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NUCLEOPHILIC REACTIONS OF 9-ISOPROPYL-2,4-DIMETHOXY-7,12-DIMETHYL-3-(PHENYLSULFONYL)BENZO[*a*]HEPTALENE WITH LITHIUM DIALKYLAMIDES

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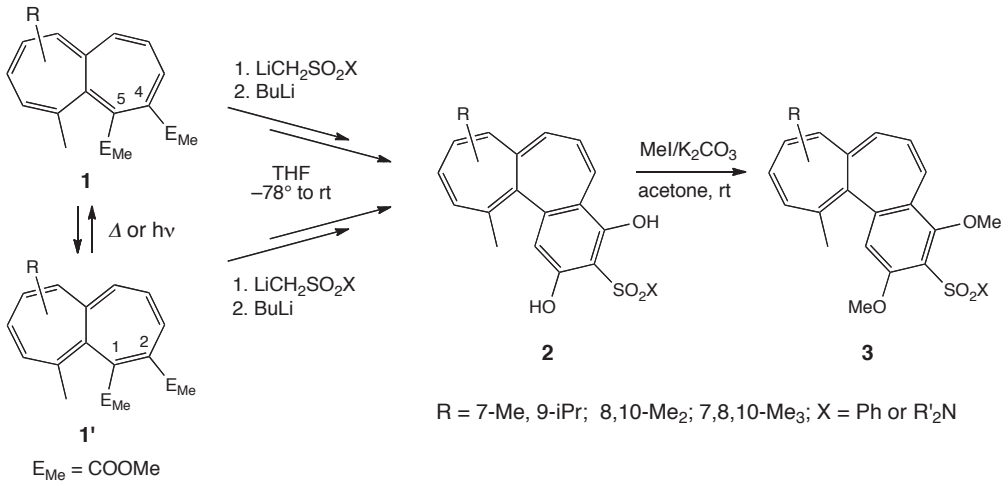
Dedicated to Professor Dr. Albert Eschenmoser on the occasion of his 85th birthday

Abstract – Treatment of the title compounds with lithium piperidinide in THF at –5 °C leads to an exchange of the two methoxy groups by piperidino substituents (Scheme 2). On the other hand, lithium diisopropylamide (LDA) in THF at –5 °C induces the formation heptaleno-annulated dibenzothiophenes.

INTRODUCTION

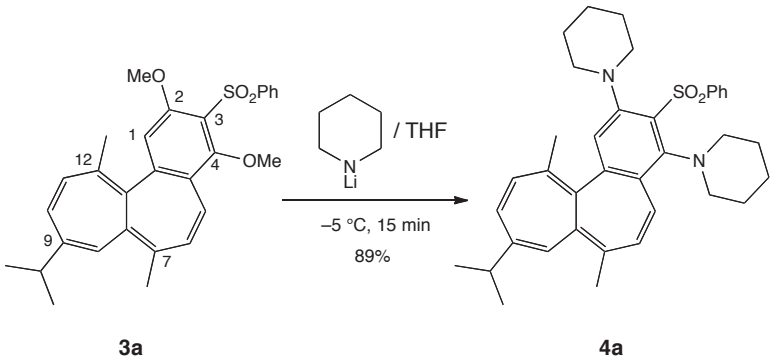
Already several years ago, we found by chance a new benzo-annulation reaction of dimethyl heptalene-4,5- and -1,2-dicarboxylates with lithiomethyl sulfones as C_1 carrier in the presence of an excess of butyl lithium (BuLi) to yield 2,4-dihydroxy-3-(X-sulfonyl)benzo[*a*]heptalenes.[1] We have improved this new "one-pot access" to benzo[*a*]heptalenes in the meantime continuously (see reference 2 and literatures cited there), so that colchicine-like compounds of type **1** and **2** became available in yields of > 80% (Scheme 1). The sulfonyl group in **3** can be reductively removed[3] and the third MeO group can be introduced by lithiation of C(3), followed by oxidation of the lithio species with air and then O-methylation.[4] On the other hand, the sulfonyl substituent of **2** should allow nucleophilic substitution reactions at C(2) and/or C(4) with MeO as a leaving group. In the following part, we report on the reaction of **3a** (R = 7-Me, 9-iPr) with lithium dialkylamides.



