

A DMAP Catalyzed Approach to the Industrial Scale Preparation of N-6-Demethylated 9,10-Dihydrolysergic Acid Methyl Ester: a Key Cabergoline and Pergolide Precursor

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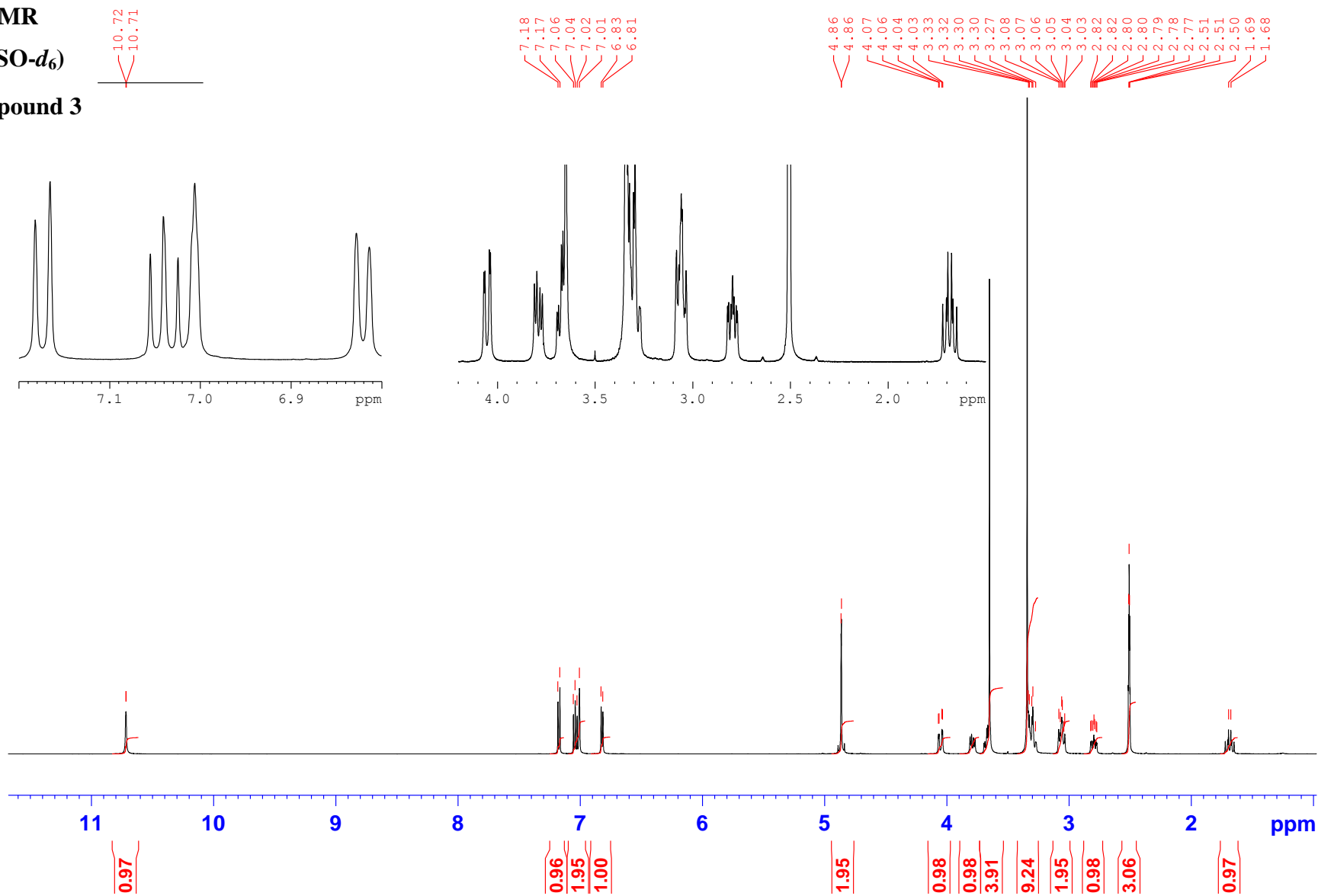
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^1H NMR

(DMSO- d_6)

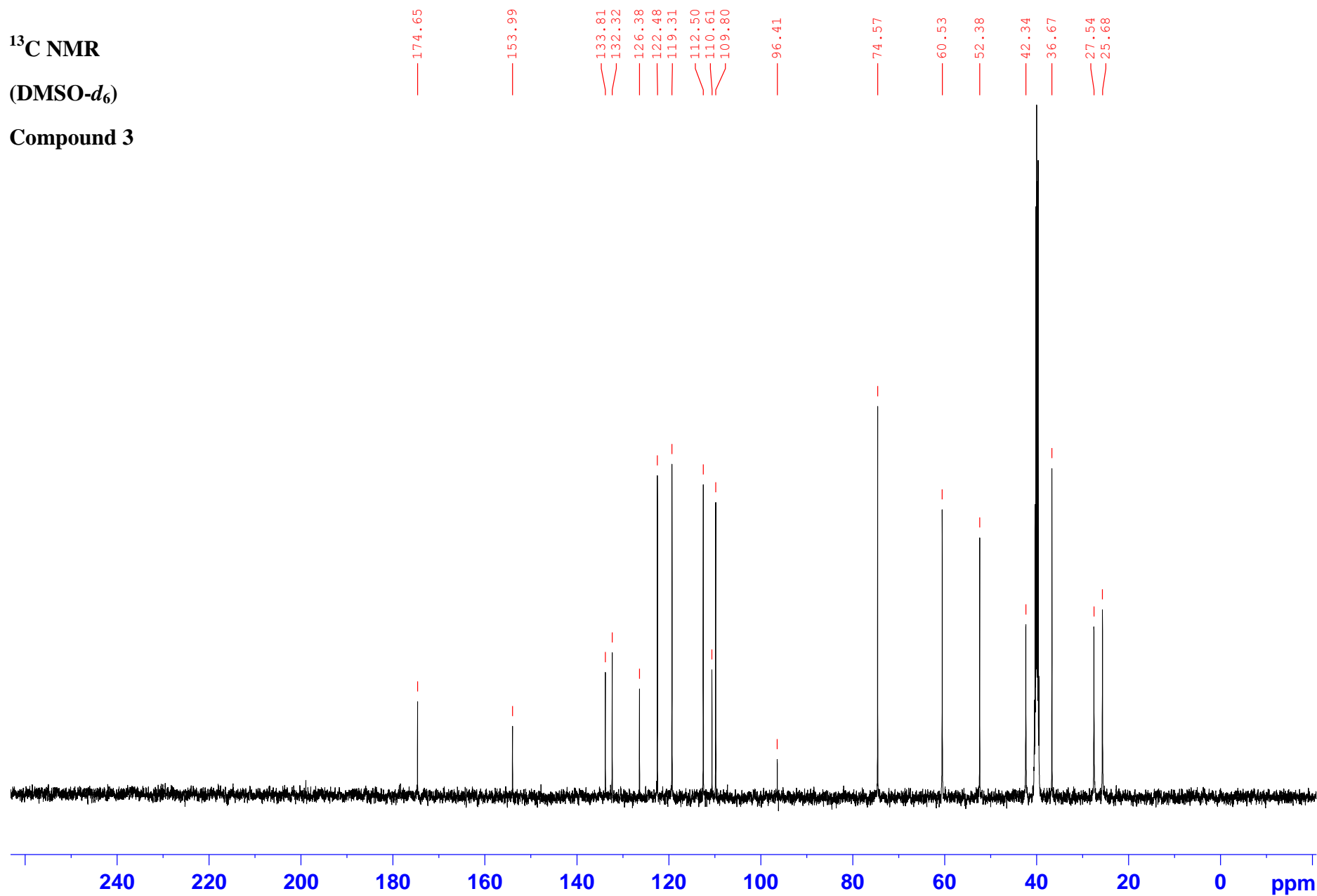
Compound 3



^{13}C NMR

(DMSO- d_6)

