Supporting Information

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Synthesis scheme of 1,1,4a,6-tetramethyl-1,2,3,4,4a,9b-hexahydrodibenzo[*b,d*]thiophene (Me_4H_6DBT) The synthesis starts (scheme is illustrated in **Figure 1**) with the commercially available 2-methylthiophenol (**1**) which on direct ortho-lithiation gives lithium 2-lithio-6-methylbenzenethiolate (**2**). After addition of 2,2,6-trimethylcyclohexanone (**3**), 2,2,6-trimethyl-1-(3-methyl-2-sulfanylphenyl)-cyclohexanol (**4**) is formed and eliminates water to give 2-methyl-6-(2,2,6-trimethylcyclohex-1-en-yl-)-benzenethiol (**5**) which subsequently undergoes cyclization, both steps acid-promoted, to yield the desired product **6**.

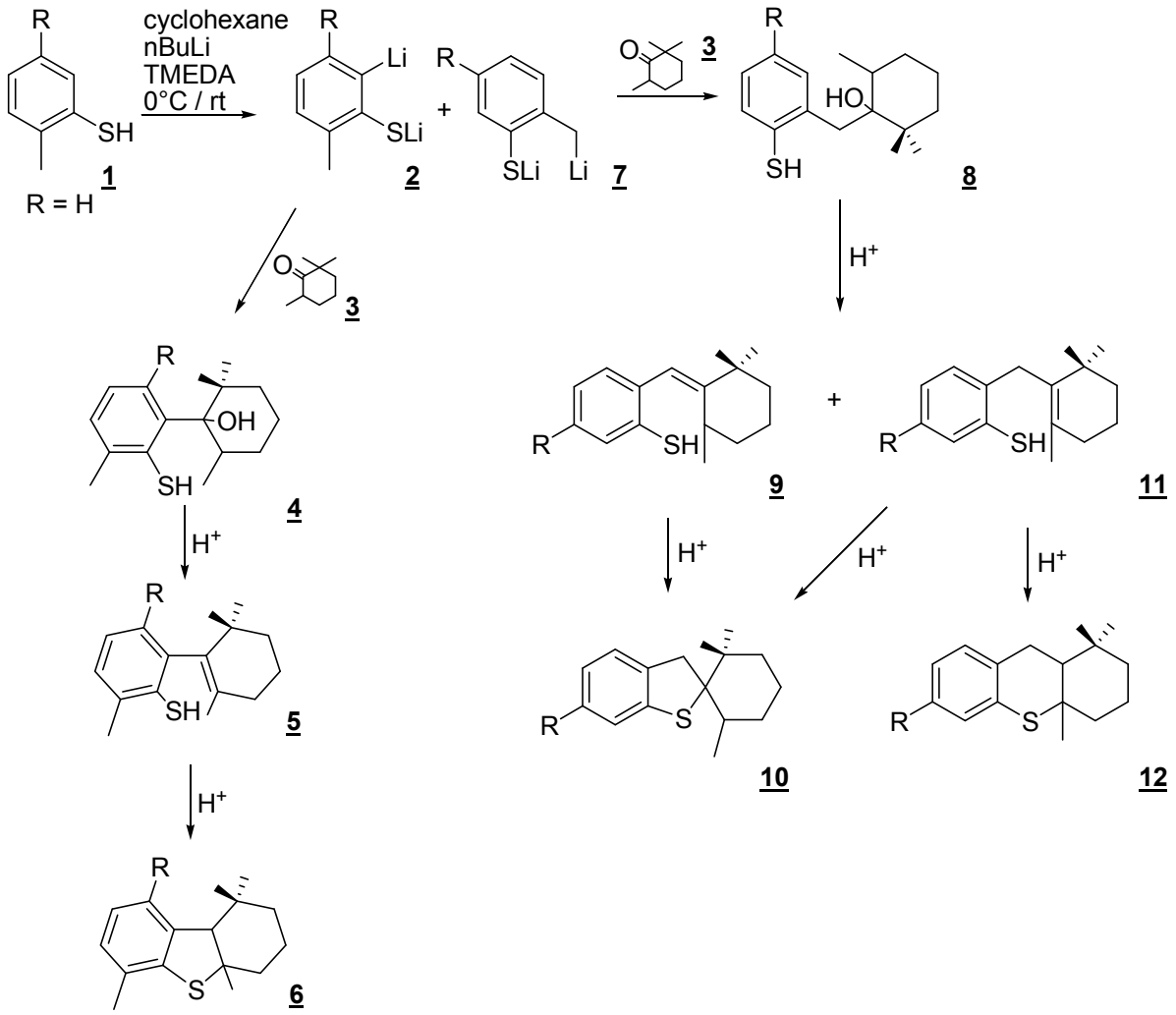

Figure 1. Synthesis scheme applied for the synthesis of Me_4H_6DBT.

The dilithiation is not cleanly regioselective since the methyl group is acidic enough to be lithiated[1,2] and this position contributes strongly to the total conversion[1]. The result is the formation of 75% of lithium (2-sulfidobenzyl)lithium (**7**) which can also couple with **3** to yield compound **8**. The acid-promoted elimination of water can lead to two products (**9** + **11**), only differing in the orientation of the double bonds. Each of those can now undergo ring-closure reactions in two directions. In each case, both carbon atoms of the double bonds can be attacked by the sulfur atom.

The protonation of the double bond compound **5** would either lead to a four-membered ring or the desired Me_4H_6DBT **6**. The formation of a four-membered ring is highly unlikely because of the ring strain, so that only the formation of Me_4H_6DBT is considered here.

The acid-promoted cyclization of compound **9** would also result in a four-membered ring and a spiro compound **10** (2',2',6-trimethyl-3*H*-spiro[1-benzothiophene-2,1'-cyclohexane]). Again, the four-membered ring is highly unlikely. Compound **11** yields the spiro-compound **10** and the six-membered ring **12** (1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-thioxanthene), both products are likely to be formed. Figure 2 shows a gas chromatogram of the obtained synthesis mixture.

