From thiophene *S*-oxides to 7-thiabicyclo[2.2.1]hept-5-enes

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Oligocycles with a 7-thiabicyclo[2.2.1]hept-5-ene unit have been prepared stereoselectively by cycloaddition of thiophene *S*-oxides to alkenes and subsequent deoxygenation of the sulfoxy bridge of the cycloadducts with PBr_3.

Keywords: thiophene *S*-oxides, cycloaddition, phosphorus tribromide, deoxygenation

Thiophene *S*-oxides such as **4a–c**, which can be prepared by oxidation of thiophenes with *m*-CPBA in the presence of $BF_3{\cdot}Et_2O$[1] or with H_2O_2 in the presence of a protic acid,[2] are good dienes in cycloaddition reactions.[3] With alkenes as dienophiles, they yield 7-thiabicyclo[2.2.1]hept-5-ene *S*-oxides[3] (see also Scheme 2). These cycloadducts are good precursors to multifunctionalised arenes,[4] to cyclohexadienes[5] and in certain cases to diaryl disulfides.[6] Previously, the authors have used this combination of reaction to construct such diverse molecules as crown ethers,[7] cyclophanes[8] and amino acids.[9] We have reported one example of a transformation of a 7-thiabicyclo[2.2.1]heptene *S*-oxide to a 7-thiabicyclo[2.2.1] heptene.[5] We now report that this deoxygenation of bridged sulfoxides to bridged sulfides is a general reaction.

Thiophene *S*-oxides **4** undergo facile cycloaddition to alkenes **3**, **5**, and **8** (Scheme 2). Thus, a solution in chloroform of 3,4-dibromo-2,5-thiophene *S*-oxide (**4a**), accessible from 3,4-dibromo-2,5-dimethylthiophene in one step, was heated with dibutyl maleate (**5**) to give cycloadduct **6** in good yield. Cycloadduct **6** is formed stereoselectively as the *endo*-product. Cycloadducts **9a**/**b** are also *endo*-products and are formed as one stereoisomer only, with the lone electron pair on sulfur being on the same side as the newly formed double bond of the cycloadducts. Compounds **9a**/**b** can also be formed in a one-pot oxidation-cycloaddition reaction of the corresponding thiophenes and *N*-phenylmaleimides **8a**/**b** by the action of meta chloroperoxybenzoic acid (*m*-CPBA) in the presence of $BF_3{\cdot}Et_2O$.[1,3] The yield of the cycloaddition of the isolated thiophene *S*-oxides **4b**/**c** and the thiophene *S*-oxides formed *in situ* in the one-pot procedure are comparable. Compound **7** is formed as the *exo-endo* product, with all nine stereocentres controlled over the course of two consecutive cycloaddition reactions. The first of these cycloadditions involves the synthesis of a dienophile 3,4-dibenzoyl-tricyclo[4.2.$10^{2,5}$] nona-3,7-diene (**3**) itself, which is achieved by reaction of quadricyclane (**1**) with dibenzoylacetylene (**2**) (Scheme 1), reminiscent of the reaction of quadricyclane with alkynes, published previously.[10] The stereochemical outcome of the reactions can be predicted from extensive work on single crystal X-ray analysis on cycloadducts of thiophene *S*-oxides and alkenes carried out by us and others.[3,11-13]

Reaction with PBr_3 deoxygenates 7-thiabicyclo[2.2.1] heptene *S*-oxides **6**, **7**, and **9a**/**b** efficiently to 7-thiabicyclo-[2.2.1]heptenes **10**, **11**, and **12a**/**b**, respectively. A temperature of 0°C must be maintained carefully during the addition of PBr_3. Temperatures higher than 25 °C should also be avoided during the reaction itself. Elevated temperatures favour the extrusion of the entire SO-bridge and lead to mixtures of aromatic systems and cyclohexadienes.

