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Synthesis of Chiral Pyrrolo[1,2-*c*]thiazoles via Intramolecular Dipolar Cycloaddition of Münchnones: An Interesting Rearrangement to Pyrrolo[1,2-*c*]thiazines

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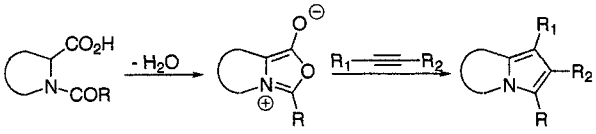
Intramolecular dipolar cycloaddition of bicyclic münchnones, 5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates, derived from cyclodehydration of 2-substituted-*N*-acylthiazolidine-4-carboxylic acids are reported. A range of new pyrrolo[1,2-*c*]thiazole derivatives (**7**, **14**, **15**, **20**, **23**, and **26**) were obtained as single enantiomers from 2-phenylthiazolidines, 2-benzoylthiazolidines, and 2-methylthiazolidine-4-carboxylates. Pyrrolo[1,2-*c*][1,4]thiazine derivative **27** was also obtained from pyrrolo[1,2-*c*]thiazole derivative **26.** The structures of methyl (2*R*,4*R*)-2-(*p*-methoxybenzoyl)thiazolidine-4-carboxylate (**17a**), methyl (2*R*,4*R*)-2-(*p*-methoxybenzoyl)-*N*-(prop-2-ynyloxyacetyl)thiazolidine- 4-carboxylate (**18**), and 3-oxo-4-phenyl-3,4,6,8-tetrahydro-1*H*-furo[3′,4′:2,3]pyrrolo[1,2-*c*][1,4]thiazine **(27)** were determined by X-ray crystallography. Chirooptical studies of the pyrrolo[1,2-*c*]thiazoles were done by confirming the absolute configuration at the chiral center C-3.

Introduction

The 1,3-dipolar cycloaddition is the most general approach to the synthesis of five-membered heterocyclic compounds. In particular the cycloaddition of oxazolium-5-oxides (münchnones) has proved to be a useful method for the synthesis of pyrroles.[1] This mesoionic ring system acts as cyclic azomethine ylide in the reaction with alkynes leading to the corresponding cycloadduct, followed by cycloreversion of carbon dioxide generating pyrrole derivatives. Bicyclic mesoionic ring systems provide a route to heterocycles in which another ring system is annulated to pyrrole. This type of münchnone can be generated by cyclodehydration of cyclic *N*-acyl-α-amino acids with reagents such as acetic anhydride or carbodiimides (Scheme 1).

Thus, *N*-acylthiazolidine-4-carboxylic acids have been used to generate bicyclic münchnones, 5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates, which give some examples of intermolecular 1,3-dipolar addition, namely the addition to dimethyl acetylenedicarboxylate,[2] to α-chloroacrylonitrile,[3] and to imines.[4] The products from dimethyl acetylenedicarboxylate are 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives, and this type of heterocyclic compound can also be obtained from the reaction with α-chloroacrylonitrile.

Scheme 1



In our study the intermolecular dipolar cycloaddition of 5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates was extended to other dipolarophiles namely methyl propiolate, ethyl and methyl vinyl ketone, and acrylonitrile leading to the synthesis of a range of new chiral 1*H*,3*H*-pyrrolo-[1,2-*c*]thiazole derivatives and of interesting new spiro compounds.[5] We have also described the first examples of intramolecular 1,3-dipolar cycloaddition of 5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates which led to the synthesis of new 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives as single enantiomers (**1** and **2**).[6]

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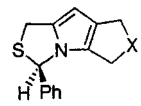
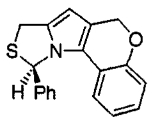
10.1021/jo010807p CCC: $22.00



1a X = O
1b X = S



2

In this paper we further explore the scope of the intramolecular 1,3-dipolar cycloaddition of 5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates thus obtaining new 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives, heterocyclic compounds with potential biological activity.[2c,d,3b,7]

Results and Discussion

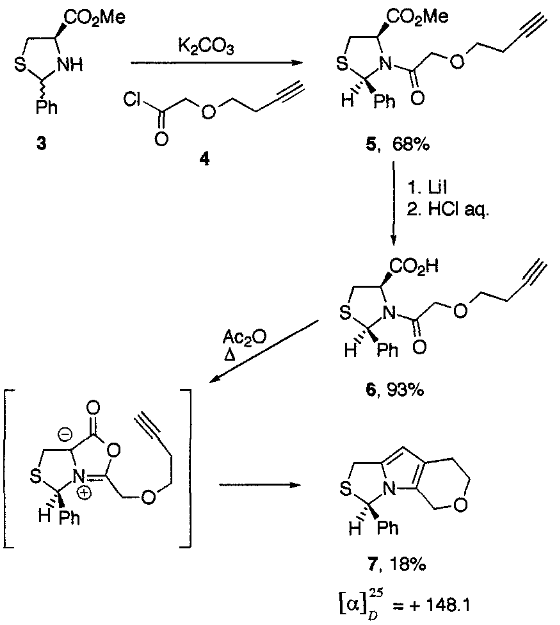
The synthetic strategy for the generation of 5-substituted-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates containing internal dipolarophiles involves the *N*-acylation of 2-substituted thiazolidine-4-carboxylates with the appropriate acid chloride. The selectivity of this acylation is crucial since it modulates the stereochemistry of the final adducts: *N*-acyl-2-substituted thiazolidine-4-carboxylates in diastereoisomeric pure form will lead to chiral pyrrolo[1,2-*c*]thiazole derivatives since the chirality at C-4 of the thiazolidine will be lost and the chirality at C-2 (C-3 in the product) will be retained.[2b,5,6]

2-Substituted-1,3-thiazolidine-4-carboxylates are obtained from the reaction of aldehydes and *L*-cysteine esters in a process where a new chiral center at C-2 position of the thiazolidine is created leading to a mixture of the (2*S*,4*R*) and (2*R*,4*R*) diastereoisomers. The acylation of the diastereoisomeric mixture with acetic anhydride or with acid chlorides can lead to the selective synthesis of *N*-acyl-2-substituted-1,3-thiazolidine-4-carboxylates as pure stereoisomers with (2*R*,4*R*) or (2*S*,4*R*) stereochemistry depending on the reaction conditions. In fact 2-substituted-1,3-thiazolidine-4-carboxylates can undergo selective inversion at C-2 through a mechanism involving the opening of the ring, but the protection with the acyl group prevents this epimerization and allows the isolation of pure diastereoisomers.[8]

Previous results showed that starting with methyl 1,3-thiazolidine-4-carboxylate, bearing a phenyl group at C-2, as a mixture of the (2*R*,4*R*) and (2*S*,4*R*) diastereoisomers, *N*-acylation, using our reaction conditions, lead to the selective formation of methyl *N*-acyl-2-phenyl-1,3-thiazolidine-4-carboxylate with (2*R*,4*R*) stereochemistry.[6] The dehydration of the corresponding *N*-acyl-2-phenyl-1,3-thiazolidine-4-carboxylic acids generates 5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates containing internal dipolarophiles which undergo cycloaddition giving 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives as single enantiomers and with *R* configuration (**1** and **2**).[6]

This synthetic methodology is now explored to include the dipolar cycloaddition of new 5-substituted-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates. *N*-acylations of thiazolidines with phenyl, methyl, and benzoyl groups at C-2 were made using the reaction conditions previously described[6] to evaluate if the nature of this substituent would have any influence on its selectivity.

Scheme 2



As a first objective we decided to prepare new 5-phenyl-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates containing internal dipolarophiles and promote their cycloaddition. The synthetic strategy used is outlined in Scheme 2. (But-3-ynyloxy)acetic acid was prepared from the reaction of 3-butyn-1-ol and chloroacetic acid and converted into the corresponding acid chloride **4** by the reaction with thionyl chloride. This acetylenic acid chloride was used to acylate thiazolidine **3** giving compound **5** as a single stereoisomer with (2*R*,4*R*) stereochemistry, in 68% yield. Thiazolidine **6** was obtained by reacting compound **5** with lithium iodide in ethyl acetate followed by treatment with aqueous HCl. Heating a solution of *N*-acylthiazolidine **6** in acetic anhydride led to the generation of the corresponding mesoionic species which underwent an intramolecular 1,3-dipolar cycloaddition with the unactivated terminal alkyne. A new chiral 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivative having a fused dihydro-2*H*-pyran ring with $[\alpha]_D^{25} = +148.1$ (**7**) was obtained in 18% yield.

Attempts were made to promote this type of intramolecular dipolar cycloaddition using a terminal alkene as the dipolarophile. (Prop-2-enyloxy)acetic acid was prepared by a known method,[9] and its reaction with thionyl chloride gave the acid chloride **8**. N-acylation of thiazolidine **3** with this acid chloride gave compound **9** in 60% yield, which was converted into the carboxylic acid **10** (46%). However, with heating of compound **10** in acetic anhydride, no cycloadduct was obtained (Scheme 3). This indicates the need for dipolarophile activation.

The thiazolidine **11** bearing a methyl group at C-2 was prepared and isolated as a mixture of the (2*S*,4*R*) and (2*R*,4*R*) diastereoisomers. The reaction of this compound with (prop-2-ynyloxy)acetic acid chloride, prepared from the reaction of (prop-2-ynyloxy)acetic acid[10] with thionyl chloride, gave compound **12** in 63% yield. The ^{1}H NMR spectrum of thiazolidine **12** at ambient temperature was

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(7) Davidson, S. K.; Summers, J. B.; Albert, D. H.; Holms, J. H.; Robin Heyman, H.; Magoc, T. J.; Conway, R. G.; Rhein, D. A.; Carter, G. W. *J. Med. Chem.* **1994**, *37*, 4423–4429.