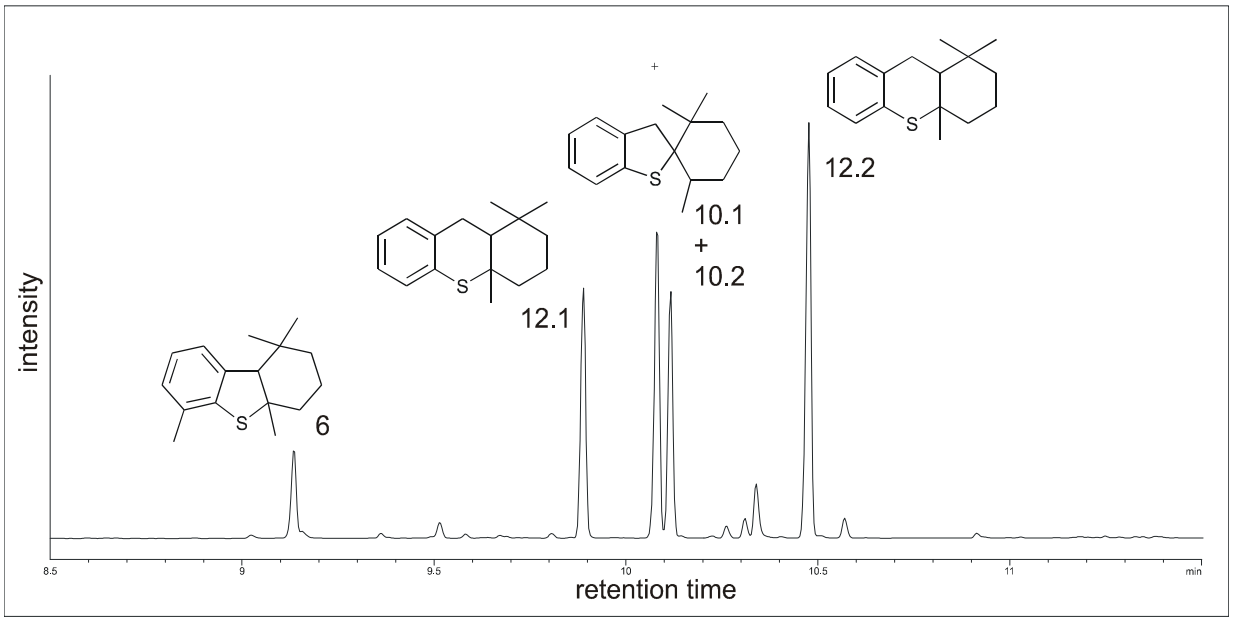

Figure 2. Gas chromatogram showing the obtained synthesis mixture.

Isolation of the desired product is difficult since all the products formed show the same elemental composition and therefore the same molecular mass and a similar polarity. Normal-phase chromatography based on silica or alumina is unsuccessful. Gas chromatography with a preparative fraction collector (PFC, Gerstel GmbH, Mülheim, Germany) and a capillary column with a higher capacity (30 m x 0.53 mm x 0.5 µm) enabled enough material to be collected from each product to make an identification by NMR possible. With the PFC it is possible to use the very high resolution of capillary gas chromatography to isolate compounds from mixtures that are very complex, although it is still necessary to fractionate the sample several hundred times to accumulate enough material for NMR experiments. The use of a capillary column with a diameter of 0.53 mm and a film thickness of 0.5 µm

increases the capacity tenfold compared to a column of 0.25 mm inner diameter and 0.25 µm film thickness, as used regularly for analytical purposes.

Synthesis of 1,1,4a,6-tetramethyl-1,2,3,4,4a,9b-hexahydrodibenzo[*b,d*]thiophene (Me_4H_6DBT)

To a solution of 5.1 mL N,N,N′,N′-tetramethylethylenediamine (TMEDA, 33 mmol, 2.2 equiv.) in 25 mL silica-dried cyclohexane (CH) and 20.5 mL 1.6 M n-butyllithium (33 mol, 2.2 equiv.) in *n*-hexane, 1.86 g (15 mmol, 1 equiv.) 