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Novel Synthetic Route to 5-Substituted Indoles

Helen Y. Chen

Loyola University Chicago

LOYOLA UNIVERSITY CHICAGO

A NOVEL SYNTHETIC ROUTE TO 5-SUBSTITUTED INDOLES

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HELEN Y. CHEN

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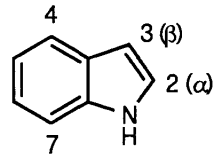
CONTENTS

LIST OF ABBREVIATIONS

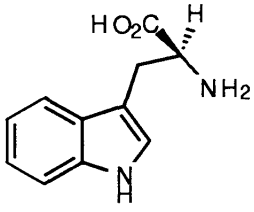
DME	Ethylene glycol dimethyl ether
DMF	N,N-Dimethylformamide
eq	equivalents
h	hours
NMP	1-Methyl-2-pyrrolidinone
PPA	Polyphosphoric acid
r.t.	room temperature

CHAPTER I

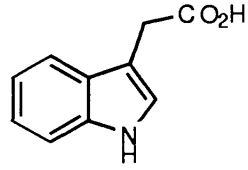
HISTORICAL INTRODUCTION



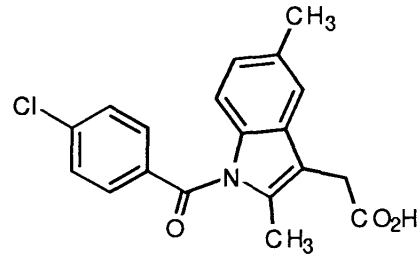
The indole skeleton, shown above, is one of the most widely distributed heterocyclic systems in nature. This ring system is not only present in dyes and alkaloids, but can also be found in the plant growth-regulating hormone indol-3-ylacetic acid, the essential amino acid tryptophan, and tryptamine. It is a building block for preparing a number of biologically active compounds including Indomethacin, one of the major treatments for rheumatoid arthritis, and several central nervous system depressants.



tryptophan



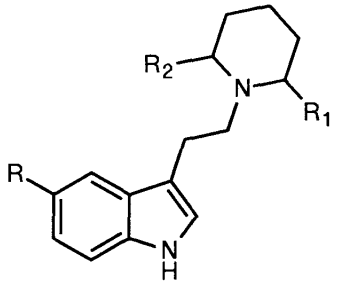
indol-3-ylacetic acid



Indomethacin

Substituted indoles are versatile intermediates in the synthesis of compounds possessing biological activity. For example, 5-substituted indoles have found their utility as starting materials in multi-step syntheses of several pharmaceutical drug targets. For instance, 5-bromoindole has been

used in the synthesis of selective serotonin (5-hydroxytryptamine) antagonists of the general formula ***1*** for the treatment of disorders of the central nervous system.[1] In the synthesis of peptidoleukotriene antagonists for the treatment of asthma, 5-nitroindole was alkylated to give, after a multi-step sequence of reactions, compounds with the general formula ***2***.[2]



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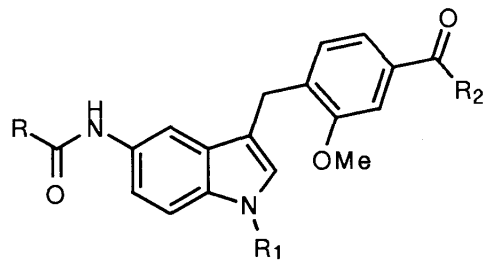
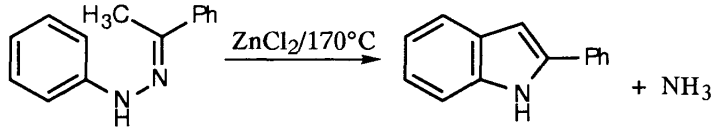


2

Due to their significance to biological systems, the indole nucleus has been a target and problem in organic synthesis for almost a century.[3] Perhaps the most widely explored and used route for the synthesis of indoles is the classical Fischer synthesis.[4] In its simplest form, the Fischer indole synthesis, first discovered in 1883, involves the acid-catalyzed rearrangement of an arylhydrazone, such as ***3***, with the liberation of ammonia.



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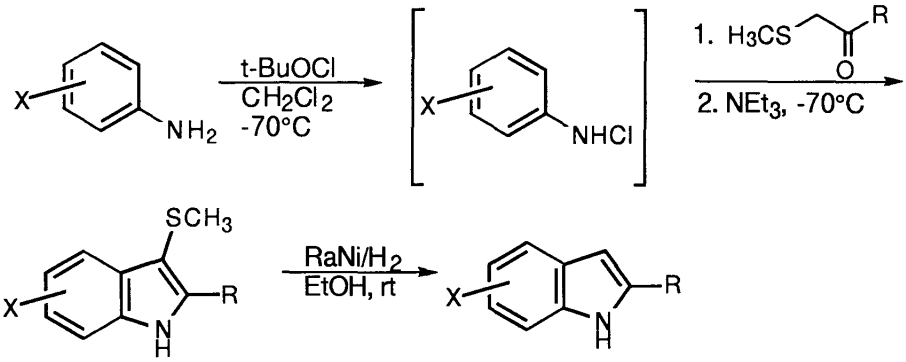
Although the Fischer synthesis is quite general, it is not applicable for the preparation of 2,3-unsubstituted indoles. In addition, for substitution in the 4, 5, 6, or 7 positions of the indole nucleus, the method requires the appropriately substituted arylhydrazones which are often not readily available.

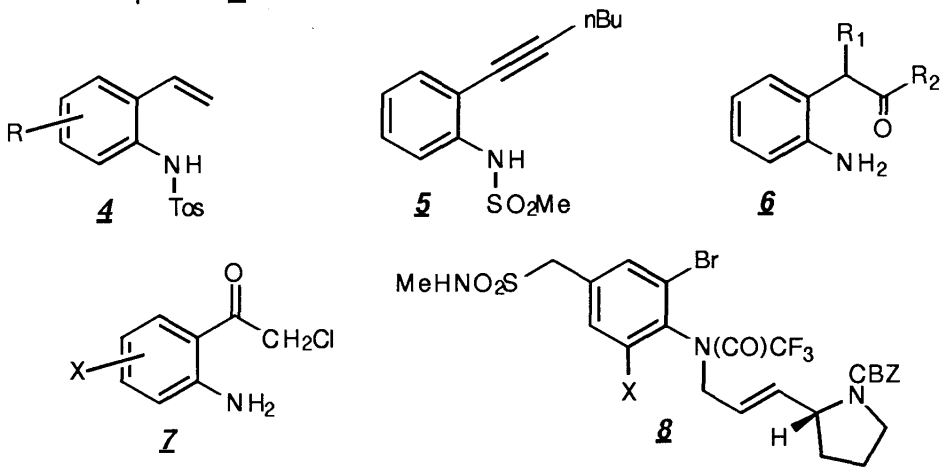
Therefore, an efficient conversion of commercially available anilines to indoles would be a useful synthetic goal. Several routes in the past have been developed to accomplish this. The Gassman indole synthesis[5] involves a one pot reaction in which hypohalite and base are added sequentially to an aniline to produce 3-thioalkoxyindoles. Raney-nickel reduction then yields the desulfurized indole.



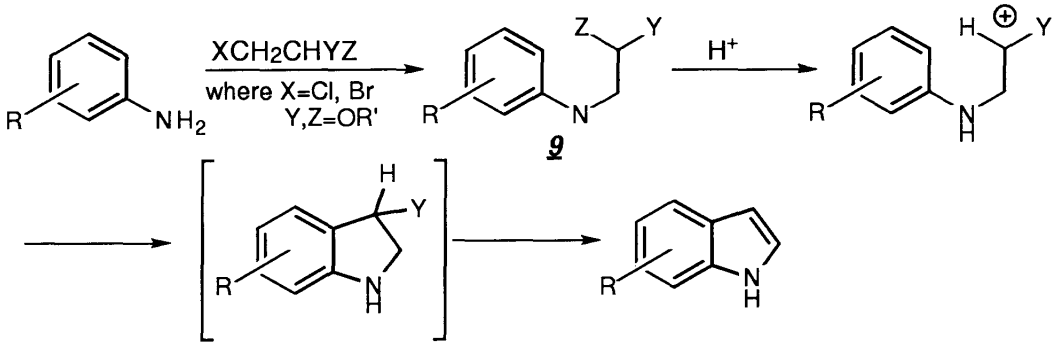
The Gassman synthesis has good generality not only for 2-substituted indoles, but also for 2,3-unsubstituted indoles. One major drawback of this route, however, is its ineffectiveness in preparing indoles such as 5-methoxyindole and 7-methoxyindole. Both the Fischer and the Gassman methods require a sigmatropic rearrangement to effect the crucial ortho substitution.

Other syntheses that convert anilines to indoles depend on having the appropriate ortho substituent built into the reactant. Although these routes tend to be regioselective, like the Fischer indole synthesis, the availability of starting materials is again a cause for concern. Some of these syntheses[6] include cyclization of 2-vinyl-N-tosylanilines (***4***) in the presence of a Pd(II) catalyst[7], palladium-catalyzed cyclization of o-alkynylanilines (***5***)[4], generation of ortho-(2-oxoalkyl)anilines (***6***)[8] from a $S_{RN}1$ reaction of o-iodoaniline followed by intramolecular cyclization, reductive cyclization of o-

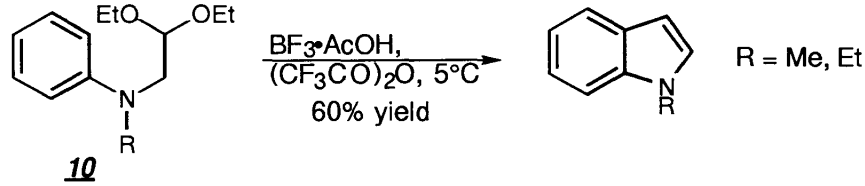
chloroacetylated anilines (***7***)[9], and cyclization via an intramolecular Heck reaction on compound ***8***[10].



Another conceptually attractive approach to indoles from anilines involves cyclization of α-anilino acetals (***9***) via an acid-catalyzed intramolecular electrophilic aromatic substitution. α-Anilino acetals can be obtained simply by treating the corresponding aniline with acetal derivatives of an α-haloaldehyde.

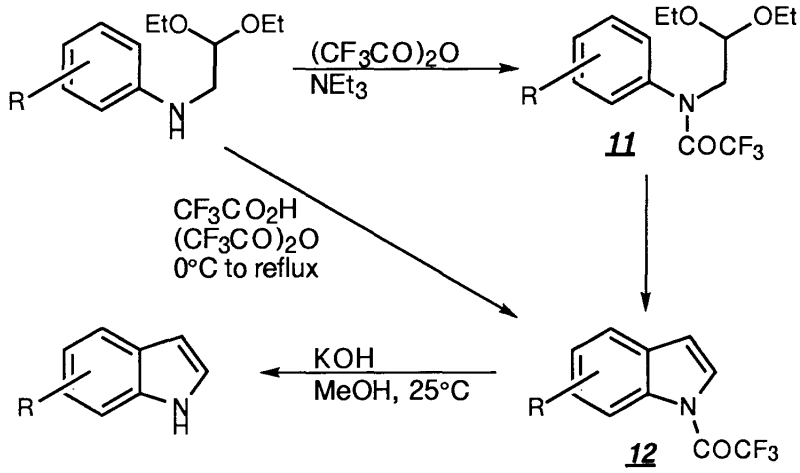


Initially, only limited success was obtained by Forbes and co-workers, who observed that cyclizations only occurred for N-alkylated acetals ***10***.[11]



In general, good yields (60% and above) were obtained for 4-methoxy-N-methylindole and 6-methoxy-N-methylindole. As Sundberg and co-workers pointed out[12], the failed cyclization of N-unsubstituted indoles could be attributed to two potential problems associated with this approach. First, protonation or coordination at the free nitrogen would disfavor cyclization by retarding the desired electrophilic substitution. Secondly, N-unsubstituted indoles are unstable to protic and Lewis acid conditions so that subsequent reaction of the initial product could occur. In another instance, Jackson and co-workers[13] observed a considerable amount of polymerization after attempting cyclization of an N-unsubstituted system, *m*--methoxyanilinoacetaldehyde diethyl acetal, with dilute HCl in dioxane.

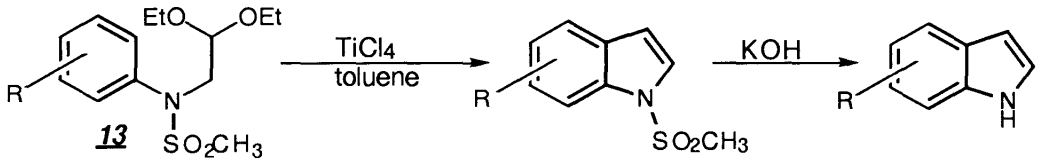
Not until recently did several groups, including Sundberg's and Nordlander's, demonstrate the feasibility of this approach for N-unsubstituted indoles. Nordlander[14] addressed the potential problems discussed above by developing the following scheme:



Appropriately substituted N-(trifluoroacetyl)-α-anilino acetals (***11***) produced N-(trifluoroacetyl)indoles (***12***) in high yields simply by refluxing with

trifluoroacetic acid and excess trifluoroacetic anhydride. By first incorporating the trifluoroacetyl group before cyclization, the basicity of the aniline nitrogen was decreased and the final product indole was stabilized. In addition, N-unsubstituted indoles could readily be obtained in quantitative yields by saponification of the initially-formed amide (***12***) with potassium hydroxide. For example, 5-methylindole was produced in 86% yield after 72 hours of heating. Unfortunately, the process failed for generating 7-substituted indoles and for substrates with electron withdrawing groups on the benzene ring (i.e. Br).

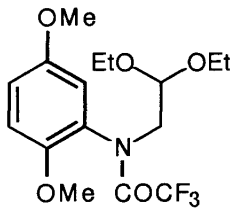
A few years later, Sundberg and co-workers[12] showed that the methanesulfonamide derivatives of N-(2,2-diethoxyethyl)anilines (***13***) could also be cyclized to indoles in aromatic solvents by treatment with titanium tetrachloride.



13

Like the trifluoroacetyl group, the methanesulfonyl group could then be removed simply by basic hydrolysis conditions. The temperature at which cyclization proceeded relied heavily on the nature of the substituents on the ring. For substrates with strongly activating groups, reaction occurred at 0°C; whereas, rings containing mildly deactivating substituents required heating to 110-130°C. Specifically, 5-methylindole was produced in 83% yield after heating at 110°C for 15-30 minutes. Interestingly, Sundberg also noted the failure of this approach towards the preparation of 7-substituted indoles.

The general concept of this method has recently been applied to the synthesis of several natural products for which other cyclization conditions have also been developed. For example, Cherif and colleagues[15] have shown that 4,7-dimethoxyindoles could be synthesized in 63% yield via cyclization of N-(trifluoroacetyl)-α-(2,5-dimethoxyanilino)acetaldehyde diethyl acetal (***14***) in refluxing xylene and PPA. Researchers at Banyu Pharmaceutical[16] have also successfully used this method in their total synthesis of a new topoisomerase II inhibitor BE 10988. Cyclization on the N-alkylated amine ***15*** proceeded in 42% yield upon treatment with $ZnCl_2$ in DMF.



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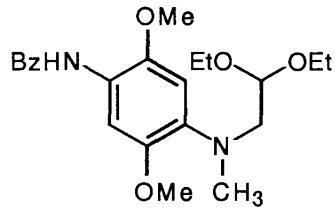

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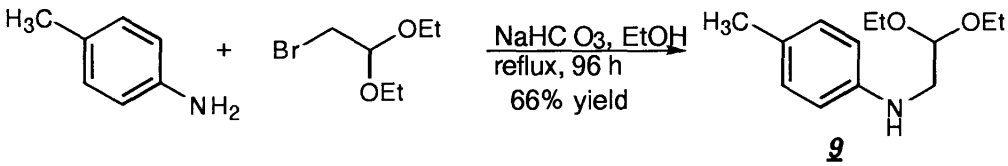
In conclusion, cyclization of acetal derivatives of α-anilino acetaldehydes has been demonstrated to be a viable synthetic route to indoles, especially 5-substituted indoles, for which the regioselectivity is fixed. Sundberg writes, "In terms of being a practical indole synthesis, this route appears to compare favorably with other methods which start from substituted anilines and is particularly suitable for 5-substituted indoles with electron-donor substituents."[12]

CHAPTER II

STATEMENT OF PROBLEM

Although the existing literature has demonstrated the feasibility of this route for the synthesis of 5-substituted indoles with cyclizations proceeding in 60-86% yields, the formation of the key synthetic intermediate, an acetal derivative of α-anilino acetaldehyde (***9***), by the conventional alkylation of aniline with α-haloacetaldehyde acetals requires high temperatures and extended reaction times. A typical procedure includes refluxing the appropriately substituted aniline (1.5 eq.) in DMF or EtOH with an acetal derivative of bromoacetaldehyde (1.0 eq.) and $NaHCO_3$ (1.5 eq.) for >48 h to 96 h.[14,15] A specific example for p-toluidine is given below.



