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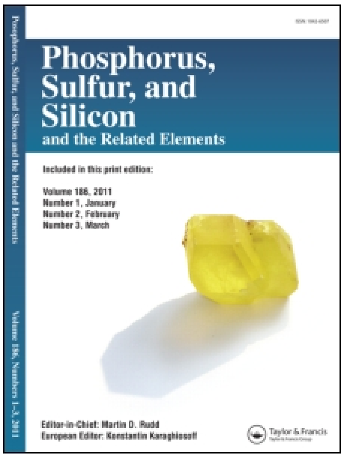

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FUNCTIONALIZATION OF (±)-2-METHYL-3-(2-THIENYL)-1-PROPANOL, A VERSATILE BUILDING BLOCK FOR THE SYNTHESIS OF 2-METHYL-1-ALKANOLS

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FUNCTIONALIZATION OF (±)-2-METHYL-3-(2-THIENYL)-1-PROPANOL, A VERSATILE BUILDING BLOCK FOR THE SYNTHESIS OF 2-METHYL-1-ALKANOLS

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Regioselective functionalizations (bromination, lithiation, stannylation) of the thiophenes **1** and **2** provide an easy access to building blocks for the synthesis of 5-substituted derivatives. The usefulness of the new building blocks is exemplified by the introduction of several pyridine-derived substituents.

Key words: Thiophenes, bromination, lithiation, organostannanes, palladium catalyst, 2-methyl-1-alkanols.

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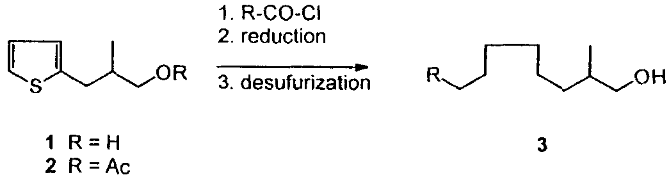
INTRODUCTION

In the past few years the thiophene derivatives **1** and **2** as well as their pure enantiomers[1,2] have attracted considerable interest, since they can be used advantageously for the preparation of long-chain 2-methyl-1-alkanols **3**, which on the other hand are versatile intermediates for the synthesis of alkaloids,[2] pheromones,[3,4] and ferroelectric liquid crystals.[4] Thus, the acetate **2** is subjected to regioselective Friedel-Crafts acylation at C-5 of the thiophene ring followed by Huang-Minlon reduction of the keto group with concomitant ester hydrolysis. Finally, reductive desulfurization of the thiophene ring with Raney nickel yields the long chain saturated alcohol **3** (Scheme I).

In an earlier publication[5] we described methodologies for the functionalization of the terminal hydroxy group of **1** to give the corresponding aldehyde, alkyl bromide and various amines with antifungal activities. In this paper we communicate the development of methods other than Friedel-Crafts acylation for functionalization at C-5 of the thiophene ring. The new building blocks **4**, **5** and **6** allow the introduction of substituents by electrophilic as well as nucleophilic substitution reactions. All syntheses described here were performed with racemic compounds.



SCHEME I

RESULTS AND DISCUSSION

Preparation of the Building Blocks

The bromo compound **4** was obtained in high yield by reaction of the ester **2** with bromine in dichloromethane at low temperature. **4** should be a useful building block for the nucleophilic introduction of substituents via Pd-catalyzed cross-coupling reactions[6] with organometallic compounds, e.g. organostannanes or organoboranes. Complementary to **4**, the stannylated thiophene **6** should permit Pd-catalyzed coupling reactions with inversed reactivities compared to those mentioned above. **6** was prepared in high yield from the alcohol **1** by conversion to the tetrahydropyranyl (THP) ether **5** and subsequent direct lithiation at the 5-position of the thiophene ring with *n*-butyllithium and stannylation with trimethyltin chloride (Scheme II). Attempts to prepare an organostannane by reaction of the aryl bromide **4** with hexamethylditin/$Pd(Ph_3P)_4$[7] were unsuccessful.

