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July 25, 1991
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U. S. Department of Energy
Pittsburgh Energy Technology Center
Acquisition and Assistance Division
P. O. Box 10940
Pittsburgh, PA

Attention: Jeffrey C. Bogdan:

Dear Mr. Bogdan:

The fourth quarterly Technical Progress Report for Task I: Synthesis of 6-Methyl-9-*n*-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,

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DOE/PC/90035-T4

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July 25, 1991
Quarterly Technical Progress Report No. 4 (draft copy)
Report period: April 25-July 25, 1991

CONTRACT TITLE AND NUMBER:
Task I: Synthesis of 6-Methyl-9-n-propyldibenzothiophene-4-ol
DE-AC22-90PC 90035

CONTRACTOR NAME: Oklahoma State University
Stillwater, OK 74078

CONTRACT PERIOD: July 25, 1990- July 24, 1992

CONTRACT OBJECTIVE: Synthesis and purification of the title compound.

Technical Summary: The material covered in this report has been described to some extent in Status Reports 9, 10 and 11 and can be divided into two parts: (a) further cyclization experiments on 1,4-diethyl-2-[(2'-methoxyphenyl)thio]benzene (**5c**, analogous to **5a** of Scheme I) and its sulfone both by chemical and photochemical means, and (b) progress toward the synthesis of the modified target molecule, 9-isopropyl-4-methoxy-6-methyldibenzo-thiophene (**5a**, Scheme II).

Part A: Further cyclization experiments on 1,4-diethyl-2-[(2'-methoxyphenyl)thio]benzene (5c) *and its sulfone* (8c) . Several small-scale cyclization experiments were carried out on the single isomer 1,4-diethyl-2-[(2'-methoxyphenyl)thio]benzene (**5c**) using:

1. $(Ph_2Li)Na$ in diethyl ether
2. hv/pyrex, CH_2Cl_2, $(CN)_2C{=}C(CN)_2$
3. Amberlyst-15, 1,2-dichlorobenzene, reflux.

We have also attempted photocyclization of the corresponding sulfone **(8c)**, as well as, reaction of the latter with $VOCl_3$, CF_3COOH, and CH_2Cl_2 at O °C. A summary of our findings follow.

The first of these reaction conditions (diphenyllithium-sodium in ether) was reported by Wittig and Benz[1] to cyclize diphenyl sulfide to dibenzothiophene in 57% yield. Treatement of diethyl sulfide **5c** with freshly-prepared $(Ph_2Li)Na$ in anhydrous ether at room temperature for 69 h and at reflux for 3 days (*as prescribed in the literature procedure*) resulted in a product mixture consisting of more than 24 components (by GC).

The second reaction condition [hv/pyrex, CH_2Cl_2, $(CN)_2C{=}C(CN)_2$] was employed by Bendig et al[2] to convert methoxy-substituted stilbenes to phenanthrenes in high yield. *Tetra* cyanoethylene acts as a scavenger of any hydrogen produced in the second (aromatization) step of the transformation. We carried out this reaction as described in the experimental section and followed its progress by removing and analyzing aliquots at regular time intervals. The GC analysis showed that at short irradiation times (6 h or 18 h) about 3% conversion had taken place, but at long irradiation times (36 h), the reaction mixture consisted of:

unreacted sulfide [88%, t_R (retention time) = 10.50 min], fragmentation product (4%, t_R = 7.81min) and unidentified products (6%, t_R = 12.22 min and 2%, t_R = 13.18 min).

The diethyl sulfide **5c** and Amberlyst-15 were heated at reflux (125 °C) in chlorobenzene for 4 h and then in chlorobenzene/*o*-dichloro-benzene (1:2) and Amberlyst-15 at 164-166 °C for 29 h.[3] GC analysis of the reaction mixture at regular time intervals revealed that the sulfide remained unchanged during the 4 h of reflux in chlorobenzene.[4] During reflux in 1:2 chloro-benzene/*o*-dichlorobenzene (164-166 °C) two major new peaks (with t_R's very close to that of the starting sulfide) started growing with time. The heating was stopped after 29 h of reflux at which point the product mixture was shown by GC and GC-MS analysis to consist of 36% unreacted **5c**, 30% demethylated **5c**, 18% $C_{10}H_{13}SC_{10}H_{13}$ and three impurities (7%).