2-methylthiophenol in 5 mL of CH is added at 0 °C and under an argon atmosphere during a period of 30 minutes with stirring. The clear solution turns yellow and after complete addition of the thiophenol, the lithiated species precipitates after some time as a yellow slurry. Stirring is continued for 12 h at 0 °C. 2.2 g (15 mol, 1 equiv.) of 2,2,6-trimethylcyclohexanone in 5 mL dried cyclohexane is added over a period of 30 minutes and the mixture is stirred for another 12 hours. During the ketone addition the slurry clears up and the intense color vanishes to give a pale yellow solution. This solution is quenched through the addition of 50 mL of diluted 2 M hydrochloric acid. An initial precipitate dissolves shortly after addition of the acid. The product is extracted using 3 x 30 mL cyclohexane. Drying over sodium sulfate and removal of the solvents results in a yellow oil. A sample of the oil is dissolved in 5 mL of cyclohexane and two drops of trifluoromethanesulfonic acid are added under vigorous stirring. After 6 hours, the solution is filtered through a small column filled with alkaline alumina and the solvent removed in vacuo.

^{1}H (400 MHz, $CDCl_3$; Me_4Si) 7.03 (3 H, m, Ph), 2.50 (1 H, s, 9b-H), 2.23 (3 H, s, 6-Me), 2.15-2.05 (2 H, m, 4-H), 1.95-1.75 (2 H, m, 2-H), 1.60-1.45 (2 H, m, 3-H), 1.38 (3 H, s, 4a-Me), 1.01 (3 H, s, 1-Me) and 0.61 (3 H, s, 1-Me).

^{13} C (50 MHz, $CDCl_3$; Me_4Si) 142.3 (9a-C), 133.0 (6-C), 132.3 (4b-C), 130.1 (8-C), 127.7 (7-C), 123.6 (9-C), 77 ($CDCl_3$), 63.0 (9b-C), 58.6 (4a-C), 39.9 (2-C), 35.8 (4-C), 35.0 (10-C), 34.9 (1-C), 32.2 (12-C), 21.9 (11-C), 20.8 (13-C) and 19.1 (3-C).