Scheme 1. Formation of 2,4-dihydroxy-3-(X-sulfonyl)benzo[*a*]heptalenes

RESULTS AND DISCUSSION

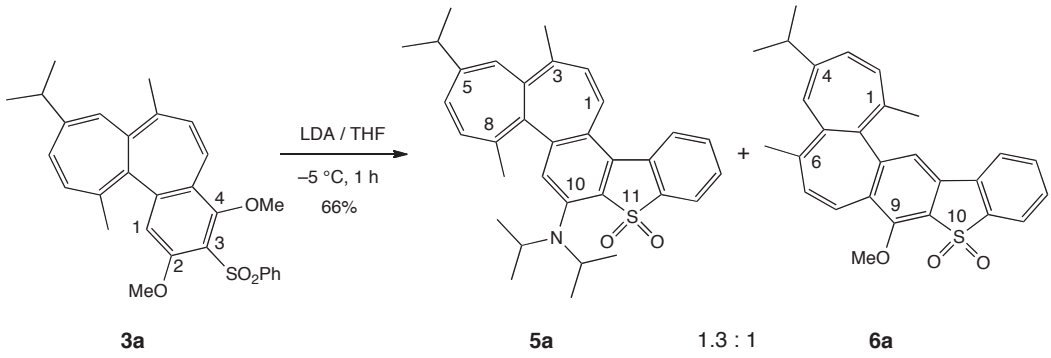
The reaction of **3a** with a 5-fold molar excess of lithium piperidide, generated by the reaction of piperidine with butyllithium (BuLi), took place smoothly at –5 °C in THF. The sole product that we isolated after recrystallization from CH_2Cl_2/Et_2O in excellent yield was the corresponding 2,4-dipiperidino-3-(phenylsulfonyl)benzo[*a*]heptalene (**4a)** (Scheme 2). When we repeated the reaction with only one equivalent of lithium piperidide, we found beside non-reacted **3a** only the bispiperidino substituted **4a**. The reaction of **3a** at –40 °C instead of –5 °C gave again only **4a**, but the reaction took a longer time. It seems that the entrance of the first piperidino substituent, presumably at C(4), where C- or N-nucleophiles enter preferentially 3-sulfonylbenzo[*a*]heptalenes **3**,[5] accelerates appreciably the introduction of the second one.



Scheme 2. Formation of **4a** by nucleophilic substitution

Normally, lithium diisopropylamide (LDA), also generated by deprotonation of diisopropylamine in THF at –5 °C, is used as sterically hindered base for selective deprotonations. We checked its quality as a

nucleophile in the reaction with **3a** at –5 °C and got an astonishing result. The two main products that we isolated after chromatography and recrystallization in a pure form and in nearly equal amounts turned out to be the heptaleno-annulated dibenzothiophene dioxides **5a** and **6a** (Scheme 3).



3a **5a** 1.3 : 1 **6a**

Scheme 3. Formation of heptaleno-annulated dibenzothiophene dioxides **5a** and **6a**

