Intramolecular Capture of a Cyclobutylthionium Ion for the Synthesis of New Strained Heterocycles and Carbocycles: A Rapid Assembly of the BCD Ring Sequence of Penitrems

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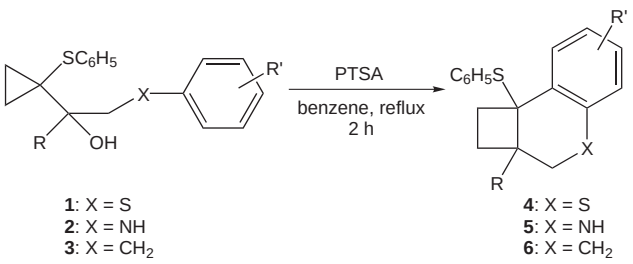
Abstract: The first example of intramolecular interception of a cyclobutyl thionium ion for the synthesis of cyclobutathiochromenes, hexahydrocyclobutaquinolines and hexahydrocyclobutanaphthalenes is reported.

Key words: heterocycles, carbocycles, ring expansion, tandem reaction, rearrangement

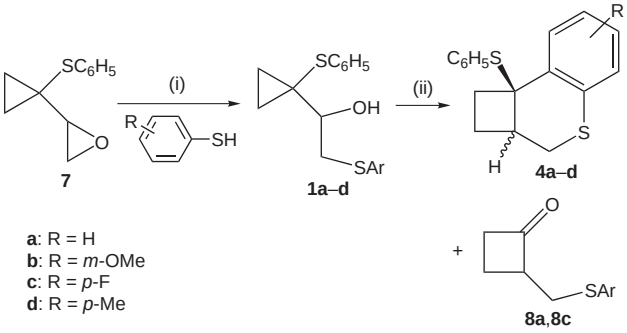
The preparation of complex carbocyclic[1] and heterocyclic[2] compounds continues to be an important target in organic synthesis that requires a constant development of new methodologies and a strategic deployment of known methods. One way of constructing molecular complexity is by combining two or more distinct reactions into a single transformation. In this context the generation of a thionium ion from a sulfoxide in a Pummerer reaction and its intramolecular interception by carbon- or hetero-nucleophiles, represents an important tool for the synthesis of both carbocycles and heterocycles.[3] We recently reported that a cyclobutylthionium ion, generated through an acid-catalyzed cyclopropylcarbinyl–cyclobutyl ring expansion, was captured by a pendant aryloxy group to furnish new strained versatile cyclobutachromenes.[4] The synthetic potential of this method is greatly increased by the results we are here reporting on the synthesis of derivatives **4**–**6** by the tandem acid-catalyzed ring-enlargement–annulation reaction of the cyclopropyl carbinols **1**–**3** (Scheme 1).



Scheme 1

We started by examining the reactivity of derivatives **1a**–**d** prepared by nucleophilic addition of the appropriate thiophenol on the cyclopropyl epoxide **7** (Scheme 2).

Derivatives **4a**–**d** were obtained in reasonable yields (40–72%) as mixtures of diastereoisomers deriving from the different *cis* or *trans* ring fusion (Table 1). The derivative **4b** was obtained as a single geometric isomer, mixture of two regioisomers in a 70:30 ratio.



Scheme 2 *Reagents and conditions*: (i) MeOH, MeONa, r.t.; (ii) PTSA 10%, dry benzene, reflux, 2 h.

Table 1 Synthesis of Cyclobutathiochromenes **4a**–**d**

Compd	R	Yield of **1** (%)	Yield of **4** (%)	Ratio of geometric isomers (**4**)[a]
a	H	75	72	75:25
b	*m*-OMe	72	70	100:0
c	*p*-F	65	40	80:20
d	*p*-Me	70	70	80:20

[a] The *cis* or *trans* configuration was not attributed for each individual isomer.

Variable, but small, amounts of cyclobutanones **8** were always present except in the case of **4a** and **4c** where the corresponding cyclobutanones **8a** and **8c** were obtained in 10% and 20% probably as a consequence of the reduced nucleophilicity of the aromatic ring in comparison with **4b** and **4d**.

