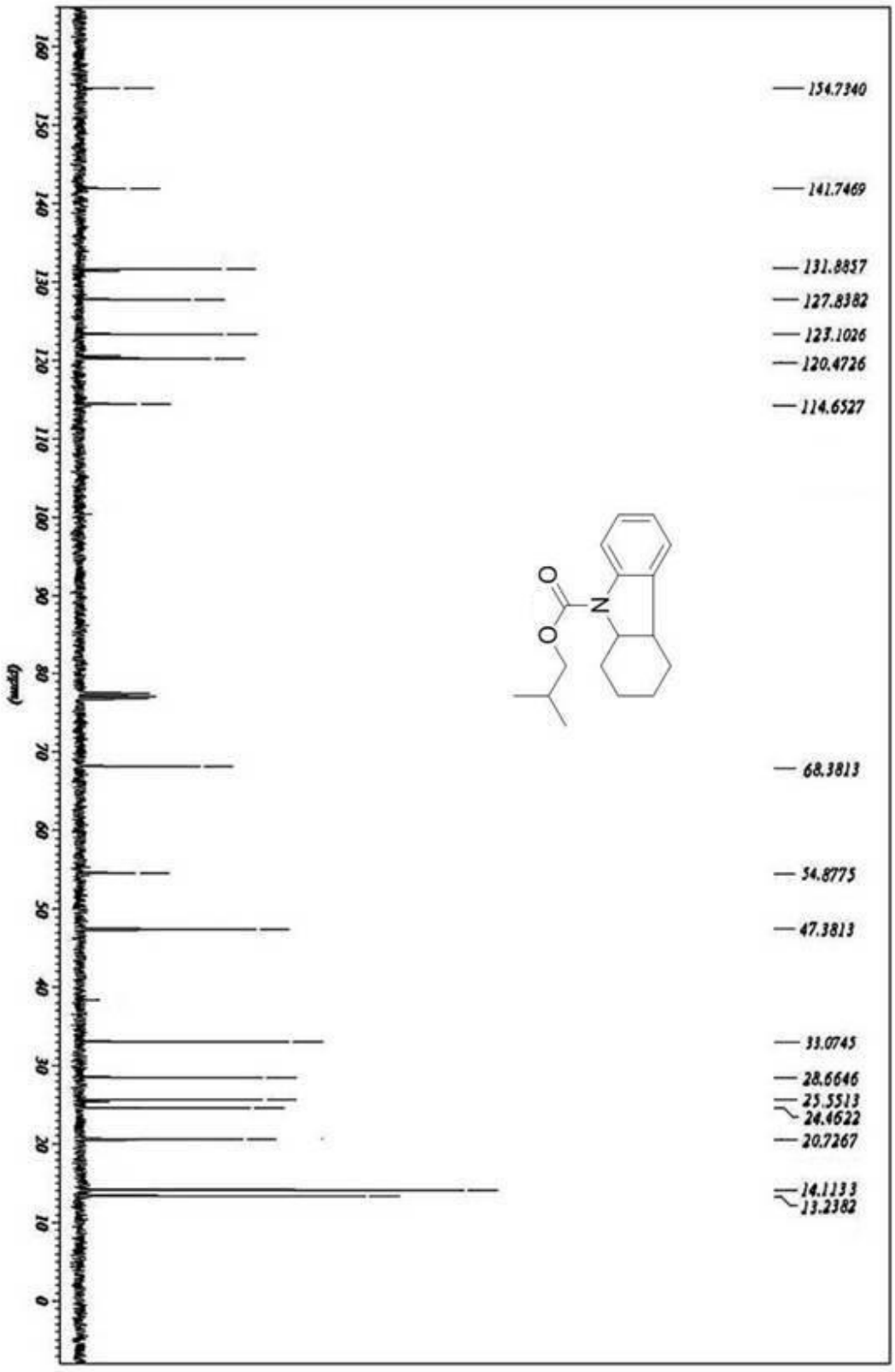
0.8821
BAS-244-1



Chromatogram for compound 2a

Column : OJ-H
Solvent : Hex/^{i}PrOH 99/1,
Flow : 1 mL/min,
Wavelength : 254 *nm*