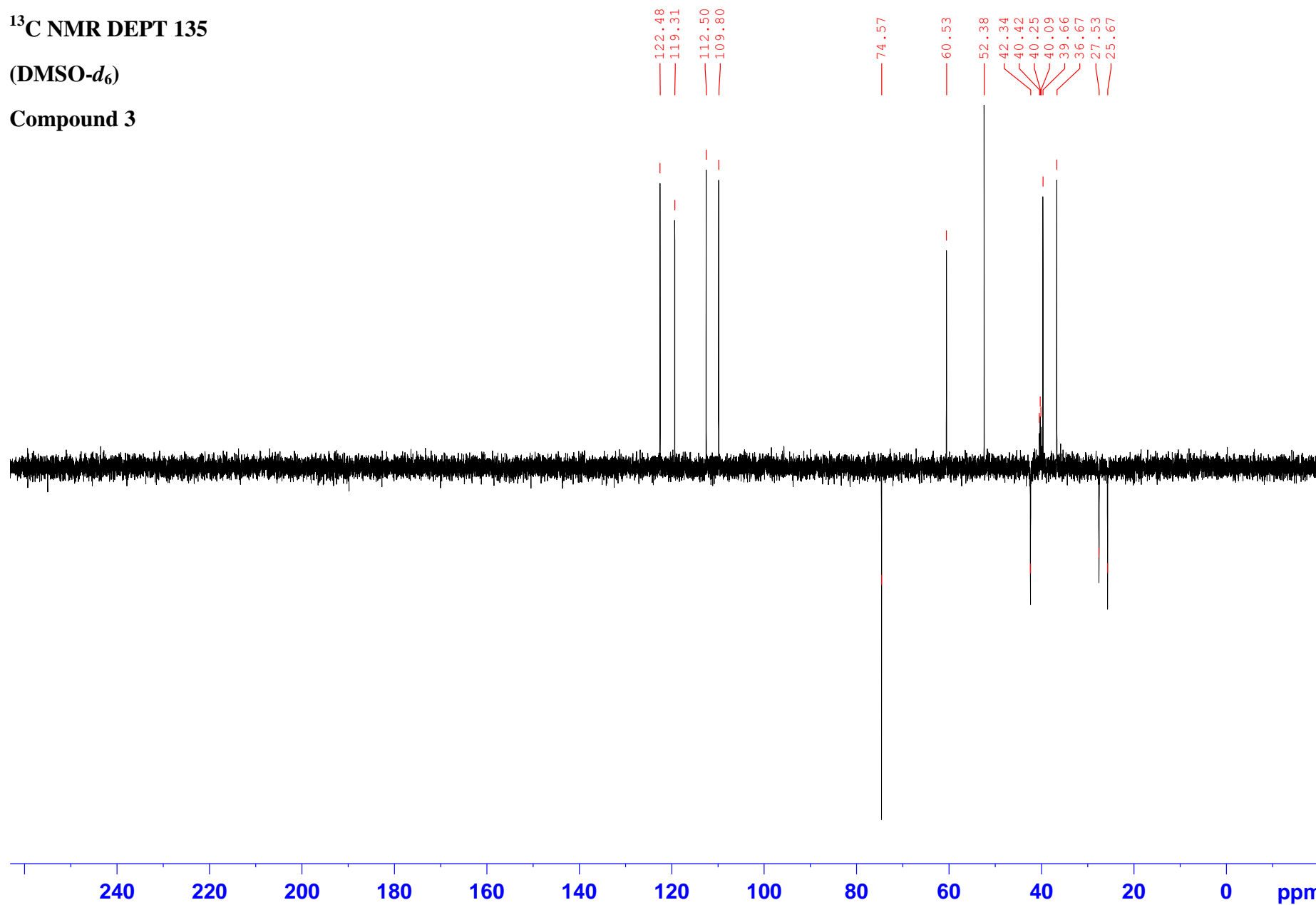
Compound 3



^{13}C NMR DEPT 135

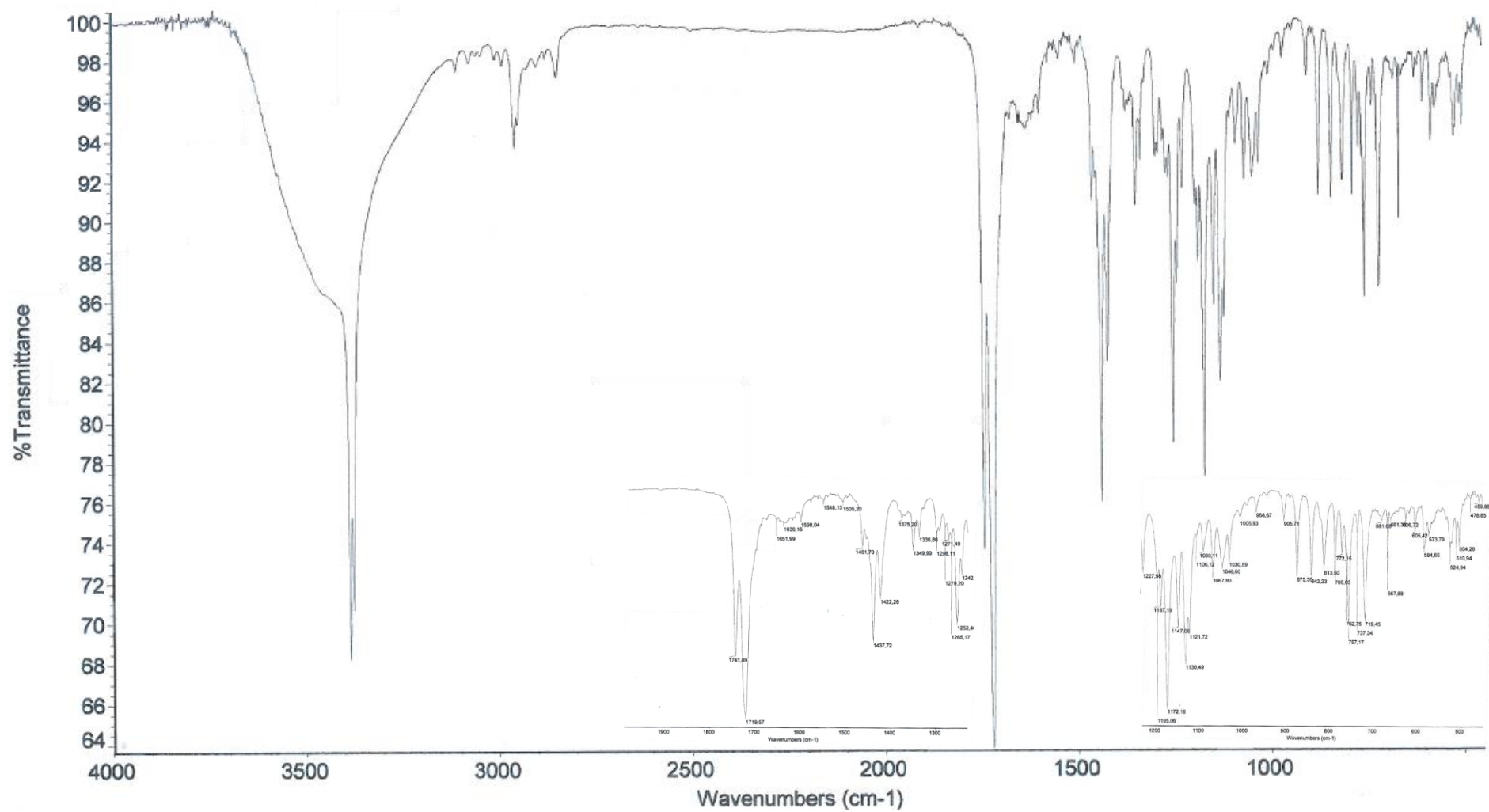
(DMSO- d_6)

