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Efficient synthesis of chiral Δ^2-1,3,4-thiadiazolines from α-pinene and verbenone

Gabriela P. Sarmiento [a], Pablo D. Rouge [a], Lucas Fabian [b], Daniel Vega [a,b,c], Rosa M. Ortuño [c], Graciela Y. Moltrasio [a], Albertina G. Moglioni [b,*]

[a] Department of Organic Chemistry, Faculty of Pharmacy and Biochemistry, Universidad de Buenos Aires, 956 Junín St., (1113) Buenos Aires, Argentina
[b] Department of Pharmacology, Faculty of Pharmacy and Biochemistry, Universidad de Buenos Aires, 956 Junín St., (1113) Buenos Aires, Argentina
[c] Faculty of Sciences, Universidad Autónoma de Barcelona, Bellaterra, Spain

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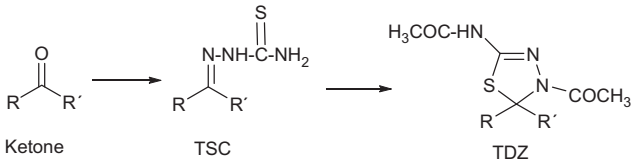
ABSTRACT

The synthesis of chiral cyclobutane 1,3,4-thiadiazoline derivatives starting from (−)-α-pinene and (−)-verbenone was studied. The diastereoisomeric excesses of the products obtained depended strongly upon the starting chiral ketone. The stereochemical assignments of the synthesized compounds were performed by NMR spectroscopy, X-ray analysis, and theoretical calculations.

1. Introduction

Thiadiazolines and their derivatives constitute a group of compounds that possess a wide range of biological activities.[1] One of the most commonly used routes to obtain 1,3,4-thiadiazolines (TDZ) is the heterocyclization of thiosemicarbazones (TSC) prepared from aldehydes and ketones (Scheme 1) under acylation conditions, usually acetic anhydride and pyridine.[2]



Scheme 1. General procedure to obtain a TDZ from a ketone.

Using this methodology, we have described the synthesis and biological activity of several TSC and TDZ compounds, derived from aromatic ketones, indanones, tetralone, and terpenones.[3,4] From prochiral ketones, the corresponding TDZ compounds were formed as a racemic mixture. In the case of chiral ketones, we have found some examples, in addition to those previously described, where we verified the influence of the steric hindrance present in the TSC to favor the π-facial selectivity in the ring closure.[4,5]

Herein we report the results obtained in the preparations of TSC compounds from ketones prepared through the oxidative cleavage of α-pinene and verbenone, respectively, and the heterocyclization of a suitable intermediate leading to two types of Δ^2-1,3,4-thiadiazoline compounds (types I and II) (Fig. 1).

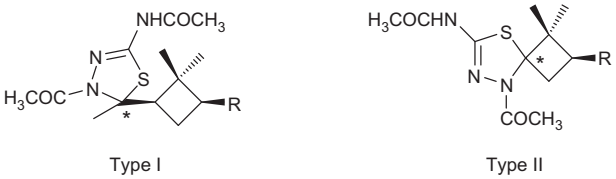


Figure 1. General structures for the TDZ compounds synthesized.

2. Results and discussion

As stated in the introduction, the precursors used for the synthesis of these compounds (types I or II) were ketones obtained by C=C oxidative cleavage of α-(−)-pinene and (−)-verbenone through synthetic pathways previously described by our group. Methylcyclobutyl ketones **1**,[6] **2**,[6] **3**,[7] **6**,[7] **8**, and a substituted cyclobutanone **9**[8] were precursors for the synthesis of types I and II compounds, respectively (Scheme 2). Ketone **8** was prepared from hydroxy ketal **5**[6] by treatment with *t*-butyldiphenylsilyl chloride and subsequent deprotection of the ketone group.

Ketones **1**–**3**, **6**, **8**, **9** were reacted with thiosemicarbazide in ethanol, avoiding the use of mineral acids, to form enantiopure thiosemicarbazones **7**–**10** (Scheme 3). Experimental observations indicated that the use of sulfuric acid as a catalyst led to the formation of a mixture of isomeric thiosemicarbazones. It was not

* Corresponding author.
E-mail address: amoglio@ffyb.uba.ar (A.G. Moglioni).

