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Synthesis of sulfur-containing *exo*-bicyclic dienes and their Diels-Alder reactions to access thiacycle-fused polycyclic systems

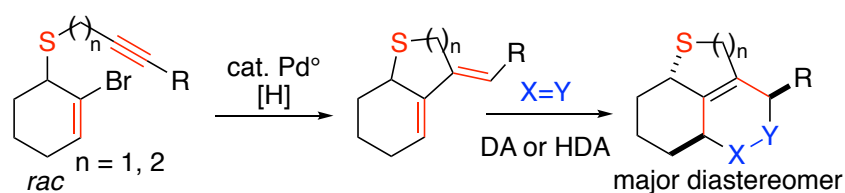
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Abstract. The stereocontrolled synthesis of unprecedented sulfur-containing *exo*-bicyclic 1,3-dienes is reported through a palladium-catalyzed reductive cyclization of sulfur-linked 2-bromoalkynes. The fused bicyclic structure provides a better stability to the thiacyclic diene, compared to the simple 3,4-dimethylenetetrahydrothiophene. Their reactivity towards several dienophiles has been investigated and various original thiacycle-fused polycyclic systems have been obtained, with high or total diastereoselectivity. Moreover, they are the first *exo*-bicyclic dienes used in Diels-Alder reactions. The relative configurations of four cycloadducts have been unambiguously assigned by X-ray crystallographic analysis. Mechanistic details of the cycloadditions have been examined by computational means.

Introduction

Sulfur-heterocycles (often called thiacycles) are important constituents of biologically active molecules for pharmaceutical industry.¹ Therefore, providing new complex structures containing a thiacycle as potential drug candidates, represents a topical research subject.

As part of our interest in accessing various S-heterocycles, we have envisioned to access new sulfur-containing fused polycyclic systems via [4+2] cycloadditions involving *exo*-thiacyclic 1,3-dienes. Indeed, *exo*-cyclic 1,3-dienes² are widely used partners in Diels-Alder (DA) reactions, due both to their high reactivity provided by their fixed *s-cis* conformation, and their synthetic usefulness consisting in the direct access to fused bicyclic structures, which are often found in natural products.³ Various efficient methodologies have been developed to synthesize *exo*-cyclic dienes, including palladium-catalyzed⁴ and radical cyclizations.⁵

As far as the sulfur series is concerned, *exo*-thiacyclic 1,3-diene **I**, namely the 3,4-dimethylenetetrahydrothiophene (Figure 1), has been prepared by Gaoni and Sadeh from 2,3-bis(bromomethyl)-1,3-butadiene and sodium sulfide, then used in a Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMADC) as dienophile.⁶ The authors noted the instability of this diene resulting mostly in its transformation into the corresponding 3,4-dimethylthiophene and its very fast polymerization in the free states. *Exo*-bicyclic S-containing dienes of type **II** (Figure 1) should provide a better stability due to hyperconjugation effect brought by the substituents on the double bonds and the bicyclic structure. Therefore, we decided to synthesize these hitherto unknown 1,3-dienes and to investigate their reactivity in [4+2] cycloadditions. Access to these bicyclic structures bearing a stereogenic carbon center next to the sulfur atom was first envisaged in the racemic form. After cycloaddition, the thiacycle-fused polycyclic cycloadducts thereby produced should have interesting 3D-structures, the stereochemistry of the newly formed stereogenic centers being governed both by the existing stereocenter and by the cycloaddition process itself, in line with modern concepts in drug discovery.⁷

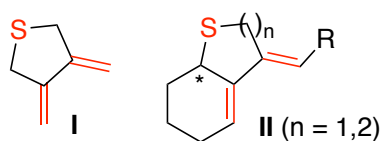


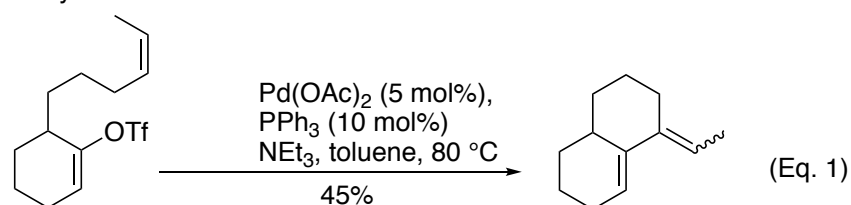
Figure 1. Known *exo*-thiacyclic diene **I** and envisaged more stable *exo*-bicyclic dienes **II**

A literature survey revealed that while *exo*-monocyclic dienes are abundant, *exo*-bicyclic dienes are rarely encountered. Only a few examples of these 1,3-dienes have been reported (Scheme 1): the carbo-bicyclic (Eq. 1),⁸ and aza-bicyclic (Eq. 2)⁹ dienes were obtained *via* an intramolecular Heck reaction, and the oxacyclic dienes were generated via radical cyclizations using Bu₃SnH/AIBN system or SmI₂ (Eq. 3).¹⁰ These methods afforded

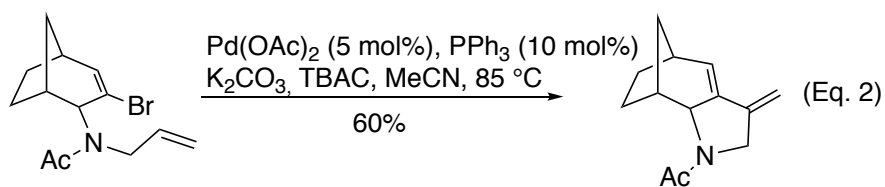
the 1,3-dienes as a mixture of *E/Z* isomers.¹¹ Noteworthy, the reactivity in Diels-Alder reactions of these *exo*-bicyclic dienes has not been examined so far.

The powerful synthetic tool represented by the palladium-catalyzed domino cyclizations¹² together with our experience in using sulfides as substrates for these reactions,¹³ prompted us to envisage 5- or 6-*exo*-dig *syn*-cyclocarbopalladation/reduction sequences to generate the sulfur containing *exo*-bicyclic 1,3-dienes. This process should lead to an exclusive *Z*-geometry of the generated double bond, as a result of the well established *syn*-carbopalladation mechanism.⁴ We report herein the preparation of racemic dienes **II** and their use in Diels-Alder or hetero-Diels-Alder (HDA) reactions to access unprecedented S-containing polycyclic compounds (Scheme 1, Eq. 4).

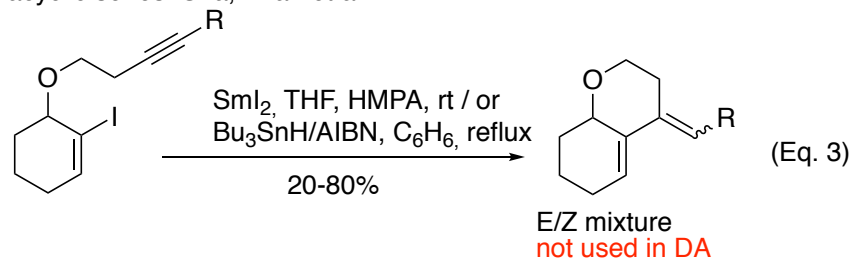
Carboxylic series: Tietze et al.⁸



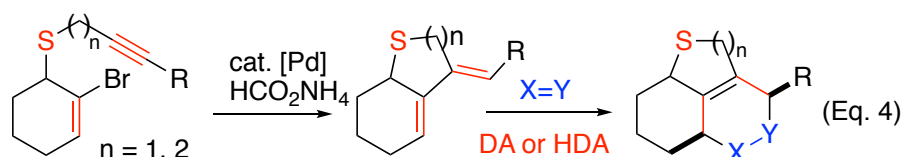
Azacyclic series: Grigg et al.⁹



Oxacyclic series: Sha, Zhan et al.¹⁰



Thiacyclic series: **this work**

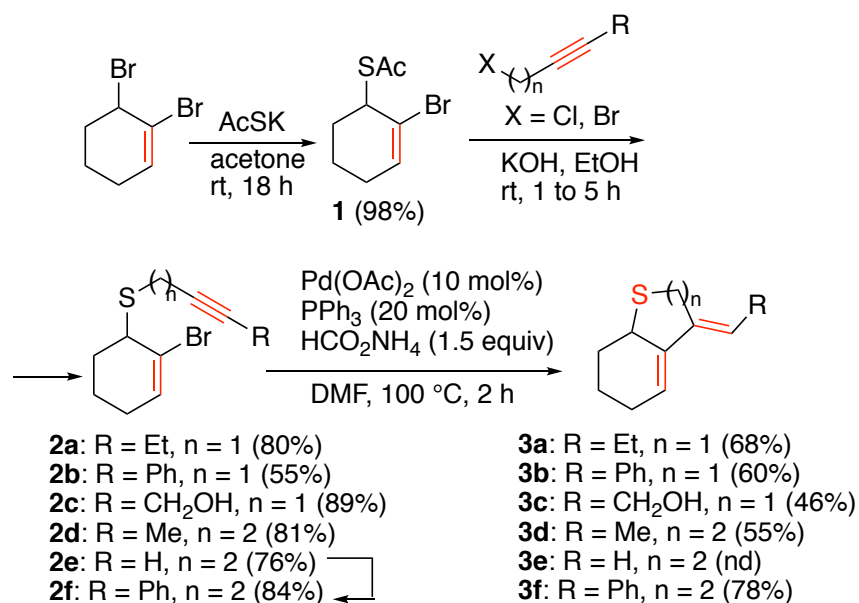


Scheme 1. Syntheses of *exo*-bicyclic dienes

Results and discussion

We first prepared thioacetic ester **1** from 1,6-dibromocyclohex-1-ene and potassium thioacetate, then used it as the starting material to access sulfur-linked 2-bromo-1,6- and 2-bromo-1,7-enynes **2**, which are the suitable precursors of the desired dienes **3** (Scheme 2).

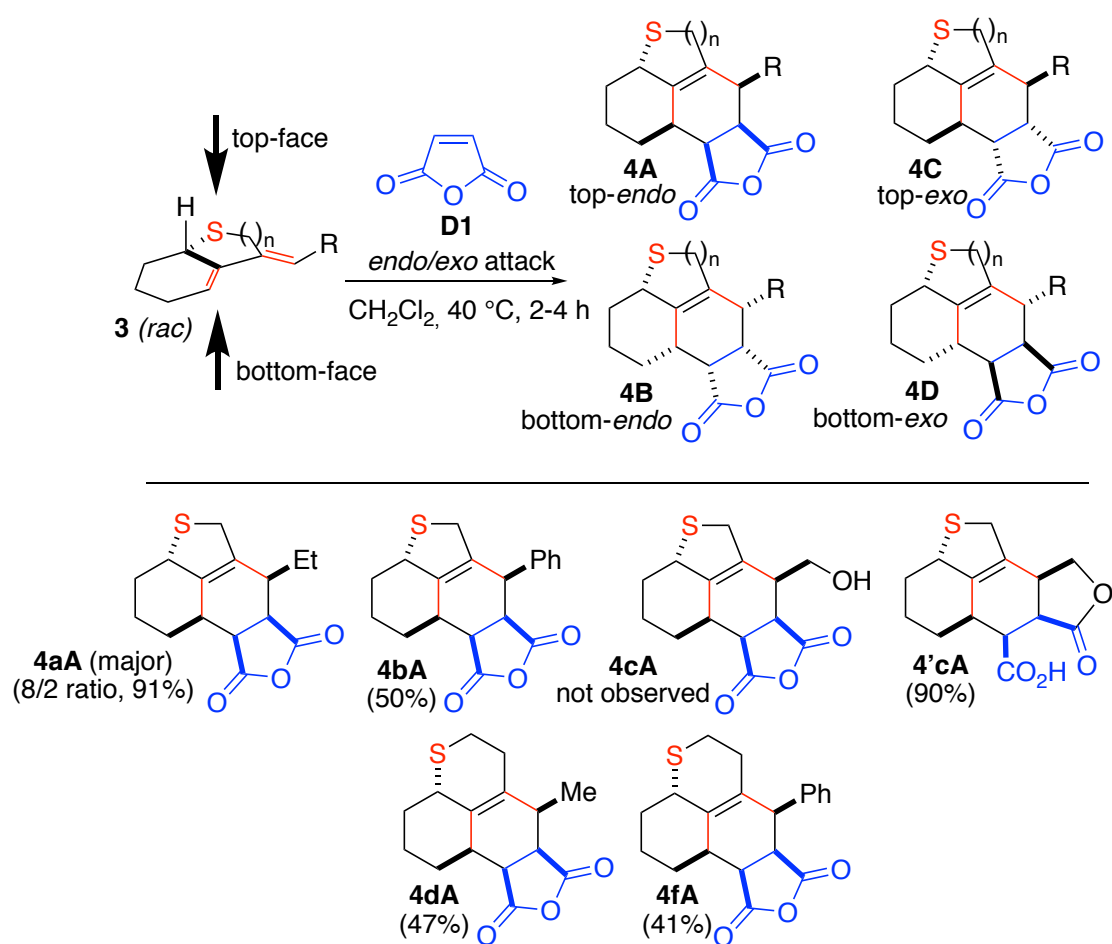
Sulfides **2a-f** have been synthesized with satisfactory yields from **1** and the corresponding propargyl or homopropargyl halide, with different R substituents on the triple bond. Sulfide **2f** was obtained by introducing a phenyl group on the terminal alkyne of **2e** via a Sonogashira cross-coupling. These substrates have been then reacted under Pd-catalyzed reaction conditions in the presence of ammonium formate as the hydrogen donor.¹⁴ Gratifyingly, the reductive cyclization sequence led to the desired *exo*-bicyclic dienes **3a-d,f** in moderate to good yields. The *Z*-geometry of the newly formed double bond is assumed considering the *syn*-carbopalladation/reduction process, and no trace of another isomer of the diene was detected by NMR analysis. Once again the use of sulfur-containing compounds was compatible with the Pd-catalysis conditions. Only diene **3e** (R = H) was obtained in a disappointing yield (22% by ¹H NMR) and could not be isolated in a pure form. This is probably due to competitive S-depropargylation reaction in the presence of the palladium catalyst, occurring more easily on the terminal alkynyl substrate **2e**.¹⁵ The method is efficient for both accessing 5- and 6-membered rings bearing either alkyl, phenyl or hydroxymethyl terminal groups. Indeed, the fused bicyclic dienes provide a better stability to these thiacyclic dienes, compared to 3,4-dimethylenetetrahydrothiophene **I**, as they can be isolated by column chromatography and stored at least one week at room temperature.



