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# Facile Synthesis of Trisubstituted Thioindoles via a Novel Tricyclic Thiolactone Intermediate

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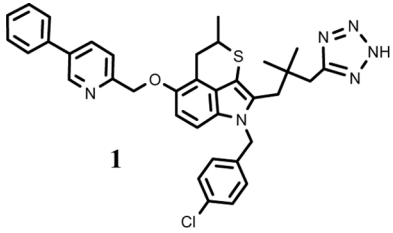
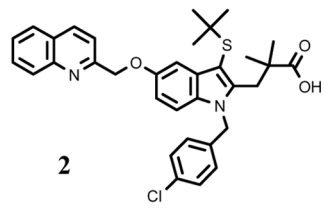
**Abstract:** Methodology to conveniently and systematically prepare biologically active indole **9** is described.

**Keywords:** Alkylation, demethylation, substituted indole, thiolactone

## INTRODUCTION




**1**




**2**

Substituted indoles exhibit wide-ranging biological activity and as a result have been the focus of tremendous interest by the pharmaceutical industry.[1] In particular, 3-thioindole analogs have been investigated for the potential treatment of asthma,[2a] inflammation,[2b] obesity,[2c] cancer,[2d] and heart disease.[2e] We have discovered that analogs of modified thiopyranoindole **1**[3] and 3-*t*-butylthio-indole **2**[4] showed interesting biological activity in an ongoing drug discovery program. This prompted us to find a

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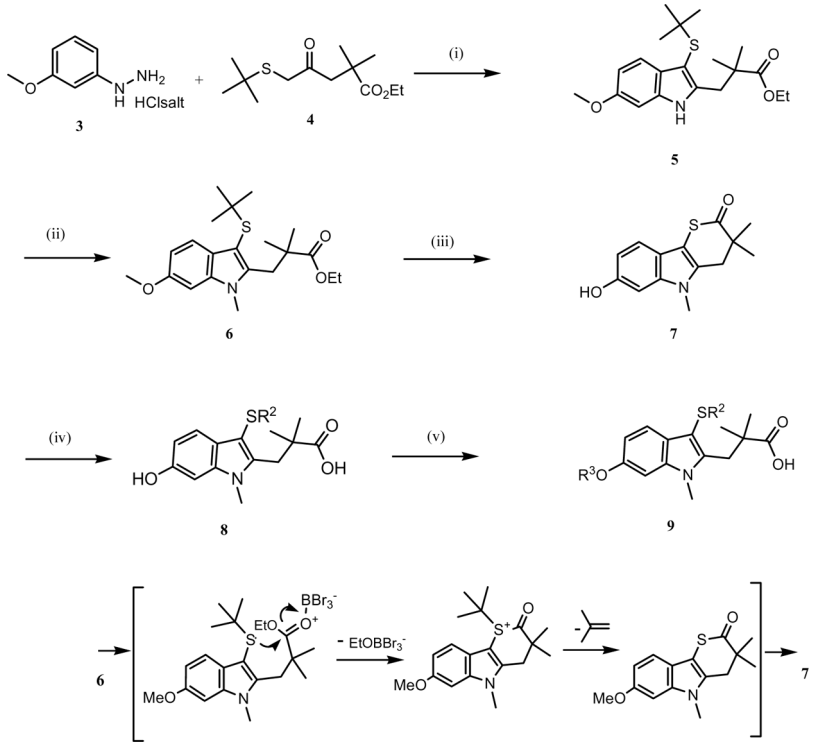
convenient method for the preparation of 6-alkoxy compounds **9**. We report here a facile synthesis of **9** via a novel thiolactone intermediate **7,** which allows for sequential modification of the thiol and phenol moieties.

Analogs of 3-thioindole compounds are generally prepared by Fisher indole synthesis,[5] Gassman indole synthesis,[6a,6b] and various electrophilic aromatic sulfenylations of indoles.[7a–h] To efficiently explore structure–activity relationships (SAR) around structure **9**, we envisioned preparation of compound **5**, alkylation of the indole nitrogen to afford **6**, then selective deprotection and modification of the orthogonally protected thiol and phenol moieties to allow for sequential modification of these groups in either order.