Compound 3



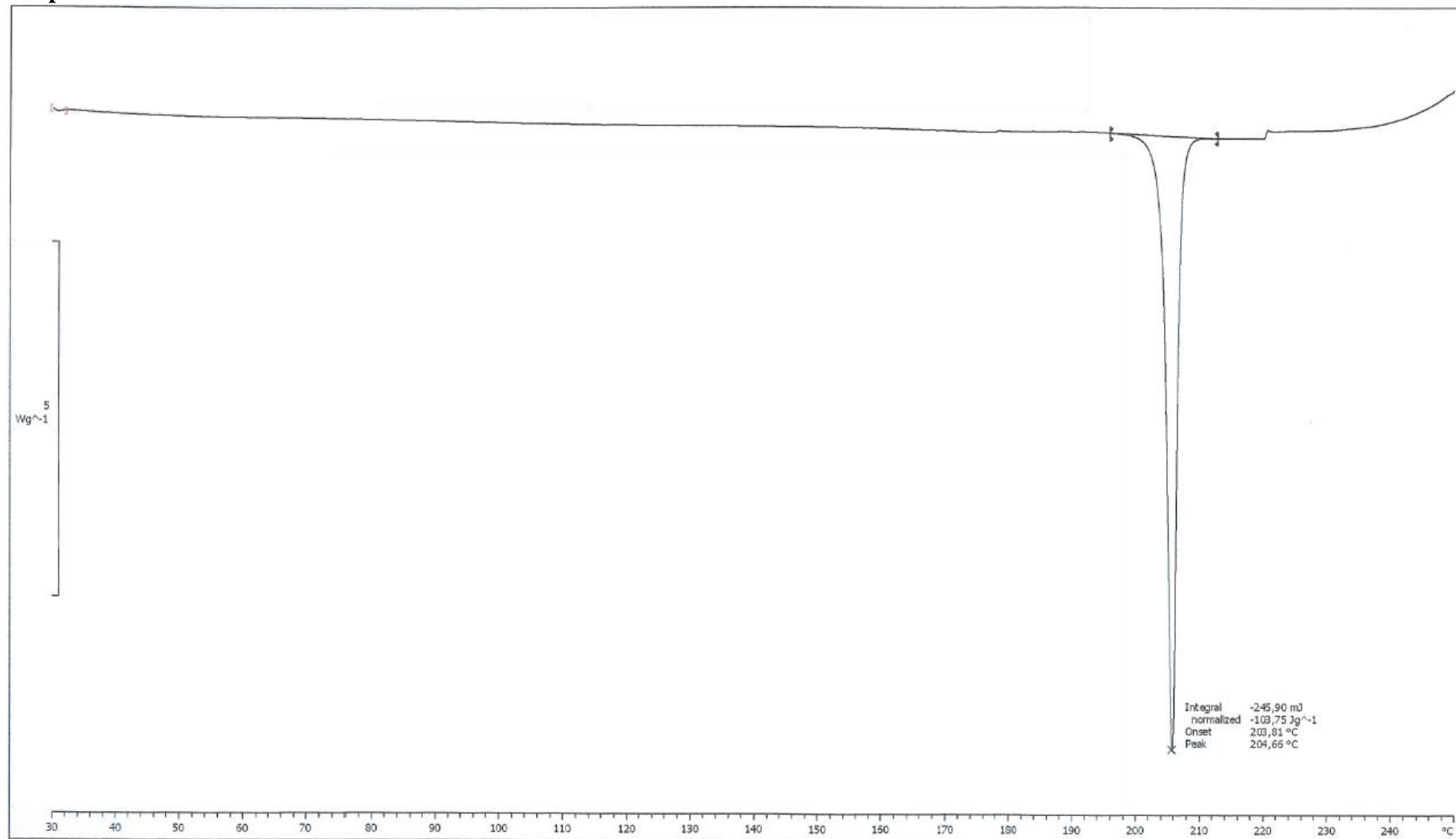
IR spectra (KBr disk)

Compound 3



DSC thermogram

Compound 3



Comparative experimental procedures and reaction kinetic data for demethylation of 1 to 3 with 2

1. Repeated literature procedure from A. M. Crider *et al.*, *J. Pharm. Sci.* 1981, 70, 1319-1321:

“6-Nor-6-(2,2,2-trichloroethoxycarbonyl)-9,10-dihydrolysergic acid methyl ester

A mixture of 9,10-dihydrolysergic acid methyl ester (0.425 g, 0.0015 mol), potassium bicarbonate (0.729 g, 0.0073 mol), and 2,2,2-trichloroethyl chloroformate 2 (0.619 g, 0.0029 mol) in 60 mL of absolute dichloromethane was refluxed for 24 hours. 2,2,2-Trichloroethyl chloroformate 2 (1.48 g, 0.0070 mol) was added and refluxing was continued for an additional 24 hours. The reaction mixture was cooled, filtered, and evaporated under reduced pressure to yield a white solid. Recrystallization from absolute methanol gave 0.602 g (90%) of crystalline product, mp 208-210°; IR(KBr): 3485 (N-H, indole) and 1740 (C=O, ester an carbamate) cm^{-1} ; NMR (dimethyl sulfoxide- d_6): δ 3.70 (s, 3H, COOCH_3), 4.90 (s, 2H; OCH_2CCl_3), 6.67-7.20 (m, 4H, aromatic), and 7.27 (s, 1H, NH). Anal.-Calc. For $\text{C}_{19}\text{H}_{19}\text{Cl}_3\text{N}_2\text{O}_4$: C, 51.19; H, 4.30; Cl, 23.86; N, 6.29. Found: C, 51.14; H, 4.20; Cl, 24.21; N, 6.13.”

Two batches were performed according to the above described original procedure of Crider *et al.* on 2.13 g scale:

2.13 g of **1**

3.645 g of KHCO_3

300 mL of CH_2Cl_2

2.01 mL of **2** reflux 24 h

4.80 mL of **2** reflux 24 h

First batch

Kinetics of the reaction:

t (h)	1 [HPLC A%]	3 [HPLC A%]
4	93.69	5.55
24	81.70	15.54
29	73.71	25.32
48	62.95	35.85

Second batch

Kinetics of the reaction:

t (h)	1 [HPLC A%]	3 [HPLC A%]
4	93.08	5.53
24	83.77	15.53
29	73.53	25.54
48	49.38	50.62

The reaction mixture was cooled, filtered, and evaporated under reduced pressure to yield a white solid.

Recrystallization from absolute methanol gave:

first batch: 1.02 g (30%) of crystalline product **3**; HPLC: 99.67 area%

second batch: 1.16 g (35%) of crystalline product **3**, HPLC: 99.40 area%

2. Optimized chemical reaction system, lab scale (5 g).

A gradual addition of 2, the use of sodium bicarbonate and filtration of the reaction mixture over the aluminium oxide.

5.00 g (17.58 mmol) of 9,10-dihydrolysergic acid methyl ester **1** was dissolved in 200 mL of absolute dichloromethane, after 7.2 g (85.8 mmol) of sodium bicarbonate were added and mixture was heated to reflux. Then 16.5 mL ($\rho = 1.539$ g/mL, 25.39 g, 120 mmol) of 2,2,2-trichloroethyl chloroformate were slowly added in 24 hours. After complete addition the reaction mixture was refluxed further for 24 hours. After 48 hours the reaction mixture was cooled, filtered over aluminium oxide (10 g), washed with 150 mL of dichloromethane and evaporated under reduced pressure and 50 mL of absolute methanol were added and stirred for 2 hours. Crystalline product was filtered and dried to yield a 5.92 g (76%) of product **3** as a white solid.

Kinetics of the reaction:

t [h]	1 [HPLC A%]	3 [HPLC A%]
2	95.35	3.95
4	90.45	8.68
6	84.00	16.00
8	71.59	27.81
13	49.95	49.41
22	23.98	72.58
31	17.27	81.09
48	15.69	83.25

3. Optimized chemical reaction system, kilo lab scale (600 g).

A gradual addition of 2, the use of sodium bicarbonate, azeotropic distillation of dichloromethane before the addition of 2, an additional excess of 2, a prolonged reaction time, filtration of the reaction mixture over aluminium oxide and the use hexane for the precipitation of the product.

600 g (2.11 mol) of 9,10-dihydrolysergic acid methyl ester **1** was dissolved in 24 L of absolute dichloromethane, after 864 g (10.3 mol) of sodium bicarbonate were added. The obtained mixture was heated to reflux and ca. 2 L of dichloromethane was distilled off. Then 2.515 L ($\rho = 1.539$ g/mL, 3.87 kg, 18.3 mol) of 2,2,2-trichloroethyl chloroformate were added in four portions ($t_{0h} = 640$ mL, $t_{11.5h} = 625$ mL, $t_{28h} = 625$ mL, $t_{70h} = 625$ mL). Reaction mixture was refluxed for 90 hours, and then the reaction mixture was cooled, filtered over aluminium oxide (6.2 kg), washed with 20 L of dichloromethane and evaporated under reduced pressure to 4 L. After, 4.5 L of *n*-hexane were added and stirred for 2 hours at 0 °C. Crystalline product was filtered and dried to yield a 553 g (59 %) of product **3** as white solid.