Scheme 2. Synthesis of sulfur-containing *exo*-bicyclic dienes **3**

With these thiacyclic dienes in hands, we then envisaged their involvement in Diels-Alder reactions with a range of four electron-deficient symmetrical dienophiles: maleic anhydride **D1**, N-phenylmaleimide **D2**, dimethylacetylene dicarboxylate **D3**, and 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione **D4**. All products are obtained in a racemic form and their relative configurations are represented in all schemes.

First, all isolated dienes were reacted with maleic anhydride **D1**, in dichloromethane, at 40 °C (Scheme 3). A complete consumption of the diene was observed within 2 to 4 hours. Theoretically, the cycloaddition between diene **3** and dienophile **D1** can lead to four couples of diastereomeric cycloadducts **4A-D**, arising from the four possible approaches: two from the top/bottom face of the diene and two according to the *endo/exo* orientations. The reaction with **3a** led to a mixture of two inseparable diastereomers in 8:2 ratio (91% yield). NMR analyses (NOEDIFF correlations) indicated that the major cycloadduct resulted from the expected *endo*-attack, however it was difficult to distinguish between **4aA** and **4aB**.



Scheme 3. Diels-Alder reactions of *exo*-bicyclic dienes **3** with **D1** (ratio diene/**D1** 1.1:1)

In the case of the phenyl substituted diene **3b**, the formation of a single diastereomer was observed. The relative stereochemistry of the isolated adduct **4bA** (50% yield) was unambiguously assigned by an X-ray crystallographic analysis (Figure 2) and confirmed the favored *endo* approach from the less hindered face of the diene (top-face), opposite to the S-containing ring. Then, in the reaction between **D1** and diene **3c** the product **4'cA** was obtained as the only adduct in 90% yield. In this case the cycloaddition was followed by an intramolecular lactonization occurring on cycloadduct **4cA** and leading to **4'cA**.¹⁶ X-Ray crystallographic analysis on a monocrystal also confirmed the structure and the relative stereochemistry of the product in this case (Figure 3). The cycloaddition of **D1** with the 6-membered ring *exo*-bicyclic dienes **3d** and **3f** led to a single diastereomer, **4dA** (47% yield) and **4fA** (41% yield), respectively. Crystals obtained from **4fA** allowed to obtain an X-ray structure (Figure 4), which revealed that its relative stereochemistry was similar to **4bA**. The relative configurations of **4aA** and **4dA** were then assigned by analogy with the previous results.

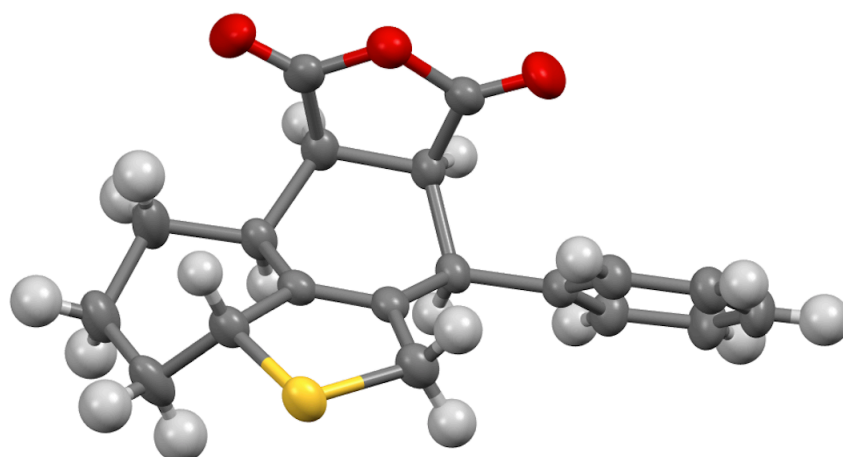


Figure 2. X-ray structure of **4bA** (50% probability ellipsoids)

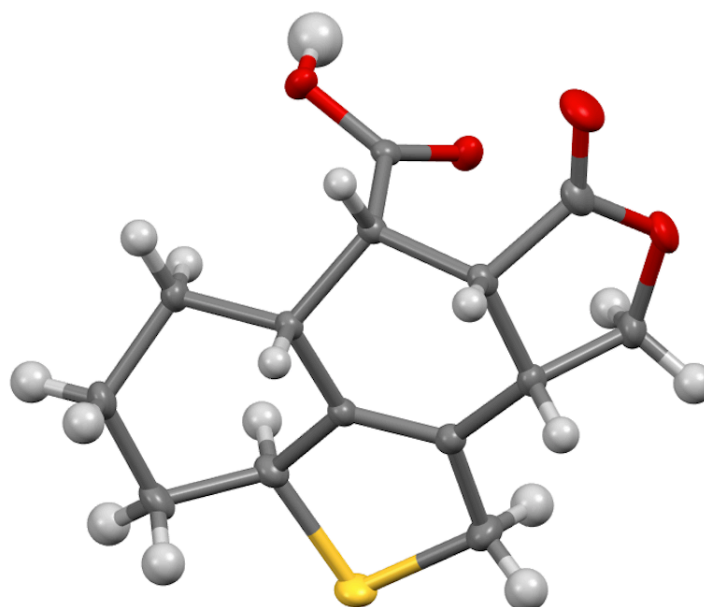


Figure 3. X-ray structure of **4cA** (50% probability ellipsoids)

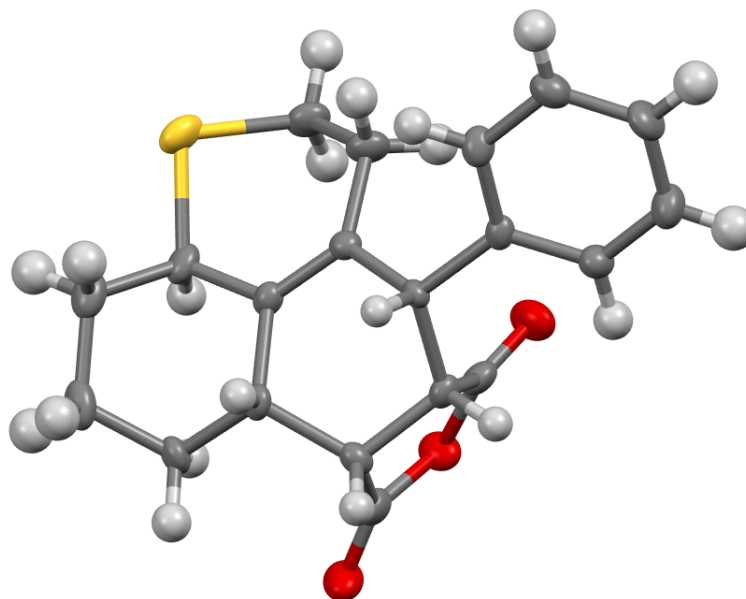
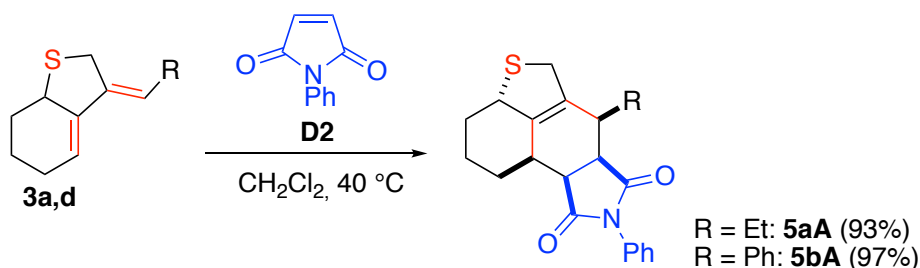


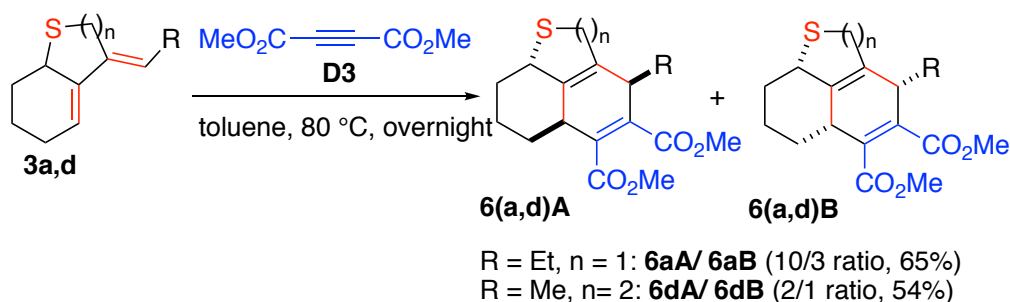
Figure 4. X-ray structure of **4fA** (50% probability ellipsoids)

N-Phenylmaleimide **D2** was then reacted with dienes **3a** and **3b** under the same reaction conditions. In both cases only one diastereomer was formed and we assume that they are respectively **5aA** (93% yield) and **5bA** (97% yield), having the same relative configurations than those obtained with **D1** (Scheme 4).



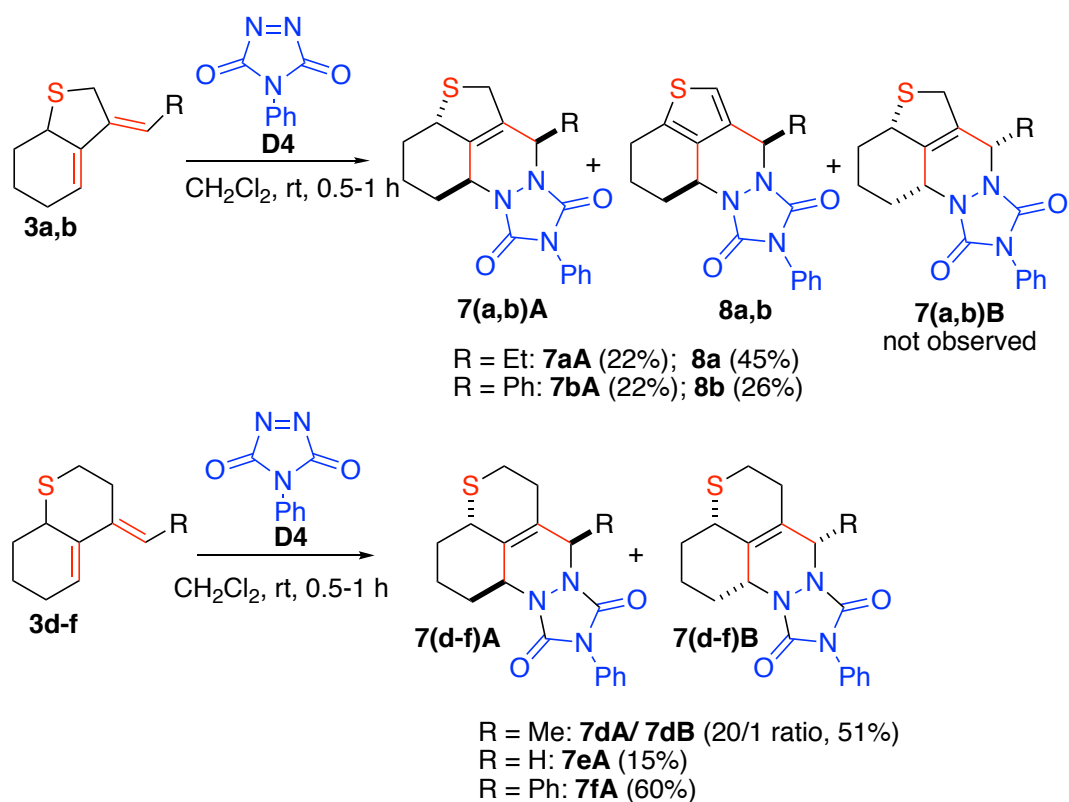
Scheme 4. Diels-Alder reactions of *exo*-bicyclic dienes **3a,b** with **D2** (ratio diene/**D2** 1.1:1)

Dimethylacetylene dicarboxylate **D3** was then reacted with dienes **3a**, **3b**, and **3d**. Heating in toluene at 80 °C overnight was necessary to get completion in this case. Cycloadducts **6a** and **6d** were obtained as a mixture of two diastereomers (A/B) in 10:3 and 2:1 ratio, respectively (Scheme 5). Very probably, similarly to the previous cases, the major products are respectively **6aA** and **6dA**, resulting from the top-face approach of the diene. The product resulting from **3b** decomposed and could not be characterized.