The synthesis of nitrogen-containing heterocycles by the tandem acid-catalyzed ring-enlargement–annulation reaction of cyclopropyl carbinols **2** presents a real challenge.

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Within the acidic reaction conditions used to generate the thionium ion, the nitrogen atom should be the first to be protonated, being more basic than the oxygen atom of the hydroxyl group and hence the nucleophilicity of the aromatic ring will be reduced. A successful strategy would require the generation of a leaving group under non-acidic conditions (a subject of current research) or the fine-tuning of the basicity of the nitrogen atom with minimal detriment to the nucleophilicity of the aromatic ring.

Next we prepared the cyclopropyl carbinols **2a**–**c** through nucleophilic ring-opening of the cyclopropyl epoxide **7** by the corresponding aniline and treated them with TsOH in refluxing benzene (Scheme 3). Unexpectedly the ring expansion of derivatives **2** occurred cleanly only in the case of **2c** where a *p*-OMe group was present in the aromatic ring, leading to moderate yields of the dihydroquinoline **5c** (42% yield) to which the *cis* geometry was tentatively assigned. In all the other cases, the starting material was recovered even after long refluxing.

Finally, we directed our attention to the reactivity of the cyclopropyl carbinols of type **3** (X = CH_2). They appeared to our eyes particularly interesting because their successful cyclization to give type **6** derivatives would represent an easy access to the important BCD ring sequence present in the family of the biologically active penitrems (Figure 1).[5] The penitrems represent a class of novel indole alkaloids that have attracted attention as a result of their potent neurotoxic activity and complex architectures.[6]

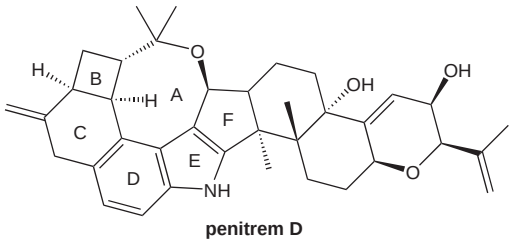


Figure 1

In addition, there are relatively few examples in the literature of cationic cyclization reactions for the synthesis of carbocycles involving the intramolecular cyclization of carbon-centered nucleophiles onto, in situ generated carbenium ion or heteroatom-stabilized carbocation, through a sequential, tandem cascade or domino reaction.[7a–d,8a–e] In connection with this, our previous attempt to cyclize a type **3** cyclopropyl carbinol which lacks the *ipso*-oxygen[4] led only to the corresponding cyclobutanone probably as a consequence of the insufficient nucleophilicity of the aromatic ring. We therefore reasoned that the introduction of an electron-donating substituent in the aromatic ring should favor the capture of the intermediate cyclobutyl thionium ion.

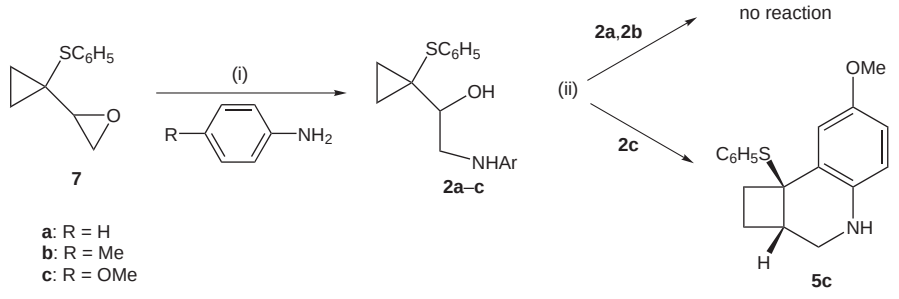
Table 2 Synthesis of Hexahydrocyclobutanaphthalenes **6b**–**e**

	R	R′	R″	Yield of **3** (%)	Yield of **6** (%)
a	Me	*p*-OMe	H	61	0
b	Me	*m*-OMe	H	60	68
c	Me	*m*-Me	H	70	79[a]
d	H	*m*-OMe	H	60	67
e	H	*m*-Me	COOMe	66	65[a]

