JOC Article

# New Resolution of 2-Formyl-1,4-DHP Derivatives Using CIDR Methodology. Facile Access to New Chiral Tricyclic Thiolactam

Štefan Marchalín,[†] Katarína Cvopová,[†] Miroslav Križ,[‡] Peter Baran,[§] Hassan Oulyadi,[||] and Adam Daïch*

*Department of Organic Chemistry, Slovak University of Technology, SK-81237 Bratislava, Slovak Republic, Synkola Mlynska dolina CH-2, Faculty of Natural Sciences, Comenius University, SK-84215 Bratislava, Slovak Republic, Department of Chemistry, University of Puerto Rico, Rio Piedros, P.O. Box 23346, San Juan 00931-3346, Puerto Rico, IRCOF-UMR 6014 CNRS, Place Emile Blondel, Université de Rouen, F-76131 Mt-St-Aignan Cedex, France, and URCOM, EA 3221, UFR des Sciences & Techniques, l'Université du Havre, 25 rue Philippe Lebon, BP: 540, F-76058 Le Havre Cedex, France*

*adam.daich@univ-lehavre.fr*

*Received February 20, 2004*

(*R*)- and (*S*)-α-phenylethylamine (α-PEA: **7**) have been used separately to resolve successfully a racemate 2-formyl-1,4-DHP derivative **4**. The process was based on the difference of the solubility of both Schiff bases (**6**) since one of them crystallized out from the solution. These imines obtained by condensation of (*R*)-α-PEA (**7**) or (*S*)-α-PEA (**7**) with aldehyde (*rac*-**4**) were separated and analyzed by X-ray diffraction, and their exposition to an hydrochloric hydrolysis conditions led to the enantiopure (4*R*)-**4** or (4*S*)-**4** in excellent yields. Separate condensation of other chiral (**8** and **13**) and racemic (**18**) amino thiols as auxiliary with *rac*-**4**, (4*S*)-**4**, or (4*R*)-**4** is accompanied by an in situ crystallization-induced dynamic resolution, whereby one distereomer of thiazole template selectively precipitates and can be isolated by simple filtration in 76−82% yield with dr > 99. The thiazole species isolated from this process resulted from an amino aldehyde condensation followed by a spontaneous thiol−imine cycloaddition. Finally, the racemate (±)-(4*R*,2′*R*)-**19** and the diastereomerically pure homologous (4*S*,2′*R*)-**23** and (4*R*,2′*S*)-**20** (obtained in good yields (79−82%) from 2-aminoethanethiol (**18**) and 2-formyl-1,4-DHP derivative *rac*-**4**, (4*S*)-**4**, or (4*R*)-**4**, respectively) were converted conveniently in a one-pot procedure into newly tricyclic thiolactams in the DHP series in racemic ((±)-(6*R*,9b*R*)-**21**, 72% yield)) and enantiopure ((6*S*,9b*R*)-**24**, 71% yield); (6*R*,-9b*S*)-**24**, 70% yield) forms.

## Introduction

Calcium channel blockers (CCBs) of the 1,4-dihydropyridine derivatives (DHPs), exemplified by nifedipine (Adalat) and nilvadipine (Nivadil), are well-known as clinically important drugs since they first appeared on the market in 1975. To date, these compounds have become almost indispensable for the clinical treatment of cardiovascular diseases such as angina pectoris, hypertension, and cardiac arrhythmias.[1,2] Also, interest in them is growing toward other pharmacological activities such as neurotropic, antidiabetic, antiviral, antibacterial, and membrane protecting as well as anticancer.[3]

Interestingly, it has been now recognized that the absolute configuration at the $C_4$ position of the 1,4-DHP nucleus is indispensable for activity modulation. Indeed, enantiomers of an unsymmetrical 1,4-DHP usually differ in their biological properties, and sometimes they could have exactly the opposite action profile (calcium antagonist vs calcium agonist for example).[4] Consequently, the synthesis of enantiomerically pure 4-aryl-1,4-DHPs and their biological evaluation continue to present significant challenge for the scientific community.

Three general methods have been reported for the preparation of enantiomeric 4-aryl-1,4-DHPs: (i) the optical resolution of 1,4-DHP-monocarboxylic acids **1**,[1] (ii) the enantioselective Hantzsch-type synthesis using chiral auxiliary on the DHP-nitrogen atom **2**[1,5,6] or the ester function **3**,[4b] or (iii) the chemoenzymatic approaches by hydrolyzing the alkyl ester(s) function(s) at the position

* To whom correspondence should be addressed. Tel: (+33) 02-32-74-44-03. Fax: (+33) 02-32-74-43-91.
[†] Slovak University of Technology.
[‡] Slovak Comenius University.
[§] University of Puerto Rico.
[||] Université de Rouen.

(1) For reviews, see: (a) Bossert, F.; Vater, W. *Med. Res. Rev.* **1989**, *9*, 291. (b) Goldmann, S.; Stoltefuss, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1559 and references therein. (c) Marchalín, Š.; Chudík, M.; Mastihuba, V.; Decroix, B. *Heterocycles* **1998,** *48*, 1943 and references therein.

(2) Chudík, M.; Marchalín, Š.; Daïch, A.; Decroix, B. *Res. Adv. Synth. Org. Chem.* **2000**, *1*, 1.

(3) (a) Sobolev, A.; Franssen, M. C. R.; Vigante, B.; Cekavicus, B.; Makarova, N.; Duburs, G.; de Groot, A. *Tetrahedron: Asymmetry* **2001**, *12*, 3251. (b) Sobolev, A.; Franssen, M. C. R.; Vigante, B.; Cekavicus, B.; Zhalubovskis, R.; Kooijman, H.; Spek, A. L.; Duburs, G.; de Groot, A. *J. Org. Chem.* **2002**, *67*, 401 and references therein.

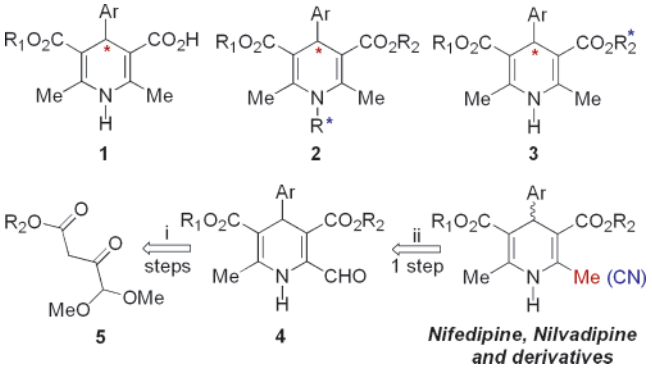
(4) (a) Vo, D.; Matowe, W. C.; Ramesh, M.; Iqbal, N.; Wolowyk, M. W.; Howlett, S. E.; Knaus, E. E. *J. Med. Chem.* **1995**, *38*, 2851. (b) Shan, R.; Howlett, S. E.; Knaus, E. E. *J. Med. Chem.* **2002**, *45*, 955.

(5) Kosugi, Y.; Hori, M.; Nagasaka, T. *Heterocycles* **1994,** *39*, 591.

(6) (a) Iqbal, N.; Vo, D.; McEwen, C. A.; Wolowyk, M. W.; Knaus, E. E. *Chirality* **1994**, *6*, 515. (b) Peri, R.; Padmanabhan, S.; Rutledge, A.; Singh, S.; Triggle, D. J. *J. Med. Chem.* **2000**, *43*, 2906.

10.1021/jo049706s CCC: $27.50 
Published on Web 05/11/2004

**SCHEME 1. Retrosynthetic Scheme Leading to the Nifedipine 1,4-DHPs Class**[a]




[a] Key: (i) see refs 2, 8, and 9; (ii) see refs 2 and 11.

$C_3$ and/or $C_5$ of the 3,5-dialkyl-4-aryl-1,4-DHP carboxylate(s).[1,3,7] In all these reported methods, only the 1,4-DHP nucleus with a methyl group at the $C_2$ and $C_6$ positions was studied.

## Results and Discussion

As a part of our research program directed toward 1,4-DHP chemistry, we have recently explored the utility of 2-formyl-1,4-DHP derivatives **4** as remarkable synthons for the synthesis of various pyrrolo[3,4-*b*]-1,4-DHPs,[8] highly functionalized indolizines with different degrees of unsaturation,[9] bis-1,4-DHPs,[10] and nilvadipine.[2] In this paper, we report for the first time optical resolution of 2-formyl-1,4-DHP derivatives **4** and their use to access new racemic and chiral tricyclic thiolactams **17** and **24**. Similar substrates to 2-formyl-1,4-DHPs **4**, which could be also used as the precursors to the synthesis of some optically active CCBs of the 1,4-DHPs class, have been used in racemic form to successfully produce nilvadipine and its derivatives in a multiple-step sequence.[11]

The proposed resolution consists of the use of α-phenylethylamine (α-PEA: **7**)[12] as a chiral auxiliary, covalently bonded to a racemic substrate via the aldehyde function. The substrate is represented by the cheaper racemic 2-formyl-4-(thien-2-yl)-1,4-DHP **4** ($R_1 = R_2 = CO_2Et$) (Scheme 1), which could be prepared from ethyl 4,4-dimethoxy-3-oxobutanoate (**5**) using a three-step sequence described previously by us.[2,8−10] This substrate was chosen as a starting material[13] for its stability and easy preparation relative to other 4-aryl-2-formyl-1,4-DHP derivatives.

The imine function of **6** (Scheme 2) is easily generated from an equimolar amount of epimerizable racemic aldehyde *rac*-**4** and pure (*R*)-α-PEA (**7**) in ethanol at room temperature. We obtained a mixture of two diastereomers with a dr of approximately 1:1. In the product **6**, the chiral auxiliary is too distant from the newly created stereogenic center (position $C_4$ of the DHP nucleus) for inducing significant differences of physical properties of the two diastereomers (4*R*,1′*R*)-**6** and (4*S*,1′*R*)-**6**; nevertheless, one of them, the (4*S*,1′*R*)-**6**, being poorly soluble, preferentially crystallized out from the solution.[14,15] The dissolution−precipitation of **6** was best obtained using dry ethanol at room temperature. Both the heat of the reaction (up to reflux of the solvent) and the use of other solvents such as methanol, $CH_2Cl_2$, $CHCl_3$, DMSO, and THF was accompanied by minor decomposition of compounds which decreased the crystallization of the imine (4*S*,1′*R*)-**6**. In some cases, no crystallization was observed. Having isolated the crystalline imine **6** (32% yield) which showed a (4*S*,1′*R*) configuration (its structure was confirmed by a single-crystal X-ray diffraction),[16] its acidic hydrolysis using 6 N hydrochloric acid solution in $CH_2Cl_2$ led to the enantiopure (4*S*)-2-formyl-1,4-DHP derivative **4** in a yield of 91%.

Similarly (Scheme 2), using again the racemic aldehyde *rac*-**4** and chiral (*S*)-α-PEA (**7**) as the formyl partner in dry ethanol gave a 1/1 mixture of (4*R*,1′*S*)-**6** and (4*S*,1′*S*)-**6**. The enantiomeric imine (4*R*,1′*S*)-**6** crystallized out was separated and collected by filtration after 2 h of the reaction (30% yield), and its structure was confirmed again by X-ray analysis.[16] Further, its hydrochloric acid hydrolysis produced similarly the enantiopure (4*R*)-2-formyl-1,4-DHP product **4** in 96% yield.