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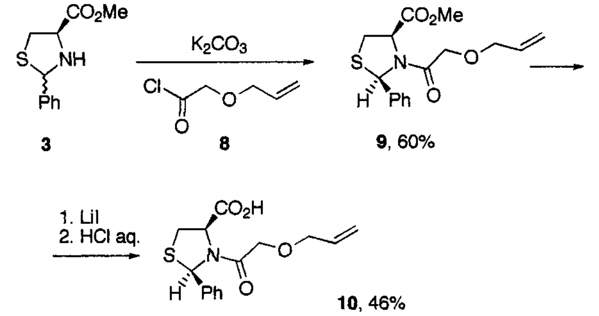
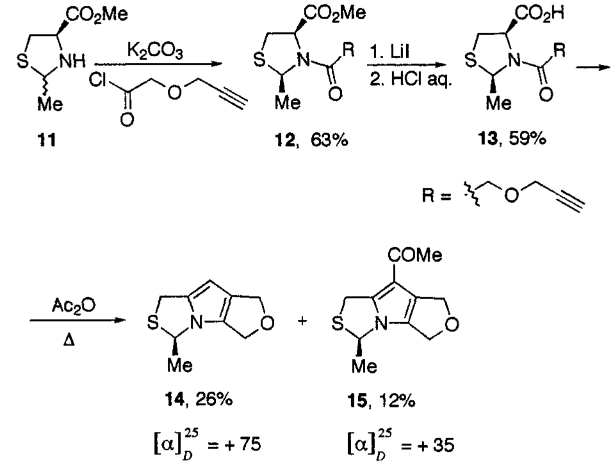
Scheme 3



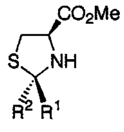
Scheme 4



complicated by the existence of separated rotamers but when recorded in DMSO-d_6 at 65 °C showed signals for a single diastereoisomer. Thiazolidine **12** was converted into the 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **14** using a synthetic approach similar to the one described in Scheme 2. This product (**14**) was obtained in 26% yield as a single enantiomer with *R* configuration $[\alpha]_D^{25} = +75$. The acetylated product **15** ($[\alpha]_D^{25} = +35$) was also isolated in 12% yield (Scheme 4).

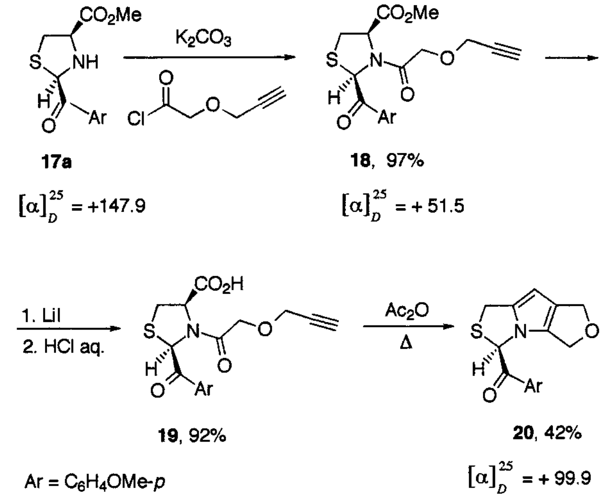
The reaction of phenylglyoxal and *L*-cysteine methyl ester gives also a thiazolidine as a mixture of the (2*S*,4*R*) and (2*R*,4*R*) diastereoisomers. However, in this case the two diastereoisomers of methyl 2-benzoylthiazolidine-4-carboxylate (**16a,b**) can be separated by chromatography proving that the interconversion of these isomers through a reversible ring opening mechanism is difficult.[11]

(*p*-Methoxyphenyl)glyoxal, obtained by oxidation of 4-methoxyacetophenone with aqueous hydrobromic acid and dimethyl sulfoxide,[12] reacts with *L*-cysteine methyl ester giving a mixture of diastereoisomeric thiazolidines (**17a,b**), which can also be separated but this time by selective crystallization.



16a $R^1 = COPh; R^2 = H$
16b $R^1 = H; R^2 = COPh$
17a $R^1 = COC_6H_4OMe\text{-}p; R^2 = H$
17b $R^1 = H; R^2 = COC_6H_4OMe\text{-}p$

Scheme 5



The stereochemistry of the methyl (2*R*,4*R*)-2-(*p*-methoxybenzoyl)thiazolidine-4-carboxylate (**17a**) was established by X-ray crystallography (see Supporting Information). The compound crystallizes in the noncentrossymmetric *P*21 space group. The puckering parameters of the five-membered ring are $Q(2) = 0.357(3)°$ and $\phi(2)=271.1(4)°$. The methyl carboxylate substituent bonds to C4 in an equatorial geometry as shown by the angle between the C4–C41 bond and the normal to the Cremer and Pople plane, 63.90(19)°. The *p*-methoxybenzoyl group bonds to the ring in a bisecting geometry as shown by the corresponding angle 52.31(19)°. The conformation is stabilized by one bifurcated intramolecular hydrogen bond N3–H3···O21, O41 with short distances, 2.680(4) and 2.724(3) Å, although narrow angles, 107(3) and 102(3)°, respectively. The absolute structure was determined by taking advantage of the sulfur small anomalous dispersion at the Mo Kα wavelength. The Flack parameter refined to 0.03(10), confirming the expected *R*,*R* chirality.

The ^1H NMR spectra of 2-(*p*-methoxybenzoyl) derivative **17a** are characterized by having the sum of the coupling constants between geminal protons H(5a), H(5b) with H(4) larger than the corresponding sum of these coupling constants for the thiazolidine **17b**. This is in agreement with previous observation that the sum of $J_{(5a),(4)}$ with $J_{(5b),(4)}$ of the (2*R*,4*R*) isomer of 2-substituted thiazolidine-4-carboxylic acid derivatives is greater than that of the (2*S*,4*R*) isomer.[8] The comparison of these spectra with the ^1H NMR spectra of **16a,b** allowed us to conclude that **16a** is the (2*R*,4*R*) isomer and **16b** the (2*S*,4*R*) isomer (see Supporting Information).

The unique possibility of isolating pure diastereoisomers of 2-substituted thiazolidines characterized by the an unfavorable interconversion between the (2*R*,4*R*) and (2*S*,4*R*) isomers led us to explore the use of **16a**,**b** and **17a**,**b** as precursors of 5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates with internal dipolarophiles and to promote the dipolar cycloaddition in the hope of retaining the configuration of the starting thiazolidine at C-2. This could lead to chiral dipolar cycloadducts with *R* and *S* configurations.

The reaction of thiazolidine **17a** with (prop-2-ynyloxy)-acetic acid chloride in the presence of potassium carbonate led to *N*-acylthiazolidine **18** meaning that retention of configuration at C-2 has occurred (Scheme 5). This *N*-acylthiazolidine showed a positive value for the optical rotation ($[\alpha]_D^{25} = +51.5$) which is consistent with the

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[11] Gilchrist, T. L.; Rocha Gonsalves, A. M. d'A.; Pinho e Melo, T. M. V. D. *Tetrahedron* **1994**, *50*, 13709–13724.

[12] Brawner Floyd, M.; Du, M. T.; Fabio, P. F.; Jacob, L. A.; Johnson, B. D. *J. Org. Chem.* **1985**, *50*, 5022–5027.

(2*R*,4*R*) stereochemistry. In fact, a positive value for the optical rotation of 2-substituted *N*-acyl-1,3-thiazolidine-4-carboxylates is normally associated with (2*R*,4*R*) stereochemistry and a negative value with (2*S*,4*R*) stereochemistry.[5,6,8a]

Meanwhile the structure of thiazolidine **18** was confirmed by X-ray crystallography (see Supporting Information). The compound crystallizes in the noncentrosymmetric $P2_12_12_1$ space group. The five-membered ring adopts an envelope conformation on S1 with puckering parameters $Q(2) = 0.409(3)$ Å and $\varphi(2) = 354.3(4)°$. The (prop-2-ynyloxy)acetyl ring substituent bonds to N3 in an equatorial position as seen by the angle between the C31−N3 bond and the normal to the Cremer and Pople plane, 69.1(2)°. The *p*-methoxybenzoyl and methyl carboxylate groups are positioned in axial and bisecting positions, respectively, as seen by the corresponding angles, 15.8(2) and 49.7(2)°.

The structure shows no classical hydrogen bonds. Cohesion is maintained by C−H···O and C−H···π intermolecular bonding. Both terminal methyl groups have one of their hydrogens atoms directed toward the π cloud of the benzoyl ring with distances of 2.870 and 2.784 Å between the hydrogens and the centroid of the ring. Oxygen atom O21 accepts one proton from C24 [C24−H24···O21^{i}, 3.453(4) Å; i = $-1/2 + x$, $3/2 - y$, $-z$]. O31 accepts two protons coming from the same neighbor molecule [C32−H32A···O31^{ii}, 3.293(4) Å; C33−H33A···O31^{ii}, 3.435(4) Å; ii = $1 - x$, $-1/2 + y$, $-z$]. O41 accepts two protons from the (prop-3-ynyloxy)acetyl group of two neighboring symmetry-related molecules [C26−H26···O41^{iii}, 3.306(4) Å; C35−H35···O41^{iv}, 3.313(5) Å; iii = x, $-1 + y$, z; iv = $-x$, $-1/2 + y$, $-z$].

Absolute structure was determined by taking advantage of the small anomalous dispersion of the sulfur atom at the Mo Kα wavelength. The Flack parameter was refined to 0.01(9), confirming the expected *R*,*R* configuration of the C2 and C4 atoms.