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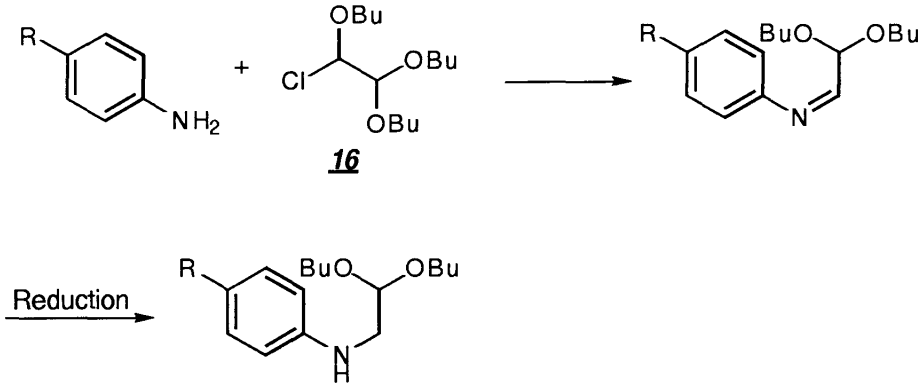
Yields generally range from 54-71% depending on the electronic nature of the substituents. However, in cases where coupling was performed using N-alkylated anilines with several substituents on the benzene ring, yields appeared to be lower (26-32% yield).[16,17] Few attempts have been made to improve this route. Sundberg and his co-workers briefly examined the use of 2-(bromomethyl)-1,3-dioxolane in place of the bromoacetaldehyde diethyl acetal

in his alkylation of N-methanesulfonyl anilines. He was able to reduce the reaction time from 48-60 h to <20 h.[12]

We propose an alternative route to 5-substituted indoles using 2-chloro-1,1,2-tributoxyethane (***16***), a much more reactive alkylating reagent than bromoacetaldehyde diethyl acetal, to alkylate the aniline. 2-Chloro-1,1,2-tributoxyethane can be readily prepared from inexpensive glyoxal in two steps. Subsequent alkylation of the aniline with ***16*** affords an imine, which upon reduction produces essentially the same substrate ***9*** (differing only in the OR group of the acetal) necessary for the cyclization conditions developed by Nordlander.[14]



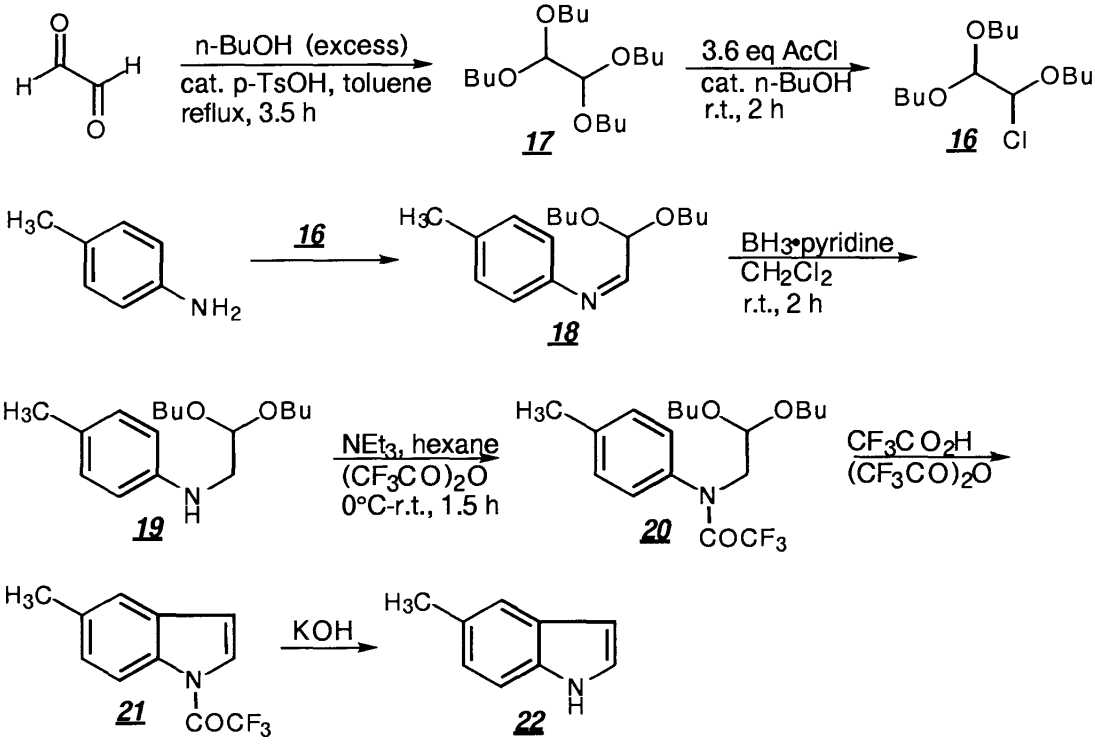
A similar alkylation has recently been demonstrated by J. Babler to occur in 82% yield when benzylamine is treated with α-chloroether ***16***.[18] Therefore this route would offer another option for converting substituted anilines to indoles.

CHAPTER III

RESULTS AND DISCUSSION

This thesis presents preliminary results obtained by applying the novel synthetic route outlined in Scheme I to the preparation of 5-methylindole. As the first test case of this methodology, p-toluidine was primarily chosen in view of its greater capability, relative to aniline, for nucleophilic attack on 2-chloro-1,1,2-tributoxyethane.

Scheme I



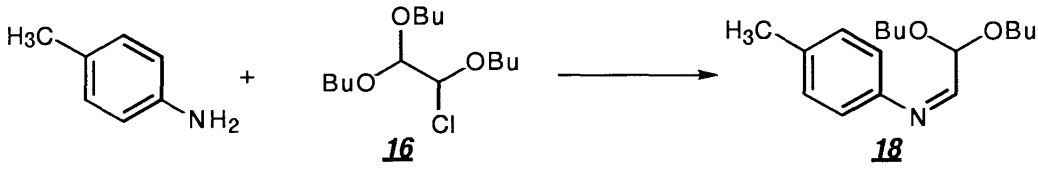
p-Toluidine was N-alkylated using 2-chloro-1,1,2-tributoxyethane (***16***) under mildly basic conditions in CH_3CN and the resulting imine (***18***) subsequently reduced with BH_3•pyridine to give the key synthetic intermediate (***19***) in 30% overall yield over the two-step process. Subsequent treatment of ***19*** with trifluoroacetic anhydride gave the corresponding trifluoroacetamide derivative (***20***) in quantitative yield. Cyclization of ***20*** to generate 5-methylindole could then be achieved using literature procedures reported by Nordlander.[14]

The alkylating agent, 2-chloro-1,1,2-tributoxyethane, was prepared using a modification of Babler's literature procedure.[18] Aqueous glyoxal was converted to the corresponding bis(dibutyl acetal) (***17***) by refluxing with excess 1-butanol and a catalytic amount of p-toluenesulfonic acid in toluene. Typical yields for acetal formation ranged from 74-85% yield. 2-Chloro-1,1,2-tributoxyethane was subsequently obtained in 78% yield by treating glyoxal bis(dibutyl acetal) with excess acetyl chloride.

Several reaction conditions were explored to optimize the key alkylation of p-toluidine with 2-chloro-1,1,2-tributoxyethane. These are given in Table I.

Table I

Alkylation of p-Toluidine

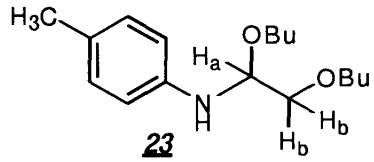


Rxn	Solvent	Conditions	Results	^{1}H NMR (Appendix 1)
1	DMF	0°C to r.t., 17 h 60°C, 3.5 h	31% chrom. yield of ***18***	A,B
2	2.0 eq ***16***	95°C, 5 min	*unidentified products	C
3	2.0 eq ***16***	80-90°C, 10 min (+$K_2C\ O_3$)	*unidentified products	D
4	1,2-DME	r.t., 6-7 h	*decomposition of ***16***	E
5	dioxane	r.t., 6-7 h	*$ArNH_2$•HCl, hydrolysis of ***16***	F
6	pyridine	0°C to r.t., 1.5 h	*decomposition of ***16***	G
7	NMP	0°C to r.t., 1.5 h r.t., 17 h	*decomposition of ***16***	H
8	CH_3CN	0°C to r.t., 3 h	crude: 2:1 ***18***/unidentified prod.; $ArNH_2$•HCl	I, J

*Unidentified products or structures tentatively assigned by ^{1}H NMR; Further data (IR, MS, ^{13}C NMR) necessary to unequivocally identify reaction products.

The reaction was critically dependent on solvent and temperature conditions. Most of the difficulties encountered were related to the reactivity of the alkylating agent ***16*** not only to the desired SN_2 reaction with p-toluidine, but also to the competing elimination reaction. In general, by increasing the polarity of the solvent and lowering the temperature, higher yields of the desired product could be obtained.

Initially, I examined reaction conditions (DMF, K_2CO_3, 0°C) reported by Babler[23] to give alkylation of benzylamine by α-chloroether ***16*** in 82% yield. However, in the case of p-toluidine, the same conditions afforded the desired imine ***18*** in just 31% chromatographed yield even after heating at 60°C for 3.5 h. The reaction appeared sluggish with more than 50% of the p-toluidine being recovered unreacted. Proton NMR analysis of the reaction product mixture also revealed the formation of a significant amount of an unidentified by-product. When the crude reaction mixture was directly reduced with $NaBH_4$ in EtOH to the corresponding amino acetal ***19*** , a major contaminant isolated from the reaction appeared to be a 1:1 mixture of p-toluidine and compound ***23*** (tentatively assigned). Proton NMR ($CDCl_3$) analysis appeared to be consistent with the structure drawn with H_a appearing as a triplet at 4.53 ppm and H_b appearing as a doublet at 3.58 ppm. However, more data would be required to unequivocally identify the side product.



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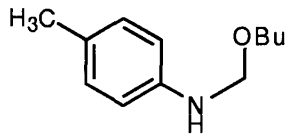
When the alkylation was carried out neat at elevated temperatures, as shown in reactions 2 and 3 in Table I, p-toluidine was completely consumed

within 5-10 minutes as determined by TLC and a considerable amount of tar was observed. However, no desired product was isolated from either one of those reactions. Instead, the major fraction isolated from plate layer chromatography in reaction 2 contained two unidentified products. By proton NMR analysis, these two products appeared very symmetrical as evident by the convergence of the -$OCH_2CH_2CH_3$ multiplet, present in the starting material and in the desired product, to a single triplet. Similarly, the product isolated from reaction 3 (with addition of K_2CO_3) also suggested a symmetrical compound. One possible structure that might fit the available data is the fragmented piece shown below or some derivative/polymer of it:



However, further characterization is necessary to unequivocally identify the structure.

In the more basic solvents such as NMP, pyridine, and 1,2-DME (reactions 4, 6, and 7 in Table I), decomposition of 2-chloro-1,1,2-tributoxyethane via competing elimination reactions appeared to be faster than reaction with p-toluidine. No desired products were isolated from these reactions. Similarly, in a relatively non-polar solvent such as dioxane (entry 5 in Table I), alkylation of p-toluidine failed. Instead generation of the hydrochloride salt of p-toluidine and hydrolysis of 2-chloro-1,1,2-tributoxyethane to an aldehyde-containing compound was detected in the crude proton NMR spectrum (C<u>H</u>O, 9.46 ppm).

After some exploration of alternative reaction conditions, satisfactory results were achieved by using CH_3CN as the solvent, as indicated in entry 8

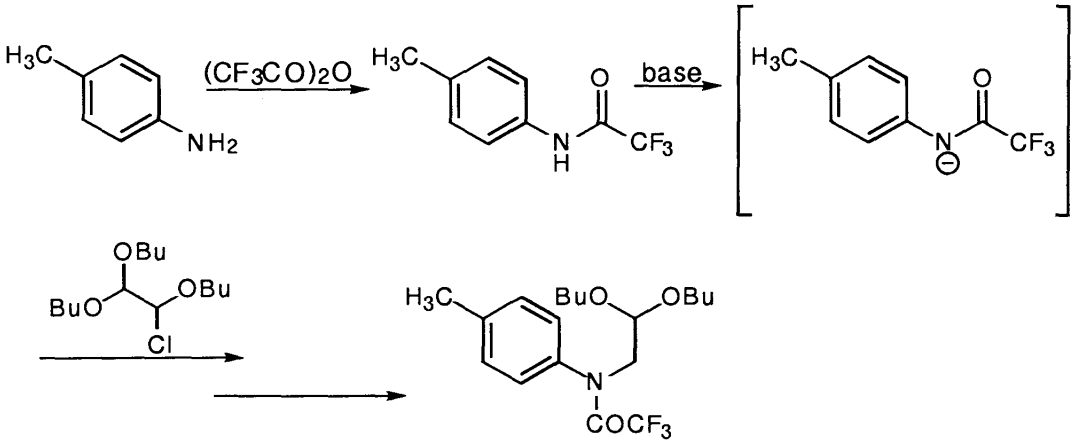
in Table I. A typical procedure is as follows: 1.2 equivalents of p-toluidine was treated with 1.0 equivalent of 2-chloro-1,1,2-tributoxyethane and 1.3 equivalents of K_2CO_3 in CH_3CN at 0°C and subsequently stirred at room temperature for 2 hours. The reaction proceeded more cleanly and more efficiently in CH_3CN than in DMF as evident from the crude product's proton NMR spectrum. Also improving the yield were shortened reaction times and lower temperatures. Interestingly, a significant amount of white solid precipitated from the crude product after standing at room temperature or storage at 0°C for 24 h. Characterization of the precipitate by proton NMR analysis revealed it to be the p-toluidine hydrochloride. The remainder of the crude product, however, contained a 2:1 mixture of the desired imine and an unidentified side product also observed in the DMF reaction. Efforts to reduce the amount of this side product by maintaining the reaction temperature at 0°C overnight, proved fruitless. At 0°C, the reaction afforded mainly unreacted 2-chloro-1,1,2-tributoxyethane with trace amounts of the undesired side product.

Due to the sensitivity of imine ***18*** to chromatography on silica gel, reduction was performed on the crude product. Initial attempts to reduce imine ***18*** with $NaBH_4$ in EtOH failed, giving rise to incomplete reactions and recovery of the starting material. Even overnight stirring at room temperature did not effect the desired transformation. In contrast, treatment of imine ***18*** with BH_3•pyridine in methylene chloride accomplished the reduction within two hours at room temperature. β-amino acetal ***19*** was thus obtained in 30-36% chromatographed yields from the starting 2-chloro-1,1,2-

tributoxyethane. Its proton NMR spectrum compared favorably with literature references.[19]

In summary, we have shown the aforementioned route to be a viable alternative synthesis to amide-acetal ***20*** which can be readily cyclized to give 5-methylindole. Unlike the current conventional methods, alkylation of p-toluidine can be accomplished at room temperature within 3 hours using 2-chloro-1,1,2-tributoxyethane. In addition to offering a more reactive alkylating agent, this method also utilizes inexpensive and readily available starting materials. However, its one major drawback in comparison to other routes is the inferior yields obtained from the key alkylation of p-toluidine. This can be attributed to the instability of 2-chloro-1,1,2-tributoxyethane to the reaction conditions when the rate of nucleophilic attack is slow.

Further research would be required to provide cleaner and more efficient alkylation conditions. One possibility might be to generate a more nucleophilic aniline equivalent by an in situ generation of a negative charge on nitrogen. This could theoretically be accomplished by initially converting the substituted aniline to its N-trifluoroacetyl derivative, followed by abstraction of the NH proton by a base.



A similar transformation has been done in the literature. Sundberg has successfully alkylated N-methylsulfonyl derivatives of anilines by initial treatment with NaH followed by addition of bromoacetaldehyde diethyl acetal. In this way, the yield of alkylation was increased from 66% yield after 96 hours in refluxing ethanol to 79% yield after 48-60 hours of heating in DMF at 110°C.[12] In addition, further work would need to be directed at exploring the limits and application of this synthetic route to other substituted aniline systems.

CHAPTER IV

EXPERIMENTAL

General Methods. Proton NMR (^{1}H NMR) spectra were recorded on a GE-300 (300 MHz) instrument with Me_4Si as the internal standard and $CDCl_3$ as the solvent. IR spectra were recorded using a Perkin-Elmer model No.1320 spectrophotometer. Elemental analyses and mass spectra were performed by the Physical Methodology Department, Searle Laboratories, G.D. Searle & Co.

Glyoxal Bis(Dibutyl Acetal) (*17*). A mixture of 40% wt. glyoxal (Aldrich, 4.193 g, 0.03 mol), 1-butanol (10.53 g, 0.14 mol), and p-toluenesulfonic acid (0.207 g, 0.97 mmol) in toluene (20 mL) was heated to reflux with continuous azeotropic removal of water (3.5 mL) for 3.5 h. The cooled reaction mixture was diluted with ether (20 mL) and washed with saturated aqueous $NaHCO_3$ (2X40 mL) followed by brine (40 mL). The organic layer was collected, dried over Na_2SO_4, and filtered. Concentration in vacuo gave the desired product as a pale yellow oil (7.3 g, 85% yield). ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 12 H, J=7.5 Hz, $C\underline{H}_3$), 1.40 (sept., 8 H, $C\underline{H}_2CH_3$), 1.58 (sept., 8 H, $C\underline{H}_2CH_2CH_3$), 3.50-3.70 (m, 8 H, $OC\underline{H}_2$), 4.32 (s, 2 H, $C\underline{H}(OR)_2$). ^{13}C NMR ($CDCl_3$, DEPT): δ CH_3 14.28; CH_2 19.75, 32.41, 67.81; CH 102.95.

IR υ_{max} (neat): 2860-2980 (C-H), 1080 (C-O) cm^{-1}.

Anal. Calcd. for $C_{18}H_{38}O_4$*: C, 67.88; H, 12.03.

Found: C, 66.80; H, 12.15.

*The large discrepancy in the elemental analysis between the calculated carbon content and those experimentally found may be attributed to contamination of the sample with toluene. Trace amounts of toluene were also detected in the proton NMR spectra. Glyoxal Bis(Dibutyl Acetal) ***17*** is a known compound reported in the literature (F. Chastrette et al., *Synth. Commun.*, **1988**, *18*, 1343).

2-Chloro-1,1,2-tributoxyethane (*16*). To a solution of ***17*** (3.005 g, 11.4 mmol) in acetyl chloride (2.9 mL, 41 mmol) was added 1-butanol (0.42 mL, 4.6 mmol) under argon. After stirring at r.t. for 2 h, the reaction was concentrated in vacuo and the residue was azeotroped with toluene to remove low boiling impurities. The desired product was obtained as a pale yellow oil (2.071 g, 78% yield).

^{1}H NMR ($CDCl_3$): δ 0.92 (t, 9 H, J=7.5 Hz, CH_3), 1.40 (m, 6 H, CH_2CH_3), 1.60 (m, 6 H, $CH_2CH_2CH_3$), 3.50-4.00 (m, 6 H, OCH_2), 4.54 (d, 1 H, J=5.5 Hz, $CH(OR)_2$), 5.43 (d, 1 H, J=5.5 Hz, CHCl).

^{13}C NMR ($CDCl_3$, DEPT): δ CH_3 14.20, 14.33; CH_2 19.60, 19.72, 31.24, 31.39, 32.20, 32.34, 68.28, 68.57, 70.99; CH 97.48, 103.66.

IR υ_{max} (neat): 2880-2960 (C-H), 1080, 1110 (C-O) cm^{-1}.

Anal. Calcd. for $C_{14}H_{29}O_3Cl$: C, 59.88; H, 10.41.

Found: C, 60.05; H, 10.64.

MS: 245 (M-Cl), 280.3 (M^+).

4-Methyl N anilino-2,2-dibutoxyethanimine (*18*). A mixture of ***16*** (2.071 g, 7.4 mmol), p-toluidine (Aldrich, 0.92 g, 8.6 mmol), and anhydrous K_2CO_3 (1.296, 9.3 mmol) in CH_3CN (HPLC-grade, 25 mL) was stirred under argon at 0°C for 1 h, then warmed to r.t. for 2 h. The reaction mixture was subsequently partitioned between water and ethyl acetate. The

organic layer was collected, washed with brine, and dried over $MgSO_4$. Concentration in vacuo gave an orange/yellow oil which darkened upon standing at room temperature. The oil was slurried with hexane and the undissolved white solid filtered off. The filtrate was reconcentrated in vacuo to give an orange/red oil (2.26 g, quantitative).