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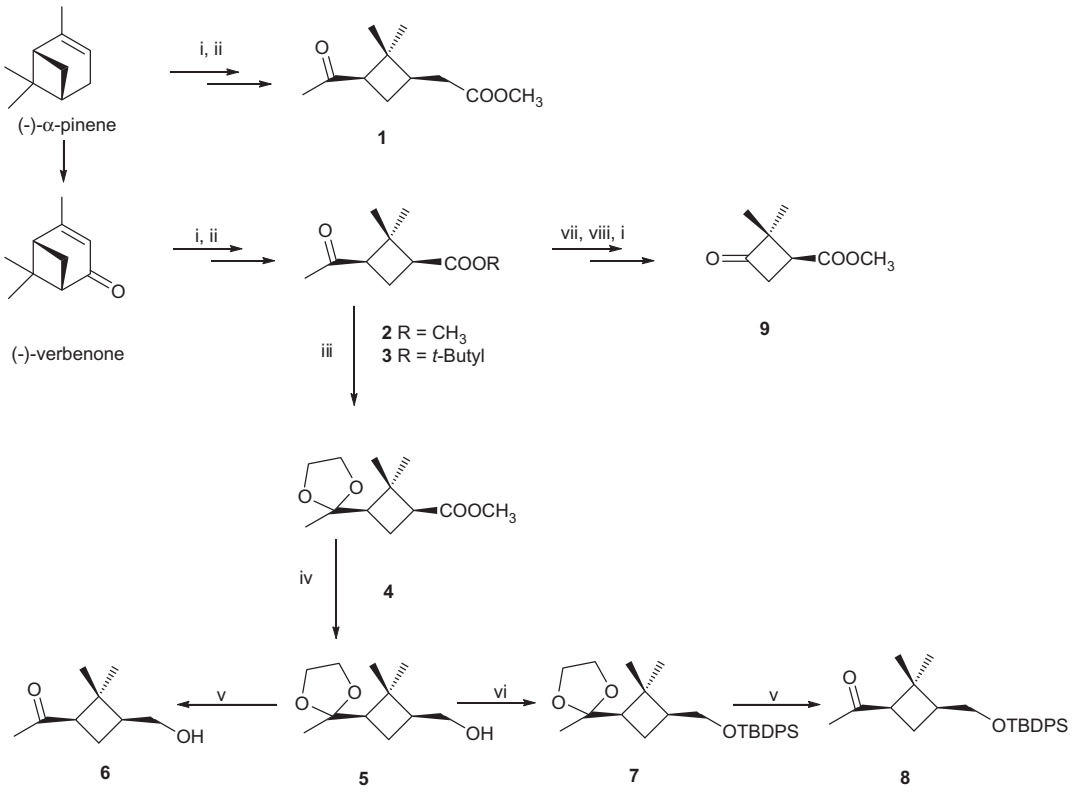
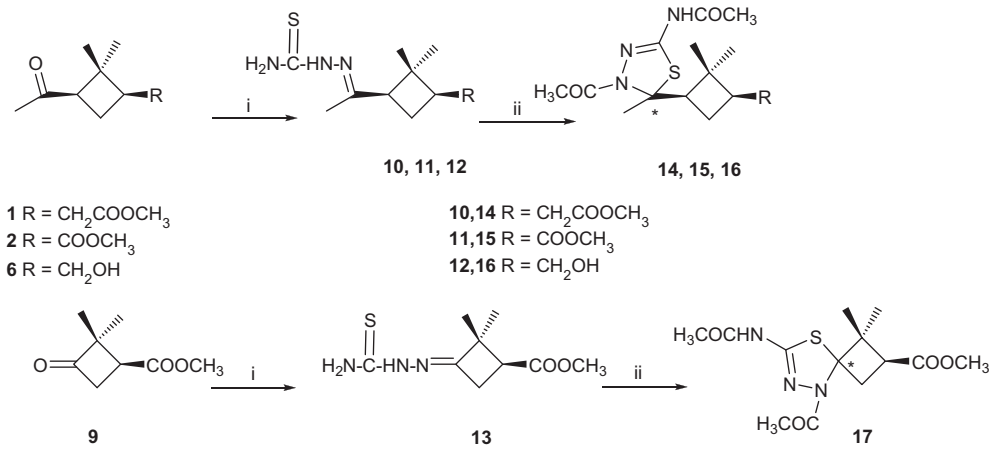


Scheme 2. Synthesis of ketones **1**–**3**, **6**, **8**, **9**. Reagents and conditions: (i) $NaIO_4/RuO_n/CH_3CN/Cl_4C/H_2O$; (ii) CH_2N_2/ether; (iii) ethylene glycol/PPTS/heat; (iv) $LiBH_4$/THF; (v) acetone/PPTS/heat; (vi) Cl-TBDPS/DMAP/Cl_2CH_2; (vii) *m*-CPBA/Cl_2CH_2; (viii) K_2CO_3/H_2O/ethanol.



Scheme 3. Synthesis of TSC **10**–**13** and TDZ **14**–**17**. Reagents and conditions: (i) thiosemicarbazide/ethanol/heat; (ii) acetic anhydride/pyridine/heat.

possible to obtain the corresponding TSC for compounds **3** and **8**, which was attributed to the steric hindrance exerted by the bulky substituent at the 1,3-*cis* position on the cyclobutane ring.

The configuration of the C=N double bond was assigned to be the *trans*-isomer, for compounds **10**–**12**, according to that observed in the crystallographic structure of compound **12** (Fig. 2). X-ray crystallography of compound **12** also confirmed the 1,3-*cis* relative stereochemistry between the substituents present in the cyclobutane ring, after six reaction steps from verbenone. The compound crystallizes with one molecule in the asymmetric unit (Fig. 2). The crystal cohesion is mainly due to the three hydrogen bonds provided by H-12, H-8, and H-14B. These hydrogen bonds determine a chain of molecules running along the c direction. The packing can be described as a piling up of parallel chains along the b direction.

