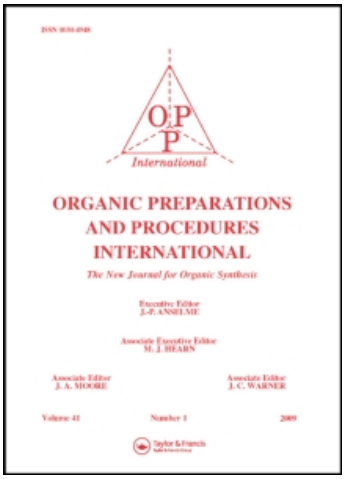

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A CONTINUOUS PROCEDURE FOR PREPARATION OF para FUNCTION ALIZED AROMATIC THIOLS USING NEWMAN-KWART CHEMISTRY

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A CONTINUOUS PROCEDURE FOR PREPARATION OF *para* FUNCTIONALIZED AROMATIC THIOLS USING NEWMAN-KWART CHEMISTRY

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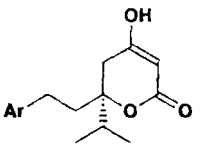
3-Arylthio-4-hydroxy-5,6-dihydropyrones such as CI-1029 (**8a**) and PD 190497 (**8b**) are members of a new class of HIV protease inhibitors which are nonpeptidic, competitive, reversible inhibitors of the protease enzyme.[1,2] The 3-arylthio-4-hydroxy-5,6-dihydropyrones enjoy low cross resistance relative to currently marketed peptidomimetic protease inhibitors. S-Arylsulfonyl derivatives (**6**) of 2-tert-butyl-4-hydroxymethyl-5-methylthiophenol (**5**) are key intermediates required for the synthesis of PD 190497 and CI-1029.[1,2] In this process, a tosyl group is displaced as a leaving group in a coupling reaction of **6** with the enol activated nucleophilic center found in suitably substituted 4-hydroxy-5,6-dihydropyrones such as **7**. [2,3]



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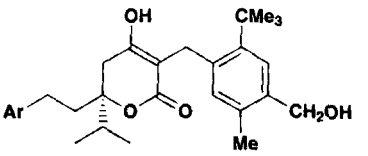


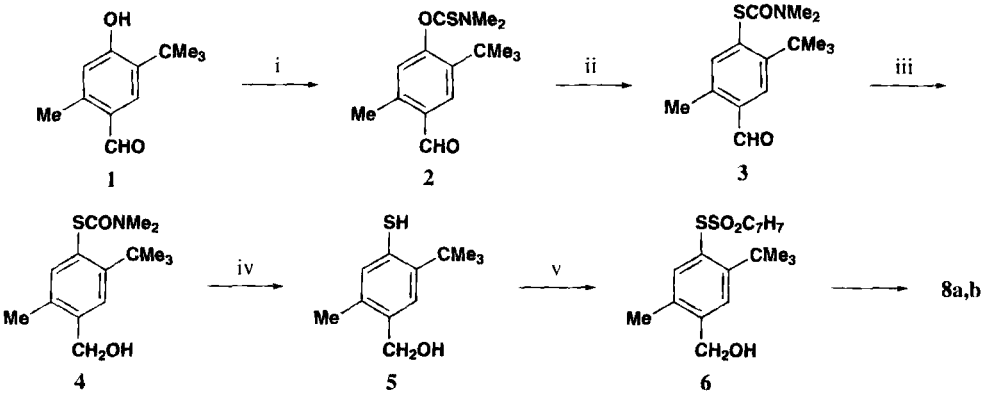
8

Ar = a) *p*-$H_2NC_6H_4$- b) 3-Thienyl

We now report a rapid, safe and cost effective method for preparation of **6** (Scheme 1). In the course of this work, a method for *in situ* generation of tosyl bromide was developed to permit use of inexpensive tosyl chloride for preparation of the labile thiosulfonate function. Secondly we will describe a procedure for carrying out a continuous Newman-Kwart rearrangement reaction, a method that provides a convenient, economical approach to the thiocarbamate rearrangement products and their thiol derivatives. Finally the new method for **6** proceeds in high overall yield and avoids hazardous reagents used previously, including chloromethyl methyl ether, bromine, n-butyllithium, NaH and DIBAL.