^1H NMR ($CDCl_3$): δ 0.92 (t, 6 H, *J*=7.5 Hz, CH_3), 1.40 (sept., 4 H, CH_2CH_3), 1.61 (sept., 4 H, $CH_2CH_2CH_3$), 2.36 (s, 3 H, $ArCH_3$), 3.55-4.00 (m, 4 H, OCH_2), 4.94 (d, 1 H, *J*=5.0 Hz, $CH(OR)_2$), 7.04 (d, 2 H, *J*=9.0 Hz, Ar), 7.17 (d, 2 H, *J*=9.0 Hz, Ar), 7.73 (d, 1 H, *J*=5.0 Hz, N=CH).

"**Reduction of Imine *18* "(*19*)**. To a solution of ***18*** (2.26 g, 7.4 mmol) in CH_2Cl_2 was added BH_3•pyridine (Aldrich, 0.91 mL, 9.0 mmol) at 20°C under argon. After 2 h, the reaction was quenched with water and the resulting mixture extracted with ethyl acetate (2X). The combined organic layers were then washed with brine, and dried over $MgSO_4$. Concentration in vacuo afforded the desired product as an orange oil. The oil was purified by column chromatography (100 g Merck silica gel, mesh size 230-400) using 5% ethyl acetate/hexane as the eluent and the desired product (***19***) was isolated as a yellow oil (0.61 g, 30% yield).

^1H NMR ($CDCl_3$): δ 0.92 (t, 6 H, *J*=7.5 Hz, CH_3), 1.40 (sept., 4 H, CH_2CH_3), 1.58 (sept., 4 H, $CH_2CH_2CH_3$), 2.22 (s, 3 H, $ArCH_3$), 3.21 (d, 2 H, *J*=5.5 Hz, $NHCH_2$), 3.49 (m, 2 H, OCH_2), 3.65 (m, 2 H, OCH_2), 3.73 (b, 1 H, NH), 4.66 (t, 1 H, *J*=5.5 Hz, $CH(OR)_2$), 6.55 (d, 2 H, *J*=9.0 Hz, Ar), 6.99 (d, 2 H, *J*=9.0 Hz, Ar).

^{13}C NMR ($CDCl_3$, DEPT): δ *C*H_3 14.43, 20.91; *C*H_2 19.92, 32.52, 47.14, 67.03; *C*H 101.65, 113.83, 130.26; *C* 127.35, 146.26.

IR υ_{max} (neat): 3400 (2° N-H); 2870-2960 (C-H); 1620, 1520 (Ar), 810 (p-substitution, Ar) cm^{-1}.

Anal. Calcd. for $C_{17}H_{29}O_2$: C, 73.07; H, 10.46; N, 5.01.

Found: C, 72.88; H, 10.66; N, 4.61.

MS: 280 ($M+H^+$).

Conversion of Amine *19* to the Corresponding Trifluoroacetamide Derivative (*20*). To a solution of ***19*** (0.307 g, 1.1 mmol) in hexane (3 mL) was added triethylamine (0.17 mL, 1.3 mmol) followed by trifluoroacetic anhydride (0.17 mL, 1.2 mmol) at 0°C under argon. The reaction was allowed to warm to room temperature and was subsequently stirred for 1.5 h. The reaction was then quenched with cold water and extracted with ether. The organic layer was collected, washed in succession with water and brine, and dried over $MgSO_4$. The solvent was removed in vacuo to give a yellow oil which darkened to red upon standing at room temperature. (0.41 g, 100% yield).

^1H NMR ($CDCl_3$): δ 0.83 (t, 6 H, *J*=7.5 Hz, CH_3), 1.29 (sept., 4 H, CH_2CH_3), 1.45 (sept., 4 H, $CH_2CH_2CH_3$), 2.30 (s, 3 H, $ArCH_3$), 3.48 (m, 2 H, OCH_2), 3.50 (m, 2 H, OCH_2), 3.73 (d, 2 H, *J*=5.5 Hz, NCH_2), 4.70 (t, 1 H, *J*=5.5 Hz, $CH(OR)_2$), 7.10 (s, 4 H, Ar).

^{13}C NMR ($CDCl_3$, DEPT): δ *C*H_3 14.31, 21.58; *C*H_2 19.77, 32.34, 54.26, 67.02; *C*H 99.40, 128.56, 130.19; *C* 115, 117, 137.65, 139.44.

IR υ_{max} (neat): 2880-2960 (C-H); 1620, 1700 (C=O), 1510 (Ar), 830 (p-substitution, Ar) cm^{-1}.

Anal. Calcd. for $C_{19}H_{28}NO_3F_3$: C, 60.79; H, 7.52; N, 3.73.

Found: C, 60.84; H, 7.34; N, 3.74.

MS: 376 ($M+H^+$).

Literature Procedure[14] **for Conversion of *11* to *12***

(Analogous for conversion of ***19*** to ***21***). To 50 mL of 50% (v/v) $(CF_3CO)_2O$ in CF_3CO_2H at 0°C under nitrogen was added 5.0 g (24 mmol) of ***11***. After 30 min, the cold mixture was diluted with 40 mL of CF_3CO_2H and boiled under reflux for 72 h. Distillation gave 4.8 g (23 mmol, 95 %) of ***12***.

Literature Procedure[14] **for Hydrolysis of*12* to 5-Methylindole**

(Analogous for hydrolysis of ***21***). Treatment of 3.0 g (14 mmol) of N-(trifluoroacetyl)indole (***12***) with 40 mL of 5% methanolic KOH at room temperature overnight, rotary evaporation of the bulk of the methanol, standard extractive workup with ether, and distillation (1 mm) gave 1.6 g (13.5 mmol, 86%) of 5-methylindole.

APPENDIX 1

SPECTRA ACCOMPANYING TABLE I

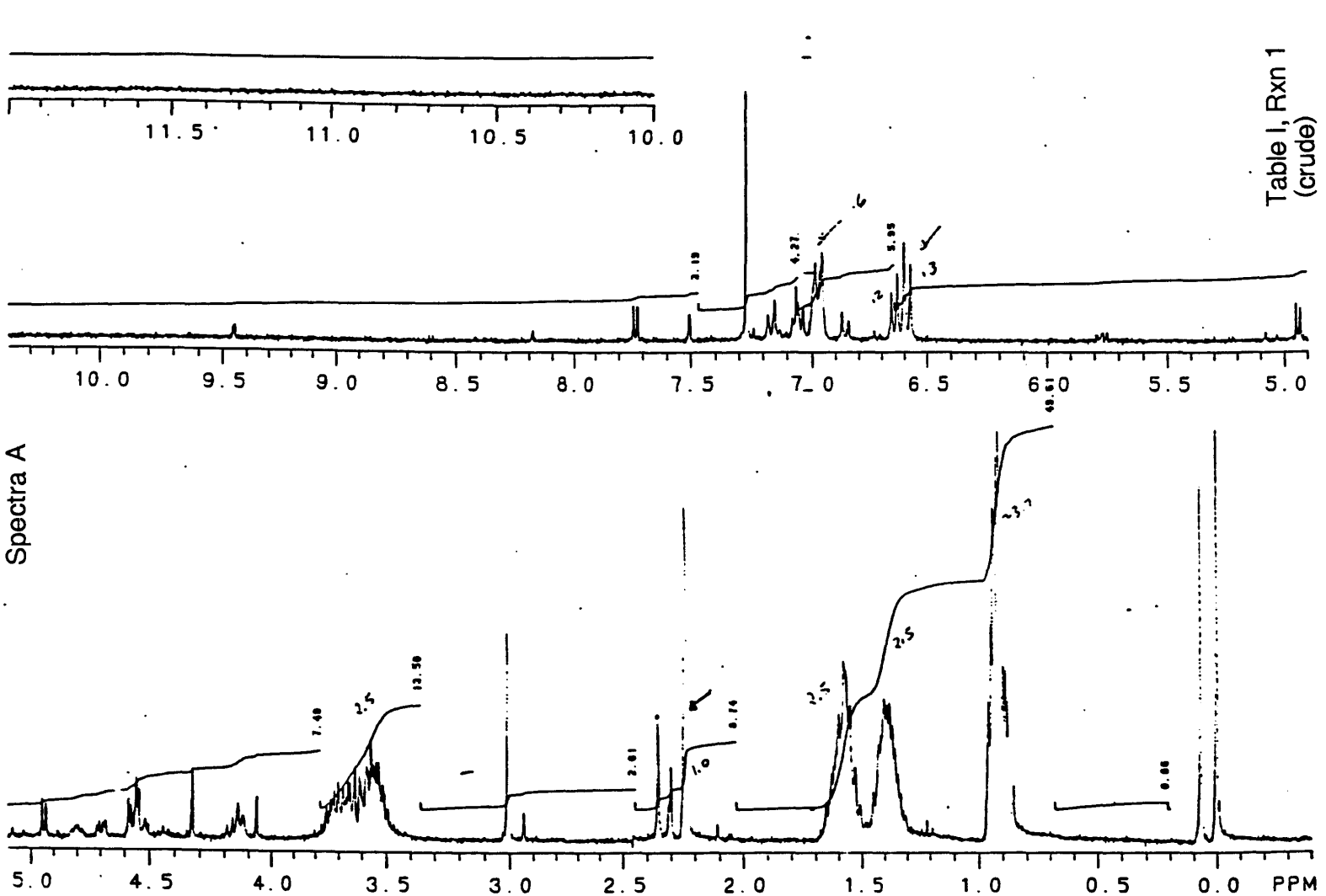


Table I, Rxn 1
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Spectra A
PPM

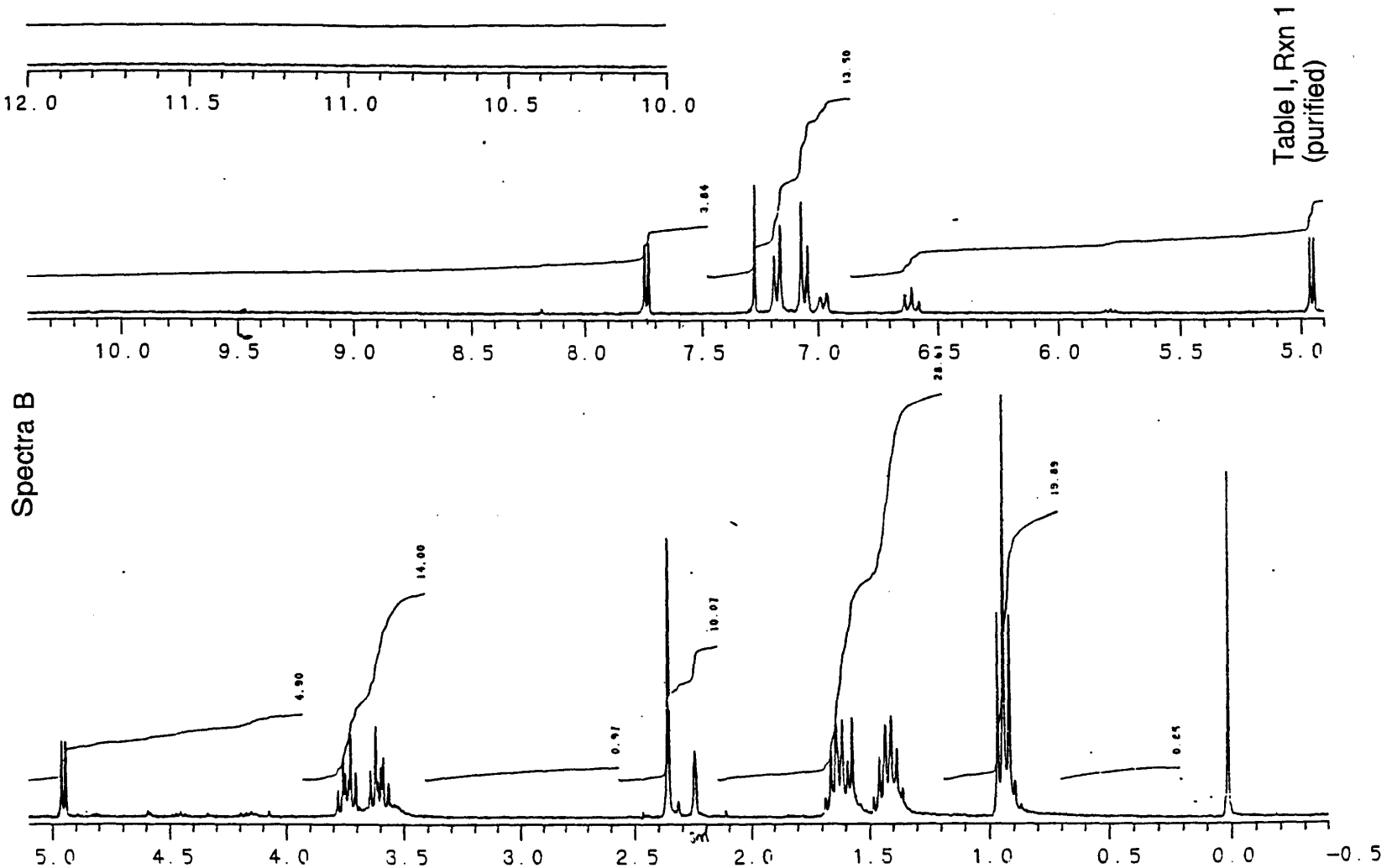


Table I, Rxn 1
(purified)
Spectra B

Spectra C

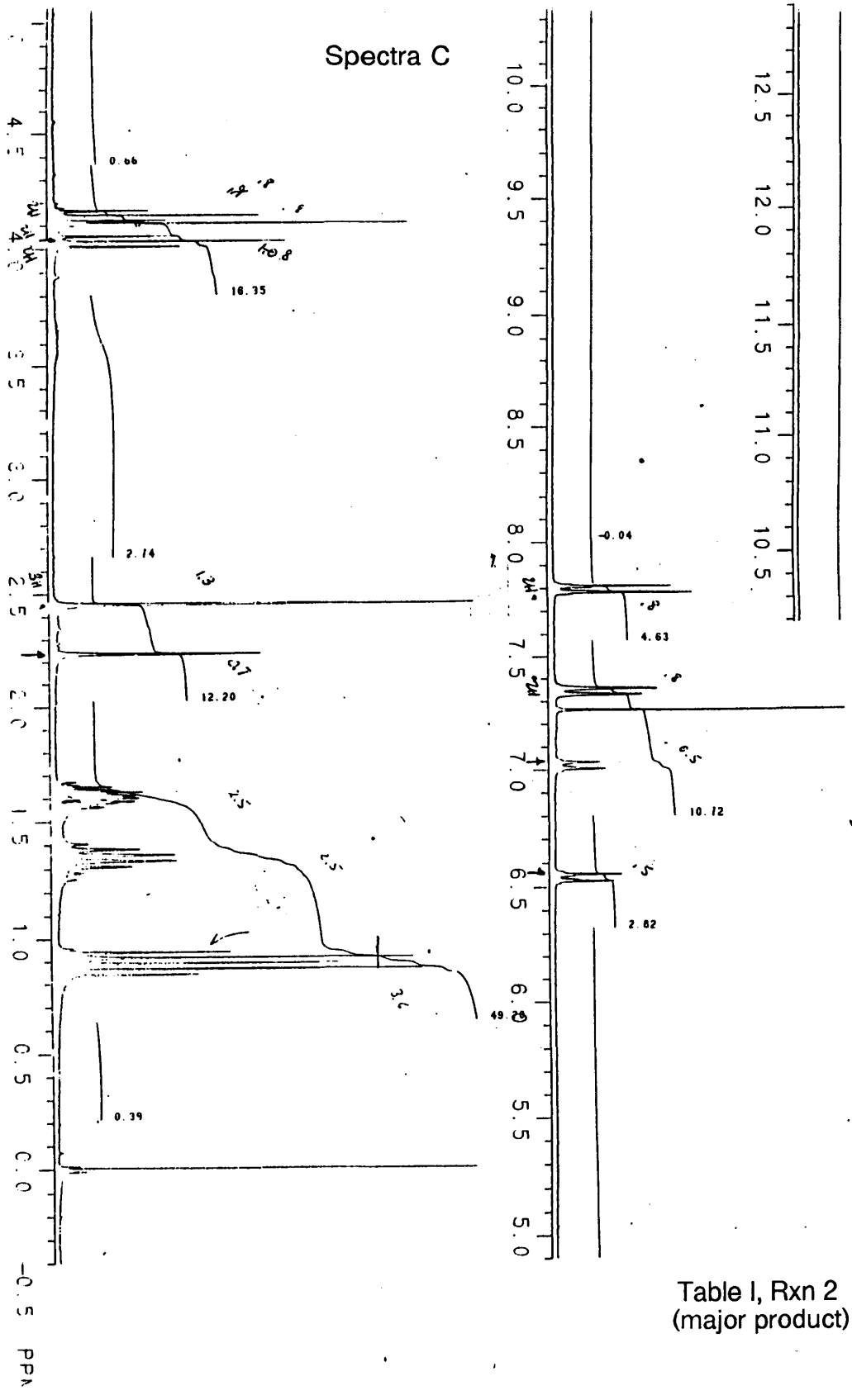
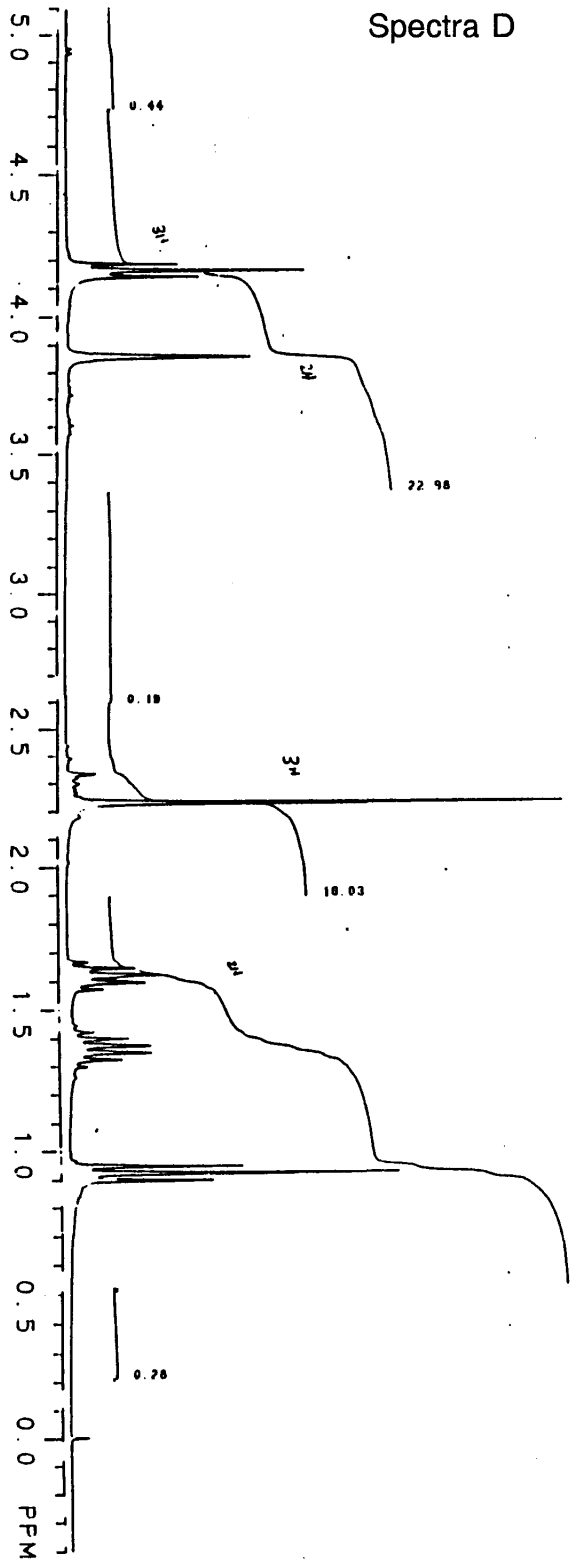


