

November 20, 1990
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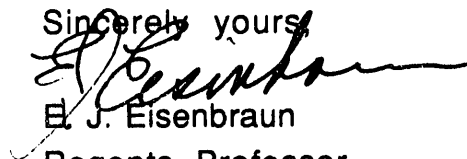
U. S. Department of Energy
Pittsburgh Energy Technology Center
Acquisition and Assistance Division
P. O. Box 10940
Pittsburgh, P. A.

Attention: Jeffrey C. Bogdan:

Dear Mr. Bogdan:

The first quarterly Technical Progress Report for Task I: Synthesis of 6-Methyl-9-propyldibenzothiophene-4-ol (DE-AC22-90PC 90035) is enclosed. According to Part III, Section J, Attachment B, of the contract, this is to be a draft copy. I have labeled this version of the report accordingly. I assume that you will contact me for changes which are to be included in the final draft.

Sincerely yours,



E. J. Eisenbraun

Regents Professor

Principal Investigator

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"U. S./DOE Patent Clearance is not required prior to publication of this document."

November 20, 1990

Technical Progress Report No. 1 (draft copy)

Report period: July 25, 1990-Oct. 25, 1990

CONTRACT TITLE AND NUMBER:

Task I: Synthesis of 6-Methyl-9-propyldibenzothiophene-4-ol
DE-AC22-90PC 90035

CONTRACTOR NAME: Oklahoma State University
Stillwater, OK 74078

CONTRACT PERIOD: July 25, 1990- July 25, 1992

CONTRACT OBJECTIVE: Synthesis and purification of the title compound.

The Synthesis Plan: The synthesis route for the preparation of the title compound, shown as number **7** in the enclosed synthesis sequence, has been carried, on a small scale, to the preparation of **5** as a mixture of isomers. The conversion of this material to **6** and an isomer is currently under study.

TECHNICAL SUMMARY:

The conversion of commercially available 4'-methylpropiophenone (**1**) to 1-methyl-4-*n*-propylbenzene (**2**) was accomplished in high yields (86 % of distilled product)¹. We do not anticipate problems in increasing the scale of the reaction to provide needed quantities of **2**.

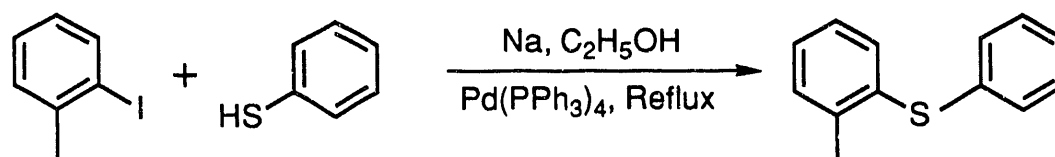
Literature reports^{2,3} claiming specificity in the bromination of **2** to 2-methyl-5-*n*-propyl-1-bromobenzene (**3**) were found to be in error and instead a mixture of **3** and the isomer, 5-methyl-2-*n*-propyl-1-bromobenzene, was obtained in a 2.3:1 ratio. The yield of this mixture was 94%. This reaction most likely favors **3** as the

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major product of the two isomers. We do not plan to separate isomers at this stage.

This material was used to study the conversion of **3** and its isomer to a mixture of **5** and the corresponding isomer through treatment with sodium butoxide and 2-methoxybenzenethiol in the presence of the $\text{Pd}[\text{P}(\text{C}_6\text{H}_5)_3]_4$ in 1-butanol solvent⁴. This is shown in the synthesis sequence as the step in the direct conversion of **3** to **5**. This reaction provided the mixture of **5** and an isomer (GC ratio 1.7:1) in 60 % yield. The reaction was sluggish, with recovered starting material, despite 18 h of reflux. To determine whether the ortho-alkyl group in **3** and its isomer could be exerting an adverse steric hindrance in the reaction and to learn whether the iodo analog of **3** would be superior, a model reaction substituting 2-iodotoluene for **3** and benzenethiol for 2-methoxy-benzenethiol was run, as shown below. It is known that the reactivity of aryl halides in this reaction is $\text{ArI} > \text{ArBr} > \text{ArCl}$. An additional change was to run the reaction in ethanol rather than 1-butanol. This is an advantage because it was found that the removal of 1-butanol from the product mixture in the preparation of **5** was difficult.



Gas Chromatography studies showed that all of the 2-iodotoluene had been consumed and that the crude product showed two peaks in the ratio 97:3. The theoretical weight of crude product was observed. This result suggested that the iodo-analog of **3** would be superior to **3** as a starting material.

