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Masked constrained cysteines: diastereoselective and enantioselective synthesis of 1-amino-2-mercaptocyclopropanecarboxylic acid derivatives

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Abstract—A diastereoselective and enantioselective synthesis of (*Z*)-1-benzoylamino-2-tritylsulfanylcyclopropanecarboxylic acid derivatives **8a**,**b** and **9a**,**b** was achieved starting from (−)- or (+)-menthyl 2-benzoylamino-3-tritylsulfanylacrylates **3a**,**b**. Compounds **3** were reacted with diazomethane giving the corresponding pyrazolines **4a**,**b** and **5a**,**b**. These compounds, on melting, were transformed, under steric control, into the cyclopropaneamino acid derivatives (*R*,*R*)-**8a**,**b** and (*S*,*S*)-**9a**,**b**. The synthesis of a large class of chiral 2-*S*-alkyl-1-aminocyclopropanecarboxylic acid derivatives is possible after removing the trityl protecting group and subsequent alkylation reactions.

1. Introduction

Recently,[1] we reported the synthesis of a series of 1-amino-2-mercaptocyclopropanecarboxylic acid derivatives having different substituents on the sulfur. We found that the compound substituted at sulfur with a trityl group could be used as the key starting material for the preparation of a large number of the above compounds in which an alkyl group is present.

In addition to their biological interest as single molecules,[2] new classes of cyclopropylamino acid derivatives are worth synthetic effort due to the possibility of using them in the synthesis of special peptides.[3] The choice of cyclopropylamino acid derivatives is very interesting owing to the possibility of making the peptide skeleton stiff because of hindered rotation around the Cα–Cβ bond by the cyclopropyl ring. Furthermore, when a β-substituent is present on the cyclopropyl ring, the possibility of choosing the *cis* (β-substituent to respect nitrogen atom) or *trans* stereoisomer allows the evaluation of the substituent effect on the interaction between the drug and the receptor site.

Clearly, diastereoselective and, most of all, enantioselective syntheses are of general interest and our research toward the syntheses of constrained cysteine derivatives **8**,**9** are proceeding in this direction. We now report the diastereoselective and enantioselective synthesis of (1*R*,2*R*)- and (1*S*,2*S*)-1-benzoylamino-2-tritylsulfanylcyclopropanecarboxylic acid derivatives, which, as underlined before, are interesting key starting materials. For their preparation, new chiral aminoacrylate derivatives **3** were prepared.

2. Results and discussion

The new chiral aminoacrylates **3a**,**b** were obtained in 66–84% yield when 2-phenyl-4-(tritylsulfanylmethylene)-5(4*H*)-oxazolone **1** was reacted with (−)- or (+)-menthol **2a**,**b**, respectively, in a benzene solution and in the presence of bis-(dibutylchlorotin)oxide as catalyst[5] (Scheme 1). The use of this catalyst is essential for product formation because nucleophiles can react both at the carbonyl group and at the double bond when the starting oxazolone is functionalized at the double bond with an heteroatom. When **1** was reacted with the menthol under the classical basic or acidic conditions, the reaction was not successful and a mix-

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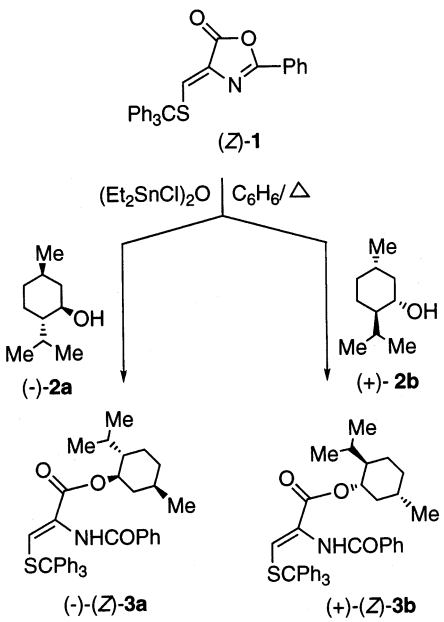