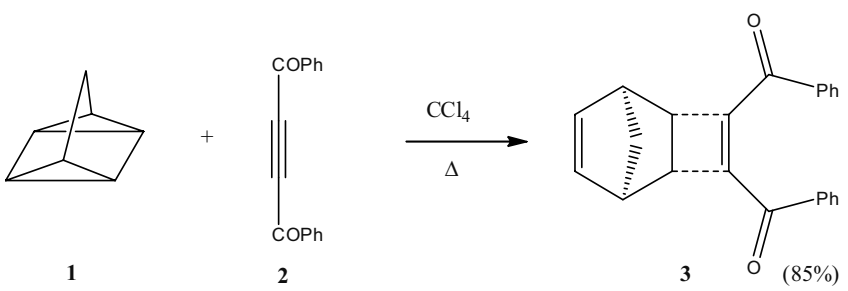
In conclusion, we have shown that oligocycles with a 7-thiabicyclo[2.2.1]hept-5-ene unit can be prepared with total stereochemical control in very few steps.

Experimental

General

Melting points were determined on a Mitamurariken MELT THERMO and are uncorrected. IR spectra were recorded on a JASCO-102 spectrometer. NMR spectra were recorded at 270 MHz (proton) and at 67.8 MHz (carbon-13) with a JEOL EX-270 spectrometer. The chemical shifts are relative to TMS (solvent $CDCl_3$, unless noted otherwise). DEPT (Distortionless Enhancement by Polarisation Transfer) was used to help assign the carbon signals, where (+) denotes primary and tertiary, (–) secondary and C_{quat} quaternary carbons. Mass spectra were measured with a JMS-01-SG-2 spectrometer (EI, 70 eV). Column chromatography was carried out Wako gel C300. Thiophene *S*-oxides **4** were prepared by oxidation of the corresponding thiophenes with *meta*-chloroperoxybenzoic acid (*m*-CPBA) in the presence of $BF_3{\cdot}Et_2O$, as reported previously.[14] **9a**[1] was prepared analogous to **9b** (see below). DMF was dried over CaH_2 and distilled. PBr_3 was distilled before use.

3,4-Dibenzoyltricyclo[4.2.$10^{2,5}$]nona-3,7-diene (**3**): A solution of tetracyclo[3.2.0.$0^{2,7}0^{4,6}$]heptane (**1**, 100 mg, 1.09 mmol) and dibenzoylacetylene (**2**, 234 mg, 1.00 mmol) in CCl_4 (2 mL) was held at reflux for 48 h. Thereafter, CCl_4 was removed *in vacuo* and the residue was subjected to column chromatography on silica gel (hexane/ether 1:2) to give **3** (270 mg, 85%) as a pale yellow solid, m.p. 104 °C. (Found: M^+, 326.1309. $C_{23}H_{18}O_2$ requires M^+,



Scheme 1 Synthesis of dienophile 3,4-dibenzoyl-tricyclo[4.2.$10^{2,5}$]nona-3,7-diene (**3**).