Kinetics of the reaction:

t [h]	1 [HPLC A%]	3 [HPLC A%]
4	75.15	22.47
12	54.02	42.98
28	26.53	71.05
70	21.45	75.04
72.5	19.45	71.35
90	17.90	76.80

4. Optimized chemical reaction system, pilot scale (4.6 kg).

The use of sodium bicarbonate, a prolonged reaction time, filtration of the reaction mixture over the aluminium oxide and the use hexane for the precipitation of the product.

Dry nitrogen inertized 250 L reactor was charged with 4.6 kg (16.18 mol) **1**, 6.6 kg (78.56 mol) sodium bicarbonate and 210 kg of dry dichloromethane. Then 2,2,2-trichloroethyl chloroformate **2** (7.0 kg, 33.03 mol) was charged into the reactor. The mixture was heated to reflux and stirred at reflux for 92 hours. Additional quantity (18.5 kg, 87.32 mol) of 2,2,2-trichloroethyl chloroformate **2** was charged into the reactor gradually during the stirring at reflux. After the reaction mixture was cooled to 10 ± 5 °C and filtered through a pad of alumina. Fractions containing the product were collected, concentrated and cooled 10 ± 5 °C. Then heptane is added to the concentrated solution and the precipitated product was collected by centrifugation. After drying, 4.1 kg (56%) of product **3** was obtained.

Kinetics of the reaction:

t [h]	1 [HPLC A%]	3 [HPLC A%]
0	100	0
4	78.16	21.27
20,5	50.98	48.74
27	45.35	54.34
44	36.73	63.01
68.5	34.73	64.98
74	34.53	65.18
76.5	34.20	65.43
92	26.84	72.70

5. Head to head comparison of literature known process and application of organic base catalysis

The following two experiments were performed on the same scale, the same solvent and temperature regime were applied, all other reagents were added in the same amount and the reaction time was the same.

	KHCO ₃ mediated process	DMAP catalyzed process
Procedure	A 2000 mL flask containing a 1400 mL of dry dichlorometane 10.0 g (30.3 mmol) of 1 (unstoichiometric toluene solvate), 17.15 g (171.3 mmol) of KHCO ₃ and 9.25 mL ($\rho = 1.539$ g/mL, 14.24 g, 67.2 mmol) of 2,2,2-trichloroethyl chloroformate 2 were added. The mixture was heated to reflux and refluxed for 24 hours. 22 mL ($\rho = 1.539$ g/mL, 33.9 g, 159.8 mmol) of 2,2,2-trichloroethyl chloroformate 2 was added and refluxing was continued for additional 24 hours. After the reaction mixture was cooled, filtered and evaporated under reduced pressure to yield a white solid. Product was crystallized from 120 mL of methanol and dried.	A 2000 mL flask containing a 1400 mL of dry dichlorometane 10.0 g (30.3 mmol) of 1 (unstoichiometric toluene solvate), 200 mg (1.64 mmol) of DMAP and 9.25 mL ($\rho = 1.539$ g/mL, 14.24 g, 67.2 mmol) of 2,2,2-trichloroethyl chloroformate 2 were added. The mixture was heated to reflux and refluxed for 24 hours. 22 mL ($\rho = 1.539$ g/mL, 33.9 g, 159.8 mmol) of 2,2,2-trichloroethyl chloroformate 2 was added and refluxing was continued for additional 24 hours. After the reaction mixture was cooled, filtered and evaporated under reduced pressure to yield a white solid. Product was crystallized from 120 mL of methanol and dried.
Reactants	Dichlorometane: 1400 mL 1 : 10.0 g (87.4% assay); 30.7 mmol; 1.0 eq. 2 : (9.25 + 22 mL); 48.1 g; 227 mmol; 7.4 eq. KHCO ₃ : 17.15 g; 171 mmol; 5.6 eq.	Dichlorometane: 1400 mL 1 : 10.0 g (87.4% assay); 30.7 mmol; 1.0 eq. 2 : (9.25 + 22 mL); 48.1 g; 227 mmol; 7.4 eq. DMAP: 200 mg; 1.64 mmol; 0.05 eq.
m _(product)	8.01 g	9.52 g
Yield _(mol.)	58.5 %	69.5%
HPLC _(of the dried product)	3 : 98.84 area% 1 : 1.16 area%	3 : 96.50 area% 1 : 3.50 area%
Assay _(HPLC external standard)	83.9% (low assay is due to the carbonate impurities as evidenced by GC-MS analysis; see page S17-S24).	101.3%

The above head to head comparison clearly demonstrates favorable effect of an organic base catalyst on the outcome of the reaction. In particular, application of organic base catalyst instead of the KHCO_3 in the process described in A. M. Crider *et al.* in *J. Pharm. Sci.* **1981**, *70*, 1319-1321 has significant advantage. This advantage is reflected in 69.5% yield obtained when DMAP catalyst is used compared to 58.5% yield by in the literature known procedure where KHCO_3 is used. In addition, the product obtained via the literature known procedure has low assay (ca. 84%) due to the high level of carbonate impurities which are not detectable by HPLC but only through GC-MS analysis.

6. Head to head comparison of literature known and DMAP catalyzed process with application of water elimination procedure.

The use of organic catalyst can be further improved by appropriate design of the overall process by total elimination of water as disclosed in the process described below. Both experiments were performed on the same scale, the same solvent and temperature regime were applied, all other reagents were added in the same amount and the reaction time was the same. This clearly demonstrates favorable effect of DMAP catalyst on the outcome of the reaction.

	KHCO ₃ mediated process	DMAP catalyzed process
Procedure	A 1000 mL flask containing a 560 mL of dry dichlorometane was charged with 22.2 mL ($\rho = 1.539$ g/mL, 34.2 g, 161.3 mmol) 2,2,2-trichloroethyl chloroformate 2 at 20 °C. The mixture was heated to reflux and refluxed for 1 hour. After the mixture was cooled to 20 °C. The flask was purged with nitrogen and charged with 17.15 g (171.3 mmol) of KHCO ₃ at 20 °C. The obtained mixture was then stirred at 20 °C for 15 min. The flask was purged with nitrogen for 15 min. and charged with 10.0 g of 1 (toluene solvate) (30.3 mmol) at 20 °C. The obtained mixture was then heated to reflux and refluxed for 22 hours. After the reaction mixture was cooled to 10 ± 5 °C and filtered through a pad of alumina 1-2 cm. Dichloromethane was evaporated off and 200 mL of <i>n</i> -heptane was added and the precipitated product was collected by filtration. After drying 13.70 g of 3 is obtained.	A 1000 mL flask containing a 560 mL of dry dichlorometane was charged with 22.2 mL ($\rho = 1.539$ g/mL, 34.2 g, 161.3 mmol) 2,2,2-trichloroethyl chloroformate 2 at 20 °C. The mixture was heated to reflux and refluxed for 1 hour. After the mixture was cooled to 20 °C. The flask was purged with nitrogen and charged with 200 mg (1.64 mmol) of DMAP at 20 °C. The obtained mixture was then stirred at 20 °C for 15 min. The flask was purged with nitrogen for 15 min. and charged with 10.0 g of 1 (toluene solvate) (30.3 mmol) at 20 °C. The obtained mixture was then heated to reflux and refluxed for 22 hours. After the reaction mixture was cooled to 10 ± 5 °C and filtered through a pad of alumina 1-2 cm. Dichloromethane was evaporated off and 200 mL of <i>n</i> -heptane was added and the precipitated product was collected by filtration. After drying 13.55 g of 3 is obtained.
Reactants	dichlorometane: 560 mL 1 : 10.0 g (87.4%); 30.7 mmol; 1.0 eq. 2 : 22.2 mL; 161.3 mmol; 34.2 g; 5.2 eq. KHCO ₃ : 17.15 g; 171 mmol; 5.6 eq.	dichlorometane: 560 mL 1 : 10.0 g (87.4%); 30.7 mmol; 1.0 eq. 2 : 22.2 mL; 161.3 mmol; 34.2 g; 5.2 eq. DMAP: 200 mg; 1.64 mmol; 0.05 eq.
$m_{\text{(product)}}$	13.70 g	13.55 g
Yield (mol.)	100% (mixture of 1 and 2)	98.9%
HPLC <small>(of the dried product)</small>	3 : 69.71 area% 1 : 30.21 area%	3 : 98.32 area% 1 : 1.68 area%
Assay <small>(HPLC external standard)</small>	73.8% (low assay is due to the unreacted 1 and carbonate impurities as evidenced by GC-MS analysis; see page S17-S24).	97.4%

When the new process using water elimination procedure was used, the KHCO_3 mediated reaction was not complete, as evidenced by the presence of ca. 30% of starting **1** in the precipitated product. When this new concept was combined with DMAP organocatalysis, the reaction was complete and **3** was isolated in excellent 98.9% yield and high purity (> 97% assay).