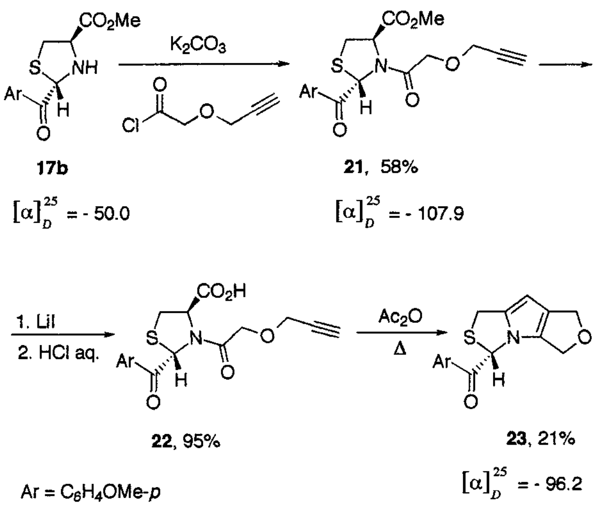
Compound **18** reacted with lithium iodide in ethyl acetate followed by treatment with aqueous HCl, and the corresponding acid **19** was obtained. This compound was heated in a solution of acetic anhydride to generate a mesoionic species which underwent an internal 1,3-dipolar cycloaddition. The chiral 3-benzoyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivative **20** was obtained with *R* configuration ($[\alpha]_D^{25} = +99.9$).

The thiazolidine **21** was obtained from the acylation of thiazolidine **17b** with (prop-2-ynyloxy)acetic acid chloride (Scheme 6). The compound obtained showed a negative value for the optical rotation suggesting stereochemistry (2*S*,4*R*). Thiazolidine **21** was converted into the corresponding carboxylic acid **22**, which was heated in acetic anhydride giving the cycloadduct **23** ($[\alpha]_D^{25} = -96.2$), the enantiomer of compound **20**.

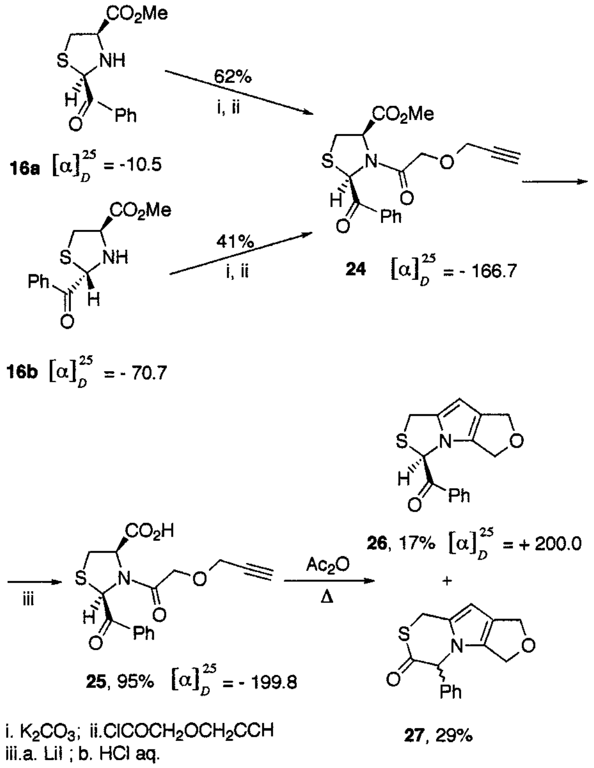
Our study showed that with methyl 2-(*p*-methoxybenzoyl)thiazolidine-4-carboxylates **17a,b** as starting material 3-benzoyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives can be obtained as single enantiomers with retention of configuration at C-2 of the starting thiazolidine.

In contrast with the results obtained with 2-(*p*-methoxybenzoyl)thiazolidines the acylation reaction of 2-benzoylthiazolidines **16a,b** led to products which showed identical ^{1}H NMR (Scheme 7). They both led to the same thiazolidine (**24**) with *R* configuration at C-2 ($[\alpha]_D^{25} = -166.7$). This observation indicates that the acylation of thiazolidine **16a** occurs with retention of configuration whereas thiazolidine **16b** undergoes inversion of configuration at C-2.

Scheme 6



Scheme 7



Compound **24** reacted with lithium iodide in ethyl acetate followed by treatment with aqueous HCl giving thiazolidine **25**. With heating of *N*-acylthiazolidine **25** in acetic anhydride, two products were obtained, the chiral 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivative **26** in 17% yield and compound **27** in 29% yield. The absolute configuration of compound **26** was confirmed by chirooptical studies (see below) as being the *R* configuration ($[\alpha]_D^{25} = +200.0$).

The structure of the pyrrolo[1,2-*c*][1,4]thiazine derivative **27** was established by X-ray crystallography (see Supporting Information). The unit cell contains a pair of enantiomeric molecules.

The furan and pyrrole rings are practically planar; the largest deviation from the least-squares plane is 0.0145(13) Å (atom C3). The thiazine ring has a distorted boat conformation with puckering parameters $Q = 0.640(2)$ Å, $\theta = 85.5(2)°$, and $\phi = 51.81(14)°$ as defined by Cremer and Pople. The dihedral angle between the least-squares planes of the furan and pyrrole rings is 0.30(7)°, and that between the pyrrole and thiazine rings is 23.86(8)°.

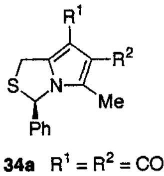
Bond lengths and angles show no unusual values. There is a significant asymmetry between the two S−C bond lengths [C5−S1, 1.817(2) Å; C7−S1, 1.749(2) Å], reflecting the different hybridization of the C5 and C7 atoms. Although there is a large asymmetry between the valence angles around N1, the sum of these angles adds up to 359.6(3)°, indicating no significant pyramidal character of the N1 atom. The environment around the asymmetric C8 atom is close to tetrahedral, with bond angles in the range 110.80(14)−112.72(13)°. The phenyl ring is in an axial position with respect to the thiazine ring with torsion angles −87.78(16)° [S1−C7−C8−C10] and 75.32(19)° [C4a−N1−C8−C10]. The dihedral angle between the least-squares planes of the phenyl and thiazine rings is 83.78(7)°.

No classical hydrogen bonds are present in the structure, and cohesion of the crystal is achieved mainly through van der Waals interactions. The short carbonyl C7═O71 [1.211(2) Å] bond distance is in agreement with an O atom not involved in strong hydrogen bonding. An inspection of the close contact distances shows that C15−H15···N1 [2.843(3) Å] and C11−H11···O71 [3.216(3) Å] are possible weak intramolecular interactions.

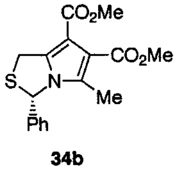
The pyrrolo[1,2-*c*][1,4]thiazine derivative **27** could also be obtained by heating a solution of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivative **26** in acetic anhydride. This result clearly indicates that compound **27** was formed from pyrrolo[1,2-*c*]thiazole derivative **26** and not from the *N*-acyl-1,3-thiazolidine **25**.

The mechanism proposal for the synthesis of the pyrrolo[1,2-*c*][1,4]thiazine derivative **27** is outlined in Scheme 8. The first step is the acetylation of the sulfur atom with acetic anhydride giving **28**. Two possible ways in which this intermediate could be converted into the final product are shown in the scheme. Further studies are underway to clarify the mechanism for the formation of pyrrolo[1,2-*c*][1,4]thiazine **27**.

Isotropic UV and CD Spectra. The UV isotropic and CD spectra for some pyrrolo[1,2-*c*]thiazoles were obtained (see Supporting Information and Figure 1). The study includes compounds whose synthesis has been previously described[2b,5,6] (**1a,b**, **34a,b**, **35**, and **36**) and pyrrolo[1,2-*c*]thiazoles prepared during this work (**14**, **15**, **20**, **23**, and **26**). Dimethyl (3*R*)- and (3*S*)-3,5-dimethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (**37a,b**) were also prepared as outlined in Scheme 9 to be used in comparative CD studies.



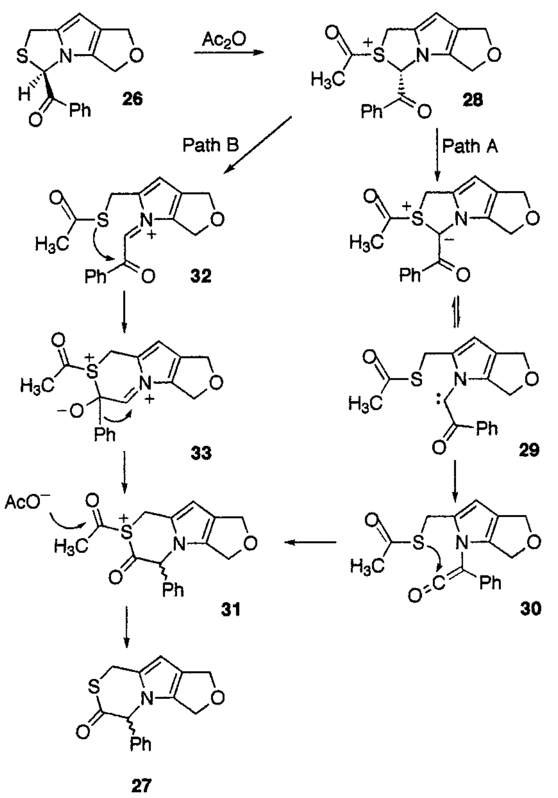
34a $R^1 = R^2 = CO_2Me$
35 $R^1 = CO_2Me$; $R^2 = H$
36 $R^1 = COEt$; $R^2 = H$



34b

Strong bands are found in the UV isotropic spectra of the C-3-aryl- and C-3-benzoyl-substituted substances. In contrast the C-3-alkyl-substituted compounds show medium bands. The same applies for the CD spectra, particularly the bands that originate from the aryl rings.