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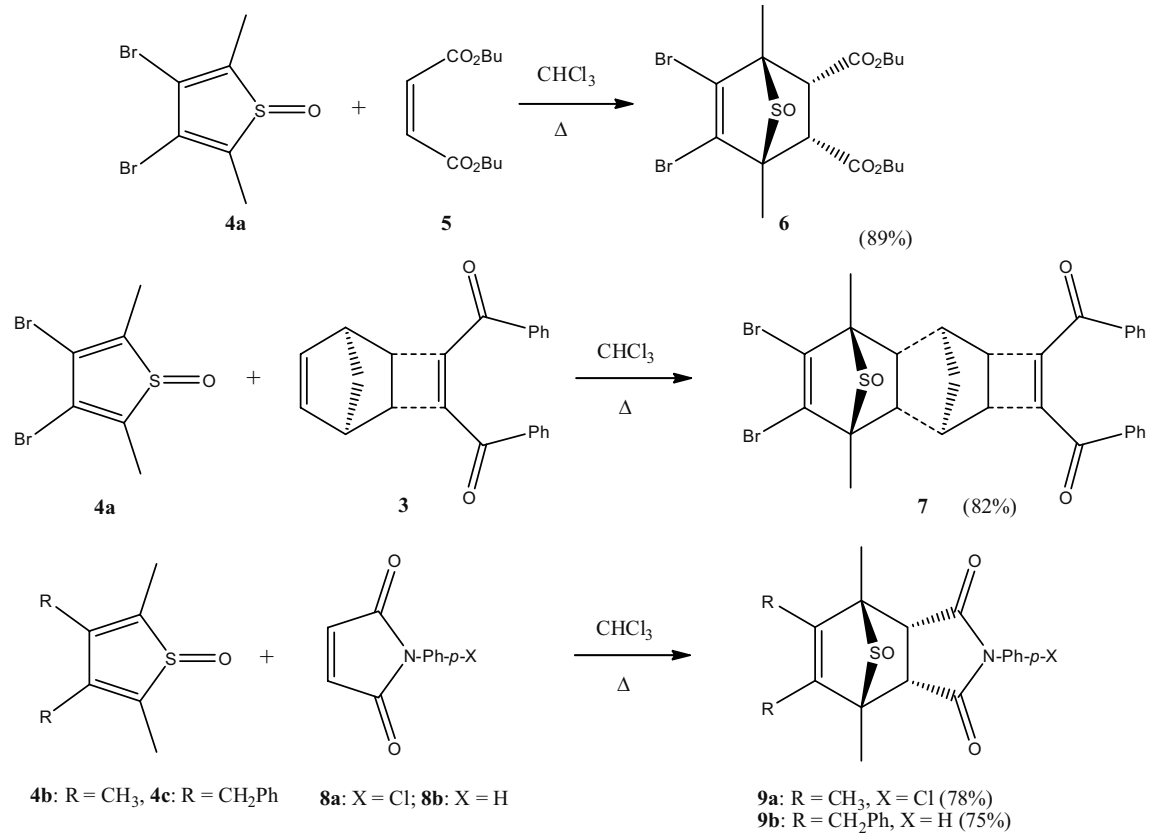


Scheme 2 Cycloaddition of thiophene S-oxides to alkenes.

326.1307). ν_{max} (neat/cm^{-1}) 2994, 2974, 2948, 1648, 1598, 1449, 1317, 1290, 1279, 947, 865, 703, 660; δ_H (270 MHz, $CDCl_3$) 1.55 (1H, d, ^2J = 9.6 Hz), 1.74 (1H, d, ^2J = 9.6 Hz), 2.89 (2H, d, J = 1.7 Hz), 2.91 (2H, brs), 6.52 (2H, s), 7.22–7.72 (10H, m); δ_C (67.8 MHz, $CDCl_3$) 39.4, 40.1, 45.4, 128.5, 128.8, 133.2, 136.0, 136.7, 149.9, 190.8; MS (EI, 70 eV) *m/z* (%) = 326 (M^+) (30).