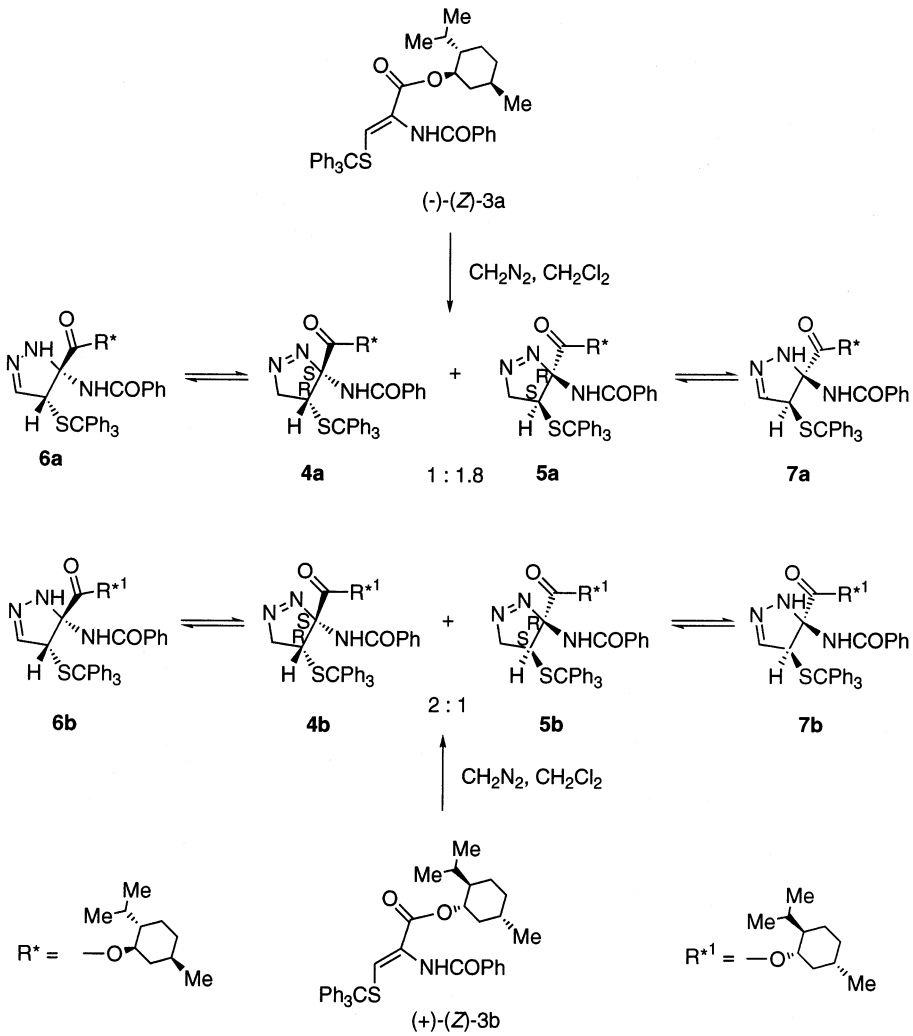
Scheme 1.

ture of compounds or the starting oxazolone was obtained.

The structure of the enantiomeric acrylates **3** was determined by analytical and spectroscopic data. The ^{1}H NMR spectrum is characterized by a singlet at 7.93 δ (NH) and at 7.03 δ associated with the olefinic proton. The NOESY experiment evidenced the spatial proximity between the H-3 and the menthyl protons, thus assuring the *Z* stereochemistry of the double bond.

Compound **3a** was reacted in dichloromethane at room temperature with an excess of diazomethane. Two diastereoisomeric pyrazoline derivatives **4a** and **5a** were detected by ^{1}H NMR and HPLC in a 1:1.8 ratio and were separated by column chromatography. During this process partial isomerization of the Δ^1-pyrazolines **4a**,**5a** to Δ^2-pyrazolines **6a**,**7a** was observed. The overall reaction yield was good (93%) and the Δ^1/Δ^2-pyrazoline ratio is about 5.2:1 (Scheme 2).

Under the above reaction conditions, the diastereoisomeric pyrazoline derivatives **4b** and **5b** were obtained



Scheme 2.

(2:1) when starting from the acrylate **3b**. These compounds also partially isomerized to the Δ^2-pyrazolines **6b**,**7b** during chromatography on silica gel, and compounds **4**–**7b** were obtained in 88% ($\Delta^1/\Delta^2 = 5.7:1$) overall yield (Scheme 2). The Δ^1-pyrazolines **4a**,**5b**, with respect to compounds **5a**,**4b**, isomerize slowly to the corresponding Δ^2-isomers.

Pyrazolines **4a** and **5b** showed identical ^{1}H and ^{13}C NMR spectra. Furthermore, they are characterized by the same absolute value of specific rotation (**4a**: +125.4; **5b**: −125.4). On the basis of these results, we can conclude that **4a** and **5b** are enantiomers. On the same basis, the enantiomeric relationship between **5a** and **4b** was established ($[\alpha]_D = -202$, +202 for **5a** and **4b**, respectively).