Scheme 8



Among the compounds studied there are three enantiomeric pairs: **20**/**23**, **34a**/**34b**, and **37a**/**37b**. The CD spectra recorded corroborate the presence of these three sets of compounds as enantiomers, but the optical purity is somewhat better for the compounds with the *R* configuration at C-3 than for those with *S* configuration.

The CD spectra in the range 200−330 nm show a rather complex set of bands with variable intensities. At least five bands are normally detected. We note that the sign of the CD bands of the compounds depends, with few exceptions (see below), on the configuration of the chiral center C-3.

Benzene presents bands at 203.5 (K-band) and 254 nm (B-band), and pyrrole, bands at ∼200 nm.[13] It is known that substitution on the aromatic rings, particularly by groups that extend conjugation, leads to λ_{max} of bands at wavelengths longer that those observed for nonsubstituted aromatic rings.[13,14] Therefore we expect that groups such as −R or −COR (R = pyrrolo[1,2-*c*]thiazoles) and −COOMe will induce a bathochromic effect on these bands. This affects the type of spectra and the broadness of the bands; moreover, the Cotton effects observed in some compounds may overlap and only show up as shoulders in the CD spectra of other compounds.

The assignment of individual bands was done in analogy to the similar compounds already studied.[2b,8b,15]

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(13) Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*, 5th ed.; McGraw-Hill: London, 1995; pp 1−27.

(14) Silverstein, R. M.; Bassler, C. C.; Morril, T. C. *Spectrometric Identification of Organic Compounds*, 5th ed.; John Wiley & Sons: New York, 1991; pp 289−315.

(15) Györgydeák, Z.; Kajtár, J.; Kajtár, M.; Kajtár-Peredy, M. *Liebigs Ann. Chem.* **1990**, 281−286.

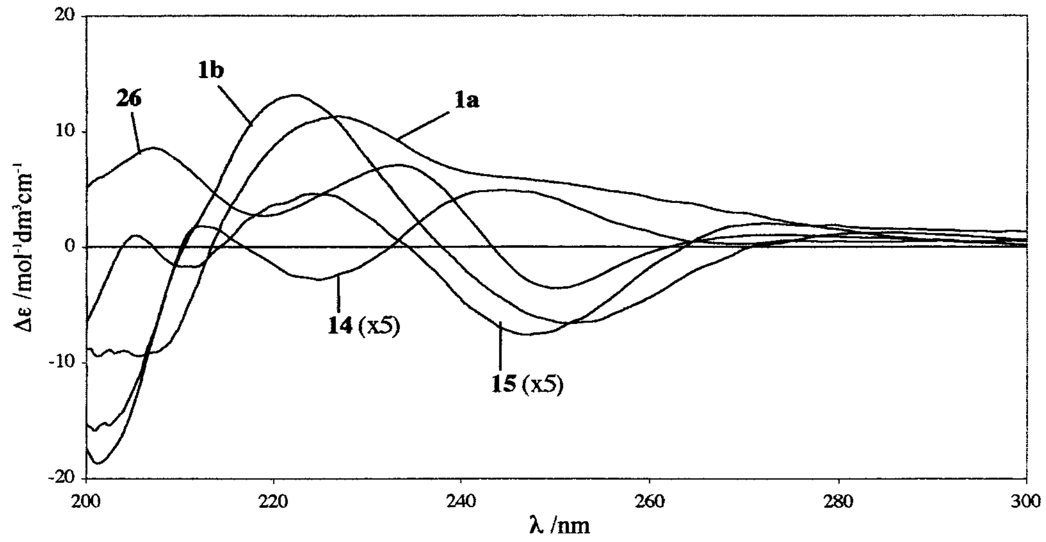
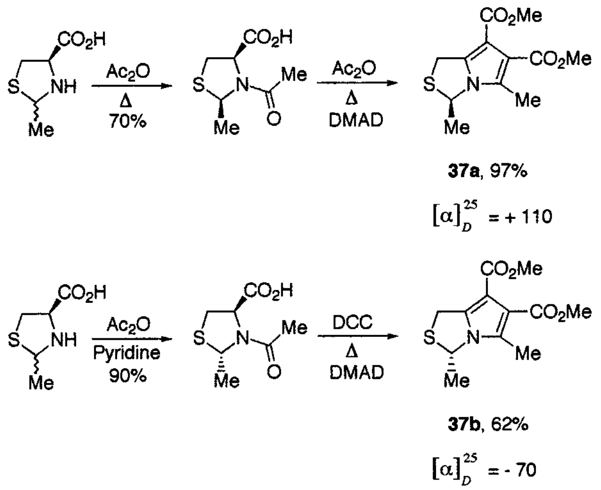


Figure 1. CD spectra for chiral C-3 substituted pyrrolo[1,2-*c*]thiazoles (**1a,b**, **14**, **15**, and **26**).

Scheme 9



Compounds containing the carbonyl (ketone) group also show bands in the 300–330 nm range due to the n → π* transition of the carbonyl group. The derivatives containing ester groups (e.g. **34**, **35**, and **37a,b**) show this band around 220 nm. As found in these studies,[2b,8b,15] the sign of the 205 nm band (band V) correlates in the spectra of our compounds with the absolute configuration of the chiral center C-3: the (3*R*) derivatives show a negative Cotton effect at 205 nm. Exceptions to this behavior are compounds **20**, **23**, and **26**. This band is assigned to a π→π* transition of the S–C–N–C(pyrrole) group, the sign and amplitude of which is determined by the helicity of the chromophore and the type of group attached to the C-3 atom.

To better understand the factors that determine the sign of the Cotton effect associated with the band at ~205 nm we used the program HyperChem (Polak–Ribiere optimization) to estimate the structure of the compounds (therefore the conformation of the thiazolidine ring). The calculated structures agree reasonably well with those obtained from single-crystal X-ray diffraction studies, particularly for **1a**, reported earlier.[6] Except for the S atom, all atoms of the thiazolidine pyrrole (and furan) rings are approximately in the same plane, this corresponding to a rather rigid disposition of atoms. The thiazolidine rings are obtained with an envelope conformation, the S atom being opposite to the substituent at C-3 for all compounds except **20**, **23**, and **26**.

Earlier determinations have suggested that the sign of the Cotton effect associated with band V is related with the torsion angle N–C–C–S, a negative value corresponding to a negative Cotton effect at 205 nm. In our molecular mechanics calculations negative torsion angles N–C–C–S were obtained for compounds with the *R* configuration at C-3 and positive angles for the similar compounds with the *S* configuration. The same applies for the torsion angle N–C–S–C, while for the torsion angle C–N–C–S positive values were found for compounds with *R* configuration at C-3 and negative values for the compounds with *S* configuration at C-3. Compounds **20**, **23**, and **26** are exceptions to this rule, the torsion angles N–C–C–S, N–C–S–C, and C–N–C–S showing signs opposite to those of the other compounds, the same applying to the sign of the 205 nm band. Nevertheless, from the results of the molecular mechanics calculations, it may be stated that for all compounds the relative positions of the atoms of the thiazolidine ring and of the substituents at C-3, as measured by the signs of the torsion angles, determine unambiguously the Cotton effect of band V. In fact, negative values for the torsion angles N–C–C–S and N–C–S–C and positive for C–N–C–S always correspond to a negative Cotton effect for the band at 205 nm.

Although the methyl-substituted compounds normally correspond to greater torsion angles, the increased intensity of the bands of the aryl- or benzoyl- substituted compounds is explained by the mixing of the transitions of the aryl (and pyrrole) rings with those of the S–C–N chromophores.

Summarizing the chirooptical studies of the pyrrolo[1,2-*c*] thiazoles, we confirm that the absolute configuration of the chiral center C-3 can be determined unambiguously via the sign of the 205 nm band. The molecular mechanics studies suggest that this is possible due the rigidity of the thiazolidine ring that is condensed with the pyrrole ring, the torsion angles characterizing the disposition of the most relevant atoms all having the same sign for the *R* (or for the *S*) derivatives. Exceptions to this general behavior are the compounds with the benzoyl group at the chiral center C-3, where torsion angles with opposite signs to those of the other compounds were found in the molecular mechanics calculations. Accordingly, the sign for the Cotton effect of the 205 nm transition is the opposite in these compounds.

Conclusion

The reactivity of 5-substituted-5*H*,7*H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates containing internal dipolarophiles is described. The synthetic strategy involves the *N*-acylation of 2-substituted thiazolidine-4-carboxylates which are used as precursors of the mesoionic species. Depending on the nature of the substituent at C-2 of the thiazolidine, *N*-acyl derivatives with different stereochemistry were obtained. If one starts with methyl 2-phenylthiazolidine-4-carboxylate or methyl 2-methylthiazolidine-4-carboxylate as a mixture of the (2*R*,4*R*) and (2*S*,4*R*) diastereoisomers, a pyrrolo[1,2-*c*]thiazole with *R* configuration was obtained (**7**, **14**, and **15**). Using methyl (2*R*,4*R*)-2-(*p*-methoxybenzoyl)thiazolidine-4-carboxylate and methyl (2*S*,4*R*)-2-(*p*-methoxybenzoyl)thiazolidine-4-carboxylate in diastereoisomeric pure form, 7-(*p*-methoxybenzoyl)pyrrolo[1,2-*c*]thiazole derivatives with *R* and *S* configuration, respectively, were obtained (**20** and **23**) with retention of configuration at C-2 of the starting thiazolidine. In the case of 2-benzoylthiazolidines both diastereoisomers led to the same *N*-acyl derivative allowing for the synthesis of compound **26** with *R* configuration. An interesting conversion of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivative **26** to pyrrolo[1,2-*c*][1,4]thiazine derivative **27** was also achieved. Chirooptical studies of the pyrrolo[1,2-*c*]thiazoles were done by confirming the absolute configuration at the chiral center C-3.