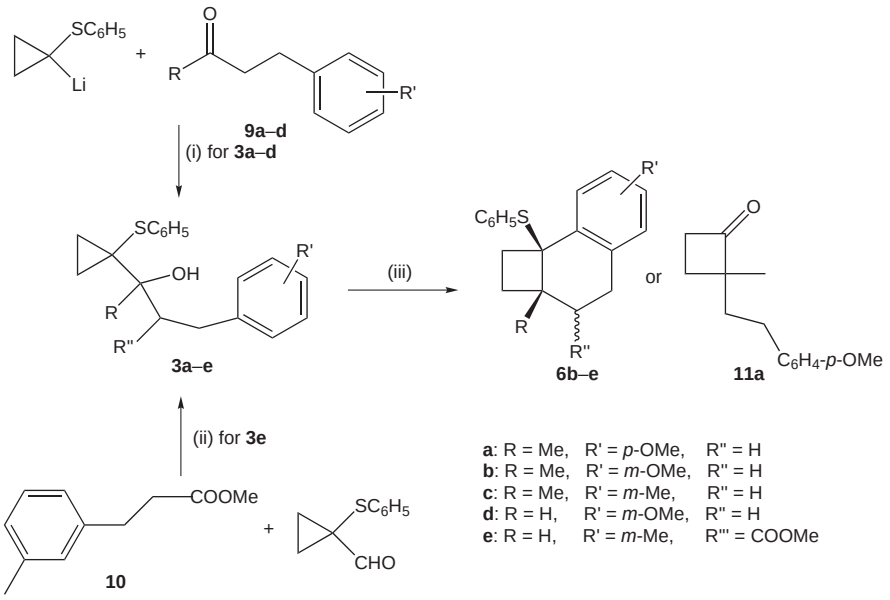
[a] Traces of cyclobutanone were evident.

Consequently, we prepared the derivative **3a** (path i) with a *p*-OMe substituent in the aromatic ring by reaction of the lithium salt of cyclopropylphenylsulfide[9] with **9a** (Scheme 4). Ring expansion of **3a** by treatment with PTSA in C_6H_6 led only to the formation of the cyclobutanone **11a**. Next we prepared, in the same way, the derivatives **3b**–**d** with a methoxy or a methyl group in the *meta* position of the aromatic ring that is suitably placed to activate an electrophilic attack to form a six-membered ring. Successive acid-catalyzed ring expansion, gratifyingly, led cleanly to the formation of the expected three-ring carbocycles **6b**–**d** (Table 2).[10,11] Ring expansion of **3e** obtained by reaction of **10** with 1-phenylthiocyclopropyl carboxaldehyde (path ii) led successfully to **6e**[10,11] carrying an ester group as a suitable precursor of the double bond present in the cyclohexyl moiety of the BCD ring sequence of penitrems.

In summary, we have demonstrated that the synthetic potentialities of the acid-catalyzed ring expansion of 1-phenylthio cyclopropyl carbinols can be extended to create new carbo- and heterocyclic derivatives containing the



Scheme 3 *Reagents and conditions*: (i) dry EtOH, reflux; (ii) PTSA 1.1 equiv, dry benzene, reflux, 2 h.



Scheme 4 *Reagents and conditions*: (i) THF, 0 °C to r.t.; (ii) LDA, THF, –78 °C; (iii) PTSA (10 mol%), dry benzene, reflux, 2 h.

cyclobutyl moiety if a suitably activated aromatic ring is tethered to the cyclopropyl ring.[12] New examples of the capture of a cyclobutylthionium ion to create new heterocycles will be reported in due course.

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(10) Derivatives **6b**–**e** are inseparable mixtures of the two possible regioisomers of cyclization (**6b** and **6d** in the ratio of 90:10, while **6c** in a ratio of 82:18 and **6e** in a ratio of 66:34).

(11) A *cis* geometry was tentatively assigned to the R group and the phenylthio group of derivatives **6b**–**e**, on the basis of the steric constraints present during the cyclization step. In any case, we were not able to register any NOE effects between the protons of the phenylthio and the methyl group of compound **6b**, but we recorded the presence of a NOE effect between the benzylic proton and the methyl group of the

compound obtained by desulfuration of **6b** with Raney nickel.