Initially it was necessary to prepare the substrate required for the Newman-Kwart rearrangement.[4] For this purpose we developed a Schotten-Baumann method to convert 5-tert-butyl-4-hydroxy-2-methylbenzaldehyde (**1**) into its N,N-dimethylthiocarbamic ester derivative (**2**). We discovered early that this was not a straight forward Schotten-Baumann reaction. The bulky ortho tert-butyl group has an unfavorable effect on the rate of this substitution reaction. However, a reliable procedure was developed by carefully controlling pH in the 11.5 – 12.5 range while carrying out addition of 45% KOH along with addition of a THF solution of dimethylthiocarbamoyl chloride – both added simultaneously to an aqueous THF solution of the potassium salt of **1**. A yield of 77% was achieved on large scale.

The method provided high purity material needed for the rearrangement step (HPLC: 100 area %; ROI: 0.03%). Laboratory experience showed that yields could be increased to 84% by application of vacuum to concentrate the reaction mixture during the simultaneous addition procedure, thus increasing the rate of the bimolecular reaction. Vacuum concentration of the reaction mixture was started after approximately 70% of the simultaneous addition process had been completed.



i) Me_2NCSCl, KOH, THF, H_2O ii) TEGDME, heat iii) $NaBH_4$, MeOH, H_2O
iv) NaOH, heat, HCl, toluene v) $C_7H_7SO_2Cl$, pyridine, LiBr, toluene, EtOAc

The *para* formyl substituent [5] in **2** was selected for the rearrangement in preference to other groups such as the ester function used previously [2] for several reasons. First, the aldehyde group could be converted to the required hydroxymethyl group in **6** under mild, safe conditions using inexpensive, commercially available $NaBH_4$ in 14M aqueous NaOH. The NaOH is needed for cleavage of the N,N-dimethylthiocarbamate ester group after rearrangement and reduction are complete. Secondly the strong electron withdrawing formyl substituent nicely activated the Newman-Kwart rearrangement allowing it to proceed more cleanly at lower temperatures than for the ester analog. Lastly, the required 5-tert-butyl-4-hydroxy-2-methylbenzaldehyde (**1**) and its N,N-dimethylthiocarbamate ester derivative (**2**) were easy to prepare from 2-tert-butyl-5-methylphenol. The aldehyde **1** can be readily obtained by formylation of inexpensive 2-tert-butyl-5-methylphenol under a variety of conditions. [6]

In early work, the rearrangement of **2** to give dimethylthiocarbamic acid S-(2-tert-butyl-4-hydroxy-methyl-5-methylphenyl) ester (**3**) was carried out in 1-1.5 parts of phenyl ether solvent at an oven temperature of 270°. Although this reaction afforded **3** in excellent yield with crude HPLC purity of about 95 %, two low level (1-2%) impurities [7] were present which proved difficult to remove. In the case of CI-1029, they were consistently carried through to final product at levels ranging from 0.3 to 0.6%. Alternate solvents and reaction conditions were investigated for the rearrangement reaction leading finally to an acceptable process. Solvents examined included mineral oil, tetraethylene glycol, tetraethylene glycol dimethyl ether, and tetrachlorobenzene. Tetraethylene glycol dimethyl ether proved most effective in avoiding impurities. A statistically designed process variable study was completed to determine the effects of concentration (25 to 75% substrate), temperature (250 to 300°C) and reaction time (20 to 180 minutes) on product quality. The design showed that reaction concentration had the largest effect on purity; the more dilute the substrate concentration, the better the product. This conclusion was not helpful in our efforts to increase throughput. However, the experimental design also showed that if the reaction temperature was increased, reaction time could be shortened thus increasing throughput to an acceptable level. Final reaction temperatures and concentrations selected for large scale runs were 1 part substrate in 3 parts solvent at 300°C with a 15 to 20 minute residence time. HPLC purity of crude **3** (excluding solvent) was better than 97 area % and the level of each of the offending impurities were reduced to well below 0.1% in final CI-1029 product prepared from **3** using this revised method. In addition to reduced equipment costs, the choice of a continuous process over a batch process has the advantage of better temperature control – an issue which becomes more important as the scale of the process is increased. The reaction was run continuously in the tubular reactor described in the experimental section. During large scale runs, samples of the reactor effluent were analyzed by HPLC. The results of the analysis were used to make appropriate adjustments in flow rate depending on the amount of unreacted **2** that remained in the reaction mixture. As the demand for **6** increased, a larger oven was employed having a volume of 11 ft^3. This permitted a 10 fold increase in reactor volume from 0.5 to 5 liters. Production of thiocarbamate **3** could then be increased from 6 to 50 kg per day.