Experimental Section

General Methods. ^{1}H NMR spectra (300 MHz) were recorded in $CDCl_3$ as solvent; chemical shifts are expressed in parts per million related to internal TMS, and coupling constants (*J*) are in Hz. Mass spectra (*m*/*z*) were recorded under electron impact at 70 eV or, where indicated, by chemical ionization with ammonia (CI). Optical rotations were recorded at the sodium D line. The circular dichroism spectra were run on a spectropolarimeter with the UV−vis (170−700 nm) photomultiplier. Flash column chromatography was performed with Merck 9385 silica as the stationary phase. 2-Phenylthiazolidine-4-carboxylate (**3**) was prepared by a procedure described earlier, starting from L-cysteine methyl ester hydrochloride, and was isolated as a mixture of the (2*R*,4*R*) and (2*S*,4*R*) diastereoisomers (66:34).[11] (Prop-2-ynyloxy)acetic acid chloride was prepared from the reaction of (prop-2-ynyloxy)acetic acid with thionyl chloride by a procedure described in the literature.[10]

(But-3-ynyloxy)acetic Acid. This was prepared from 3-butyn-1-ol (10.91 g, 170 mmol) and chloroacetic acid (17.96 g, 190 mmol) by a procedure described in the literature for the synthesis of (prop-2-ynyloxy)acetic acid:[10] ^{1}H NMR 2.06 (t, 1H, $J = 2.7$), 2.45−2.56 (m, 2H), 3.80 (t, 2H, $J = 6.3$), and 4.13 (s, 2H); MS (EI) 129 (MH^+, 15%), 83 (19), 79 (100), 61 (48), and 53 (71).

(Prop-2-enyloxy)acetic Acid. This was prepared from prop-2-enyl alcohol (30 mL) and chloroacetic acid (11.7 g, 124 mmol) by a procedure described in the literature.[9] This compound was purified by distillation at 120 °C (0.5 mmHg) (9.94 g, 68.5%): ^{1}H NMR 4.11−4.15 (m, 4H), 5.24−5.37 (m, 2H), 5.85−5.98 (m, 1H), and 11.27 (s, 1H); MS (CI) 134 [$(M + NH_4)^+$, 100%]. Anal. Calcd for $C_5H_8O_3$: C, 51.7; H, 6.9. Found: C, 52.4; H, 7.1.

General Procedure for the Synthesis of Thiazolidines.[11] L-Cysteine methyl ester hydrochloride (3.45 g, 20 mmol) was dissolved in water (15 mL), and potassium hydrogen carbonate (2.0 g, 20 mmol) was added following the addition of a solution of the aldehyde (22 mmol) in ethanol (15 mL). The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with water and extracted with dichloromethane. The organic extracts were concentrated, and the residue was purified as stated for each compound.

Methyl (2*R*,4*R*)- and (2*S*,4*R*)-2-Methylthiazolidine-4-carboxylate (11). The thiazolidine, obtained in 77% yield, was purified by flash chromatography [hexanes−ethyl acetate (1:1)]. The ^{1}H NMR spectrum showed the presence of two diastereoisomers (ratio 63:37, determined by GC-MS). *Major component*: ^{1}H NMR 1.61 (d, 3H, $J = 6.3$), 2.35 (s, 1H, NH), 2.94 (dd, 1H, $J = 9.3, 10.5$), 3.32 (dd, 1H, $J = 7.2, 10.5$), 3.79 (s, 3H), 3.84 (dd, 1H, $J = 7.2, 9.3$), and 4.57 (q, 1H, $J = 6.3$). *Minor component*: ^{1}H NMR 1.50 (d, 3H, $J = 6.3$), 2.35 (s, 1H, NH), 3.13 (dd, 1H, $J = 6.0, 10.6$), 3.34 (dd, 1H, $J = 7.2, 10.6$), 3.77 (s, 3H), 4.21 (dd, 1H, $J = 6.0, 7.2$), and 4.78 (q, 1H, *J* 6.3).

Methyl (2*R*,4*R*)-2-Benzoylthiazolidine-4-carboxylate (16a) and Methyl (2*S*,4*R*)-2-Benzoylthiazolidine-4-carboxylate (16b). The thiazolidine was obtained in 68% yield. The ^{1}H NMR spectrum showed the presence of two diastereoisomers (ratio 55:45), which were separated by flash chromatography [petroleum ether−ethyl acetate (3:1), petroleum ether−ethyl acetate (1:1), and then ethyl acetate] giving (in order of elution) the following: methyl (2*R*,4*R*)-2-benzoylthiazolidine-4-carboxylate (**16a**) (the major isomer:) [mp 116.8−119.2 °C (from ethyl ether−hexane); ^{1}H NMR 2.80 (approximately t, 1H, $J = 10.2$), 3.37 (dd, 1H, $J = 5.8, 10.2$), 3.75 and 3.84 (m, 1H), 3.84 (3H), 5.80 (1H, s), 7.47−7.63 (m, 3H, Ar H), and 7.94−7.99 (m, 2H, Ar H); MS (EI) 251 (M^+, 2%), 250 (10), 226 (3), 220 (3), 192 (1), 174 (5) 146 (11), 105 (100), 87 (9), and 77 (90); HRMS calcd for $C_{12}H_{14}NO_3S$ (MH^+) 252.0694, found 252.0691; $[\alpha]_D^{25} = -10.5$ ($c = 0.95$, CH_2Cl_2)]; methyl (2*S*,4*R*)-2-benzoylthiazolidine-4-carboxylate (**16b**) (the minor isomer) [mp 62.2−64.6 °C (from ethyl ether−hexane); ^{1}H NMR 3.08 (dd, 1H, $J = 6.6, 10.7$), 3.40 (dd, 1H, $J = 2.6,10.7$), 3.82 (3 H), 4.69 (dd, 1H, $J = 2.6, 6.6$), 5.99 (s, 1H), 7.47−7.53 (m, 2H, Ar H), 7.59−7.64 (m, 1H, Ar H), and 7.94−7.98 (m, 2H, Ar H); MS (EI) 252 (MH^+, 24%), 146 (100), 105 (24), 86 (69), and 77 (27); HRMS calcd for $C_{12}H_{14}NO_3S$ (MH^+) 252.0694, found 252.0685; $[\alpha]_D^{25} = -70.7$ ($c = 0.9$, CH_2Cl_2)].

Methyl (2*R*,4*R*)-2-(4-Methoxybenzoyl)thiazolidine-4-carboxylate (17a) and Methyl (2*S*,4*R*)-2-(4-Methoxybenzoyl)thiazolidine-4-carboxylate (17b). The thiazolidine was obtained in 74% yield. The ^{1}H NMR spectrum showed the presence of two diastereoisomers (ratio 73:27). The major component is separated by selective crystallization (ethyl ether). The minor component is purified by flash chromatography [petroleum ether−ethyl acetate (1:1) and then ethyl acetate] giving (in order of elution) the following: methyl (2*R*,4*R*)-2-(4-methoxybenzoyl)thiazolidine-4-carboxylate (**17a**) (the major isomer) [mp 157.5−160.3 °C; ^{1}H NMR 2.80 (approximately t, 1H, $J = 10.4$), 3.36 (dd, 1H, $J = 6.0, 10.4$), 3.83 (s, 3H), 3.88 (s, 3H), 4.04 (dd, 1H, $J = 6.0, 10.4$), 5.75 (s, 1H), 6.97 (d, 2H, $J = 8.8$, Ar H), and 7.94 (d, 2H, $J = 8.8$, Ar H); MS (EI) 281 (M^+, 1%), 222 (5), 146 (100), 135 (57), and 86 (79); $[\alpha]_D^{25} = +147.9$ ($c = 0.1$, CH_2Cl_2). Anal. Calcd for $C_{13}H_{15}NSO_4$: C, 55.5; H, 5.4; N, 5.0; S, 11.4. Found: C, 55.0; H, 5.4; N, 5.1; S, 11.4]; methyl (2*S*,4*R*)-2-(4-methoxybenzoyl)-thiazolidine-4-carboxylate (**17b**) (the minor isomer; an oil) [^{1}H NMR 3.06 (dd, 1H, $J = 6.6, 10.6$), 3.39 (dd, 1H, $J = 2.2, 10.6$), 3.83 (s, 3H), 3.87 (s, 3H), 4.68 (dd, 1H, $J = 2.2, 6.6$), 5.93 (s, 1H), 6.95 (d, 2H, $J = 8.8$, Ar H), and 7.93 (d, 2H, $J = 8.8$, Ar H); MS (EI) 281 (M^+, 1%), 222 (3), 176 (4), 146 (100), 135 (29), and 86 (48); HRMS calcd for $C_{13}H_{15}NO_4S$ 281.0722, found 280.9824; $[\alpha]_D^{25}$ -50.0 ($c = 0.1$, CH_2Cl_2)].

General Procedure for the Synthesis of Methyl *N*-Acylthiazolidine-4-carboxylate.

(a) Acid Chlorides 4 and 5. Freshly distilled thionyl chloride (15 mL) was added to (prop-2-enyloxy)acetic acid or (but-3-ynyloxy)acetic acid (28.5 mmol). After the solutions were heated at reflux for 30 min, the solvent was evaporated off. The residue was dissolved in toluene and the organic solvent evaporated off giving the corresponding acetylenic acid chloride, which was used without further purification.