The combination vanadium oxychloride-trifluoroacetic acid has been used as a strong Lewis-acid catalyst in electrophilic aromatic substitutions. For example, Liepa and Summons[5] used them in methylene chloride at 0 °C to effect the rapid conversion of methoxy-substituted stilbenes to the corresponding phenanthrenes. The diethyl sulfone **8c** was recovered quantitatively from treatment with an excess of vanadium oxychloride-trifluoroacetic acid in methylene chloride at 0 °C for 4 h under an argon atmosphere.

Finally, UV-irradiation (Pyrex filter) of the diethyl sulfone **8c**, in methylene chloride at room temperature for 21 h in the presence of a stoichiometric amount of iodine, followed by workup, resulted in a product mixture consisting of 95% unreacted sulfone (GC tR =

12.54 min) and two fragmentation products (2.5%, tR = 4.54 min and 2.0 %, tR = 6.22 min).

Part B: Progress toward the synthesis of the modified target molecule, 9-isopropyl-4-methoxy-6-methyldibenzothiophene ***(5a, Scheme II)***. In a May 6, 1991 letter, we proposed the synthesis of 9-isopropyl-6-methyldibenzothiophene-4-ol (**6a**, Scheme II) as a modified version of the title compound. The rationale being that the starting materials for the synthesis are commercially available and that the synthetic approach is well precedented with relatively few steps. We have carried out the synthesis on a small scale using equilibrated menthone that was on hand. This menthone was not chemically pure and both epimers were present. We did not optimize reaction conditions or yields, nor did we purify intermediates. Our aim was to carry the sequence to the end to learn if any of **5a** (M^+ = 270) is formed. These efforts are described in the Experimental Section. GC and GC-MS analyses of the crude product corresponding to **5a** (Scheme II) showed it to be a mixture consisting of three isomeric **5**'s (35%), demethylated **5** (4%), two isomeric **5**'s lacking an isopropyl group (15%), and several unidentified side-products (46%). The three isomeric **5**'s were present in the relative ratios of 23:11:1.0.

Since this synthesis was quick and dirty, no effort was made to purify intermediates or optimize reaction conditions. We believed, however, that the yields and purities of the intermediates and final product could be improved considerably by using pure l-(-)-menthone and running the PPA-cyclization reaction at a lower temperature. We observed from the GC-MS results that the PPA cyclization conditions (based on literature precedent) resulted in partial cleavage of the isopropyl group and in partial cleavage of the methoxy methyl group. Cleavage of the methoxy methyl group at this step is acceptable, in principle, since it could eliminate the need for the final step in the synthesis (**5a** --> **6a**).

Once it became established that **5a** (Scheme II) had been formed, we carried out the first two steps of this synthetic sequence, using purer menthone starting material, and on a larger scale. Our objective in this larger-scale preparation was to characterize the intermediates, to decide on suitable points for purification, and to modify the literature conditions in order to reduce the number of side-products that were observed in the small-scale run. The large-scale experiments carried out thus far are described in the Experimental Section. GC analyses indicate that these reactions are proceeding as anticipated with the expected isomers forming the major constituent of the crude products. The conversion in the bromination reaction was substantial but not complete and was accompanied by some equilibration of the unreacted menthone starting material. The conversion can, however, be improved further in future runs by increasing the reaction time. The preparation of the keto sulfide **3a**, on the other hand, proceeded to completion but was accompanied by some dimerization of 2-methoxy-benzenethiol to 2,2'-dimethoxydiphenyl disulfide as a white crystalline solid. This, however, is not a problem since this disulfide is separable from **3a** by selective precipitation. We have observed that the unreacted menthone (carried over from the bromination step) can also be separated to a great extent from the keto sulfide by steam distillation of the former, although the stability of the keto sulfide itself to the steam distillation procedure is still not satisfactorily ascertained.

Current and Future Effort:

We are currently carrying out the dehydrative cylization of the keto sulfide **3a** on the larger scale. We shall then proceed with the aromatization step using both palladium/carbon and selenium metal in order to learn if the use of the highly toxic and malodorous selenium can be avoided. If gas chromatographic and spectroscopic evidence shows the aromatization to be successful, then we intend to rigorously purifiy **5a** before carrying out the last demethylation step. we anticipate phenol **6a** will be difficult to purify by base extraction owing to the formation of emulsions.