Accordingly, **2** was iodinated using iodine with periodic acid as an oxidant⁵. As expected from our experience in the bromination

of **2**, the product was found by gas chromatography to be a 2.8:1. The reaction was run with the hydrocarbon in excess so recovery of hydrocarbon was expected. The gas chromatography ratio, including the hydrocarbon (first peak) was 43:13:36. It is expected that the major isomer will prove to be the desired 2-methyl-5-*n*-propyl-1-iodobenzene. This product mixture, after distillation to concentrate the iodo product, is being used in preparing the sulfide **5** and its isomer.

The sulfide mixture, represented by **5** and its isomer, is being photocyclized in the presence of iodine as shown in Step 5 of the synthesis sequence. The initial studies are being carried out using the sulfide prepared from brominated material.

A decision to use iodination vs. bromination will be made when more data are accumulated. In addition, we intend to explore the preparation of **5** via **4** to be certain that we have the most efficient route before large-scale work will be attempted.

The current work and work planned for the new quarter include finishing the preparation of **6** and **7**, separating isomers, establishing the structures as well as determining the properties of the products in the synthesis scheme. We shall attempt isomer separation at both **6** and **7** in the synthesis sequence since we anticipate both **6** and **7** to be solids.

EXPERIMENTAL

Wolff-Kishner Reduction of 4-Methylpropiophenone (1) to 1-Methyl-4-*n*-propylbenzene (2). 4-Methylpropiophenone (101.4 g, 0.63 mol), hydrazine hydrate (150 mL), sodium hydroxide (27 g, 0.67 mol), potassium hydroxide (43 g, 0.66 mol) and diethylene glycol (500 mL) were added to a stainless steel apparatus containing a magnetic stirring bar. The apparatus was fitted with a thermocouple probe, Dean-Stark trap, stainless-steel water

condenser and a nitrogen inlet tube. This apparatus, constructed mainly of stainless steel, was specifically designed for this type of reaction in order to avoid the attack of alkali on glass¹.

The apparatus was flushed with nitrogen and heating with stirring was carried out at such a rate that nitrogen from the decomposing hydrazone was vigorous. As the reaction proceeded, the hydrocarbon product distilled and was collected in the Dean-Stark trap as an upper layer [107.4 mL (103.7 mL theoretical)].

The product was transferred to a separatory funnel, dissolved in 500 mL of ether, washed with dilute hydrochloric acid (2x50 mL), water (3x50 mL), dried (MgSO₄), filtered, concentrated (rotary evaporation) to 87.0 g (98%) of a pale yellow oil. Gas chromatography studies using OV-101 substrate at 130 °C showed approximately 95% purity. Vacuum distillation, using a Kugelrohr apparatus, gave 76.2 g (86 %) of colorless liquid. The ¹H and ¹³C NMR spectra, copies of which are enclosed, verified the structure of the product as 1-methyl-4-n-propylbenzene (2).

Bromination of 1-Methyl-4-n-propylbenzene⁶. A 500 mL, 3-neck flask was fitted with condenser, magnetic stir-bar, thermocouple probe and pressure-equalized dropping funnel. The top joint of the condenser was connected to an empty trap which, in turn, led to a second trap containing magnetically stirred 10% sodium hydroxide. This alkali trap absorbs hydrogen bromide produced by the reaction. 1-Methyl-4-n-propylbenzene (134 g, 1.0 mol), iodine (2 crystals) and iron powder (2.5 g, 325 mesh) were added to the reaction flask. The flask was then immersed in an ice-salt bath and cooled to -6 °C. Bromine (45 mL, 139.8 g, 0.88 mol, 0.9 equiv.) was added to the stirred reaction mixture during 2.5 h. The inside temperature was maintained around -3 °C during addition. The reaction mixture was allowed to warm to room temperature overnight.

The brown reaction mixture was poured into water (500 mL) and the mixture was then transferred to a separatory funnel. This operation was carried out in a hood. The layers were separated and the aqueous layer was extracted with hexane (3 x 300 mL). The organic layers were combined, washed with 10 % NaOH (200 mL) and water (3 x 200 mL), dried (MgSO_4), filtered, concentrated (rotary evaporation) and then pumped to constant weight (189 g, 102 % yield) of light brown oil. Kugelrohr distillation gave a clear colorless oil (175 g, 94 % yield) and 12.6 g of dark brown pot residue. The ^1H and ^{13}C NMR spectra of the distillate showed it to be a mixture of the expected product and an impurity. There is a characteristic pmr peak at $\delta = 7.34$ (s, 1H, ArH). The ratio of expected product: isomer: unknown was 2.3:1.0:0.1.