To generalize this process, we examined the effect of other chiral amines which bear an ester function with or without an additional methyl group at the stereogenic center $C_2$ of the chiral auxiliary. The condensation of racemic aldehyde *rac*-**4** with (*R*)-cysteine ethyl ester hydrochloride (**8**) in absolute ethanol at room temperature with 1.1 equiv of sodium acetate as base gave imines **I** and **II** which spontaneously cyclized via an intramolecular thiol−imine addition (Scheme 3).[17] Interestingly, four thiazoles, namely (4*S*,2′*R*,4′*R*)-**9**, (4*S*,2′*S*,4′*R*)-**10**, (4*R*,2′*R*,4′*R*)-**11**, and (4*R*,2′*S*,4′*R*)-**12**, were observed according to NMR essay of the reaction mixture. Furthermore, when the obtained crude solid **9** was taken up in ethanol as solvent followed by a slow evaporation, a crystalline product **9** as a single stereomer separated and could be obtained by simple filtration (44% yield). The

(7) (a) Holdgrüm, X. K.; Sih, C. J. *Tetrahedron Lett.* **1991**, *32*, 3465. (b) Ebiike, H.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1991**, *32*, 5805. (c) Ebiike, H.; Maruyama, K.; Achiwa, K. *Tetrahedron: Asymmetry* **1992**, *3*, 1153.

(8) Chudík, M.; Marchalín, Š.; Knesl, P.; Daïch, A.; Decroix, B. *J. Heterocycl. Chem.* **2000**, *37*, 1549.

(9) (a) Chudík, M.; Marchalín, Š.; Havrilová, K. *Collect. Czech. Chem. Commun.* **1998**, *63*, 826. (b) Chudík, M.; Marchalín, Š.; Pham-Huu, D.-P., Humpa, O.; Friedl, Z. *Monatsh. Chem.* **1999,** *130*, 1241. (c) Marchalín, Š.; Cvopová, K.; Pham-Huu, D.-P.; Chudík, M.; Kožíšek, J.; Svoboda, I.; Daïch, A. *Tetrahedron Lett.* **2001**, *42*, 5663.

(10) Marchalín, Š.; Chudík, M.; Cvopová, K.; Kožíšek, J.; Leško, J.; Daïch, A. *Tetrahedron* **2002**, *58*, 5747.

(11) (a) Satoh, Y.; Ichihashi, M.; Okumura, K. *Chem. Pharm. Bull.* **1991**, *39*, 3189. (b) Satoh, Y.; Okumura, K.; Shiokawa, Y. *Chem. Pharm. Bull.* **1992**, *40*, 1799.

(12) For use of the popular α-phenylethylamine (α-PEA) as the chiral resolving agent, see: Juaristi, E.; Escalante, J.; Léon-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmetry* **1998**, *9*, 715.

(13) The starting material, 1,4-DHP derivative **4**, could be obtained in large scale—up to 20 g in a single preparative step.

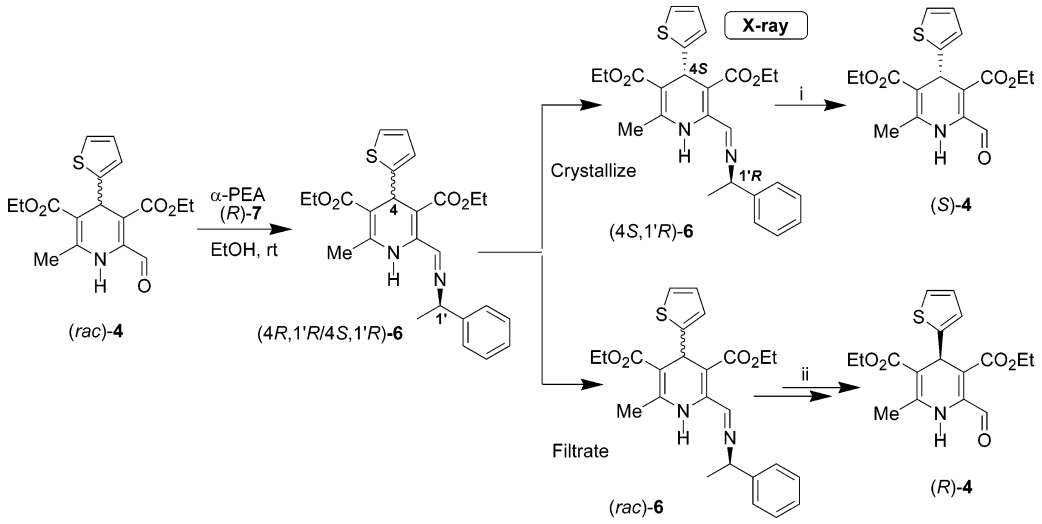
(14) (a) For recent review related to this subject, see: Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447 and references therein. (b) For recent examples, see: (c) Boesten, W. H. J.; Seerden, J.-P. G.; De Lange, B.; Dielemans, H. J. A.; Elsenberg, H. L. M.; Kaptein, B.; Moody, H. M.; Kellogg, R. M.; Broxterman, Q. B. *Org. Lett.* **2001**, *3*, 1121. (d) Košmrlj, J.; Weigel, L. O.; Evans, D. A.; Downey, C. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 3208.

(15) The proximity of a chiral auxiliary to the labile stereocenter in the crystallization process is sometimes no as important. See ref bellow 14.

(16) See the Supporting Information for the ORTEP drawing of the enantiopures imines (4*S*,1′*R*)-**6** and (4*S*,1′*R*)-**6**.

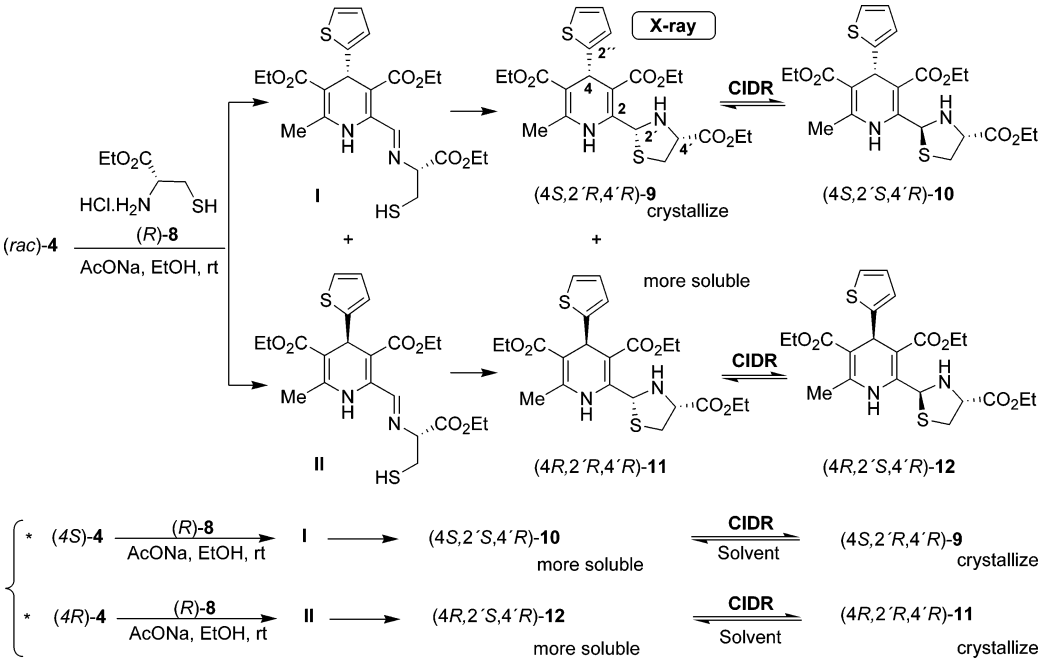
(17) For representative references, see: (a) Vernin, G.; Metzger, J. *Bull. Soc. Chem. Belg.* **1981**, *30*, 553. (b) Fernandez, X.; Fellous, R.; Duñach, E. *Tetrahedron Lett.* **2000**, *41*, 3381.

**SCHEME 2. Resolution of 2-Formyl-1,4-DHPs Derivative 4 at the Imine Function 6 by the Simple Selective Precipitation out from the Solution**[a]




[a] Key: (i) 6 N HCl, $CH_2Cl_2$, rt; (ii) (1) acidic hydrolysis as in (i); (2) (*S*)-α-PEA-(**7**), EtOH, rt; (3) filtration; (4) acidic hydrolysis as in (i).

**SCHEME 3. Deracemization of 2-Formyl-1,4-DHP Derivative 4 with Aminothiol (*R*)-8 via CIDR of Thiazoles 9 and 11**




4*S*, 2′*R*, and 4′*R* configurations of the three stereocenters were proven by X-ray structural analysis (Scheme 4).[18] In addition, this enantiopure thiazole derivative **9** in other solvents as MeOH, $CD_3OD$, DMSO-$d_6$, and $CDCl_3$ at room temperature furnished a mixture of **9** and **10** in equilibrium within 1.5, 2, 6, and 24 h, respectively. Since the recovery of diastereomer (4*S*,2′*S*,4′*R*)-**10**, which was not present initially in the solution, it is clear that the crystallization occurs under CIDR conditions.

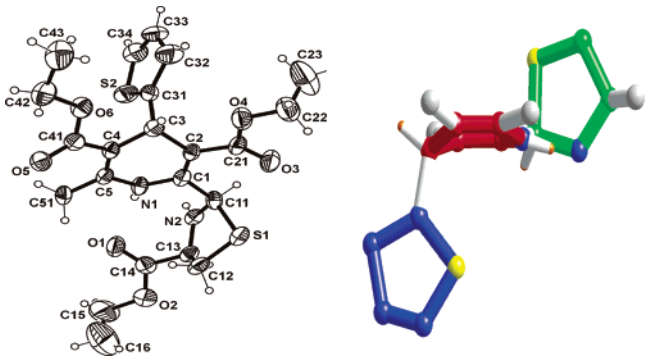
On the basis of these observations, it seemed that the solvent could play an important role for setting the appropriate CIRD conditions. In fact, if a protic solvent such as methanol is better for the kinetic interconversion of epimers (the epimerization process equilibration was reached in 1.5 h at room temperature), the ethanol is one in which the solubility of the arising 2-(2′-thiazolidinyl)-1,4-DHP (4*S*,2′*R*,4′*R*)-**9** is low. In addition, it is noteworthy that the in situ epimerization under CIDR conditions, observed here, might have been initiated by the excess of sodium acetate. This fact was confirmed by further study from the enantiopure (4*S*,2′*R*,4′*R*)-**9** in ethanol which showed a slow or rapid epimerization process upon addition of catalytic amounts of PTSA and *t*-BuOK, respectively.[19] In all these cases, the enantiopure (4*S*,2′*R*,4′*R*)-**9** was the main isomer obtained in different ratios compared to other epimers.

(18) (a) For the X-ray single-crystal structure determination of (4*S*,2′*R*,4′*R*)-**9**, see the crystallographic characteristics in the Supporting Information (SI1). (b) See also: Vrábel, V.; Kožíšek, J.; Marchalín, Š. *Acta Crystallogr.* **2003**, *E59*, 1064.