The ^{1}H NMR spectra of enantiomeric compounds **4a** and **5b** showed the presence of a singlet at 8.35 δ (NH), a multiplet at 4.76–4.70 associated to the CHO of menthyl group. An ABX system is present and the chemical shift values at low fields ($\delta = 4.62$, 3.97, 3.05; $J = 18.9$, 9.4, 6.8 Hz) are in good agreement with the values expected for a pyrazoline structure.

Analogous results were observed for the couple of enantiomers **5a** and **4b** having ^{1}H NMR spectra characterized by a singlet at 8.22 δ (NH), a multiplet at 4.65–4.54 δ (CHO) and an ABX system at $\delta = 4.65$, 4.07, 3.10 ($J = 19.0$, 9.4, 6.2 Hz).

Through a NOESY experiment on the pyrazoline derivative **4a**, positive Overhauser effects between H-4 ($\delta = 3.05$) and H-5 ($\delta = 3.97$) and between the latter and H-5′ ($\delta = 4.62$) were observed. Analogously, in the case of the diastereoisomeric compound **5a**, spatial proximity was observed between H-4 ($\delta = 3.10$) and H-5 ($\delta = 4.07$) and between the latter and H-5′ ($\delta = 4.65$). In both diastereoisomeric compounds **4a** and **5a** the Overhauser effect was not detected between H-4 and the proton linked to the nitrogen atom (Fig. 1).

These data confirm the assigned configuration which is the same of the starting olefin **3**. Furthermore, the *J*

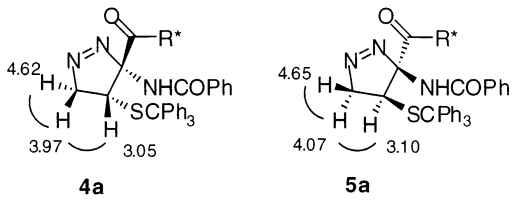


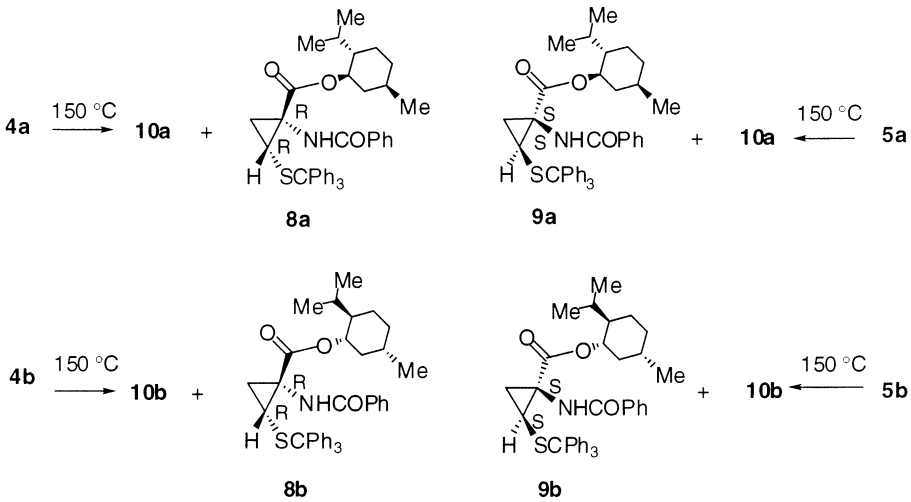
Figure 1.

values observed in the ABX system confirms the assigned regiochemistry.

These results are in agreement with the literature[2a,4] data concerning the diazomethane addition reaction to α-aminoacrylate derivatives. In fact, it has been reported that the dipolar cycloaddition reaction usually occurs under charge control giving a single regioisomer for which the relationship between the two substituents is maintained. In our case, the asymmetric induction of the menthyl group is better in respect to other auxiliary alcohols used for the esterification of aminoacrylate derivatives.[4b]

The structure of the Δ^2-pyrazolines **6b**,**7a** was assigned on the basis of their identical ^{1}H NMR spectra, which are characterized by the presence of signals associated with the amidic proton ($\delta = 7.94$), and with the NH proton of the Δ^2-pyrazolinyl ring ($\delta = 7.12$) and by an AX system ($\delta = 6.29$, 3.99, $J = 1.4$ Hz) associated with H-3 and H-4. Analogous data were observed for enantiomers **6a**, **7b** ($\delta = 8.05$, NH; $\delta = 6.58$, NH; $\delta = 6.14$, 4.09, $J = 1.5$ Hz, AX system).