Experimental Section

Reaction of 1,4-Diethyl-2-[(2'-methoxyphenyl)-thio]benzene (5c) with Diphenyl Lithium-Sodium. Phenyl lithium (3.9 mL, 7.02 mmol) and 0.62 g of sodium were added to a solution of 1.13 g of diphenyl mercury in anhydrous ether. After stirring for 2 h at 25 °C under argon, 1.38 g of sulfide **5c** in 7 mL of anhydrous ether was added. The resulting dark-brown reaction mixture was stirred at 25 °C for 69 h and then heated at reflux for three days. Methanol (20 mL) and water (20 mL) were cautiously added to the cooled reaction suspension under argon. The mixture was made slightly acidic (pH 4) with dilute hydrochloric acid, the layers were separated and the aqueous layer was extracted with 3 x 100 mL of ether. The combined ether extracts were washed with 2 x 30 mL of sat'd sodium bicarbonate, 30 mL of water, dried ($MgSO_4$), filtered, rotorvaped and pumped (oil pump,1 h) affording 1.43 g (106 %) of the crude product as a pale-yellow wax. GC analysis of this material showed it to consist of more than 24 components.

Photocyclization of 1,4-Diethyl-2-[(2'-methoxyphenyl)thio]benzene (5c). Sulfide **5c** (1.37 g), tetracyanoethylene (0.65 g) and methylene chloride (500 mL) were charged into a standard photochemical reactor and the resulting solution was deaerated with a steady stream of argon bubbles for 1h. It was then irradiated thru a Pyrex filter with an UV lamp under argon at 25 °C for 36 h during which aliquots were removed at regular intervals. GC analysis of these aliquots showed that at short irradiation times (6h or 18 h) about 3% conversion had taken place, but at long irradiation times (36 h), the reaction mixture consisted of: unreacted sulfide (88%, t_R = 10.50 min), fragmentation product (4%, t_R = 7.81min) and two unidentified products (6%, t_R = 12.22 min and 2%, t_R = 13.18 min).

Reaction of 1,4-Diethyl-2-[(2'-methoxyphenyl)thio]benzene (5c) with Amberlyst-15. Sulfide **5c** (1.40 g), Amberlyst-15 (5.0 g) and chlorobenzene (70 mL) were charged into a 100-mL, 2-neck, round-bottom flask fitted with a thermocouple probe, a stir bar, a reflux condenser and a Dean-Stark trap. The reaction mixture was heated at reflux under nitrogen for 4 h and aliquots were removed after 1h, 2h, 3h and 4h for GC analysis. Most of the chlorobenzene (55 mL) was then removed by distillation and 30 mL of *o*-dichlorobenzene were added. Heating at reflux (164-166 °C) was then resumed for 29 h during which time more aliquots were taken at regular time intervals. During this second reflux period, two major new peaks (with t_R's very close to that of the starting sulfide) grew with time. The heating was stopped after 29 h of reflux at which point the product mixture was shown by GC and GC-MS analysis to consist of 36% unreacted **5c**, 30% demethylated **5c**, 18% $C_{10}H_{13}SC_{10}H_{13}$ and three impurities (7%).

Reaction of 1,4-Diethyl-2-[(2'-methoxyphenyl)-thionyl]-benzene (8c) with Vanadium Oxychloride. The sulfone **8c** (1.52 g) in 5 mL of dichloromethane was added under argon at 0 °C to a solution of vanadium oxychloride (2.0 mL) in trifluoroacetic acid (15 mL). The resulting dark-brown reaction solution was stirred at 0 °C for 4 h. Water (50 mL) was cautiously added and the aqueous layer was extracted with 5 x 50 mL of dichloromethane. The combined dichloromethane extracts were washed with sat'd sodium bicarbonate (30 mL), water (50 mL), dried (MgSO4), filtered, rotorvaped, and pumped (oil pump, 2 h) affording 1.44 g (99%) of the crude product as a dirty-white solid, mp 73-76 °C. GC analysis showed this solid to be the unreacted sulfone.

