Wagner-Meerwein rearrangement of benzo- and thieno-annelated spiroalkanols

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Dedicated to Professor Lubor Fišera on the occasion of his 60th birthday
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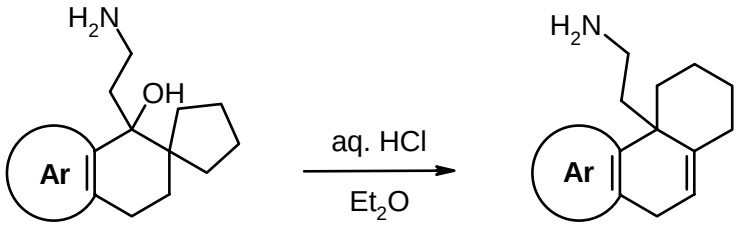
Abstract
The treatment of benzene solutions of 7,8-benzo- and 7,8-thieno-fused spiro[4.5]decan-6-ols with *p*-toluenesulfonic acid induced Wagner-Meerwein rearrangement resulting in a condensed three-ring system. In the case of the 6-methyl derivatives three different isomeric products were formed: two rearrangement products and the dehydration product featuring an exocyclic double bond. Variation of the reaction conditions led to the exclusive or preferred formation of one of the isomers.

Keywords: Wagner-Meerwein rearrangement, spiroketone, spiroalkanol

Introduction

In the course of an attempted synthesis for a thiophene analogue of the isomorphinane system we dealt with a reaction of the type shown in Scheme 1.



Scheme 1

The unusual reaction conditions and the question of the regioselectivity in the formation of the double bond prompted us to analyze this rearrangement more closely. A literature search revealed several instances of exactly the type of conversion shown in Scheme 1,[1] where Ar is a

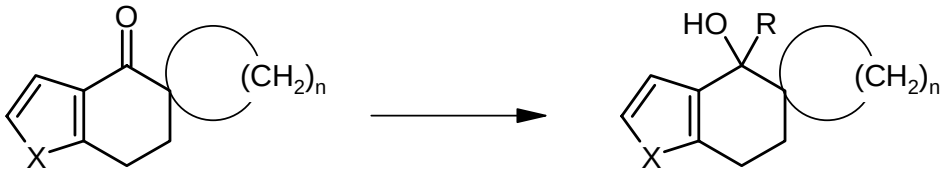
(substituted) benzene ring, but no system with an other side chain instead of an aminoalkyl group was found. Therefore, we decided to investigate this reaction utilizing a methyl group as an example for a non-basic side chain and also thieno-annelated systems.

Results and Discussion

Synthesis of the spiro alcohols

The introduction of the spiro ring was achieved by double alkylation of an appropriate ketone with an α,ω -dibromo alkane. This method for synthesizing spiro-ketones **1a**,[2] **1b**,[3] and **2**[4] has been described before, and we followed the procedure with some minor modifications that reduced the formation of side products and allowed easier purification of the products.

For reasons of simplicity and easy detection by NMR we chose the methyl group as side chain of the alcohols to be rearranged. The methyl group was introduced with methyl lithium, since in our hands methyl magnesium halide, as described for the synthesis of **3a**,[5,6] led to the formation of large amounts of the exocyclic alkenes **7** as side products. In addition, reduction with $LiAlH_4$ converted the thieno-annelated ketones **1b** and **2** into the secondary alcohols **5** and **6**, respectively (Scheme 2).