The transformation of pyrazoline derivatives **4** and **5** into the corresponding cyclopropane amino acid derivatives was not possible in solution. In fact, these compounds are stable from room temperature to 150°C. Instead, when melted at 150°C for 10 min, they were readily transformed into cyclopropane derivatives. Starting from pure **4a**, cyclopropane **8a** was isolated in 70% yield in diastereomerically pure form, as confirmed by ^{1}H NMR and HPLC. An acrylate derivative **10a**, as secondary product (17%), was also isolated. The same



Scheme 3.

behavior was observed when starting from **5a**, **4b** and **5b**. Cyclopropane derivatives **9a** (82%), **8b** (64%) and **9b** (72%) were obtained, respectively, as well as the acrylate derivative **10a** (13%) in the first case and its enantiomer **10b** (10–16%) in the other (Scheme 3).

The structure of the enantiomers **8a**/**9b** as well as the enantiomers **8b**/**9a** was demonstrated by spectroscopic data. In the ^{1}H NMR spectrum of compounds **8a**/**9b**, a singlet at 5.42 δ (amidic proton) and a multiplet at 4.64–4.58 δ (CHO) are present. The δ values of the ABX system ($\delta=2.66$, 2.21, 1.24; $J=10.2$, 7.4, 6.3 Hz) are in agreement with the values reported for similar cyclopropane compounds.[1] Analogous results were observed for the couple **8b**/**9a**. Signals at 5.09 δ (NH), 4.61–4.48 δ (CHO) and $\delta=2.73$, 2.26, 1.25 (ABX system, $J=10.1$, 7.5, 6.3 Hz) were observed.

NOESY experiments were carried out on both **8a** and **9a**. A positive Overhauser effect was observed in compound **8a** between H-2 ($\delta=2.66$) and H-3 ($\delta=2.21$). In contrast, the spatial proximity between H-2 and NH was absent, thus confirming the assigned configuration. The NOESY experiment on compound **9a** revealed spatial proximity for the latter mentioned protons also.

As demonstrated by X ray analysis of compound **8a** (Fig. 2), the absolute configuration of the two stereocenters is *R* confirming the *cis* relationship between the trityl and benzoylamino groups as in the starting pyrazoline **4a**. Accordingly, the *S* and *R* configuration at C-3 and C-4 was assigned.

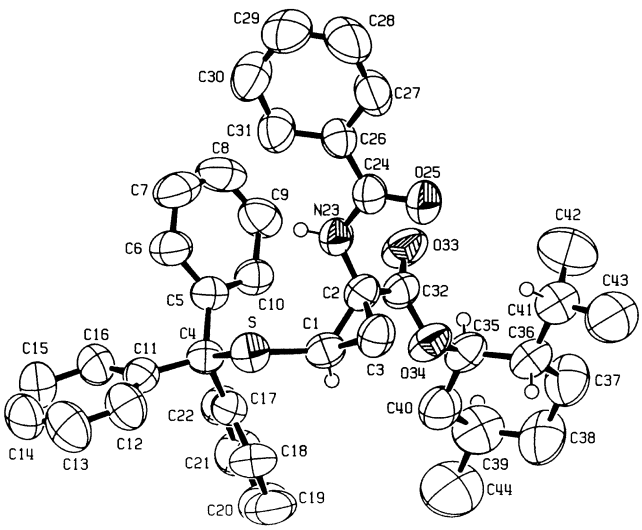


Figure 2. Projection of **8a** with the crystallographic numbering scheme. Ellipsoids at 50% probability level. For clarity H atoms of phenyl, CH_2 and CH_3 groups are omitted.

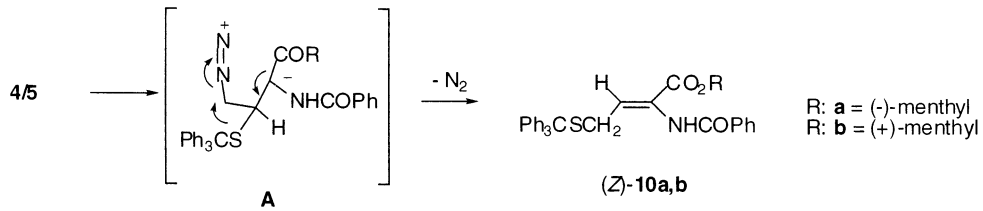
On the basis of the above analytical and spectroscopic data, it was concluded that the contraction of the pyrazoline ring into the cyclopropane is sterically controlled and retention of configuration exists at C-α of the amino acid derivatives. As a consequence of this observation and on the basis of the experimental results illustrated below (hydrolysis of compound **9a**), the *S*,*S* configuration was assigned to the stereoisomer **9a**. Any attempt to prepare suitable crystals for X-ray analysis of this compound failed.