**TABLE 1. Chemicals Shifts ($\delta$ in ppm) in the $^1$H and $^{13}$C NMR Spectra of All Four Diastereomers 9−12 in $CDCl_3$ Solution**

| | compounds **9**−**12** | | | |
|---|---|---|---|---|
| proton/carbon | (4*S*,2′*R*,4′*R*)-**9** | (4*S*,2′*S*,4′*R*)-**10** | (4*R*,2′*R*,4′*R*)-**11** | (4*R*,2′*S*,4′*R*)-**12** |
| $CH_3$ at C-6/C-6 | 2.45 s/18.8 | 2.33 s/19.6 | 2.41 s/19.2 | 2.38 s/19.6 |
| H-5′/C-5′ | 3.17−3.24 m/35.8 | 3.17−3.24 m/34.7 | 3.18−3.23 m/35.6 | 3.18−3.23 m/33.8 |
| H-4′/C-4′ | 4.35 t/64.9 | 4.34 t/65.0 | 4.35 t/65.2 | 4.35 t/64.8 |
| H-4/C-4 | 5.33 s/34.6 | 5.34 s/34.6 | 5.35 s/34.6 | 5.34 s/34.6 |
| H-2′/C-2′ | 6.32 s/63.9 | 6.28 s/62.6 | 6.52 s/64.2 | 6.13 s/61.0 |
| NH/$CO_2$Et at C-2′ | 9.23 s/174.1 | 7.85 s/171.7 | 9.07 s/173.9 | 7.86 s/171.8 |

**SCHEME 4. Molecular Structure and Absolute Configuration of (4*S*,2′*R*,4′*R*)-9 (Arbitrary Numbering of Atoms, 30% Probability Ellipsoids)[a]**

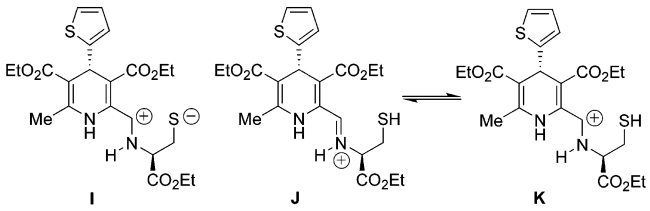



[a] A side view showing mutual orientation of molecule fragments in which ester groups are marked with their parent carbon atoms only.

To identify and characterize all diastereomers **9**, **10**, **11**, and **12**, the enantiopure aldehyde (4*S*)-**4** was subjected to the reaction with (*R*)-**8** under similar conditions as outlined above (Scheme 3). Only two diastereomers of **9** and **10** are present in the solution, out of which only the isomer (4*S*,2′*R*,4′*R*)-**9** crystallized out and was collected by suction (79% in total yield). A similar profile was obtained with (4*R*)-**4** and (*R*)-**8** under the effective protocol. Interestingly, the diastereomer (4*R*,2′*R*,4′*R*)-**11** was isolated as white crystals in 76% yield and its structure was determined by an array of monodimensional NMR analysis including the NOE difference measurements. After that, structure of the other epimers such as (4*S*,2′*S*,4′*R*)-**10** and (4*R*,2′*S*,4′*R*)-**12** was tentatively assigned and the obtained results of significant signals summarized in Table 1 (see also the Experimental Section for complete NMR attribution).

Thus, from these results, the CIDR process was effective and the interconversion of epimers could be explained by the formation of the intermediate **J** in equilibrium with **K** when the reaction is under acidic catalysis conditions (Chart 1). In contrast, when a base was used as catalyst, the zwitterionic intermediate **I** could be assumed. These observations have previously been suggested for the analogous 1,3-thiazolidines. The epimerization process had been observed in different conditions: in alkaline medium,[20] in neutral solution with

**CHART 1. Possible Intermediates Formed during the Epimerization Process**




protic solvent,[21] as well as in acidic conditions.[22] In these latter processes, the zwitterionic species were also evoked but their detection was not proven. In addition, in both cases the imine(s) **I** and/or **II** as the open-chain form of corresponding thiazole(s) have never been observed in the NMR spectra made during the epimerization process (CIDR) (Chart 1). These remarks are in contrast to those evoked, in general, during the ring-chain tautomerism studies of 1,3-thiazolidine heterocycles.[23] But, at the same time, a few examples of 1,3-thiazolidines do not contain detectable amounts of the related open chain form.

Similar crystallization-induced asymmetric resolutions (CIDRs), commonly known as the asymmetric transformations of a second order,[24] under conditions in which one of each enantiomer or diastereomer is converted to the other with an excellent selectivity, were reported. In these asymmetric disequilibrating transformations, the process occurred with the substrate epimerization in the presence of a nucleophile acting as a base and/or an additional base during the nucleophilic substitution reaction,[14,25] a catalytic amount of 1,5-diazabicyclo-[4.3.0]non-5-one (DBN),[14] a catalytic amount of aryl aldehyde,[14] a ketone−enol tautomerism,[26] and a reversible hetero-Diels−Alder cycloaddition.[27] However, only two special reports dealing with the formation of optically active compounds in which the crystallization process is governed by a second-order asymmetric transformation (without influence of base) were described. The latter

(19) (a) For similar results, see the following review: Ebbes, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. A. *Tetrahedron* **1997**, *53*, 9417 and references therein. (b) Napolitano, E.; Farina, V. *Tetrahedron Lett.* **2001**, *42*, 3231.

(20) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 364−665.

(21) Pesek, J. J.; Frost, J. H. *Tetrahedron* **1975**, *31*, 907.

(22) Nagasawa, H. T.; Goon, D. J. W.; Shirota, F. M. *J. Heterocycl. Chem.* **1981**, *18*, 1047.

(23) Hamri, A.; Péra, M.-H.; Fillion, H. *J. Heterocycl. Chem.* **1987**, *24*, 1629.

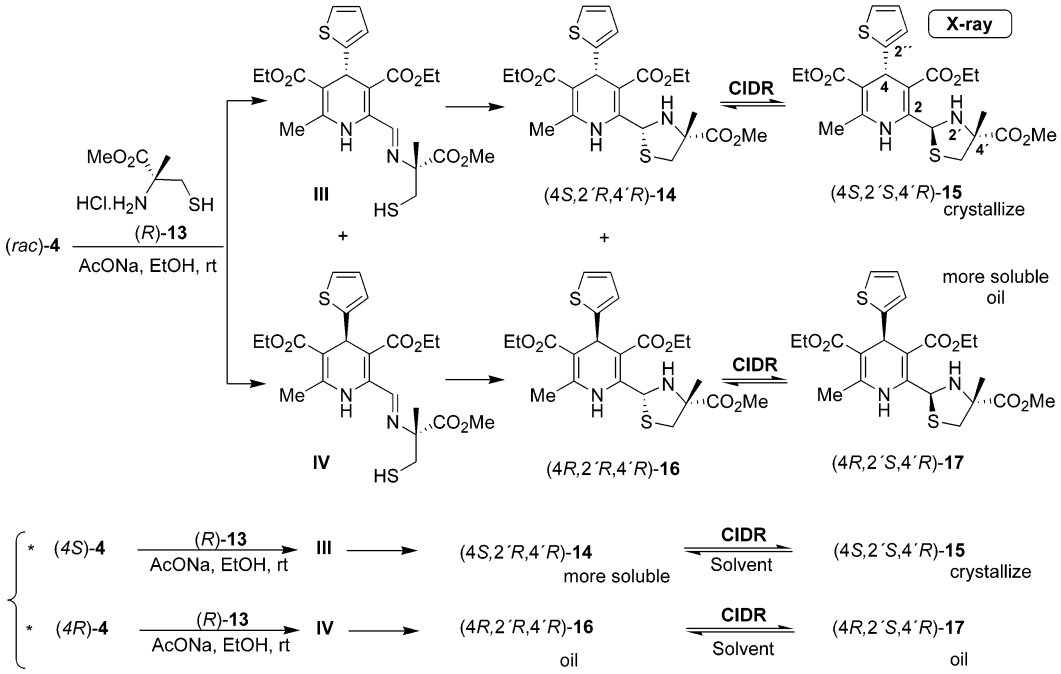
(24) For example of spectroscopic study on 1,3-thiazoles, see: Fülöp, F.; Mattinen, J.; Pihlaja, K. *Tetrahedron* **1990**, *46*, 6545 and references therein.

(25) (a) Caddick, S.; Jenkins, K. *Tetrahedron Lett.* **1996**, *37*, 1301. (b) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K. I. *J. Org. Chem.* **1997**, *62*, 5830. (c) O'Meara, J. A.; Gardee, N.; Jung, M.; Ben, R. N.; Durst, T. *J. Org. Chem.* **1998**, *63*, 3117. (d) Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700. (e) Lee, S.-K.; Lee, S. Y.; Park, Y. S. *Synlett* **2001**, 1941.

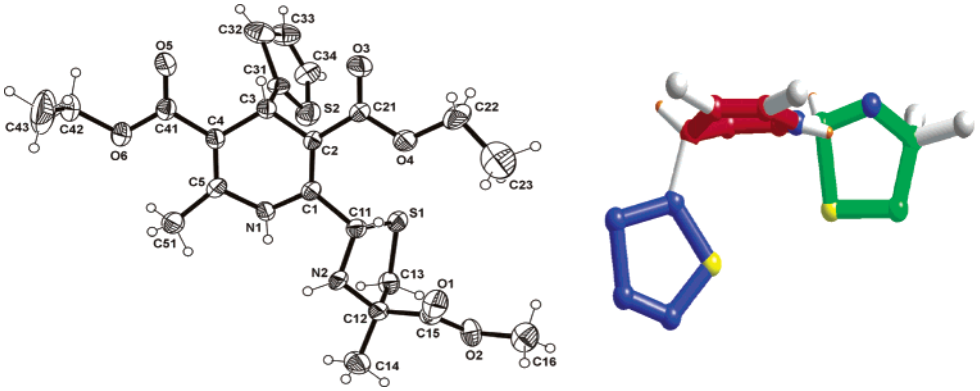
(26) Shieh, W.-C.; Carlson, J. A.; Zaunius, G. M. *J. Org. Chem.* **1997**, *62*, 8217.

(27) Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. *J. Org. Chem.* **2001**, *66*, 4759.

**SCHEME 5. Deracemization of 2-Formyl-1,4-DHP Derivative 4 with the Aminothiol (*R*)-13 via CIDR of Thiazoles 14−17**




**SCHEME 6. Molecular Structure and Absolute Configuration of (4*S*,2′*S*,4′*R*)-15 (Arbitrary Numbering of Atoms, 30% Probability Ellipsoids)[a]**



[a] A side view showing mutual orientation of molecule fragments in which ester groups are marked with their parent carbon atoms only.

processes occurred under achiral synthetic conditions[28] and with chiral amino alcohol as a reactant,[29] respectively.

In view of these promising CIDR results, we explored a second structural variation related to the chiral aminothiol type **8**. In this case, a commercially available (*R*)-2-methylcysteine methyl ester hydrochloride (**13**) was used as a substrate. In fact, standard treatment of the aldehyde *rac*-**4** with (*R*)-**13** in ethanol resulted in formation of four diastereomers in different proportions (Scheme 5). As for the reaction between aldehyde *rac*-**4** and (*R*)-**8**, the condensation of aminothiol (*R*)-**13** with *rac*-**4** produced imines **III** and **IV**, not detectable in the reaction medium. This condensation produced a rapid cyclization into the 2-(2′-thiazolidinyl)-1,4-DHP derivatives **14**−**17** without stereocontrol (Scheme 5). The diastereomer **15** which crystallized out of the solution (41% in total yield) had 4*S*, 2′*S*, and 4′*R* absolute configurations at $C_4$, $C_{2'}$ and $C_{4'}$ stereocenters, respectively, as observed by X-ray crystallography analysis (Scheme 6).[30] Interestingly, it has the opposite configuration at the *N*,*S*-acetal carbon $C_{2'}$ in comparison with the same one of the (4*S*,2′*R*,4′*R*)-**9** obtained above from *rac*-**4** or (4*S*)-**8** and (*R*)-**8** as starting materials (Schemes 3 and 4).