Applications of the Building Blocks

The usefulness of the new building blocks described above was demonstrated by the introduction of several pyridine-derived substituents (Scheme III). The products should be practical intermediates for the synthesis of lower homologs of the marine alkylpyridine alkaloids ikimine A and niphatesine C following the synthetic strategies described by us recently.[2]

Pd-catalyzed cross-coupling of the organostannane **6** with 3-bromopyridine followed by acidic hydrolysis gave the biaryl **7**. Direct lithiation of **5**, as described above, followed by reaction with pyridine-3-carboxaldehyde and subsequent O-deprotection offered an easy access to the diol **8**.

The introduction of a vinyl group into the ring was accomplished by Pd-catalyzed cross-coupling of the bromothiophene **4** with tri-*n*-butyl-vinylstannane.[8] The resulting vinyl compound **9** was further applied to the preparation of an arylethyl derivative of **1**. Thus, hydroboration of the alkene **9** with 9-BBN gave a terminal organoborane, which was directly used for a Pd-catalyzed coupling reaction[9] with 3-bromopyridine. Finally, hydrolysis of the ester group gave the primary alcohol **10**.

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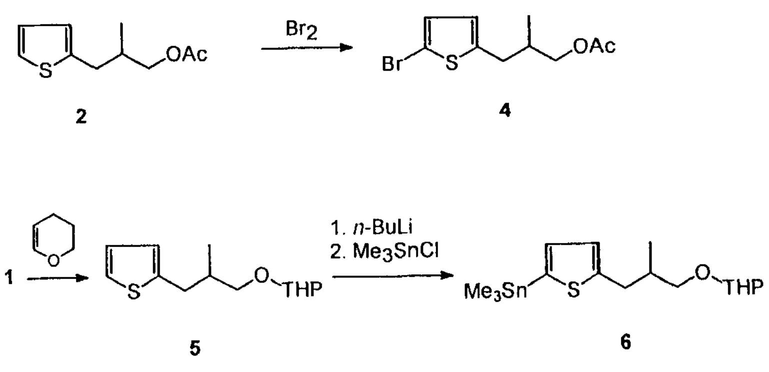
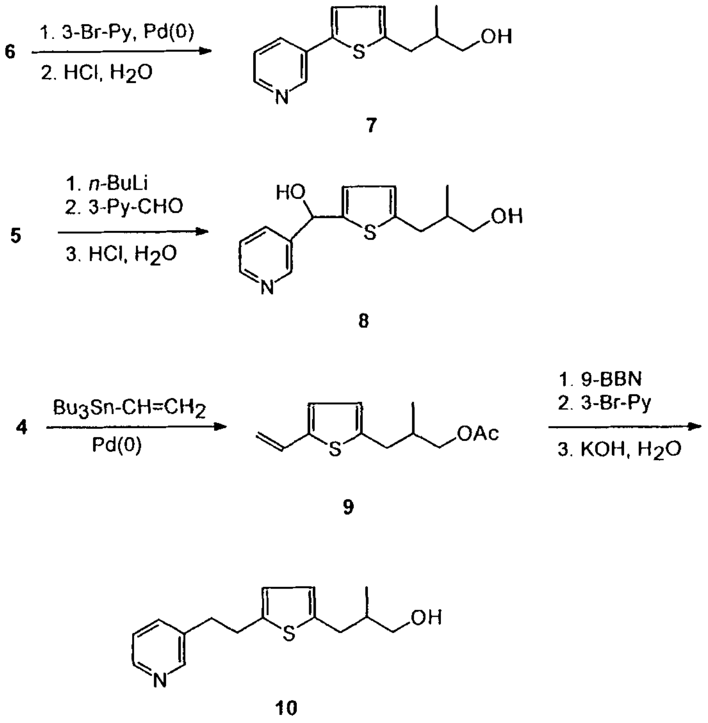


SCHEME II



SCHEME III

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In conclusion, the new building blocks **4**, **5** and **6** allow easy introduction of aryl, hydroxyalkyl, vinyl and arylethyl substituents into the 5-position of the thiophene **1**. These results should lead to an ever broader application of the hydroxyalkylthiophene **1** and its pure enantiomers in the synthesis of 2-methyl-1-alkanols and derivatives thereof.