Tetraethylene glycol dimethyl ether also has the advantage of high solubility in water. Thus the rearrangement product is precipitated by addition of water. Filtration of the mixture in the reactor without removing the product from the reactor, permits facile separation of a water solution of tetraethylene glycol dimethyl ether from the precipitated aldehyde, **3**. This replaces a series of hexane solvent extractions used in the initial process to remove the phenyl ether solvent. The aldehyde function in **3** is reduced under mild, safe conditions with 12% $NaBH_4$ in14M NaOH at low temperature in an aqueous methanol solvent system.

After stirring at 15-25° for 30 to 60 minutes the corresponding alcohol, **4**, is obtained. However, in the developed method the alcohol is not isolated, but instead saponified directly to 2-tert-butyl-4-hydroxymethyl-5-methylthiophenol (**5**) by addition of more NaOH and then heating to reflux for 2-3 hours. Attempts to reduce and saponify simultaneously by heating to reflux immediately after

$NaBH_4$ addition, led to dark colored reaction mixtures and low yields.

The initial procedure [2,3] for conversion of the thiophenol **5** to toluene-4-thiosulfonic acid S-(2-tert-butyl-4-hydroxymethyl-5-methylphenyl)ester (**6**) involved the reaction of **5** with tosyl bromide [8] using modified literature methods. [9] The use of tosyl bromide remained a major cost issue in the method to make **5**. Thus we searched for a process that would use less expensive tosyl chloride. Initially conditions could not be found that avoided appreciable formation of a long retention time HPLC impurity. However, generation of tosyl bromide *in situ* by reaction of tosyl chloride with lithium bromide for 1-2 hours in THF followed by addition of a solution of **5** and pyridine in toluene at 35-45° gave a convenient, high yield procedure for conversion of **5** to **6**. In place of THF, other solvents such as ethyl acetate, acetone and acetonitrile were tried and found to be less effective. The thiophenol **5** is, of course, quite susceptible to air oxidation giving rise to the disulfide derivative. Therefore, as with intermediates **3** and **4**, the thiophenol is also not isolated . Solutions of **5** were analyzed by HPLC and found to contain 80-90% of the thiol with a major late running impurity (tentatively assigned as the disulfide derivative based on LC-MS data) and many minor impurities.

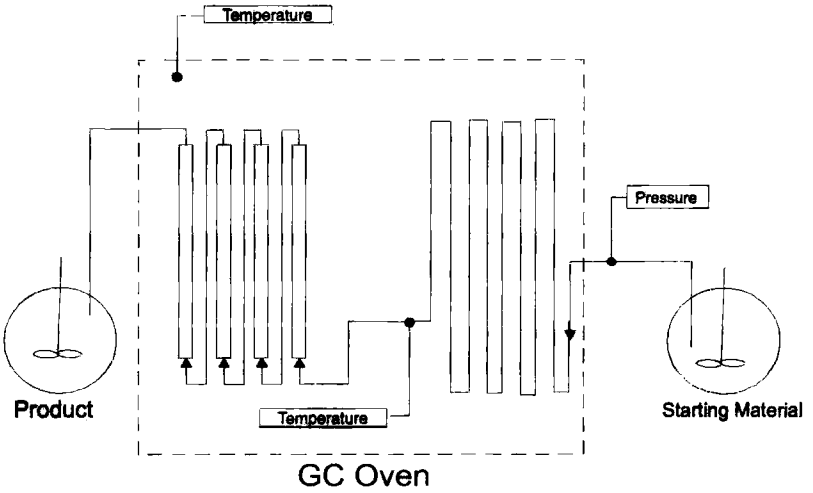
In summary, the overall method for preparing **6** from **2** *via* unisolated intermediates **3**, **4** and **5** takes place in four combined steps in 70-72% overall yield to give material with better than 98% HPLC purity. The product is not contaminated with any significant quantity of impurities noted earlier, that would carry through to our targeted, protease inhibitors, CI-1029 and PD 190497.