To obtain other information on the CIDR process, additional reactions were performed. So again, the chiral aldehyde (4*S*)-**4**, when subjected to a reaction with aminothiol (*R*)-**13**, yielded the diastereomer (4*S*,2′*S*,4′*R*)-**15** in 76% yield. After that, mother liquor partially

(28) Okada, Y.; Takebayashi, T.; Hashimoto, M.; Kasuga, S.; Sato, S.; Tamura, C. *J. Chem. Soc., Chem. Commun.* **1983**, 784.

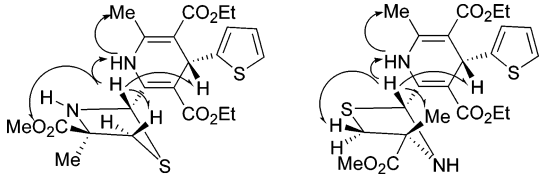
(29) Kolarovic, A.; Berkes, D.; Baran, P.; Povazanec, F. *Tetrahedron Lett.* **2001**, *42*, 2579.

(30) For the X-ray single-crystal structure determination of (4*S*,2′*S*,4′*R*)-**15**, see the crystallographic characteristics in the Supporting Information.

**TABLE 2. Chemicals Shifts ($\delta$ in ppm) in the $^1$H NMR Spectra of All Four Diastereomers 14−17 in $CDCl_3$ Solution**

| | compounds **14**−**17** | | | |
|---|---|---|---|---|
| proton | (4*S*,2′*R*,4′*R*)-**14** | (4*S*,2′*S*,4′*R*)-**15** | (4*R*,2′*R*,4′*R*)-**16** | (4*R*,2′*S*,4′*R*)-**17** |
| $CH_3$ at C-4′ | 1.60 s | 1.56 s | 1.62 s | 1.57 s |
| $CH_3$ at C-6 | 2.46 s | 2.33 s | 2.41 s | 2.41 s |
| H-5′ | 2.85 d, 3.44 d | 2.90 d, 3.34 d | 2.88 d, 3.45 d | 2.82 d, 3.35 d |
| H-4 | 5.33 s | 5.34 s | 5.33 s | 5.33 s |
| H-2′ | 6.37 s | 6.13 s | 6.56 s | 5.99 s |
| NH (H-1) | 9.10 s | 8.01 s | 9.03 s | 8.05 s |

**CHART 2. Selected NOE NMR Experiments for Diastereomers 14 and 15**



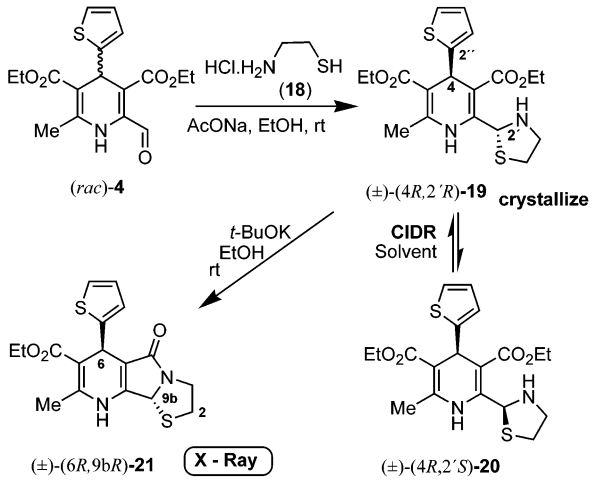
enriched in diastereomer (4*S*,2′*R*,4′*R*)-**14** was obtained, and further manipulations resulted in the equilibrium mixture but the minor product (4*S*,2′*R*,4′*R*)-**14** was not isolated (Scheme 5). Similar as above, (4*R*)-**4** was condensed with aminothiol (*R*)-**13** under the typical thiazole formation conditions; an equilibrium mixture of (4*R*,2′*R*,4′*R*)-**16** and its $C_{2'}$ epimer (4*R*,2′*S*,4′*R*)-**17** was obtained. The diastereomer (4*R*,2′*R*,4′*R*)-**16** was deposited as yellow oil in 75% yield but other tentative conventional recrystallization or trituration with other solvents immediately resulted in rapid epimerization into its diastereomer (4*R*,2′*S*,4′*R*)-**17** without any precipitation.

Structural assignment of these epimers was based on NMR data including NOE difference experiments (Chart 2) and the comparison with results obtained on the stereochemistry and conformational behavior of related 1,3-oxazolidines and 1,3-thiazolidines (Table 2). From these results, it seemed that (when the nitrogen atom is not bearing any substitution) the cis arrangement between the $C_{2'}$ and $C_{4'}$ substituents of the thiazole nucleus constitutes the principal factor for the epimeric stability as outlined previously.[31] These arguments are in accordance with our results obtained from aldehyde *rac*-**4** with aminothiol (*R*)-**8** or (*R*)-**13** and are responsible for the $C_{2'}$ absolute configuration inversion in diastereomer (4*S*,2′*S*,4′*R*)-**15** compared to the (4*S*,2′*R*,4′*R*)-**9** one as the major crystallized isomers.

To better understand the origin of this highly effective CIDR protocol, we have investigated reactions with other aminothiols. In fact, the success of this one-pot CIDR process was not restricted to the use of chiral aminothiol substrates. So, as depicted in Scheme 7, an ethanolic solution of 2-aminoethanethiol hydrochloride (**18**) reacted efficiently with the aldehyde *rac*-**4** and gave the racemate thiazole (±)-(4*R*,2′*R*)-**19** which was collected by simple filtration in an overall 82% yield. Similar to that shown above in the initial process, ethanol is a well-used solvent as a partner of the tandem imination/thiazole cyclization reaction. The use of other solvents led to similar results as shown above.

We have sought to address conveniently the relative absolute configuration at the $C'_2$ and $C_4$ positions of the

**SCHEME 7. Deracemization of 2-Formyl-1,4-DHP Derivative 4 with 2-Aminoethanthiol (18) and Access To Racemate Bicyclic Thiolactam 21**



bicyclic system **19** and to illustrate the potential of the one-pot thiazole formation protocol by the synthesis of some bicyclic thiolactams.[32] These structures constitute in the DHP series new, sophisticated, and interesting scaffolds, both of synthetic and pharmacological interest. In this sense, and on the basis of the preceding results,[8] the thiazole ester derivative (±)-(4*R*,2′*R*)-**19** was allowed to react under various cyclization conditions (Scheme 7). So, (±)-(4*R*,2′*R*)-**19** with a catalytic amount of *t*-BuOK in ethanol for 3 h at room temperature led to the bicyclic thiolactam (±)-(6*R*,9b*R*)-**21** (Scheme 8) in a yield of 72%; prolonged reaction time (up to 12 h) left the yield unchanged. The reaction proceeded via the classical intramolecular amino-ester cyclization in a basic medium. Interestingly, the same product (±)-(6*R*,9b*R*)-**21** was obtained in a comparable yield (70%) when a catalytic amount of PTSA in ethanol was used.

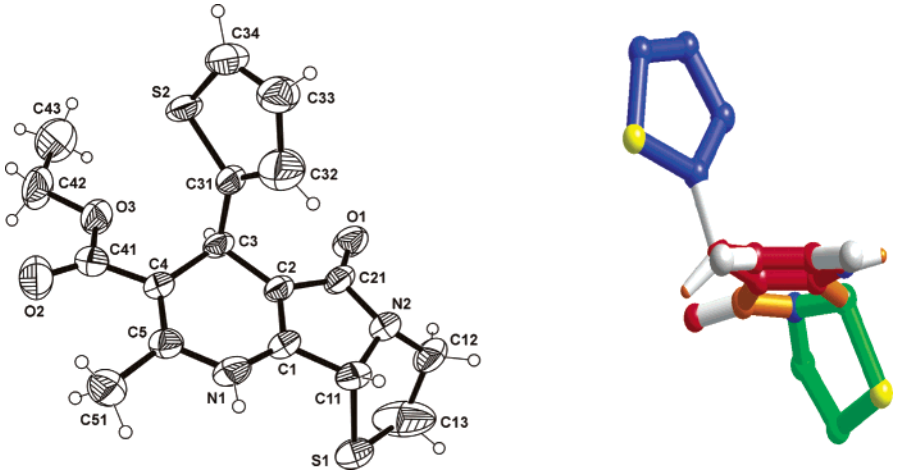
Crystals of (±)-**21** were grown from dry ethanol, and the (*R*) configuration at the $C_4$ position of the 1,4-DHP nucleus and the bridgehead stereocenter, respectively, was proven by X-ray structural analysis.[33] Interestingly, these results in addition to others that performed an independent X-ray crystallography of the monocrystal of (±)-**19** indicated clearly that the cyclization process occurred with total retention of the configuration of the angular stereocenter $C'_2$. From these results and that

(31) For the stereochemical study of optically active thiazolidines, see: Cruz, A.; Vásquez-Badillo, A.; Ramos-García, I.; Contraras, R. *Tetrahedron: Asymmetry* **2001**, *12*, 711.

(32) The oxygenated heterologues of these tricyclic lactams were elegantly and fully exploited by numerous groups, notably by Meyers. For more information, see the following reviews: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (b) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *54*, 9843.

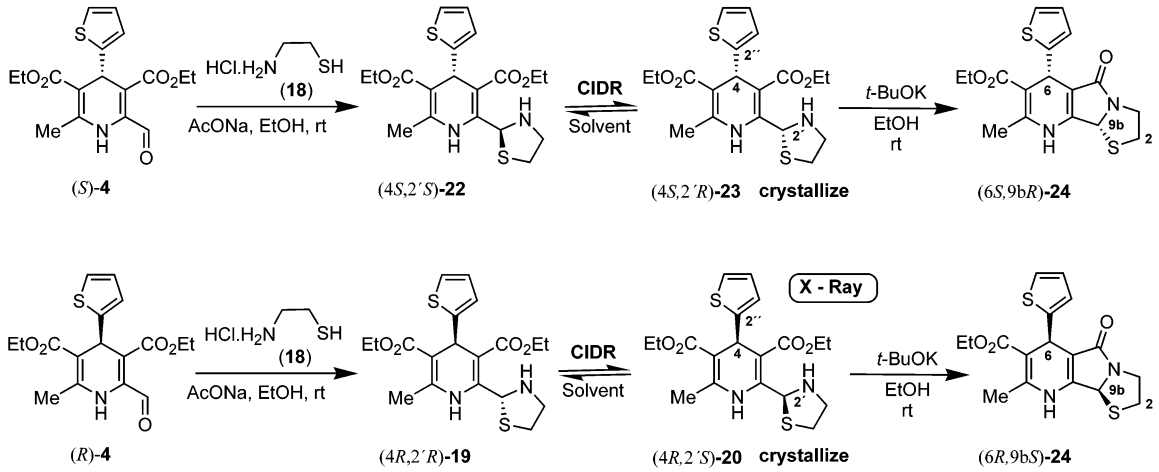
(33) For the X-ray single-crystal structure determination of (±)-(6*R*,-9b*R*)-**21**, see the crystallographic characteristics in the Supporting Information.

**SCHEME 8. Molecular Structure and Absolute Configuration of (±)-(4*R*,2′*S*)-21 (Arbitrary Numbering of Atoms, 50% Probability Ellipsoids)[a]**




[a] A side view showing mutual orientation of molecule fragments in which ester groups are marked with their parent carbon atoms only.

**SCHEME 9. Deracemization of Chiral 2-Formyl-1,4-DHP Derivative 4 with 2-Aminoethanethiol (18) and Access to Enantiopure Bicyclic Thiolactams 24**




obtained with chiral aminothiols developed above (Schemes 3 and 5), it seemed that the 1,4-DHP system via its stereocenter $C_4$ constitutes the principal factor which plays a pivotal role for the configuration of the $C'_2$ stereocenter being formed. Furthermore, the substitution at $C'_4$ position of the thiazole ring, constitutes a steric factor which leads to a high degree of stereogenic discrimination during the dynamic crystallization.