Photocyclization of 1,4-Diethyl-2-[(2'-methoxyphenyl)-thionyl]benzene (8c). This reaction was carried out for 21 h as described for the corresponding sulfide **5c** except that a stoichiometric amount of iodine was substituted for tetracyanoethylene. Again aliquots were removed at regular time intervals and analyzed by GC. Workup after 21 h resulted in a product mixture consisting of 95% unreacted sulfone (tR = 12.54 min) and two fragmentation products (2.5%, tR = 4.54 min and 2.0 %, tR = 6.22 min).

6-Bromomenthone (2, Scheme II).[6,7] Lithiumdiisopropyl amide (LDA) was generated in anhydrous tetrahydrofuran (THF) at -78 °C and under an argon atmosphere from 0.113 mol of n-butyllithium and 0.110 mol of diisopropyl amine. Cold THF solutions of chlorotrimethylsilane (0.701 mol, 7.0 equiv) and menthone (0.100 mol; equilibrated and racemic) were then added at -78 °C followed by the rapid addition of a cold solution of bromine (0.101 mol,1.0 equiv) in dichloromethane. After stirring for a short time at -78 °C, 200 mL of cold saturated sodium bicarbonate were added. The resulting mixture was diluted with water (200 mL) and extracted with 4 x 100 mL of low-boiling petroleum ether. The organic extracts were combined, washed with sat'd sodium bicarbonate, water, dried ($MgSO4$), filtered, rotorvaped at room temperature and pumped (r.t., 2 mm, 16 h) affording 23.6 g of the crude product **2** as a light brown liquid.

6-Isopropyl-2-[(2'-methoxyphenyl)thio]-3-methyl-cyclohexanone (3).[8] Sodium hydroxide (0.101 mol), ethyl alcohol (25 mL), water (25 mL), and 2-methoxybenzenethiol (0.100 mol) were stirred under nitrogen at room temperature for 15 minutes. Crude bromomenthone (23.6 g) in ethyl alcohol (35 mL) was then added dropwise over 40 minutes. The resulting mixture was heated under nitrogen to reflux over 0.5 h and at reflux for 5 h. After cooling to room temperature, the mixture was treated with water (300 mL) and extracted with ether (200 mL). The layers were separated and the aqueous layer was further extracted with 3 x 100 mL of ether. The combined ether extracts were washed with water, dried ($MgSO4$), filtered, rotorvaped and pumped affording 24.9 g of presumed crude **3** as a brown liquid. The residual basic aqueous layer was acidified with conc. hydrochloric acid and extracted with 3 x 50 mL of ether. These combined ether extracts were washed with water, dried ($MgSO4$), filtered, rotorvaped and pumped (oil pump) affording 1.2 g of acidic fraction as a brown liquid with a strong mercaptan odor.

9-Isopropyl-4-methoxy-6-methyl-6,7,8,9-tetrahydrodibenzothiophene (4a). Crude **3** (24.9 g) and 311 g of polyphosphoric acid (PPA) were heated with mechanical stirring under nitrogen to 190 °C over 3.25 h and 190-225 °C over 1.5 h. The chocolate-brown, syrupy reaction mixture was poured onto 1L of ice, diluted with 1L of water and extracted with 5 x 200 mL of dichloromethane. The combined organic extracts were washed with water (2 x 100 mL), brine (2 x 200 mL), dried (MgSO4), filtered, rotorvaped and pumped (oil pump) affording 15.3 g of crude **4a** as a black, thick liquid with a mild asphalt-like odor. GC and GC-MS analyses showed this material to contain, among others, three components with the desired $M^+ = 274$ and amounting to about 50%. These three isomers were present in the relative ratios of 2.8:1.0:3.8

9-Isopropyl-4-methoxy-6-methyldibenzothiophene (5a). Crude **4** (15.3 g) and powdered selenium metal (16.0 g) were heated with stirring under an argon atmosphere in a well-ventillated hood to 300 °C over 0.5 h and at 300 °C for 2.3 h. The effluent gas from this reaction was passed first through an empty trap and then through a trap containing copper sulfate solution in order to scrub the hydrogen selenide produced. Ethyl alcohol (80 mL) was then added to the reaction flask and the heterogeneous mixture was heated at reflux under argon for 1h. It was filtered while hot and the filter cake was washed repeatedly with hot dichloromethane. The resulting black filtrate was boiled with activated charcoal, filtered again and the new filtrate was rotorvaped and pumped (oil pump) affording 10.3 g of crude **5** as a black amorphous paste. This material was eluted with hexanes (3 h) thru neutral alumina in a

Soxhlet apparatus. Concentration of the hexane extract afforded 2.6 g of a first fraction that was shown by GC and GC-MS analysis to be made up of three isomeric **5**'s (35%), de-methylated **5** (4%), two isomeric **5**'s lacking an isopropyl group (15%), and several unidentified side-products (46%). The three isomeric **5**'s were present in the relative ratios of 23:11:1.0.