Scheme 5. Diels-Alder reactions of *exo*-bicyclic dienes **3** with **D3** (ratio diene/**D3** 1:1.5)

Hetero-Diels-Alder (HDA) reactions have been then attempted with an aza-dienophile, the 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione **D4** (Scheme 6). The reactions were performed in dichloromethane, at room temperature, until complete consumption of the substrates was observed (0.5 to 1 hour). Both 5-membered ring dienes **3a** and **3b** led to a mixture of two separable products in 1:2 and 1:1 ratio, respectively. The two products derived from **3a** have been identified as cycloadduct **7aA** (22% yield) and the corresponding thiophene derivative **8a** (45% yield), formed by a dehydrogenative aromatization of the dihydrothiophene ring of the cycloadduct **7a**. Dienophile **D4** is probably involved in this latter transformation and further studies will be done to propose a plausible mechanism. Similarly, products **7bA** and **8b** resulting from diene **3b** have been isolated in 22% and 26% yield, respectively. The structure of **8b** was confirmed by X-ray crystallographic analysis (Figure 5). In the cases of 6-membered ring exocyclic dienes, the oxidation of the thiacycle did not occur, and only the expected cycloaddition products were obtained. The reaction between **D4** and diene **3d** led to a 20:1 mixture of diastereomers, whereas diene **3f** led to a single diastereomer, which was isolated in 60% yield. By adding **D4** at room temperature to the crude diene **3e**, the expected product was also obtained as a single diastereomer, however with a low isolated yield of 15%. Assignments of the relative configurations of the major (or single) cycloadducts (**7aA**, **7bA**, **7dA**, **7eA**, **7fA**) were done by analogy with the previous results, which correspond to a top-face approach of the diene (Scheme 6).



Scheme 6. Hetero-Diels-Alder reactions of *exo*-bicyclic dienes **3** with **D4** (ratio diene/**D4** 1:2)

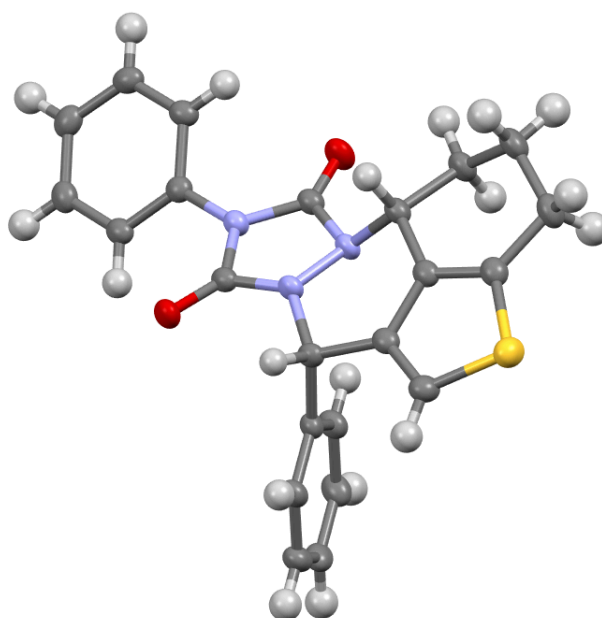
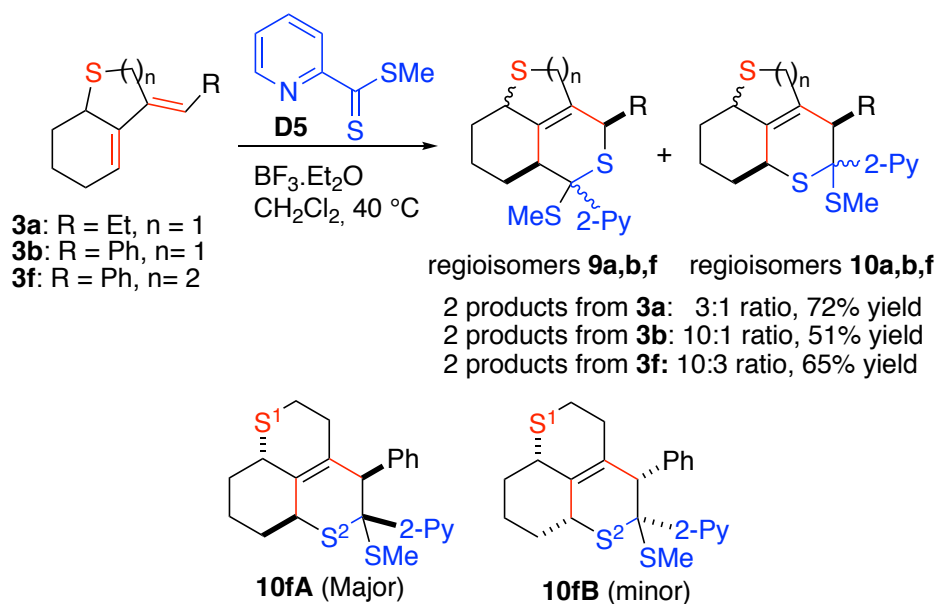


Figure 5. X-ray structure of **8b** (50% probability ellipsoids)

We finally explored the more challenging HDA-reaction with the dithioester heterodienophile **D5**,¹⁷ in order to obtain structures containing two sulfur-heterocycles

(Scheme 7). As this dienophile is non-symmetric, two regioisomeric cycloadducts can be expected, each one with four relative stereochemistries mentioned before. The reaction was performed in dichloromethane, at room temperature, in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as Lewis acid to activate the dienophile. An inseparable mixture of two products in 3:1 ratio, was obtained with diene **3a**, however we were not able to determine their structures, since the products decomposed fast. The reactions of **D5** with dienes **3b** and **3f** also afforded mixtures of two products in a ratio of 10:1 and 10:3, respectively. In the case of the two cycloadducts resulted from **3f**, a series of NMR experiments indicate that they correspond to two diastereomers of regioisomer **10f**, of which the relative configurations differ at the CHS^1 carbon-stereocenter, as the result of the top/bottom approaches. It was however difficult to categorically conclude on the relative configurations at the CHS^2 carbon-stereocenter (*endo* vs *exo* approach relative to pyridyl), although several NOESY-2D and selective NOESY-1D experiments match well with products **10fA** (major) and **10fB** (minor) having pyridyl and phenyl substituents in a *cis* relationship (*endo* approach). Geometry optimization of **10fA** and **10fB** (DFT calculations) is also in agreement with this assignment (see in Supporting Information).

The overall results showed that the stereochemical course of the Diels-Alder reaction involving *exo*-bicyclic dienes **3** did not depend on the tethered ring-size, as both five and six-membered thiacyclic dienes give high selectivities. The cycloadducts resulting from five-membered thiacyclic dienes and aza-dienophile **D4** are prone to aromatization into the corresponding thiophene derivatives. Concerning the nature of the substituent on the triple bond, a phenyl substituent led to slightly better selectivity than an alkyl one.



Scheme 7. thia-Diels-Alder reactions of *exo*-bicyclic dienes **3** (ratio diene/**D5** 1.1:1)

Theoretical study

In order to get a better insight into the mechanistic details of these cycloadditions, we then examined the course of the reaction by computational means. DFT calculations were performed at the wB97XD/6-31+G(d,p) level of theory, including dispersion terms, which proved appropriate for similar organic systems¹⁸ (see SI for the results obtained with other functionals, basis sets and inclusion of solvent effects). Computations were first effected with diene **3b** and maleic anhydride (**D1**) as dienophile. Optimization of the diene conformation expectedly showed a half-chair conformational preference for the cyclohexenyl moiety. An energy minimum was found for the conformer with a C=C-C=C dihedral angle of 42.2°. Evaluation of the frontier orbitals energies confirmed the preferential interaction between the HOMO of diene **3b** and the LUMO of dienophile **D1**, and thus the normal electron demand character of the cycloaddition process. Quantitative evaluation of the preferred pathway on the activation energy was then undertaken, by localization of the transition states (TS) of the cycloaddition. Four arrangements were considered, depending on the face approach: top/bottom approach of the dienophile and the *endo/exo* orientations (Figure 6). The cycloaddition proved exergonic in each case. The most favored transition states were found to be 20.57 kcal.mol⁻¹ above the reactants for the top-*endo* approach (**A**) and 23.57 kcal.mol⁻¹ for the top-*exo* one (**C**). The bottom-*endo* TS (**B**) was slightly higher in energy (24.37 kcal.mol⁻¹) while the bottom-*exo* (**D**) one proved to be the least favorable (27.68 kcal.mol⁻¹).

Considering the reaction is under kinetic control, the 3.00 kcal.mol⁻¹ difference between the two most favoured TS should thus allow for a good if not complete stereocontrol of the cycloaddition. Experimentally, the only stereoisomer formed and isolated when interacting **3b** with **D1** proved to be **4bA**. These DFT calculations are thus in line with these results since the top-*endo* TS indeed leads to cycloadduct **4bA**. The process appeared to be concerted and slightly asynchronous, the lengths of the forming bonds CH^{cyclo}-C^{dienophile} and CH^{Ph}-C^{dienophile} being in the same range, 2.10 Å and 2.36 Å, respectively for the most favored top-*endo* TS. The phenyl substituent of the diene moiety was not conjugated with the double bond but the dihedral angle C^{diene}=C^{diene}H-C^{Ph}=C^{Ph}H was small (23.95°). All attempts to find zwitterionic intermediates were unsuccessful.

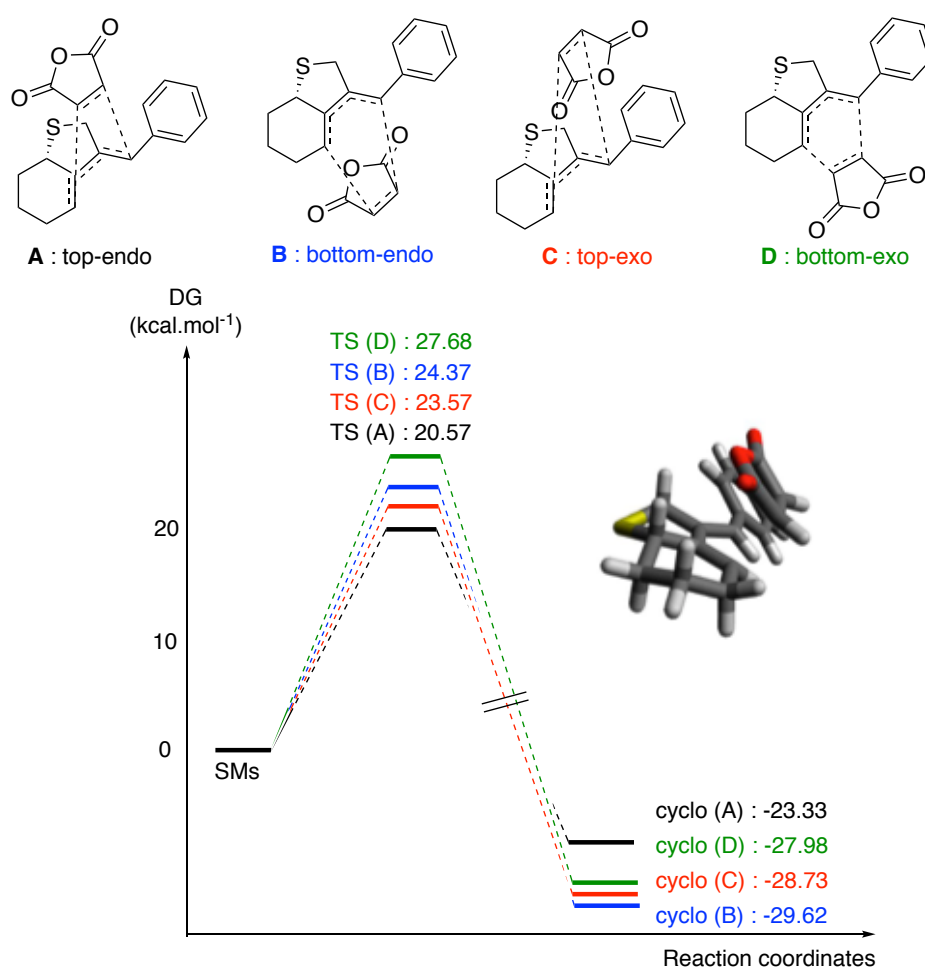


Figure 6. Schematic representation of the energy profile for the cycloaddition between **3b** and **D1**