(b) Methyl *N*-Acylthiazolidine-4-carboxylates. The thiazolidine-4-carboxylate (28.5 mmol) was dissolved in dry dichloromethane (60 mL). Anhydrous potassium carbonate (6 g, 43.4 mmol) was added followed by a solution of the acid chloride in dichloromethane (20 mL). The reaction mixture was stirred under nitrogen at room temperature for 18 h. The organic solution was washed with water and the solvent evaporated off. The crude product was purified by flash chromatography [hexanes−ethyl acetate].

Methyl (2*R*,4*R*)-2-phenyl-*N*-(but-3-ynyloxyacetyl)thiazolidine-4-carboxylate (5): yield 68%; ^{1}H NMR 2.35 (m, 1H), 3.20−3.35 (m, 2H), 3.44−3.55 (m, 2H), 3.69−3.82 (m, 2H), 3.85 (s, 3H), 3.93−4.08 (m, 2H), 4.71 and 5.05 (2 × m, 1H), 6.19 and 6.25 (2 × s, 1H), 7.31−7.41 (m, 3H, Ar H) and 7.61−7.68 (m, 2H, Ar H); MS (EI) 333 (M^+, 1%), 274 (28), 222 (32), 77 (27), and 53 (100). Anal. Calcd for $C_{17}H_{19}NSO_4$: C, 61.2; H, 5.7; N, 4.2. Found: C, 59.9; H, 5.6; N, 4.0.

Methyl (2*R*,4*R*)-2-phenyl-*N*-(prop-2-enyloxyacetyl)thiazolidine-4-carboxylate (9): yield 60%; mp 60.2−62.3 °C; ^{1}H NMR 3.24−3.30 (m, 2H), 3.84 (s, 3H), 3.94−3.99 (m, 4H), 5.04−5.21 (m, 3H), 5.77 (m, 1H), 6.21 (s, 1H), 7.27−7.37 (m, 3H, Ar H), and 7.64−7.66 (m, 2H, Ar H); MS (EI) 321 (M^+, 1%), 222 (31), 162 (36), 121 (77), 77 (31), 59 (56) and 41 (100). Anal. Calcd for $C_{16}H_{19}NSO_4$: C, 59.8; H, 6.0; N, 4.4. Found: C, 59.7; H, 5.9; N, 4.3.

Methyl (2*R*,4*R*)-2-methyl-*N*-(prop-2-ynyloxyacetyl)thiazolidine-4-carboxylate (12): yield 63%, obtained as an oil; ^{1}H NMR 1.61 and 1.66 (d, 3H, $J = 6.3$), 2.50 (s, 1H), 3.31−3.43 (m, 2H), 3.78 and 3.81 (s, 3H), 4.22−4.35 (m, 4H), 4.99−5.06 (m, 1H), 5.31 and 5.48 (q, 1H, $J = 6.3$); MS (EI) 258 (MH^+, 43%), 198 (20), 188 (15), 174 (18), 160 (14), and 69 (100). Anal. Calcd for $C_{11}H_{15}NSO_4$: C, 51.4; H, 5.9; N, 5.4. Found: C, 50.9; H, 6.0; N, 5.3.

Methyl (2*R*,4*R*)-2-(*p*-methoxybenzoyl)-*N*-(prop-2-ynyloxyacetyl)thiazolidine-4-carboxylate (18): yield 97%; mp 113.5−114.5 °C (from ethyl acetate−hexane); ^{1}H NMR 2.16−2.37 (m, 1H), 3.38−3.68 (m, 2H), 3.85−3.90 (m, 6H), 3.94 and 3.96 (m, 1H), 4.22−4.56 (m, 3H), 5.16−5.28 (m, 1H), 6.44 and 6.48 (2 × s, 1H, C*H*COAr), 6.93−6.98 (m, 2H, Ar H), and 7.90−7.95 (m, 2H, Ar H); MS (EI) 378 (MH^+, 5%), 242 (86), 214 (85), 184 (32), and 135 (100). Anal. Calcd for $C_{18}H_{19}NSO_6$: C, 57.3; H, 5.1; N, 3.7; S, 8.5. Found: C, 57.2; H, 5.1; N, 4.0; S, 8.6. $[\alpha]_D^{25} = +51.5$ ($c = 0.1$, CH_2Cl_2).

Methyl (2*S*,4*R*)-2-(*p*-methoxybenzoyl)-*N*-(prop-2-ynyloxyacetyl)thiazolidine-4-carboxylate (21): yield 58%, obtained as an oil; ^{1}H NMR 2.35−2.50 (m, 1H), 3.14−3.61 (m, 2H), 3.84 (s, 3H), 3.88 and 3.89 (2 × s, 3H), 3.92−3.94 (m, 1H), 4.05−4.33 (m, 3H), 5.31 (dd, 1H, $J = 6.4$, 13.6), 6.45 and 6.58 (2 × s, 1H, C*H*COAr), 6.94−6.99 (m, 2H, Ar H), and 7.90−7.94 (m, 2H, Ar H); MS (EI) 378 (MH^+, 3%), 242 (100), 214 (77), 184 (28), 135 (67), and 69 (50); HRMS calcd for $C_{18}H_{20}NO_6S$ (MH^+) 378.1010, found 378.1011; $[\alpha]_D^{25} = -107.9$ ($c = 0.1$, CH_2Cl_2).

Methyl (2*R*,4*R*)-2-benzoyl-*N*-(prop-2-ynyloxyacetyl)thiazolidine-4-carboxylate (24): yield 62%, obtained as an oil; ^{1}H NMR 2.34−2.51 (m, 1H), 3.14−3.60 (m, 2H), 3.80 and 3.84 (2 × s, 3H), 3.77−3.89 (m, 1H), 4.01−4.36 (m, 3H), 5.28−5.36 (m, 1H), 6.47 and 6. 63 (2 × s, 1H, C*H*COMe), 7.31−7.64 (m, 4H, Ar H), and 7.92−7.95 (m, 1H, Ar H); MS (EI) 348 (MH^+, 12%), 242 (100), 214 (98), 184 (45), and 105 (45); $[\alpha]_D^{25} = -166.7$ ($c = 0.1$, CH_2Cl_2).

General Procedure for the Synthesis of Thiazolidine-4-carboxylic Acids. The methyl *N*-acylthiazolidine-4-carboxylate (1 mmol) and LiI (4 mmol) were dissolved in ethyl acetate (1.3 mL). The reaction mixture was protected from light and heated at reflux for 6 h. Water was added (5 mL), and the solution was acidified with 1 M HCl and extracted with ethyl acetate. The organic phase was washed with water and with a saturated aqueous solution of NaCl. The organic solvent was evaporated off. To the residue a saturated aqueous solution of $NaHCO_3$ was added, and the solution was washed with DCM. The aqueous solution was acidified with concentrated HCl and extracted with ethyl acetate. The organic phase was dried, and the solvent was evaporated giving the *N*-acyl-2-phenylthiazolidine-4-carboxylic acid. The following acids were isolated by this procedure:

(2*R*,4*R*)-2-Phenyl-*N*-(but-3-ynyloxyacetyl)thiazolidine-4-carboxylic acid (6): yield 92%, obtained as an oil; ^{1}H NMR 2.38 (m, 1H), 3.27−3.63 (m, 6H), 3.84−4.16 (m, 2H), 4.74 and 5.09 (2 × m, 1H), 6.23 and 6.29 (2 × s, 1H), 7.32−7.47 (m, 3H, Ar H), and 7.54−7.81 (m, 2H, Ar H); MS (EI) 320 (MH^+, 0.7%), 248 (6), 77 (33), and 53 (100); HRMS calcd for $C_{16}H_{18}NO_4S$ (MH^+) 320.0957, found 320.0962.

(2*R*,4*R*)-2-Phenyl-*N*-(prop-2-enyloxyacetyl)thiazolidine-4-carboxylic acid (10): yield 46%, obtained as an oil; ^{1}H NMR 3.05−3.57 (m, 2H), 3.75−4.27 (m, 4H), 4.79 (m, 1H), 5.03−5.26 (m, 2H), 5.69 and 5.87 (2 × m, 1H), 6.18 and 6.35 (2 × s, 1H), 7.30−7.37 (m, 3H, Ar H), and 7.52−7.69 (m, 2H, Ar H); MS (EI) 307 (M^+, 1%), 208 (16), 77 (32), and 41 (100).

(2*R*,4*R*)-2-Methyl-*N*-(prop-2-ynyloxyacetyl)thiazolidine-4-carboxylic acid (13): yield 59%, obtained as an oil; ^{1}H NMR 1.64 (d, 3H, J 5.7), 2.52 (s, 1H), 3.37−3.47 (m, 2H), 4.19−4.36 (m, 4H), 4.97−5.09 (m, 1H) and 5.32−5.48 (m, 1H); MS (EI) 244 (MH^+, 62%), 228 (8), 141 (43), 86 (51), and 69 (100); HRMS calcd for $C_{10}H_{16}NO_4S$ (MH^+) 244.0644, found 244.0647.

(2*R*,4*R*)-2-(*p*-Methoxybenzoyl)-*N*-(prop-2-ynyloxyacetyl)thiazolidine-4-car boxylic acid (19): yield 92%, obtained as an oil; ^{1}H NMR 2.37−2.56 (m, 1H), 3.44−3.79 (m, 2H), 3.89 and 3.93 (2 × s, 3H), 4.25−4.45 (m, 4H), 4.97−5.36 (m, 1H), 6.48, 6.58, 6.65, and 6.73 (4 × s, 1H, C*H*COAr), 6.94−7.03 (m, 2H, Ar H), 7.90−7.95 (m, 1H, Ar H), and 7.98−8.05 (m, 1H, Ar H); MS (EI) 364 (MH^+, 1%), 228 (47), 200 (41), 135 (100), 107 (9), and 69 (41); HRMS calcd for $C_{17}H_{17}NO_6S$ (MH^+) 364.0855; found 364.0855.