Table I, Rxn 2
(major product)

Spectra D



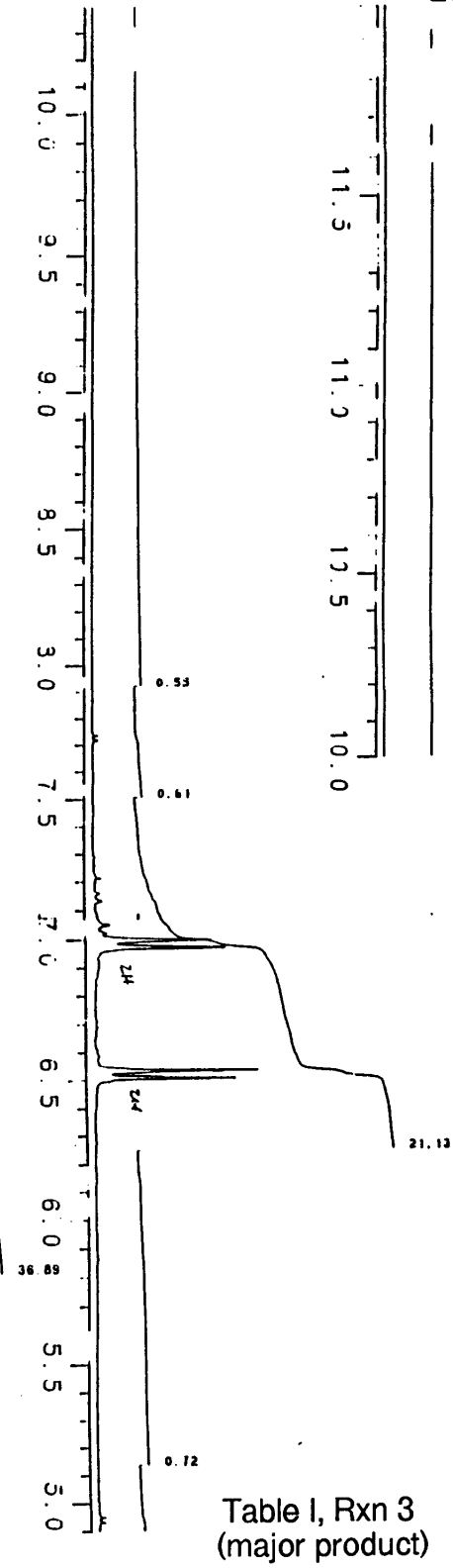


Table I, Rxn 3
(major product)

Spectra E

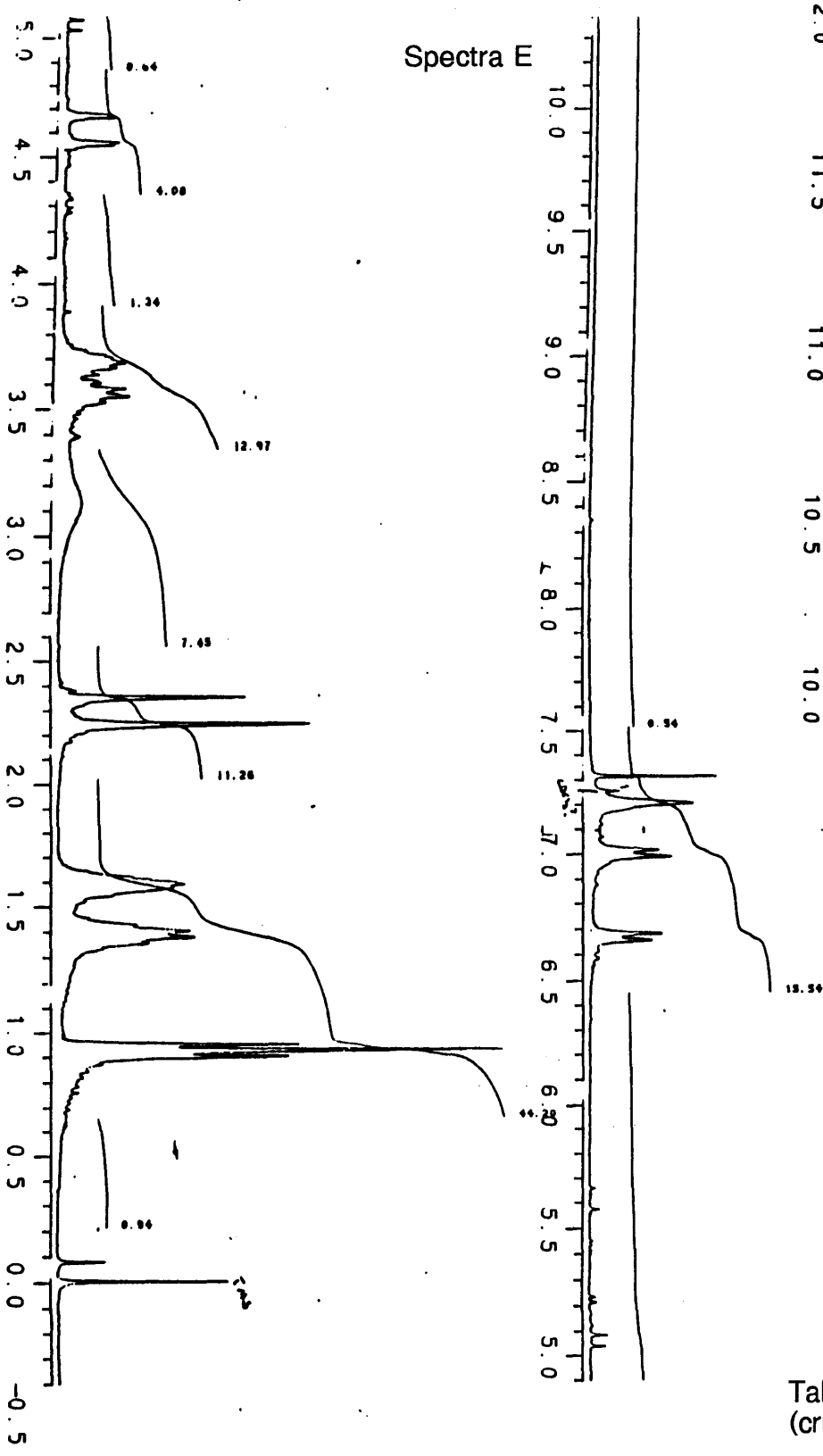


Table I, Rxn 4
(crude)

Spectra F

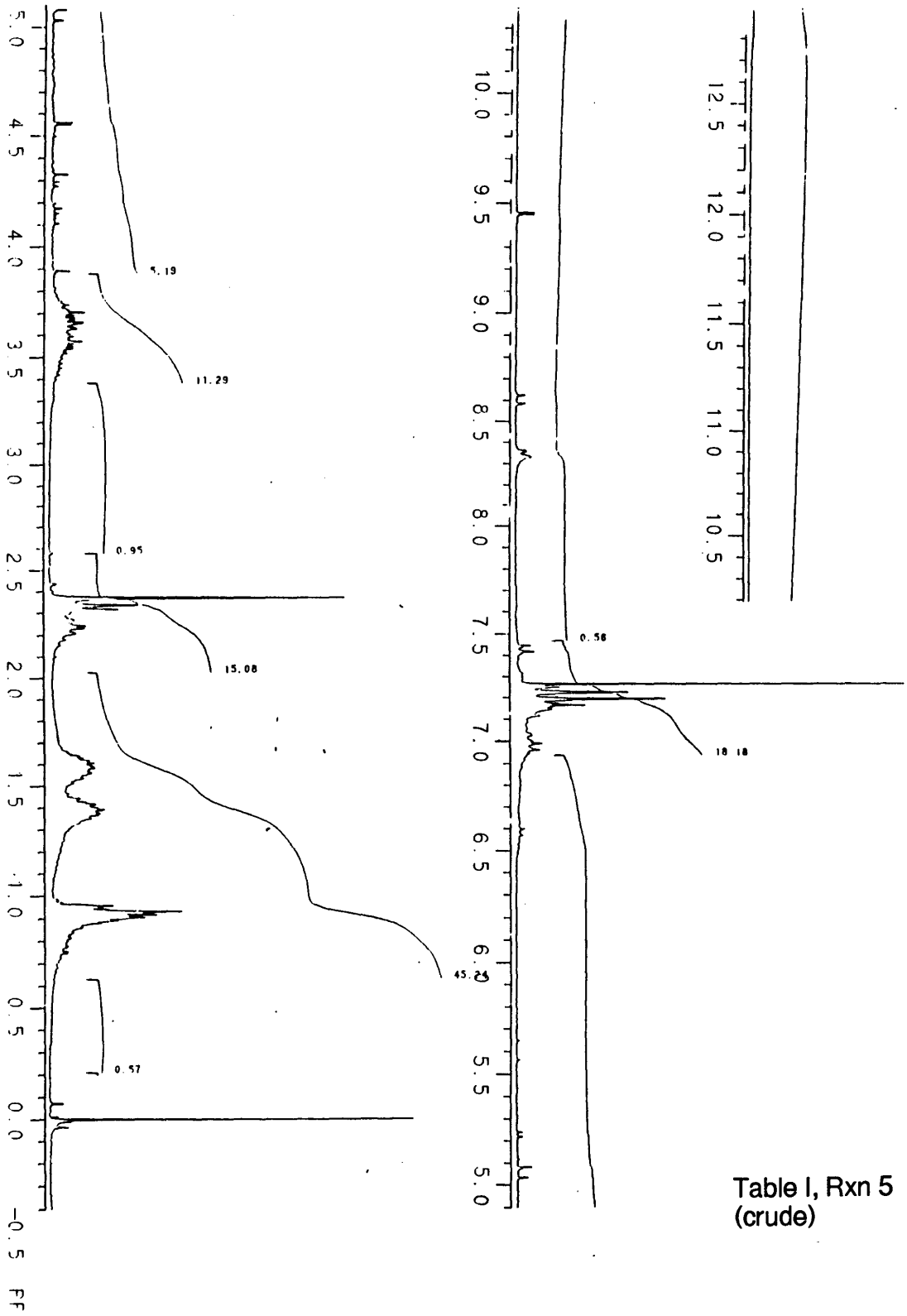
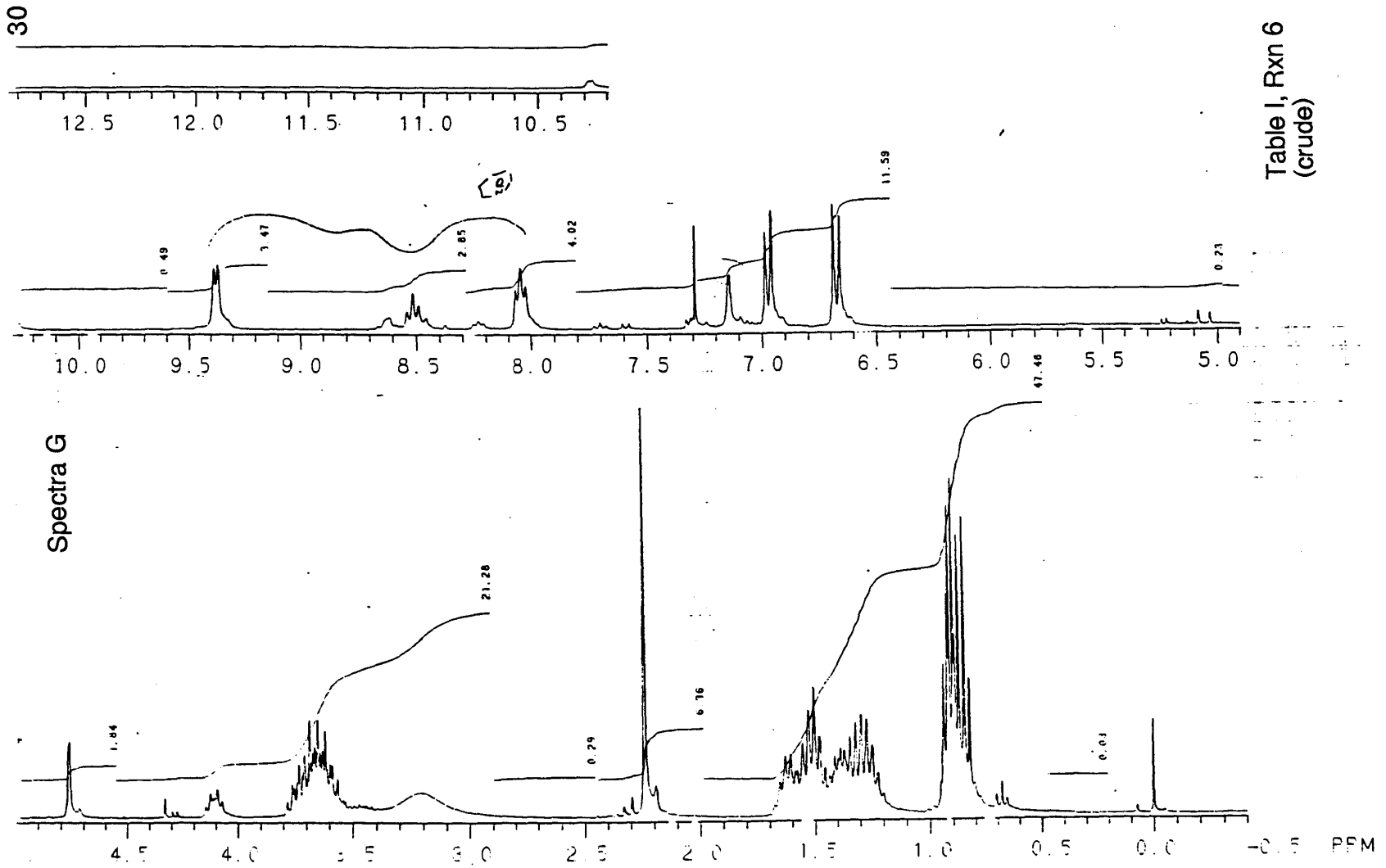


Table I, Rxn 5 (crude)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10.5
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6.0
5.5
5.0
Spectra G
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0.29
6.16
47.48
0.04
4.5
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PPM

Spectra H

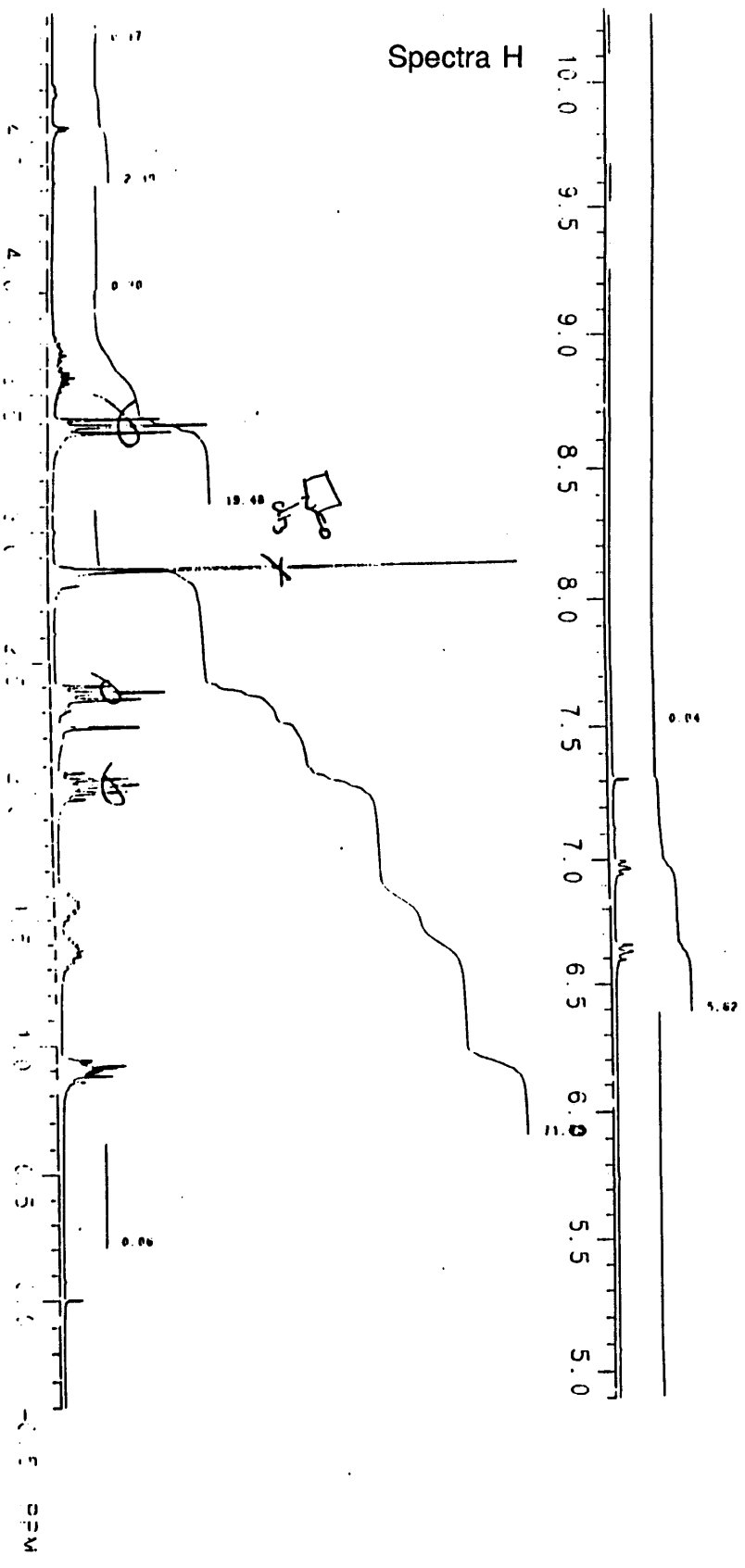

Table I, Rxn 7
(crude)