MS: m/z (EI, 70 eV) 246 (M^+, 57%), 231 (15, M^+ - CH_3), 163 (100, $[C_{10}H_{11}S]^+$).

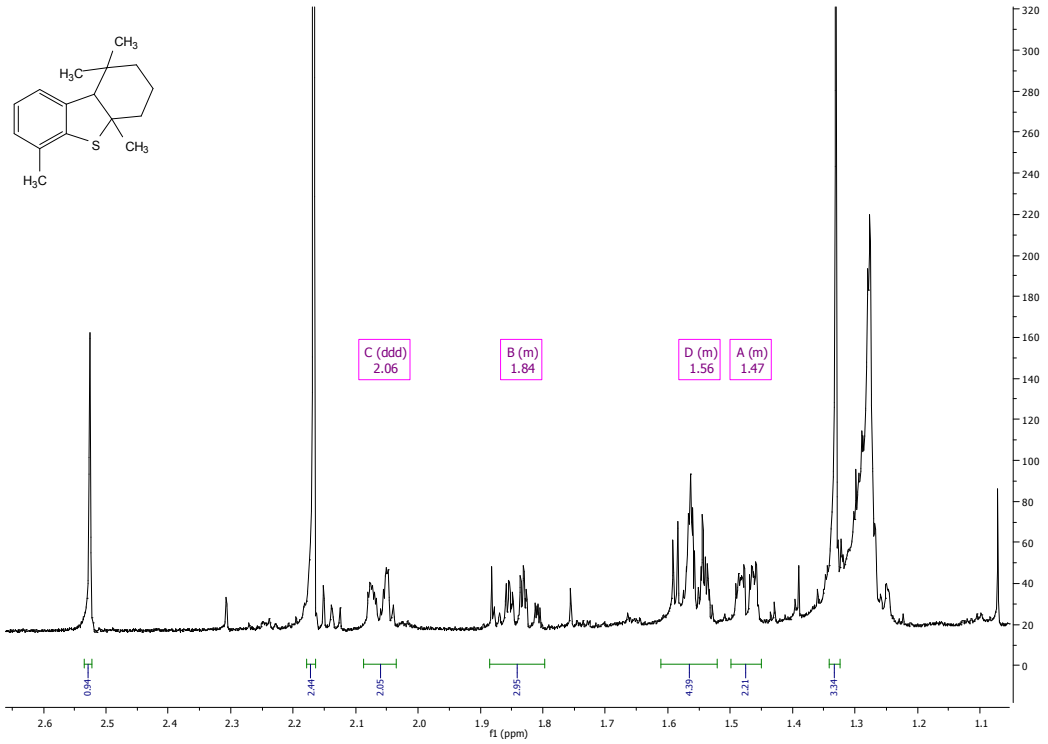

Figure 3. ^{1}H-NMR-spectrum of Me_4H_6DBT in the range between 0 and 2.6 ppm (300 MHz instrument, sample dissolved in $CDCl_3$).