(2*S*,4*R*)-2-(*p*-Methoxybenzoyl)-*N*-(prop-2-ynyloxyacetyl)thiazolidine-4-carb oxylic acid (22): yield 95%, obtained as an oil; ^{1}H NMR 2.37−2.55 (m, 1H), 3.16−3.64 (m, 2H), 3.88 and 3.90 (2 × s, 3H), 4.09−4.16 (m, 1H), 4.20−4.31 (m, 3H), 5.31−5.40 (m, 1H), 6.48 and 6.57 (2 × s, 1H, C*H*COAr), 6.94−7.03 (m, 2H, Ar H), and 7.90−7.94 (m, 2H, Ar H); MS (EI) 327 [$(M - CH_2O_2)^+$, 6%], 228 (28), 200 (32), 135 (100), 86 (30), 77 (40), and 69 (52).

(2*R*,4*R*)-2-Benzoyl-*N*-(prop-2-ynyloxyacetyl)thiazolidine-4-carboxylic acid (25): yield 95%; mp 162.8−165.2 °C (from ethyl ether−hexane); ^{1}H NMR 2.35−2.58 (m, 1H), 3.33−3.49 (m, 2H), 3.85−3.89 (m, 1H), 4.09−4.34 (m, 3H), 5.32−5.42 (m, 1H), 6.51 and 6.63 (2 × s, 1H, C*H*COMe), 7.43−7.52 (m, 4H, Ar H), and 7.92−7.95 (m, 1H, Ar H); MS (EI) 228 [$(M - COPh)^+$, 22%], 200 (26), 105 (100), 86 (30), 77 (81), and 69 (75); $[\alpha]_D^{25} = -199.8$ ($c = 0.1$, CH_2Cl_2).

General Procedure for the Synthesis of Adducts 7, 14, 15, 20, 23, 26, and 27. The *N*-acylthiazolidine-4-carboxylic acid (5 mmol) was dissolved in Ac_2O (20 mL), and the solution was heated at reflux for 6 h. The reaction mixture was cooled to room temperature and was diluted with CH_2Cl_2 (50 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ and with water, dried (Na_2SO_4), and evaporated off. The crude product was purified by flash chromatography (hexanes−ethyl acetate).

(6*R*)-6-Phenyl-1,2-dihydro-4*H*,6*H*,8*H*-pyro[3′,4′:2,3]pyrrolo[1,2-*c*][1,3]thiazole (7): yield 18%; mp 100−125 °C (from ethyl ether−hexane); ^{1}H NMR 2.60−2.62 (m, 2H), 3.68−3.76 (m, 1H), 3.78−3.86 (m, 2H), 4.15 (d, 1H, $J = 12.9$), 4.27 (d, 1H, $J = 12.3$), 4.31 (d, 1H, $J = 12.9$), 5.77 (s, 1H), 6.17 (s, 1H), 7.19−7.35 (m, 5H, Ar H); MS (EI$^+$) 257 (M^+, 83%), 136 (94), 121 (100), 105 (94), and 77 (93); HRMS calcd for $C_{15}H_{15}NOS$ 257.0874, found 257.0872; $[\alpha]_D^{25} = +148.1$ ($c = 0.1$, CH_2Cl_2).

(7*R*)-7-Methyl-1,3-dihydro-5*H*,7*H*-furo[3′,4′:2,3]pyrrolo[1,2-*c*][1,3]thiazole (14): yield 26%; mp 54.6−59 °C; ^{1}H NMR 1.66 (d, 3H, $J = 6.0$), 4.07 (s, 2H), 4.85−4.89 (m, 4H), 5.37 (q, 1H, $J = 6.0$) and 5.67 (s, 1H); MS (EI) 181 (M^+, 100%), 122 (54), 93 (50), and 65 (42). Anal. Calcd for $C_9H_{11}NSO$: C, 59.6; H, 6.1; N, 7.7. Found: C, 59.6; H, 6.2; N, 7.7. $[\alpha]_D^{25} = +75$ ($c = 1.0$, CH_2Cl_2).

(7*R*)-4-Acetyl-7-methyl-1,3-dihydro-5*H*,7*H*-furo-[3′,4′:2,3]pyrrolo[1,2-*c*][1,3]thiazole (15): yield 12%; mp 181.8−184.3 °C (from ethyl ether); ^{1}H NMR 1.68 (d, 3H, J = 6.3), 2.26 (s, 3H), 4.30 (d, 1H, J = 15.3), 4.38 (m, 1H), 4.89−4.9 (m, 2H), 5.04−5.06 (m, 2H) and 5.41 (q, 1H, J = 6.3); MS (EI) 223 (M$^+$, 100%), 208 (60), 136 (19), and 43 (51). Anal. Calcd for $C_{11}H_{13}NSO_2$: C, 59.2; H, 5.9; N, 6.3. Found: C, 58.8; H, 5.9; N, 6.6. $[\alpha]_D^{25}$ = +35 (c = 1.0, CH_2Cl_2).

(7*R*)-7-(*p*-Methoxybenzoyl)-1,3-dihydro-5*H*,7*H*-furo-[3′,4′:2,3]pyrrolo[1,2-*c*][1,3]thiazole (20) was obtained as a solid which was washed with ethyl ether (42%): mp 144.5−145.4 °C; ^{1}H NMR 3.92 (s, 3H), 4.13 (d, 1H, J = 12.6), 4.22 (d, 1H, J = 12.6),4.78 (bs, 2H), 4.90−4.95 (m, 2H), 5.82 (s, 1H), 6.28 (s, 1H), 7.01 (d, 2H, J = 8.9, Ar H), and 7.91 (d, 2H, J = 8.9, Ar H); MS (EI) 301 (M$^+$, 5.4%), 166 (78), 135 (100), 92 (25), and 77 (31). Anal. Calcd for $C_{16}H_{15}NSO_3$: C, 63.7; H, 5.0; N, 4.7; S, 10.6. Found: C, 63.4; H, 5.0; N, 4.9; S, 11.2. $[\alpha]_D^{25}$ = +99.9 (c = 0.1, CH_2Cl_2).

(7*S*)-7-(*p*-Methoxybenzoyl)-1,3-dihydro-5*H*,7*H*-furo-[3′,4′:2,3]pyrrolo[1,2-*c*][1,3]thiazole (23) was obtained as a solid that was washed with ethyl ether (21%): mp 148.2−150.3 °C (from ethyl ether); ^{1}H NMR 3.90 (s, 3H), 4.11 (d, 1H, J = 12.6), 4.20 (d, 1H, J = 12.6), 4.76 (bs, 2H), 4.88−4.93 (m, 2H), 5.81 (s, 1H), 6.26 (s, 1H), 6.92 (d, 2H, J = 8.9, Ar H), and 7.89 (d, 2H, J = 8.9, Ar H); MS (EI) 301 (M$^+$, 8%), 166 (69), 135 (100), 121 (23) 92 (18), and 77 (22). Anal. Calcd for $C_{16}H_{15}NSO_3$: C, 63.7; H, 5.0; N, 4.7; S, 10.6. Found: C, 63.5; H, 5.1; N, 4.8; S, 10.6. $[\alpha]_D^{25}$ = −96.2 (c = 0.1, CH_2Cl_2).

(7*R*)-7-Benzoyl-1,3-dihydro-5*H*,7*H*-furo[3′,4′:2,3]pyrrolo-[1,2-*c*][1,3]thiazole (26): yield 17%; mp 167.8−170.3 °C (from ethyl ether); υ (KBr) 1662 and 2856 cm^{-1}; ^{1}H NMR 4.09 (d, 1H, J = 12.5), 4.20 (dd, 1H, J = 1.3, 12.5), 4.76−4.78 (m, 2H), 4.86−4.96 (m, 2H), 5.82 (s, 1H), 6.29 (d, 1H, J 1.3), 7.50−7.54 (m, 2H, Ar H), 7.62−7.67 (m, 1H, Ar H), and 7.89−7.92 (m, 2H, Ar H); MS (EI) 271 (M$^+$, 8%), 166 (100), 122 (30), 105 (35), 94 (28), and 77 (44). Anal. Calcd for $C_{15}H_{13}NSO_2$: C, 66.4; H, 4.8; N, 5.2. Found: C, 66.7; H, 4.9; N, 5.2. $[\alpha]_D^{25}$ = +200.0 (c = 0.3, CH_2Cl_2).

3-Oxo-4-phenyl-3,4,6,8-tetrahydro-1*H*-furo[3′,4′:2,3]pyrrolo[1,2-*c*][1,4]thiazine (27): yield 29%; mp 122.6−124.3 °C (from ethyl ether); υ (KBr) 1678 and 2873 cm^{-1}; ^{1}H NMR 3.91 (d, 1H, J = 14.9), 4.17 (dd, 1H, J = 1.3, 14.9), 4.77−4.83 (m, 2H), 4.93−4.97 (m, 2H), 5.73 (s, 1H), 6.05 (bs, 1H), 7.01−7.08 (m, 2H, Ar H), and 7.37−7.39 (m, 3H, Ar H); MS (EI) 271 (M$^+$, 37%), 211 (100), 182 (30), 121 (23), and 77 (22). Anal. Calcd for $C_{15}H_{13}NSO_2$: C, 66.4; H, 4.8; N, 5.2. Found: C, 66.7; H, 5.0; N, 5.3. $[\alpha]_D^{25}$ = −0 (c = 0.3, CH_2Cl_2).