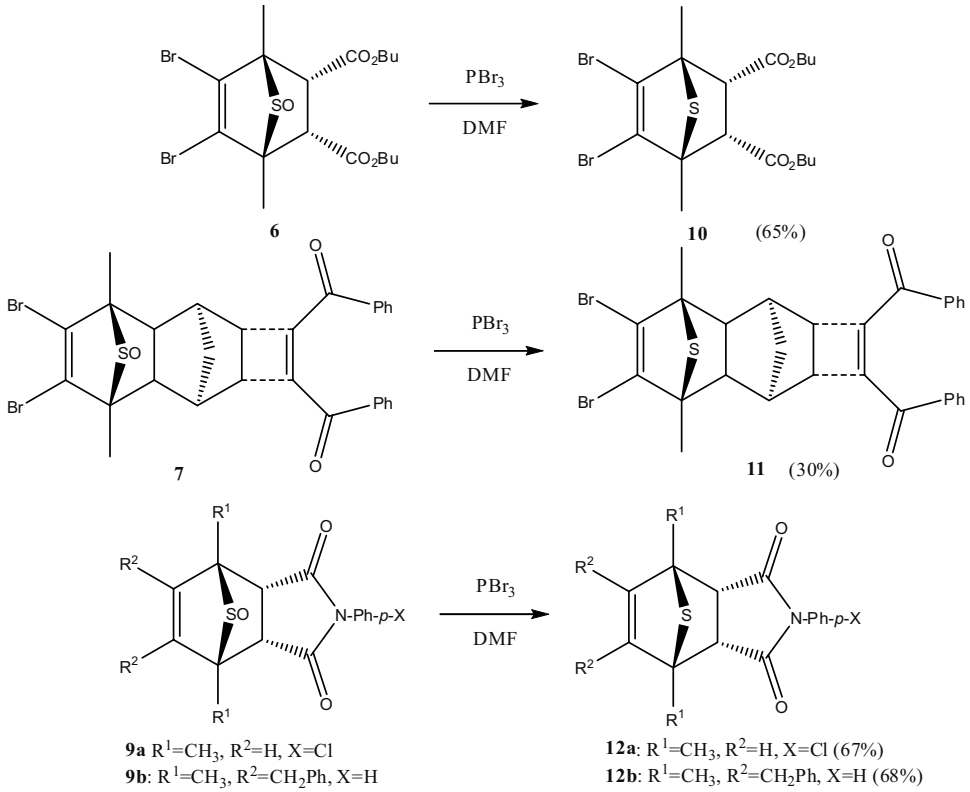
Dibutyl 2,3-dibromo-1,4-dimethyl-7-thiabicyclo[2.2.1]hept-2-ene-5,6-dicarboxylate 7-oxide (**6**): A mixture of 3,4-dibromo-2,5-dimethylthiophene *S*-oxide (**4a**) (150 mg, 0.52 mmol) and dibutyl maleate (**5**) 237 mg, 1.04 mmol) in chloroform (2 mL) was heated under reflux for 24 h. Thereafter, the solution was cooled and concentrated *in vacuo*. The residue was subjected to column chromatography on silca gel (hexane/ether 2:1) to give **6** (240 mg, 89%) as a colourless solid; m.p. 69–70 °C. (Found: M^+, 513.9848. $C_{18}H_{26}O_5{}^{79}Br^{81}BrS$ requires M^+, 513.9847). ν_{max} (neat/cm^{-1}) 2960, 2870, 1737, 1566, 1450, 1383, 1328, 1282, 1246, 1171, 1146, 1110, 1084, 1063, 1025, 950. δ_H (270 MHz, $CDCl_3$) 0.93 (6H, t, ^3J = 7.2 Hz, 2 CH_3), 1.36 (4H, m), 1.59 (4H, m), 1.68 (6H, s, 2 CH_3), 3.89 (2H, s), 4.04 (4H, m); δ_C (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) 13.7 (+, 2C, CH_3), 15.5 (+, 2C, CH_3), 19.1 (–, 2C), 30.4 (–, 2C), 52.7 (+, 2C, CH), 65.6 (–, 2C), 75.2 (C_{quat}, 2C), 125.4 (C_{quat}, 2C), 169.1 (C_{quat}, 2C). MS (70 eV) *m/z* (%) = 516 ([$^{81}Br_2$]M^+, 4), 514 ([$^{81}Br^{79}Br$]M^+, 8), 512 ([$^{79}Br_2$]M^+, 4), 468 ([$^{81}Br_2$] M^+-SO, 38), 264 (100).