1, **2** **3** - **6**

	n	X
1a	4	CH=CH
1b	4	S
2	5	S

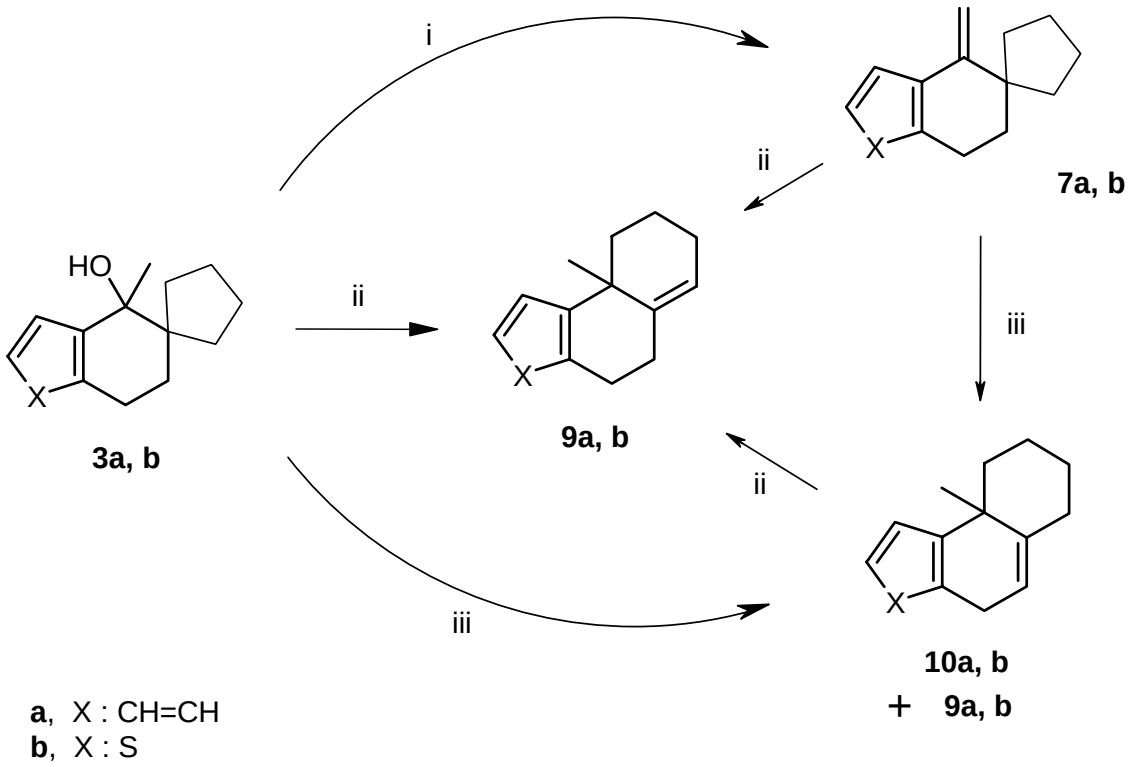
	n	X	R	Yield
3a	4	CH=CH	Me	89%
3b	4	S	Me	98%
4	5	S	Me	98%
5	4	S	H	96%
6	5	S	H	96%

Scheme 2

Rearrangements

Already the first experiments showed that three isomers were formed: Treatment of **3a** with *p*-toluenesulfonic acid (TosOH) in benzene at 50 °C for 1 h produced a mixture of the exo-alkene **7a** and the Wagner-Meerwein products **9a** and **10a** (Scheme 3). Variations of the reaction conditions allowed the selective synthesis of two of them: The reaction of of **3a** with TosOH in a

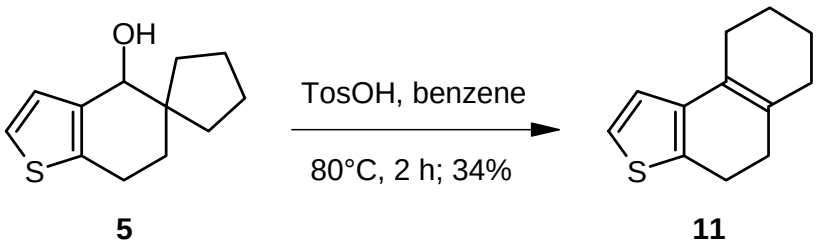
benzene solution at ambient temperature for 1 h afforded **7a**, which can be synthesized by this method under much milder conditions than it was reported before[6] by heating to 170 °C with $KHSO_4$. Heating a benzene solution of **3a** and TosOH at reflux temperature for 6 hours formed exclusively **9a**.



Scheme 3. All conversions carried out using TosOH/benzene. i, 1h, 20 °C; ii, 6h, 80 °C; iii, 7d, 35 °C.