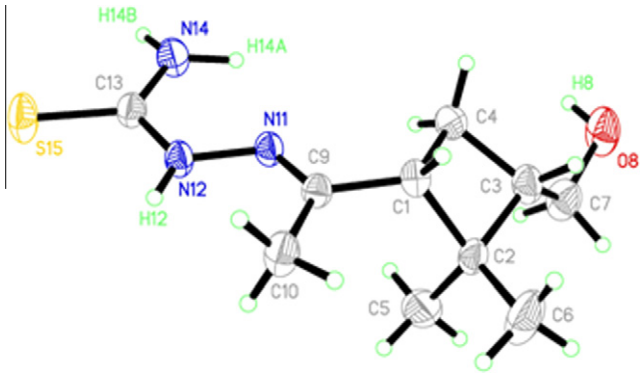


Figure 2. Crystal structure of compound **12**.

The reaction of thiosemicarbazones under acetylating conditions is the best known pathway known for the synthesis of thiadiazoline derivatives.[2,9] Accordingly, heating of homochiral TSC **10**–**12** with anhydride acetic in pyridine gave the expected thiodiazolines **14**–**16** (Scheme 3).

Specifically, TDZ compounds **14**–**16** were obtained as a mixture of diasteroisomeric products in a 1:1 ratio, which were not resolvable by any traditional chromatographic methods such as thin layer or column chromatography. The ^{13}C NMR spectra of these compounds presented several duplicated signals, for example two signals for C-2 and C-5 corresponding to the heterocyclic moiety. Our earlier experience working with 1,3-*cis*-disubstituted methylcyclobutyl ketones indicated that the isomerization from a *cis*- to a *trans*-structure via the keto-enol equilibrium was a probable reaction.[6] Aiming to establish which stereogenic center was modified during the reaction of heterocyclization, the complete assignment of the pair of diastereoisomers **16** was carried out. Compound **16**, obtained as an acetate, was selected because, regardless of the presence of three stereogenic centers in the molecule, only two centers, C-1′ and C-5, could be stereochemically modified. The new stereogenic center generated in this reaction (C-5) could be (*R*) or (*S*). Otherwise, according to the mechanism accepted for this reaction (Scheme 4),[2] C-1′ could be modified via transposition to an intermediate carbocation. The proposed mechanism (Scheme 4) for the formation of these thiadiazolines can be explained on the basis of the hard and soft acid and base principle.[2] The harder acylating reagent reacts with the harder nitrogen atom, rather than the softer sulfur atom, and this acylation favors the cyclization of TSC to a Δ^2-1,3,4-TDZ.

The separation of the diastereoisomeric products in the mixture of **16** was accomplished by analytical HPLC using a chiral column. Under these conditions, the two *cis*-diastereoisomers **16a** and **16b,** which differed at the C-5 configuration, were isolated. The assignment of the configuration at C-1′ of **16** was made on the basis of mono- and bi-dimensional NMR experiments, with the latter being fundamental in establishing the unequivocal proton–carbon relationship. In addition, the NOESY spectra confirmed the identity of *cis*-**16a** and *cis*-**16b** (Fig. 3). However, the C-5 configuration could not be assigned.

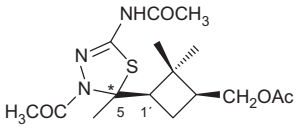


Figure 3. Structure of the *cis* diastereoisomers **16a** and **16b**.

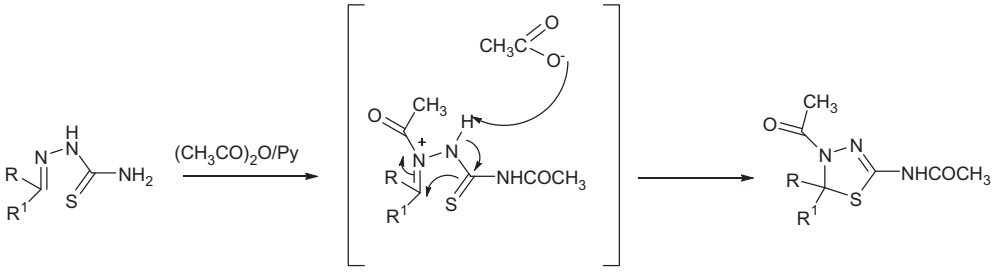
When the heterocyclization reaction was performed on **13**, high diastereoselectivity was observed, with stereoisomer **17a** being obtained as the main product. This was in accordance with the behavior displayed by other TDZ derivatives obtained from verbanone, camphor, and fenchone.[4] After concentration of the mother liquor, a relatively low amount of minor isomer **17b** was isolated. The configuration of both isomers **17a** and **17b** was elucidated from NMR data and theoretical calculations. The signal assignment of each H and C was unequivocally performed on the basis of HMQC experiments. Further structural insight was obtained from NOESY experiments. In the case of **17a**, protons bonded to C-3 (δ 30.9 ppm) showed shifts of δ 2.90 and 3.33 ppm ($\Delta\delta$ 0.43 ppm), the proton bonded at C-2 (δ 45.7 ppm) appeared at δ 3.78 ppm (triplet). On the other hand, for **17b**, the protons at C-3 (δ 31.8 ppm) presented a $\Delta\delta$ at 2.25 ppm (δ 2.55 and 4.80 ppm, respectively), the methine proton was found at δ 2.60 ppm (Fig. 4). The selectivity of the process may be governed by two factors, the relative stability of the two products or the rates of formation. To determine whether one or both factors had an influence on the results of the reaction, the stabilities of the two possible diastereoisomers **17a** and **17b** were studied by theoretical methods. The geometry optimizations were performed at the B3LYP/6-31**G level with the Gaussian G03 program package.[10] Conformational minima obtained for both epimers are shown in Figure 4. The calculated energy difference for them is low (ΔE = 1.87 kcal/mol) with a slight minimum for the configuration where the sulfur atom is in a *cis*-position with regard to the carboxymethyl group at C-2 of the cyclobutane ring. It is proposed that there is a considerable amount of steric hindrance to the ring-closure from one side of the ring at C-4 which might be explained on the basis that while the sulfur atom is more bulky than the nitrogen atom, the N–$COCH_3$ group becomes more bulky than the sulfur atom during cyclization. Thus the thiadiazoline ring closure at C-4, by the preferential attack of the sulfur atom to the more hindered side, leaves the bulky (N–$COCH_3$) group on the less sterically hindered side, to give **17a**.