The formation of by-products **10a**,**b** can be explained as an insertion olefin reaction typical for pyrazoline ring decomposition (Scheme 4).

As a consequence of breaking the bond between the pyrazoline nitrogen and the quaternary carbon, an intermediate A is formed, which rearranges to the acrylate derivatives **10** with formation of the double bond and transposition of the S-trityl group to C-4 on nitrogen elimination. The structure of compounds **10** was confirmed by spectroscopic data. In the ^{1}H NMR spectrum a doublet at $\delta=3.12$ and a triplet at $\delta=6.82$ associated with H-4 and H-3, respectively ($J=7.7$ Hz), are present. A Hetcor reverse experiment allowed association of these protons to the corresponding carbons, which values were in agreement with the proposed structure (C-3: $\delta=132.4$; C-4: $\delta=31.0$). Finally, a NOESY experiment allowed confirmation of the *Z* geometry of the double bond because spatial proximity was demonstrated between H-3 and the protons of the menthyl group.

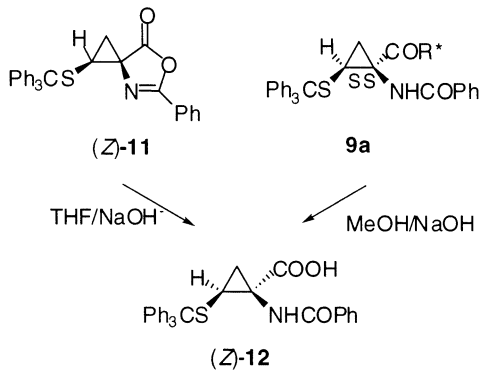
The behavior of the Δ^1-pyrazolines was also tested under ultraviolet light. The reaction was carried out both in a dichloromethane solution and in acetone starting from the pyrazoline **4a** using a HPK-Philips 125 W high pressure Hg lamp. The reactions were monitored by ^{1}H NMR and by HPLC. After 3 h the reaction was complete and the above analyses revealed the formation of the cyclopropane derivative **8a** and of the acrylate **10a** in a 1.5:1 ratio, when using CH_2Cl_2 and 1:1 ratio when using acetone. However, this procedure was not considered convenient for the preparation of compounds **8** and **9** considering the increase in the amount of unwanted compound **10**.

The hydrolysis of the ester function in compound **9a** was carried out in methanol in the presence of sodium



Scheme 4.

hydroxide. The reaction gave the chiral acid **12**, which was characterized by the same ^{1}H NMR of the racemic acid obtained when the known spiro compound **11**[1] was hydrolyzed in THF and in the presence of NaOH (Scheme 5). This result confirms indirectly the *cis* relationship between nitrogen and sulfur atoms, and the absolute configuration *S* was assigned at the two stereocenters in compound **9a**.



Scheme 5.

On the basis of the above results, we conclude that the new chiral synthons **3** are useful key starting materials for the preparation of amino acid derivatives **8**/**9** with diastereoselective and enantioselective control. Even though the ratio between the two pyrazolines **4**/**5** was not very high (about 1:2), the complementary distribution of the latter compounds, when starting from **3a** (**4a**/**5a**, 1:1.8) or **3b** (**4b**/**5b**, 2:1), the good yields and the easy separation of the diastereoisomers and, most of all, the possibility of transforming the pyrazolines **4**/**5** into the cyclopropane derivatives **8**/**9** in a stereocontrolled way, make this synthetic procedure satisfying.

3. Experimental

Melting points were determined using an Electrothermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ as the solvent with Bruker Avance 300 and Varian Gemini 200 instruments. Coupling constants values (*J*) are given in hertz. HPLC using Hipersil column (250×4.6 mm; CH_2Cl_2/AcOEt, 100: 2.5; $T=30$°C; flow = 1 mL/min, $\lambda=254$). Ethanol-free CH_2Cl_2 was used in all experiments. Oxazolone **1** and spirooxazolone **11** are known compounds.[1]