Although analogues of **10a** bearing an aminoalkyl side chain are known from isomorphinane syntheses, we failed in obtaining this isomer selectively. After testing several reagents (including ethanolic HCl, trifluoroacetic acid, boron trifluoride/acetic acid, and dioxane/sulfuric acid under various conditions), best results were achieved with a benzene solution of **3a** and TosOH kept at 35 °C. Complete conversion of **3a** required 7 days yielding a mixture of **10a** and **9a** (85:15) which we could not separate; both alkenes show almost identical R_f values and boiling points (Scheme 3, X = CH=CH). The thieno-annelated alcohol **3b** behaved completely analogous to **3a**, except that the product ratio in the synthesis of **10b** was slightly better (Scheme 3, X = S).

The experiments with spiranols were extended to the secondary alcohol **5**; treatment of **5** with TosOH in a benzene solution at reflux temperature for 2 h furnished alkene **11** as the rearrangement product (Scheme 4).

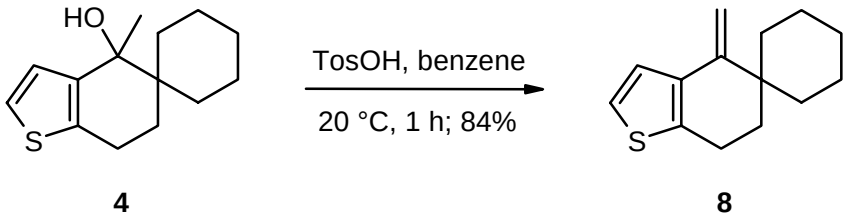


5 **11**

Scheme 4

The reaction conditions applied to **3a** and **3b** affording the rearrangement products **9** and **10** converted also the exocyclic alkenes **7a** and **7b** into the respective isomers **9** and **10** with identical results. Even the conversion of the alkenes **10** into the thermodynamically more stable isomers **9** was possible under the same conditions that were utilized for the synthesis of the latter from the alcohols **3**.

The above-described reaction conditions applied to spiro-cyclohexane alcohols gave different results. The tertiary alcohol **4** yielded only the exocyclic alkene **8** as the dehydration product (Scheme 5). All experiments aiming at the conversion of **6** resulted in complete decomposition. We did not detect any rearrangement product derived from a – presumably thermodynamically much less favorable – cycloheptano-annelated skeleton.



4 **8**

Scheme 5

Experimental Section

General Procedures. Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Anhydrous diethyl ether and tetrahydrofuran were obtained by distillation from sodium/benzophenone, dry benzene by refluxing over P_2O_5. After isolation all products were purified by bulb-to-bulb distillation. TLC was performed on precoated plates (Merck TLC aluminium sheets silica $60F_{254}$) with detection by UV light. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX-90 spectrometer (TMS as internal standard, $CDCl_3$ as solvent, δ values in ppm).

The starting materials 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one[7] and 3,4-dihydronaphthalen-1(2*H*)-one[8] and from these the spiro-ketones **1a**,[2] **1b**,[3] and **2**[4] were synthesized according to known procedures.

3',4′-Dihydro-1'-methylspiro[cyclopentane-1,2'(1'*H*)-naphthalen]-1'-ol (3a). Methyl lithium (46 mL of a 0.5 M solution in diethyl ether, 23 mmol) was cooled to –10 °C under a nitrogen atmosphere, and a solution of ketone **1a** (4 g, 20 mmol) in anhydrous diethyl ether (40 mL) was added dropwise. The mixture was stirred for further 15 min, poured into water and extracted several times with diethyl ether. The combined organic layers were dried and evaporated. Yield 3.85 g (89%), colorless oil; TLC: R_f = 0.25 (light petroleum/EtOAc, 4:1); bp 116-118 °C (0.05 mm Hg); ^{1}H NMR ($CDCl_3$): δ 7.49 (m, 1H), 7.15–6.90 (m, 3H), 2.77 (m, 2H), 1.90–1.15 (m, 10H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 139.8 (s), 138.6 (s), 128.7 (d), 127.2 (d), 126.1 (d), 125.8 (d), 74.8 (s), 44.6 (s), 30.9 (t), 30.2 (t), 29.6 (t), 27.5 (t), 25.7 (t), 25.2 (t), 22.4 (q).