The apparent disparity in the ^1H NMR shifts, corresponding to isomer **17b**, especially in the case of H-3 at δ 4.80 ppm, indicates high deshielding due to the anisotropic effect of the two C=O groups, the acetyl moiety bound to N-8 and the methoxycarbonyl group bound to C-2, both of the spirane system (see Fig. 4). This phenomenon was also observed for the proton bound to the C-2 of the cyclobutane in **17a**, found at lower fields than the one corresponding to **17b** ($\Delta\delta$ 1.2 ppm).

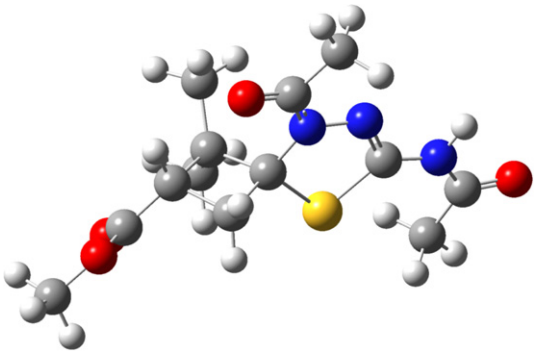
The ^1H chemical shifts were calculated with the B3LYP/6-31**G optimized geometries of diastereoisomers **17a** and **17b** (Fig. 4) by the GIAO method.[11] A good correlation with the observed experimental values was found (Table 1).

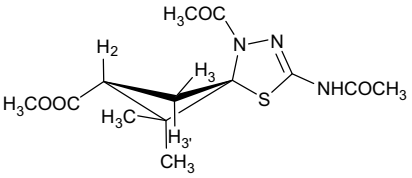
3. Conclusion

Herein we have studied the stereoselectivity of the cyclization procedure to obtain Δ^2-1,3,4-TDZ compounds from the corresponding TSC precursors. While the TSC derived from methylcyclobutyl ketones gave mixtures of heterocyclic derivatives, the TSC of a cyclobutanone gave a main product, in accordance to those previously described for other cycloalkanones, showing the influence of the steric hindrance during the ring closure process. We have also reported spectroscopic and theoretical studies to confirm our hypothesis regarding the influence of this effect on the observed diastereoselectivity.



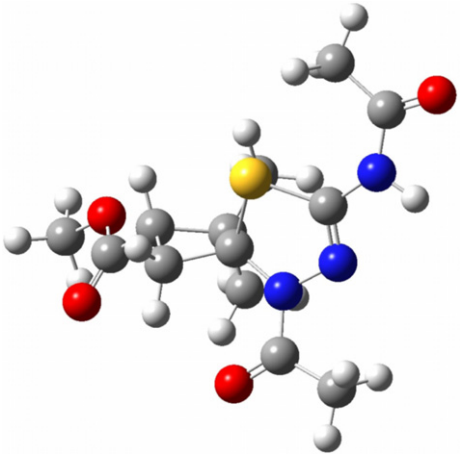
Scheme 4. The mechanism of reaction of TSC with acetic anhydride.

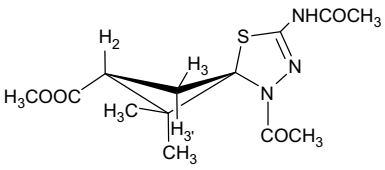




(2*S*,4*R*)-**17a**

17 a





(2*S*,4*S*)-**17b**

17 b

Figure 4. Conformational minima obtained by theoretical calculations for epimers **17a** and **17b**.