## RESULTS AND DISCUSSION

As depicted in Scheme 1, 3-*t*-butyl thiol indole **5** was prepared via Fischer indole condensation of 3-methoxy phenyl hydrazine **3** and a tert-butyl thioketone **4**. Methylation of the indole nitrogen under conditions ii (listed in Scheme 1) afforded **6**.[8] Subsequent deprotection of the methyl ether with 5 equivalents of $BBr_3$ unexpectedly occurred with concomitant formation of the thiolactone to form **7** in high yield, the structure of which was confirmed by x-ray analysis (Fig. 1). Less $BBr_3$ resulted in a low-yielding reaction with a number of side products. One of the side products was 7-methoxy-3,3,5-trimethyl-4,5-dihydrothiopyrano[3,2-*b*]indol-2(3*H*)-one. Close examination of the reaction progress indicated that thiolactone formation occurred prior to demethylation. We hypothesize that the thiolactone formed as shown at the bottom of Scheme 1, involving nucleophilic addition of the sulfur atom in **6** to the $BBr_3$ coordinated carbonyl group[9] and the resulting thiolactone sulfonium intermediate eliminating isobutylene to give the thiolactone. Such isobutylene elimination of t-butyl sulfonium cations to afford sulfides have been reported previously.[10] Alternatively, conversion of **6** to **7** may proceed through $BBr_3$ deprotection of the t-butyl thioether followed by ring closure to the thiolactone.[11] We expected that alkylation of the thiolactone **7** would occur on the phenol. To our surprise, however, alkylation with a slight excess of alkylating reagent $R^2X$ with NaH under anhydrous conditions, followed by base hydrolysis, proceeded preferentially on the thiol to provide **8**. No desired peak was observed based on LC-MS analysis of the most of NaH-induced (anhydrous condition) alkylation reactions. The obtained chromatograph shows a dimer and a number of later-eluting peaks. Hydrolysis gives the product, indicating that ester linkages could exist in the initial alkylation product. The same product was obtained when aqueous NaOH was used instead of NaH in the first




***Scheme 1.*** (i) t-Butanol, 95 °C; (ii) $CH_3I$, NaH, DMF, −10 °C; to rt; (iii) $BBr_3$, DCM, −78 °C to rt; (iv) $R^2X$, NaH, DMF, rt or 70 °C; 3 N NaOH, dioxane/MeOH, 50 °C; (v) $R^3X$, NaH, DMF, rt or 70 °C; 3 N NaOH, dioxane/MeOH, 50 °C.

alkylation. It appears that NaOH hydrolyzes thiolactone, followed by alkylation of thiolate, however, phenolate displacement cannot be ruled out.

Prior to saponification, liquid chromatographic–mass spectrographic (LC-MS) analysis of the NaH alkylation reaction revealed ester dimer **10** (Fig. 2) and what appeared to be higher order structures, implicating phenolate displacement of thiolactone, followed by alkylation of the resultant thiolate, as the basis for the observed selectivity. The reaction scope and mechanism is still not clear and is a subject of future investigation. Subsequent alkylation of **8** with excess alkylating reagent $R^3X$ and base, followed by hydrolysis of the resultant ester, afforded **9** as the final product.