Spectra I

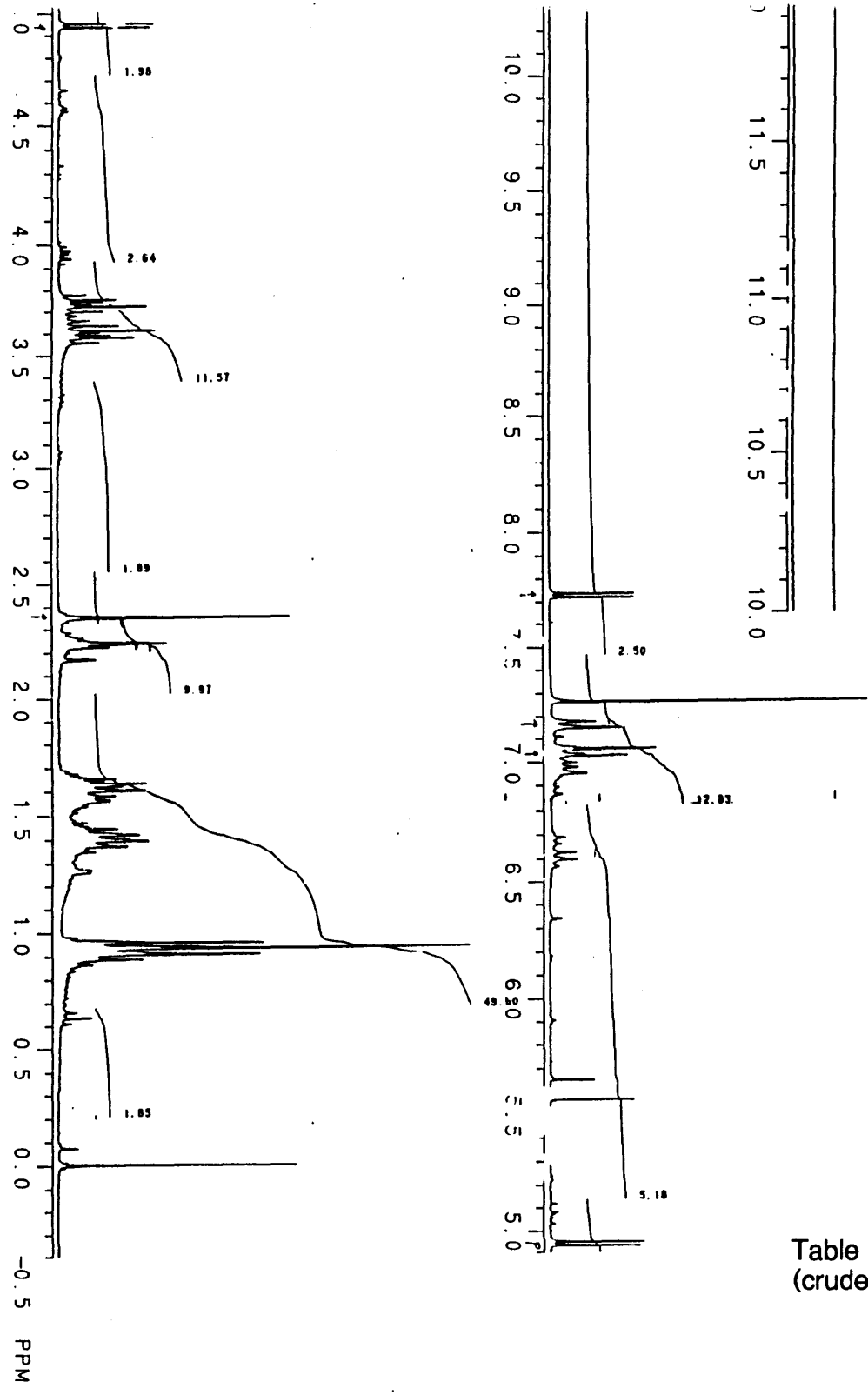

Table I, Rxn 8
(crude)

Spectra J

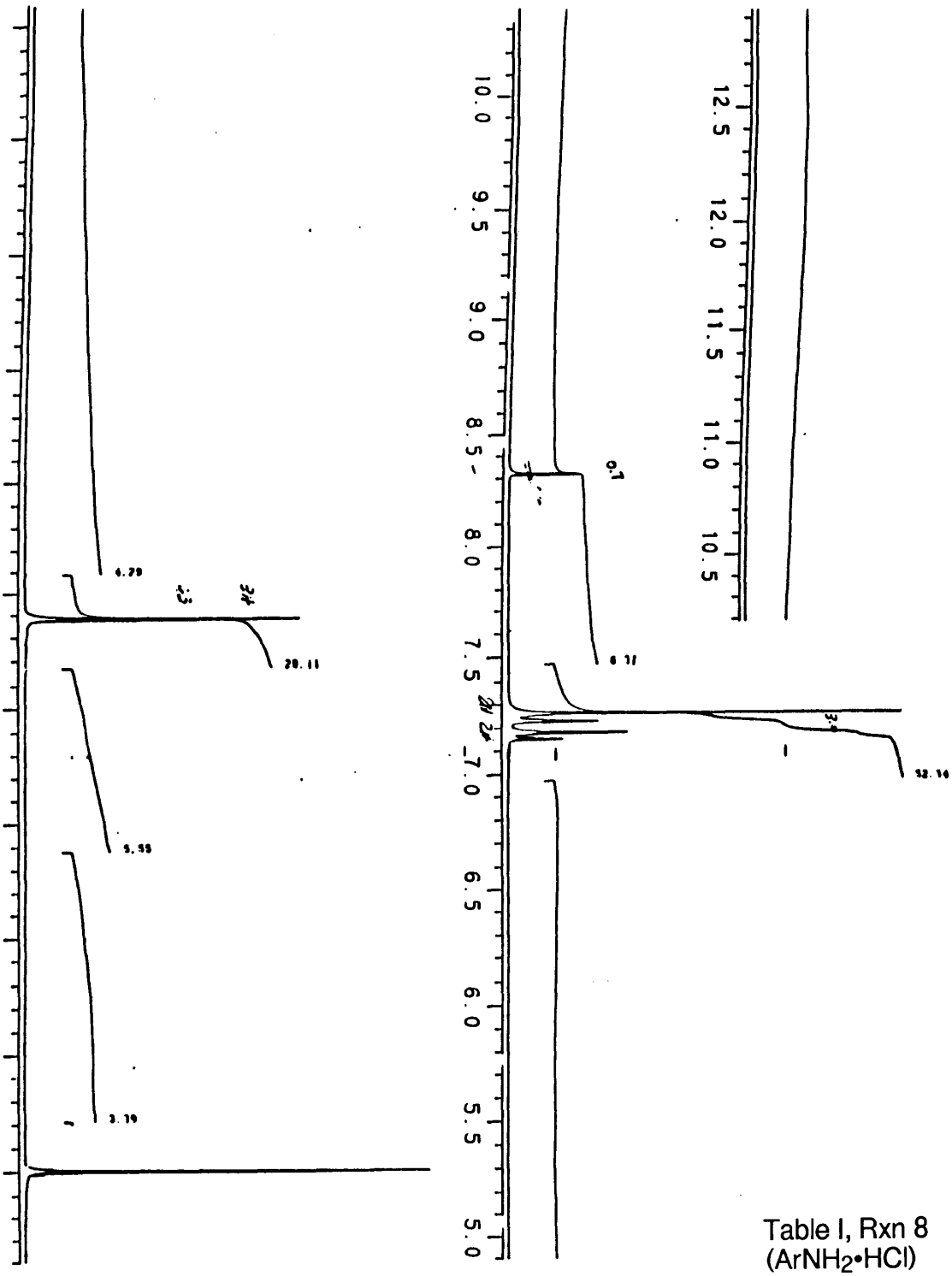

Table I, Rxn 8
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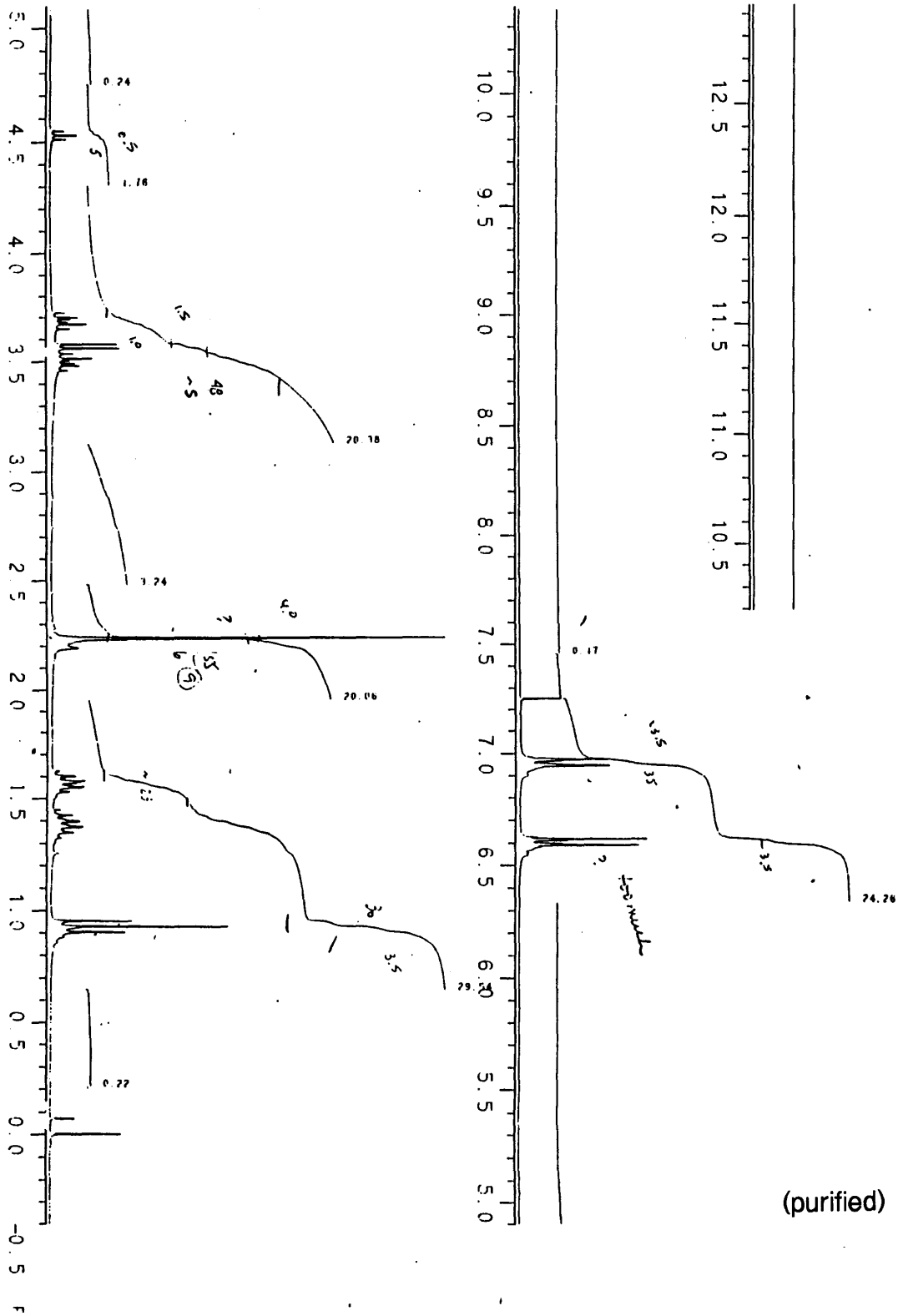
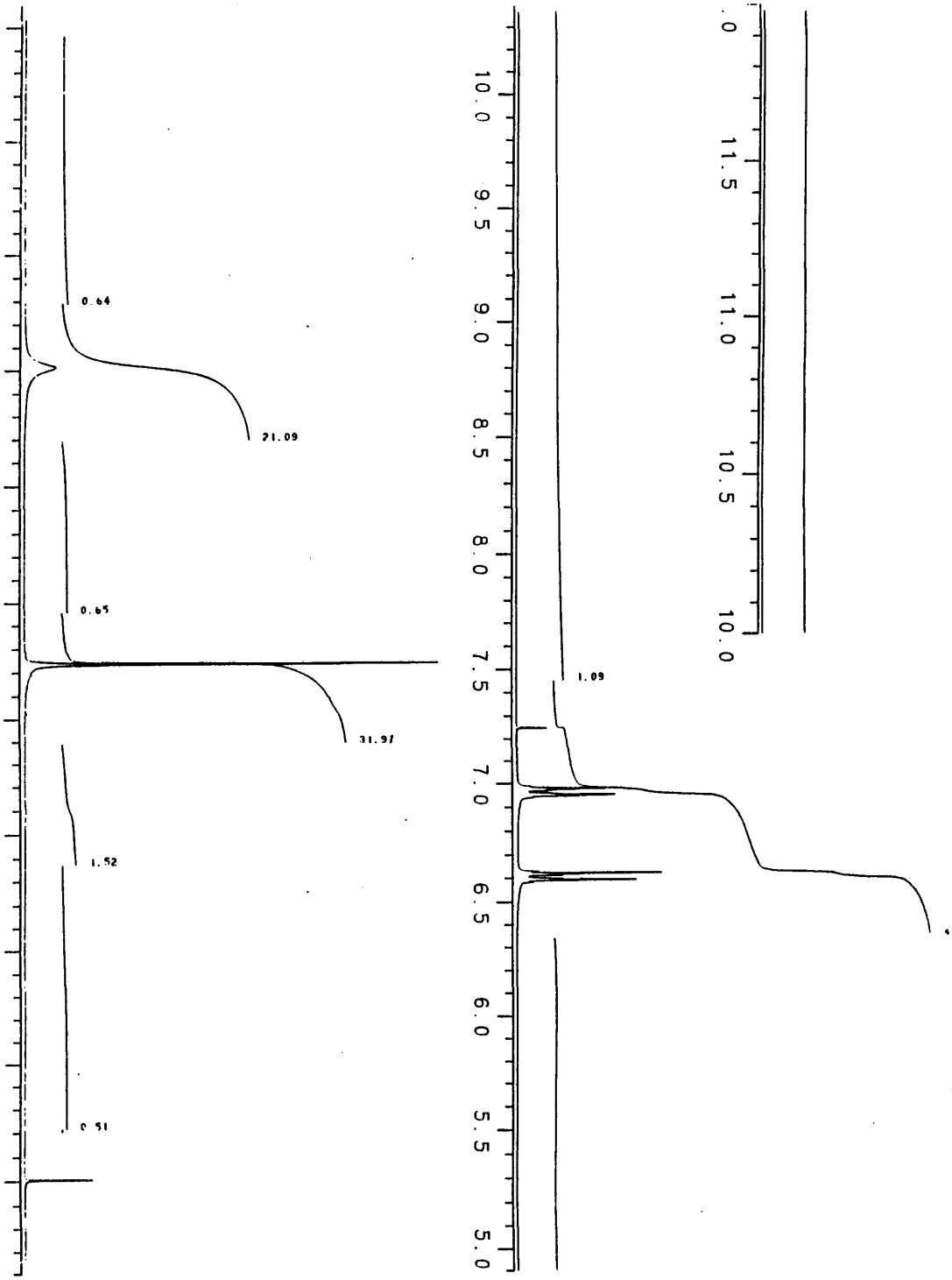
Compound ***23***



(purified)

P-toluidine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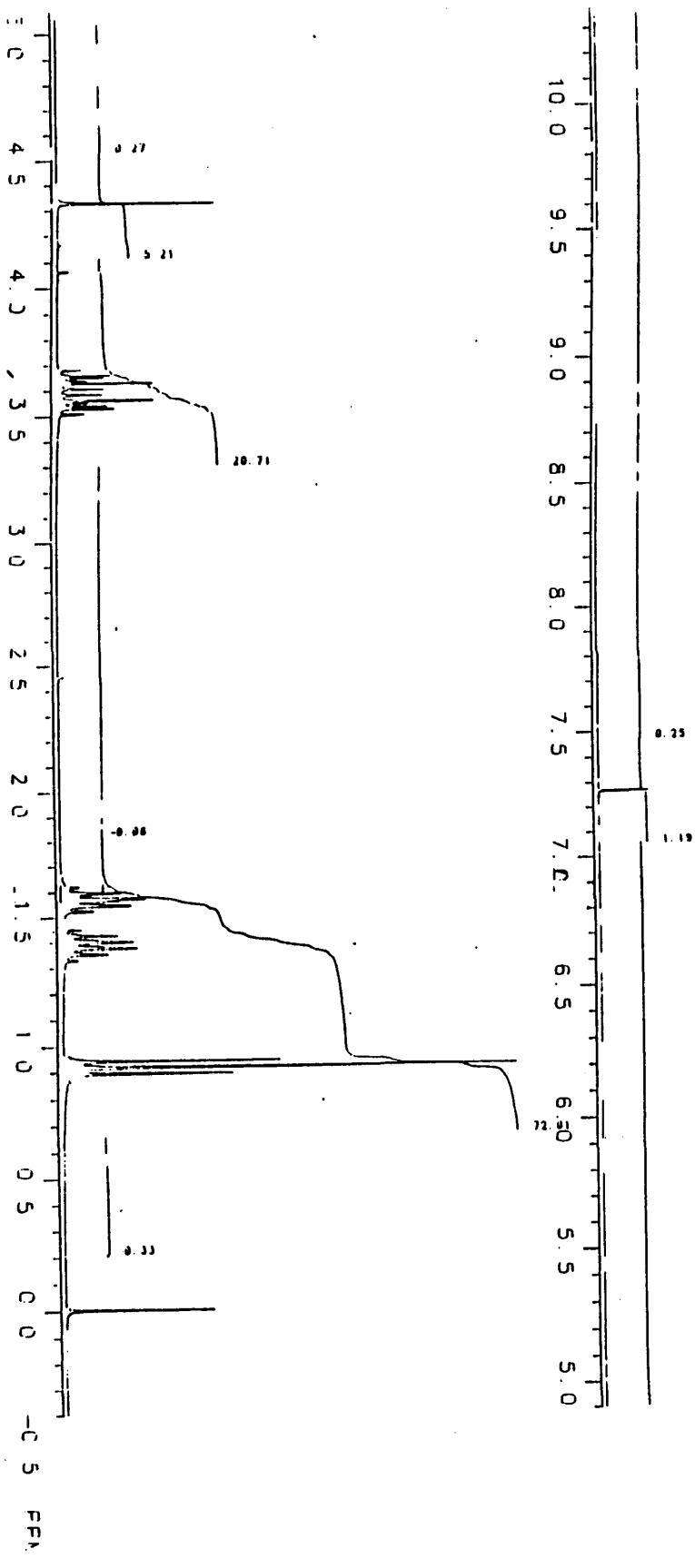
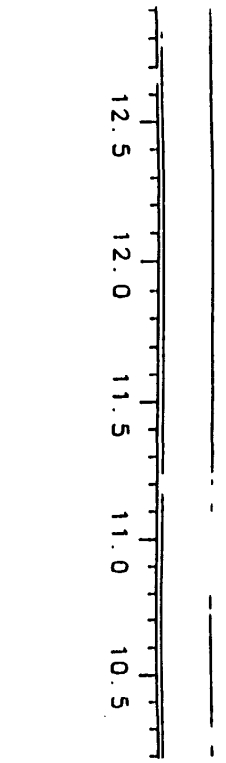
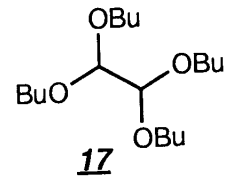
10.0