Table 1
Chemical shifts found and calculated for H-2, H-3 and H-3′for compounds **17a** and **17b**

H	**17a** Exp. δ (ppm)	**17a** Calcd δ (ppm)	**17b** Exp. δ (ppm)	**17b** Calcd δ (ppm)
H-2	3.78	4.02	2.60	2.89
H-3	3.34	3.40	4.80	5.46
H-3′	2.90	3.17	2.45	2.46

4. Experimental

4.1. General

Melting points were measured in a Unimelt or in an Electrothermal IA 9000 apparatus. FT-IR spectra were recorded as a film from chloroform with a Spectrum one FT-IR spectrometer Perkin–Elmer. ^{1}H, ^{13}C NMR spectra, heteronuclear correlation spectroscopy and NOESY experiments were recorded in a Bruker 400-MHz or in a Bruker 300-MHz spectrometers. Chemical shifts are expressed in ppm (relative to the solvent). High resolution mass spectra (HRMS) were determined in a VG AutoSPec (Micromass Inst.). Thin layer chromatography (TLC) and preparative thin layer chromatography were performed on Silica Gel GF254 (Merck). Optical rotations were measured with Perkin–Elmer 141 polarimeter at 23 °C. Single crystal X-ray diffraction data were collected at room temperature, using a Gemini A diffractometer (Oxford Diffraction, UK). Data-collection strategy and data reduction followed standard procedures implemented in the CrystAlisPro software.[12] The structures were solved using program SHELXS-97[13] and refined using the full-matrix LS procedure with SHELXL-97.[13] Anisotropic displacement parameters were employed for non-hydrogen atoms and H atoms were treated isotropically with U_{iso} = 1.2 (for those attached to aromatic O and to N atoms) or 1.5 times (for those bonded to C atoms) the U_{eq} of the parent atoms. All H atoms were located at the expected positions and they were refined using a riding model. In the final cycle of refinement, LS weights of the form $w = 1/[\sigma_2(F_o^2) + (a * P)^2 + b * P]$, where $P = [(F_o^2) + 2 * F_c^2)]/3$, were employed. Routines employed to create CIF files are from WinGX package.[14] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre[15] as supplementary publications N° CCDC 833332. Theoretical calculations were performed using B3LYP/6-31**G level with the Gaussian G03 program package.[10] The GIAO method[11] was used for the simulation of ^{1}H NMR spectra.

4.2. Procedures and analytical data

4.2.1. (1*R*,3*S*)-3-Butyldiphenylsilyloxymethyl-2,2-dimethyl-cyclobutylmethylketone 8

A mixture of alcohol **5**[6](1 mmol) and DMAP (3 mmol) in anhydrous methylene chloride (1 mL) was stirred under a nitrogen atmosphere until complete dissolution at room temperature. The solution was cooled at 0 °C and and *tert*-butyldiphenylsilylchloride

(2 mmol) was added dropwise. The flask was sealed with a septum and the reaction was left at room temperature with stirring under a nitrogen atmosphere for 12 h. Then the mixture was diluted with a mixture of methylene chloride and HCl 1% (5 mL). The organic phase was separated, washed with water (2 × 10 mL), dried over Na_2SO_4, and the solvent was removed until dryness. The compound obtained was purified by preparative TLC (solvent Cl_2CH_2/hexane; 1:1) and the fraction with the higher R_f was eluted with Cl_2CH_2. Product **7** was characterized by ^{1}H NMR and used without further purification in the next step. Compound **7** (1 mmol) was dissolved in acetone (15 mL) and PPTS (0.33 mmol) was added. The mixture was heated at reflux for 5 h. Then the solvent was removed and the residue was diluted with diethyl ether (15 mL). The organic phase was washed with $NaHCO_3$ (saturated solution) and dried over Na_2SO_4. The crude product obtained was purified by preparative TLC eluting with hexane/chloroform (2:1). The fraction with the higher R_f corresponded to compound **8** and was isolated as an oil (yield 52%); IR ν_{max} (cm^{-1}) (film) 2956, 1706 (C=O), 1427, 1112 (Si–O–C). ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 3H), 1.04 (s, 9H), 1.41 (s, 3H), 1.60–1.75 (m, 1H), 1.85 (dd, 1H, J = 7.4 Hz, J = 10.0 Hz), 2.04 (s, 3H), 2.20–2.30 (m, 1H), 2.83 (dd, 1H, J = 10.7 Hz, J = 21.5 Hz), 3.50–3.60 (m, 2H), 7.30 (m, 3H) and 7.65 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 17.6, 19.8, 27.5 (three carbons), 30.8, 32.0, 44.0, 44.1, 50.2, 54.4, 64.8, 128.3 (two carbons), 130.3, 134.4, 136.2 (two carbons) and 208.7 ppm. HRMS: Calcd for $C_{25}H_{34}NaO_2Si$ 417.22203. Found 417.22327. $[\alpha]_D^{23} = -46.0$ (c 0.5, chloroform).

4.2.2. Synthesis of thiosemicarbazones. General procedure

An ethanolic solution of ketone and thiosemicarbazide in equimolecular quantities was heated at reflux (for approximately 36 h) and the reaction monitored by TLC. The corresponding thiosemicarbazones were isolated after evaporation of the solvent under reduced pressure. Thiosemicarbazones were purified by preparative TLC (solvent: chloroform) or recrystallization as indicated for each case.

4.2.3. Synthesis of thiadiazolines. General procedure

Thiosemicarbazones (0.25 mmol) were dissolved in a pyridine/acetic anhydride mixture (1:1, 0.5 mL) and the mixtures were heated with magnetic stirring at 110 °C for 1.5 h. Crude products were purified by preparative TLC eluting with hexane/ethylacetate/chloroform (3.5:2.0:1.5) or by recrystallization as indicated in each case.