Coupling of 1-Bromo-2-methyl-5-*n*-propylbenzene and 1-Bromo-5-methyl-2-*n*-propylbenzene with 2-Methoxybenzenethiol⁴.

A 500-mL, 3-neck, round-bottom flask was fitted with two reflux condensers, stopper and Teflon-coated stirring bar. Nitrogen was introduced and vented through the two condensers. The system was purged with nitrogen while 1-butanol (200 mL) and freshly-cut pieces of sodium (3.05 g, 0.133 g. atom, 2.7 equiv.) were introduced. This heterogeneous mixture was stirred at room temperature until all of the sodium had reacted (0.5 h). A solution of the mixture of title bromo compounds (10.66 g, 0.050 mol) and 2-methoxybenzenethiol (5.75 g, 0.040 mol) in 50 mL of 1-butanol was then added followed by 0.62 g (5.37×10^{-4} mol, 1.1 mol %) of $\text{Pd}[\text{P}(\text{C}_6\text{H}_5)_3]_4$ catalyst. This reaction mixture was heated, under nitrogen, at reflux for 18 h during which a dark color developed.

The cooled reaction mixture was concentrated under vacuum (rotary evaporator) to a dark grey slush. Since washing the slush with hexane was ineffective, the product was transferred to a separatory funnel containing 300 mL of water and the mixture was extracted with hexane (3 x 300 mL). The combined extracts were washed with water (3 x 100 mL), dried (MgSO_4), and filtered through a pad of basic alumina. The filtrate was concentrated under vacuum

(rotary evaporator) and further stripped using a vacuum pump to 14.86 g (138 %) of colorless oil. At this point, some 1-butanol remained. GC analysis (programming from 120 to 290 °C at 20 °/min) of this liquid showed unreacted starting material (36 %) and two product peaks in the ratio of 57:33. The estimated yield of coupled product, based on GC studies, is 60%. Steam distillation of the distilled reaction mixture was effective in separating the starting bromo material from the product but some of the product slowly steam distilled.

Coupling of 2-Iodotoluene and Benzenethiol⁴. The apparatus described above was charged with 200 mL of absolute ethanol and freshly-cut sodium (5.52 g, 0.24 g-atom, 4.8 equiv.) was added in small pieces. After all of the sodium had reacted, a solution of 2-iodotoluene (11.12 g, 0.05 mol) and benzenethiol (5.52 g, 0.05 mol) in 50 mL of absolute ethanol was added followed by addition of Pd[P(C₆H₅)₃]₄ (0.51 g, 4.4 x 10⁻⁴ mol, 0.88 mol %).

A dark-brown color developed during 16 h of heating at reflux. The cooled reaction mixture was transferred to a separatory funnel, diluted with 300 mL of water, extracted with hexane (4 x 75 mL) and the combined extracts were washed with 10% sodium hydroxide (2 x 30 mL), water (3 x 50 mL), dried (MgSO₄), filtered, concentrated under vacuum, and pumped (oil pump) for 4 h affording 10.05 g (100 %) of crude brown-colored but clear oil. GC analysis at 220 °C showed 2-iodotoluene (4.4 min) to be absent and the presence of a major product (97%) and two minor impurities (3%).

Iodination of 1-Methyl-4-n-propylbenzene (2)⁵. To a 1-L, round-bottom flask containing a magnetic stir-bar and fitted with a thermometer, was added 1-methyl-4-n-propylbenzene (60.4 g, 0.45 mol), glacial acetic acid (170 mL), periodic acid (H₅IO₆, 15.40 g, 0.068 mol), iodine (33.90 g, 0.134 mol), and sulfuric acid (6.0 mL diluted with 32 ml of water). The resulting dark-brown reaction mixture was heated with stirring to 56 °C during 1 h and then maintained at 52-56 °C for four additional hours. The cooled

reaction mixture was then transferred to a separatory funnel using water and dichloromethane. The layers were separated and the top (aqueous) layer was extracted with dichloromethane (4 x 200 mL). All of the dichloromethane layers were combined, washed with saturated sodium bicarbonate (2 x 200 mL), dilute sodium bisulfite (2 x 200 mL), and water (2 x 200 mL). The residual organic layer was dried (MgSO_4), filtered, concentrated (rotary evaporation) and pumped (oil pump) affording 92.5 g of crude product as a dark-pink liquid which was shown by gas chromatography (DB-1, 130 °C to 290 °C at 20 °C/min) to consist of unreacted hydrocarbon (43 %), monoiodo compound (13%), second monoiodo compound (36 %) and diiodo impurity (9%). The presence of unreacted hydrocarbon was expected since less than one equivalent of iodine was used in this trial run in order to minimize the formation of polyiodo side products. The unreacted hydrocarbon appears to be separable from the iodo products by fractional distillation.