APPENDIX 2

DATA FOR EXPERIMENTAL SECTION







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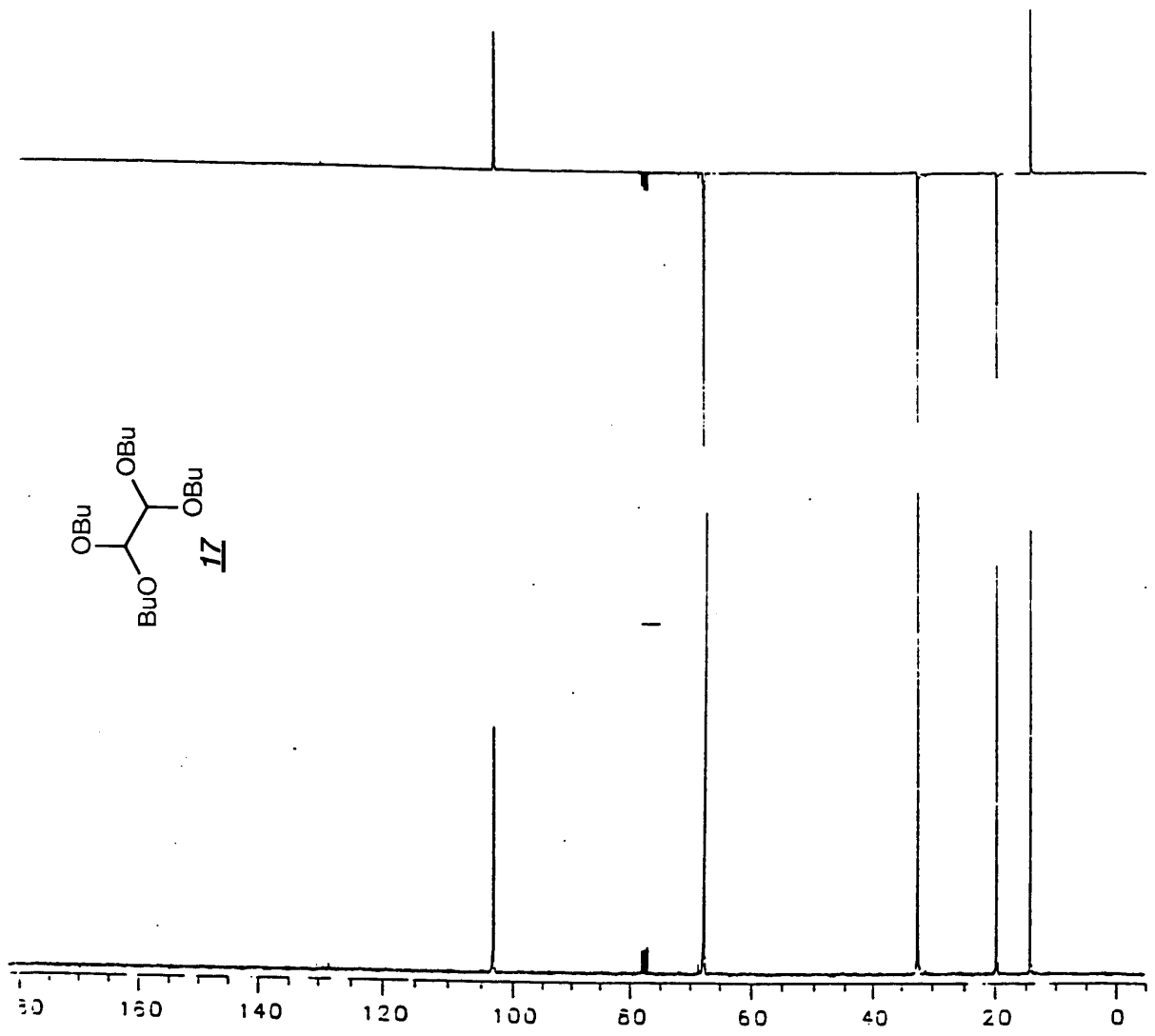

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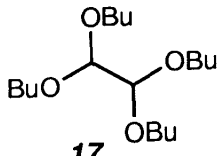

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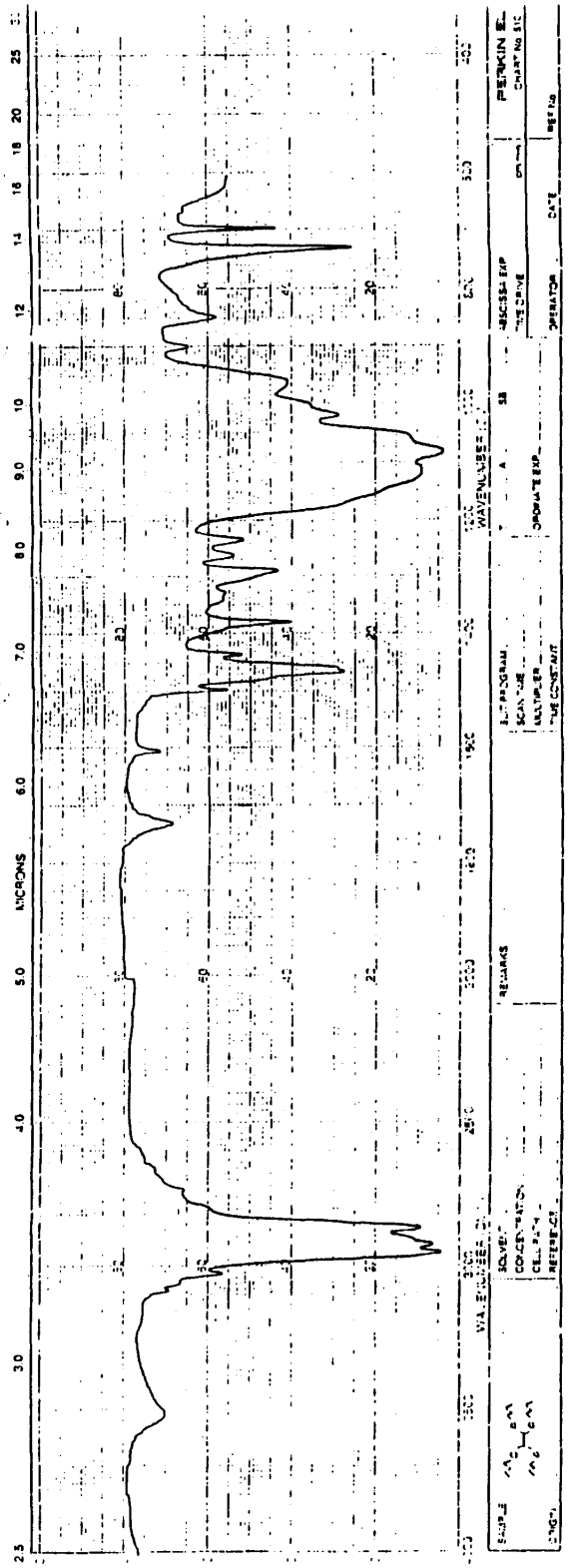

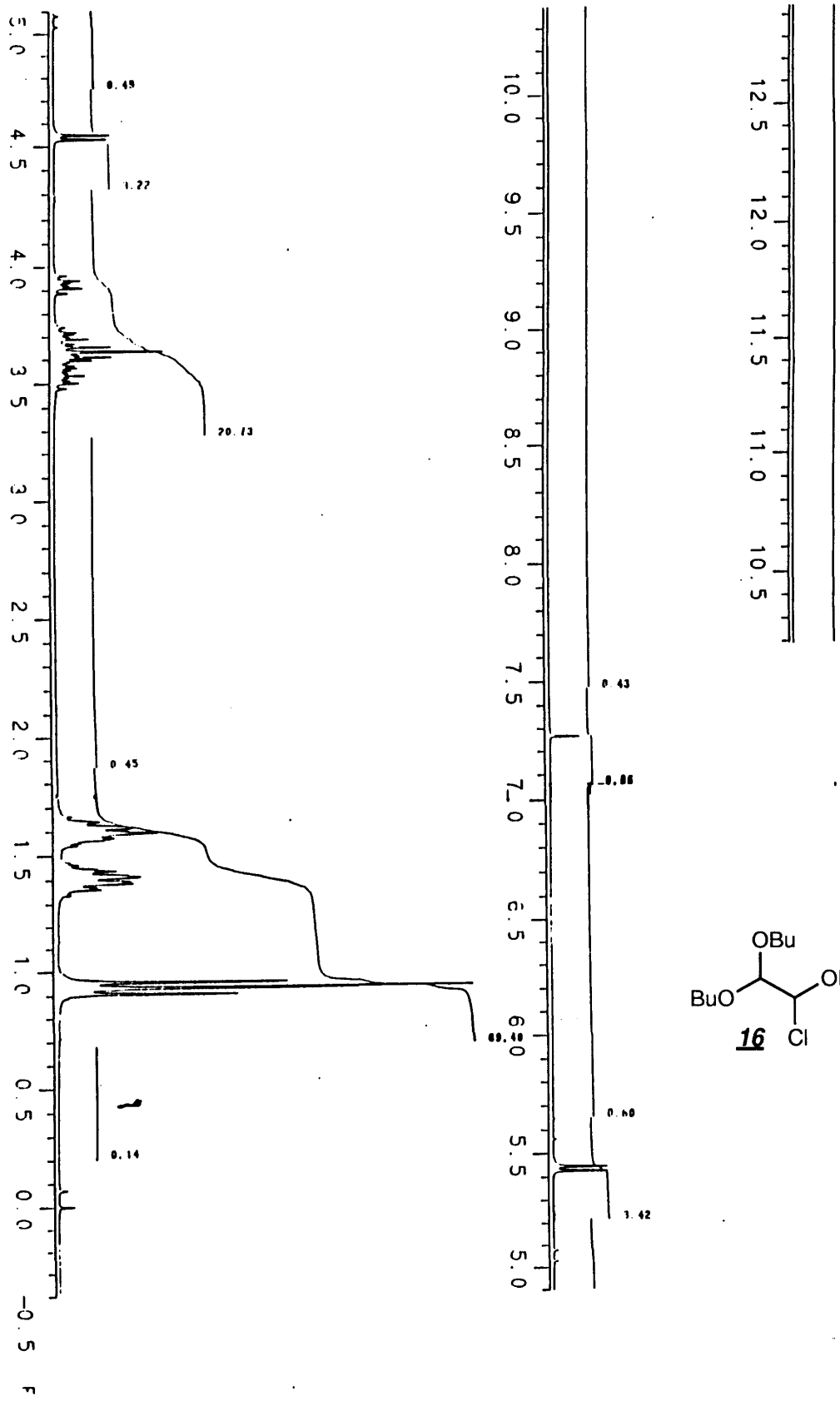

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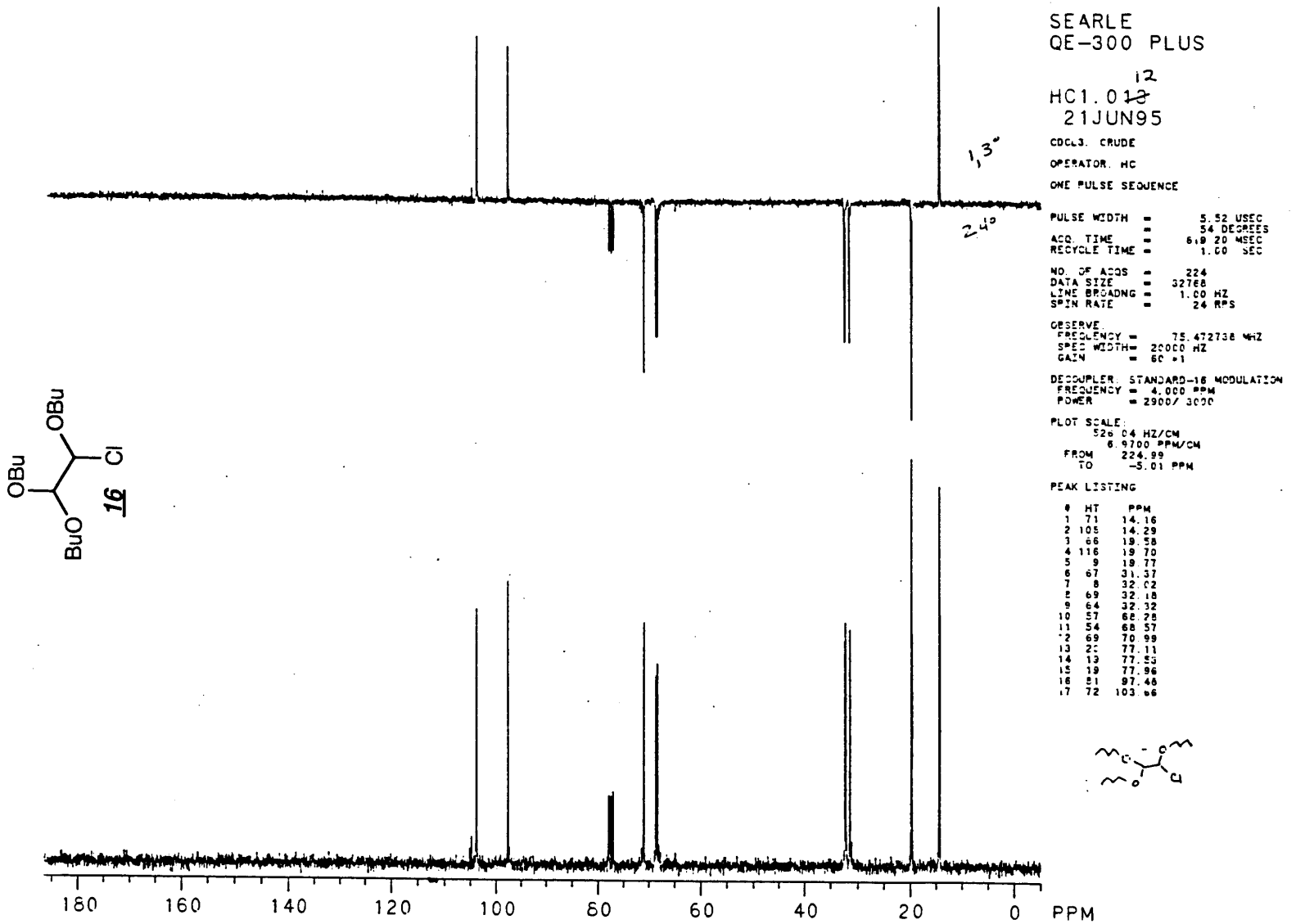
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21JUN95
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TO -5.01 PPM
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9 64 32.32
10 57 68.28
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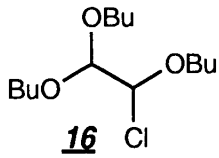
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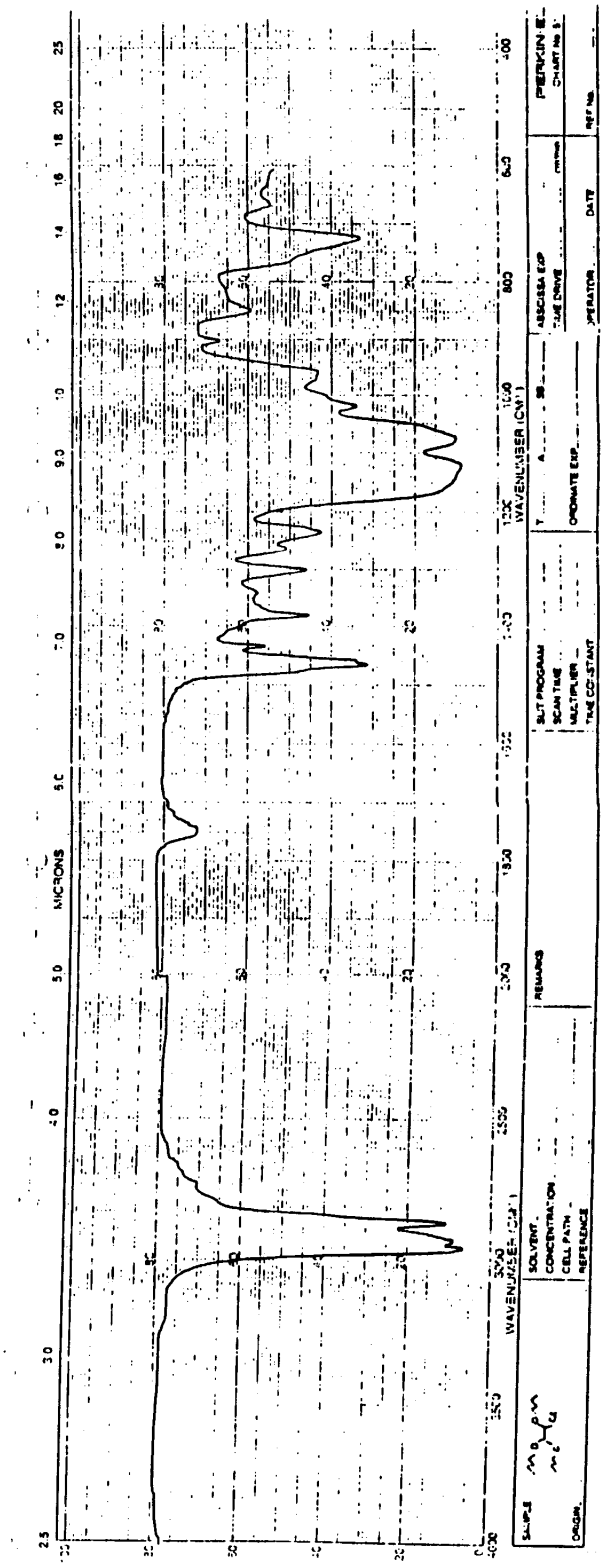
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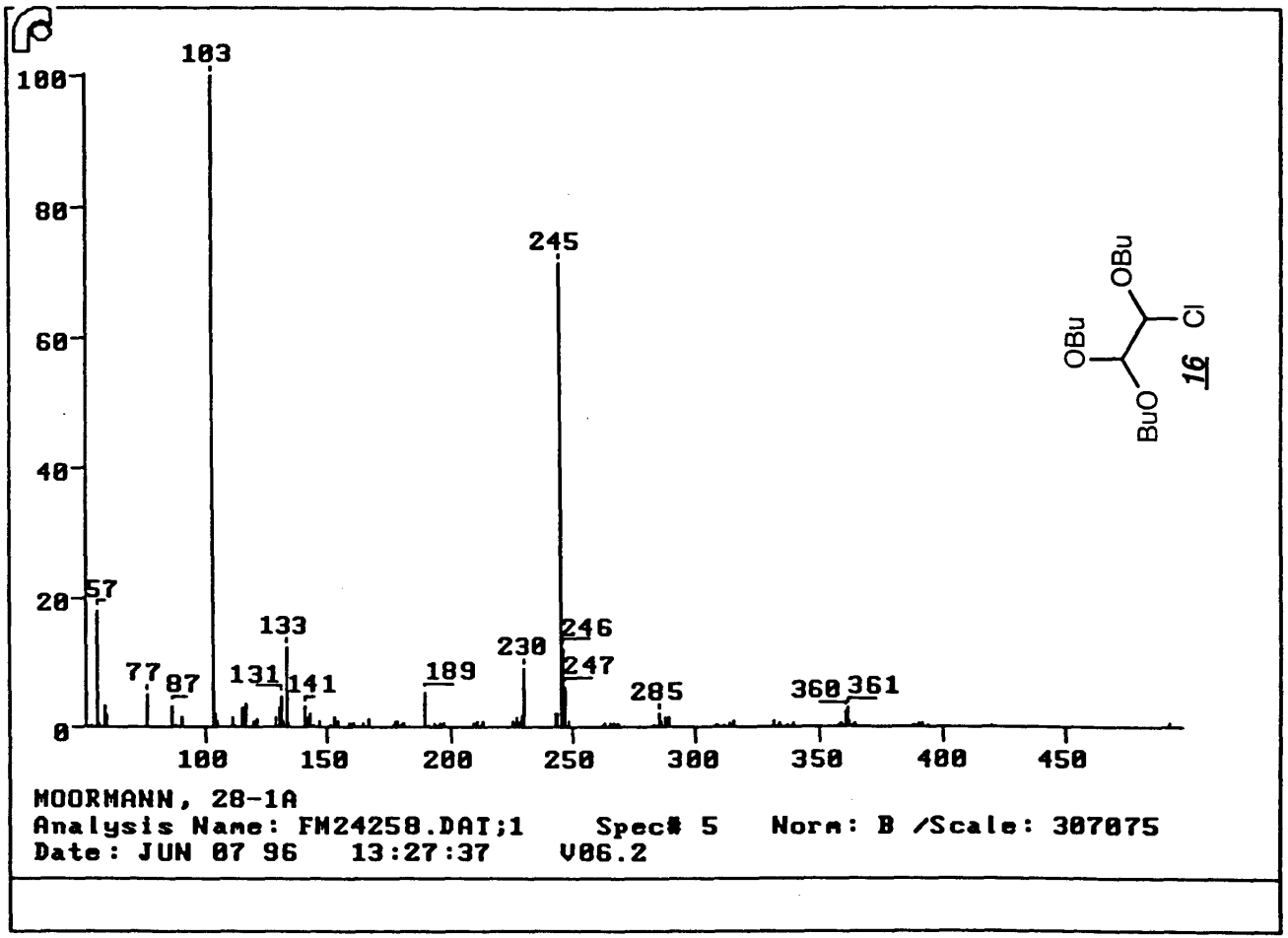
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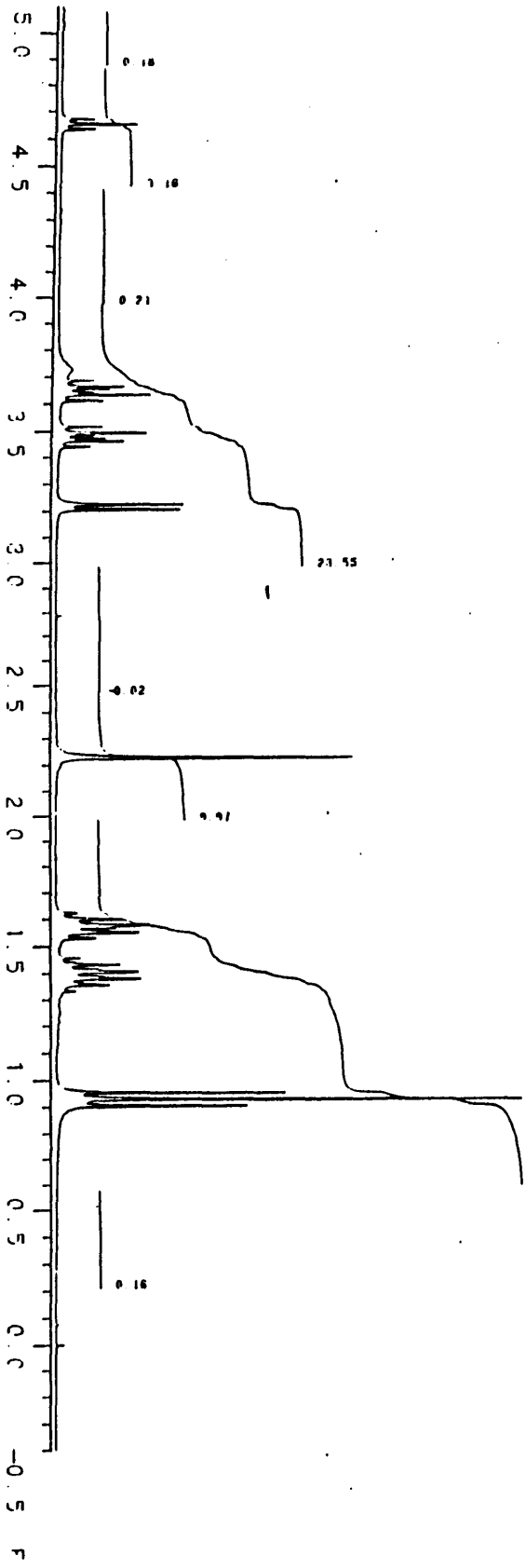