The described alkylation sequence is illustrated by the synthesis of **9a** and **9b** shown in Scheme 2. Reaction of **7** with 4-(chloromethyl)-1, 2-diphenylethane in NaH/dimethylformanide (DMF) followed by

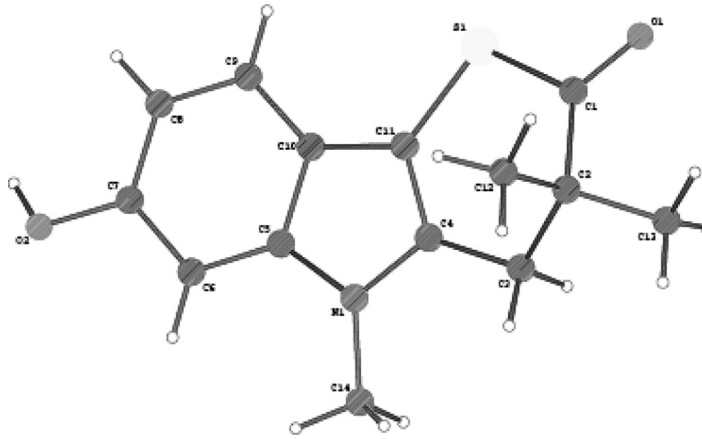
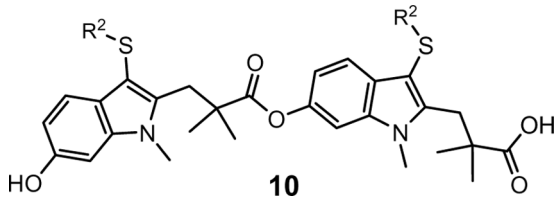


*Figure 1.* X-ray structure of the tricyclic thiolactone **7**.

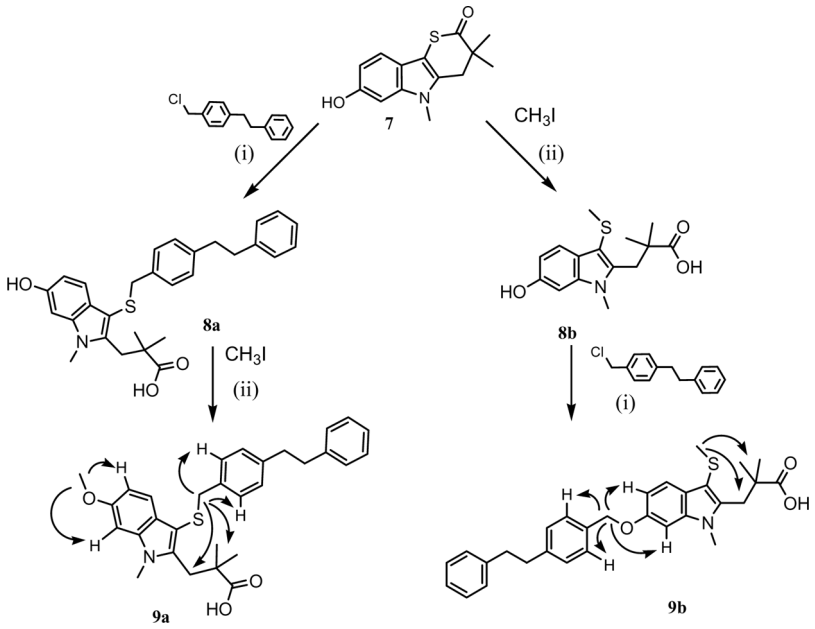
reaction with MeI provided **9a**. Reversal of the alkylation sequence afforded **9b**. The structural assignments of **9a** and **9b** were confirmed by nuclear Overhauser effect (NOE).

In the case of first alkylation, where 4-(chloromethyl)-1,2-diphenylethane was used as alkylating reagent, the irradiation of the proton on carbon next to the sulfur atom in **9a** resulted in the enhancement of the protons on the ortho-carbons of the phenyl group and methylene and gem dimethyl groups in the carboxylic acid side chain. For the second alkylation, where $CH_3I$ was employed as alkylating reagent, irradiation of the protons on the methoxy group resulted in enhancements of protons on carbons adjacent to the methoxy group. Reversal of the alkylation sequence afforded compound **9b,** in which irradiation of the protons on the thiol methyl group resulted in enhancement of the protons on methylene and gem dimethyl groups in the carboxylic acid side chain. Irradiation of the proton on the methylene next to the oxygen atom resulted in enhancements of protons on the ortho-carbons of the phenyl group and the indole.