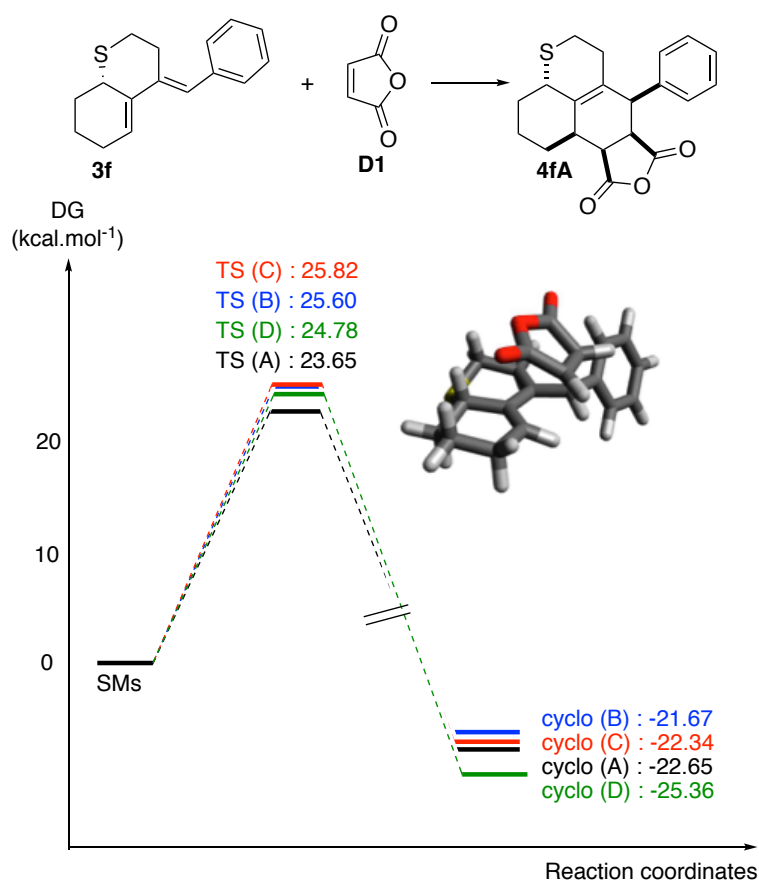


Figure 7. Schematic representation of the energy profile for the cycloaddition between **3f** and **D1**

Computations involving the 6-membered ring diene **3f** and diene **D1** led to similar results. In this case also the *top-endo* approach (**A**) is also the most favored one, in line with the experimental results, albeit a much lower energy difference between the two most favorable TS is observed (Figure 7). Interestingly, the phenyl moiety of the diene is not conjugated with the dienic part (with a $C^{\text{diene}}=\text{CH}-\text{C}=\text{C}(\text{Ph})\text{H}$ dihedral angle of 54.5°) in the optimized diene and is quasi perpendicular to the dienic part in the *top/endo* most favored TS (the $C^{\text{diene}}=\text{C}^{\text{diene}}\text{H}-\text{C}^{\text{Ph}}=\text{C}^{\text{Ph}}\text{H}$ dihedral angle being 78.48°), in sharp contrast with the 5-membered ring system. The process remains a concerted, asynchronous one with the lengths of the forming bonds being 2.47 \AA and 2.08 \AA $\text{CH}^{\text{cyclo}}-\text{C}^{\text{dienophile}}$ and $\text{CH}^{\text{Ph}}-\text{C}^{\text{dienophile}}$, respectively for the most favored *top-endo* TS. Noteworthy, the asynchronicity is more important, with the 6-membered ring system, and the smallest forming bond is not the same, highlighting the strong influence of the thiacycle on the cycloaddition reaction.

Conclusions

In summary, we developed a stereocontrolled synthesis of new sulfur-containing *exo*-bicyclic 1,3-dienes, based on palladium-catalyzed reductive cyclization of sulfur-linked 2-bromoenyne. The method is efficient for both accessing 5- and 6-membered thiacyclic dienes. They have been reacted with several electron-deficient dienophiles leading to various original thiacycle-fused polycyclic systems, with high or total diastereoselectivity. Mechanistic details of the cycloadditions have been examined by computational means and the conclusions were in agreement with the experimental results.

Experimental Part

General information. Reagents were obtained from commercial sources and used without any further purification. Thin layer chromatography was performed on silica gel 60 F254 plates.

NMR spectra were recorded at 400 or 500 MHz for ^1H and at 100 or 125 MHz for ^{13}C . Chemical shifts are reported in parts per million (ppm) relative to residual solvent and coupling constants (J) are reported in hertz (Hz). CDCl_3 was filtered previously on basic alumina. Assignments of ^1H and ^{13}C signal were made by DEPT, COSY, HSQC, HMBC, ADEQUATE, NOESY-2D, and selective NOESY-1D experiments. HRMS were performed with a Q-TOF analyzer Agilent 1200, using either electrospray ionization (ESI) at $T_{\text{source}} = 340\text{ }^\circ\text{C}$, $V_{\text{cap}} = 4000\text{ V}$, or atmospheric pressure chemical ionization (APCI) at $T_{\text{gas}} = 300\text{ }^\circ\text{C}$, $T_{\text{vap}} = 380\text{ }^\circ\text{C}$, $V_{\text{corona}} = 4\mu\text{A}$, or with an Agilent 7890 analyzer by using GC-MS (FI or EI). Melting points were determined in open capillary tubes and are uncorrected.

(2-bromocyclohex-2-en-1-yl) ethanethioate (1). To a solution of 1,6-dibromocyclohex-1-ene (240 mg, 1 mmol, 1 equiv) in acetone (200 mL), potassium thioacetate (126 mg, 1.1 mmol, 1.1 equiv) was added. The reaction mixture was stirred at room temperature for one night. After filtration of the potassium bromide salts, the filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (heptane) to afford thioacetate **1** (235 mg, 100% yield).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 1.59 (m, 1H), 1.75 (m, 1H), 1.96 (m, 1H), 2.09-2.18 (m, 3H), 2.35 (s, 3H, CH_3), 4.37 (bs, 1H, SCH), 6.19 (t, $J = 4.0\text{ Hz}$, 1H, $\text{C}=\underline{\text{CH}}$). $^{13}\text{C NMR}$ (CDCl_3 , 100.6 MHz) δ 17.9 (CH_3), 27.4 (CH_2), 30.5 (CH_2), 31.7 (CH_2), 48.2 (SCH), 120.3 (CBr), 133.8 ($\text{C}=\underline{\text{CH}}$), 194.6 ($\text{C}=\text{O}$).

Synthesis and characterization of sulfides (2a-f)

(2-bromocyclohex-2-en-1-yl)(pent-2-yn-1-yl)sulfane (2a) To a solution of KOH (657 mg, 11.7 mmol, 1.5 equiv) in ethanol (130 mL), thioacetate **1** (1.83 g, 7.80 mmol, 1 equiv) and 3-(ethyl)propargyl bromide (1.26 g, 8.58 mmol, 1.1 equiv) were added successively. The reaction mixture was stirred at room temperature for 15 min. After evaporation of the solvent, hydrolysis by water and extraction with ether, the organic layers were separated, dried with MgSO_4 and the solution was concentrated

under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: heptane) to afford **2a** (1.6 g, 80% yield).

¹H NMR (CDCl₃, 400 MHz) δ 1.16 (t, *J* = 7.5 Hz, 3H, CH₃), 1.71 (m, 1H), 1.86 (m, 1H), 2.04-2.17 (m, 4H, 2xCH₂), 2.24 (tq, *J* = 2.3, 7.6 Hz, 2H, CH₃CH₂), 3.39 (t, *J* = 2.3 Hz, 2H, SCH₂), 3.70 (s, 1H, SCH), 6.16 (t, *J* = 3.8 Hz, 1H, BrC=CH). **¹³C NMR** (CDCl₃, 100.6 MHz) δ 12.5 (CH₃), 14.0 (CH₃CH₂), 13.3 (SCH₂), 20.9 (CH₂), 20.5 (CH₂), 30.9 (CH₂), 49.4 (SCH), 74.9 (Cq), 85.4 (Cq), 122.4 (CBr), 132.5 (BrC=CH). **HRMS (FI+eiFi) m/z:** [M⁺] calculated for C₁₁H₁₅BrS 258.0078, found 258.0083.

(2-bromocyclohex-2-en-1-yl)(3-phenylprop-2-yn-1-yl)sulfane (2b) To a solution of KOH (716 mg, 12.8 mmol, 1.5 equiv) in ethanol (78 mL), thioacetate **1** (2 g, 8.5 mmol, 1 equiv) and (3-chloroprop-1-yn-1-yl)benzene (1.28 g, 8.5 mmol, 1 equiv) were added successively. The reaction mixture was stirred at room temperature for one hour. After evaporation of the solvent, hydrolysis by water and extraction with ether, the organic phases were separated, dried with MgSO₄ and the solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (heptane) to afford **2b** (1.43 g, 55% yield).

¹H NMR (CDCl₃, 400 MHz) δ 1.70 (m, 1H), 1.85 (m, 1H), 1.94-2.17 (m, 4H, CH₂), 3.62 (s, 2H, SCH₂), 3.77 (bs, 1H, SCH), 6.11 (t, *J* = 4.0 Hz, 1H, BrC=CH), 7.21-7.26 (m, 3H), 7.37-7.39 (m, 2H). **¹³C NMR** (CDCl₃, 100.6 MHz) δ 17.5 (SCH₂), 21.5 (CH₂), 27.74 (CH₂), 31.19 (CH₂), 49.90 (SCH), 83.70 (Cq), 85.54 (Cq), 122.37 (Cq), 123.1 (Cq), 128.4 (CH), 128.5 (2xCH), 131.9 (2xCH), 133.0 (CBr). **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₁₅H₁₆BrS 307.0151, found 307.0143.

4-((2-bromocyclohex-2-en-1-yl)thio)but-2-yn-1-ol (2c) To a solution of KOH (286 mg, 5.10 mmol, 1.5 equiv) in ethanol (40 mL), thioacetate **1** (800 mg, 3.40 mmol, 1 equiv) and 4-chlorobut-2-yn-1-ol (391 mg, 3.74 mmol, 1.1 equiv) were added successively. The reaction mixture was stirred at room temperature for 5 hours. After evaporation of the solvent, hydrolysis by NH₄Cl and extraction with ether, the organic layers were separated, dried on Na₂SO₄ and the solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (heptane/AcOEt 80/20) to afford **2c** (789 mg, 89%).

¹H NMR (CDCl₃, 400 MHz) δ 1.71 (m, 1H), 1.83 (m, 1H), 2.04-2.17 (m, 4H, 2xCH₂), 3.41 (s, 2H, SCH₂), 3.66 (s, 1H, SCH), 4.30 (d, *J* = (5.1 Hz, 2H, OCH₂), 6.15 (dd, *J* = 4.6, 3.5 Hz, 1H, BrC=CH). **¹³C NMR** (CDCl₃, 100.6 MHz) δ 17.5 (CH₂), 20.7 (CH₂), 27.7 (CH₂), 31.1 (SCH₂), 49.7 (SCH), 51.5 (OCH₂), 81.7 (Cq), 82.1 (Cq), 122.2 (CBr), 133.0 (C=CH). **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₁₀H₁₄BrOS 260.9943, found 260.9938.

(2-bromocyclohex-2-en-1-yl)(pent-3-yn-1-yl)sulfane (2d) To a solution of KOH (260 mg, 4.6 mmol, 1.5 equiv) in ethanol (40 mL), S-(2-bromocyclohex-2-en-1-yl) thioacetate **1** (730 mg, 3 mmol, 1 equiv), 18-crown-6 (170 mg ; 0,46 mmol, 0,15 equiv), and then 5-bromopent-2-yne (670 mg, 3.7

mmol, 1.2 equiv) were added successively. The reaction mixture was stirred at room temperature for 3 hours. After evaporation of the solvent, ether was added, then the insoluble solid removed by filtration. The solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (heptane/AcOEt 99:1) to afford **2d** (653 mg 81% yield).

¹H NMR (CDCl₃, 400 MHz) δ 1.67 (m, 1H), 1.77 (s, 3H, CH₃), 1.79 (m, 1H), 2.03-2.08 (m, 4H, 2xCH₂), 2.43-2.45 (m, 2H, CH₂), 2.75 (t, J = 7.4 Hz, 2H, SCH₂), 3.46 (s, 1H, SCH), 6.08 (t, J = 3.8 Hz, 1H, CBr=CH). ¹³C NMR (CDCl₃, 100.6 MHz) δ 3.7 (CH₃), 17.5 (CH₂), 20.7 (CH₂), 27.6 (CH₂), 31.7 (CH₂), 32.3 (CH₂), 50.1 (SCH), 70.0 (≡C), 76.9 (≡C), 122.9 (CBr), 132.3 (=CH). **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₁₁H₁₆BrS 259.0151, found 259.0141.