EXPERIMENTAL

General Comments: NMR spectra were performed on a Bruker AM 400 spectrometer. IR spectra were recorded on a Philips Analytical PU 98000 FTIR spectrometer. Mass spectra were recorded on a Finnigan MAT 8430 spectrometer (EI, 70 eV). Elemental analyses: Carlo Erba CHNO-Elemental Analyzer. Flash column chromatography (FCC) was performed on Merck Kieselgel 60 (230–400 mesh).

(±)-2-Methyl-3-(5-bromo-2-thienyl)-1-propyl acetate (4)

The thiophene **2**[2a] (10.0 g, 50.4 mmol) was dissolved in dichloromethane (300 ml) and the solution was cooled to 0°C. Then a solution of bromine (8.10 g, 50.7 mmol) in dichloromethane (50 ml) was added dropwise with stirring within 40 min. Stirring was continued for 60 min and then the mixture was extracted with $NaHSO_3$ solution and with water. The organic layer was dried and concentrated *in vacuo*. The oily residue was purified by distillation to give **3** (12.4 g, 89%) as a colourless oil, $b.p._{0.1} = 90°C$. IR (NaCl): 1963, 1740, 1445, 1375, 1365, 1240, 1042, 964, 792 cm^{-1}. MS (m/e, %): 278 (M^+, 18) 276 (M^+, 17), 218 (76), 216 (74), 177 (100), 175 (96), 137 (78), 122 (40), 96 (38). ^1H NMR ($CDCl_3$): δ 6.85 (d, $J = 4$ Hz, 1H, ArH), 6.54 (d, $J = 4$ Hz, 1H, ArH), 3.93 (d, $J = 6$ Hz, 2H, OCH_2), 2.83 (dd, $J = 15$ Hz/6 Hz, 1H, Ar—C*H*H), 2.62 (dd, $J = 15$ Hz/8 Hz, 1H, Ar—CH*H*), 2.07 (m, 1H), 2.06 (s, 3H, CH_3), 0.96 (d, $J = 7$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 171.0, 144.1, 129.5, 125.9, 109.3, 68.0, 34.6, 34.0, 20.8, 16.5. Anal. Calcd. for $C_{10}H_{13}BrO_2S$: C, 43.33; H, 4.73. Found: C, 43.23; h, 4.85.

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(±)-2-[2-Methyl-3-(2-thienyl)-1-propyloxy]-tetrahydropyran (**5**) (*mixture of isomers*)

A solution of 1^{1b} (1.00 g, 6.4 mmol), 3,4-dihydropyran (0.80 g, 9.5 mmol) and pyridinium *p*-toluenesulfonate (0.16 g, 0.64 mmol) in anhydrous dichloromethane (10 ml) was stirred at room temperature for 4 h. Then the solution was washed with 10% $NaHCO_3$ solution and with water, dried and evaporated. The oily residue was purified by FCC to give **5** (1.20 g, 78%) as a colourless oil. IR (NaCl): 2941, 1454, 1441, 1379, 1352, 1136, 1123, 1078, 1060, 1033, 692 cm^{-1}. MS (m/e, %): 240 (M^+, 1), 168 (16), 138 (24), 97 (36), 85 (100). ^1H NMR ($CDCl_3$): δ 7.11 (dd, J = 5 Hz/1 Hz, 1H, 5-H), 6.91 (dd, J = 5 Hz/3 Hz, 1H, 4-H), 6.77 (br. d, J = 3 Hz, 1H, 3-H), 4.57 (t, J = 3 Hz, 1H), 3.85 (m, 1H), 3.63 (m, 1H), 3.51 (m, 1H), 3.24 (m, 1H), 3.00 (m, 1H), 2.66 (m, 1H), 2.07 (m, 1H), 1.83 (m, 1H), 1.70 (m, 1H), 1.52 (m, 4H, CH_2—CH_2), 0.96 (d, J = 7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 143.5/143.2, 126.6, 125.2/125.1, 123.2/123.1, 98.9/98.8, 71.9/71.7, 62.1, 35.9/35.8, 33.8/33.7, 30.7/30.6, 25.5, 19.5, 16.8/16.7. Anal. Calcd. for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.39. Found: C, 65.02; H, 9.05.