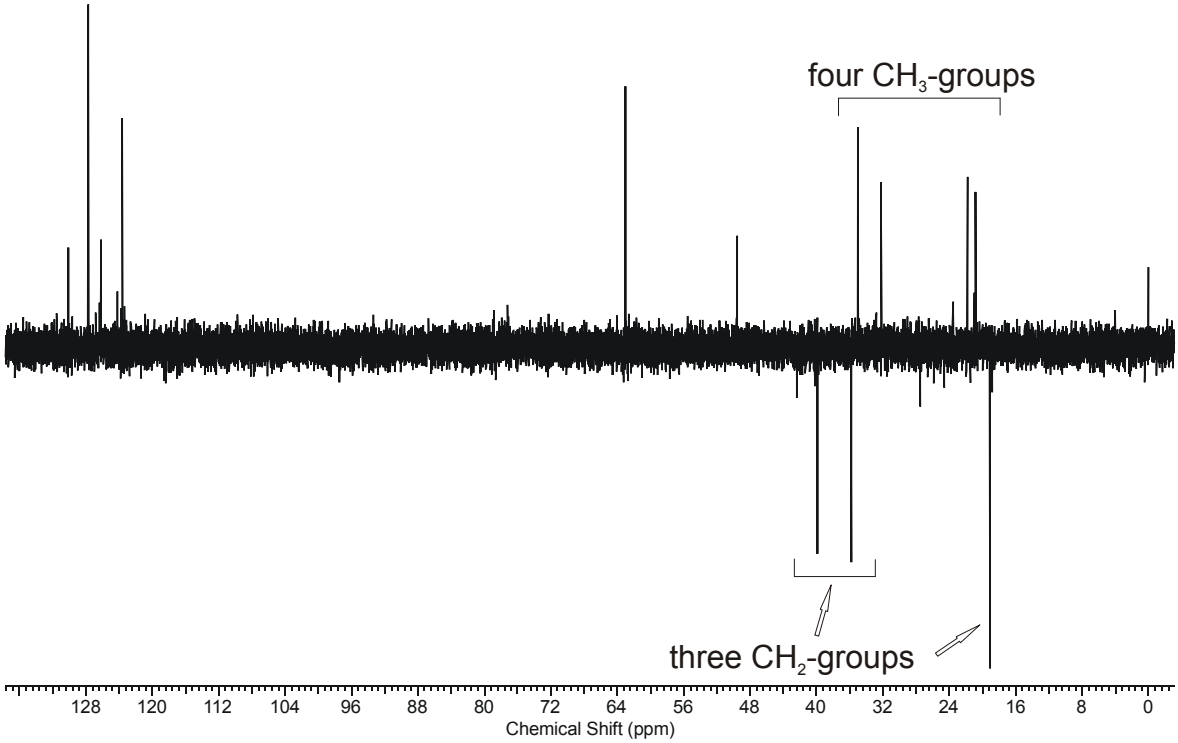

Figure 4. DEPT135-spectrum of Me_4H_6DBT showing the distinctive four signals for the CH_3- and the three signals for the CH_2-groups.