The structure of both compounds could be derived unequivocally from their spectral data, in particular, their ^{1}H-NMR spectra, in comparison with those of the starting material **3a**. We observed in the IR spectra ($CHCl_3$) of **5a** and **6a**, a shift in the wavenumbers of ν_{as}/ν_s of the SO_2 group[6] from 1375/1154 cm^{-1} of the 4-Me analog of **3a** to 1306/1159 and 1304/1157 cm^{-1} of **5a** and **6a**, respectively, speaking for a change in the bonding situation of the SO_2 fragment in going from **3a** to **5a** and **6a**. Full support of the presence of a dibenzothiophene 5,5-dioxide substructure in **5a** and **6a** came from their ^{1}H-NMR spectra ($CDCl_3$). The general ^{1}H-signal pattern of the phenylsulfonyl group of **3a** (d for H_o, t for H_p and H_m in a ratio of 2 : 1 : 2) appeared in the products (**5a** and **6a)** as d, t, t, d pattern in a ratio of 1 : 1 : 1 : 1, typical for non-symmetrically 1,2-substituted benzene derivatives. All further signals and coupling patterns could be derived from COSY and NOESY experiments, including the assignments of the ^{13}C-signals of both new compounds. It was also of importance to note that **5a** showed no signals for the presence of a MeO substituent, instead we found the signals of two further, non-equivalent that means diastereotopic with respect to the presence of the axis of chirality of the heptalene part, i-Pr groups. On the other hand, **6a** exhibited the signals of one MeO group (^{1}H: δ 4.19; ^{13}C: δ 63.89), which showed, in ^{1}H-NOE experiments, the spatial neighborhood of an H-atom at δ 7.10, appearing as d with ^3J = 11.8 Hz, a fact, which was only in accordance with an H-atom linked to a heptalene C=C bond. These findings together with all other NMR data were in perfect agreement with the proposed structures of **5a** and **6a**. The structure of **5a**, crystallized from $CDCl_3$, was finally established by an X-ray crystal-structure analysis (Figure 1), which showed that the asymmetric unit contains one heptalene and one $CDCl_3$ molecule.

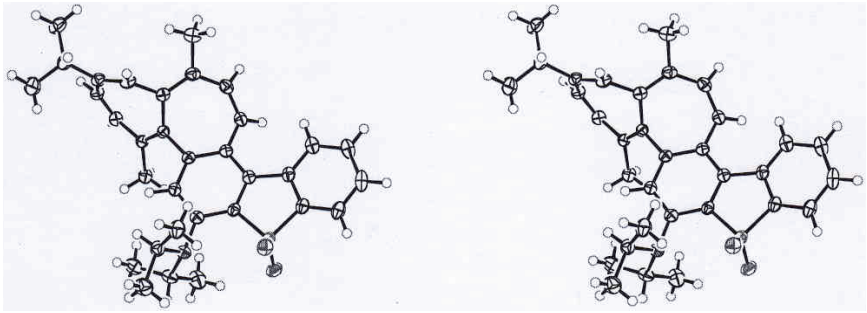
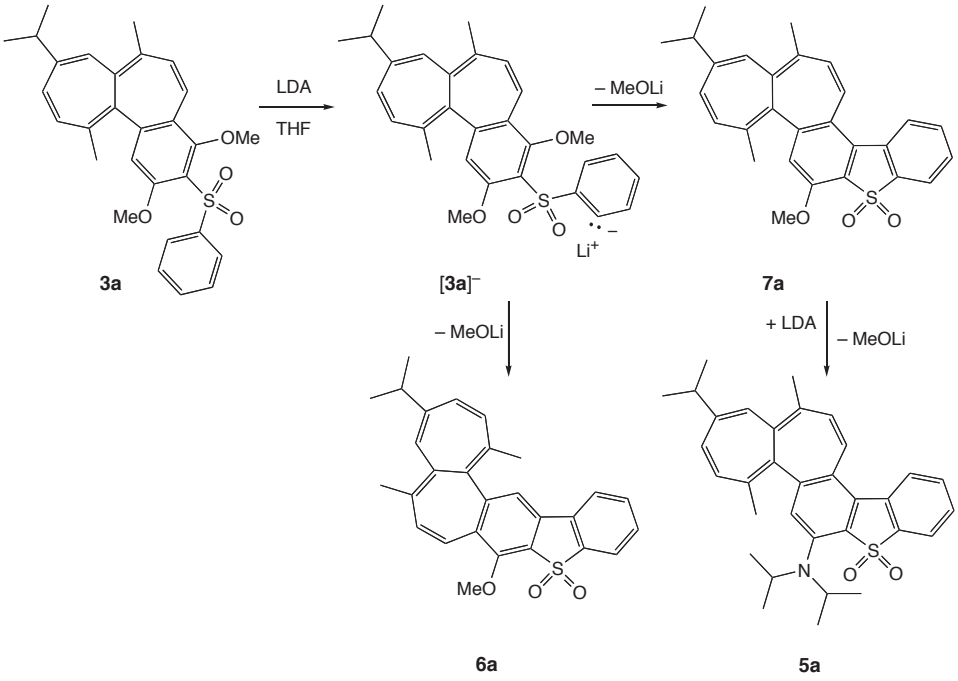