**10**

*Figure 2.* Structure of dimer **10**.




***Scheme 2.*** (i) NaH/DMF, 70 °C, 1 h; 3 N NaOH, dioxane/MeOH, 50 °C, 1 h, 55%; (ii) NaH/DMF, rt, 1 h; 3 N NaOH, dioxane/MeOH, 50 °C, 1 h, 57%.

In conclusion, we have described an efficient and practical route for the direct synthesis of biologically active compounds **9** via a key thiolactone intermediate **7**, which allows for sequential modification of –N, –S, and –O groups.

## EXPERIMENTAL

$^1$H NMR spectra were recorded on a 500-MHz or 600-MHz spectrometer. LC-MS data were recorded by the RP-LC/MS system [0.05% trifluoroacetic acid (TFA) or formic acid, acetonitrile/water, 10–100% gradient]. Flash chromatography was performed using Si 40 S/M cartridges.

### Ethyl 5-(*tert*-Butylthio)-2,2-dimethyl-4-oxopentnaoate (4)

*N*,*N*-Diisopropylethylamine (DIEA) (0.96 mL, 5.5 mmol) was added slowly to a solution of ethyl 5-bromo-2,2-dimethyl-4-oxopentanoate (1.10 g, 4.4 mmol) and *tert*-butyl thiol (0.52 mL, 4.6 mmol) in dry

$CH_3CN$ (4 mL) at 0 °C. The mixture was stirred at room temperature for 3.5 h, quenched with $H_2O$, and extracted with EtOAc/hexanes (2/1). The organic layer was washed with 1 N HCl, $H_2O$ (2×), and brine and dried with $Na_2SO_4$. Removal of the solvent in vacuo afforded 1.13 g of crude product **4** as a colorless oil, which was used without further purification in the next step.

### Ethyl 3-[3-(*tert*-Butylthio)-6-methoxy-1*H*-indol-2-yl]-2,2-dimethylpropanoate (5)

A mixture of **3** (1.34 g, 7.6 mmol), the crude ketone **4** (1.54 g, 5.9 mmol), and *tert*-butanol (24 mL) in a sealed reaction vessel was stirred at 90 °C overnight. The solution was cooled, poured into saturated $NaHCO_3$, and extracted with DCM (2×). The combined organic layers were concentrated in vacuo. The crude residue was purified by silica-gel chromatography, eluting with a gradient of 28% to 38% EtOAc/hexanes to provide the compound **5** as yellow oil (1.42 g, 66%). LC-MS (ESI): $m/z = 364.2$ $[M + H]^+$. $^1H$ NMR (500 MHz, $CD_2Cl_2$): $\delta$ 9.06 (s, 1H), 7.54 (d, $J = 9.0$ Hz, 1H), 6.85 (d, $J = 2.0$ Hz, 1H), 6.77 (dd, $J = 9.0$ Hz, 2.0 Hz, 1H), 4.21 (quartet, $J = 7.5$ Hz, 2H), 3.66 (s, 3H), 3.21 (s, 2H), 1.28 (t, $J = 7.5$ Hz, 3H), 1.26 (s, 9 H), 1.21 (s, 6H).