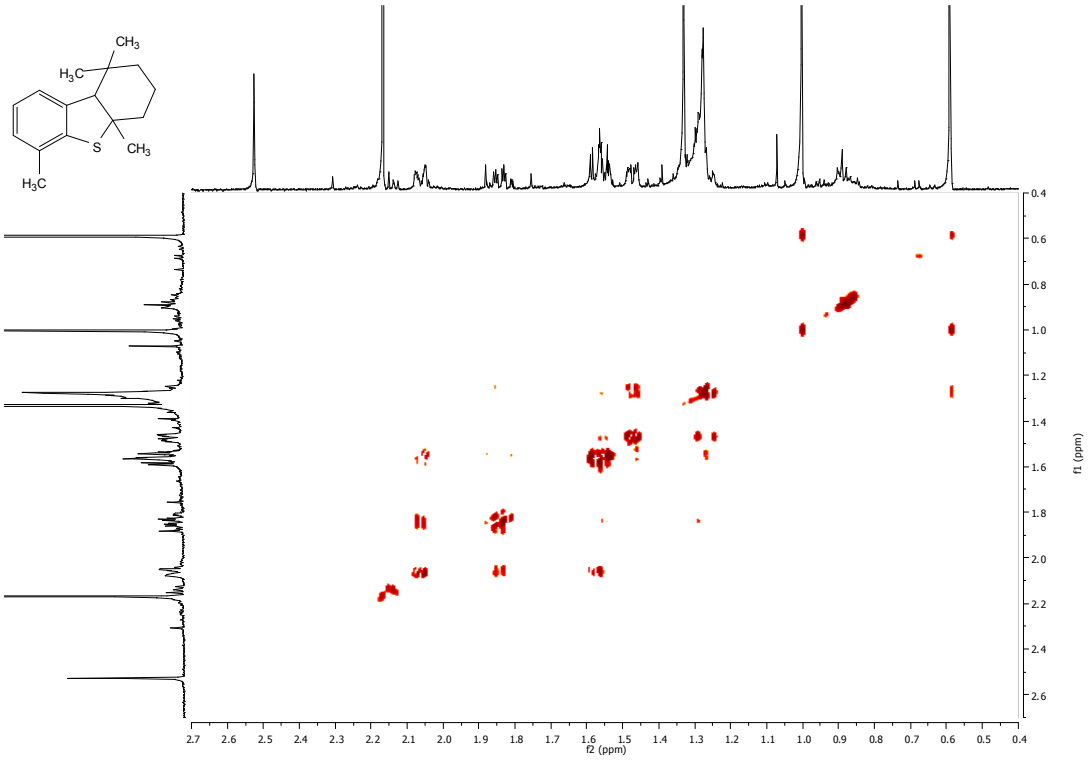

Figure 5. Two-dimensional $^{1}H,^{1}H$-COSY-spectrum of Me_4H_6DBT correlating the different signal groups.

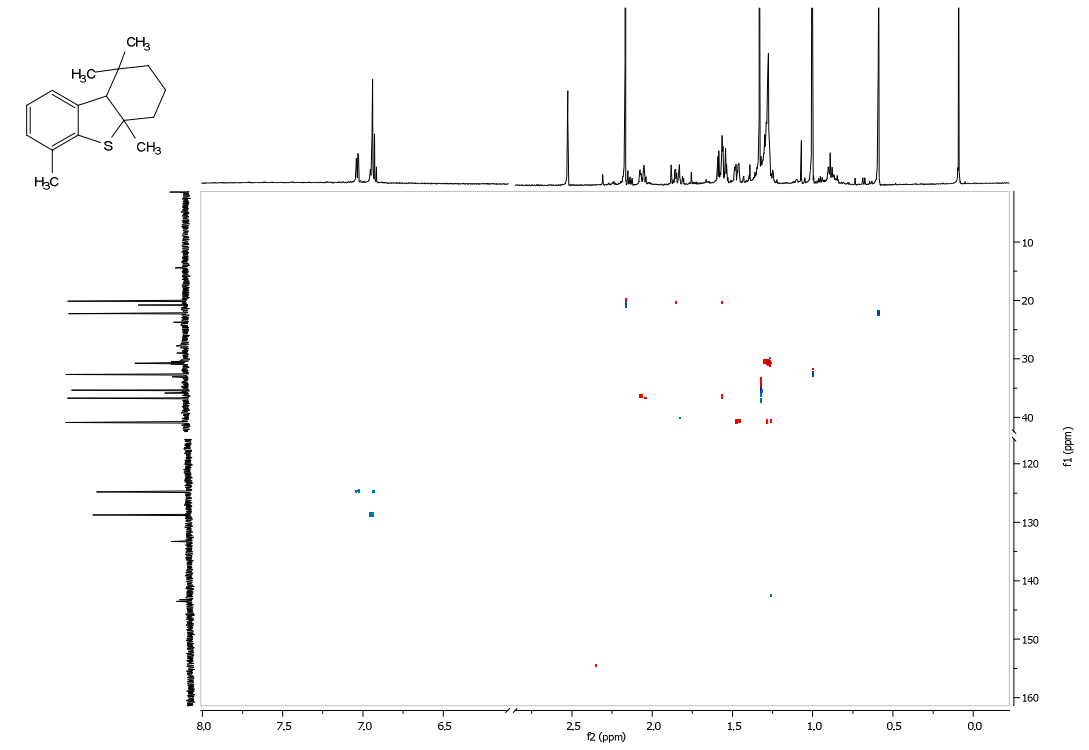

Figure 6. ^{1}H, ^{13}C-HSQC spectrum of Me_4H_6DBT illustrating the correlations between carbon and hydrogen.