4.2.4. [(1*R*,3*R*)-3-Methylacetate-2,2-dimethylcyclobut-1-yl] methyl thiosemicarbazone 10

Compound **10** was obtained as an oil (yield 30%); IR ν_{max} (cm^{-1}) (film) 3428, 3267, 2952 (NH and NH_2), 1732 (C=O), 1591 (C=N), and 1504 (C=S). ^{1}H NMR (acetone-d_6) δ 0.75 (s, 3H), 1.25 (s, 3H), 1.80 (s, 3H), 1.90–2.05 (m, 2H), 2.15–2.35 (m, 3H), 2.65–2.70 (m, 1H), 3.65 (s, 3H), 6.55 (br s, 1H), 7.24 (br s, 1H) and 8.75 (br s, 1H) ppm. ^{13}C NMR (acetone-d_6) δ 17.7, 18.0, 25.7, 35.9, 39.4, 44.2, 50.6, 51.6, 52.1, 153.4, 174.1, 181.5 ppm. HRMS: Calcd for $C_{12}H_{22}N_3O_2S$ 272.14272. Found 272.14377. $[\alpha]_D^{23} = -33.8$ (c 0.3, acetone).

4.2.5. (1′*R*,3′*R*,5*S*)- and (1′*R*,3′*R*,5*R*)-2-Acetamido-4-acetyl-5-(3′-methylacetate-2′,2′-dimethylcyclobutyl)-5-methyl-Δ^2-1,3,4-thiadiazoline 14

Compound **14** was obtained as an oil (yield 62%); IR ν_{max} (cm^{-1}) (film) (as a mixture) 3240, 3170, 3083 (NH and NH_2), 1737, 1712, 1666, 1621 (C=O), 1504 (C=N). ^{1}H NMR ($CDCl_3$) (as a mixture) δ 1.00 (s, 3H), 1.02 (s, 3H), 1.15 (s, 3H), 1.18 (s, 3H), 1.90 (s, 3H), 1.50–2.00 (m, 4H), 2.00 (s, 3H), 2.10–2.50 (m, 6H), 2.15 (s, 6H), 2.20 (s, 6H), 3.14 (m, 1H), 3.45 (m, 1H), 3.65 (s, 6H) and 8.30 (br s, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ 16.2, 17.3, 23.4 (two carbons), 24.2, 24.6, 26.7, 27.3, 28.6, 28.9, 31.0, 31.2, 34.7 (two carbons), 38.4, 38.8, 42.1, 42.9, 47.2, 48.5, 51.5 (two carbons), 83.3, 84.4, 142.7, 143.3, 168.1 (two carbons), 169.2, 169.6 and 173.4 (two carbons) ppm. HRMS: Calcd for $C_{16}H_{25}N_3O_4S$ 355.15658. Found 355.15672.

4.2.6. [(1*R*,3*S*)-3-Methoxycarbonyl-2,2-dimethylcyclobut-1-yl] methyl thiosemicarbazone 11

Compound **11** was obtained as a crystalline solid (yield 25%); mp: 134.4–134.9 °C (ethanol); IR ν_{max} (cm^{-1}) 3427, 3256, 3156 (NH and NH_2), 1720 (C=O), 1583 (C=N), 1501 (C=S). ^{1}H NMR (DMSO-d_6) δ 0.70 (s, 3H), 1.30 (s, 3H), 1.80 (s, 3H), 1.70–1.80 (m, 1H), 2.45–2.65 (m, 1H), 2.70–2.90 (m, 2H), 3.60 (m, 3H), 7.51 (br s, 1H), 8.15 (br s, 1H) and 9.95 (br s, 1H) ppm. ^{13}C NMR (DMSO-d_6) δ 17.3, 17.7, 19.9, 29.8, 40. 6, 44.2, 44.3, 51.1, 152.7 172.6 and 178.6 ppm. HRMS: Calcd for $C_{11}H_{19}N_3NaO_2S$ 280.10902. Found 280.10996. $[\alpha]_D^{23} = -45.0$ (c 1.1, acetone).

4.2.7. (1′*R*,3*S*′,5*S*)- and (1′*R*,3*S*′,5*R*)-2-Acetamido-4-acetyl-5-(3′-methoxycarbonyl-2′,2′-dimethylcyclobutyl)-5-methyl-Δ^2-1,3,4-thiadiazoline 15

Compound **15** was obtained as an oil (yield 55%); IR ν_{max} (cm^{-1}) (as a mixture) 3171 and 3085 (N–H), 1734, 1713, and 1665 (C=O), and 1621(C=N). ^{1}H NMR ($CDCl_3$) (as a mixture) δ 0.95 (s, 3H), 1.02 (s, 3H), 1.10 (s, 3H), 1.20 (s, 3H), 1.80 (s, 3H), 1.86 (s, 3H), 1.95–2.00 (1H, m), 2.06 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 2.18–2.21 (m, 1H), 2.30–2.48 (m, 1H), 2.55–2.65 (m, 2H), 3.10–3.14 (m, 1H), 3.38–3.42 (m, 1H) and 11.50 (br s, 2H) ppm. ^{13}C NMR ($CDCl_3$) (as a mixture) δ 16.9, 17.9, 21.0, 21.8, 23.0, 24.0, 24.2, 24.4, 27.1, 28.2, 31.2, 31.4, 44.4, 45.3, 45.5, 46.0, 46.4, 48.2, 51.3, 51.5, 82.0, 83.1, 144.0, 144.5, 169.4, 169.5, 169.6, 169.9, 172.8 and 173.2 ppm. HRMS: Calcd for $C_{15}H_{23}N_3O_4S$ 341.14093. Found 341.13907.