As shown in Scheme 9, we have investigated two additional reactions starting from 2-aminoethanethiol (**18**) and enantiopure (*S*)-**4** and (*R*)-**4**, respectively, under preferred conditions. Interestingly, the enantiopure thiazole-esters (4*S*,2′*R*)-**23** and (4*R*,2′*S*)-**20** (Scheme 10) were isolated in 82 and 81% yield, respectively.[34] Similarly as above, treatment of these substrates in ethanol with *t*-BuOK as a catalyst yielded enantiopure tricyclic thiolactam (6*S*,9b*R*)-**24** ($[\alpha]_D = -54.9$, *c* 0.5) and its enantiomer (6*R*,9b*S*)-**24** ($[\alpha]_D = +54.2$, *c* 0.5) in 70 and 71% yields, respectively. Interestingly, in both cases the protons $H_{2'}$ and $H_4$ at the stereogenic centers were in a cis relationship. Conversely, the same protons in the racemate (±)-(4*R*,2′*S*)-**21** described above were in a trans relationship.

Finally, these structures and particularly enantiopure products **17** deserve interest as analogues to a wide range of naturally occurring and/or bioactive substances. These compounds are exemplified by (2′*R*)-cephalexin and derivatives (**25**),[35] 6,5-fused bicyclic thiazolidinlactams (**26**),[36] and substituted (9*bR*)-9*b*-phenylthiazolo[2,3-*a*]isoindolin-5-one (**27**),[37] which have shown to be excellent antibiotics of considerable commercial and pharmaceutical relevance,[38] constrained dipeptides as active-site inhibitors of enzymes,[39] and a nonnucleosidic HIV-reverse transcriptase inhibitors (Chart 3).[37]

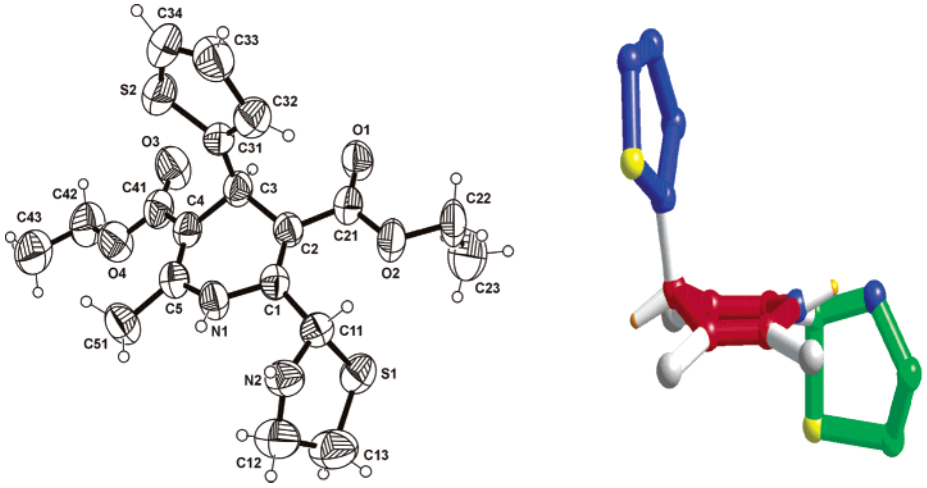
(34) For the X-ray single-crystal structure determination of (4*R*,2′*S*)-**20**, see the crystallographic characteristics in the Supporting Information.

(35) Cooper, J.; Humber, D. C.; Long, A. G. *Synth. Commun.* **1986**, *16*, 1469.

(36) Tremmel, P.; Brand, J.; Knapp, V.; Geyer, A. *Eur. J. Org. Chem.* **2003**, 878.

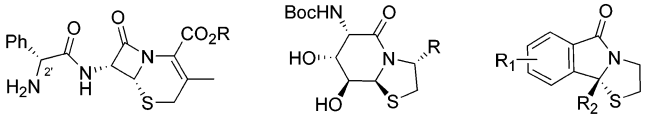
(37) (a) Mertens, A.; Zilch, H.; Koenig, B.; Schaefer, W.; Poll, T.; Kampe, W.; Seidel, H.; Leser, U.; Leinert, H. *J. Med. Chem.* **1993**, *36*, 2526. (b) Jingshan, R.; Esnouf, R. M.; Hopkins, A. L.; Stuart, D. I.; Stammers, D. K. *J. Med. Chem.* **1999**, *42*, 3845.

**SCHEME 10. Molecular Structure and Absolute Configuration of (4*R*,2′*S*)-20 (Arbitrary Numbering of Atoms, 50% Probability Ellipsoids)[a]**




[a] A side view showing mutual orientation of molecule fragments in which ester groups are marked with their parent carbon atoms only.

**CHART 3. Representative Bicyclic Thiolactam Structures**




(2′*R*)-Cephalexin/R=H (**25**) Thiazolidinlactams (**26**) Thiolactams (**27**)

## Conclusions

In conclusion, by means of a amino-aldehyde condensation involving the crystallization out of the solution of one diastereomer of the formed imines, we have disclosed a concise and efficient resolution protocol of 2-formyl-1,4-DHP derivative (**4**) from enantiopure (*R*)- and (*S*)-α-PEA (**7**). The use of other chiral amines bearing a thiol group as a second nucleophile as typified by (*R*)-cysteine ethyl ester (**8**) and (*R*)-methylcysteine methyl ester (**13**) under the same synthetic approach conditions led to enantiopure 2-(2′-thiazolidinyl)-1,4-DHP derivatives **9**−**12** and **14**−**17**, respectively, in variable yields (41 to 76%). These enantiopure thiazoles were also obtained as crystalline products by simple filtration when chiral amines (**8** and **13**) were exposed to react with enantiopure 2-formyl-1,4-DHP derivative (**4**) in ethanol as solvent. The structure of these products was secured by X-ray crystallographic analysis.

The formation of these tricyclic systems involves an amino-aldehyde condensation followed by an in situ spontaneous sulfur−imine cyclization proceeding in a stereocontrolled manner. Interestingly, under these conditions, a crystallization-induced dynamic resolution occurred depending on the temperature of the reaction and the nature of solvent.

Owing to the efficiency and simplicity of this new methodology, this protocol followed by an intramolecular peptidic coupling in alkaline medium between amine and ester functions were used to access in a two steps reaction pathway, using a CIDR process of 2-(2′-thiazolidinyl)-1,4-DHPs (obtained by the tandem amino-aldehyde condensation/thiol-imine cyclization), interesting enantiomerically pure tricyclic thiolactams in 1,4-DHP series **24** (70 and 71% yields). These *N*,*S*-acetals might find application as building blocks in asymmetric synthesis of a potentially bioactive compounds.[32] Studies along this line are currently underway in our laboratory, and the results will be published soon.

## Experimental Section

**General Remarks.** Melting points were taken with a capillary melting point apparatus and are uncorrected. UV spectra were determined in methanol. The infrared (IR) absorption spectra were determined as solutions in potassium bromide and are indicated in $cm^{-1}$. The $^1H$ and $^{13}C$ NMR spectra were recorded as solutions in $CDCl_3$ or DMSO-$d_6$ at 200 or 300 MHz ($^1H$) and 50.3 or 75 MHz ($^{13}C$), respectively, and chemical shifts ($\delta$) are expressed in ppm relative to TMS as internal standard. Thin-layer chromatography (TLC) was performed using of silica gel analytical plates ($F_{254}$) of 0.25 mm thickness. The detection on TLC plates was performed by UV light at 254 or 365 nm or using iodine vapor. Mass spectra (MS) were measured on a mass spectrometer using electron impact ionization (EI, 70 eV). Optical rotations were determined at 25 °C in acetone. The analytical results of elemental analysis are within 0.4% of theoretical values.

**(±)-Diethyl 2-Formyl-6-methyl-4-(thien-2′-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4).**[10] A mixture of thiophene-2-carboxaldehyde (1.12 g, 10 mmol), ethyl 4,4-dimethoxy-3-oxobutanoate **5** (1.9 g, 10 mmol), and piperidine (90 mg, 1 mmol) in benzene (10 mL) was refluxed with a Dean−Stark apparatus for 5 h. The solvent was evaporated under reduced pressure to give an oily olefin, which was used in the next step without any additional purification. To this oily residue was added ethyl 3-aminobutenoate (1.29 g, 10 mmol), and the resulting mixture was stirred at 100−120 °C for 3 h. After cooling, viscous oil was dissolved in acetone (37 mL) and 6 N hydrochloric acid (6.5 mL) was added dropwise. The solution was stirred at room temperature for 3 h. The organic solvent

(38) Substitution of the phenyl ring of cephalexin with certain substituents does not appear to modify significantly the antibacterial properties of cephalexin (R = H). For more information, see: Ryan, C. W.; Simon, R. L.; Van Heyningen, E. M. *J. Med. Chem.* **1969**, *12*, 310.

(39) (a) Elhkorn, F. A.; Guo, T.; Lipton, M. A.; Goldberg, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1994**, *116*, 10412. (b) Wagner, J.; Kallen, J.; Ehrhardt, C.; Evenou, J.-P.; Wagner, D. *J. Med. Chem.* **1998**, *41*, 3664.

was removed in vacuo, and the residue was poured onto water (10 mL) and neutralized with 10% solution of $NaHCO_3$. After classical workup, the solid residue was purified by recrystallization from ethanol and gave 2.55 g of 4-(thien-2′-yl)-2-formyl-1,4-DHP product (±)-**4** in 73% yield: mp 108−109 °C (ethanol) (lit.[40] mp 67−68.5 °C); $^1$H NMR ($CDCl_3$) $\delta$ 1.27 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.34 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.43 (s, 3H, $CH_3$), 4.15−4.21 (m, 2H, $OCH_2$), 4.28−4.33 (m, 2H, $OCH_2$), 5.46 (s, 1H, H-4), 6.81−6.89 (m, 2H, H-3″ and H-4″), 7.10−7.13 (m, 2H, H-5″ and NH), 10.52 (s, 1H, CH=O); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2 ($CH_3$), 14.3 ($CH_3$), 19.4 ($CH_3$ at C-6), 35.3 (C-4), 60.2 ($OCH_2$), 61.5 ($OCH_2$), 102.4, 115.0 (C-3 and C-5) 124.3, 124.3, 126.7 (C-3″, C-4″ and C-5″), 138.5, 144.6 (C-2 and C-6), 148.7 (C-2″), 165.5 ($CO_2$), 166.7 ($CO_2$), 186.8 (CH=O); IR (KBr) $\nu$ 3288 (s, NH), 2989 (m, CH), 1686 (s, C=O), 1675 (s, C=O), 1627 (m, C=C), 1598 (m, C=C), 1477 (s), 1378 (m), 1318 (m), 1272 (s), 1203 (s), 1088 (s), 1032 (m), 858 (w), 800 (m) cm$^{-1}$; UV $\lambda_{max}$ nm (log $\epsilon$) 231 (3.34), 353 (2.77); MS $m/z$ 350 (13), 349 M$^{\bullet+}$ (58), 320 (20), 304 (10), 278 (10), 177 (18), 276 (100), 275 (18), 274 (10), 166 (18), 248 (15), 246 (23), 202 (10), 192 (10), 164 (10). Anal. Calcd for $C_{17}H_{19}NO_5S$ (349.40): C, 58.44; H, 5.48; N, 4.01. Found: C, 58.16; H, 5.29; N, 3.96.