(12) All new compounds have been fully characterized by ^{1}H NMR (300 MHz), ^{13}C NMR (75.4 MHz), IR, GLC mass spectra (70 eV) and elemental analyses. Selected analytical data for some representative derivatives are reported.

General Procedure for the Synthesis of 1a–d.

To a stirred solution of Na (119.8 mg, 5.21 mmol) in MeOH (20 mL) at r.t. under argon, thiophenol (0.57 mg, 5.21 mmol) in MeOH (5 mL) was added dropwise. After 30 min, epoxide **7** (1 g, 5.21 mmol) was added and the reaction mixture was stirred for 16 h. After this time the MeOH was evaporated under vacuum and the residue dissolved in Et_2O. The ethereal solution was washed with 1 N NaOH, brine, dried on anhyd Na_2SO_4 and concentrated under vacuum. The crude product was purified by chromatography on silica gel column using light PE–Et_2O (1:1) as eluent.

2-(Phenylsulfanyl)-1-[1-(phenylsulfanyl)cyclopropyl]ethanol (**1a**): yellow oil; yield 75%. IR (neat): 3420 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.90–1.21 (m, 4 H), 2.60 (br s, 1 H), 2.95 (dd, 1 H, *J* = 14.0, 9.9 Hz), 3.51–3.58 (m, 2 H), 7.12–7.42 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ = 12.0, 14.4, 29.3, 39.8, 72.0, 126.0, 126.2, 128.7, 128.9, 128.9, 129.3, 135.0, 135.8. MS: *m/z* (%) = 302 (45) [M$^+$], 285 (2), 193 (43), 175 (62), 162 (28), 149 (28), 123 (91), 109 (100), 91 (58), 77 (67), 45 (58). Anal. Calcd for $C_{17}H_{18}OS_2$: C, 67.51; H, 6.00; S, 21.20. Found: C, 67.48; H, 6.01; S, 21.22.

General Procedure for the Synthesis of 2a–c

A solution of the appropriate amine (2.3 mmol) and of the 2-[1-(phenylsulfanyl)cyclopropyl]epoxide (**7**, 450 mg, 2.3 mmol) in dry EtOH (10 mL) was refluxed for 16 h. After this time the solvent was evaporated under vacuum and the residue was purified by chromatography on a silica gel column using light PE–Et_2O (1:1) as eluent.

1-[1-(Phenylsulfanyl)cyclopropyl]-2-(4-toluidino)ethanol (**2b**): yellow oil; yield 45%. IR (neat): 3340 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.96–1.19 (m, 4 H), 2.22 (s, 3 H), 3.11 (dd, 1 H, *J* = 9.3, 12.0 Hz), 3.13 (br s, 1 H), 3.48 (dd, 1 H, *J* = 3.3, 12.0 Hz), 3.59 (dd, 1 H, *J* = 3.3, 9.3 Hz), 6.49 (d, 2 H, *J* = 8.4 Hz), 6.57 (d, 2 H, *J* = 8.4 Hz), 6.94 (d, 2 H, *J* = 8.4 Hz), 7.14–7.29 (m, 2 H), 7.46 (d, 1 H, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$): δ = 12.7, 13.8, 20.3, 28.8, 48.9, 73.4, 113.5, 115.2, 126.2, 128.8, 129.1, 129.7, 136.1, 145.6. MS: *m/z* (%) = 299 (16) [M$^+$], 190 (3), 172 (2), 120 (100), 109 (2), 91 (12), 77 (9). Anal. Calcd for $C_{18}H_{21}NOS$: C, 72.20; H, 7.07; N, 4.68; S, 10.71. Found: C, 72.18; H, 7.08; N, 4.69; S, 10.71.