5,6-Dibenzoyl-11,12-dibromo-1,10-dimethyl-14-thiapentacyclo-[8.2.1.1.^{3,8}0.^{2,9}0.^{4,7}]penta-deca-5,11-diene 14-oxide (**7**): A solution of **3** (100 mg, 0.31 mmol) and **4a** (44 mg, 0.15 mmol) in chloroform (1.5 mL) was held at reflux for 21 h. Then, the cooled solution was concentrated *in vacuo* and subjected to column chromatography on silica gel (ether/hexane 1 : 1) to give **7** (75 mg, 82%) as a colourless solid; m.p. 184 °C. (Found: MH^+, 612.9870. $C_{29}H_{25}O_3{}^{79}Br^{81}BrS$ requires MH^+, 612.9873 [FAB]). ν_{max} (KBr/cm^{-1}) 3054, 3026, 2960, 2920, 1653, 1597, 1444, 1315, 1286, 1110, 712, 687, 656; δ_H (270 MHz, $CDCl_3$) 1.48 (2H, m), 1.65 (6H, s, 2 CH_3), 2.51 (2H, bs), 2.52 (2H, bs), 3.07 (2H, bs), 7.18–7.24 (4H, m), 7.33–7.39 (2H, m), 7.60–7.63 (4H, m); $^{13}\delta_C$ (67.8 MHz, $CDCl_3$, DEPT, DEPT 135) 16.2 (+, 2C, CH_3), 27.8 (–, 2C), 35.0 (+, 2C, CH), 42.3 (+, 2C, CH), 53.3 (+, 2C, CH), 77.2 (C_{quat}, 2C), 125.8 (C_{quat}, 2C), 128.5 (+, 4C, CH), 128.8 (+, 4C, CH), 133.4 (+, 2C, CH), 136.4 (C_{quat}, 2C), 145.9 (C_{quat}, 2C), 190.5 (C_{quat}, 2C, C=O); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 613 (MH^+, 35), 564 (15).

N-Phenyl-5,6-benzyl-1,4-dimethyl-7-thiabicyclo[2.2.1]hept-5-ene-2,3-carboxamide 7-oxide (**9b**): A solution of 3,4-dibenzyl-2,5-dimethylthiophene *S*-oxide (**4c**, 406 mg, 1.32 mmol) and *N*-phenylmaleimide (**8b**, 250 mg, 1.45 mmol) in $CHCl_3$ (4 mL) was stirred at 60°C for 18 h under an inert atmosphere. Thereafter, the solvent was evaporated *in vacuo* and the residue was subjected to a short column chromatography on silica gel (ether/$CHCl_3$/hexane 2:1:1) to give **9b** (475 mg, 75%) as a colourless solid, m.p. 73 °C. (Found: M^+, 481.1718. $C_{30}H_{27}NO_3S$ requires M^+, 481.1712). ν_{max} (KBr/cm^{-1}) 1700, 1060; δ_H (270 MHz, $CDCl_3$) 1.67 (6H, s, 2 CH_3), 3.56 (2H, d, ^2J = 16.0 Hz), 3.76 (2H, s), 3.82 (2H, d, ^2J = 16.0 Hz), 7.04–7.52 (15H, m); δ_C (67.8 MHz, $CDCl_3$) 13.5, 32.7, 51.2, 73.9, 126.1, 126.8, 128.4, 128.7, 128.8, 129.0, 129.1, 131.6, 137.0, 137.1, 174.1; MS (EI, 70 eV) *m/z* (%) = 433 (M^+-SO, 47), 342 (6.9), 193 (100). Anal Calcd for $C_{30}H_{27}NO_3S$ (481.60): C, 74.82; H, 5.65; N, 2.91. Found: C, 74.82; H, 5.84; N, 2.83%.