EXPERIMENTAL SECTION

Melting points were obtained using a Büchi B-545 melting point apparatus. ^{1}HNMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 200MHz on a Varian XL 200 NMR spectrometer. Chemical shifts are reported downfield in ppm from an internal tetramethylsilane standard. Analytical high-performance liquid chromatography (HPLC) was carried out using a Hitachi Model L-6200 pump, a Hitachi Model L-7400 variable wavelength UV detector set at 254 nm using a 4.6 mm x 25 cm 5 μ C18 Phenomenex Luna column with mobile phases consisting of (A) 50 parts CH_3CN and 50 parts of a mixture of 0.2 % acetic acid adjusted to pH 5.1 with NH_4OH and (B) 100 parts CH_3CN in a gradient mode at a flow rate of 1.0 mL/min.

The continuous Newman-Kwart rearrangement process of **2** to **3** was carried out on large scale using a converted Hewlett Packard 5890A gas chromatograph with a hole cut through one side so that the stainless steel tubing could be inserted into the oven chamber. Calculation of the internal volume of the tubing allows determination of the flow rate based on the desired residence time inside the oven chamber. Initial scale-up was targeted to allow rearrangement of 17 kg of **2** within a one to two day period. The tubular reactor begins with a 40 ft long 1/8 inch (outside) diameter section of stainless steel tubing placed before the larger 3/4 inch diameter sections to ensure that the incoming reaction mixture reaches the desired temperature prior to entering the larger tubes. The reaction mixture than flows into ten 3/4 inch diameter, 10 inch long sections of stainless steel tubing connected by 2 ft long 1/8 inch diameter sections to give a total reactor volume of about 0.5 L. (The diagram in the figure below shows only four of the ten, 10 inch long 3/4 inch diameter sections.) The 3/4 inch diameter

sections were placed vertically in the oven chamber and then connected by the 1/8 inch diameter sections using compression fittings. The direction of flow of the reaction mixture needs to proceed as shown in the figure in order to avoid entrapment of air when the system is filled. The use of the 1/8 inch connecting tubes is necessary in part to permit rapid heating of the reaction mixture as it travels between the larger sections of tubing.



Small scale studies were carried out early in the development program. The gas chromatograph is fitted with a 26 ft long 1/8 inch (outside) diameter stainless steel tube, which is filled with solvent. Solvent is recirculated through the system until the temperature equilibrates at about 250-260°. The feed line is then placed into a warm (about 50°) solution of **2** in 1 - 3 parts solvent and this solution passed through the tubular reactor at 250-260°, at such a rate to permit 98-99% conversion of **2** to **3,** as judged by HPLC analysis of samples taken from the tube exiting the reactor. When the feed reservoir is empty, additional solvent is added, and this passed through the reactor to transfer the remaining product solution into the product reservoir.

Dimethylthiocarbamic acid O-(2-tert-Butyl-4-formyl-5-methylphenyl) Ester (2).- To a solution of 5-tert-butyl-4-hydroxy-2-methylbenzaldehyde (**1**) (33.7 Kg, 162 mol correcting for a GC purity of 92.5%) in water (60 L) and THF (45 L) under a nitrogen atmosphere was added potassium hydroxide (5.0 Kg of a 45% aqueous solution) to adjust the pH of the solution to 12. The resulting solution was stirred at 10-19° while a solution of dimethylthiocarbamoyl chloride (28.7 Kg) in THF (36 L) was added over a 2.5 hour period with simultaneous addition of 45% KOH (22.2 Kg) in order to hold the pH of the reaction mixture between 11.8 and 12.1. The vessel containing the dimethylthiocarbamoyl chloride - THF solution was rinsed with THF (5 L) and the rinse combined with the whole. Additional 45% KOH (3.8 Kg) was added to the mixture over a 2 hour period at 15-19° in order to maintain a basic pH in the range 11.7-11.8. Stirring at 18-19° was continued for another 70 minutes. Ethyl acetate (45 Kg) and heptane (34 Kg) were added. Phase separation was assisted by the addition of NaCl (22 Kg) in water (60 L). After separation, the aqueous layer was extracted with a solution of ethyl acetate