6-Bromomenthone (2).[6,7] Lithium diisopropyl amide (LDA) was generated in anhydrous tetrahydrofuran (THF) at -78 °C and under an argon atmosphere by addition over 1.5 h of 0.690 mol of n-butyllithium in hexanes to 0.660 mol of diisopropyl amine. Cold THF solutions of chlorotrimethyl-silane (3.93 mol, 6.6 equiv) and (-)-menthone (0.600 mol; Aldrich; contaminated with 5% isomenthone) were then added at -78 °C over 1.6 h and 1.8 h, respectively. This was followed by the rapid addition (15 min) of a cold (-15 °C) solution of bromine (0.626 mol, 1.0 equiv) in dichloro-methane. After stirring for a short time at -78 °C, 200 mL of cold saturated sodium bicarbonate were added over 0.5 h. The Dry Ice-acetone bath was then replaced by an ice bath and the reaction mixture was diluted further with sat'd sodium bicarbonate (3.8 L) and then solid sodium bicarbonate until gas evolution ceased and the pH rose to 7-8. The resulting homogeneous solution was extracted with 4 x 300 mL of low-boiling petroleum ether. The organic extracts were combined, washed with water, dried (MgSO4), filtered, rotorvaped at *room temperature* and pumped (oil pump, r.t., 2 mm, 16 h) affording 143 g of the crude product (**2**) as a brown liquid possessing a minty odor.

6-Isopropyl-2-[(2'-methoxyphenyl)thio]-3-methyl-cyclohexanone (3).[8] Sodium hydroxide (0.654 mol), ethyl alcohol

(350 mL), water (150 mL), and 2-methoxybenzenethiol (0.656 mol) were stirred under nitrogen at room temperature for one hour. Crude bromomenthone (0.595 mol) in ethyl alcohol (250 mL) was then added dropwise over 0.7 h. The resulting heterogeneous mixture was heated under nitrogen to reflux over 0.7 h and at reflux for 4 h. After cooling to room temperature under nitrogen, the mixture was treated with water (700 mL) and extracted with ether (6 x 200 mL). The combined ether extracts were washed with brine (4 x 100 mL), dried ($MgSO_4$), filtered, rotorvaped and pumped affording 141 g of presumed crude **3** as a brown liquid. After steam-distillation and similar workup, There was obtained 14 g of a steam-volatile fraction as a clear minty-smelling liquid, which is presumably unreacted menthone (**1**), and 124 g of a non-steam-volatile fraction as a brown, viscous liquid. These samples have been submitted for GC and GC-MS analysis locally.

References and Notes

1. Wittig, G.; Benz, E. *Chem. Ber.* **1958**, *91* , 873-882.

2. Bendig, J.; Beyermann, M.; Kreysig, D. *Tet. Lett.* **1977**, 3659-3660.

3. Amberlyst-15 is a strongly acidic ion-exchange resin commonly used for effecting electrophilic aromatic substitution/cyclization reactions.

4. Since the boiling point of chlorobenzene is 132 °C, this shows that sulfide **5c** is remarkably thermally stable. This treatment also demonstrated the stability of **5c** under these acidic conditions.