(2-bromocyclohex-2-en-1-yl)(but-3-yn-1-yl)sulfane (**2e**). To a solution of KOH (358 mg, 6.3 mmol, 1.5 equiv) in ethanol (40 mL), S-(2-bromocyclohex-2-en-1-yl) thioacetate **1** (1 g, 4.25 mmol, 1 equiv), 18-crown-6 (169 mg, 0.63 mmol, 0.15 equiv), and 4-bromobut-1-yne (566 mg, 4.25 mmol, 1 equiv) were added successively. The reaction mixture was stirred at room temperature for 3 hours. After evaporation of the solvent, ether was added, then the insoluble solid was removed by filtration. The solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (heptane/AcOEt) to afford **2e** (791 mg 76% yield).

¹H NMR (CDCl₃, 400 MHz) δ 1.67 (m, 1H), 1.83 (m, 1H), 2.03-2.12 (m, 5H, 2xCH₂ & C≡CH), 2.49-2.56 (m, 2H, CH₂), 2.82 (t, J = 7.4 Hz, 2H, SCH₂), 3.47 (s, 1H, SCH), 6.11 (t, J = 3.8 Hz, 1H, CBr=CH). ¹³C NMR (CDCl₃, 100.6 MHz) δ 17.4 (CH₂), 20.4 (CH₂), 27.6 (CH₂), 31.7 (2xCH₂), 50.2 (SCH), 69.6 (HC≡), 82.7 (≡C), 122.7 (CBr), 132.5 (=CH). **HRMS (APCI/Q-TOF) m/z:** [M+H⁺] calculated for C₁₀H₁₄BrS 245.0000, found 244.9987

(2-bromocyclohex-2-en-1-yl)(4-phenylbut-3-yn-1-yl)sulfane (**2f**). Under argon atmosphere, were added successively copper iodide (0.1 equiv, 0.04 mmol, 7.7 mg), Pd(OAc)₂ (4.6 mg, 0.02 mmol, 0.05 equiv), PPh₃ (10.7 mg, 0.04 mmol, 0.1 equiv), phenyl iodide (120 mg, 0.4 mmol, 1 equiv), then the mixture was dissolved in distilled diisopropylamine (1 mL). Then, homopropargyl sulfide **2e** (107 mg, 0.4 mmol, 1 equiv) was added and the mixture was stirred at room temperature for 12h. The reaction mixture was then filtered through Celite to eliminate the metal traces and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent: heptane/AcOEt 95/5), to afford pure **2f** (108 mg 84% yield).

¹H NMR (CDCl₃, 400 MHz) δ 1.67 (m, 1H), 1.86 (m, 1H), 2.07-2.11 (m, 4H, 3xCH₂), 2.75-2.78 (m, 2H, CH₂), 2.87-2.91 (m, 2H, SCH₂), 3.54 (s, 1H, SCH), 6.15 (t, J = 3.8 Hz, 1H, CBr=CH), 7.26-7.28 (m, 3H), 7.39-7.41 (m, 2H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 17.5 (CH₂), 21.5 (CH₂), 27.6 (CH₂), 31.7 (CH₂), 32.0 (CH₂), 50.2 (SCH), 81.8 (≡C), 88.3 (PhC≡), 122.9 (Cq), 123.7 (Cq), 128.0 (CH), 128.4 (2xCH), 131.8 (2xCH), 132.5 (CH). **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₁₆H₁₈BrS 321.0313, found 321.0309.

Synthesis and characterization of dienes (3a-f). General procedure: To a solution of sulfide **2** (1 equiv) in DMF, were successively added ammonium formate (1.5 equiv), Pd(OAc)₂ (0.1 equiv) and PPh₃ (0.2 equiv). After 2 h at 100 °C, the reaction mixture was cooled to room temperature and water was added to remove the DMF. After extraction with ethyl acetate, the combined organic phases were washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/toluene 95/5) to give diene **3**.

(Z)-3-propylidene-2,3,5,6,7,7a-hexahydrobenzo[*b*]thiophene (**3a**). Following the general procedure, sulfide **2a** (456 mg, 1.76 mmol, 1 equiv) was used with ammonium formate (166 mg, 2.64 mmol, 1.5 equiv), Pd(OAc)₂ (39 mg, 0.18 mmol, 0.1 equiv) and PPh₃ (92 mg, 0.35 mmol, 0.2 equiv) to afford diene **3a** as colorless oil (217 mg, 68%).

¹H NMR (CDCl₃, 400 MHz) δ 1.01 (t, *J* = 7.6 Hz, 3H, CH₃), 1.38 (m, 1H), 1.50 (m, 1H), 1.90 (m, 1H), 2.05-2.11 (m, 2H, CH₂CH₃), 2.13-2.22 (m, 3H), 3.49 (s, 2H, SCH₂), 3.74 (m, 1H, SCH), 5.75 (t, *J* = 7.5 Hz, 1H, C=CH), 5.89 (bs, 1H, C=CH). ¹³C NMR (CDCl₃, 100.6 MHz) δ 14.0 (CH₃), 22.4 (CH₂), 22.9 (CH₂), 25.0 (CH₂), 29.5 (CH₂), 31.7 (SCH₂), 46.4 (SCH), 117.6 (C=CH), 122.5 (Cq), 137.7 (C=CH), 140.8 (Cq). HRMS (APCI/Q-TOF) *m/z*: [M+H⁺] calculated for C₁₁H₁₇S 181.1045, found 181.1041.

(Z)-3-benzylidene-2,3,5,6,7,7a-hexahydrobenzo[*b*]thiophene (**3b**). Following the general procedure, sulfide **2b** (498 mg, 1.63 mmol, 1 equiv) was used with ammonium formate (154 mg, 2.44 mmol, 1.5 equiv), Pd(OAc)₂ (36 mg, 0.16 mmol, 0.1 equiv) and PPh₃ (85 mg, 0.32 mmol, 0.2 equiv) to afford diene **3b** as colorless oil (223 mg, 60%).

¹H NMR (CDCl₃, 400 MHz) δ 1.39-1.49 (m, 1H, CH₂), 1.58-1.63 (m, 1H, CH₂), 1.93-1.98 (m, 1H, CH₂), 2.24-2.27 (m, 3H, CH₂), 3.77-3.83 (m, 1H, SCH), 3.84 (s, 2H, SCH₂), 6.13 (s, 1H, C=CH), 6.77 (s, 1H, C=CH), 7.21-7.24 (m, 1H), 7.31-7.35 (m, 4H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 17.5 (CH₂), 21.5 (CH₂), 27.7 (CH₂), 31.2 (SCH₂), 49.9 (SCH), 122.4 (C=CH), 123.2 (C=CH), 128.4 (CH), 128.5 (2xCH), 128.6 (C=CH), 129.0 (Cq), 131.9 (2xCH), 133.0 (C=CH). HRMS (ESI/Q-TOF) *m/z*: [M+H⁺] calculated for C₁₅H₁₇S 229.1045, found 229.1044.

(Z)-2-(5,6,7,7a-tetrahydrobenzo[*b*]thiophen-3(2*H*)-ylidene)ethan-1-ol (**3c**). Following the general procedure, sulfide **2c** (100 mg, 0.38 mmol, 1 equiv) was used with ammonium formate (36 mg, 0.57 mmol, 1.5 equiv), Pd(OAc)₂ (9 mg, 0.04 mmol, 0.1 equiv) and PPh₃ (20 mg, 0.07 mmol, 0.2 equiv) to afford diene **3c** as colorless oil (32 mg, 46%).

¹H NMR (CDCl₃, 400 MHz) δ 1.32-1.41 (m, 2H), 1.55 (m, 1H), 1.90 (m, 1H), 2.13-2.22 (m, 3H), 3.54 (s, 2H, SCH₂), 3.72 (m, 1H, SCH), 4.24 (d, *J* = 6.8 Hz, 2H, OCH₂), 5.93 (t, *J* = 7.0 Hz, 1H, C=CH), 6.01 (bs, 1H, C=CH). ¹³C NMR (CDCl₃, 100.6 MHz) δ 22.1 (CH₂), 24.9 (CH₂), 29.2 (CH₂), 31.4 (CH₂), 45.9 (SCH), 60.5 (OCH₂), 118.4 (C=CH), 119.7 (C=CH), 140.3 (Cq), 140.6 (Cq). HRMS (ESI/Q-TOF) *m/z*: [M+H⁺] calculated for C₁₀H₁₅OS 183.0838, found 183.0829.

(*E*)-4-ethylidene-3,4,6,7,8,8a-hexahydro-2H-thiochromene (**3d**). Following the general procedure, sulfide **2d** (286 mg, 1.1 mmol, 1 equiv) was used with ammonium formate (104 mg, 1.65 mmol, 1.5 equiv), Pd(OAc)₂ (24 mg, 0.11 mmol, 0.1 equiv) and PPh₃ (58 mg, 0.22 mmol, 0.2 equiv), in 1 mL DMF, to afford diene **3d** as colorless oil (110 mg, 55%).

¹H NMR (CDCl₃, 400 MHz) δ 1.53-1.59 (m, 1H), 1.62 (d, *J* = 6.7 Hz, 3H, CH₃), 1.73-1.79 (m, 1H), 1.99-2.05 (m, 2H), 2.11 (m, 1H), 2.28 (m, 1H), 2.67-2.80 (m, 3H), 2.90 (m, 1H), 3.49 (m, 1H, SCH), 5.44 (q, *J* = 7.2 Hz, 1H, C=CH), 5.65 (bs, 1H, C=CH). ¹³C NMR (CDCl₃, 100.6 MHz) δ 13.3 (CH₃), 21.1 (CH₂), 25.9 (CH₂), 29.2 (CH₂), 30.0 (CH₂), 30.7 (CH₂), 40.5 (SCH), 119.8 (CH), 122.1 (CH), 140.2 (Cq), 141.0 (Cq). HRMS (APCI/Q-TOF) *m/z*: [M+H⁺] calculated for C₁₁H₁₇S 181.1045, found 181.1041.

4-methylene-3,4,6,7,8,8a-hexahydro-2H-thiochromene (**3e**). Following the general procedure, sulfide **2e** (100 mg, 0.41 mmol, 1 equiv) was used with ammonium formate (39 mg, 0.61 mmol, 1.5 equiv), Pd(OAc)₂ (9 mg, 0.041 mmol, 0.1 equiv) and PPh₃ (21 mg, 0.082 mmol, 0.2 equiv), in 2 mL DMF, to afford diene **3e**. The crude product obtained (characterized by ¹H-NMR) after extraction was directly used in cycloaddition.

¹H NMR (CDCl₃, 400 MHz) δ 1.5 (t, *J* = 7.5 Hz, 1H), 1.62-1.64 (m, 2H), 2.04-2.07 (m, 2H), 2.48-2.55 (m, 2H), 2.64-2.70 (m, 2H), 2.79-2.86 (m, 1H), 3.46-3.51 (m, 1H), 4.66 (s, 1H, =CH), 4.86 (s, 1H, =CH), 5.78 (s, 1H, =CH).

(*E*)-4-benzylidene-3,4,6,7,8,8a-hexahydro-2H-thiochromene (**3f**). Following the general procedure, to a solution of sulfide **2f** (264 mg, 0.8 mmol, 1 equiv) in DMF (5 mL), were successively added ammonium formate (78 mg, 1.2 mmol, 1.6 equiv, 0.5 mmol), Pd(OAc)₂ (18 mg, 0.08 mmol, 0.1 equiv) and PPh₃ (43 mg, 0.2 mmol, 0.2 equiv). After 2 h at 100 °C, the reaction mixture was cooled to room temperature and water was added to remove the DMF. After extraction with ethyl acetate, the combined organic phases were washed with water, dried with MgSO₄, filtered and concentrated under reduced pressure. The crude material was purified by chromatography (cyclohexane/toluene 95/5) to afford diene **3f** as colorless oil (151 mg, 78%).

¹H NMR (CDCl₃, 400 MHz) δ 1.53-1.59 (m, 2H), 1.81 (m, 1H), 2.08-2.20 (m, 3H), 2.44-2.80 (m, 3H), 3.16 (m, 1H, SCHH), 3.59 (m, 1H, SCH), 5.88 (bs, 1H, C=CH), 6.49 (s, 1H, C=CH), 7.21-7.26 (m, 3H), 7.32-7.34 (m, 2H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 22.0 (CH₂), 26.1 (CH₂), 29.3 (CH₂), 30.0 (CH₂), 32.2 (CH₂), 40.4 (SCH), 123.8 (CH), 125.7 (CH), 126.7 (CH), 128.3 (2xCH), 129.4 (2xCH), 137.8 (Cq), 140.8 (Cq), 142.1 (Cq). HRMS (ESI/Q-TOF) *m/z*: [M+H⁺] calculated for C₁₆H₁₉S 243.1207, found 243.1195.