Figure 1. Stereoscopic view of the X-ray crystal structure of the heptaleno-annulated dibenzothiophene **5a** (50% probability ellipsoids)

The results with LDA demonstrate that LDA acts in a first line as a base that deprotonates the phenylsulfonyl substituent at C(3) of **3a** in the *ortho*-position of the benzene ring. The nucleophile thus formed substitutes intramolecularly the adjacent MeO groups at C(2) as well as at C(4) via Meisenheimer-type intermediates (Scheme 4). The first step in the formation of **5a** seems to be the appearance of the intermediate (**7a)**, the MeO group of which is then substituted by LDA. We cannot exclude the possibility that **3a** reacts first with LDA, followed by ring closure to **5a**. However, the absence of the product derived by further reaction of 6a with LDA under the reaction conditions indicates that the first steps are the ring closure reaction to **6a** and **7a**, and only **7a** carries a sterically less hindered MeO for the subsequent intermolecular substitution reaction with LDA.



Scheme 4. Intramolecular substitution of the MeO groups of **3a**

Little is known about the formation of dibenzothiophene 5,5-dioxides by ring closure of corresponding diphenylsulfone precursors. The main procedures for the synthesis of dibenzothiophene 5,5-dioxides utilize the formation of dibenzothiophenes, which are then oxidized, for example, with 30% aqueous H_2O_2 in glacial acetic acid to the corresponding 5,5-dioxides (see, e.g.[7]). Nevertheless, Pol and Kulkarni reported on the synthesis of 2,3,7,8-tetramethoxy-dibenzothiophene 5,5-dioxide by heating (2-bromo-3',4,4',5-tetramethoxy)diphenyl sulfone in the presence of EtONa in Ph_2O,[8] which follows obviously a similar mechanism as discussed above for **3a** with LDA as the base and MeO^- as the leaving group. Lithiation in the *ortho*-position of diphenyl sulfone dioxide with BuLi in THF/Et_2O at –60 °C and then heating at 45 °C has also been used for the synthesis of dibenzothiophene (72%), whereby formed LiH seems to be responsible for the reduction of the primarily generated dibenzothiophene 5,5-dioxide.[9]

In conclusion, we can say that the *ortho*-deprotonated (lithiated) diphenyl sulfones with the *ortho*-MeO group(s) at the second phenyl group react smoothly to the corresponding dibenzothiophene 5,5-dioxides, whereby LDA as the sterically hindered reactant acts primarily as the strong base and not as the nucleophile, thereby avoiding intermolecular nucleophilic substitution reactions with the *ortho*-MeO group(s).

EXPERIMENTAL

General: THF was purified and dried by reflux over sodium benzophenone and was distilled just before use. All reactions were performed under an atmosphere of Ar. Melting points (mp) were measured on a Büchi FP5 apparatus. They are not corrected. TLC on aluminum sheets coated with silica gel 60 F_{254} (Merck). Column chromatography (CC) was performed on silica gel 60 (40-63 μm; Chemie Uetikon AG*)*. IR spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. Band positions are given in wavenumbers (cm^{-1}). Transmissions are classified as vs = very strong (< 10%), s = strong (10-30%), m = middle (30-50%), and w = weak (> 60%). ^{1}H-NMR and ^{13}C-NMR spectra ($CDCl_3$) were measured at 300 K on a Bruker 600 AMX spectrometer; δ in ppm related to internal TMS (= 0 ppm) and adjusted to the solvent signals 7.26 ppm and 77.00 ppm, respectively, *J* in Hz. Assignments of the signals are based on additional DEPT 90, DEPT 135, COSY, NOSEY, NOE, HSQC, HMBC, and TOCSY measurements. Mass spectra (MS) were measured on a Finnigan MAT 95 instrument; chemical ionisation (CI) with NH_3, 70 eV, at a temp. of 250 °C.