Dibutyl 2,3-dibromo-1,4-dimethyl-7-thiabicyclo[2.2.1]hept-2-ene-5,6-dicarboxylate (**10**): A solution of **7** (114 mg, 0.22 mmol) and PBr_3 (110 μL, 313 mg, 1.16 mmol) in dry DMF (2.0 mL) was set at 0 °C and stirred at r.t. for 25 min. Thereafter, the mixture was cooled again to 0 °C and ether (10 mL) was added. Then, water (300 μL) was added dropwise. The mixture was extracted with water (15 mL) and ether (2 × 15 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography on silica gel (hexane/ether 2.5 : 1) gave **10** (71 mg, 65%) as a colourless oil. (Found: M^+, 497.9896. $C_{18}H_{26}O_4{}^{79}Br^{81}BrS$ requires M^+, 497.9899). ν_{max} (neat/cm^{-1}) 2956, 2854, 1748, 1587, 1459, 1382, 1195; δ_H (270 MHz, $CDCl_3$) 0.92 (6H, t, ^3J = 7.5 Hz, 2 CH_3), 1.20–1.34 (4H, m), 1.56 (4H, m), 1.78 (6H, s, 2 CH_3), 3.94 (2H, s), 3.92–4.10 (4H, m); δ_C (67.8 MHz, $CDCl_3$) 13.7 (+, 2C, CH_3), 19.2 (+, 2C, CH_3 and 2C, CH_2), 30.5 (–, 2C), 60.7 (+, 2C, CH), 65.1 (–, 2C), 65.9 (C_{quat}, 2C), 132.3 (C_{quat}, 2C), 169.3 (C_{quat}, 2C, C=O); MS (70 eV) *m/z* (%) = 500 ([$^{81}Br_2$]M^+, 10), 498 ([$^{79}Br^{81}Br$]M^+, 19), 496 ([$^{79}Br_2$]M^+, 10), 419 (M^+-Br, 31), 417 (M^+-Br, 30), 308 (94), 271 (52), 269 (100), 267 (50).

5,6-Dibenzoyl-11,12-dibromo-1,10-dimethyl-14-thiapentacyclo-[8.2.1.1.^{3,8}0.^{2,9}0.^{4,7}]penta-deca-5,11-diene (**11**): A solution of **7** (67 mg, 0.11 mmol) and PBr_3 (110 μL, 313 mg, 1.16 mmol) in dry DMF (1.5 mL) was set at 0 °C and stirred at r.t. for 25 min. Thereafter, the mixture was cooled again to 0 °C and ether (10 mL) was added. Then, water (300 μL) was added dropwise. The mixture was extracted with water (15 mL) and ether (2 × 15 mL). The combined



Scheme 3 Deoxygenation of compounds with a 7-thiabicyclo[2.2.1]heptene *S*-oxide subunit.

organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane/ether 3 : 1) to give **11** (19 mg, 30%) as a colourless solid, m.p. 176–179 °C. (Found: MH^+, 596.9922. $C_{29}H_{25}O_2{}^{79}Br^{81}BrS$ requires MH^+, 596.9923 [FAB]). ν_{max} (KBr/cm^{-1}) 3058, 2960, 2922, 2856, 1651, 1598, 1446, 1314, 1284, 1262, 866, 741, 713, 689; δ_H (270 MHz, $CDCl_3$) 1.56 (2H, bs), 1.72 (6H, s, 2 CH_3), 2.38 (2H, s), 2.62 (2H, s), 2.99 (2H, s), 7.17–7.23 (4H, m), 7.32 – 7.38 (2H, m), 7.60–7.63 (4H, m); δ_C (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) 20.5 (+, 2C, CH_3), 35.4 (+, 2C, CH), 50.0 (+, 2C, CH), 62.3 (+, 2C, CH), 68.2 (+, 2C, CH), 128.9 (+, 4C, CH), 129.3 (+, 4C, CH), 132.5 (C_{quat}, 2C), 133.8 (+, 2C, CH), 137.0 (C_{quat}, 2C), 146.4 (C_{quat}, 2C), 191.1 (C_{quat}, 2C, CO); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) = 599 ([$^{81}Br_2$]MH^+, 0.9), 597 ([$^{79}Br^{81}Br$]MH^+, 1.5), 595 ([$^{79}Br_2$]MH^+, 0.85).