Diels-Alder reactions. Synthesis and characterization of cycloadducts (4-10)

Cycloadditions of diene (3a)

6-ethyl-1,2,3,3a,6,6a,9a,9b-octahydro-5H-thieno[4',3',2':4,5]naphtho[1,2-*c*]furan-7,9-dione (**4aA**)

A mixture of diene **3a** (50 mg, 0.28 mmol, 1.1 equiv) and maleic anhydride **D1** (27 mg, 0.25 mmol, 1 equiv) was stirred 2 h at 40 °C in dichloromethane (0.5 mL). The product was then purified by flash chromatography (heptane/ethyl acetate 9/1) and obtained as an inseparable mixture of two diastereomers in 8/2 ratio, as a white paste (63 mg, 91%).

Major stereoisomer 4aA: ¹H NMR (CDCl₃, 400 MHz) δ 1.12 (t, *J* = 7.2 Hz, 3H, CH₃), 1.73 (m, 1H), 1.78 (m, 1H), 1.84-1.95 (m, 2H), 1.98-2.01 (m, 2H), 2.10-2.16 (m, 2H), 2.53-2.42 (m, 2H), 3.43 (m, 1H, H_c), 3.54 (dd, *J* = 4.5, 9.0 Hz, 1H, H_b), 3.77-3.90 (m, 2H, SCH₂), 4.26 (bs, 1H, SCH_e). ¹³C NMR (CDCl₃, 100.6 MHz) δ 12.7 (CH₃), 20.9 (CH₂CH₃), 21.5 (CH₂), 22.1 (CH₂), 30.2 (CH₂), 35.5 (CH), 39.1 (CH₂), 39.6 (CH), 44.7 (CH_b), 45.0 (CH_c), 49.7 (SCH_e), 136.1 (C=C), 140.2 (C=C), 170.9 (C=O), 171.4 (C=O). **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₁₅H₁₈O₃S 279.1049, found 279.1057.

Minor stereoisomer (characteristic signals different from **4a**): ¹H NMR (CDCl₃, 400 MHz), δ 1.02 (t, *J* = 7.2 Hz, 3H, CH₃), 4.00 (bs, 1H, SCH_e). ¹³C NMR (CDCl₃, 100.6 MHz) δ 12.4 (CH₃), 23.4 (CH₂CH₃), 26.3 (CH₂), 29.8 (CH₂), 31.3 (CH₂), 34.1 (CH), 36.1 (CH₂), 38.2 (CH), 39.7 (CH), 43.3 (CH), 55.5 (CH), 131.0 (C=C), 137.0 (C=C), 170.70 (C=O), 170.72 (C=O).

6-ethyl-8-phenyl-2,3,3a,5,6,6a,9a,9b-octahydrothieno[4',3',2':4,5]naphtho[1,2-c]pyrrole-7,9(1H,8H)-dione (5aA). A mixture of diene **3a** (43 mg, 0.24 mmol, 1.1 equiv) and N-phenylmaleimide **D2** (35 mg, 0.2 mmol, 1 equiv) was stirred 2 h at 40 °C in dichloromethane (0.5 mL). The product **5aA** was then purified by flash chromatography (heptane/ethyl acetate 9/1) and obtained as single diastereomer, as a white paste (65 mg, 93%).

¹H NMR (CDCl₃, 400 MHz) δ 1.16 (t, *J* = 7.3 Hz, 3H, CH₃), 1.58-1.68 (m, 2H), 1.77-1.96 (m, 3H), 1.99 (m, 1H), 2.18 (m, 1H), 2.27 (m, 1H), 2.38-2.49 (m, 2H), 3.31 (t, *J* = 8.1 Hz, 1H), 3.42 (dd, *J* = 4.6, 8.1 Hz, 1H), 3.80-3.90 (m, 2H, SCH₂), 4.27 (bs, 1H, SCH), 7.12-7.14 (m, 2H), 7.38 (m, 1H), 7.42-7.46 (m, 2H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 13.1 (CH₃), 21.3 (CH₂CH₃), 21.9 (CH₂), 22.5 (CH₂), 30.5 (CH), 36.5 (CH₂), 39.2 (SCH₂), 40.4 (CH), 44.2 (CH), 44.7 (CH), 49.8 (SCH), 126.8 (2xCH), 128.8 (CH), 129.3 (2xCH), 132.0 (C_q), 135.8 (C=C), 139.9 (C=C), 176.1 (C=O), 176.7 (C=O). **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₂₁H₂₃NO₂S 354.1522, found 354.1530.

dimethyl 3-ethyl-3,5a,6,7,8,8a-hexahydro-2H-naphtho[1,8-bc]thiophene-4,5-dicarboxylate (6a)

A mixture of diene **3a** (50 mg, 0.28 mmol, 1 equiv) and dimethyl acetylenedicarboxylate **D3** (60 mg, 0.42 mmol, 1.5 equiv) was stirred overnight at 80 °C in toluene (3 mL). The product was then purified by flash chromatography (heptane/ethyl acetate 9/1) and obtained as an inseparable mixture of two diastereomers in 10/3 ratio, as a colorless oil (57 mg, 65%).

Major stereoisomer 6aA: ¹H NMR (CDCl₃, 400 MHz) δ 0.63 (t, *J* = 7.5 Hz, 3H, CH₃), 1.39 (m, 1H), 1.52-1.60 (m, 2H), 1.63-1.73 (m, 2H), 1.78-1.93 (m, 2H), 2.19 (m, 1H), 3.18 (m, 1H), 3.36 (m, 1H), 3.54 (m, 1H), 3.72 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 3.78 (m, 1H), 4.18 (m, 1H, SCH). ¹³C NMR (CDCl₃, 100.6 MHz) δ 8.6 (CH₃), 21.0 (CH₂), 23.2 (CH₂CH₃), 23.5 (CH₂), 25.9 (CH₂), 36.3 (CH),

38.8 (SCH₂), 39.2 (CH), 49.8 (SCH), 52.1 (2xOCH₃), 129.7 (C=C), 135.1 (C=C), 138.6 (C=C), 139.5 (C=C), 167.8 (C=O), 168.5 (C=O).

Minor stereoisomer 6aB: ¹H NMR (CDCl₃, 400 MHz) characteristic signals different from **6aA**: δ 0.70 (t, *J* = 7.5 Hz, 3H, CH₃), 3.97 (m, 1H, SCH). ¹³C NMR (CDCl₃, 100.6 MHz) δ 8.5, 22.9, 25.8, 33.7, 39.5, 39.6, 39.9, 52.2, 54.9, 127.1, 136.6, 137.1, 137.8, 167.8, 168.5.

6aA/B: HRMS (ESI/Q-TOF) m/z: [M+H⁺] calculated for C₁₇H₂₃O₄S 323.1312, found 323.1308.

6-ethyl-9-phenyl-1,2,3,3a,6,11a-hexahydro-5H,8H-thieno[4,3,2-de][1,2,4]triazolo[1,2-a]cinnoline-8,10(9H)-dione (7aA) and 6-ethyl-9-phenyl-1,2,3,11a-tetrahydro-6H,8H-thieno[4,3,2-de][1,2,4]triazolo[1,2-a]cinnoline-8,10(9H)-dione (8a)

A mixture of diene **3a** (23 mg, 0.13 mmol, 1 equiv) and 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione **D4** (43 mg, 0.26 mmol, 2 equiv) was stirred 1 h, at room temperature, in dichloromethane (0.5 mL). The product was then purified by flash chromatography (heptane/ethyl acetate 9/1) and obtained as a mixture of **7aA** and **8a** in 1:2 ratio. Each one was isolated as a single diastereomers: **7aA** as an amorphous white solid (11 mg, 22%) of and **8a** as a viscous oil (23 mg, 45%).

Product 7aA: ¹H NMR (CDCl₃, 400 MHz) δ 0.94 (t, *J* = 7.7, 3H, CH₃), 1.47-1.58 (m, 4H), 1.74 (m, 1H), 1.95 (m, 1H), 2.13-2.0 (m, 2H), 2.96 (m, 1H), 3.85 (mAB, 2H, CH₂), 4.19 (m, 1H), 4.21 (m, 1H), 4.63 (bs, 1H), 7.32-7.36 (m, 2H), 7.42-7.51 (m, 3H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 9.4 (CH₃), 23.5 (CH₂), 24.8 (CH₂), 33.3 (CH₂), 38.0 (CH₂), 38.3 (CH₂), 53.3 (CH), 54.6 (CH), 57.3 (CH), 125.6 (CH), 128.1 (Cq), 128.2 (CH), 129.2 (CH), 131.4 (Cq), 135.1 (Cq), 149.5 (C=O), 153.4 (C=O). **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₂₃H₂₂N₃O₂S 404.1433, found 404.1449.

Product 8a: ¹H NMR (CDCl₃, 400 MHz) δ 0.88 (t, *J* = 7.7, 3H, CH₃), 1.81-1.91 (m, 3H), 2.15 (m, 1H), 2.22 (m, 1H), 2.75-2.98 (m, 2H), 3.05 (m, 1H), 4.45 (m, 1H), 5.31 (m, 1H), 7.32-7.36 (m, 2H), 6.90 (s, 1H), 7.25-7.28 (m, 1H), 7.46-7.54 (m, 4H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 9.5 (CH₃), 21.7 (CH₂), 24.0 (CH₂), 27.1 (CH₂), 28.5 (CH₂), 56.0 (CH), 59.5 (CH), 117.2 (CH), 125.6 (2xCH), 128.3 (CH), 129.2 (2xCH), 131.1 (Cq), 131.4 (Cq), 136.1 (Cq), 151.1 (C=O), 155.8 (C=O). **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₂₃H₁₉N₃O₂S 401.1198, found 401.1204.

Cycloaddition between diene (3a) and dithioester (D5). 2-(Methylsulfanyl)carbothiopyridine **D5** (47 mg, 0.28 mmol, 1 equiv) and boron trifluoride diethyl etherate (0.035 mL, 0.28 mmol, 1 equiv) were mixed in dichloromethane (0.6 mL). After 5 min, diene **3a** (54 mg, 0.3 mmol, 1.1 equiv) was added in dichloromethane (0.2 mL). Then the reaction mixture was stirred 1 h at 40 °C in DCM. The mixture was washed with a saturated solution of NaHCO₃ and the product was extracted with dichloromethane. The organic layers were then dried with MgSO₄ and evaporated under *vacuum*. After purification by flash chromatography (heptane/ethyl acetate 9/1) the product was obtained as an inseparable mixture of two cycloadducts (ratio 3:1), as an orange oil (70 mg, 72%). The structures have been not assigned.

Major cycloadduct 10a: $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 1.02 (m, 1H), 1.13 (t, $J = 7.1$ Hz, 3H, CH_3), 1.37 (m, 1H), 1.47 (m, 1H), 1.54 (m, 1H), 1.70 (m, 1H), 1.80 (s, 3H, SMe), 1.85 (m, 1H), 1.99 (m, 1H), 2.10 (m, 1H), 2.69 (m, 1H), 3.66-3.72 (m, 2H), 3.97-4.02 (m, 2H), 7.17 (m, 1H, H_{Py}), 7.69-7.73 (m, 2H, H_{Py}), 8.56 (m, 1H, H_{Py}). $^{13}\text{C NMR}$ (CDCl_3 , 100.6 MHz) δ 12.0 (CH_3), 13.1 (SMe), 24.5 (CH_2CH_3), 26.2 (CH_2), 31.3 (CH_2), 39.1 (SCH_2), 40.9 (CH_2), 41.9 (CH_2), 50.8 (CH_2), 56.8 (CH), 68.8 (Cq), 122.3 (CH_{Py}), 122.4 (CH_{Py}), 127.9 ($\text{C}=\text{C}$), 136.7 (CH_{Py}), 141.0 ($\text{C}=\text{C}$), 148.3 (CH_{Py}), 161.1 (Cq). **HRMS (ESI/Q-TOF) m/z:** $[\text{M}+\text{H}^+]$ calculated for $\text{C}_{18}\text{H}_{24}\text{NS}_3$ 350.1065, found 350.1058.

Cycloadditions of diene (3b)

6-phenyl-1,2,3,3a,6,6a,9a,9b-octahydro-5H-thieno[4',3',2':4,5]naphtho[1,2-c]furan-7,9-dione (4bA)

A mixture of diene **3b** (21 mg, 0.09 mmol, 1.1 equiv) and maleic anhydride **D1** (8 mg, 0.08 mmol, 1 equiv) was stirred 2 h at 40 °C in dichloromethane (1 mL). The product **4bA** was then purified by trituration in pentane and obtained as single diastereomer, as a white solid with mp = 137 °C (13 mg, 50%).