6,7-Dihydro-4-methylspiro[benzo[*b*]thiophene-5(4*H*),1'-cyclopentan]-4-ol (3b). Ketone **1b** (4.95 g, 24 mmol) and methyl lithium (56 mL of a 0.5-m solution in diethyl ether, 28 mmol) were reacted as described for **3a**. Yield 5.23 g (98%), colorless oil; TLC: R_f = 0.25 (light petroleum/EtOAc, 4:1); bp 110-112 °C (0.07 mm Hg); ^{1}H NMR ($CDCl_3$): δ 7.06 (s, 2H), 2.80 (m, 2H), 2.00–1.30 (m, 10H), 1.47 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 143.1 (s), 135.9 (s), 125.2 (d), 122.4 (d), 73.6 (s), 49.3 (s), 32.7 (t), 32.1 (t), 31.5 (t), 25.7 (t), 25.5 (t), 25.3 (t), 21.7 (q).

6,7-Dihydro-4-methylspiro[benzo[*b*]thiophene-5(4*H*),1'-cyclohexan]-4-ol (4). Ketone **2** (4.41 g, 20 mmol) and methyl lithium (46 mL of a 0.5-m solution in diethyl ether, 23 mmol) were reacted as described for **3a**. Yield 4.63 g (98%), colorless oil; TLC: R_f = 0.40 (light petroleum/EtOAc, 4:1); bp 116-118 °C (0.04 mm Hg); ^{1}H NMR ($CDCl_3$): δ 7.05 (s, 2H), 2.70 (m, 2H), 2.10–1.00 (m, 12H), 1.40 (s, 3H); ^{13}C NMR: δ 142.2 (s), 135.4 (s), 125.4 (d), 122.3 (d), 72.4 (s), 39.0 (s), 29.0 (t), 27.4 (t), 26.0 (t), 25.0 (t), 24.2 (t), 21.8 (2t), 21.0 (q).

6,7-Dihydrospiro[benzo[*b*]thiophene-5(4*H*),1'-cyclopentan]-4-ol (5). Ketone **1b** (3.1 g, 15 mmol) was dissolved in anhydrous tetrahydrofuran (100 mL) under nitrogen atmosphere, solid $LiAlH_4$ (0.57 g, 15 mmol) was added and the mixture stirred for 30 min. Water was then added carefully until the evolution of hydrogen ceased and the hydroxide slurry was filtered by suction and washed with THF. The combined organic solutions were dried and evaporated. Yield 3.03 g (96%), colorless oil; TLC: R_f = 0.20 (light petroleum/EtOAc, 4:1); bp 110-113 °C (0.06 mm Hg) [lit[3b]: 124-128 °C (1.3 mm Hg)]; ^{1}H NMR ($CDCl_3$): δ 6.95 (d, 1H, J=5.1Hz), 6.82 (d, 1H, J=5.1Hz), 4.10 (s, 1H), 2.70 (m, 2H), 2.00–0.95 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 138.1 (s), 137.8 (s), 127.4 (d), 123.0 (d), 72.0 (d), 46.7 (s), 34.5 (t), 33.8 (t), 30.2 (t), 25.1 (t), 25.0 (t), 22.7 (t).

6,7-Dihydrospiro[benzo[*b*]thiophene-5(4*H*),1'-cyclohexan]-4-ol (6). Ketone **2** (2.2 g, 10 mmol) and $LiAlH_4$ (0.38 g, 10 mmol) were reacted as described for **5**. Yield 2.13 g (96%), colorless oil; TLC: R_f = 0.20 (light petroleum/EtOAc, 4:1); bp 115-118 °C (0.04 mm Hg); ^{1}H NMR ($CDCl_3$): δ 7.09 (d, 1H, J=4.5Hz), 6.98 (d, 1H, J=4.5Hz), 4.30 (s, 1H), 2.73 (m, 2H), 2.10–1.10 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 137.1 (s), 136.8 (s), 127.3 (d), 122.2 (d), 71.4 (d), 36.2 (s), 31.4 (t), 31.2 (t), 26.9 (t), 26.1 (t), 21.5 (t), 21.2 (2t).