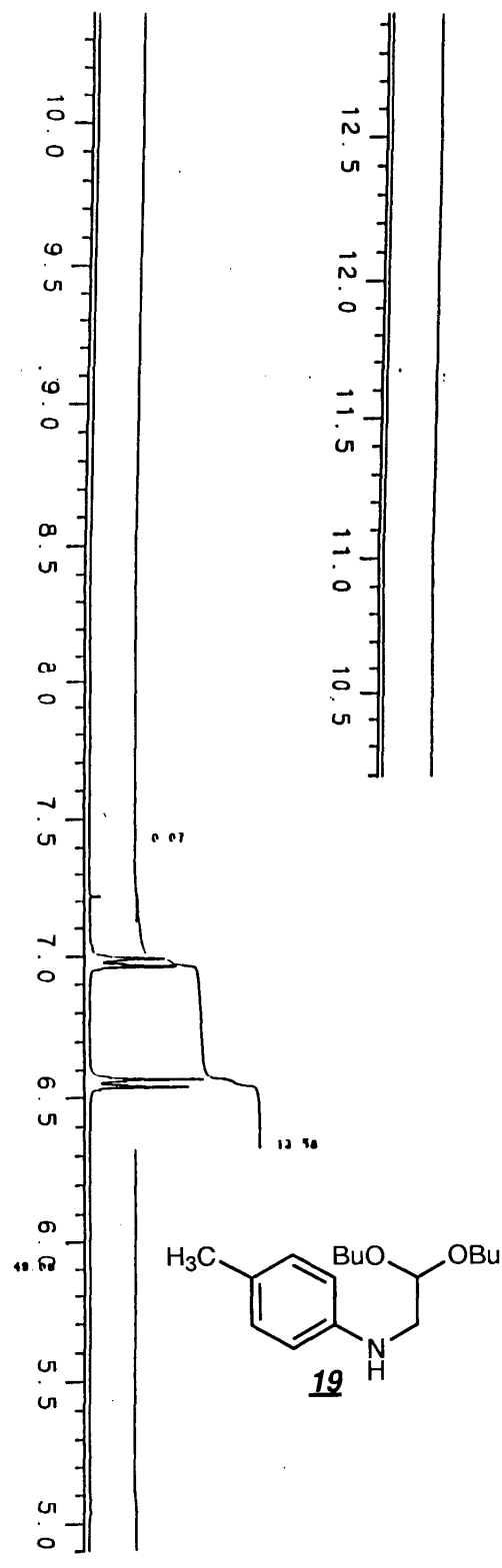

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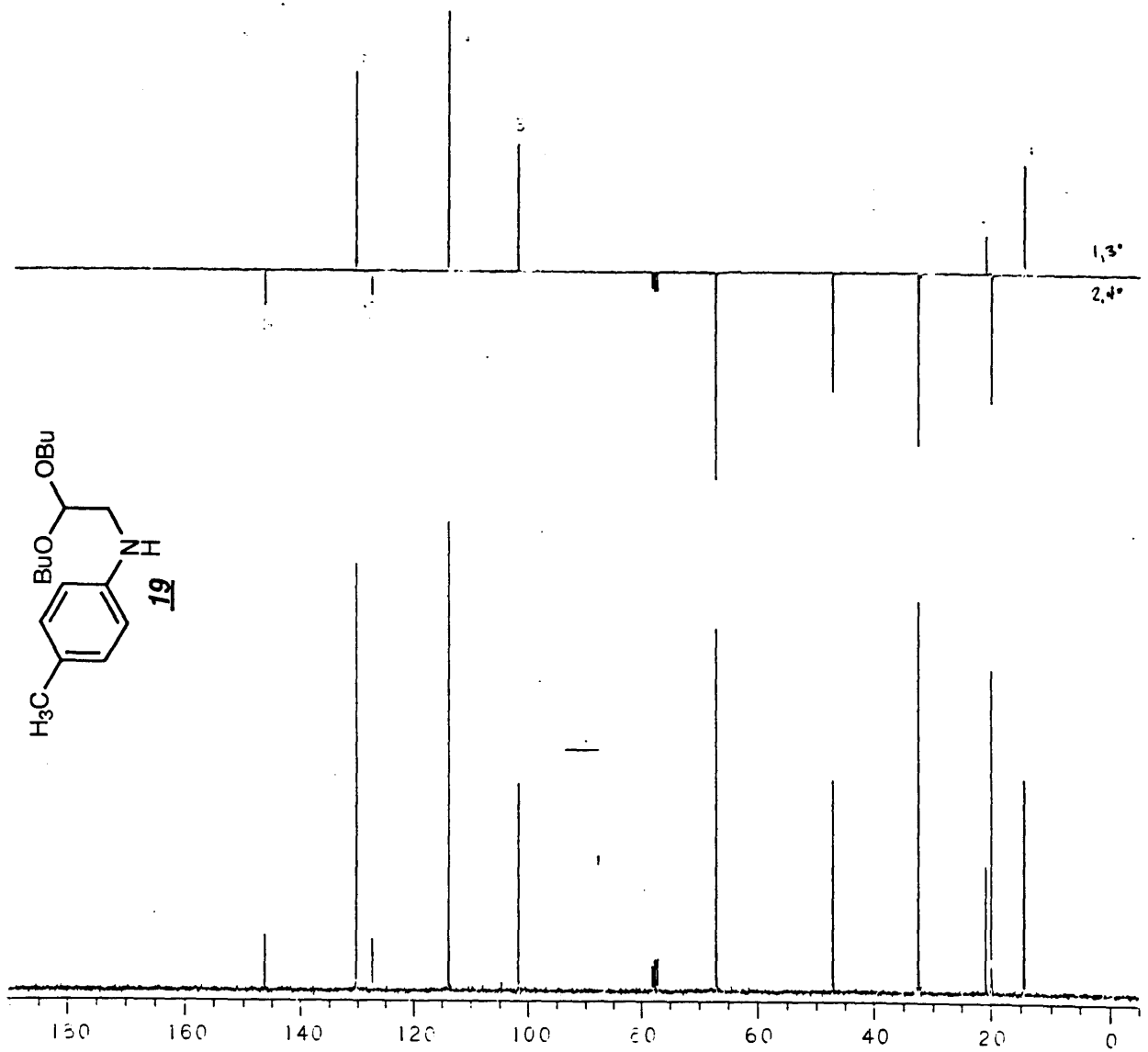

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HC1.031 30FI
31JAN96

CDCL3 PLATE CHROM.

OPERATOR HC

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RECYCLE TIME	=	1.00 SEC
NO OF ACQS	=	224
DATA SIZE	=	32768
LINE BROADNG	=	1.00 HZ
SPIN RATE	=	11 RPS

OBSERVE
FREQUENCY = 75.472736 MHZ
SPEC WIDTH= 20000 HZ
GAIN = 60 +1

DECOUPLER STANDARD-16 MODULATION
FREQUENCY = 4.000 PPM
POWER = 2500/ 3000

PLOT SCALE
526.04 HZ/CM
6.9700 PPM/CM
FROM 224.89
TO -5.01 PPM

PEAK LISTING

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5	58	47.14
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7	6	77.20
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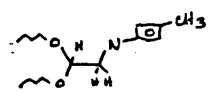
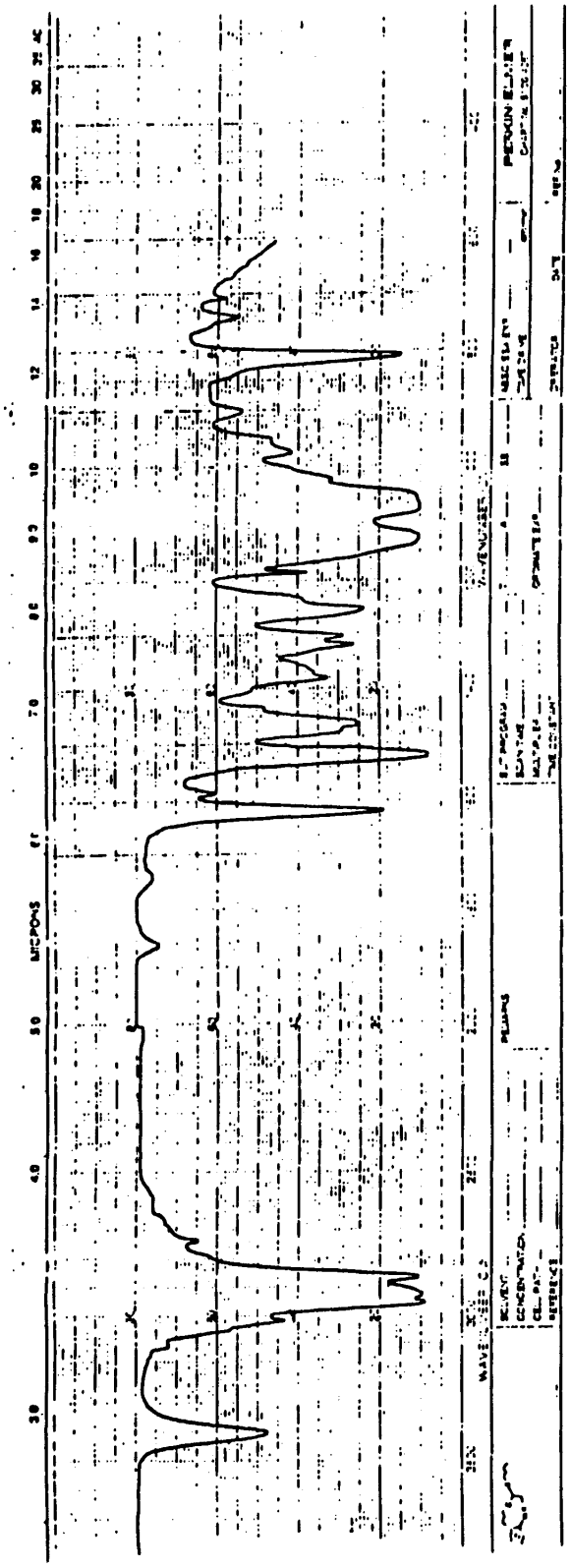
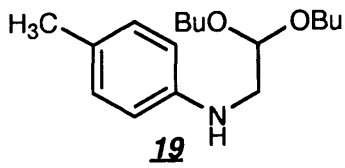
10	119	113.93
11	12	127.35
12	107	130.26
13	13	146.26