(23 Kg) and heptane (17 Kg). The combined organic layers were diluted with ethyl acetate (50 Kg) and extracted with 15% KOH (2x35 L) followed by 10% aqueous sodium chloride (2x33 Kg). The organic product solution was concentrated to approximately 45 L. This was treated with 45% KOH (50 gm) and diluted with methanol (40 L) and the resulting solution cooled to 43°. Water (7 L) was added over 15 to 30 minutes while maintaining the temperature between 40 and 45°. The solution was cooled slowly with addition of seed crystals. Crystallization began at 40°. The mixture was stirred and cooled over several hours to 2°. The mixture was filtered and the solid washed with a solution of methanol (25 L) and water (6 L) followed by water (20 L) and vacuum dried at 40-45° overnight until the water content was 0.03%. This gave dimethylthiocarbamic acid O-(2-tert-butyl-4-formyl-5-methylphenyl) ester (**2**): 34.8 Kg (125 mol, 77 %); mp: 79.5-81°; ^{1}H NMR ($CDCl_3$): d 1.39 (s, 9H), 2.62 (s, 3H), 3.41 (s, 3H), 3.50 (s, 3H), 6.94 (s, 1H), 7.86 (s, 1H), 10.22 (s, 1H); HPLC: 100.0 area %; ROI: 0.03%.

Toluene-4-thiosulfonic Acid S-(2-tert-Butyl-4-hydroxymethyl-5-methylphenyl) Ester (6).- Dimethylthiocarbamic acid O-(2-tert-butyl-4-formyl-5-methylphenyl) ester (**2**) (17.0 Kg, 60.8 mol) was treated with tetraethylene glycol dimethyl ether (51 Kg) and the mixture stirred and heated under an argon atmosphere to 38-42° to give a solution. This was pumped through the tubular reactor described above with the oven temperature maintained at 300° at a flow rate of 34-38ml/min. The effluent containing dimethylthiocarbamic acid S-(2-tert-butyl-4-formyl-5-methylphenyl) ester (**3**) was collected in an argon inerted reactor. The product solution was cooled to 11° and water (175 L) was added while maintaining the temperature between 10 and 17°. The resulting precipitate was allowed to settle and the supernatent transferred to a second reactor through a cloth filter. The residue was washed with water (175 L) and treated with toluene (95 L). The lower aqueous waste layer was discarded and the toluene solution of **3** concentrated under vacuum to a solid. This was treated with methanol (50 L) and toluene (7 L) and the solution stirred and cooled to 5°. A 12 weight percent solution of $NaBH_4$ in 14 M aqueous sodium hydroxide (10.0 Kg) was added followed by methanol (5 L) while maintaining the temperature below 19°. The resulting solution was allowed to stir at 15-28° for 35 minutes. Sodium hydroxide 50% aqueous solution (7.1 Kg) was added followed by methanol (3 L) and the mixture heated to reflux where it was maintained for 135 minutes. The solution was cooled to 30° and water (25 L) and toluene (40 L) added. The solution was cooled to 11° and acidified with 37% hydrochloric acid (24.5 Kg) to pH 1.5 while maintaining the temperature below 14°. The aqueous layer was separated and extracted with toluene (2x7 L). The combined toluene extracts containing 2-tert-butyl-4-hydroxymethyl-5-methylthiophenol (**5**) were treated with pyridine (4.61 Kg) and the resulting toluene solution slowly added over 2 hours at 38-42° to a prestirred (105 minutes at 21-26°) solution of toluenesulfonyl chloride (11.6 Kg) and lithium bromide (5.7 Kg) in THF (53 L). The resulting mixture was allowed to stir at 39-42° for 2 hours and then for 9 hours at 15-25°. Water (50 L) was added. After mixing and settling, the layers were separated and the organic layer extracted with 10% HCl (2x33 L) followed by water (18 L) and concentrated under vacuum to a volume of 40 L which was warmed to 48°. Heptane (22 L) was added followed by seed crystals. Crystallization began