Synthesis of Dimethyl (3*R*)-3,5-dimethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (37a) and Dimethyl (3*S*)-3,5-dimethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (37b).

The diastereoisomeric mixture (2*R*,4*R*)- and (2*S*,4*R*)-2-methylthiazolidine-4-carboxylic acid was prepared as described in the literature[11] and was obtained as a white solid (95%): mp 144.0−188.6 °C (from ethyl ether); ^{1}H NMR (minor isomer) 1.51 (d, 3H, J = 6.1), 3.16 (dd, 2H, J = 6.2, 10.5), 4.18 (approximately t, 1H, J = 6.6), 4.79 (q, 1H, J = 6.5); ^{1}H NMR (major isomer) 1.60 (d, 3H, J = 6.1), 3.36 (dd, 2H, J = 8.3, 16.5), 3.82 (approximately t, 1H, J = 8.3), 4.58 (q, 1H, J = 6.1). Anal. Calcd for $C_5H_9NO_2S$: C, 40.8; H, 6.2; N, 9.5; S, 21.8. Found: C, 40.9; H, 6.3; N, 9.1; S, 21.7.

(2*R*,4*R*)-*N*-Acetyl-2-methylthiazolidine-4-carboxylic acid was prepared from 2-methylthiazolidine-4-carboxylic acid as described in the literature[8a] and was obtained as a white solid (70%): mp 94.5−99.5 °C (from ethyl ether); ^{1}H NMR 1.59 and 1.63 (2 × d, together 3H, J = 6.2, J = 6.5), 2.12 and 2.25 (2 × s, together 3H), 3.32−3.53 (m, 1H), 3.55−3.79 (m, 1H), 4.78 and 4.96 (dd and approximately t, together 1H, J = 4.2, 6.9 and J = 7.8), 5.17 and 5.49 (2 × q, together 1H, J = 6.5 and J = 6.2); MS (EI) (the product was treated with diazomethane giving the corresponding methyl ester) 203 (M$^+$, 4%), 146 (53), 117 (100), 102 (79), and 86 (26). Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.4; H, 5.9; N, 7.4; S, 16.9. Found: C, 44.0; H, 6.0; N, 7.4; S, 16.6.

(2*S*,4*R*)-*N*-Acetyl-2-methylthiazolidine-4-carboxylic acid was prepared from 2-methylthiazolidine-4-carboxylic acid as described in the literature[8a] and was obtained as a yellow oil (90%): ^{1}H NMR 1.58 and 1.63 (2 × d, together 3H, J = 6.2 and J = 6.3), 2.10 and 2.25 (2 × s, together 3H), 3.28−3.57 (m, 2H), 4.75−4.98 (m, 1H), 5.16 and 5.39 (2 × q, together 1H, J = 6.3 and J = 6.2); MS (EI) (the product was treated with diazomethane giving the corresponding methyl ester) 203 (M$^+$, 3%), 146 (55), 117 (96), 102 (100), and 86 (31).

Dimethyl (3*R*)-3,5-Dimethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (37a). (2*R*,4*R*)-*N*-Acetyl-2-methylthiazolidine-4-carboxylic acid (0.74 g, 3.9 mmol), DMAD (0.72 mL, 5.9 mmol), and Ac_2O (4.5 mL) were heated at 110−120 °C for 3 h. The reaction was cooled to room temperature and was diluted with CH_2Cl_2. The organic phase was washed with saturated aqueous solution of $NaHCO_3$ and with water, dried ($MgSO_4$), and evaporated off. The crude product was purified by flash chromatography [hexanes−ethyl acetate (2:1 and 1:1)] giving compound **37a** as a white solid (97%): mp 70.0−72.2 °C (from ethyl ether−hexane); ^{1}H NMR 1.71 (d, 3H, J = 6.2), 2.39 (s, 3H), 3,79 (s, 3H), 3.84 (s, 3H), 4.18 (d, 1H, J = 15.0), 4.35 (dd, 1H, J = 1.7, 15.0), 5.38 (dq, 1H, J = 1.7, 6.2); MS (EI) 269 (M$^+$, 42%), 237 (100), 222 (28), 178 (82), and 151 (32). Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.5; H, 5.6; N, 5.2; S, 11.9. Found: C, 53.8; H, 5.7; N, 5.5; S, 12.4. $[\alpha]_D^{25}$ = +110.0 (c = 1.0, CH_2Cl_2).

Dimethyl (3*S*)-3,5-Dimethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (37b). (2*S*,4*R*)-*N*-Acetyl-2-methylthiazolidine-4-carboxylic acid (0.79 g, 4.2 mmol) was dissolved in toluene (15 mL). DCC (0.86 g, 4.2 mmol) was added followed by DMAD (0.77 mL, 6.3 mmol). The reaction mixture was stirred at 100−110 °C for 3 h. The reaction was cooled to room temperature, and water was added. The organic phase was separated off, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were joined, dried ($MgSO_4$), and evaporated off. The product was isolated by flash chromatography [hexanes−ethyl acetate (1:1)] giving compound **37b** as a white solid (62%): mp 90.3−92.7 °C (from ethyl ether−hexane); ^{1}H NMR 1.72 (d, 3H, J = 6.2), 2.39 (s, 3H), 3,80 (s, 3H), 3.84 (s, 3H), 4.18 (d, 1H, J = 15.0), 4.35 (dd, 1H, J = 1.6, 15.0), 5.38 (dq, 1H, J = 1.6, 6.2); MS (EI) 269 (M$^+$, 42%), 237 (100), 222 (33), 178 (88), and 151 (29). Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.5; H, 5.6; N, 5.2; S, 11.9. Found: C, 53.1; H, 5.6; N, 5.1; S, 11.8. $[\alpha]_D^{25}$ = −70.0 (c = 1.0, CH_2Cl_2).

Crystal Data for Compound Methyl (2*R*,4*R*)-2-(4-Methoxybenzoyl)thiazolidine-4-carboxylate (17a). X-ray diffraction analysis on compound was carried out on an Enraf-Nonius CAD-4 diffractometer at room temperature. The structure of this compound was determined using a transparent crystal of dimensions 0.34 × 0.20 × 0.12 mm, space group $P21$ with unit cell a = 8.258(3) Å, b = 9.463(3) Å, c = 9.063(2) Å, β = 108.033(16)°, and V = 673.5(2) Å^3. It contains two molecules/unit cell. D_x = 1.387 g cm^{-3}, and μ = 0.250 mm^{-1}. Mo Kα radiation was used with λ = 0.710 73 Å. A total of 2393 reflections were used with $I > 2\sigma(I)$; R_w = 0.035.

Crystal Data for Compound Methyl (2*R*,4*R*)-2-(*p*-methoxybenzoyl)-*N*-(prop-2-ynyloxyacetyl)thiazolidine-4-carboxylate (18). X-ray diffraction analysis on compound **18** was carried out on an Enraf-Nonius CAD-4 diffractometer at room temperature. The structure of this compound was determined using a prismatic crystal of dimensions 0.49 × 0.49 × 0.10 mm (space group $P2_12_12_1$) with unit cell a = 7.5427(10) Å, b = 9.277(4) Å, c = 25.805(4) Å, and V = 1805.7(9) Å^3. It contains four molecules/unit cell. D_x = 1.388 g cm^{-3}, and μ = 0.214 mm^{-1}. Mo Kα radiation was used (λ = 0.710 73 Å). A total of 3010 reflections with $I > 2\sigma(I)$ were used; R = 0.033.

Crystal Data for 3-Oxo-4-phenyl-3,4,6,8-tetrahydro-1*H*-furo[3′,4′:2,3]pyrrolo[1,2-*c*][1,4]thiazine (27). X-ray diffraction analysis on compound **27** was carried out on a Enraf-Nonius CAD-4 diffractometer at room temperature. The structure of this compound ($C_{15}H_{13}NO_2S$, M_r = 271.32 amu) was determined from a transparent and colorless prismatic crystal of dimensions 0.15 × 0.25 × 0.41 mm (space group $P\bar{1}$) with unit cell a = 8.747(6) Å, b = 8.903(5) Å, c = 9.047(3) Å, α = 73.27(4)°, β = 89.55(4)°, γ = 73.64(5)°, and V = 645.3(6)

Å^3. It has two molecules/unit cell. $D_x = 1.396$ g cm^{-3}, and $\mu = 0.247$ mm^{-1}. Mo Kα radiation was used ($\lambda = 0.710\,73$ Å). A total of 2387 unique reflections were collected, with 1978 having $I > 2\sigma(I)$. R ($I > 2\sigma(I)$) = 0.0336, and $R_w = 0.0952$.

Circular Dichroism. The solutions were prepared using ethanol (Riedel-deHaën Spectranal grade). Spectra were run in either 1 or 0.1 cm quartz cells in concentrations of ca. 10^{-4} M (1 cm cell) or ca. 10^{-3} M (0.1 cm cell). Normally at least two accumulations were made when recording each CD spectrum.

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Supporting Information Available: Crystallographic tables and ORTEP diagrams for compounds **17a**, **18**, and **27**, CD spectra for the enantiomeric pair **20**/**23**, chemical shifts and coupling constants for the thiazolidine ring protons of **16a,b** and **17a,b**, CD and UV absorption data for some chiral C-3 substituted pyrrolo[1,2-*c*]thiazoles, torsion angles obtained from structures calculated with the HyperChem program (Polak−Ribiere optimization), and CD bands for the 3*R* enantiomers of pyrrolo[1,2-*c*]thiazoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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