General Procedure for the Synthesis of 3a–d

To a solution of cyclopropylphenylsulfide (1.8 g, 12 mmol) in dry THF (40 mL), under Argon *n*-BuLi (7.5 mL, 12 mmol, 1.6 M solution in hexane) was added dropwise at 0 °C. After stirring for 5 h the resulting mixture was cooled to –40 °C and the ketone or aldehyde (12 mmol) was added. After 16 h, the reaction mixture was quenched with sat. aq NH_4Cl (10 mL) and extracted with Et_2O. The organic layer was dried on anhyd Na_2SO_4 and concentrated under vacuum. The crude oil was purified by chromatography on a silica gel column using light PE–Et_2O (1:1) as eluent.

4-(3-Methoxyphenyl)-2-[1-(phenylsulfanyl)cyclopropyl]butanol (**3b**): colorless oil; yield 60%. IR (neat): 3460 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.92–1.32 (m, 4 H), 1.25 (s, 3 H), 1.78 (s, 1 H), 1.90–2.10 (m, 2 H), 2.65–2.77 (m, 2 H), 3.78 (s, 3 H), 6.71–6.77 (m, 4 H), 7.15–7.48 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ = 13.4, 24.6, 30.3, 35.0, 42.2, 55.1, 74.6, 111.0, 114.0, 120.7, 126.0, 128.6, 129.2, 129.4, 136.9, 144.0, 159.5. MS: *m/z* (%) = 219 (4) [M$^+$ – 109], 189 (13), 179 (14), 150 (24), 135 (39), 121 (100), 109 (22), 91 63), 77 (29), 43 (27). Anal. Calcd for $C_{20}H_{24}O_2S$: C, 73.13; H, 7.36; S, 9.76. Found: C, 73.10; H, 7.37; S, 9.78.

Procedure for the Synthesis of Methyl 3-Hydroxy-2-(3-methylbenzyl)-3-[1-(phenylthio)cyclopropyl]propanoate (3e).

To a stirred solution of lithium diisopropylamide (LDA), prepared from diisopropylamine (1.3 mL, 9.2 mmol) and *n*-BuLi (1.2 M in hexane; 7.66 mL, 9.2 mmol) in dry THF (30 mL) in the customary manner, cooled at –78 °C, a solution of methyl 3-(3-methylphenyl)propanoate (1.64 g, 9.2 mmol) in THF (10 mL) was added dropwise. After stirring for 1 h at the same temperature, the 1-(1-phenylsulfanyl)cyclopropyl carbaldehyde (1.64 g, 9.2 mmol) in THF (10 mL) was added. After 16 h, the mixture was diluted with Et_2O and washed with 10% $NaHCO_3$. The organic layer was dried over anhyd Na_2SO_4 and concentrated under vacuum. The residue was purified by chromatography on a silica gel column using light PE–Et_2O (1:1) as eluent. Spectral data refer to a 50:50 mixture of two inseparable diastereoisomers. Yellow oil; yield 66%. IR (neat): 3470, 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.85–1.26 (m, 8 H), 2.28 (s, 3 H), 2.31 (s, 3 H), 2.82–2.92 (m, 2 H), 3.13–3.20 (m, 2 H), 3.39–3.68 (m, 4 H), 3.49 (s, 3 H), 3.61 (s, 3 H), 6.92–7.50 (m, 18 H). ^{13}C NMR: δ = 11.5, 13.6, 13.9, 14.6, 21.3, 22.6, 29.3, 31.9, 33.8, 36.2, 49.8, 51.4, 51.8, 52.1, 74.3, 75.9, 125.8, 126.3, 126.4, 127.0, 127.2, 128.1, 128.3, 128.7, 128.8, 129.5, 129.9, 135.3, 135.8, 137.8, 138.0, 138.9, 174.8, 176.0.

General Procedure for the Synthesis of Derivatives 4a–d, 5c, 6b–e.

A stirred solution of cyclopropylcarbinol **1**–**3** (1.2 mmol) and PTSA (20 mg, 0.12 mmol for **1a**–**d**, **3a**–**d**; 220 mg, 1.3 mmol for **2c** and **3e**) in dry benzene (10 mL) was refluxed for 2 h in a Dean–Stark apparatus. The reaction mixture was then washed with 10% $NaHCO_3$ and brine, dried over anhyd Na_2SO_4 and concentrated under vacuum. The residue was chromatographed on a silica gel column using Et_2O–light PE (1:1) as eluent.