7. Preparation of (**3**) by application of DMAP catalyst on pilot scale (reaction kinetics) (4.4 kg).

Kinetics of the reaction:

t [h]	1 [HPLC A%]	3 [HPLC A%]
0	100	0
1	90.87	8.71
2	63.55	36.10
4	53.10	46.32
6	34.28	65.07
8	30.20	69.14
10	27.12	71.77
12	20.38	78.44
14	15.98	83.34
18	12.39	86.01
20	12.08	86.62
22	11.67	86.90

8. Industrial process for the preparation of (3) using DMAP (reaction kinetics) on 51 kg scale.

Kinetics of the reaction:

t [h]	1 [HPLC A%]	3 [HPLC A%]
0	100	0
4	35.7	64.30
9	83.05	16.95
26	5.86	94.14
30	5.89	94.11

GC-MS chromatograms and spectra of 3 and mother liquors obtained after precipitation of 3

Analyses were conducted on the following instrument:

- Agilent G1888 Headspace Sampler
- Agilent 6890 gas chromatographic (GC) system
- Agilent, mass selective detector 5973 EI
- Agilent, mass selective detector 5973 EI
- GC/MSD ChemStation
- NIST/EPA/NIH Mass Spectral Library and Search Software

Sample preparation:

100 μ L of the reaction mixture was transferred into the 20 mL vial of the gas sampler (HS vial), reaction mixture was tempered (15 min) and through transport tube (transfer line) injected into 1 mL of gas phase.

Instrumental method:

Headspace sampler settings:

Agilent G1888 Headspace sampler

Temperature of the oven: 85 °C

Temperature of the loop: 100 °C

Temperature of the transport tube: 115 °C

Time of the GC cycle: 45 min

Time of the vial stabilization: 15 min

Time of the pressure build up in the vial: 0.20 min

Time of the loop charging: 0.20 min

Time of the loop stabilization: 0.05 min

Time of injection: 0.20 min

Vial shaking: strong

Pressure on the vial: 15 psi vial

Volume of injection: 1 mL of gas phase

Instrument: GC Agilent 6890

Capillary column: Phenomenex Zebron, ZB-5ms 30m \times 0.25mm \times 0.25 μ m

Injector: Volatiles interface, Split/splitless, split ratio 80:1, T = 250 °C.

Carrying gas: Helium, constant pressure 2.0 psi, (Average velocity: 28 cm/s)

Temp. gradient: 30 °C (5 min) $\xrightarrow{10^\circ\text{C}/\text{min}}$ 240 °C (10 min)

Tem. MSD Transfer Line: T = 280 °C (MSD Transfer Line)

MSD settings (MS ACQUISITION PARAMETERS):

Source : EI (Electron ionization)

Tune File : atune.u

Acquisition Mode : Scan [Low Mass: 15.0, High Mass: 550.0, Threshold: 150]

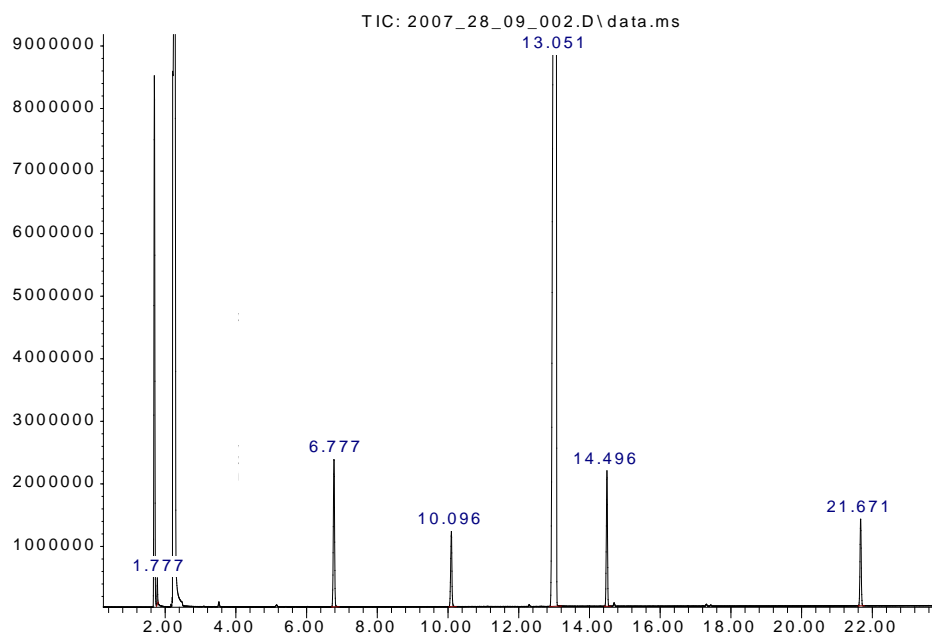
MS Source : 230 °C maximum 250 °C

MS Quad : 150 °C maximum 200 °C



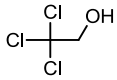
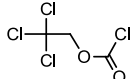
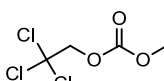
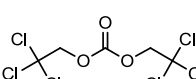
Reaction mixture after 33 h of reaction time in NaHCO₃ mediated demethylation reaction of **1** with **2**.

TIC chromatogram:

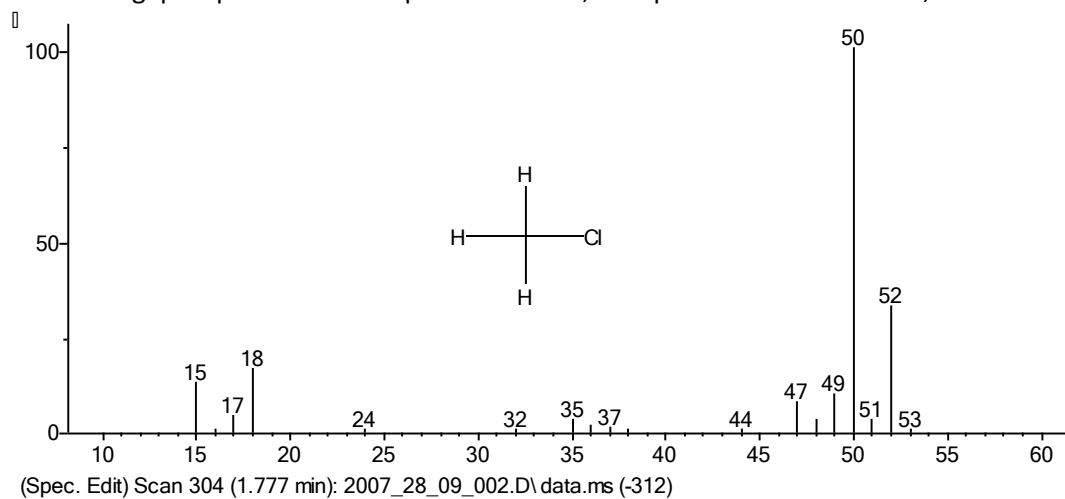
Abundance



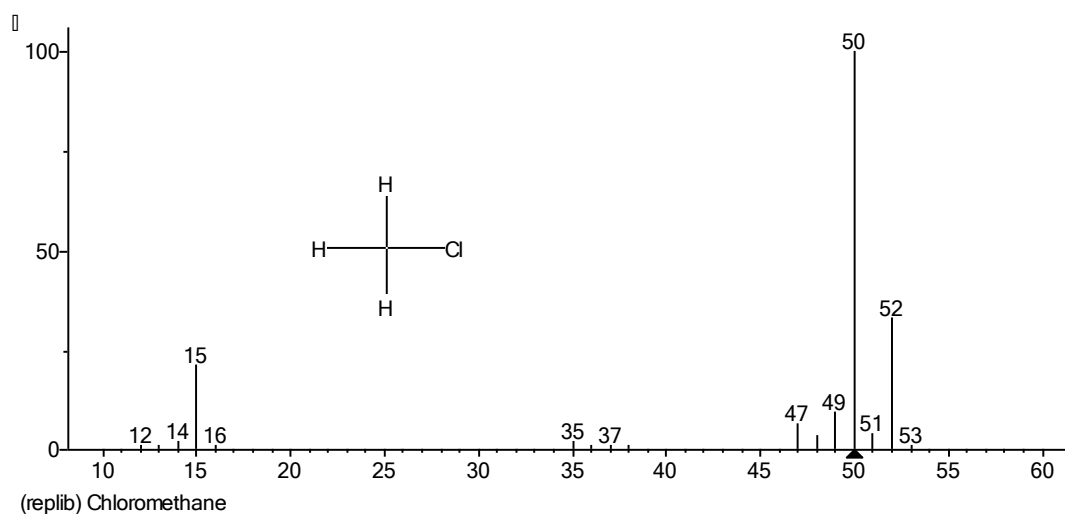
Toluene is detected in the reaction mixture, when **1** as toluene solvate is used as a starting material for the reaction.