N-(p-Chlorophenyl)-1,4-dimethyl-7-thiabicyclo[2.2.1]hept-5-ene-2,3-dicarboxamide (**12a**): PBr_3 (300 μL, 855 mg, 3.16 mmol) at 0 °C and within 25 min was added to a solution of **9a** (100 mg, 0.30 mmol) in dry DMF (2.5 mL). The resulting slurry was stirred at r.t. for 25 min, then cooled to 0 °C and ether (15 mL) was added. Then, water (300 μL) was added dropwise. Thereafter, the mixture was extracted with water (15 mL) and ether (2 × 15 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane/ether 2 : 1) to give **12a** (64 mg, 67%) as colourless needles, m.p. 153–154 °C. (Found: M^+, 320.0518. $C_{16}H_{15}O_2N^{35}ClS$ requires M^+, 320.0512). ν_{max} (KBr/cm^{-1}) 3098, 2966, 2928, 2870, 1703, 1492, 1453, 1378, 1181, 1167, 1087, 836, 804, 741; δ_H (270 MHz, $CDCl_3$) 1.95 (6H, s, 2 CH_3), 3.83 (2H, s), 6.31 (2H, s), 7.09 (2H, d, ^3J = 8.6 Hz), 7.40 (2H, d, ^3J = 8.6 Hz); δ_C (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) 18.3 (+, 2C, CH_3), 57.8 (+, 2C, CH), 64.6 (C_{quat}, 2C), 127.6 (+, 2C, CH), 129.3 (+, 2C, CH), 129.9 (C_{quat}), 134.5 (C_{quat}), 141.2 (+, 2C, CH), 173.4 (C_{quat}, 2C, C=O); MS (70 eV) *m/z* (%) = 321 ([^{37}Cl]M^+, 3), 319 ([^{35}Cl]M^+, 8), 207 (13), 112 (100). Anal Calcd for $C_{16}H_{14}NO_2ClS$ (319.81): C, 60.09; H, 4.41; N, 4.38. Found: C, 60.17; H, 4.45; N, 4.43%.

N-Phenyl-5,6-benzyl-1,4-dimethyl-7-thiabicyclo[2.2.1]hept-5-ene-2,3-carboxamide (**12b**): A solution of **9b** (50 mg, 0.10 mmol) and PBr_3 (150 μL, 427 mg, 1.58 mmol) in dry DMF (2.0 mL) was reacted (addition time 20 min. at 0°C, reaction time 20 min. at r.t.) and worked-up analogous to the preparation of **12a**. Column chromatography on silica gel (hexane/ether 3 : 1) gave **12b** (33 mg, 68%) as colourless needles, m.p. 152–153 °C (hexane). (Found: M^+, 465.1766; $C_{30}H_{27}O_2NS$ requires M^+, 465.1763). ν_{max} (KBr/cm^{-1}) 3060, 3024, 2980, 2930, 2870, 1775, 1706, 1600, 1494, 1453, 1382, 1184, 1029, 750, 728, 714, 692; δ_H (270 MHz, $CDCl_3$) 1.77 (6H, s, 2 CH_3), 3.30 (2H, d, ^2J = 15.9 Hz), 3.76 (2H, d, ^2J = 15.9 Hz), 3.85 (2H, s), 7.15–7.32 (12H, m), 7.42–7.53 (3H, m); δ_C (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) 18.0 (+, 2C, CH_3), 33.2 (–, 2C, $\underline{C}H_2Ph$), 59.0 (+, 2C, CH), 66.5 (C_{quat}, 2C), 126.2 (4C, +, CH), 126.4 (2C, +, CH), 128.4 (4C, +, CH), 128.6 (2C, +, CH), 128.8 (2C, +, CH), 129.3 (+, CH), 131.5 (2C, C_{quat}), 138.6 (2C, C_{quat}), 144.8 (C_{quat}), 173.6 (2C, C_{quat}, C=O); MS (70 eV) *m/z* (%) = 465 (M^+, 3), 433 (M^+-S, 38), 292 (100), 173 (44). Anal. Calcd for $C_{30}H_{27}NO_2S$ (465.61): C, 77.39; H, 5.85; N, 3.01. Found: C, 77.21; H, 5.86; N, 2.99%.

Received 29 September 2009; accepted 19 October 2009
Paper 09/0803 doi: 10.3184/030823409X12562932030738
Published online: 16 November 2009

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