4.2.8. [(1*R*,3*S*)-3-Hydroxymethyl-2,2-dimethylcyclobut-1-yl] methyl thiosemicarbazone 12

Compound **12** was obtained as a crystalline solid (yield 60%); mp 183.2–184.2 °C (ethanol). IR ν_{max} (cm^{-1}) 3438, 3290, 3164 (NH and NH_2), 1597 (C=N), and 1501 (C=S). ^{1}H NMR (DMSO-d_6) δ 0.78 (s, 3H), 1.23 (s, 3H), 1.60–1.70 (m, 1H), 1.81 (s, 3H), 1.90–2.10 (m, 2H), 2.60–2.70 (m, 1H), 3.20–3.45 (m, 2H), 7.43 (s, 1H), 8.07 (s, 1H) and 9.89 (br s, 1H) ppm. ^{13}C NMR (DMSO-d_6) δ 17.4, 22.1, 25.9, 31.9, 43.5, 44.7, 51.0, 63.4, 153.4, 172.4 ppm. HRMS: Calcd for $C_{10}H_{19}N_3OS$: 229.12488. Found 229.12441. $[\alpha]_D^{23} = -19.0$ (c 0.4, acetone). Unit cell: a: 7.9523(3) Å, b: 9.2675(3) Å, c: 9.6965(3) Å, α: 63.517(3)°, β: 83.499(3)°, γ: 82.073(3)°, V: 632.43(4) Å^3, number of collected reflections: 15070, R_{int}: 0.023, number of independent reflections: 3060, number of reflection with $I > 2\sigma(I)$: 2064, number of parameters: 136, R_1 ($I > 2\sigma(I)$): 0.052, wR_2 (all refl.): 0.166, S: 1.104.

4.2.9. (1′*R*,3′*S*,5*S*)- and (1′*R*,3′*S*,5*R*)-2-Acetamido-4-acetyl-5-(3′-acetoxymethyl-2′,2′-dimethylcyclobutyl)-5-methyl-Δ^2-1,3,4-thiadiazoline 16

Compound **16** was obtained as an oil (yield 32%). IR ν_{max} (cm^{-1}) (as a mixture) 3170, 3084 (N–H), 1740, 1712, 1666, (C=0), and 1621 (C=N). Separation of **16a** TDZ and **16b** TDZ was performed using HPLC (Waters 996 PDA HPL System) using methanol as a mobile phase in an isocratic mode and with a chiral column CHIRADEX (MERCK) of 250 mm × 4.6 mm, with 5 μm of particle size.

Compound **16a** ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 3H), 1.19 (s, 3H), 1.65 (m, 1H), 1.92 (s, 3H), 2.00–2.25 (m, 2H), 2.04 (s, 3H), 2.16 (s, 3H), 2.19 (s, 3H), 3.21 (dd, 1H, J = 8 Hz, J = 12 Hz), 4.00–4.15 (m, 2H), 8.00 (br s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 16.7, 21.7, 24.1, 24.8, 26.5, 29.3, 32.6, 41.4, 43.2, 49.0, 65.3, 82.3, 151.2, 170.0, 170.3, 171.7 ppm.

Compound **16b** ^{1}H NMR (CDCl3) δ 1.11 (s, 3H), 1.21 (s, 3H), 1.75–1.95 (2H, m), 1.98 (s, 3H), 2.04 (s, 3H), 2.10–2.20 (1H, m), 2.16 (s, 3H), 2.19 (s, 3H), 3.50 (dd, 1H, J = 8 Hz, J = 12 Hz), 3.99

(dd, 1H, J = 8 Hz, J = 10 Hz), 4.09 (dd, 1H, J = 6 Hz, J = 8HZ), 7.98 (br s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 17.7, 21.7, 24.1 (two carbons), 25.3, 28.1, 32.4, 41.0, 42.4, 47.5, 65.3, 85.0, 145.9, 170.0, 170.3, 171.7 ppm. HRMS (as a mixture): Calcd for $C_{16}H_{25}N_3O_4S$: 355.15668. Found 355.15662.

4.2.10. (3*S*)-3-Methoxycarbonyl-2,2-dimethylcyclobutanone thiosemicarbazone 13

Compound **13** was obtained as a crystalline solid (yield 75%); mp: 223.4–224.2 °C (ethanol); IR ν_{max} (cm^{-1}) 3408, 3247, 3149 (NH and NH_2), 1718 (C=O), 1600 (C=N), 1525 (C=S). ^{1}H NMR (DMSO-d_6) δ 1.04 (s, 3H), 1.29 (s, 3H), 2.90–3.00 (m, 1H), 3.05–3.15 (m, 2H), 3.64 (s, 3H), 7.41 (s, 1H), 7.97 (s, 1H) and 10.48 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6) δ 21.0, 25.6, 31.8, 42.5, 51.1, 51.6, 158.6, 172.4 and 178.2 ppm. HRMS: Calcd for $C_9H_{16}N_3O_2S$ 230.09577. Found 230.09660. $[\alpha]_D^{23} = -16.0$ (c 0.9, acetone).