$^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.63 (m, 1H), 1.75 (m, 1H), 1.89 (m, 1H), 2.00 (m, 1H), 2.15-2.20 (m, 2H), 2.56 (m, 1H, H_d), 3.29 (m, 1H, SCH_d), 3.49 (dd, $J = 8.7, 6.6$ Hz, 1H, H_c), 3.68 (dd, $J = 8.7, 7.7$ Hz, 1H, H_b), 3.83 (m, 1H, H_a), 3.88 (m, 1H, SCH_d), 4.41 (m, 1H, SCH_e), 7.27-7.32 (m, 2H), 7.33-7.35 (m, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 125.7 MHz) δ 20.7 (CH_2), 21.7 (CH_2), 29.4 (CH_2), 34.4 (CH_d), 40.6 (SCH_2), 43.9 (CH_a), 45.7 (CH_c), 48.4 (CH_b), 50.0 (SCH_e), 128.2 (Cq), 128.7 (2xCH), 129.9 (2xCH), 133.1 (Cq), 136.5 (Cq), 142.4 (Cq), 170.2 ($\text{CH}_c\text{C}=\text{O}$), 170.8 ($\text{CH}_b\text{C}=\text{O}$). **HRMS (ESI/Q-TOF) m/z:** $[\text{M}+\text{H}^+]$ calculated for $\text{C}_{19}\text{H}_{18}\text{O}_3\text{S}$ 327.1049, found 327.1037.

6,8-diphenyl-2,3,3a,5,6,6a,9a,9b-octahydrothieno[4',3',2':4,5]naphtho[1,2-c]pyrrole-7,9(1H,8H)-dione (5bA)

A mixture of diene **3b** (30 mg, 0.13 mmol, 1.1 equiv) and N-phenylmaleimide **D2** (15 mg, 0.09 mmol, 1 equiv) was stirred 2 h at 40 °C in dichloromethane (1 mL). The product **5bA** was then purified by flash chromatography (heptane/ethyl acetate 9/1) and obtained as a single diastereomer, as an amorphous white solid (35 mg, 97%).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 1.63-1.83 (m, 2H), 1.96-2.02 (m, 2H), 2.11-2.22 (m, 2H), 2.66 (m, 1H), 3.36-3.42 (m, 2H, H_b and SCH_d), 3.62 (t, $J = 7.4$ Hz, 1H, H_c), 3.87-3.92 (m, 2H, H_a and SCH_d), 4.41 (m, 1H, SCH_e), 6.99 (d, $J = 8.0$ Hz, 2H, H_{ar}), 7.28-7.34 (m, 6H, H_{ar}), 7.38 (t, $J = 7.4$ Hz, 2H, H_{ar}). $^{13}\text{C NMR}$ (CDCl_3 , 100.6 MHz) δ 21.1 (CH_2), 22.3 (CH_2), 29.6 (CH_2), 35.3 (CH_d), 40.6 (SCH_2), 44.7 (CH_a), 44.8 (CH_b), 47.7 (CH_c), 50.2 (SCH_e), 126.4 (2xCH), 127.7 (CH), 128.5 (2xCH), 128.6 (CH), 129.2 (2xCH), 130.4 (2xCH), 131.8 (Cq), 133.2 ($\text{C}=\text{C}$), 137.7 (Cq), 141.7 ($\text{C}=\text{C}$), 175.7 ($\text{C}=\text{O}$), 175.9 ($\text{C}=\text{O}$). **HRMS (ESI/Q-TOF) m/z:** $[\text{M}+\text{H}^+]$ calculated for $\text{C}_{25}\text{H}_{23}\text{NO}_2\text{S}$ 402.1528, found 402.1529.

6,9-diphenyl-1,2,3,3a,6,11a-hexahydro-5H,8H-thieno[4,3,2-de][1,2,4]triazolo[1,2-a]cinnoline-8,10(9H)-dione (7bA) and 6,9-diphenyl-1,2,3,11a-tetrahydro-6H,8H-thieno[4,3,2-de][1,2,4]triazolo[1,2-a]cinnoline-8,10(9H)-dione (8b)

A mixture of diene **3b** (30 mg, 0.13 mmol, 1 equiv) and 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione **D4** (46 mg, 0.26 mmol, 2 equiv) was stirred 30 min, at room temperature, in dichloromethane (0.5 mL). The product was then purified by flash chromatography (heptane/ethyl acetate 9/1) and obtained as a mixture of **7bA** and **8b** in 1:1 ratio. Each one was isolated as a single diastereomer: **7bA** as a viscous oil (11 mg, 22%) and **8b** as a white solid with mp = 184 °C (13 mg, 26%).

(7bA): ¹H NMR (CDCl₃, 400 MHz) δ 1.69 (m, 1H), 1.94 (m, 1H), 1.98-2.05 (m, 2H), 2.10 (m, 1H), 3.05 (m, 1H), 3.36 (m, 1H, SCHH), 3.41 (m, 1H, SCHH), 4.34 (m, 1H), 4.45 (m, 1H), 5.63 (s, 1H), 7.35-7.39 (m, 10H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 19.7 (CH₂), 22.3 (CH₂), 25.1 (CH₂), 38.3 (CH₂), 49.2 (CH), 57.1 (CH), 58.4 (CH), 125.6 (2xCH), 128.0 (CH), 128.2 (CH), 129.8 (2xCH), 130.2 (Cq), 131.2 (Cq), 136.2 (Cq), 137.8 (Cq), 149.9 (C=O), 154.9 (C=O). **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₂₃H₂₂N₃O₂S 404.1433, found 404.1449.

(8b): ¹H NMR (CDCl₃, 400 MHz) δ 1.94-1.99 (m, 2H), 2.28 (m, 1H), 2.90-2.95 (m, 2H), 3.20 (m, 1H), 4.61 (m, 1H, CH), 6.27 (d, *J* = 1.1 Hz, 1H, NCHPh), 6.74 (d, *J* = 1.1 Hz, 1H, SCH), 7.24-7.38 (m, 10H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 21.7 (CH₂), 24.1 (CH₂), 27.2 (CH₂), 58.9 (CH), 59.6 (CH), 119.6 (SCH), 125.6 (2xCH), 128.2 (2xCH), 128.3 (CH), 128.6 (Cq), 128.8 (2xCH), 129.2 (2xCH), 131.3 (Cq), 133.0 (Cq), 136.3 (Cq), 140.3 (Cq), 151.3 (C=O), 155.6 (C=O). **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₂₃H₁₉N₃O₂S 401.1198, found 401.1204.

2-(4-(methylthio)-3-phenyl-2,3,4,5a,6,7,8,8a-octahydrothieno[4,3,2-de]thiochromen-4-yl)pyridine
(10b)

2-(Methylsulfanyl)carbothiopyridine **D5** (17 mg, 0.1 mmol, 1 equiv) and boron trifluoride diethyl etherate (0.0127 mL, 0.1 mmol, 1 equiv) were mixed in dichloromethane (0.2 mL). After 5 min, diene **3b** (25 mg, 0.11 mmol, 1.1 equiv) was added in dichloromethane (0.2 mL). Then the reaction mixture was stirred 1 h at 40 °C in DCM. The mixture was washed with a saturated solution of NaHCO₃ and the product was extracted with dichloromethane. The organic layers were then dried with MgSO₄ and evaporated under *vacuum*. After purification by flash chromatography (heptane/ethyl acetate 9/1) the product was obtained as an inseparable mixture of two cycloadducts (ratio 10:1), as a yellow oil (20 mg, 51%).

Major cycloadduct 10b: ¹H NMR (CDCl₃, 400 MHz) δ 1.71-2.11 (m, 6H, (CH₂)₃), 1.83 (s, 3H, SMe), 3.26-3.38 (m, 2H, SCH₂), 3.88 (s, 1H, CH_a), 3.93-3.96 (m, 1H, CH_d), 4.46 (m, 1H, SCH_e), 6.09 (m, 1H, H_{py}), 6.95-7.10 (5H), 7.15-7.19 (m, 1H), 7.50 (td, *J* = 7.8, 1.8 Hz, 1H, H_{py}), 7.67 (m, 1H, H_{py}), 8.22 (dd, *J* = 5.0, 1.8 Hz, 1H, H_{py}). ¹³C NMR (CDCl₃, 100.6 MHz) δ 13.7 (SMe), 21.2 (CH₂), 22.8 (CH₂), 27.2 (CH₂), 36.6 (CH_d), 40.6 (SCH₂), 50.7 (SCH_e), 55.6 (CHPh), 73.1 (Cq), 122.1 (CH_{py}), 123.2 (CH_{py}), 127.0 (CH), 127.6 (2xCH), 129.8 (2xCH), 132.8 (Cq), 135.9 (CH_{py}), 137.7 (Cq), 138.5 (Cq), 147.8 (CH_{py}), 159.8 (Cq). The ionization to perform the mass analysis led to the oxidation of the compound with loss of two hydrogen atoms: **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₂₂H₂₂NS₃ 396.0914, found 396.0897.

Cycloaddition of diene (3c)

7-oxo-2a,3,4,5,5a,6,6a,7,9,9a-decahydro-1H-thieno[2',3',4':8,1]naphtho[2,3-c]furan-6-carboxylic acid (4'cA)

A mixture of diene **3c** (30 mg, 0.16 mmol, 1.1 equiv) and maleic anhydride **D1** (15 mg, 0.15 mmol, 1 equiv) was stirred 2.5 h at 40 °C in dichloromethane (1 mL). The product **4'cA** was then purified by flash chromatography (heptane/ethyl acetate 8/2) and obtained as a single diastereomer, as pale yellow solid with mp = 151 °C (38 mg, 90%).

¹H NMR (CDCl₃, 400 MHz) δ 1.57-1.63 (m, 2H), 1.72-1.78 (m, 2H), 1.94 (m, 1H), 2.10 (m, 1H), 2.63 (m, 1H), 3.11 (m, 1H), 3.31-3.37 (m, 2H), 3.45 (m, 1H, SCHH), 3.75 (m, 1H, SCHH), 4.20 (dd, *J* = 9.6, 7.8 Hz, 1H, CH-O), 4.26 (m, 1H, SCH), 4.50 (dd, *J* = 8.6, 7.8 Hz, 1H, CH-O). **¹³C NMR** (CDCl₃, 100.6 MHz) δ 20.6 (CH₂), 22.8 (CH₂), 28.2 (CH₂), 35.5 (CH), 36.9 (CH), 38.8 (CH₂), 41.5 (CH), 43.3 (CH), 49.9 (CH), 71.0 (CH₂O), 128.8 (C=C), 138.9 (Cq), 175.8 (Cq), 177.7 (C=O). **HRMS (ESI/Q-TOF) m/z:** [M+H⁺] calculated for C₁₄H₁₇O₄S 281.0848, found 281.0844.

Cycloadditions of diene (3d)

7-methyl-1,2,3,3a,5,6,7,7a,10a,10b-decahydrobenzo[8,1]isothiochromeno[6,7-c]furan-8,10-dione (4dA)

A mixture of diene **3d** (40 mg, 0.22 mmol, 1.1 equiv) and maleic anhydride **D1** (25 mg, 0.22 mmol, 1 equiv) was stirred 2.5 h at 40 °C in dichloromethane (0.3 mL). The product **4dA** was then purified by flash chromatography (pentane/diethyl ether 8/2) and obtained as single diastereomer, as an amorphous white solid (29 mg, 47%).

¹H NMR (CDCl₃, 500 MHz) δ 1.44 (d, *J* = 7.5 Hz, 3H, CH₃), 1.49-1.55 (m, 2H), 1.75 (m, 1H), 1.85-2.12 (m, 2H), 2.15-2.40 (m, 4H), 2.55-2.65 (m, 3H), 3.18-3.25 (m, 2H), 3.6 (m, 1H, SCH). **¹³C NMR** (CDCl₃, 125.7 MHz) δ 13.6 (CH₃), 20.3 (CH₂), 22.4 (CH₂), 25.5 (CH₂), 27.0 (CH₂), 27.7 (CH₂), 34.0 (CH), 35.2 (CH), 37.0 (CH), 46.9 (CH), 45.7 (CH), 134.0 (Cq), 135.3 (Cq), 171.7 (2xC=O). **HRMS (APCI/Q-TOF) m/z:** [M+H⁺] calculated for C₁₅H₁₈O₃S 279.1049, found 279.1037.

dimethyl-4-methyl-2,3,4,6a,7,8,9,9a-octahydrobenzo[de]thiochromene-5,6-dicarboxylate (6dA/6dB)

A mixture of diene **3d** (50 mg, 0.28 mmol, 1 equiv) and dimethyl acetylenedicarboxylate **D3** (59 mg, 0.42 mmol, 1.5 equiv) was stirred overnight at 80 °C in toluene (1 mL). The resulted product was obtained as an inseparable mixture of two diastereomers in 2/1 ratio, as a colorless oil (49 mg, 54%) and purified by flash chromatography (heptane/ethyl acetate 9/1). A small fraction enriched in minor isomer **6dB** was isolated (ratio 2/10).