**Resolution of (±)-Diethyl 2-Formyl-6-methyl-4-(thien-2″-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4) via Diastereomeric Imines 6.** To a suspension of (±)-2-formyl-1,4-dihydropyridine (**4**) (10.1 g, 29 mmol) in ethanol (40 mL) was added (*R*)-α-phenylethylamine (**7**) (3.51 g, 29 mmol). After the mixture was stirred at room temperature for 2 h, the precipitated crystals of diastereomer (4*S*,1′*R*)-**6** were filtered off and washed with ethanol. The filtrate, containing the excess of the diastereomer (4*R*,1′*R*)-**6**, was evaporated to dryness. To the solid residue in dichloromethane (100 mL) were added water (10 mL) and 6 N HCl (12 mL). After the mixture was stirred at room temperature for 6 h (monitored by TLC), the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with sodium hydrogenocarbonate and water and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure to give the crude 1,4-dihydropyridine **4** as a yellow solid ($m$ = 7.16 g). To a suspension of this 2-formyl-1,4-dihydropyridine derivative **4** in ethanol (40 mL) was added (*S*)-α-phenylethylamine (**7**) (2.42 g, 20 mmol). After the mixture was stirred at room temperature for 2 h, the precipitated crystals of the diastereomer (4*R*,1′*S*)-**6** were filtered off and washed with cold ethanol.

**Diethyl (4*S*,1′*R*)-6-Methyl-2-[(1′-phenylethylimino)-methyl]-4-(thien-2″-yl)-1,4-dihydropyridine-3,5-dicarboxylate (6).** This diastereomer was obtained in 32% yield ($m$ = 4.16 g): mp 105−106 °C (propan-2-ol); $[\alpha]_D$ = −129.5 ($c$ 1); $^1$H NMR ($CDCl_3$) $\delta$ 1.26 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.30 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.55 (d, 3H, $CHCH_3$, $J$ = 6.6 Hz), 2.42 (s, 3H, $CH_3$), 4.14−4.24 (m, 4H, 2 × $OCH_2$), 4.64 (q, 1H, CH, $J$ = 6.6 Hz), 5.43 (s, 1H, H-4), 6.85−6.88 (m, 2H, H-3″ and H-4″), 7.09 (d, 1H, H-5″, $J$ = 3.9 Hz), 7.25−7.36 (m, 5H, H-arom), 7.87 (s, 1H, NH), 9.12 (s, 1H, CH=N); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2 ($OCH_2CH_3$), 14.3 ($OCH_2CH_3$), 19.7 ($CH_3$ at C-6), 24.3 ($CH_3$), 35.1 (C-4), 59.9 ($OCH_2$), 60.7 ($OCH_2$), 68.6 (CH), 102.1, 109.4 (C-3 and C-5) 123.7, 123.7, 126.5, 126.6, 126.6, 127.3, 128.6 (C-3″, C-4″, C-5″, 5 × CH-arom), 139.5, 143.8, 145.2 (C-2, C-6 and C-arom), 150.2 (C-2′), 153.1 (CH=N), 166.5 ($CO_2$), 167.2 ($CO_2$); IR (KBr) $\nu$ 3354 (s, NH), 3104 (w, =CH), 2985 (m, CH), 1705 (m, C=O), 1688 (s, C=O), 1613 (m, C=C), 1597 (m, C=C), 1470 (s), 1321 (m), 1275 (s), 1211 (m), 1105 (m), 1049 (w), 858 (m), 705 (m) cm$^{-1}$; UV $\lambda_{max}$ nm (log $\epsilon$) 197 (3.42), 255 (3.41), 375 (2.77); MS $m/z$ 453 (6), 452 M$^{+\cdot}$ (22), 379 (14), 378 (55), 368 (10), 359 (6), 319 (6), 300 (12), 275 (10), 274 (53), 264 (14), 228 (22), 218 (8), 106 (10), 105 (100), 103 (8), 79 (16), 77 (12). Anal. Calcd for $C_{25}H_{28}N_2O_4S$ (452): C, 66.35; H, 6.24; N, 6.19. Found: C, 66.22; H, 6.01; N, 5.97.

(40) Yoshinari, S.; Japanese Patent. FR 2,315,930, 1977; US 4,145,-432, 1977; *Chem. Abstr.* **1977**, *86*, 189726.

**Diethyl (4*R*,1′*S*)-6-Methyl-2-[(1′-phenylethylimino)-methyl]-4-(thien-2″-yl)-1,4-dihydropyridine-3,5-dicarboxylate (6).** This diastereomer was obtained in 30% yield ($m$ = 3.95 g): mp 104−105 °C (propan-2-ol); $[\alpha]_D$ = +133.8 ($c$ 1). Anal. Calcd for $C_{25}H_{28}N_2O_4S$ (452): C, 66.35; H, 6.24; N, 6.19. Found: C, 66.15; H, 6.04; N, 6.07.

**Enantiopure Diethyl 2-Formyl-6-methyl-4-(thien-2′-yl)-1,4-dihydropyridine-3,5-dicarboxylates (4).** To a solution of the corresponding imine (4*S*,1′*R*)-**6** or (4*R*,1′*S*)-**6** in dichloromethane (25 mL) were added water (10 mL) and 6 N HCl (6 mL). After the mixture was stirred at room temperature for 6 h (monitored by TLC), the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with sodium hydrogenocarbonate and water and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure, and the solid residue was purified by recrystallization from ethanol to give both enantiomers of 2-formyl-1,4-dihydropyridines **4**.

**Diethyl (4*S*)-2-Formyl-6-methyl-4-(thien-2′-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4).** This enantiomer was obtained from the imine (4*S*,1′*R*)-**6** in 91% yield: mp 128−129 °C; $[\alpha]_D$ = −414.9 ($c$ 1). Anal. Calcd for $C_{17}H_{19}NO_5S$ (349): C, 58.44; H, 5.48; N, 4.01. Found: C, 58.26; H, 5.30; N, 3.91.

**Diethyl (4*R*)-2-Formyl-6-methyl-4-(thien-2′-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4).** This enantiomer was obtained from the imine (4*R*,1′*S*)-**6** in 96% yield: mp 128−129 °C; $[\alpha]_D$ = +411.9 ($c$ 1). Anal. Calcd for $C_{17}H_{19}NO_5S$ (349): C, 58.44; H, 5.48; N, 4.01. Found: C, 58.20; H, 5.33; N, 3.85.

**Diethyl 2-(4′-Ethoxycarbonyl-2′-thiazolidinyl)-6-methyl-4-(thien-2″-yl)-1,4-dihydropyridine-3,5-dicarboxylates (9−12).** To a suspension of 2-formyl-1,4-dihydropyridine *rac*-**4** (0.70 g, 2.0 mmol) and (*R*)-cysteine ethyl ester hydrochloride (**8**) (0.37 g, 2.0 mmol) in ethanol (5 mL) was added AcONa (0.18 g, 2.2 mmol) over 15 min. After being stirred at room temperature for 3 h, the mixture was poured into crushed ice. The precipitated crude product was filtered off, washed with water, and recrystallized from ethanol.

**Diastereomer (4*S*,2′*R*,4′*R*)-9: Method A.** Starting from the aldehyde *rac*-**4**, the mixture of diastereomers **9**−**12** was obtained in a 1:1 ratio. Diastereomer (4*S*,2′*R*,4′*R*)-**9** was isolated in a yield of 44% after crystallization from ethanol: mp 162−166 °C; $[\alpha]_D$ = +268.8 ($c$ 1); $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.27 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.31 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.45 (s, 3H, $CH_3$), 2.79 (s broad, 1H, NH), 3.17−3.24 (m, 2H, $CH_2$), 4.11−4.22 (m, 4H, 2 × $OCH_2$), 4.25 (q, 2H, $OCH_2$, $J$ = 7.2 Hz), 4.35 (t, 1H, CH, $J$ = 6.6 Hz), 5.33 (s, 1H, H-4), 6.32 (s, 1H, CH), 6.80−6.85 (m 2H, H-3″ and H-4″), 7.04 (dd, 1H, H-5″, $J$ = 1.2, 4.8 Hz), 9.23 (s broad, 1H, NH); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2 ($CH_3$), 14.3 ($CH_3$), 14.4 ($CH_3$), 18.8 ($CH_3$ at C-6), 34.6 (C-4), 35.8 ($CH_2$), 59.7 ($OCH_2$), 60.0 ($OCH_2$), 62.0 ($OCH_2$), 63.9 (CH), 64.9 (CH), 101.2, 103.4 (C-3 and C-5),123.1, 126.3 (C-3″, C-4″ and C-5″), 146.2, 149.4, 151.7 (C-2, C-6, C-2″), 166.8 ($CO_2$), 167.5 ($CO_2$), 174.1 ($CO_2$); IR (KBr) $\nu$ 3382 (m, NH), 3237 (m, NH), 3096 (w, =CH), 2981 (m, CH), 2932 (w, CH), 1736 (s, C=O), 1686 (s, C=O), 1678 (s, C=O), 1633 (m, C=C), 1585 (m, C=C), 1466 (s), 1365 (w), 1281 (s), 1202 (s), 1101 (s), 1052 (m), 782 (w), 710 (w), 686 (w) cm$^{-1}$; UV $\lambda_{max}$ nm (log $\epsilon$) 235 (3.41), 358 (2.88); MS $m/z$ 480 M$^{\bullet+}$ (19), 408 (19), 407 (72), 398 (17), 397 (66), 396 (17), 323 (15), 321 (28), 287 (19), 277 (30), 276 (15), 275 (75), 238 (15), 229 (19), 160 (66), 87 (15), 86 (34), 59 (26), 42 (15), 39 (17), 29 (100), 27 (36). Anal. Calcd for $C_{22}H_{28}N_2O_6S_2$ (480): C, 54.98; H, 5.87; N, 5.83. Found: C, 54.82; H, 5.81; N, 5.73. **Method B.** The same isomer **9** was prepared from the enantiopure aldehyde (*S*)-**4** in 79% yield: mp 163−166 °C; $[\alpha]_D$ = +269.8 ($c$ 1).

**Diastereomer (4*S*,2′*S*,4′*R*)-10:** $^1$H NMR ($CDCl_3$) $\delta$ 1.23 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.27 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.32 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 2.33 (s, 3H, $CH_3$), 2.79 (s broad, 1H, N−H), 3.17−3.24 (m, 2H, $CH_2$), 4.11−4.22 (m, 4H, 2 × $OCH_2$), 4.25 (q, 2H, $OCH_2$, $J$ = 7.2 Hz), 4.34 (t,

1H, CH, $J$ = 6.6 Hz), 5.34 (s, 1H, H-4), 6.28 (s, 1H, CH), 6.80−6.85 (m 2H, H-3″ and H-4″), 7.05 (dd, 1H, H-5″, $J$ = 1.2, 4.8 Hz), 7.85 (s broad, 1H, NH); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2 ($CH_3$), 14.3 ($CH_3$), 14.4 ($CH_3$), 19.6 ($CH_3$ at C-6), 34.6 (C-4), 34.7 ($CH_2$), 59.9 ($OCH_2$), 60.1 ($OCH_2$), 62.0 ($OCH_2$), 62.6 (CH), 65.0 (CH), 100.2, 104.0 (C-3 and C-5), 123.4, 126.3 (C-3″, C-4″ and C-5″), 144.2, 148.8, 151.0 (C-2, C-6, C-2″), 166.9 ($CO_2$), 167.3 ($CO_2$), 171.7 ($CO_2$).