3',4'-Dihydro-1'-methylenespiro[cyclopentane-1,2'(1'*H*)-naphthalene] (7a). The tertiary alcohol **3a** (0.65 g, 3 mmol) was dissolved in anhydrous benzene (10 mL) and treated with TosOH (0.34 g, 2 mmol). The mixture was stirred for 1 h at ambient temperature, poured into

saturated sodium bicarbonate solution and extracted with diethyl ether. The combined organic layers were dried and evaporated. Yield 0.48 g (81%), pale brown oil; TLC: R_f = 0.30 (light petroleum); bp 90-93 °C (0.3 mm Hg) [lit[6]: 113-115 °C (1.5 mm Hg)]; ^{1}H NMR ($CDCl_3$): δ 7.45 (m, 1H), 7.15–6.90 (m, 3H), 5.35 (s, 1H), 4.92 (s, 1H), 2.84 (m, 2H), 1.90–1.35 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 151.1 (s), 136.3 (s), 135.8 (s), 128.6 (d), 127.1 (d), 125.6 (d), 125.3 (d), 105.9 (t), 47.7 (s), 36.6 (2t), 35.2 (t), 27.3 (t), 23.7 (2t).

6,7-Dihydro-4-methylenespiro[benzo[*b*]thiophene-5(4*H*)-1'-cyclopentane] (7b). Alcohol **3b** (0.44 g, 2 mmol) and TosOH (0.17 g, 1 mmol) were reacted as described for **7a**. Yield 0.34 g (83%), pale brown oil; TLC: R_f = 0.25 (light petroleum); bp 90-95 °C (0.25 mm Hg); ^{1}H NMR ($CDCl_3$): δ 7.13 (d, 1H, J=5.6Hz), 7.01 (d, 1H, J=5.6Hz), 5.26 (s, 1H), 4.91 (s, 1H), 2.86 (m, 2H), 1.90–1.50 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 147.7 (s), 137.1 (s), 136.1 (s), 124.3 (d), 122.2 (d), 104.2 (t), 46.8 (s), 36.8 (2t), 36.2 (t), 24.2 (t), 23.2 (2t).

6,7-Dihydro-4-methylenespiro[benzo[*b*]thiophene-5(4*H*),1'-cyclohexane] (8). Alcohol **4** (0.47 g, 2 mmol) and TosOH (0.17 g, 1 mmol) were reacted as described for **7a**. Yield 0.36 g (84%), pale brown oil; TLC: R_f = 0.25 (light petroleum); bp 100-104 °C (0.5 mm Hg); ^{1}H NMR ($CDCl_3$): δ 7.13 (d, 1H, J=5.3Hz), 7.05 (d, 1H, J=5.3Hz), 5.25 (s, 1H), 5.03 (s, 1H), 2.82 (m, 2H), 1.89 (m, 2H), 1.75–0.75 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 149.6 (s), 135.9 (2s), 124.3 (d), 122.2 (d), 104.1 (t), 36.8 (s), 34.2 (2t), 30.7 (t), 26.4 (t), 22.0 (2t), 21.5 (t).

2,3,4,4a,9,10-Hexahydro-4a-methylphenanthrene (9a). The tertiary alcohol **3a** (4.33 g, 20 mmol) was dissolved in anhydrous benzene (100 mL) and treated with TosOH (1.72 g, 10 mmol). The mixture was heated at reflux for 6 h, cooled, poured into saturated sodium bicarbonate solution and extracted with diethyl ether. The combined organic layers were dried and evaporated. Yield 3.25 g (82%), pale yellow oil; TLC: R_f = 0.30 (light petroleum); bp 95-98 °C (0.25 mm Hg) [lit[9]: 50 °C (0.02 mm Hg)]; ^{1}H NMR ($CDCl_3$): δ 7.40 (m, 1H), 7.15–6.90 (m, 3H), 6.04 (m, 1H), 2.90–2.70 (m, 2H), 2.30–1.95 (m, 2H), 1.75–1.30 (m, 6H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 140.1 (s), 134.8 (2s), 128.8 (d), 126.2 (d), 125.6 (d), 124.4 (d), 120.8 (d), 38.7 (t), 37.7 (t), 32.6 (s), 26.7 (q), 25.8 (t), 22.7 (t), 18.4 (t).