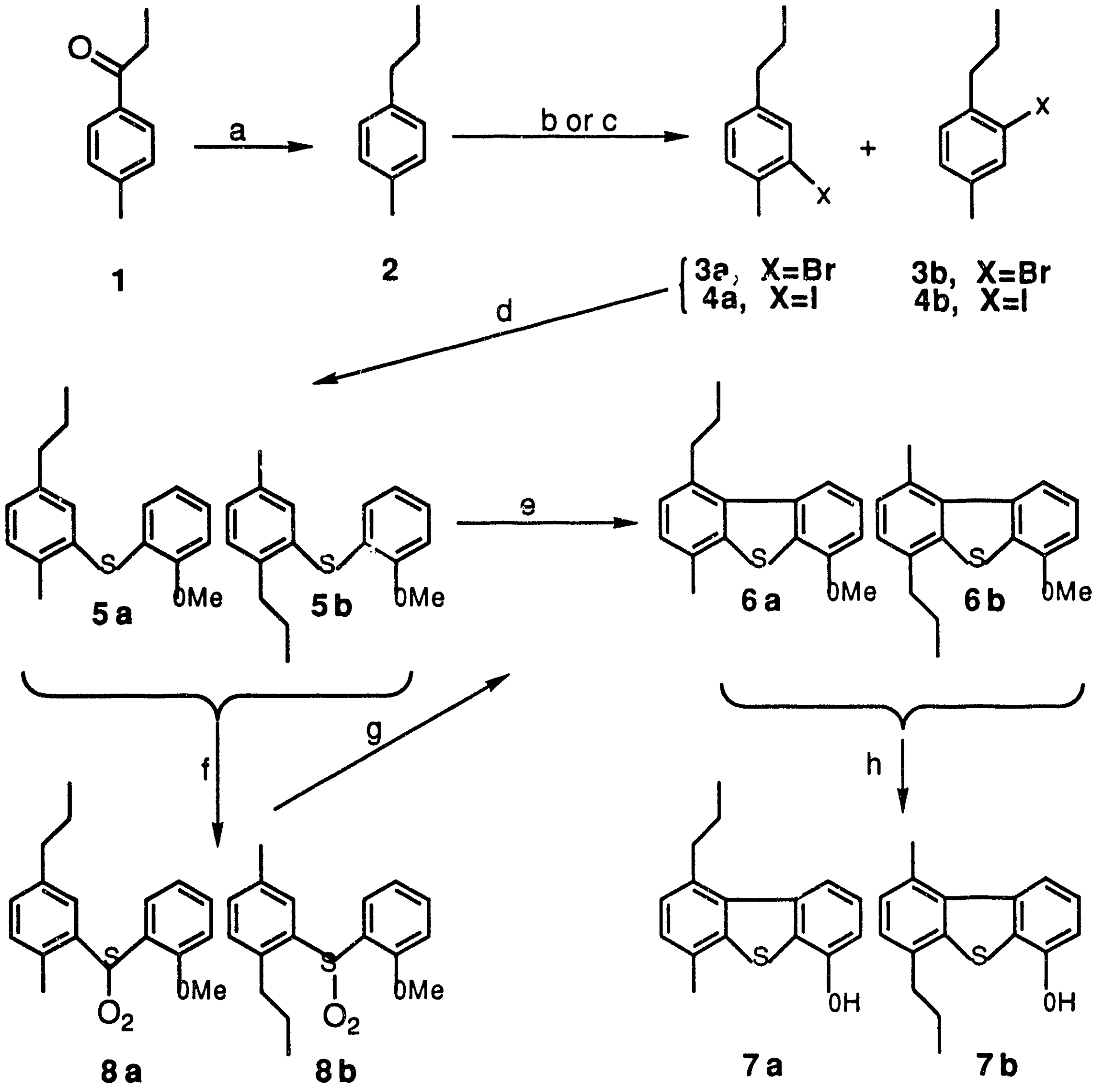
5. Liepa, A.J.; Summons, R.E. *J. Chem. Soc., Chem. Commun.* **1977**, 826-827.

6. Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* **1984**, *25*, 495-498.