**Diastereomer (4*R*,2′*R*,4′*R*)-11.** This compound was obtained from aldehyde (*R*)-**4** in 76% yield: mp 163−166 °C; $[\alpha]_D$ = +282.0 (*c* 1); $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (t, 3H, $OCH_2CH_3$, $J$ = 7.1 Hz), 1.27 (t, 3H, $OCH_2CH_3$, $J$ = 7.0 Hz), 1.31 (t, 3H, $OCH_2CH_3$, $J$ = 7.3 Hz), 2.41 (s, 3H, $CH_3$), 3.18−3.23 (m, 2H, $CH_2$), 4.08−4.25 (m, 4H, 2 × $OCH_2$), 4.26 (q, 2H, $OCH_2$, $J$ = 6.9 Hz), 4.35 (t, 1H, CH, $J$ = 6.9 Hz), 5.35 (s, 1H, H-4), 6.52 (s, 1H, CH), 6.80−6.86 (m 2H, H-3″, H-4″), 7.04 (dd, 1H, H-5″, $J$ = 1.2, 3.6 Hz), 9.07 (s broad, 1H, NH); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2 ($CH_3$), 14.3 ($CH_3$), 14.4 ($CH_3$), 19.2 ($CH_3$ at C-6), 34.6 (C-4), 35.6 ($CH_2$), 59.8 ($OCH_2$), 59.9 ($OCH_2$), 62.0 ($OCH_2$), 64.2 (CH), 65.2 (CH), 99.9, 103.0 (C-3 and C-5),123.3, 126.2 (C-3″, C-4″, and C-5″), 145.2, 149.4, 151.5 (C-2, C-6, and C-2″), 167.1 ($CO_2$), 167.6 ($CO_2$), 173.9 ($CO_2$); IR (KBr) $\nu$ 3338 (w, NH), 3278 (m, NH), 2982 (w, CH), 2930 (w, CH), 1738 (s, C=O), 1704 (s, C=O), 1673 (s, C=O), 1645 (m, C=C), 1610 (m, C=O), 1494 (s), 1370 (w), 1307 (m), 1270 (s), 1205 (s), 1148 (m), 1102 (s), 1086 (s), 1050 (w), 766 (w), 701 (s), 670 (w) cm$^{-1}$; UV $\lambda_{max}$ nm (log e) 235.4 (3.50), 359.4 (3.01); MS 480 M$^{\bullet+}$ (21), 435 (14), 409 (21), 408 (25), 407 (100), 398 (21), 397 (91), 396 (21), 365 (14), 351 (16), 350 (30), 323 (16), 321 (25), 287 (23), 277 (34), 276 (16), 275 (75), 259 (14), 238 (14), 229 (18), 220 (14), 160 (43), 86 (25), 59 (23). Anal. Calcd for $C_{22}H_{28}N_2O_6S_2$ (480): C, 54.98; H, 5.87; N, 5.83. Found: C, 54.84; H, 5.79; N, 5.75.

**Diastereomer (4*R*,2′*S*,4′*R*)-12:** $^1$H NMR ($CDCl_3$) $\delta$ 1.23 (t, 3H, $OCH_2CH_3$, $J$ = 7.1 Hz), 1.27 (t, 3H, $OCH_2CH_3$, $J$ = 7.0 Hz), 1.31 (t, 3H, $OCH_2CH_3$, $J$ = 7.3 Hz), 2.38 (s, 3H, $CH_3$), 3.18−3.23 (m, 1H, H-5′), 3.24−3.32 (m, 1H, H-5′), 4.08−4.25 (m, 4H, 2 × $OCH_2$), 4.27 (q, 2H, $OCH_2$, $J$ = 7.3 Hz), 4.35 (t, 1H, CH, $J$ = 6.9 Hz), 5.34 (s, 1H, H-4), 6.13 (s, 1H, CH), 6.80−6.86 (m, 3H, H-3″, H-4″ and NH), 7.05 (dd, 1H, H-5″, $J$ = 1.2, 3.6 Hz), 7.86 (s broad, 1H, NH); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2 ($CH_3$), 14.3 ($CH_3$), 14.4 ($CH_3$), 19.6 ($CH_3$ at C-6), 33.8 (C-4), 34.6 ($CH_2$), 59.9 ($OCH_2$), 60.2 ($OCH_2$), 61.0 (CH), 62.0 ($OCH_2$), 64.8 (CH), 102.1, 104.1 (C-3 and C-5), 123.2, 126.4 (C-3″, C-4″, and C-5″), 144.7, 148.4, 151.4 (C-2, C-6, and C-2′), 166.8 ($CO_2$), 167.3 ($CO_2$), 171.8 ($CO_2$).

**Diethyl 2-(4′-Methoxycarbonyl-4′-methyl-2′-thiazolidinyl)-6-methyl-4-(thien-2″-yl)-1,4-dihydropyridine-3,5-dicarboxylates (14−17).** To a suspension of 2-formyl-1,4-dihydropyridine *rac*-**4** (0.70 g, 2.0 mmol) and (*R*)-2-methylcysteine methyl ester hydrochloride (0.37 g, 2.0 mmol) in ethanol (5 mL) was added AcONa (0.18 g, 2.2 mmol) over 15 min. After being stirred at room temperature for 3 h, the mixture was poured into crushed ice. The precipitated crude product was filtered off, washed with water, and recrystallized from ethanol.

**Diastereomer (4*S*,2′*S*,4′*R*)-15: Method A.** Starting from the aldehyde *rac*-**4**, the mixture of diastereomers **14**−**17** was obtained in a 1:1 ratio. Diastereomer (4*S*,2′*S*,4′*R*)-**15** was isolated in 41% yield after crystallization from anhydrous ethanol: mp 163−166 °C; $[\alpha]_D$ = −16.9 (*c* 1); $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.30 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.56 (s, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$ at C-6), 2.90 (d, 1H, H-5′, $J$ = 11.1 Hz), 3.34 (d, 1H, H-5′, $J$ = 11.1 Hz), 3.79 (s, 3H, $OCH_3$), 4.09−4.21 (m, 4H, 2 × $OCH_2$), 5.34 (s, 1H, H-4), 6.13 (s, 1H, CH), 6.81−6.83 (m, 2H, H-3″ and H-4″), 7.04 (dd, 1H, H-5″, $J$ = 1.2 and 4.8 Hz), 8.01 (s broad, 1H, NH); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2 ($CH_3$), 14.3 ($CH_3$), 14.4 ($CH_3$), 18.8 ($CH_3$ at C-6), 34.6 (C-4), 35.8 ($CH_2$), 59.7 ($OCH_2$), 60.0 ($OCH_2$), 62.0 ($OCH_2$), 63.9 (CH), 64.9 (CH), 101.2, 103.4 (C-3 and C-5), 123.1, 123.4, 126.3 (C-3″, C-4″ and C-5″), 146.2, 149.4, 151.7 (C-2, C-6 and C-2″), 166.8 ($CO_2$), 167.5 ($CO_2$), 174.1 ($CO_2$); IR (KBr) $\nu$ 3310 (m, NH), 3277 (s, NH), 2981 (w, CH), 1733 (s, C=O), 1689 (s, C=O), 1656 (s, C=O), 1462 (s), 1370 (m), 1328 (m), 1272 (m), 1212 (s), 1160 (m), 1075 (m), 1024 (m), 972 (w), 769 (w), 721 (m) cm$^{-1}$; UV, $\lambda_{max}$ nm (log $\epsilon$) 198 (3.19), 235 (3.47), 357 (2.96); MS *m*/*z* 480 M$^{\bullet+}$ (24), 409 (14), 408 (77), 398 (14), 397 (77), 396 (21), 351 (14), 350 (45), 333 (17), 321 (37), 320 (17), 317 (12), 307 (33), 301 (22), 291 (25), 276 (14), 275 (95), 248 (13), 238 (21), 229 (27), 220 (12), 219 (15), 191 (15), 161 (12), 160 (100), 101 (12), 100 (39), 73 (32), 57 (13). Anal. Calcd for $C_{22}H_{28}N_2O_6S_2$ (480): C, 54.98; H, 5.87; N, 5.83. Found: C, 54.81; H, 5.77; N, 5.71. **Method B.** The same isomer (4*S*,2′*S*,4′*R*)-**15** was prepared from the enantiopure aldehyde **(*S*)-4** in 76% yield: mp 162−166 °C; $[\alpha]_D$ = −17.1 (*c* 1).

**Diastereomer (4*S*,2′*R*,4′*R*)-14:** $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.28 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.60 (s, 3H, $CH_3$), 2.46 (s, 3H, $CH_3$ at C-6), 2.85 (d, 1H, H-5′, $J$ = 11.6 Hz), 3.44 (d, 1H, H-5′, $J$ = 11.6 Hz), 3.79 (s, 3H, $OCH_3$), 4.09−4.21 (m, 4H, 2 × $OCH_2$), 5.33 (s, 1H, H-4), 6.37 (CH), 6.81−6.83 (m, 2H, H-3″ and H-4″), 7.04 (dd, 1H, H-5″, $J$ = 1.2, 4.8 Hz), 9.10 (s broad, 1H, NH).

**Diastereomer (4*R*,2′*R*,4′*R*)-16.** This compound was obtained from the enantiopure aldehyde (*R*)-**4** in 75% yield as a yellow oil, which epimerized rapidly to diastereomer (4*R*,2′*S*,4′*R*)-**17**. $^1$H NMR ($CDCl_3$) for the mixture of diastereomers **16** and **17** is as follows:

**Diastereomer (4*R*,2′*R*,4′*R*)-16:** $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.30 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.56 (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$ at C-6), 2.88 (d, 1H, H-5′, $J$ = 11.6 Hz), 3.45 (d, 1H, H-5′, $J$ = 11.6 Hz), 3.80 (s, 3H, $OCH_3$), 3.90−4.39 (m, 4H, 2 × $OCH_2$), 5.33 (s, 1H, H-4), 6.56 (s, 1H, CH), 6.81−6.83 (m, 2H, H-3″ and H-4″), 7.04 (dd, 1H, H-5″, $J$ = 1.2, 4.8 Hz), 9.03 (s broad, 1H, NH).

**Diastereomer (4*R*,2′*S*,4′*R*)-17:** $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.30 (t, 3H, $OCH_2CH_3$, $J$ = 7.2 Hz), 1.57 (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$ at C-6), 2.82 (d, 1H, H-5′, $J$ = 11.6 Hz), 3.35 (d, 1H, H-5′, $J$ = 11.6 Hz), 3.80 (s, 3H, $OCH_3$), 3.90−4.39 (m, 4H, 2 × $OCH_2$), 5.33 (s, 1H, H-4), 5.99 (s, 1H, CH), 6.81−6.83 (m, 2H, H-3″ and H-4″), 7.04 (dd, 1H, H-5″, $J$ = 1.2, 4.8 Hz), 8.05 (s broad, 1H, NH).

**Diethyl 6-Methyl-2-(2′-thiazolidinyl)-4-(thien-2″-yl)-1,4-dihydropyridine-3,5-dicarboxylates (19, 20, 22, and 23).** To a suspension of 2-formyl-1,4-dihydropyridine *rac*-**4** (0.52 g, 1.5 mmol) and cysteamine hydrochloride (**18**) (0.17 g, 1.5 mmol) in ethanol (5 mL) was added AcONa (0.14 g, 1.7 mmol) over 15 min. After being stirred at room temperature for 2 h, the mixture was poured into crushed ice. The precipitated product was filtered, washed with water, and recrystallized from ethanol.