Major stereoisomer 6dA: **¹H NMR** (CDCl₃, 400 MHz) δ 1.21 (d, *J* = 7.1 Hz, 3H, CH₃), 1.55-2.1 (m, 4H), 2.15 (m, 2H), 2.43 (m, 2H), 2.95 (m, 2H), 3.15 (m, 2H), 3.30 (m, 1H), 3.76 (6H, 2xOCH₃). **¹³C NMR** (CDCl₃, 100.6 MHz) δ 20.3 (CH₂), 22.1 (CH₃), 25.0 (CH₂), 26.5 (CH₂), 26.6 (CH₂), 26.9 (CH₂),

34.0 (CH), 36.2 (CH), 36.9 (CH), 52.2 (2xCH₃), 131.2 (Cq), 132.3 (Cq), 135.4 (Cq), 137.8 (Cq), 167.8 (C=O), 169.0 (C=O).

Minor stereoisomer 6dB: ¹H NMR (CDCl₃, 400 MHz) δ 1.21 (d, *J* = 7.1 Hz, 3H, CH₃), 1.55-2.1 (m, 4H), 2.15 (m, 2H), 2.43 (m, 2H), 2.65 (m, 2H), 2.85 (m, 2H), 3.21 (m, 1H), 3.76 (6H, 2xOCH₃). ¹³C NMR (CDCl₃, 100.6 MHz) δ 22.1 (CH₃), 23.0 (CH₂), 26.7 (CH₂), 29.7 (CH₂), 34.8 (CH₂), 37.6 (CH₂), 38.9 (CH), 39.5 (CH), 43.3 (CH), 52.3 (2xCH₃), 129.3 (Cq), 129.4 (Cq), 136.8 (Cq), 137.1 (Cq), 168.0 (C=O), 168.5 (C=O).

6dA/B: HRMS (ESI/Q-TOF) m/z: [M+Na⁺] calculated for C₁₇H₂₂O₄SNa 345.1131, found 345.1128.

7,10-diphenyl-1,2,3,3a,5,6,7,12a-octahydro-9H-thiopyrano[4,3,2-de][1,2,4]triazolo[1,2-a]cinnoline-9,11(10H)-dione (7dA/7dB). A mixture of diene **3d** (40 mg, 0.22 mmol, 1 equiv) and 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione **D4** (57 mg, 0.33 mmol, 1.5 equiv) was stirred 1 hour, at room temperature, in dichloromethane (1 mL). The product was then purified by flash chromatography (heptane/ethyl acetate 8/2) and obtained as a mixture of **7dA** and its diastereomer **7dB** in 95:5 ratio (white paste, 40 mg, 51%).

Major 7dA: ¹H NMR (CDCl₃, 400 MHz) δ 1.36 (d, *J* = 6.5 Hz, 3H, CH₃), 1.65-1.73 (m, 2H), 1.81-1.87 (m, 2H), 2.01 (m, 1H), 2.73 (m, 1H), 2.32 (m, 1H), 2.42 (m, 1H), 3.01-3.19 (m, 2H), 3.57 (m, 1H, SCH), 4.37-4.40 (m, 2H), 7.36 (m, 1H), 7.44-7.52 (m, 4H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 17.3 (CH₃), 18.7 (CH₂), 23.9 (CH₂), 24.0 (CH₂), 27.0 (CH₂), 27.9 (CH₂), 34.0 (CH), 35.2 (CH), 36.9 (CH), 51.5 (CH), 55.0 (CH), 125.7 (2xCH), 128.2 (CH), 129.2 (2xCH), 130.9 (Cq), 131.3 (Cq), 150.7 (C=O), 155.1 (C=O).

HRMS (ESI/Q-TOF) m/z: [M+H⁺] calculated for C₁₉H₂₂N₃O₂S 356.1427, found 356.1456.

Cycloadditions of diene (3e).

10-phenyl-1,2,3,3a,5,6,7,12a-octahydro-9H-thiopyrano[4,3,2-de][1,2,4]triazolo[1,2-a]cinnoline-9,11(10H)-dione (7eA) A mixture of crude diene **3e** (72 mg, 0.43 mmol, 1 equiv) and 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione **D4** (151 mg, 0.86 mmol, 2 equiv) was stirred 2 hours, at room temperature, in dichloromethane (2 mL). The product was then purified by flash chromatography (heptane/ethyl acetate 8/2) and **7eA** was obtained as a single diastereomer (yellow paste, 22 mg, 15%).

¹H NMR (CDCl₃, 400 MHz) δ 1.70-1.78 (m, 3H), 1.80-2.01 (m, 3H), 2.73 (m, 1H), 2.32 (m, 1H), 2.75 (m, 1H), 3.01-3.04 (m, 2H), 3.65 (d, *J* = 13.6, 1H), 3.92 (d, *J* = 16.1, 1H), 4.14 (d, *J* = 16.1, 1H), 4.43 (d, *J* = 13.6, 1H), 7.36 (m, 1H), 7.44-7.52 (m, 4H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 18.7 (CH₂), 22.7 (CH₂), 23.7 (CH₂), 27.0 (CH₂), 28.2 (CH₂), 37.2 (CH), 45.9 (CH₂), 54.8 (CH), 123.3 (CH), 125.8 (2xCH), 128.2 (CH), 129.3 (2xCH), 130.9 (Cq), 131.3 (Cq), 151.8 (C=O), 153.6 (C=O).

HRMS (ESI/Q-TOF) m/z: [M+Na⁺] calculated for C₁₈H₁₉N₃O₂SNa 364.1090, found 364.1098.

Cycloadditions of diene (3f).

7-phenyl-1,2,3,3a,5,6,7,7a,10a,10b-decahydrobenzo[8,1]isothiochromeno[6,7-c]furan-8,10-dione (4fA). A mixture of diene **3f** (50 mg, 0.2 mmol, 1.1 equiv) and maleic anhydride **D1** (20 mg, 0.2 mmol, 1 equiv) was stirred 5 h at 40 °C in dichloromethane (0.3 mL). The product **4fA** was then purified by flash chromatography (pentane/diethyl ether 8/2) and obtained as single diastereomer, as a white solid, mp = 142 °C (28 mg, 41%).

¹H NMR (CDCl₃, 500 MHz) δ 1.49-1.68 (m, 2H), 1.85-2.12 (m, 6H), 2.48 (m, 1H), 2.57 (m, 1H), 2.68 (m, 1H), 3.42 (t, *J* = 8.5, 1H), 3.71 (bs, 1H), 3.64 (m, 1H), 3.84 (dd, *J* = 9.0, 4.2 Hz, 1H), 7.31-7.39 (m, 3H), 7.44-7.46 (m, 2H). ¹³C NMR (CDCl₃, 125.7 MHz) δ 20.4 (CH₂), 22.8 (CH₂), 25.4 (CH₂), 27.8 (CH₂), 27.7 (CH₂), 35.4 (CH), 36.6 (CH), 45.6 (CH), 46.1 (CH), 47.2 (CH), 134.3 (Cq), 130.2 (2xCH), 128.5 (2xCH), 127.6 (CH), 136.9 (Cq), 135.2 (Cq), 171.0 (C=O), 171.5 (C=O). HRMS (APCI/Q-TOF) *m/z*: [M+H⁺] calculated for C₂₀H₂₁O₃S 341.1206, found 341.1216.

7-methyl-10-phenyl-1,2,3,3a,5,6,7,12a-octahydro-9H-thiopyrano[4,3,2-de][1,2,4]triazolo[1,2-a]cinnoline-9,11(10H)-dione (7fA). A mixture of diene **3f** (30 mg, 0.13 mmol, 1 equiv) and 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione **D4** (45 mg, 0.26 mmol, 2 equiv) was stirred 1 hour, at room temperature, in dichloromethane (0.5 mL). The product was then purified by flash chromatography (heptane/ethyl acetate 9/1) to afford **7fA** as a single diastereomer, as a white powder (30 mg, 60%).

¹H NMR (CDCl₃, 400 MHz) δ 1.67 (m, 1H), 1.77-1.86 (m, 3H), 1.88-2.01 (m, 2H), 2.33 (m, 1H), 2.64 (m, 1H), 3.21 (m, 1H), 3.66 (m, 1H, SCH), 4.41 (m, 1H), 5.19 (s, 1H, CHPh), 7.20-7.35 (m, 10H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 18.8 (CH₂), 23.9 (CH₂), 27.1 (CH₂), 27.0 (CH₂), 28.3 (CH₂), 37.2 (CH), 55.5 (CH), 59.2 (CH), 125.6 (CH), 126.8 (Cq), 128.1 (CH), 128.8 (2xCH), 128.9 (2xCH), 129.0 (CH), 129.1 (2xCH), 131.2 (Cq), 131.8 (Cq), 136.7 (Cq), 150.4 (C=O), 154.9 (C=O).

HRMS (ESI/Q-TOF) *m/z*: [M+Na⁺] calculated for C₂₄H₂₃N₃O₂SNa 440.1403, found 440.1436.

2-(2-(methylthio)-3-phenyl-3,4,5,6a,7,8,9,9a-octahydro-2H-thiopyrano[4,3,2-de]thiochromen-2-yl)pyridine (10f). 2-(Methylsulfanyl)carbothiopyridine **D5** (39 mg, 0.2 mmol, 1 equiv) and boron trifluoride diethyl etherate (0.0152 mL, 0.1 mmol, 1 equiv) were mixed in dichloromethane (0.5 mL). After 5 min, diene **3f** (62 mg, 0.22 mmol, 1.1 equiv) was added in dichloromethane (0.2 mL). Then the reaction mixture was stirred 1.5 h at 40 °C in DCM. The mixture was washed with a saturated solution of NaHCO₃ and the product was extracted with dichloromethane. The organic layers were then dried with MgSO₄ and evaporated under *vacuum*. After purification by flash chromatography (heptane/ethyl acetate 9/1) the product was obtained as an inseparable mixture of two cycloadducts (ratio 10:3), as a yellow oil (54 mg, 65%).

The regio- and stereochemical assignments of these cycloadducts have been made on the basis of the following NMR experiments: ADEQUATE: correlation between CHPh and Cq-(SMe); selective NOESY-1D on CHS²-major: correlation with SCH₃-major; weak correlation with CHS¹-major; selective NOESY-1D on CHS²-minor: correlation with SCH₃-minor; strong correlation with CHS¹-minor; selective NOESY-1D on SCH₃: similar correlations with CHS²-major and CHS²-minor;

NOESY-2D: correlation of SCH₃ with both CHPh and CHPh The analysis of the NOESY spectra match with the optimized structures obtained by computational energy minimization (see SI).

Major cycloadduct 10fA: ¹H NMR (CDCl₃, 400 MHz) δ 1.80 (s, 3H, SMe), 1.85-2.14 (m, 8H), 2.61 (m, 1H), 2.84 (m, 1H), 3.70-3.74 (m, 1H, CHS²), 3.75 (bs, 1H, CHPh), 4.04 (m, 1H, CHS¹), 6.92-6.97 (4H), 7.06-7.09 (m, 2H), 7.52 (m, 1H), 7.67 (m, 1H), 8.22 (dd, *J* = 4.6, 1.8, 1H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 13.5 (SMe), 20.7 (CH₂), 24.9 (CH₂), 25.7 (CH₂), 27.2 (SCH₂), 32.1 (CH₂), 36.1 (CHS¹), 38.2 (CHS²), 58.1 (CHPh), 69.3 (Cq-SMe), 121.9 (CH), 122.9 (CH), 126.8 (CH), 127.2 (2xCH), 130.8 (2xCH), 131.1 (Cq), 133.2 (Cq), 135.9 (CH), 139.5 (Cq), 148.1 (CH), 159.9 (Cq). **HRMS (APCI/Q-TOF) m/z:** [M+H⁺] calculated for C₂₃H₂₆NS₃ 412.1222, found 412.1188.

Minor cycloadduct 10fB: ¹H NMR (CDCl₃, 400 MHz), characteristic signals, δ 1.80 (s, 3H, SMe), 2.46-2.52 (m, 2H), 3.24 (m, 1H, CHS²), 3.62 (m, 1H, CHS¹), 3.91 (bs, 1H, CHPh), 8.29 (dd, *J* = 4.4, 1.8, 1H). ¹³C NMR (CDCl₃, 100.6 MHz) δ 13.5 (SMe), 22.7 (CH₂), 26.7, 33.4, 33.5, 37.8, 40.0 (CHS²), 42.3 (CHS¹), 59.5 (CHPh), 67.8 (Cq-SMe), 122.0, 122.9, 126.8, 130.6, 130.9, 131.5, 133.2, 136.0, 138.9, 148.2 (CH), 159.7 (Cq).

Associated Content

The Supporting Information is available free of charge on the ACS Publications website: NMR spectra, X-ray data, computational data.

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