4,5,7,8,9,9a-Hexahydro-9a-methylnaphtho[2,1-*b*]thiophene (9b). Tertiary alcohol **3b** (4.45 g, 20 mmol) and TosOH (1.72 g, 10 mmol) were reacted as described for **9a**. Yield 3.85 g (94%), pale yellow oil; TLC: R_f = 0.25 (light petroleum); bp 98-101 °C (0.3 mm Hg); ^{1}H NMR ($CDCl_3$): δ 7.06 (s, 2H), 5.92 (m, 1H), 3.05–2.70 (m, 2H), 2.35–2.10 (m, 2H), 1.95–1.15 (m, 6H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 137.3 (s), 135.2 (s), 134.4 (s), 123.4 (d), 122.1 (d), 119.0 (d), 38.3 (t), 37.4 (t), 32.2 (s), 25.7 (t), 22.7 (t), 22.0 (q), 18.1 (t).

1,2,3,4,4a,9-Hexahydro-4a-methylphenanthrene (10a). The tertiary alcohol **3a** (0.43 g, 2 mmol) was dissolved in anhydrous benzene (15 mL) and treated with TosOH (0.17 g, 1 mmol). The mixture was stirred for 7 days at 35°C, poured into saturated sodium bicarbonate solution and extracted with diethyl ether. The combined organic layers were dried and evaporated. The final product contained 15% of the isomer **9a**. Yield 0.38 g (97%), yellow oil; TLC: R_f = 0.30 (light petroleum); bp 98-101 °C (0.35 mm Hg); ^{1}H NMR ($CDCl_3$): δ 7.25–6.95 (m, 4H), 5.47 (m, 1H), 3.34 (m, 2H), 2.95–1.05 (m, 8H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 144.9 (s), 141.1 (s),

132.4 (s), 128.0 (d), 126.0 (d), 125.6 (d), 125.3 (d), 116.4 (d), 40.3 (t), 37.3 (s), 32.9 (t), 29.7 (t), 27.6 (t), 26.8 (q), 23.0 (t),

4,6,7,8,9,9a-Hexahydro-9a-methylnaphtho[2,1-*b*]thiophene (10b). Tertiary alcohol **3b** (0.44 g, 2 mmol) and TosOH (0.17 g, 1 mmol) were reacted as described for **10a**. The final product contained 10% of the isomer **9b**. Yield 0.31 g (76%), colorless oil; TLC: R_f = 0.25 (light petroleum); bp 100-105 °C (0.4 mm Hg); ^{1}H NMR ($CDCl_3$): δ 7.13 (d, 1H, J=5.3Hz), 6.92 (d, 1H, J=5.3Hz), 5.54 (m, 1H), 3.43 (m, 2H), 2.95–1.00 (m, 8H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 144.0 (s), 141.8 (s), 131.1 (s), 124.6 (d), 122.3 (d), 115.2 (d), 40.2 (t), 38.0 (s), 32.2 (t), 28.1 (t), 26.1 (q), 25.8 (t), 22.5 (t).

4,5,6,7,8,9-Hexahydronaphtho[2,1-*b*]thiophene (11). The secondary alcohol **5** (1.25 g, 6 mmol) was dissolved in anhydrous benzene (30 mL) and treated with TosOH (0.52 g, 3 mmol). The mixture was heated at reflux for 2 h, cooled, poured into saturated sodium bicarbonate solution and extracted with diethyl ether. The combined organic layers were dried and evaporated. Yield 0.39 g (34%), colorless oil; TLC: R_f = 0.40 (light petroleum); bp 87-91 °C (0.35 mm Hg); ^{1}H NMR ($CDCl_3$): δ 6.96 (d, 1H, J=5.8Hz), 6.85 (d, 1H, J=5.8Hz), 3.50–2.95 (m, 4H), 2.85–2.45 (m, 4H), 1.90–1.65 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 138.1 (s), 137.8 (s), 133.2 (s), 132.9 (s), 128.1 (d), 118.9 (d), 34.1 (t), 32.4 (t), 29.1 (t), 27.5 (t), 23.1 (t), 22.9 (t).

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