3.1. X-Ray crystallographic analysis data for compound 8a

X-Ray data were collected on a Bruker SMART-CCD area-detector diffractometer using graphite monochromated Mo-Kα radiation ($\lambda=0.71073$ Å). Crystal data: $C_{40}H_{43}NO_3S$, $M=617.81$, monoclinic, $P2_1$, room temperature, $a=9.7905(11)$, $b=9.1636(12)$, $c=19.901(2)$ Å, $\beta=102.453(2)$, $V=1743.4(3)$ Å^3, $Z=2$, $D_x=1.177$ Mg m^{-3}, $\mu=0.130$ mm^{-1}, 15523 measured reflections below $\theta=28.24$°, 7752 independent, $R_{ave}=0.0229$, 4771 with $I_o>2\sigma(I_o)$. Data collection, reduction and cell determination were carried on by SMART and SAINT;[6] no absorption correction was applied. The structure was solved by SIR92[7] and refined by SHELX97;[8] non-H atom were anisotropic, H atoms of methyl groups were fixed in calculated positions; 543 parameters refined, $R_1=0.0398$ for $I_o>2\sigma(I_o)$ and 0.0679 for all data. Quite unusually, the amino H atom does not show any relevant intermolecular interaction, being screened off by two phenyl rings.

The crystal structures have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number 169988.

3.2. General procedure for the preparation of acrylates 3

Operating under nitrogen, compound **1** (805 mg, 1.8 mmol), menthol **2** (218 mg, 1.8 mmol) and $(Et_2SnCl)_2O$ (1.1 h, 1.98 mmol) were dissolved in anhydrous benzene (20 mL). The mixture was heated at reflux for 48 h after which time the solvent was evaporated. The crude reaction mixture was crystallized giving pure compound **3**. In the case of **3b** a further crop was obtained by mother liquor purification by flash column chromatography (cyclohexane/AcOEt, 8:1; 3.5×10 cm, 20 mL/min).

3.2.1. (−)-Menthyl 2-benzoylamino-3-tritylsulfanylacrylate (3a). Yield: 78%. $[\alpha]_D^{25}=-88.6$ (c 5.2×10^{-3}, $CHCl_3$).

3.2.2. (+)-Menthyl 2-benzoylamino-3- tritylsulfanylacrylate (3b). Yield: 66%. $[\alpha]_D^{25}=+88.6$ (c 5.4×10^{-3}, $CHCl_3$).

3a,**b**: Mp 198°C (CH_2Cl_2/iPr$_2$O). IR ν_{max} 3315, 1700, 1650 cm^{-1}; ^{1}H NMR δ 0.64–2.00 (m, 18H), 4.50–4.65 (m, 1H), 7.03 (s, 1H), 7.28–7.90 (m, 20H), 7.93 (s, 1H, exch.); ^{13}C NMR δ 16.7–47.4, 70.3, 76.1, 121.2, 127.6–144.6, 163.3, 164.8; anal. calcd: C, 77.58; H, 6.84; N, 2.32. Found: C, 77.50; H, 6.80; N, 2.28.

3.3. General procedure for the cycloaddition reaction

The acrylate **3** (549 mg, 0.9 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL). An ethereal solution of diazomethane (15 mL, 0.25 M) was added at room temperature over a period of 70 h. The ^{1}H NMR and HPLC analyses revealed the presence of a mixture of compounds **4**/**5**. Starting from **3a**, the pyrazolines **4a** and **5a** were detected in 1:1.8 ratio; starting from **3b**, the pyrazolines **4b** and **5b** were detected in 2:1 ratio. The solvent was eliminated and the crude reaction mixture was chromatographed by flash column chromatography (cyclohexane/AcOEt, 5:1; 2×20 cm, 10 mL/min) giving four fractions containing, respectively, **4a** (170 mg, 28%), **5a** (304 mg, 50%), **6a** (29 mg, 5%) and **7a** (58 mg, 10%) in 93% total yield, when starting from **3a**. Pyrazolines **5b** (152 mg, 25%), **4b** (304 mg, 50%), **7b** (23 mg, 4%) and **6b** (52 mg, 9%) where isolated in 88% total yield, when starting from **3b**.

3.3.1. (−)-Menthyl (3*S*,4*R*)-3-benzoylamino-4-tritylsulfanyl-4,5-dihydro-3*H*-pyrazole-3-carboxylate 4a. $[\alpha]_D^{25} = +125.4$ (c 5.03×10^{-3}, $CHCl_3$).

3.3.2. (+)-Menthyl (3*R*,4*S*)-3-benzoylamino-4-tritylsulfanyl-4,5-dihydro-3*H*-pyrazole-3-carboxylate 5b. $[\alpha]_D^{25} = -125.4$ (c 2.1×10^{-3}, $CHCl_3$).