Retention time [min]	Compound	Structure
1.78	Chloromethane	
6.78	Toluene	
10.10	Trichloroethanol	 II
13.05	2,2,2-trichloroethyl chloroformate	 2
14.50	methyl (2,2,2-trichloroethyl) carbonate	 IV
21.67	bis(2,2,2-trichloroethyl) carbonate	 III

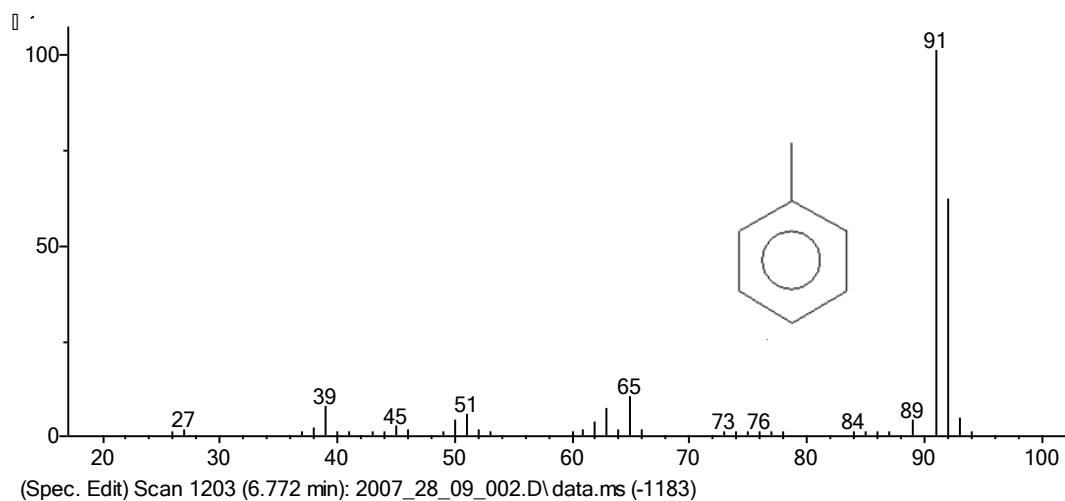
Chromatographic peak in the sample at 1.78 min, MS spectra Chloromethane, Mw = 50.49.



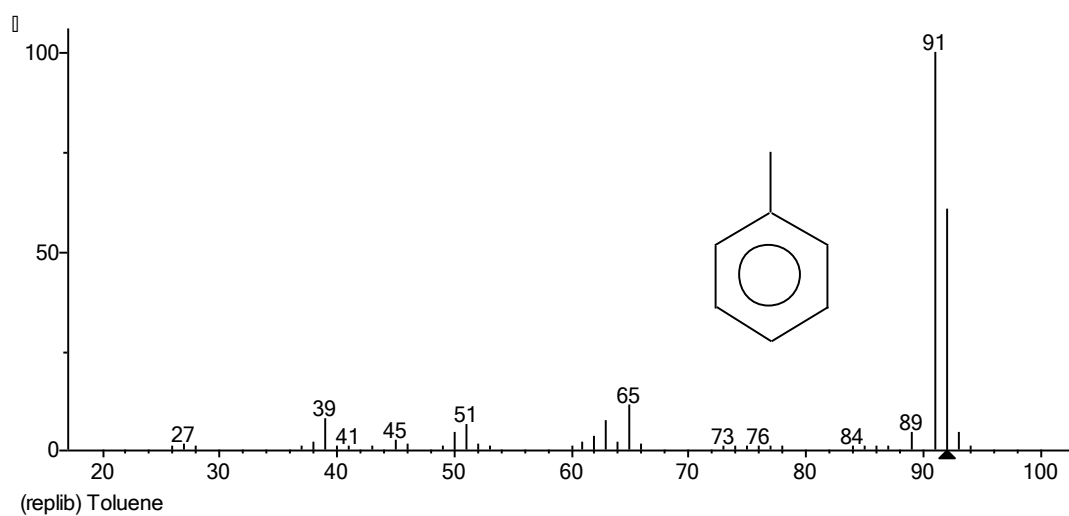
MS spectra Chloromethane, NIST library.



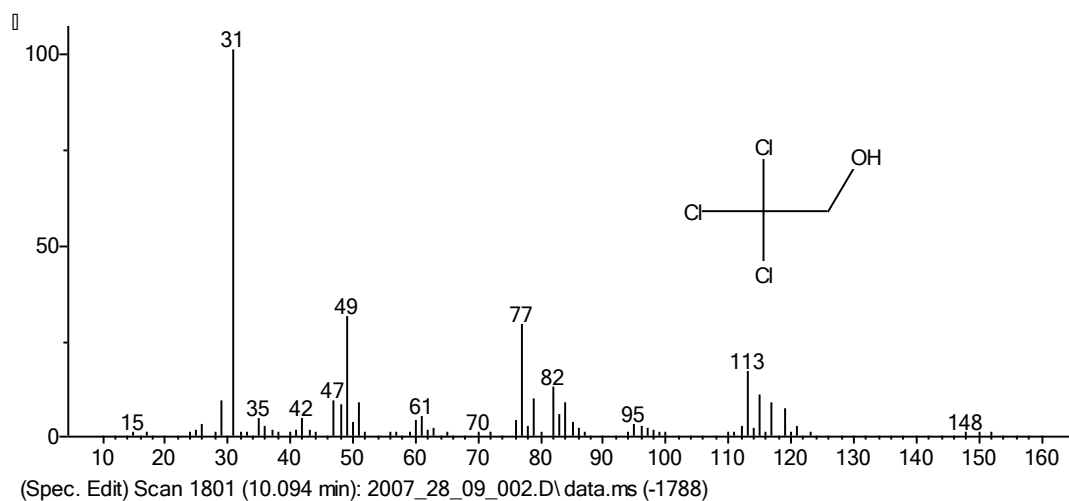
Chromatographic peak in the sample at 6.78 min, MS spectra Toluene, Mw = 92.14.



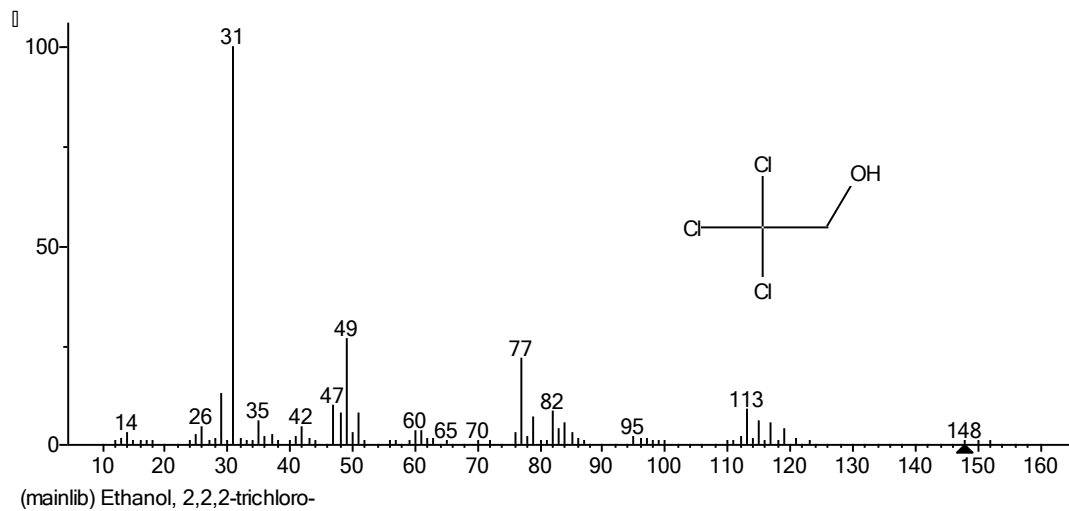
MS spectra Toluene, NIST library.