Reaction of 2,4-Dimethoxy-3-phenylsulfonylbenzo[*a*]heptalene (3) with Lithium Piperidide. – 9-Isopropyl-7,12-dimethyl-2,4-dipiperidino-3-(phenylsulfonyl)benzo[*a*]heptalene (4a). To a solution of piperidine (0.628 ml, 7 mmol) in THF (5 mL), 2.5M BuLi (2.84 mL, 7.1 mmol) were slowly added at

–5°. The yellow solution was stirred for 30 min. This solution was added by using a cannula to a solution of **3a** (0.50 g, 1.05 mmol) in THF (15 mL) at –5 °C. The reaction mixture was stirred for 15 min at –5 °C. Then, the mixture was treated with ice/4N HCl. The product was extracted with AcOEt. The organic phase was washed with brine and dried (Na_2SO_4). The solvent was distilled off in a rotatory evaporator (RE). The residue was purified by CC (silica gel; hexane/AcOEt 2 : 1) and crystallized from CH_2Cl_2/Et_2O to yield 0.55 g (89%) of pure **4a**.

Data of 4a: Yellow crystals, mp 214.2–214.6 °C. R_f (hexane/AcOEt 3 : 1) 0.69. IR (KBr): 3007m, 2926vs, 2853s, 1551vs, 1521s, 1464m, 1444vs, 1418s, 1381s, 1302vs, 1290s, 1275s, 1248m, 1213s, 1182m, 1140vs, 1123m, 1090s, 1074m, 1032m, 990s, 914w, 887w, 857m, 750s, 687s, 617s, 608vs, 562s. ^{1}H-NMR: δ 7.52 (d, ^3J = 7.4, H_o of Ph); 7.35 (t-like, H_p of Ph); 7.40 (t-like, H_m of Ph); 7.06 (d, ^3J(5,6) = 11.9, H–C(5)); 6.40 (d, ^3J(11,10) = 11.9, H–C(11)); 6.36 (dd, ^3J(10,11) = 11.9, ^4J(10,8) = 0.9, H–C(10)); 6.25 (d, ^3J(6,5) = 11.8, H–C(6)); 5.73 (s, H-C(8)); 3.47, 2.36, 2.16, 1.60, 1.21 (H of two piperidino groups); 2.56 (sept, Me_2CH–C(9)); 1.74 (s, Me–C(12)); 1.72 (s, Me–C(7)); 1.16, 1.15 (2d, ^3J = 7.9 and 7.8, Me_2CH–C(9)). ^{13}C-NMR: δ 154.77 (s, C(2)); 154.35 (s, C(4)); 147.86 (s, C_{ip} of Ph); 146.85 (s, C(9)); 144.91 (s, C(12b)); 135.74 (d, C(11)); 135.43 (s, C(12a)); 133.43 (s, C(7a)); 131.40 (d, C(10)); 131.12 (s, C(12)); 131.01 (d, C(6)); 130.74 (d, C_p of Ph); 129.81 (s, C(4a)); 128.90 (d, C(5)); 128.80 (s, C(7)); 127.94 (d, C_m of Ph); 125.19 (d, C_o of Ph); 124.39 (s, C(3)); 122.20 (d, C(8)); 115.17 (d, C(1)); 58.73/50.64 (C of piperidino groups); 34.44 (d, Me_2CH–C(9)); 25.28/24.45/24.35/23.83 (C of piperidino groups); 22.78/22.82 (2q, Me_2CH–C(9)); 20.41 (q, Me–C(12)); 16.60 (q, Me–C(7)). CI-MS ($C_{37}H_{44}N_2O_2S$; 580.84): 584.5 (6, $[M + 3]^+$); 583.5 (20, $[M + 2]^+$); 582.5 (42, $[M + 1]^+$); 581.5 (100, $[M]^+$); 442.5 (17); 441.5 (50); 439.5 (21); 388.4 (7).