(±)-2-[2-Methyl-3-(5-trimethylstannyl-2-thienyl)-1-propyloxy]-tetrahydropyran (**6**) (*mixture of isomers*)

A solution of **5** (240 mg, 1.00 mmol) in anhydrous diethyl ether (2 ml) was added dropwise with stirring to a mixture of diethyl ether (3 ml) and *n*-butyllithium solution (1.6 M in hexane; 0.70 ml, 1.12 mmol) under N_2. Stirring was continued for 1 h at room temperature and then the mixture was cooled to −80°C and a solution of trimethyltin chloride (239 mg, 1.20 mmol) in anhydrous diethyl ether (3 ml) was added over a period of 15 min. The mixture was allowed to warm up to room temperature and stirred for another 30 min. Then water (5 ml) was added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 10 ml), the combined organic layers were washed with water, dried and evaporated. The residue was purified by FCC to give **6** (390 mg, 97%) as a colourless oil. IR (NaCl): 2940, 1454, 1441, 1377, 1352, 1201, 1134, 1122, 1078, 1061, 1034, 794, 773 cm^{-1}. MS (m/e, %): 404 (M^+, 1), 389 (22), 287 (19), 137 (20), 138 (48), 123 (17), 97 (52), 85 (100), 58 (18). ^1H NMR ($CDCl_3$): δ 7.00 (d, J = 3 Hz, 1H, ArH), 6.90 (d, J = 3 Hz, 1H, ArH), 4.57 (t, J = 3 Hz, 1H), 3.84 (m, 1H), 3.61 (m, 1H), 3.50 (m, 1H), 3.24 (m, 1H), 3.03 (m, 1H), 2.68 (m, 1H), 2.08 (m, 1H), 1.85 (m, 1H), 1.70 (m, 1H), 1.53 (m, 4H, CH_2—CH_2), 0.97 (d, J = 10 Hz, 3H, CH_3), 0.33 (s, 9H, $Sn(CH_3)_3$). ^{13}C NMR ($CDCl_3$): δ 149.4/149.2, 135.2/135.1, 134.9, 126.7/126.6, 98.9/98.8, 72.1/71.9, 62.1, 36.0/35.9, 33.9, 30.7, 25.5, 19.5, 17.0, −8.3 (3C). HRMS: Calcd for $C_{16}H_{28}O_2S^{120}Sn$: 404.0833. Found: 404.0830.

(±)-2-Methyl-3-[5-(3-pyridyl)-2-thienyl]-1-propanol (**7**)

A solution of **6** (1.47 g, 3.65 mmol), 3-bromopyridine (0.89 g, 5.63 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.127 g, 0.11 mmol) in anhydrous toluene (20 ml) was refluxed under a N_2 atmosphere for 24 h and then the toluene was removed by distillation *in vacuo*. The residue was dissolved in 6 M HCl (20 ml) and refluxed for 1 h. Then the mixture was brought to pH 9 by addition of sodium carbonate and extracted with ethyl acetate (3 × 30 ml). The combined organic layers were dried and evaporated and the residue was purified by FCC to give **7** (330 mg, 39%) as a colourless oil. IR (NaCl): 3322, 2957, 2917, 2872, 1491, 1415, 1044, 794, 704 cm^{-1}. MS (m/e, %): 233 (M^+, 28), 175 (16), 174 (100), ^1H NMR ($CDCl_3$): 8.81 (s, 1H, 2-H), 8.46 (m, 1H, 6-H), 7.80 (ddd, J = 8 Hz/2Hz/1Hz, 1H, 4-H), 7.27 (dd, J = 8 Hz/5 Hz, 1H, 5-H), 7.18 (d, J = 4 Hz, 1H, ArH), 6.79 (d, J = 4 Hz, 1H, ArH), 3.56 (d, J = 6 Hz, 2H, OCH_2), 3.01 (dd, J = 15 Hz/6 Hz, 1H, Ar—C*H*H), 2.69 (dd, J = 15 Hz/8 Hz, 1H, Ar—CH*H*), 2.32 (br.s, 1H, OH), 2.00 (m, 1H), 1.00 (d, J = 7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 187.6, 146.5, 144.7, 138.0, 132.6, 130.7, 126.6, 124.0, 123.7, 67.0, 38.1, 33.8, 16.4. Anal. Calcd. for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 67.07; H, 6.18; N, 5.99.