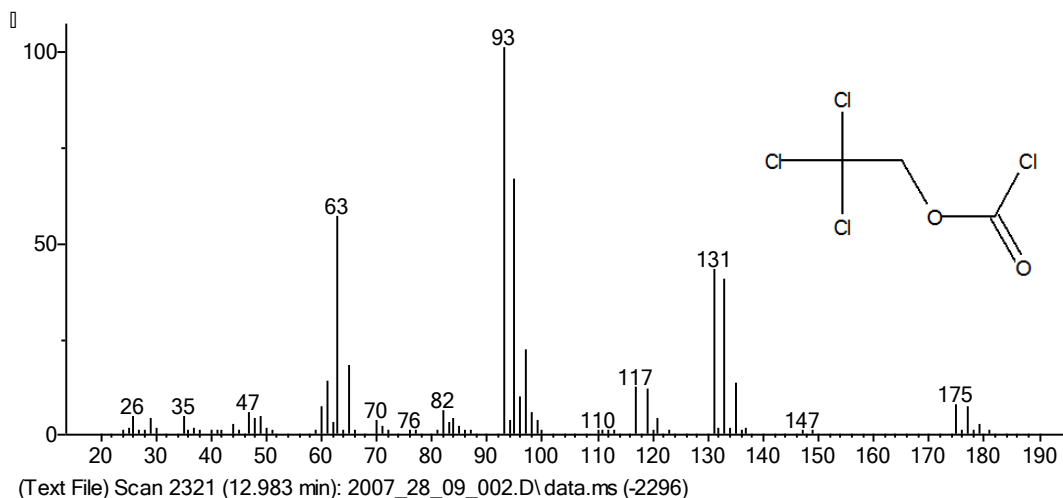
Chromatographic peak in the sample at 10.10 min, MS spectra Trichloroethanol II, Mw = 149.40.



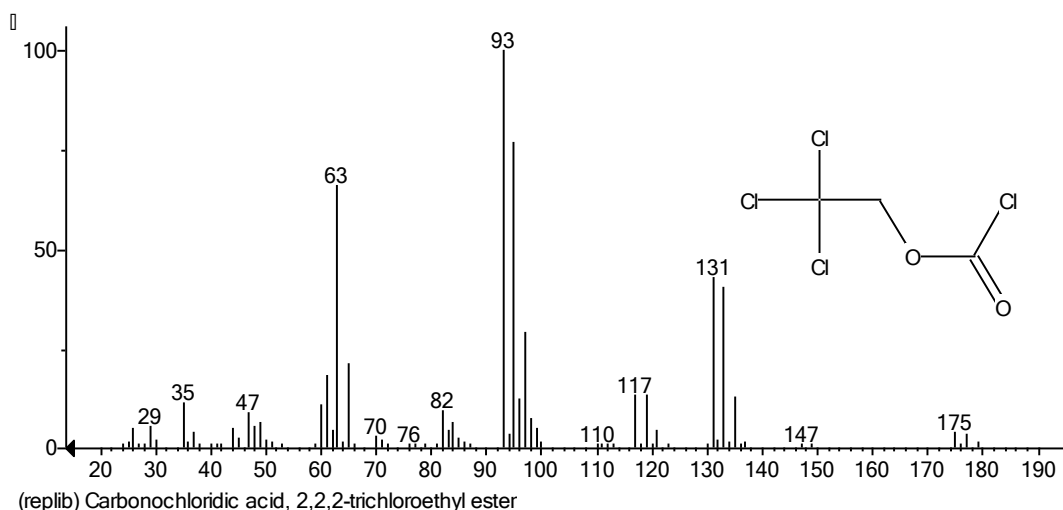
MS spectra Trichloroethanol II, NIST library.



Chromatographic peak in the sample at 13.05 min, MS spectra 2,2,2-trichloroethyl chloroformate **2**, Mw = 211.86.

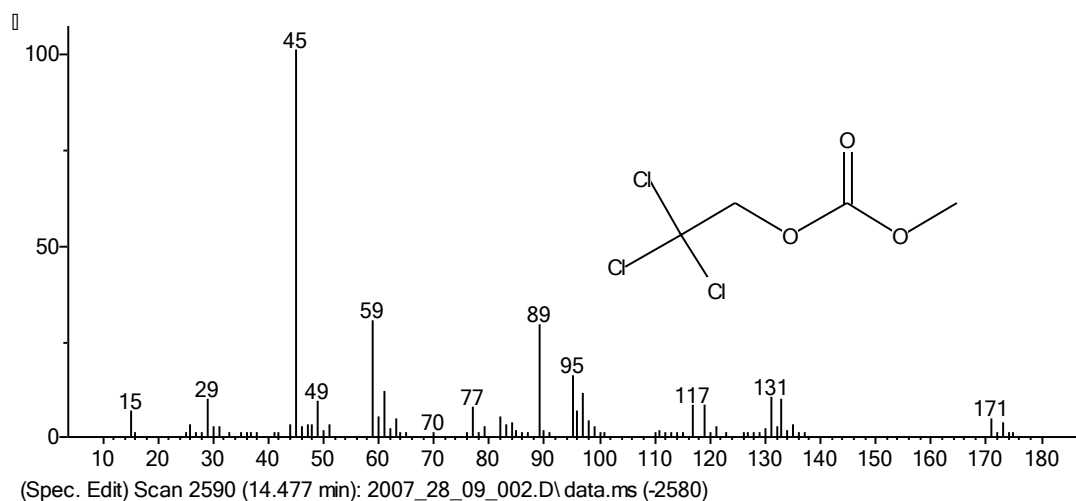


MS spectra 2,2,2-trichloroethyl chloroformate **2**, NIST library.

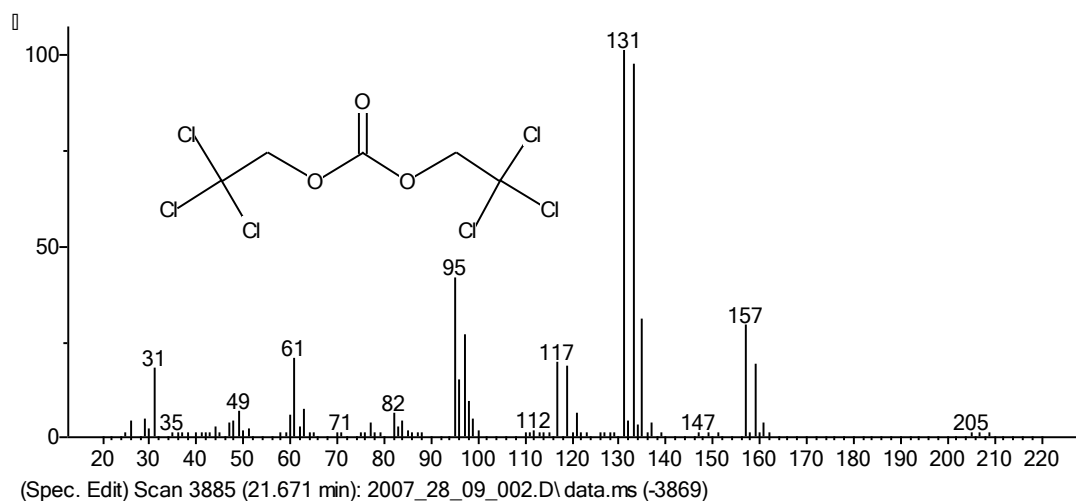


Chromatographic peak in the sample at 14.50 min, MS spectra methyl (2,2,2-trichloroethyl) carbonate **IV**, Mw = 207.44. Reference MS spectra of methyl (2,2,2-trichloroethyl) carbonate **IV** doesn't exist in NIST library.