8b-(Phenylsulfanyl)-1,2a,3,8b-tetrahydro-2*H*-cyclobuta[*c*]thiochromene (**4a**): mixture of *cis*/*trans* isomers (75:25).

Major isomer: yellow oil; yield 51%. ^{1}H NMR ($CDCl_3$): δ = 1.78–1.86 (m, 1 H), 2.29–2.40 (m, 1 H), 2.47–2.56 (m, 2 H), 2.78 (dd, 1 H, *J* = 13.2, 9.0 Hz), 3.16 (dd, 1 H, *J* = 12.9, 5.4 Hz), 2.85–2.91 (m, 1 H), 3.10–3.16 (m, 1 H), 7.04–7.44 (m, 9 H). ^{13}C NMR ($CDCl_3$): δ = 21.8, 32.1, 35.7, 44.2, 55.2, 125.7, 126.4, 128.2, 128.4, 129.5, 132.9, 134.6, 135.0, 140.1. MS: *m/z* (%) = 284 (35) [M$^+$], 256 (3), 175 (100), 160 (10), 147 (90), 134 (30), 109 (45), 89 (10), 65 (30). Anal. Calcd for $C_{17}H_{16}S_2$: C, 71.79; H, 5.67; S, 22.54. Found: C, 71.68; H, 5.61; S, 22.8.

Minor isomer: yellow oil; yield 21%. ^{1}H NMR ($CDCl_3$): δ = 1.94–2.13 (m, 4 H), 2.76–2.90 (m, 1 H), 3.01 (dd, 1 H, *J* = 13.2, 10.5 Hz), 3.16 (dd, 1 H, *J* = 13.2, 4.8 Hz), 7.19–7.63 (m, 9 H). ^{13}C NMR ($CDCl_3$): δ = 23.2, 32.1, 34.9, 46.5, 65.8, 126.2, 128.0, 128.7, 128.9, 129.9, 132.4, 134.2, 135.8, 136.4. MS: *m/z* (%) = 284 (20) [M$^+$], 256 (3), 221 (5), 175 (100), 160 (15), 147 (95), 134 (34), 109 (65), 91 (9), 77 (16), 65 (26). Anal. Calcd for $C_{17}H_{16}S_2$: C, 71.79; H, 5.67; S, 22.54. Found: C, 71.70; H, 5.60; S, 22.7.

7-Methoxy-8b-(phenylsulfanyl)-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline (**5c**): colorless oil; yield 42%. ^{1}H NMR ($CDCl_3$): δ = 1.83–1.91 (m, 2 H), 2.12–2.19 (m, 1 H), 2.41–2.51 (m, 1 H), 2.84–2.89 (m, 3 H), 3.76–3.80 (m, 1 H), 3.77 (s, 3 H), 6.47 (d, 1 H, *J* = 8.7 Hz), 6.66 (dd, 1 H *J* = 8.7, 3.0 Hz), 7.14–7.38 (m, 6 H). ^{13}C NMR ($CDCl_3$): δ = 18.6, 36.9, 41.3, 42.7, 51.0, 55.8, 114.0, 114.9, 116.2, 128.2, 128.5, 133.2, 135.8, 138.8, 152.5. MS: *m/z* (%) = 297 (11) [M$^+$], 268 (10), 253 (5), 188 (100), 173 (10), 160 (11), 145

(6), 117 (7), 96 (5), 71 (5), 57 (6), 43 (4). Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.12; N, 4.71; S, 10.78. Found: C, 72.60; H, 6.05; N, 4.73; S, 10.80.

6-Methoxy-2a-methyl-8b-(phenylsulfanyl)-1,2,2a,3,4,8b-hexahydrocyclobuta[*a*]naphthalene (**6b**): spectral data refer to a 90:10 mixture of two inseparable regioisomers. Colorless oil; yield 68%. ^{1}H NMR ($CDCl_3$): δ = 1.43 (s, 6 H), 1.45–1.89 (m, 8 H), 2.15–2.24 (m, 2 H), 2.43–2.64 (m, 6 H), 3.71 (s, 3 H), 3.77 (s, 3 H), 6.53–7.53 (m, 16 H).