### Ethyl 3-[3-(*tert*-Butylthio)-6-methoxy-1-methyl-1*H*-indol-2-yl]-2,2-dimethylpropanoate (6)

A solution of **5** (1.12 g, 3.08 mmol) in dry DMF (12 mL) was added slowly at −10 °C to a suspension of 95% NaH (84 mg, 3.38 mmol) in dry DMF (4 mL) under $N_2$ protection. After 20 min of stirring at room temperature, a solution of $CH_3I$ (0.252 mL, 4.00 mmol) in dry DMF (14 mL) was added. The mixture was stirred at −10 °C for 1 h, and then at room temperature overnight. The reaction was quenched with sat. $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with water and brine and dried with $Na_2SO_4$. The solvent was evaporated. The residue was purified by silica-gel chromatography, eluting with a gradient of 20% to 35% EtOAc/hexanes to provide the compound **6** as yellow oil (1.1 g, 94%). LCMS (ESI): $m/z = 378.2$ $[M + H]^+$. $^1H$ NMR (500 MHz, $CD_2Cl_2$): $\delta$ 7.59 (d, $J = 8.0$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.80 (s, 1H), 4.15 (quartet, $J = 7.0$ Hz, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 3.32 (s, 2H), 1.27 (t, $J = 7.0$ Hz, 3H), 1.24 (s, 9H), 1.19 (s, 6H).

### 7-Hydroxy-3,3,5-trimethyl-4,5-dihydrothiopyrano[3,2-*b*]indol-2(3*H*)-one (7)

Compound **6** (1.1 g, 2.91 mmol) was dissolved in dry DCM (15 mL). The solution was cooled at −78 °C under $N_2$. $BBr_3$ (14.5 mL) was added slowly via a syringe. The reaction mixture was stirred at −78 °C for 20 min and at room temperature for 45 min, quenched with saturated $NaHCO_3$, and extracted with EtOAc (3×). The combined organic layers were washed with water and brine and dried with $Na_2SO_4$. The solvent was evaporated. The crude solid was recrystallized from $EtOAc/CH_2Cl_2$ to provide the compound **7** as a solid (0.70 g, 92%). LC-MS (ESI): $m/z = 262.15$ $[M + H]^+$. $^1H$ NMR (500 MHz, $CD_2Cl_2$): $\delta$ 7.23 (d, $J =$ 8.5 Hz, 1H), 6.81 (d, $J =$ 2.0 Hz, 1H), 6.70 (dd, $J = 8.5$ Hz, 2.0 Hz, 1H), 3.65 (s, 3H), 3.00 (s, 2H), 1.26 (s, 6H).

### 3-(6-Hydroxy-1-methyl-3-{[4-(2-phenylethyl)benzyl]thio}-1*H*-indol-2-yl)-2,2-dimethylpropanoic Acid (8a)

To a stirred solution of **7** (26 mg, 0.1 mmol) in DMF (1 mL), 95% NaH (3.8 mg, 0.15 mmol) and 4-(chloromethyl)-1,2-diphenylethane (25 mg, 0.11 mmol) were added. The reaction mixture was stirred at 70 °C for 1 h, quenched with 1N HCl, and extracted with EtOAc (3×). The solvent was evaporated. The residue was dissolved in a mixture of dioxane (0.5 mL) and MeOH (0.5 mL) followed by addition of 3 N NaOH (0.5 mL, 1.5 mmol). The reaction mixture was stirred at 50 °C for 1 h, cooled to room temperature, acidified with 3 N HCl, and extracted with EtOA (3×). The combined organic layers were washed with brine, dried with $Na_2SO_4$, and the solvent was evaporated. The crude product **8a** (LC-MS (ESI): $m/z = 474.54$ $[M + 1]^+$) was used in the next step without further purification.

### 3-(6-Methoxy-1-methyl-3-{[4-(2-phenylethyl)benzyl]thio}-1*H*-indol-2-yl)-2,2-dimethylpropanoic Acid (9a)

To the crude product **8a** dissolved in DMF (1 mL), 95% NaH (10 mg, 0.4 mml) was added. The resultant mixture was stirred at room temperature for 10 min. Iodomethane (14 µl, 0.22 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, quenched with 1 N HCl aqueous solution, and extracted with EtOAc (3×). The solvent was evaporated. The residue was dissolved in a mixture of dioxane (0.5 mL) and MeOH (0.5 mL) followed by addition of 3 N NaOH (0.5 mL,