4a/**5b**: Oil. IR ν_{max} 3400, 1731, 1670 cm^{-1}; ^1H NMR δ 0.64–1.70 (m, 18H), 3.05, 3.97, 4.62 (ABX system, $J = 18.9$, 9.4, 6.8, 3H), 4.70–4.76 (m, 1H), 7.20–7.99 (m, 20H), 8.35 (s, 1H, exch.); ^{13}C NMR δ 14.5–47.3, 42.5, 68.6, 78.3, 88.1, 100.8, 127.3–144.8, 167.0, 168.0; anal. calcd: C, 74.39; H, 6.71; N, 6.51. Found: C, 74.20; H, 6.63; N, 6.38.

3.3.3. (−)-Menthyl (3*R*,4*S*)-3-benzoylamino-4-tritylsulfanyl-4,5-dihydro-3*H*-pyrazole-3-carboxylate 5a. $[\alpha]_D^{25} = -202$ (c 4.8×10^{-3}, $CHCl_3$).

3.3.4. (+)-Menthyl (3*S*,4*R*)-3-benzoylamino-4-tritylsulfanyl-4,5-dihydro-3*H*-pyrazole-3-carboxylate 4b. $[\alpha]_D^{25} = +202$ (c 3.0×10^{-3}, $CHCl_3$).

5a/**4b**: Mp 112°C (CH_2Cl_2/$i$$Pr_2O$). IR ν_{max} 3400, 1730, 1670 cm^{-1}; ^1H NMR δ 0.34–1.67 (m, 18H), 3.10, 4.07, 4.65 (ABX system, $J = 19.0$, 9.4, 6.2, 3H), 4.54–4.65 (m, 1H), 7.20–7.97 (m, 20H), 8.22 (s, 1H, exch.); ^{13}C NMR δ 15.9–46.7, 42.6, 68.2, 79.0, 88.5, 101.2, 127.4–144.7, 167.0, 167.9; anal. calcd: C, 74.39; H, 6.71; N, 6.51. Found: C, 74.31; H, 6.65; N, 6.40.

3.3.5. Menthyl (3*S,4*R**)-3-benzoylamino-4-tritylsulfanyl-3,4-dihydro-2*H*-pyrazole-3-carboxylate 6a,7b**. IR ν_{max} 3380, 3360, 1730, 1660 cm^{-1}; ^1H NMR δ 0.58–1.87 (m, 18H), 4.09, 6.14 (AX system, J 1.4, 2H), 4.59–4.68 (m, 1H), 6.58 (s, 1H, exch.), 7.26–7.67 (m, 20H), 8.05 (s, 1H, exch.).

3.3.6. (−)-Menthyl (3*R*,4*S*)-3-benzoylamino-4-tritylsulfanyl-4,5-dihydro-3*H*-pyrazole-3-carboxylate 7a. $[\alpha]_D^{25} = -69$ (c 5.1×10^{-3}, $CHCl_3$).

3.3.7. (+)-Menthyl (3*S*,4*R*)-3-benzoylamino-4-tritylsulfanyl-4,5-dihydro-3*H*-pyrazole-3-carboxylate 6b. $[\alpha]_D^{25} = +69$ (c 5.0×10^{-3}, $CHCl_3$).

7a/**6b**: Mp 172°C (CH_2Cl_2/$i$$Pr_2O$). IR ν_{max} 3380, 3360, 1730, 1660 cm^{-1}; ^1H NMR δ 0.58–1.87 (m, 18H), 3.99, 6.29 (AX system, $J = 1.4$, 2H), 4.59–4.68 (m, 1H), 7.12 (s, 1H, exch.), 7.26–7.67 (m, 20H), 7.94 (s, 1H, exch.); ^{13}C NMR δ 15.9–47.3, 57.7, 69.8, 77.2, 77.5, 127.6–133.1, 141.5, 144.5, 167.7, 170.1; anal. calcd: C, 74.39; H, 6.71; N, 6.51. Found: C, 74.25; H, 6.60; N, 6.38.

3.4. General procedure for the synthesis of cyclopropylamino acids 8/9

The pyrazoline derivative **4** or **5** (98 mg, 0.15 mmol) was melted at 150°C for 10 min. The ^1H NMR and HPLC analyses revealed the presence of a mixture of cyclopropane derivative **8** or **9** and the acrylate **10** (**4a**: **8a**/**10a**, 4.5:1; **5a**: **9a**/**10a**, 6.5:1; **4b**: **8b**/**10b**, 4.5:1; **5b**: **9b**/**10b**, 6:1). The residue was crystallized affording pure **8** or **9**. The mother liquors were chromatographed by flash column chromatography (cyclohexane/AcOEt, 10:1; 1×10 cm, 6 mL/min) giving two fractions: the first containing acrylate **10**, the second compound **8** or **9**.