(±)-2-Methyl-3-{5-[(3-pyridyl)hydroxymethyl]-2-thienyl}-1-propanol (**8**)

A solution of **5** (3.00 g, 12.5 mmol) in anhydrous diethyl ether (15 ml) was added dropwise over a period of 15 min to a stirred mixture of diethyl ether (15 ml) and *n*-butyllithium solution (1.6 M in hexane; 9.0 ml, 14.4 mmol) under N_2 and stirring was continued for 15 min. Then the mixture was cooled to 0°C and a solution of pyridine-3-carboxaldehyde (1.30 g, 12.1 mmol) in anhydrous diethyl ether (15 ml) was added over a period of 10 min. The mixture was refluxed for 3 h, then treated with water (50 ml) and extracted with ethyl acetate (3 × 50 ml). The combined organic layers were concentrated *in vacuo* and the residue was dissolved in 3 M HCl (40 ml) and refluxed for 2 h. After cooling to room temperature the mixture was brought to pH 9 by addition of sodium carbonate and extracted with ethyl acetate (2 × 50 ml). The combined organic layers were dried, evaporated and the residue was purified by FCC to give **8** (1.68 g, 51%) as a colourless oil. IR (NaCl): 3285, 2957, 2920, 2872, 1595, 1581, 1427, 1028, 800, 713, 634 cm^{-1}. MS (m/e, %): 263 (M^+, 80), 232 (40), 204 (60), 192 (24), 108 (40), 106 (100), 97 (30). ^1H NMR ($CDCl_3$): δ 8.55 (s, 1H, 2-H), 8.42 (d, J = 5 Hz, 1H, 6-H), 7.79 (d, J = 8 Hz, 1H, 4-H), 7.26 (dd, J = 8 Hz/5 Hz, 1H, 5-H), 6.67 (d, J = 3 Hz, 1H, ArH), 6.60 (d, J = 3 Hz, 1H, ArH), 5.98 (s, 1H, CH—O), 3.46 (m, 2H, OCH_2), 3.0–2.0 (br. s, 2H, 2 OH), 2.87 (dd, J =

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15 Hz/6 Hz, 1H, Ar—C*H*H), 2.58 (dd, J = 15 Hz/8 Hz, 1H, Ar—CH*H*), 1.90 (m, 1H), 0.92 (d, J = 7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 148.5, 147.7, 145.1, 144.1, 139.1, 134.3, 124.9, 124.8, 123.5, 70.0, 66.9, 37.9, 33.7, 16.5. Anal. Calcd. for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.76; H, 6.97; N, 4.97.

(±)-2-Methyl-3-(5-vinyl-2-thienyl)-1-propyl acetate (**9**)