In the identification of Me_4H_6DBT in the mixture obtained above, the most important signal is the one originating from the proton at position 9b. Figure 3 shows the chemical shift region between 0 and 2.6 ppm of the ^{1}H-NMR-spectrum. This region is of particular interest since it shows the characteristic signal at 2.53 ppm. A singlet indicates a sulfur-containing five-membered ring since a six-membered ring would result in a triplet due to the coupling with the adjacent protons in the positions 9 and 9a. Several large singlets and a complex pattern of overlapping multiplets can be seen as well. A clear and unambiguous assignment of those multiplets of the saturated ring is not possible in this spectrum due to the overlapping regions of the signals. A combination of DEPT-measurements[I] and a two-dimensional ^{1}H, ^{1}H-COSY-spectrum[II] (DEPT135-spectrum shown in Figure 4, ^{1}H,^{1}H-COSY-spectrum shown in **Figure 5**) helps to assign the signals to the protons. The DEPT135-spectra show the presence of four CH_3- and three CH_2-groups, as expected. In direct contrast, each of the by-products would show signals for four CH_2-groups.

The signal group at 2.06 ppm couples with both signal groups at 1.85 and 1.56 ppm, resulting in a ddd multiplicity, therefore it resembles the protons at position 3. Since both groups, at 1.85 and 1.56 ppm, couple with one adjacent group of protons, it is difficult to resolve the positions.

Figure 6 shows the corresponding ^{1}H,^{13}C-HSQC-spectrum[III] of Me_4H_6DBT. For matters of clarity, a part of the range of the chemical shift has been deleted on both axes.

[I] DEPT-measurements is a ^{13}C-NMR technique that is used to distinguish between CH_3-, CH_2- and CH-groups in ^{13}C-NMR-measurements.

[II] A ^{1}H,^{1}H-COSY-measurement is a technique used to show the coupling of different groups of protons in a molecule in a two-dimensional visualization.

[III] A ^{1}H,^{13}C-HSQC-measurement is a technique to show the coupling of protons with adjacent carbon atoms in a two-dimensional visualization.

NMR-based characterization of side-products All other fractions from the synthesis mixture were also characterized using NMR-techniques. With the products **12.1** and **12.2** being separated, identification of the compounds proves to be easy. The mass spectra show molecular masses of 246 amu with the most abundant fragments of 162 amu. This already indicates the presence of CH_2-groups bridging the aromatic and the saturated rings instead of CH_3-groups connected to the benzene rings next to the sulfur atoms. The lack of the singlet signals at a chemical shift of 2.53 ppm also backs up this assumption.

With compounds **10.1** and **10.2** collected together, identification of the different signals is difficult. Table 1 and Table 2 give all the chemical shifts and coupling constants with illustrating the numbering of the carbon atoms for the compounds.

For the compound labelled **12.1**, the chemical shifts are given in Table 3 with illustrating the numbering of the carbon atoms for the compounds **12.1** and **12.2**. The proton in the 10a-position is axially oriented (with a chemical shift of 2.08 ppm) since it exhibits a small coupling constant of 4.3 Hz with the equatorially oriented proton at carbon number 10, whilst it couples with the axially oriented proton with 13.0 Hz. The chair form of the six-membered ring results in the stereocenter in position 4a to be (*R*)-configured.

For compound **12.2**, the chemical shifts are given in Table 4. In contrast to compound **12.1**, the proton in the 10a-position is oriented equatorially, since it exhibits a small coupling constant of < 2 Hz with the equatorial proton at position 10. The coupling with the axial proton shows a constant of 7.1 Hz. Therefore, the stereocenter is (*S*)-configured.

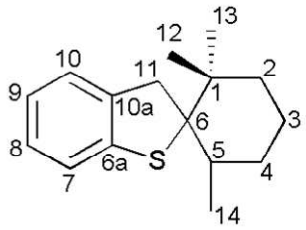

Figure 7. Numbering the carbons in compounds **10.1** and **10.2**.

Table 1. Chemical shifts [ppm] and coupling constants of compound **10.1**.