Reactions of 9-Isopropyl-2,4-dimethoxy-7,12-dimethyl-3-(phenylsulfonyl)benzo[*a*]heptalene (3a). 3,8-Dimethyl-*N*,*N*,5-tri(propan-2-yl)benzo[*b*]heptaleno[1',2':5,6]benzo[1,2-*d*]thiophen-10-amine 11, 11-dioxide (5a) and 9-Methoxy-1,6-dimethyl-4-(propan-2-yl)benzo[*b*]heptaleno[2',1':4,5]-benzo[1,2-*d*]thiophene 10,10-dioxide (6a). A solution of LDA (7.35 mmol) in THF (5 mL) was produced at –5 °C in the usual manner (see above). It was added slowly *via* a cannula to a solution of **3a** (0.50 g, 1.05 mmol) in THF (15 mL). After 1 h stirring, the mixture was treated with chopped ice/4N HCl. The products were extracted with AcOEt and then, the organic layer was washed with brine and dried (Na_2SO_4). The solvent was distilled off (RE). The residue was subjected to CC (hexane/AcOEt 3 : 1) to yield in a first fraction **5a** (0.20 g, 37%) and then **6a** (0.13 g, 29%).

Data of 5a: Orange crystals from $CDCl_3$, mp 160.6–162.8 °C. R_f: 0.49 (hexane/AcOEt 3 : 1). IR ($CHCl_3$):

2964m, 2916w, 1569m, 1459m, 1306vs, 1220m, 1159vs, 1132m, 1060m, 1030w. ^{1}H-NMR: δ 8.01 (d, J_o= 8.0, H–(15)); 7.82 (dd, J_o = 7.7, J_m = 0.7, H–C(12)); 7.59 (td, J_o = 7.7, J_m = 1.2, H–C(14)); 7.50 (t, J_o = 7.5, H–C(13)); 7.30 (d, ^3J(1,2) = 11.9, H–C(1)); 6.92 (s, H–C(9)); 6.51 (d, ^3J(2,1) = 11.9, H-C(2)); 6.44 (d, ^3J(7,6) = 12.0, H–C(7)); 6.43 (dd, ^3J(6,7) = 12.1, ^4J(6,4) = 1.1, H–C(6)); 5.79 (s, H–C(4)); 3.61 (sept, $(Me_2CH)_2$N–C(10)); 2.59 (sept, Me_2CH–C(5)); 1.76 (s, Me–C(8)); 1.74 (s, Me–C(3)); 1.17, 1.18 (4d, ^3J = 6.5, $(Me_2CH)_2$N–C(10) and 2d, ^3J = 7.1, Me_2CH–C(5)). ^{13}C-NMR: δ 148.23 (s, C(10)); 147.44 (s, C(8b)); 147.31 (s, C(5)); 139.65 (s, C (11a); 136.88 (s, C(10a)); 135.95 (s, C(3a)); 135.25 (d, C(2)); 135.11 (d, C(7)); 134.36 (s, C(8a)); 133.04 (d, C(14)); 131.96 (s, C(15c)); 131.85 (d, C(6)); 131.79 (d, C(9)); 131.55 (s, C (15a)); 131.37 (s, C(8)); 130.18 (s, C(15b); 129.46 (d, C(13)); 128.50 (d, C(1)); 128.00 (s, C(3)); 125.96 (d, C(15)); 121.94 (d, C(12)); 121.68 (d, C(4)); 50.72 (d, $(Me_2CH)_2$N–C(10)); 34.51 (d, Me_2CH–C(5)); 22.76, 22.87 (2q, Me_2CH–C(4)); 21.44, 21.56 (2q, $(Me_2CH)_2$N–C(10)); 19.97 (q, Me–C(8)); 16.40 (q, Me–C(3)). EI-MS ($C_{33}H_{37}NO_2S$; 511.73): 512.1 (10, $[M + 1]^+$); 511.1 (26, $[M]^+$); 497.1 (34, $[(M + 1) – Me]^+$); 496.0 (97, $[M – Me]^+$); 469.0 (6); 456.0 (11); 454.0 (100, $[M – iPrN]^+$); 288.9 (12); 275.9 (7); 227.1 (11); 192.5 (9).