at about 43°. The mixture was stirred and cooled to 1° and filtered and the product washed with a toluene (46 L) - heptane (72 L) solution and vacuum dried at 40-51° to give toluene-4-thiosulfonic acid S-(2-tert-butyl-4-hydroxymethyl-5-methylphenyl)ester (**6**) (15.9 Kg, 43.6 mol, 72% yield for the 4 steps): mp: 122-123°; ^{1}H NMR ($CDCl_3$): d 1.25 (s, 9H), 2.0 (bs, 1H), 2.20 (s, 3H), 2.42 (s, 3H), 4.69 (s, 2H), 7.23 (m, 3H), 7.49 (m, 3H); HPLC: 98.3 area %.

Anal. Calcd for $C_{19}H_{24}O_3S_2$: C, 62.61; H, 6.64; S, 17.59. Found: C, 62.72; H, 6.73; S, 17.24

Laboratory Preparation of 2.- Potassium hydroxide (80 mL of a 10% aqueous solution) was added to a mixture of **1** (99.0 g, 515 mmol) in water (180 mL) and THF (135 mL). This mixture was stirred at room temperature and a solution of dimethylthiocarbamoyl chloride (86.1 g) in THF (108 mL) added slowly over a 2 hour period with simultaneous addition of 10% KOH in order to hold the pH between 12.0 and 12.3. After approximately 70% of the dimethylthiocarbamoyl chloride-THF solution had been added, vacuum was applied to remove THF. During the distillation, the simultaneous additions of 10% KOH and the dimethylthiocarbamoyl chloride-THF solution were continued while maintaining the pH between 11.6 and 12.0 and the temperature between 23-25°. The distillation was continued for 10 minutes after all the dimethylthiocarbamoyl chloride-THF solution had been added. Stirring at ambient pressure and temperature was continued for another 90 minutes. During this time the pH was stable between 11.6 and 11.75. A solution of ethyl acetate (150 mL) and heptane (150 mL) was added and after stirring and settling, the layers were separated and the aqueous layer extracted with 1:1 heptane-ethyl acetate (150 mL). The combined organic extracts were washed with 10% KOH (2x105 mL) and water (2x90 mL) and concentrated to 210g. This was diluted with methanol (120 mL) and water (20 mL), and 50% NaOH (170 mg) added. The resulting solution was concentrated to an oil, which was redissolved in methanol (120 mL) at 50° and water (15 mL) added. The solution was cooled slowly with addition of seed crystals. Crystallization began at 43°. The mixture was stirred and cooled over several hours to -5°. The mixture was filtered and the solid washed with 4:1 methanol-water (75 mL) and vacuum dried at 40° overnight to give dimethylthiocarbamic acid O-(2-tert-butyl-4-formyl-5-methylphenyl) ester (**2**): 121.5 g (435 mmol, 84%); mp: 80-81°; HPLC: 99.7 area %. *Anal.* Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01; S, 11.47. Found: C, 64.28; H, 7.41; N, 5.29; S, 11.73.

Dimethylthiocarbamic Acid S-(2-tert-Butyl-4-formyl-5-methylphenyl) Ester (3).- Dimethylthiocarbamic acid O-(2-tert-butyl-4-formyl-5-methylphenyl) ester (**2**) (100 g, 358 mmol) was treated with tetraethylene glycol dimethyl ether (66.7 g) and the mixture stirred and heated under an argon atmosphere to 250° where it was maintained for 2 hours. The solution was stirred and cooled to 25° and methanol (500 mL) added. The resulting solution was slowly added to water (500 mL) at 0 to 5° and the resulting mixture stirred for 1 hour and filtered. The solid was washed with water (200 mL) and vacuum dried overnight at 40-50° to give crude **3**. This was recrystallized from toluene (40 mL) and heptane (100 mL) and the product vacuum dried at 50° to give dimethylthiocarbamic acid S-(2-tert-butyl-4-formyl-5-methylphenyl) ester (**3**): (50.0 g, 179 mmol, 50%): mp: 107-108°; ^{1}H NMR (DMSO-d_6): d 1.42 (s, 9H), 2.52 (s, 3H), 3.0 (bd, 6H). 7.34 (s, 1H), 7.86 (s, 1H), 10.21 (s, 1H);

HPLC: 97.6%.

Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01; S, 11.47. Found: C, 64.50; H, 7.48; N, 4.90; S, 11.29.

Dimethylthiocarbamic Acid S-(2-tert-Butyl-4-hydroxymethyl-5-methylphenyl) Ester (4).- Dimethylthio-carbamic acid S-(2-tert-butyl-4-formyl-5-methylphenyl) ester (**3**) (6.0 g, 21 mmol) was dissolved in THF and treated with lithium borohydride (0.8 g) in portions. The mixture was cooled in an ice bath and stirring continued for 1.5 hours. Toluene (25 mL) and water (10 mL) were added followed by cautious addition of 37% hydrochloric acid (2.8 g) to destroy excess borohydride and adjust the pH to 6.5. The aqueous layer was separated and the organic layer extracted with 1 N NaOH (2x10 mL) and water (10 mL) and concentrated to a solid. This was recrystallized from toluene and heptane and the crystals vacuum dried at 40° to give dimethylthiocarbamic acid S-(2-tert-butyl-4-hydroxymethyl-5-methylphenyl) ester (**4**) (5.6 g): mp: 135.9-136.4°; ^{1}H NMR (DMSO-d_6): d 1.38 (s, 9H), 2.15 (s, 3H), 3.0 (bs, 6H), 4.45 (d, 2H), 5.15 (t, 1H), 7.09 (s, 1H), 7.46 (s, 1H); HPLC: 99.1%.

Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98; S, 11.39. Found: C, 63.85; H, 8.08; N, 4.86; S, 11.29

Laboratory Preparation of 6.- Dimethylthiocarbamic acid O-(2-tert-butyl-4-formyl-5-methylphenyl) ester (**2**) (24.0 g, 85.9 mmol) was treated with tetraethylene glycol dimethyl ether (65 g) and the mixture stirred and heated under argon to 275° where the solution was maintained for 30 minutes. The solution was cooled and water (250 mL) added to give a precipitate. This was cooled to 0° and filtered and the solid washed with water to give **3** as a water wet solid (35.2 g). This was treated with methanol (40 mL) and THF (30 mL) followed by slow addition over 20 minutes of $NaBH_4$ (14.1 g of a 12 weight percent solution in 14 M aqueous sodium hydroxide) while maintaining the temperature below 8°. The resulting solution was allowed to stir at 20-25° for about 80 minutes. Sodium hydroxide 50% aqueous solution (4 g) was added and the mixture heated to reflux where it was maintained for 3 hours. The solution was cooled to 20° and water (110 mL) and toluene (70 mL) added and the mixture acidified with 37% hydrochloric acid (26 g) to pH 4.0. The aqueous layer was separated and extracted with toluene (2x15 mL). The combined toluene extracts containing 2-tert-butyl-4-hydroxymethyl-5-methylthiophenol (**5**) were treated with pyridine (6.12 g) and the resulting toluene solution slowly added over 3 hours at 40° to a prestirred (1 hour) solution of toluenesulfonyl chloride (16.6 g) and lithium bromide (8.0 g) in THF (75 mL). The resulting mixture was allowed to stir at 40° for 2 hours and then overnight at room temperature. Water (70 mL) and ethyl acetate (30 mL) were added. After mixing and settling the layers were separated and the organic layer extracted with 10% HCl (2x50 mL) followed by water (50 mL). The organic layer was concentrated under vacuum to a weight of 45 g which was warmed to 60°. Heptane (20 mL) was added slowly resulting in a precipitate. The mixture was stirred and cooled to 10° and filtered and the product washed with 1:1 toluene/heptane (40 mL) and vacuum dried at 40° to give toluene-4-thiosulfonic acid S-(2-tert-butyl-4-hydroxymethyl-5-methylphenyl)ester (**6**) (19.4 g, 53.2 mmol, 62% yield for the 4 steps): mp: 121-122°; HPLC: 96.3 area %.

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