7. Stotter, P.L.; Hill, K.A. *J. Org. Chem.* **1973**, *38*, 2576-2578.

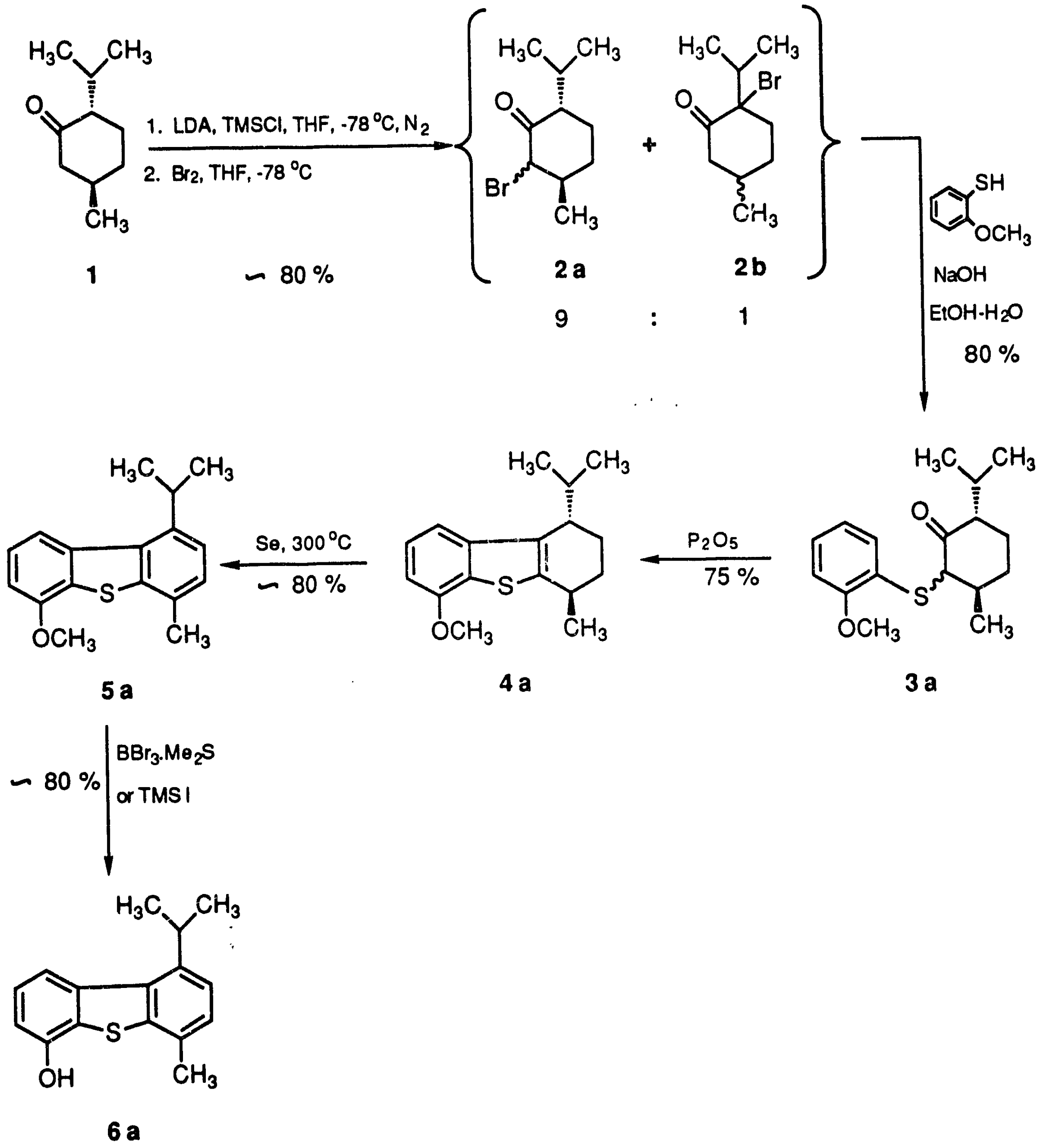
8. Tedjamulia, M.L.; Tominaga, Y.; Castle, R.N.; Lee, M.L. *J. Heterocycl. Chem.* **1983**, *20* , 1485-1495.

Scheme I



[a]NH_2NH_2, OH^-, DEG, heat. [b]Br_2, Fe, I_2 catalyst. [c]I_2, H_5IO_6, H^+, HOAc, heat. [d]Na, EtOH, 2-Methoxybenzenethiol, Tetrakis(triphenylphosphene) palladium (0), heat. [e]UV light, I_2, solvent. [f]H_2O_2 (30%), HOAc. [g]See proposed routes in Scheme II. [h]BBr_3-Me_2S complex.

Scheme II


1. LDA, TMSCl, THF, -78 °C, N2
2. Br2, THF, -78 °C
∽ 80 %
1
2a
2b
9 : 1
NaOH
EtOH-H2O
80 %
3a
P2O5
75 %
4a
Se, 300 °C
∽ 80 %
5a
BBr3.Me2S
or TMS I
∽ 80 %
6a
H3C
CH3
Br
OCH3
SH
S
OH

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