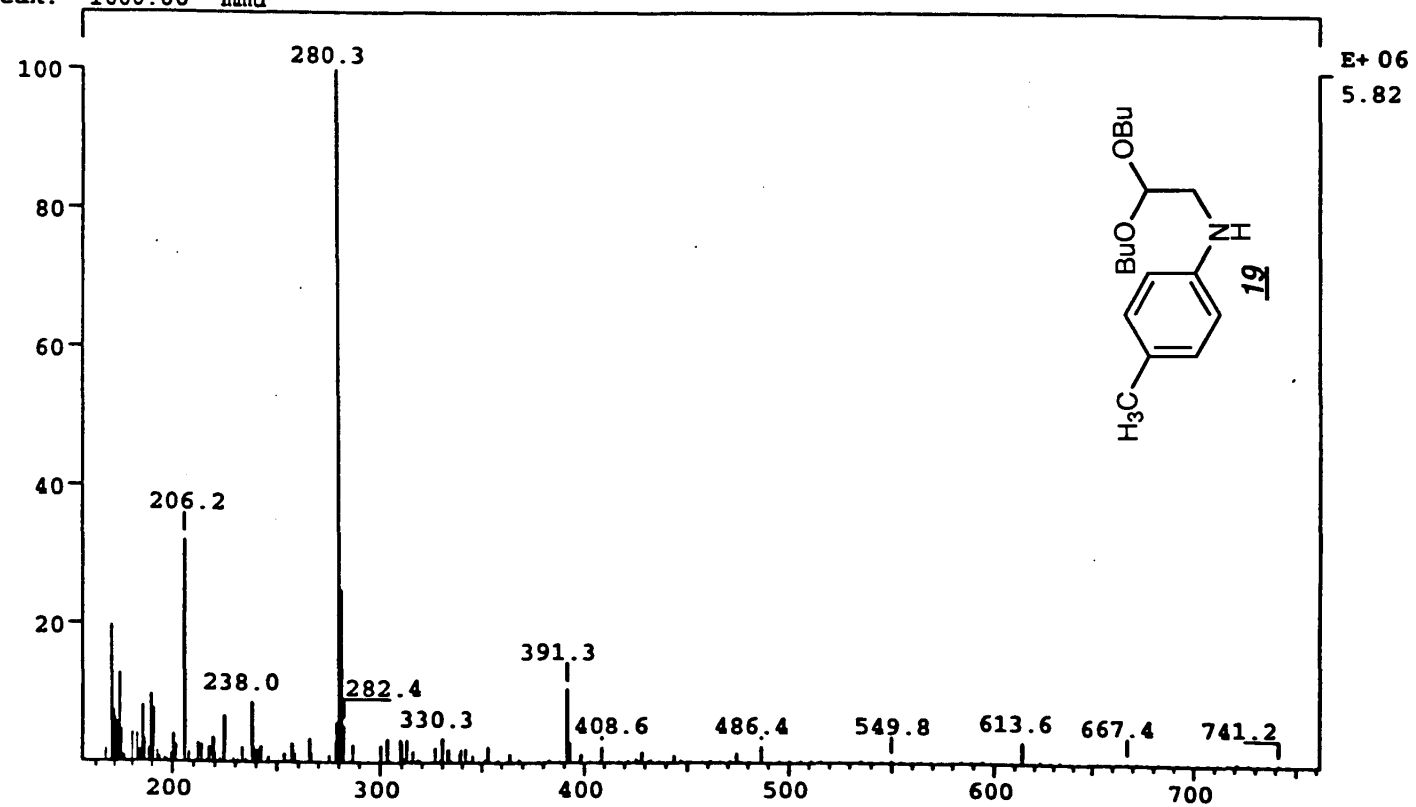


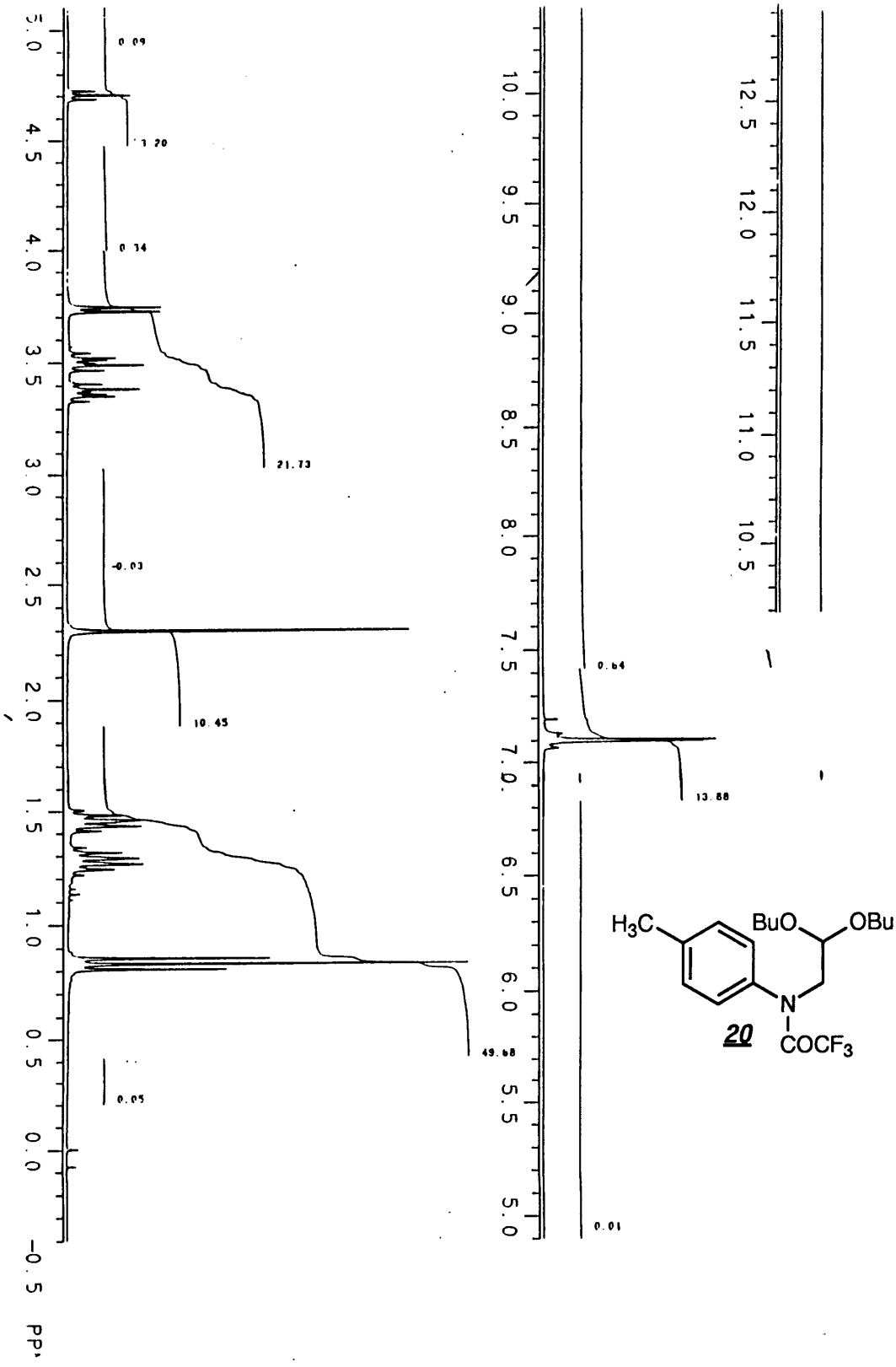




19

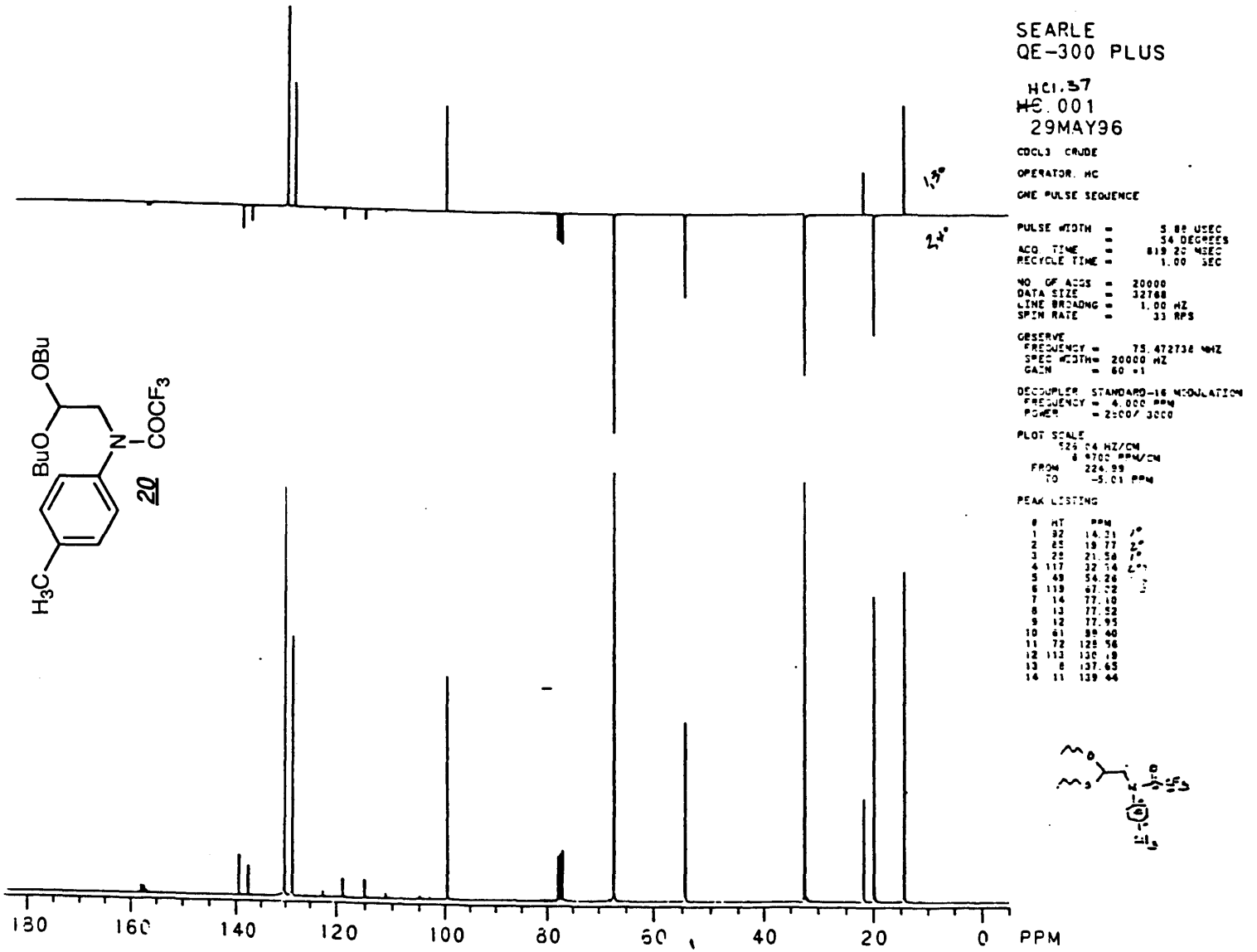
SPEC: ft11229 07-JUN-96 Elapse: 00:00:07.1 5
Samp: 28-1b Start : 13:00:06 30
Comm: APCI 500uL MW50,.5%AcA 10mL/80psi 5uA/400/150 EM1200/8,15k
Mode: +Q1MS LMR UP TREE LR Study : PA-202, MR12989
Oper: BLQ Client: Moormann Inlet :
Base: 280.3 Inten : 5822279 Masses: 165 > 750
Norm: 280.3 RIC : 26367080 #peaks: 384
Peak: 1000.00 mmu

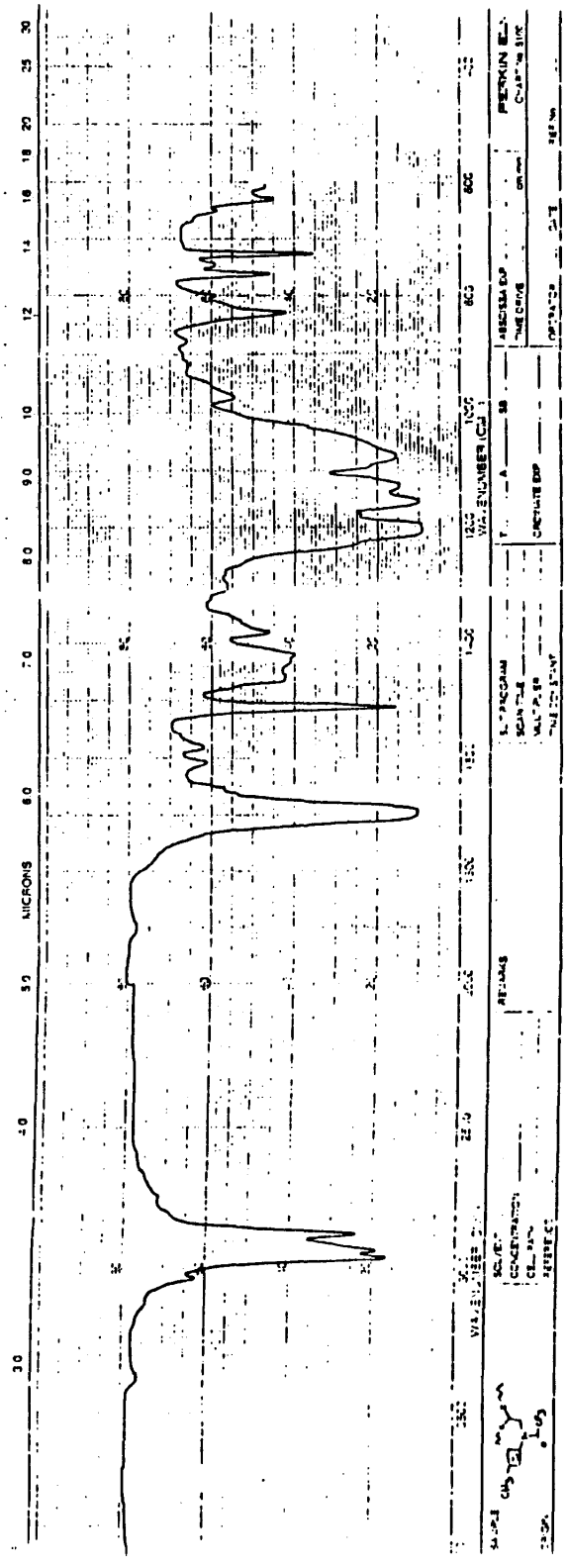


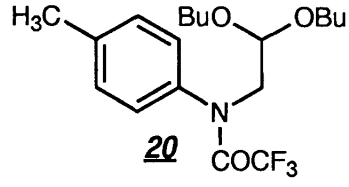

0.09
1.20
0.14
21.73
-0.03
10.45
49.68
0.05
0.64
13.88
0.01
PPM

H3C
BuO
OBu
N
COCF3

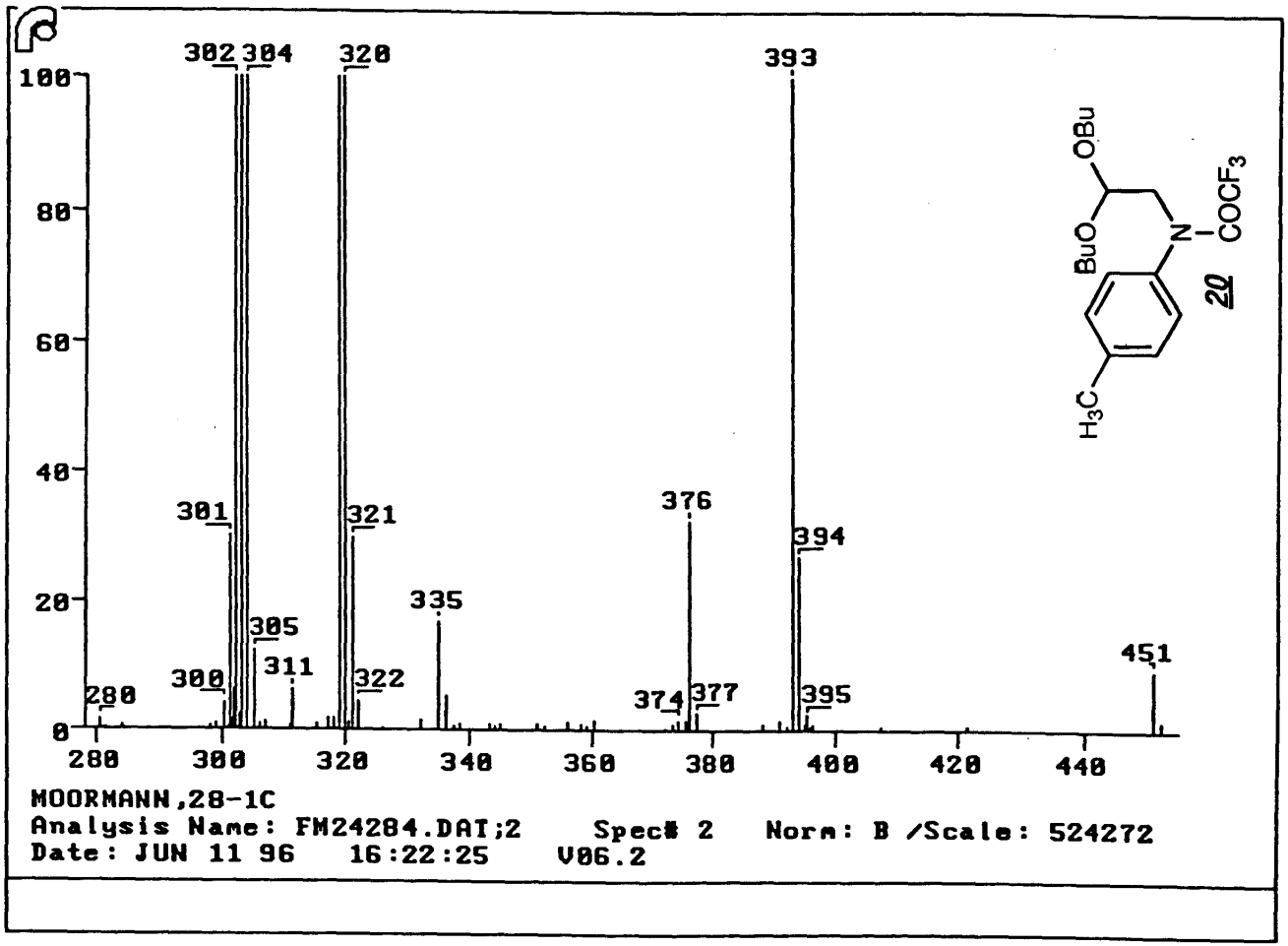
20


SEARLE
QE-300 PLUS
HC1.37
HC.001
29MAY96
CDCL3 CRUDE
OPERATOR: HC
ONE PULSE SEQUENCE
PULSE WIDTH = 5.88 USEC
= 34 DEGREES
ACQ TIME = 819.20 MSEC
RECYCLE TIME = 1.00 SEC
NO OF ACQS = 20000
DATA SIZE = 32768
LINE BROADNG = 1.00 HZ
SPIN RATE = 33 RPS
OBSERVE
FREQUENCY = 75.472738 MHZ
SPEC WIDTH= 20000 HZ
GAIN = 60 +1
DECOUPLER STANDARD-16 MODULATION
FREQUENCY = 4.000 PPM
POWER = 2500/ 3000
PLOT SCALE
526.04 HZ/CM
6.9700 PPM/CM
FROM 224.99
TO -5.01 PPM
PEAK LISTING
HT PPM
1 32 14.31
2 85 19.77
3 29 21.58
4 117 32.14
5 49 54.26
6 119 67.52
7 14 77.10
8 13 77.52
9 12 77.95
10 61 89.40
11 72 128.56
12 113 130.18
13 8 137.65
14 11 139.44
OBu
BuO
N
COCF3
H3C
20
180
160
140
120
100
80
60
40
20
0
PPM





20


302
304
320
393
100
80
60
40
20
0
301
321
376
394
335
305
311
322
300
280
374
377
395
451
280
300
320
340
360
380
400
420
440
OBu
BuO
N
COCF3
H3C
20
MOORMANN,28-1C
Analysis Name: FM24284.DAT;2
Spec# 2
Norm: B /Scale: 524272
Date: JUN 11 96
16:22:25
V06.2

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VITA

Helen (Wu) Chen graduated as Valedictorian from Haddonfield Memorial High School, NJ in 1988. In 1992, she received her Bachelors of Art degree with magna cum laude in chemistry from Bryn Mawr College, PA. Soon after graduation, she joined the Process Research group of Bristol-Myers Squibb in Princeton, NJ where she worked on thrombin antagonists and β-lactams. After 2 years, she moved to Illinois and joined the medicinal chemists at G.D. Searle working on LTA_4 antagonists and in the area of anti-cancer agents. While at Searle, she resumed her education at Loyola University of Chicago, studying under the direction of Dr. James Babler for a Master of Science degree. In 1996 , she moved back to NJ where she is currently employed at Merck & Co. as a medicinal chemist in the area of antibiotic research. She will receive her Master of Science degree in January 1998.

THESIS APPROVAL SHEET

The thesis submitted by Helen Y. Chen has been read and approved by the following committee:

James Babler, Ph.D., Director
Professor of Chemistry
Loyola University of Chicago

David Crumrine, Ph.D.
Professor of Chemistry
Loyola University of Chicago

Jonathan Zerkowski, Ph.D.
Assistant Professor of Chemistry
Loyola University of Chicago

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated and that the thesis is now given final approval by the committee with reference to content and form.

The thesis is therefore accepted in partial fulfillment of the requirements for the degree of Master of Science.

11/22/97
Date

James H. Babler
Director's Signature