3.4.1. (−)-Menthyl (1*R*,2*R*)-1-benzoylamino-2-tritylsulfanyl-cyclopropylcarboxylate 8a. $[\alpha]_D^{25} = +152$ (c 2.8×10^{-3}, $CHCl_3$).

3.4.2. (+)-Menthyl (1*S*,2*S*)-1-benzoylamino-2-tritylsulfanyl-cyclopropylcarboxylate 9b. $[\alpha]_D^{25} = -152$ (c 3.0×10^{-3}, $CHCl_3$).

8a/**9b**: Mp 179°C (CH_2Cl_2/$i$$Pr_2O$). IR ν_{max} 3400, 1740, 1670 cm^{-1}; ^1H NMR δ 0.68–1.81 (m, 18H), 1.24, 2.21, 2.66, (ABX system, J 10.2, 7.4, 6.3, 3H), 4.58–4.64 (m, 1H), 5.42 (s, 1H, exch.), 7.24–7.51 (m, 20H); ^{13}C NMR δ 16.3–47.0, 22.6, 29.9, 39.5, 66.9, 75.5, 127.2–144.4, 168.2, 169.5; anal. calcd: C, 77.76; H, 7.01; N, 2.27. Found: C, 77.40; H, 7.13; N, 2.32.

3.4.3. (−)-Menthyl (1*S*,2*S*)-1-benzoylamino-2-tritylsulfanyl-cyclopropylcarboxylate 9a. $[\alpha]_D^{25} = -235$ (c 2.8×10^{-3}, $CHCl_3$).

3.4.4. (+)-Menthyl (1*R*,2*R*)-1-benzoylamino-2-tritylsulfanyl-cyclopropylcarboxylate 8b. $[\alpha]_D^{25} = +235$ (c 3.0×10^{-3}, $CHCl_3$).

9a/**8b**: Mp 205°C (CH_2Cl_2/$i$$Pr_2O$). IR ν_{max} 3400, 1735, 1670 cm^{-1}; ^1H NMR δ 0.55–1.63 (m, 18H), 1.25, 2.26, 2.73, (ABX system, J 10.1, 7.5, 6.3, 3H), 4.48–4.61 (m, 1H), 5.09 (s, 1H, exch.), 7.21–7.55 (m, 20H); ^{13}C NMR δ 15.6–46.9, 22.4, 29.7, 39.6, 66.8, 75.6, 127.2–144.2, 168.2, 169.2; anal. calcd: C, 77.76; H, 7.01; N, 2.27. Found: C, 77.45; H, 6.90; N, 2.24.

3.4.5. Menthyl 2-benzoylamino-4-tritylsulfanylbut-2-enoate 10a,b. Oil. IR ν_{max} 3400, 1735, 1670 cm^{-1}; ^1H NMR δ 1.03–2.04 (m, 18H), 3.11, 6.27 (AX_2 system, J 7.7, 2H), 7.04–7.59 (m, 20H) 7.79 (s, 1H, exch.); ^{13}C NMR δ 16.7–47.5, 31.0, 67.7, 76.3, 126.2, 127.4–144.9, 132.4, 164.3, 165.8; anal. calcd: C, 77.76; H, 7.01; N, 2.27. Found: C, 77.50; H, 7.12; N, 2.11.

3.5. General procedure for the synthesis of 1-benzoylamino-2-tritylsulfanyl-cyclopropylcarboxylic acid 12

Ester **9a** (64 mg, 0.104 mmol) or spirooxazolone (*Z*)-**11** (47.6 mg, 0.55 mmol) was suspended in MeOH (1 mL). A solution of KOH in MeOH (1 mL, 0.31 M) and H_2O (0.1 mL) were added and the mixture was heated at 90°C for 72 h. The solvent was evaporated and the crude reaction mixture was taken up with H_2O (3 mL) and washed with AcOEt (3 mL). The water was acidified with HCl (1 mL, 10%) and extracted with CH_2Cl_2 (3×3 mL). After drying with Na_2SO_4 the solvent was evaporated and the crude mixture was recrystallized. Pure acid **12** was obtained when starting from **9a** (22 mg, 44%) or **11** (38.7 mg, 78%). Mp 216°C (CH_2Cl_2/Et_2O); IR ν_{max} 3380, 1720, 1640 cm^{-1}; ^1H NMR δ 1.03–2.04 (m, 18H), 1.23, 2.24, 2.78 (ABX system, J

10.0, 7.5, 6.2, 3H), 5.35 (s, 1H, exch.), 7.22–7.57 (m, 20H); anal. calcd: C, 75.13; H, 5.25; N, 2.92. Found: C, 75.00; H, 5.36; N, 2.78.

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