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- (3) Taylor, E. P. ; Watts, G. E. **J. Chem. Soc.** **1952**, 1123-1127.
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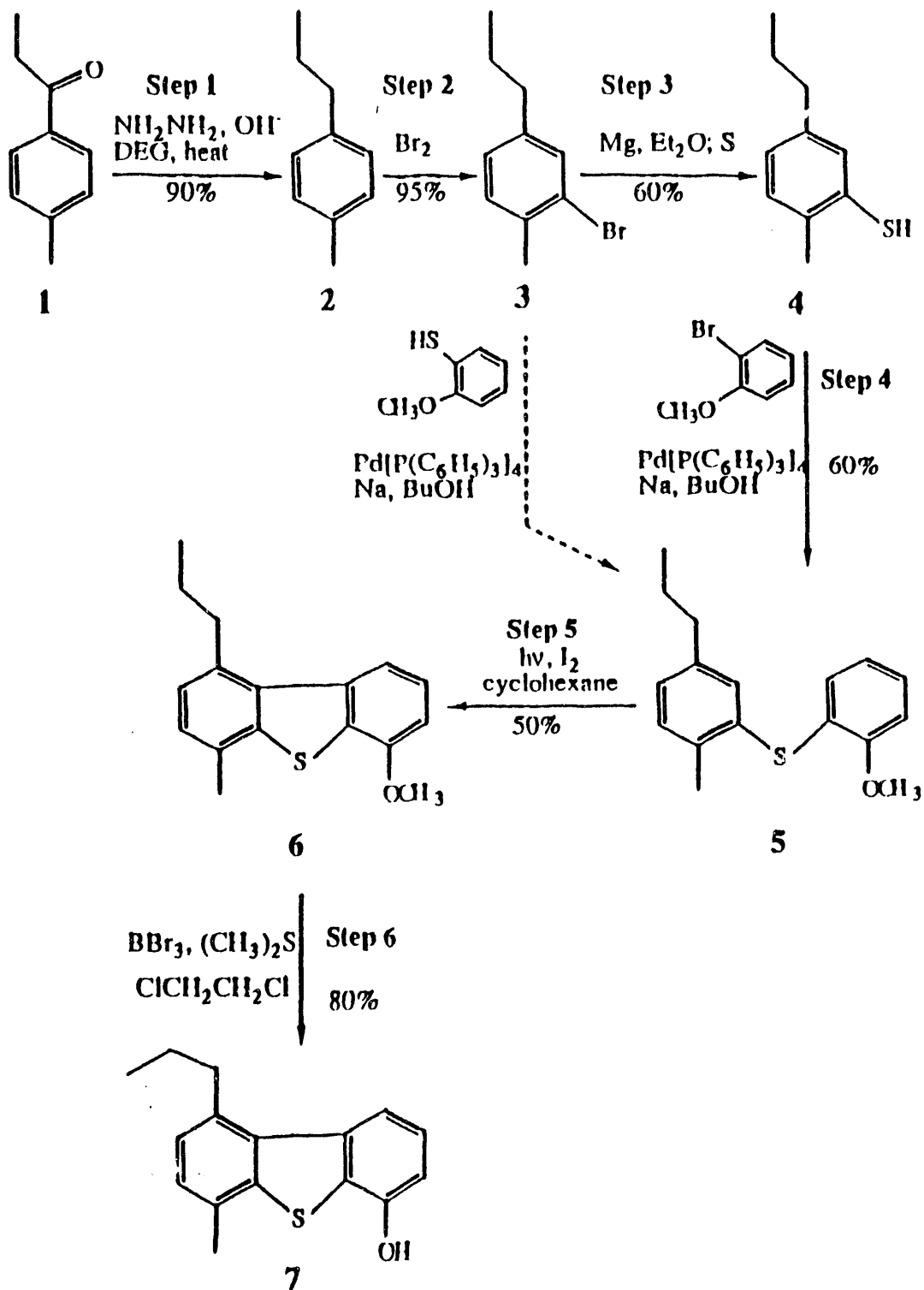