Major isomer: MS: *m/z* (%) = 228 (2) [M^+ – 28], 267 (2), 233 (4) 201 (100), 185 (4), 159 (35), 144 (10), 128 (20), 109 (85), 91 (13), 77 (30), 65 (60), 39 (40).

Minor isomer: MS: *m/z* (%) = 201 (5) [M^+ – 109], 189 (100), 185 (10), 173 (7), 156 (10), 147 (17), 121 (25), 109 (45), 91 (62), 77 (51), 65 (64), 51 (30), 39 (65).

Methyl-6-methyl-8b-(phenylsulfanyl)-1,2,2a,3,4,8b-hexahydrocyclobuta[*a*]naphthalene-3-carboxylate (**6e**): yellow oil; yield 65%. Mixture of four inseparable isomers (50:16:10:24). IR (neat): 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.62–1.86 (m, 8 H), 2.02–2.64 (m, 12 H), 2.30 (s, 3 H), 2.32 (s, 3 H), 2.46 (s, 3 H), 2.47 (s, 3 H), 2.66–3.20 (m, 12 H), 3.64 (s, 3 H), 2.65 (s, 3 H), 2.67 (s, 3 H), 2.71 (s, 3 H), 6.90–7.42 (m, 32 H).

First isomer (50%): MS: *m/z* (%) = 338 (4) [M^+], 229 (62), 197 (11), 169 (93), 154 (45), 141 (35), 128 (32), 109 (100), 91 (4), 77 (10), 65 (28).

Second isomer (16%): MS: *m/z* (%) = 338 (7) [M^+], 261 (14), 229 (75), 197 (25), 169 (93), 154 (50), 141 (52), 128 (41), 109 (100), 91 (4), 77 (15), 65 (32).

Third isomer (10%): MS: *m/z* (%) = 338 (100) [M^+], 295 (50), 250 (64), 235 (50), 221 (27), 202 (31), 197 (25), 189 (11), 147 (20), 128 (17), 115 (24), 91 (10), 77 (8), 59 (21).

Fourth isomer (24%): MS: *m/z* (%) = 338 (100) [M^+], 295 (60), 250 (62), 235 (45), 221 (27), 202 (45), 197 (25), 189 (20), 169 (75), 155 (32), 141 (44), 128 (37), 115 (47), 91 (12), 77 (21), 59 (51).

Procedure for the Synthesis of 2-[1-(Phenylsulfanyl)cyclopropyl]epoxide (7).

To a solution of dimethyloxosulfonium methylide, prepared under Argon from pentane washed NaH (0.2 g, 4.9 mmol, 60% mineral oil dispersion) trimethyloxosulfonium iodide (1 g, 4.9 mmol) and 10 mL of DMSO, was added at r.t. a solution of 1-(phenylthio)cyclopropane carbaldehyde (0.8 g, 4.5 mmol) in 5 mL of DMSO. After 6 h, 20 mL of brine was added and the mixture was extracted with Et_2O. The ethereal solution was dried on anhyd Na_2SO_4 and concentrated under vacuum. The crude product was purified by chromatography on silica gel column using light PE–Et_2O (1:1) as eluent. Colorless oil; yield 82%. ^{1}H NMR ($CDCl_3$): δ = 0.88–1.26 (m, 4 H), 2.49 (dd, 1 H, *J* = 2.4, 5.1 Hz), 2.70 (dd, 1 H, *J* = 3.9, 5.1 Hz), 3.22 (dd, 1 H, *J* = 2.4, 3.9 Hz), 7.17–7.45 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ = 11.2, 13.9, 25.1, 46.8, 54.1, 126.2, 128.7, 129.1, 135.7. MS: *m/z* (%) = 192 (4) [M^+], 147 (6), 123 (82), 110 (33), 91 (35), 77 (33), 65 (58), 45 (89), 39 (100). Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.30; H, 5.68; S, 18.04.