1.5 mmol). The reaction mixture was stirred at 50 °C for 1 h, cooled to room temperature, acidified with 3 N HCl aqueous solution, and extracted with EtOA (3×). The combined organic layers were concentrated in vacuo. The residue was purified by reverse-phase chromatography (10–90% MeCN/$H_2O$, both containing 0.05% TFA) to afford **9a** as a solid (26.8 mg, 55% in four steps). LC-MS (ESI): m/z = 488.4 $[M+1]^+$. $^1H$ NMR (500 MHz, $CD_3OD$): $\delta$ 7.45 (d, $J$ = 8.5 Hz, 2H), 7.25 (overlapping t, d, 2H), 7.16 (overlapping d, d, 2H), 6.93 (d, $J$ = 8.0 Hz, 2H), 6.88 (s, 1H), 6.77 (dd, $J$ = 8.7 Hz, 2.0 Hz, 1H), 6.73 (d, $J$ = 8.0 Hz, 2H), 3.86 (s, 3H), 3.66 (s, 2H), 3.56 (s, 3H), 2.88–2.82 (m, 4 H), 2.69 (s, 2H), 1.10 (s, 6H).

### 3-[6-Hydroxy-1-methyl-3-(methylthio)-1*H*-indol-2-yl)-2,2-dimethylpropanoic Acid (8b)

To a solution of **7** (26 mg, 0.1 mmol) in DMF (1 mL) 95% NaH (3.8 mg, 0.15 mmol) and $CH_3I$ (6.9 µl, 0.11 mmol) were added. The reaction mixture was stirred at room temperature for 1 h, quenched with 1N HCl, and extracted with EtOAc (3×). The solvent was evaporated. The residue was dissolved in a mixture of dioxane (0.5 mL), and MeOH (0.5 mL), followed by addition of 3 N NaOH (0.5 mL, 1.5 mmol). The reaction mixture was stirred at 50 °C for 1 h, cooled to room temperature, acidified with 3N HCl, and extracted with EtOA (3×). The combined organic layers were washed with brine and dried with $Na_2SO_4$, and the solvent was evaporated. The crude product **8b** (LC-MS (ESI): m/z = 294.21 $[M+1]^+$) was used in the next step without further purification.

### 2,2-Dimethyl-3-(1-methyl-3-(methylthio)-6-{[4-(2-phenylethyl)-benzyl]oxy}-1*H*-indol-2-yl) Propanoic Acid (9b)

The crude product **8b** was dissolved in DMF (1 mL), followed by addition of 95% NaH (10 mg, 0.4 mml), and stirred at room temperature for 10 min. 4-(Chloromethyl)-1,2-diphenylethane (51 mg, 0.22 mmol) was added. The reaction mixture was stirred at 70 °C for 1 h, cooled to room temperature, quenched with 1 N HCl, and extracted with EtOAc (3×). The solvent was evaporated. The residue was dissolved in a mixture of dioxane (0.5 mL) and MeOH (0.5 mL) followed by the addition of 3 N NaOH (0.5 mL, 1.5 mmol). The reaction mixture was stirred at 50 °C for 1 h, cooled to room temperature, acidified with 3 N HCl, and extracted with EtOAc (3×). The solvent was evaporated. The residue was purified by reverse-phase chromatography (10–90% MeCN/$H_2O$,

both containing 0.05% TFA) to afford the compound **9b** as a solid (28 mg, 57% in four steps). LC-MS (ESI): $m/z = 488.55$ $[M+1]^+$. $^1H$ NMR (500 MHz, $CD_3OD$): $\delta$ 7.50 (d, $J =$ 6.75 Hz, 1H), 7.36 (d, $J =$ 8.0 Hz, 2H), 7.23–7.12 (m, 7H), 6.96 (d, $J =$ 2 Hz, 1H), 6.86 (dd, $J = 8.5$ Hz, 2.5 Hz, 1H), 5.09 (s, 2H), 3.64 (s, 3H), 3.35 (s, 3H), 2.90 (s, 4H), 2.21 (s, 2H), 1.22 (s, 6H).

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