A solution of **4** (277 mg, 1.00 mmol), tri-*n*-butyl-vinylstannane (475 mg, 1.50 mmol), tetrakis(triphenylphosphine)palladium(0) (46 mg, 0.04 mmol) and a few crystals of 2,6-di-*tert*.-butyl-4-methylphenol in anhydrous toluene (15) was refluxed under a N_2 atmosphere for 3 h. Then the precipitate was removed by filtration and the filtrate was extracted with satd. NaF solution and with water. Both aqueous layers were extracted with diethyl ether and the organic layers were combined with the toluene layer. These combined organic solutions were dried and concentrated *in vacuo*. The residue was purified by FCC to give **9** (140 mg, 62%) as a colourless oil. IR (NaCl): 2963, 1740, 1620, 1365, 1240, 1037, 981, 800, 694 cm^{-1}. MS (m/e, %): 224 (M^+, 12), 164 (30) 149 (20), 138 (40), 123 (100), 97 (60), ^{1}H NMR ($CDCl_3$): δ 6.76 (d, J = 4 Hz, 1H, ArH), 6.72 (dd, J = 18 Hz/11 Hz, 1H, olefin. H), 6.62 (d, J = 4 Hz, 1H, ArH), 5.44 (d, J = 18 Hz, 1H, olefin. H), 5.06 (d, J = 11 Hz, 1H, olefin. H), 3.95 (m, 2H, OCH_2), 2.86 (dd, J = 15 Hz/6 Hz, 1H, Ar—C*H*H), 2.64 (dd, J = 15 Hz/8 Hz, 1H, Ar—CH*H*), 2.11 (m, 1H), 2.06 (s, 3H, CH_3), 0.97 (d, J = 7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$: δ 169.5, 140.1, 139.7, 128.4, 124.2, 124.1, 110.5, 66.6, 33.1, 32.4, 19.2, 14.9. Anal. Calcd. for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19. Found: C, 63.95; H, 6.88.

(±)-2-Methyl-3-{5-[2-(3-pyridyl)ethyl]-2-thienyl}-1-propanol (**10**)

The olefin **9** (350 mg, 1.56 mmol) was placed in a 10 ml round bottom flask under N_2, cooled to 0°C and treated dropwise with 9-BBN solution (0.5 M in THF; 5.0 ml, 2.5 mmol) and the mixture was stirred at room temperature for 24 h. Then the solution was transferred into a 100 ml flask containing a stirred mixture of 3-bromopyridine (395 mg, 2.50 mmol), tetrakis(triphenylphosphine)palladium(0) (170 mg, 0.15 mmol) and K_3PO_4 (660 mg, 3.10 mmol) in anhydrous THF (50 ml) under N_2. The resulting mixture was refluxed for 48 h, then cooled to 0°C, treated with 3 M NaOH (1.5 ml) and 30% H_2O_2 (1.7 ml) and then stirred at 40°C for 2 h. Then the mixture was poured into water and extracted with ethyl acetate (3 × 50 ml). The combined organic layers were dried, evaporated and the residue passed through a short silica column to receive the crude acetate of **10** (200 mg). This ester was hydrolyzed by refluxing in a solution of KOH (250 mg, 4.45 mmol) in ethanol (3.5 ml) and water (0.5 ml) for 3 h. Addition of water (20 ml) followed by extraction with ethyl acetate (2 × 30 ml), drying and evaporation gave a crude product which was purified by FCC to give **10** (110 mg, 27%) as a colourless oil. IR (NaCl): 3321, 2926, 1425, 1044, 1030, 799, 714 cm^{-1}. MS (m/e, %): 261 (M^+, 22), 231 (100), 216 (25), 202 (44), 169 (65), 151 (70), 111 (22), 93 (20), 92 (26). ^{1}H NMR ($CDCl_3$): δ 8.44 (s, 1H, 2-H), 8.40 (m, 1H, 6-H), 7.65 (m, 1H, 4-H), 7.45 (m, 1H, 5-H), 6.55 (d, J = 3 Hz, 1H, ArH), 6.52 (d, J = 3 Hz, 1H, ArH), 3.50 (m, 2H, OCH_2), 3.06 (t, J = 8 Hz, 2H, CH_2), 2.94 (t, J = 8 Hz, 2H, CH_2), 2.87 (dd, J = 15 Hz/6Hz, 1H, Ar—C*H*H), 2.60 (dd, J = 15 Hz/8 Hz, 1H, Ar—CH*H*), 2.40 (br. s., 1H, OH), 1.91 (m, 1H), 0.95 (d, J = 7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 149.8, 147.6, 141.5, 141.3, 136.1, 132.0, 128.5, 124.9, 124.3, 67.1, 38.1, 35.1, 33.8, 31.6, 16.5. HRMS: Calcd. for $C_{15}H_{19}NOS$: 261.1187. Found: 261.1187.

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