Data of 6a: Orange crystals from Et_2O/hexane, mp 244.4–246.7°. R_f: 0.45 (hexane/AcOEt 3 : 1). IR ($CHCl_3$): 2959m, 2923m, 1592m, 1551m, 1470m, 1446m, 1373s, 1303vs, 1263s, 1239m, 1165m, 1157vs, 1128s, 1057m, 1001m, 736vs, 607s, 568s, 548m. ^{1}H-NMR: δ 7.80 (d, J_o = 7.6, H–C(11)); 7.74 (d, J_o = 7.7, H–C(14)); 7.59 (t, J_o = 7.7 and 7.4, H–C(13)); 7.50 (t, J_o = 7.6 and 7.5, H–C(12)); 7.099 (s, H–C(15)); 7.097 (d, ^3J(8,7) = 11.8, H–C(8)); 6.44 (m, H–C(2,3,7)); 5.78 (s, H–C(5)); 4.19 (s, MeO–C(9)); 2.59 (sept, Me_2CH–C(4)); 1.74 (s, Me–C(6)); 1.68 (s, Me–C(1)); 1.17, 1.18 (2d, J = 7.1, Me_2CH–C(4)). ^{13}C-NMR: δ 154.70 (s, C(9)); 147.79 (s, C(4)); 144.53 (s, C(15a)); 138.32 (s, C(10a)); 135.56 (d, C(2)); 135.44 (d, C(7)); 134.31 (s, C(5a)); 133.75 (s, C(14b)); 133.59 (d, C(13) and s, C(15b)); 133.56 (s, C(8a)); 132.25 (s, C(1)); 132.17 (d, C(3)); 131.34 (s, C(14a)); 130.15 (d, C(12); 128.71 (s, C(6)); 127.45 (s, C(9a)); 124.61 (d, C(8)); 122.45 (d, C(11)); 122.12 (d, C(5)); 121.46 (d, C(14)); 117.33 (d, C(15)); 63.89 (q, MeO–C(9)); 34.57 (d, Me_2CH–C(4)); 22.78 (q, Me_2CH–C(4)); 19.36 (q, Me–C(1)); 16.99 (q, Me–C(6)). EI-MS ($C_{28}H_{26}O_3S$, 442.58): 443 (31, $[M + 1]^+$); 442 (100, $[M]^+$) 427 (38, $[M – Me]^+$); 402 (47, $[M – MeC{\equiv}CH]^+$); 387 (25); 374 (18); 305 (14); 289 (17); 276 (16); 200 (17).

2. X-ray crystal structure determination of 5a·$CDCl_3$. **Crystal data**: Crystals obtained from $CDCl_3$, $C_{33}H_{37}NO_2{\cdot}CDCl_3$, M = 631.10, monoclinic, space group: $P2_1/c$, a = 9.9303(1) Å, b = 13.6485(2) Å, c = 23.3724(3) Å, β = 98.1576(4)°, V = 3135.70(7) Å^3, Z = 4, D_x = 1.337 g cm^{-3}, $2\theta_{(max)}$ = 55°, T = –113 °C, crystal dimensions: 0.07 × 0.15 × 0.20 mm, Nonius KappaCCD area-detector diffractometer, Mo Kα radiation, λ = 0.71073 Å, μ(Mo $K\alpha$) = 0.391 mm^{-1}, 71199 measured reflections, 7173 independent

reflections, 4715 reflections with $I > 2\sigma(I)$, refinement on F with *teXsan*,[10] 370 parameters, $R(F)$ [$I > 2s(I)$ reflections] = 0.0504, $wR(F^2)$ [$I > 2\sigma(I)$ reflections] = 0.0535, goodness of fit = 1.986, $\Delta\rho_{max}$ = 0.66 e Å^{-3}. The asymmetric unit contains one molecule of **5a** and one molecule of deuteriochloroform. The non-hydrogen atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions.

CCDC-775867 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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