C	δ (^{13}C)	δ (^{1}H)	C	δ (^{13}C)	δ (^{1}H)
1	38.8		8	123.5	7.04
2	39.1	1.37	9	129.7	6.93
3	21.4	1.58: 1.49	10	131.8	7.03
4	31.5	1.45	10a	140.6	
5	38.7	1.98 ax	11	42.5	3.49; 2.95
6	74.5		12	22.2	1.08 ax
6a	126.4		13	28.8	1.12
7	125.7	7.08	14	17.4	0.82

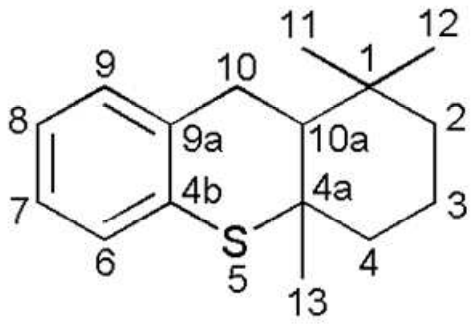

Figure 8. Numbering the carbons in compounds **12.1** and **12.2**.

Table 2. Chemical shifts [ppm] and coupling constants of compound **10.2**.

C	δ (^{13}C)	δ (^{1}H)	C	δ (^{13}C)	δ (^{1}H)
1	39.3		8	126.8	7.04
2	39.7	1.48; 1.39	9	123.3	6.93
3	21.3	1.58; 1.49	10	123.7	7.05
4	31.4	1.60; 1.27	10a	140.8	
5	37.6	2.15 ax	11	36.4	3.25; 2.18; $^{2}J_{HH}$= 17.0 Hz
6	72.9		12	27.7	1.00 eq
6a	141.8		13	24	1.14 ax
7	120.5	7.07	14	18.5	0.95 eq

Table 3. Chemical shifts [ppm] and coupling constants of compound **12.1**.

C	δ (^{13}C)	δ (^{1}H)	C	δ (^{13}C)	δ (^{1}H)
1	33.7		9	130.1	7.08
2	42.3	1.53 (m, α, eq) – 1.38 (m, β, ax)	9a	133	
3	18.8	1.56.(m, α, eq) – 1.63 (m, β, ax)	10	27.5	2.92 eq; $^{2}J_{HH}$= 17.1 Hz, $^{3}J_{HH}$=4.3 Hz
4	40.1	1.89 (m, α, eq) – 1.73 (m, β, ax)			2.79 ax; $^{2}J_{HH}$= 17.1 Hz, $^{3}J_{HH}$=13 Hz
4a	46.5		10a	49.6	
4b	133				
6	126.4	7.04	11	32.9	0.94
7	126.2	7.02	12	21	0.99
8	123.7	6.98	13	23.5	1.47

Table 4. Chemical shifts [ppm] and coupling constants of compound **12.2**.

C	δ (^{13}C)	δ (^{1}H)	C	δ (^{13}C)	δ (^{1}H)
1	34.7		9	129.7	7.08
2	42.6	1.46 (m, α, eq) – 1.27 (m, β, ax)	9a	131.8	
3	19.4	1.45 (m, α, eq) – 1.95 (m, β, ax)	10	27.5	3.01 eq; $^{2}J_{HH}$= 18.1 Hz, $^{3}J_{HH}$ < 2 Hz
4	40.6	1.84 (m, α, eq) - 1.53 (m, β, ax)			3.16 ax; $^{2}J_{HH}$= 18.1 Hz, $^{3}J_{HH}$= 7.1 Hz
4a	45.6		10a	47.7	1.48 eq
4b	134.1		11	20.6	0.94 ax
6	126.4	7.01	12	33.5	0.98 eq
7	125.7	7.01	13	34.6	1.43 ax

References:

(1) Katritzky, A.R.; Xu, Y.J.; Jain, R. A Novel Dilithiation Approach to 3,4-Dihydro-2H-1,3-benzothiazines, 3,4-Dihydro-2H-1,3-benzoxazines, and 2,3,4,5-Tetrahydro-1,3-benzothiazepines. *Journal of Organic Chemistry*, **2002**, 67, 8234-8236.

(2) Figuly, G.D.; Loop, C.K.; Martin, J.C. Directed Ortho-Lithiation of Lithium Thiophenolate - New Methodology for the Preparation of Ortho-Substituted Thiophenols and Related Compounds. *Journal of the American Chemical Society*, **1989**, 111, 654-658.