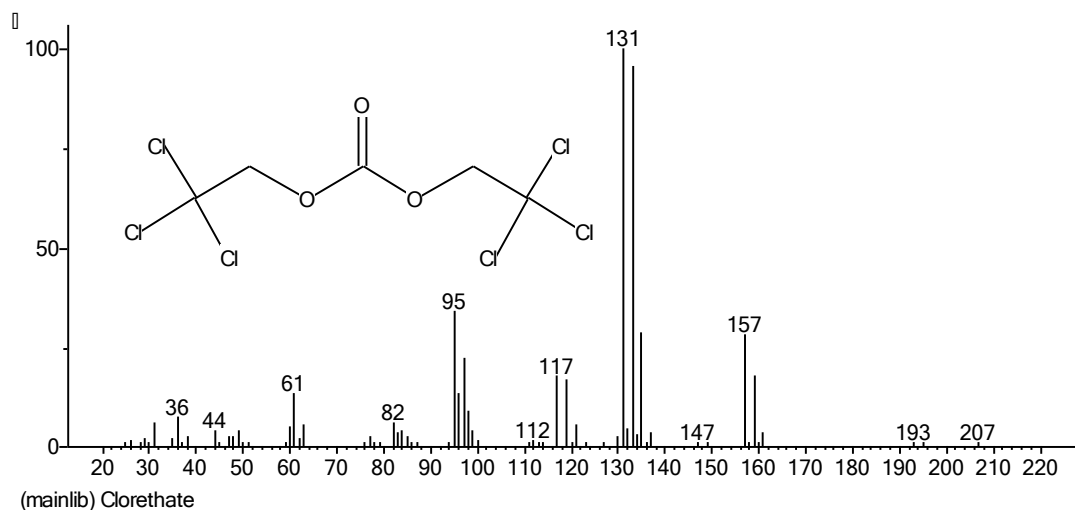
Note: $\text{Cl}_3\text{CCH}_2\text{Cl}$ (Mw = 167.85) as the other reasonable potential side product of the reaction has a lower molecular weight than the highest observed signal (171) in the mass spectrum of the compound with t_R at 14.5 min and also lower molecular weight than compound **IV** (207.44), which suggest that the side product with t_R at 14.5 min is probably compound **IV**. Furthermore, the bp of **II** is 152-154 °C and the bp of **2** is 171-172 °C, while the bp of $\text{Cl}_3\text{CCH}_2\text{Cl}$ is 138 °C. This suggest that $\text{Cl}_3\text{CCH}_2\text{Cl}$ should have the retention time lower than the one of **II** (t_R = ca. 10 min) and not the t_R over 14 min.



Chromatographic peak in the sample at 21.67 min, MS spectra bis(2,2,2-trichloroethyl) carbonate **III**
 Mw = 324.80.

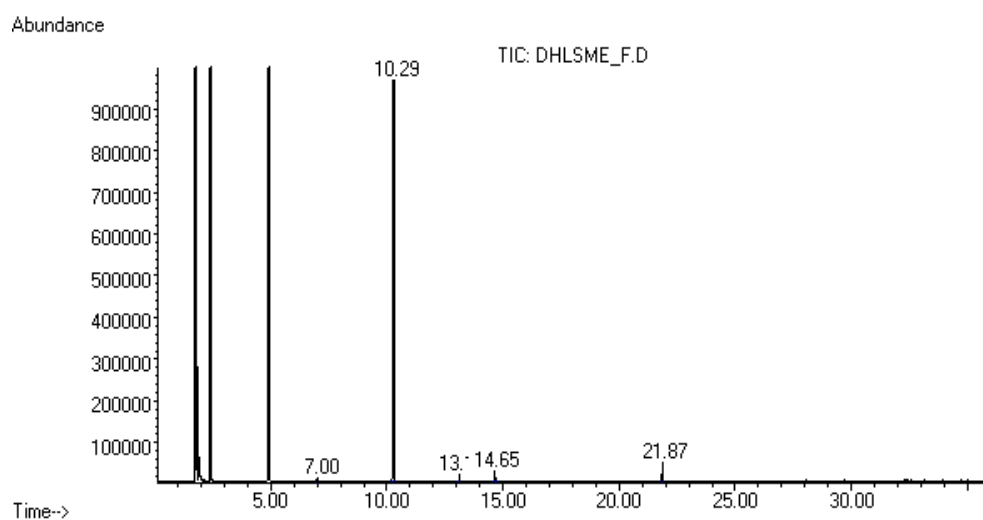


MS spectra bis(2,2,2-trichloroethyl) carbonate **III**, NIST library.



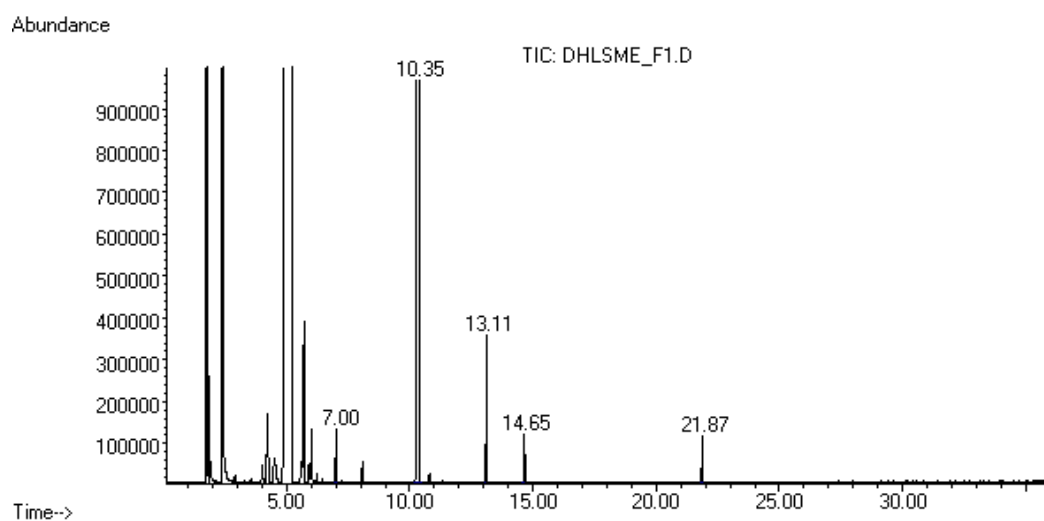
GC composition of sample of **3** after 20 hours of drying:

Peak#	Component	Ret. Time	Type	Width	Area	Start time	End time
1	PhMe	6.998	rm	0.097	27531	6.955	7.053
2	Cl ₃ CCH ₂ OH II	10.292	rm	0.219	5761403	10.194	10.414
3	Cl ₃ CCH ₂ OC(=O)Cl 2	13.105	rm	0.170	31337	13.014	13.184
4	Cl ₃ CCH ₂ OC(=O)OMe IV	14.651	rm	0.250	58230	14.560	14.810
5	[Cl ₃ CCH ₂ O] ₂ C(=O) III	21.867	rm	0.152	105222	21.812	21.964



GC composition of undried sample of **3**:

Peak#	Component	Ret. Time	Type	Width	Area	Start time	End time
1	PhMe	7.004	rm	0.134	310960	6.937	7.071
2	Cl ₃ CCH ₂ OH II	10.353	rm	0.359	20975912	10.201	10.560
3	Cl ₃ CCH ₂ OC(=O)Cl 2	13.105	rm	0.110	762941	13.044	13.154
4	Cl ₃ CCH ₂ OC(=O)OMe IV	14.652	rm	0.128	247779	14.591	14.719
5	[Cl ₃ CCH ₂ O] ₂ C(=O) III	21.867	rm	0.189	247413	21.788	21.977



GC composition of mother liquors obtained after precipitation and filtration of **3**:

Peak#	Component	Ret. Time	Type	Width	Area	Start time	End time
1	PhMe	7.065	rm	0.237	6610824	6.968	7.205
2	$\text{Cl}_3\text{CCH}_2\text{OH}$ II	10.365	rm	0.420	24062190	10.213	10.633
3	$\text{Cl}_3\text{CCH}_2\text{OC}(=\text{O})\text{Cl}$ 2	13.148	rm	0.341	23262042	13.057	13.398
4	$\text{Cl}_3\text{CCH}_2\text{OC}(=\text{O})\text{OMe}$ IV	14.689	rm	0.286	11313473	14.573	14.859
5	$[\text{Cl}_3\text{CCH}_2\text{O}]_2\text{C}(=\text{O})$ III	21.916	rm	0.378	38690081	21.794	22.172