4.2.11. (1,1-Dimethyl-2-methoxycarbonyl-6-*N*-acetyl-8-acetyl)spiro[3,4]-5-tia-7,8-diazaocta-6-eno 17

4.2.11.1. (2*S*,4*R*)-17a TDZ. Major product was obtained as a crystalline solid (yield 60%); mp: 157.5–158.8 °C (acetone); IR ν_{max} (cm^{-1}) (as a mixture) 3433 (N–H), 1733 (C=O), 1669 (C=O), 1636 (C=O) and 1615 (C=N). ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.15 (s, 3H), 2.19 (s, 3H), 2.26 (s, 3H), 2.80–3.00 (dd, 1H, J = 8 Hz, J = 15 Hz), 3.30–3.40 (dd, 1H, J = 8 Hz, J = 15 Hz), 3.68 (s, 3H), 3.80 (t, 1H, J = 8 Hz) and 8.50 (br s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 23.6, 23.9, 24.8, 25.0, 30.9, 45.7, 52.1, 53.0, 83.9, 145.1, 169.2, 171.0 and 173.9 ppm. $[\alpha]_D^{23} = +4.5$ (c 0.7, acetone). HRMS: Calcd for $C_{13}H_{20}N_3O_4S$: 314.11690. Found 314.11700.

4.2.11.2. (2*S*,4*S*)-17b TDZ. Minor product was obtained as an oil (yield 1%). ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 3H), 1.30 (s, 3H), 2.20 (s, 3H), 2.23 (s, 3H), 2.50–2.70 (m, 2H), 3.71 (s, 3H), 4.79 (dd, 1H, J = 8 Hz, J = 12 Hz) and 8.60 (br s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 20.7, 24.1, 24.8, 26.8, 31.8, 44.3, 52.3, 55.5, 82.7, 146.5, 168.9, 172.2 and 172.5 ppm.

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References

1. (a) Kirkland, P. D.; Frost, M. J.; Finlaison, D. S.; King, K. R.; Ridpath, J. F.; Gu, X. *Virol. Res.* **2007**, *129*, 126; (b) Yusuf, M.; Jain, P. *Arab. J. Chem.* **2011**. doi:10.1016/j.arabjc.2011.02.006; (c) Fatondji, H. R.; Gbaguidi, F.; Kpoviessi, S.; Bero, J.; Hannaert, V.; Quetin-Leclercq, J.; Poupaert, J.; Moudachirou, M.; Accrombessi, G. C. *Afr. J. Pure Appl. Chem.* **2011**, *5*, 59.
2. Kubota, S.; Ueda, Y.; Fujikane, K.; Toyooka, K.; Shibuya, M. *J. Org. Chem.* **1980**, *45*, 1473.
3. (a) Brousse, B. N.; Moglioni, A. G.; Martins Alho, M. A.; Moltrasio, G. Y.; ÓAccorso, N. *Arkivoc* **2002**, *3*, 14; (b) Rouge, P. D.; Brousse, B. N.; Moglioni, A. G.; ÓAccorso, N.; Moltrasio, G. Y. *Arkivoc* **2005**, *xii*, 8.
4. (a) Brousse, B. N.; García, C.; Moglioni, A. G.; Moltrasio, G. Y.; Martins Alho, M.; D'Accorso, N. B.; Carlucci, M. J.; Damonte, E. *Antivir. Chem. Chemother.* **2003**, *14*, 99; (b) Brousse, B. N.; Massa, R.; Moglioni, A. G.; Martins, M.; D'Accorso, N.; Gutkind, G.; Moltrasio, G. *J. Chilean Chem. Soc.* **2004**, *49*, 45; (c) Finkielsztein, L. M.; Castro, E. F.; Fabian, L. E.; Moltrasio, G. Y.; Campos, R. H.; Cavallaro, L. V.; Moglioni, A. G. *Eur. J. Med. Chem.* **2008**, *43*, 1767.
5. Shamsuzzamam; Aslam, M.; Salim, A. *J. Chem. Res. (S)* **1998**, 824.
6. Moglioni, A. G.; García-Expósito, E.; Aguado, G.; Parella, T.; Moltrasio, G. Y.; Ortuño, R. M. *J. Org. Chem.* **2000**, *65*, 3934.
7. Aguado, G. P.; Moglioni, A. G.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2003**, *14*, 217.
8. Rouge, P. D.; Moglioni, A. G.; Moltrasio, G. Y.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2003**, *14*, 193.
9. Somogyi, L. *Tetrahedron* **1991**, *47*, 9305.
10. 10. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A. Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Lyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, L.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmam, R. E.; Yazyev, O.; Austin, A. I.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, L. V.; Cu, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, L.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gili, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Popie, J. A. *Gaussian 03, Revision C.02*, Gaussian, Inc.: Wallingfbrd CT, 2004.
11. Wolinski, K.; Hilton, K. J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *12*, 203.
12. *CrysAlisPro*. Oxford Diffraction Ltd, Version 1.171.33.66. 2010.
13. Sheldrick, G. M. *Acta Cryst. A.* **2008**, *64*, 112.
14. Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, 837.
15. Allen, F. H. *Acta Cryst. B* **2002**, *58*, 380.