**Diastereomer (±)-(4*R*,2′*R*)-19.** This compound was prepared from *rac*-**4** in 82% yield: mp 133−135 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.23 (t, 3H, $OCH_2CH_3$, $J$ = 7.0 Hz), 1.29 (t, 3H, $OCH_2CH_3$, $J$ = 7.0 Hz), 2.32 (s broad, 4H, $CH_3$ and NH), 2.69−2.91 (m, 1H, $CH_2$), 2.93−3.07 (m, 1H, $CH_2$), 3.08−3.21 (m, 1H, $CH_2$), 3.45−3.61 (m, 1H, $CH_2$), 4.12−4.21 (m, 4H, 2 × $OCH_2$), 5.31 (s, 1H, H-4), 6.17 (s, 1H, CH), 6.82−6.85 (m, 2H, H-3″ and H-4″), 7.04 (t, 1H, H-5″, $J$ = 3.6 Hz), 7.80 (s broad, 1H, NH); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2 ($CH_3$), 14.3 ($CH_3$), 19.6 ($CH_3$ at C-6), 33.8 ($CH_2$), 34.4 (C-4), 52.6 ($CH_2$), 59.9 ($OCH_2$), 60.0 ($OCH_2$), 64.7 (CH), 100.1, 103.8 (C-3 and C-5), 123.4, 126.2 (C-3″, C-4″ and C-5″), 144.3, 149.0, 150.9 (C-2, C-6 and C-2″), 166.8 ($CO_2$), 167.3 ($CO_2$); IR (KBr) $\nu$ 3320 (s, NH), 3298 (s, NH), 2977 (m, CH), 1699 (s, C=O), 1677 (s, C=O), 1596 (m, C=C), 1463 (s), 1310 (m), 1265 (s), 1211 (s), 1093 (s), 1046 (m), 895 (w), 842 (m), 756 (m), 693 (s) cm$^{-1}$; UV, $\lambda_{max}$ nm (log $\epsilon$) 233 (3.41), 351 (2.90); MS *m*/*z* 408 M$^{\bullet+}$ (32), 363 (16), 362 (32), 337 (12), 336 (24), 335 (100), 325 (40), 324 (16), 321 (12), 289 (16), 276 (12), 275 (48), 220 (12), 219 (20), 191 (20), 88 (32), 61 (64). Anal. Calcd for $C_{19}H_{24}N_2O_4S_2$ (408): C, 55.86; H, 5.92; N, 6.86. Found: C, 55.76; H, 5.81; N, 6.73.

**Diastereomer (4*R*,2′*S*)-20.** This compound was prepared from the enantiopure aldehyde (*R*)-**4** in 81% yield: mp 119−122 °C; $[\alpha]_D$ = +339.0 (*c* 1); $^1$H NMR ($CDCl_3$) $\delta$ 1.22 (t, 3H, $OCH_2CH_3$, $J$ = 7.0 Hz), 1.27 (t, 3H, $OCH_2CH_3$, $J$ = 7.0 Hz),

2.26 (d, 1H, NH, $J$ = 4.7 Hz), 2.35 (s, 3H, $CH_3$), 2.74−2.87 (m, 1H, C$H_2$), 2.88−3.01 (m, 1H, C$H_2$), 3.12−3.29 (m, 1H, C$H_2$), 3.36−3.54 (m, 1H, C$H_2$), 4.13 (q, 2H, $OCH_2$, $J$ = 7.0 Hz), 4.17 (q, 2H, $OCH_2$, $J$ = 7.0 Hz), 5.33 (s, 1H, H-4), 6.05 (d, 1H, CH, $J$ = 4.7 Hz), 6.74−6.85 (m, 2H, H-3″ and H-4″), 7.02 (t, 1H, H-5″, $J$ = 3.9 Hz), 7.75 (s broad, 1H, NH); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2 ($CH_3$), 14.3 ($CH_3$), 19.6 ($CH_3$ at C-6), 33.3 ($CH_2$), 34.8 (C-4), 52.5 ($CH_2$), 59.8 ($OCH_2$), 60.2 ($OCH_2$), 63.6 (CH), 102.2, 103.8 (C-3 and C-5), 123.2, 126.3 (C-3″, C-4″, and C-5″), 144.8, 148.0, 151.4 (C-2, C-6, and C-2″), 166.7 ($CO_2$), 167.3 ($CO_2$); IR (KBr) $\nu$ 3317 (m, NH), 3281 (m, NH), 2985 (w, CH), 2920 (w, CH), 1666 (s, C═O), 1651 (s, C═O), 1444 (s), 1368 (m), 1326 (m), 1248 (m), 1215 (s), 1096 (m), 1028 (m), 842 (w), 786 (m), 684 (m); UV $\lambda_{max}$ nm (log $\epsilon$) 234 (3.44), 353 (2.91); MS $m/z$ 408 $M^{\bullet+}$ (20), 363 (15), 362 (28), 337 (13), 336 (23), 335 (100), 325 (40), 324 (15), 289 (15), 275 (50), 229 (25), 219 (23), 202 (13), 191 (23), 88 (38), 61 (33). Anal. Calcd for $C_{19}H_{24}N_2O_4S_2$ (408): C, 55.86; H, 5.92; N, 6.86. Found: C, 55.71; H, 5.83; N, 6.75.

**Diastereomer (4*S*,2′*R*)-23.** This compound was prepared from the enantiopure aldehyde (*S*)-**4** in 82% yield: mp 120−122 °C; $[\alpha]_D$ = −336.9 (*c* 1). Anal. Calcd for $C_{19}H_{24}N_2O_4S_2$ (408): C, 55.86; H, 5.92; N, 6.86. Found: C, 55.69; H, 5.85; N, 6.77.

**Ethyl 8-Methyl-5-oxo-6-(thien-2″-yl)-2,3,5,6,9,9b-hexahydrothiazolo[3′,2′:1,2]pyrrolo[3,4-*b*]pyridine-7-carboxylates (21).** The corresponding 2-(2′-thiazolidinyl)-1,4-dihydropyridine **19**, **20**, **22**, or **23** (0.93 g, 2.3 mmol) in ethanol (10 mL) was treated with a catalytic amount of potassium *tert*-butoxide, and the mixture was allowed to react at room temperature for 3 h. After cooling, the resulting precipitates of tricyclic systems **21** or **24** were collected by filtration and recrystallized from ethanol.

**Diastereomer (±)-(6*R*,9b*R*)-21.** This compound was prepared from (±)-(4*R*,2′*R*)-**18** in 72% yield: mp 235−239 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.22 (t, 3H, $OCH_2CH_3$, $J$ = 7.0 Hz), 2.26 (s, 3H, $CH_3$), 2.82−3.11 (m, 3H, $CH_2CH_2$), 4.01 (q, 2H, $OCH_2$, $J$ = 7.0 Hz), 4.06−4.15 (m, 1H, C$H_2$), 4.97 (s, H, H-9b), 5.50 (s, 1H, H-6), 6.72 (d, 1H, H-3″, $J$ = 3.5 Hz), 6.87 (dd, 1H, H-4″, $J$ = 3.5, 4.7 Hz), 7.27 (dd, 1H, H-5″, $J$ = 4.7, 1.2 Hz), 9.93 (s broad, 1H, NH); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 14.1 ($CH_3$), 19.0 ($CH_3$), 31.9 (C-6), 33.8 ($CH_2$), 45.4 ($CH_2$), 59.4 ($OCH_2$), 62.6 (C-9b), 102.5, 105.2 (C-3 and C-5), 123.3, 124.3, 126.8 (C-3″, C-4″, and C-5″), 145.8, 150.9, 155.0 (C-2, C-6, and C-2″), 166.7 ($CO_2$), 173.9 (CO); IR (KBr) $\nu$ 3167 (w, NH), 3072 (w, ═CH), 2985 (w, CH), 1687 (s, C═O), 1655 (s, C═O), 1509 (s), 1366 (m), 1278 (m), 1210 (m), 1093 (m), 1059 (w), 872 (w), 717 (m) cm$^{-1}$; UV $\lambda_{max}$ nm (log $\epsilon$) 198 (3.22), 232 (3.40), 355 (2.94); MS $m/z$ 363 (24), 362 $M^{+\cdot}$ (100), 333 (8), 317 (8), 315 (8), 302 (11), 301 (11), 289 (14), 288 (8), 279 (27), 273 (14), 219 (14), 191 (11), 85 (11). Anal. Calcd for $C_{19}H_{24}N_2O_4S_2$ (362): C, 56.33; H, 5.01; N, 7.73. Found: C, 56.19; H, 4.95; N, 7.59.

**Diastereomer (6*R*,9b*S*)-24.** This compound was prepared directly from the enantiopure aldehyde (*R*)-**4** via **20** and was isolated in 71% yield: mp 233−235 °C; $[\alpha]_D$ = +54.2 (*c* 0.5); $^1$H NMR (DMSO-$d_6$) $\delta$ 1.20 (t, 3H, $OCH_2CH_3$, $J$ = 7.0 Hz), 2.24 (s, 3H, $CH_3$), 2.75−2.85 (m, 1H, C$H_2$), 2.94−3.18 (m, 2H, C$H_2$), 4.00−4.11 (m, 3H, $OCH_2$ and C$H_2$), 4.98 (s, 1H, H-9b), 5.40 (s, 1H, H-6), 6.66 (d, 1H, H-3″, $J$ = 3.2 Hz), 6.85 (dd, 1H, H-4″, $J$ = 3.2, 4.8 Hz), 7.24 (d, 1H, H-5″, $J$ = 4.8 Hz), 10.00 (s broad, 1H, NH); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 14.2 ($CH_3$), 19.0 ($CH_3$), 31.6 (C-6), 34.4 ($CH_2$), 46.5 ($CH_2$), 59.4 ($OCH_2$), 62.7 (C-9b), 102.6, 103.8 (C-3 and C-5), 123.0, 124.4, 126.7 (C-3″, C-4″, and C-5″), 145.8, 151.0, 155,4 (C-2, C-6 and C-2″), 166.7 ($CO_2$), 174.7 (CO); IR (KBr) $\nu$ 3252 (m, NH), 3108 (w, ═CH), 2981 (w, CH), 1698 (s, CO), 1659 (s, CO), 1513 (s), 1384 (m), 1354 (m), 1244 (m), 1195 (m), 1090 (m), 1055 (m), 920 (w), 702 (m) cm$^{-1}$; UV $\lambda_{max}$ nm (log $\epsilon$) 197 (3.34), 231 (3.40), 352 (2.95); MS $m/z$ 363 (21), 362 $M^{+\cdot}$ (100), 360 (9), 333 (9), 315 (9). 302 (9), 301 (9), 289 (12), 279 (33), 278 (15), 273 (21), 257 (12), 233 (9), 232 (24), 229 (9), 219 (15), 204 (15), 191 (12), 84 (21). Anal. Calcd for $C_{19}H_{24}N_2O_4S_2$ (362): C, 56.33; H, 5.01; N, 7.73. Found: C, 56.10; H, 4.91; N, 7.61.

**Diastereomer (6*S*,9b*R*)-24.** This compound was prepared directly from the enantiopure aldehyde (*S*)-**4** via **23** and was isolated in 70% yield: mp 232−234 °C; $[\alpha]_D$ = −54.9 (*c* 0.5). Anal. Calcd for $C_{19}H_{24}N_2O_4S_2$ (362): C, 56.33; H, 5.01; N, 7.73. Found: C, 56.10; H, 4.91; N, 7.61.

**Acknowledgment.** We thank the Grant Agency of Slovak Republic, Grant No.1/9249/2002, and the Scientific Council of University of Le Havre, France, for their financial support for this research program. We also are grateful for many helpful comments and discussions throughout the course of this work with Professor Bernard Decroix.

**Supporting Information Available:** Spectroscopic data of products including $^1$H NMR, $^{13}$C NMR, IR, and UV spectra, ORTEP plots of imines **6**, thiazole-esters **9**, **15,** and **20**, and tricyclic thiolactam **21**, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049706S