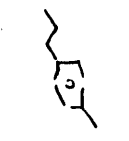
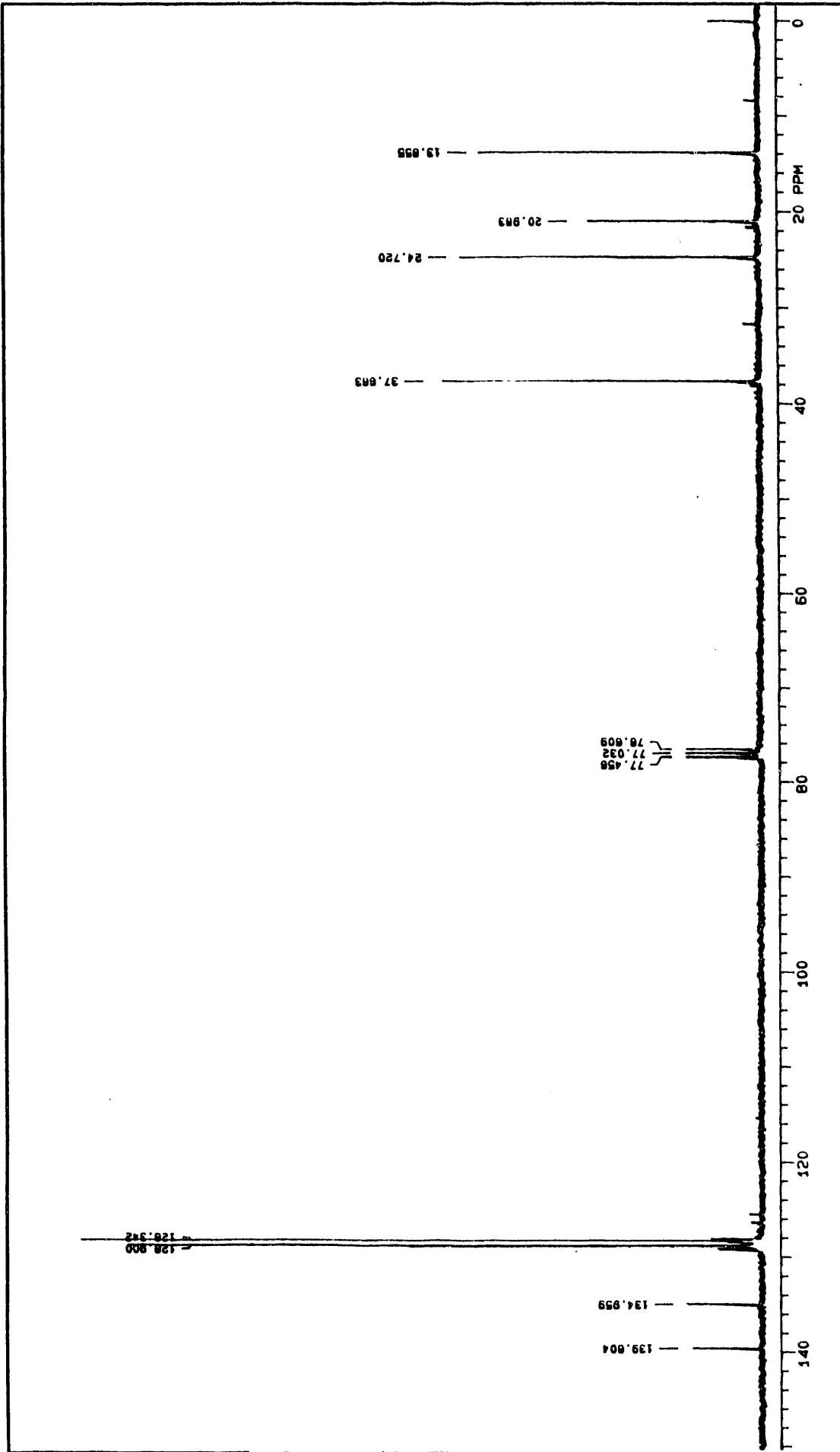
E. J. Eisenbraun

Regents Professor

Principal Investigator

Task I: Proposed Synthetic Sequence





Pulse Sequence: zgpg30
 Tube O.D.: 5 mm
 Temp.: 123.0 °C
 Solvent: CDCl3

EXPERIMENT

NUC1: 13 NUC2: 13
 P1: 6.4 P2: 6.4 P3: 6.4 P4: 6.4
 U1: 1.500 U2: 1.500 U3: 1.500 U4: 1.500
 Width: 11.453 Hz/turn Scan: -123.0 Hz/turn
 Reference: CDCl3

PROT/PROCESSING

NUC1: 13 NUC2: 13
 Mode: YVY Power: 0 dB
 Modulator Mode: 5 Freq: 7800 Hz
 Pulse Width: 17.5 µsec Power Mode: ---

DESCRIBE

NUC1: 13 NUC2: 13
 Spec. Width: 17985.6 Hz Channel: 1400 Hz
 Acq. Time: 1.112 sec Delay: 3.000 sec
 Pulse Width: 12.0 µsec Transmits: 256

REFERENCE

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