# Chiral hexahydropyrrolo[2,1-*b*][1,3]thiazoles

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**Dedicated to Professor Moreno-Manas on his 60th anniversary**

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**Abstract**

Chiral hexahydropyrrolo[2,1-*b*][1,3]thiazoles **11–16** were obtained in 56–82% yields *via* the nucleophilic substitutions of ethyl (3*R*,5*S*,7a*S*)-5-(1*H*-1,2,3-benzotriazol-1-yl)hexahydropyrrolo [2,1-*b*][1,3]thiazole-3-carboxylate **10** with benzenethiol, NaCN, triethyl phosphite, allyl silanes, silyl enol ethers, or PhZnCl. The D.e. values at the 5-position range from 50% to >99% depending on the nucleophiles.

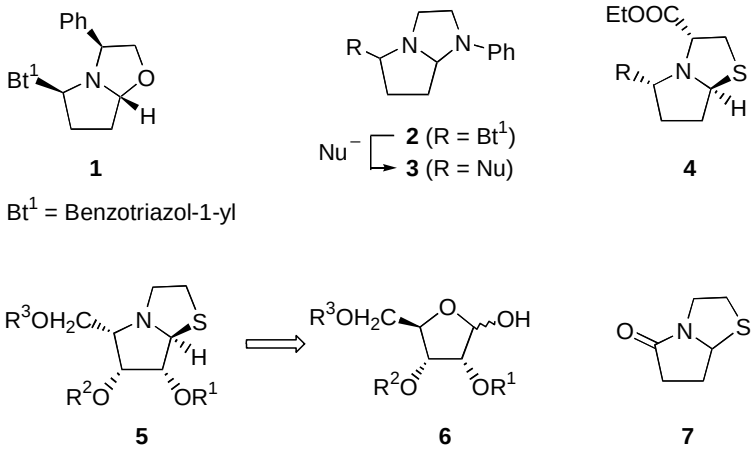
**Keywords:** Chiral hexahydropyrrolothiazoles, nucleophilic substitution, benzotriazolyl intermediates, benzenethiol, sodium cyanide, triethyl phosphite, silyl enol ether, allyl silane

## Introduction

Mannich condensation of succindialdehyde with (*S*)-2-phenylglycinol and benzotriazole forms hexahydropyrrolo[2,1-*b*][1,3]oxazole **1**, which on treatment with Grignard reagents, followed by hydrogenation, gave chiral 2,5-disubstituted pyrrolidines.[1] The nitrogen analogues, i.e., 1-phenylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazoles **2** and **3**, have also been studied.[2] We herein report stereoselective syntheses of the novel sulfur analogues, i.e., hexahydropyrrolo[2,1-*b*][1,3]thiazoles **4**.

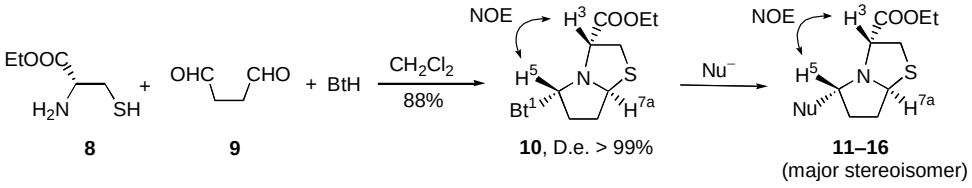
Beaupere *et al.* synthesized chiral hexahydropyrrolo[2,1-*b*][1,3]thiazoles **5** in two steps from D-ribofuranose **6** and cysteamine.[3] Hypoglycemic active tetrahydropyrrolo[2,1-*b*][1,3]thiazol-5(6*H*)-ones **7**[4] arise from condensations of 2-amino-1-ethanethiols with γ-oxo-carboxylic acids[4,5] or γ-oxo-esters.[6] However, hexahydropyrrolo[2,1-*b*][1,3]thiazoles **4** with substituents at the 3- and 5-positions appear to be novel.




## Results and Discussion

**Synthesis of chiral benzotriazolyl intermediates 10.** Reaction of *L*-cysteine ethyl ester hydrochloride **8** with succindialdehyde (**9**, obtained in situ by treatment of 2,5-dimethoxytetrahydrofuran with 0.1 M HCl) and benzotriazole in $CH_2Cl_2$ at room temperature for 24 h readily afforded benzotriazol-1-yl intermediate **10** in 88% yield as a single enantiomer (Scheme 1). The stereochemistry of **10** was determined by NOE NMR experiments. The $^1$H NMR spectrum of **10** shows that H(3), H(7a) and H(5) appear at 4.31 ppm (doublet-doublet), 5.36 ppm (doublet) and 5.94 ppm (doublet-doublet), respectively. A significant positive NOE effect was observed between H(3) and H(5), and no NOE effect was observed between H(7a) with either H(3) or H(5). Thus, NOE analysis demonstrates that in **10** H(3) and H(5) are in *cis*-orientation; while H(3) and H(7a) are in *trans*-orientation. The relative configurations in **10** are consistent with the previous oxygen analogue **1**.[1] Therefore, four new bonds are simultaneously formed in one step to generate the hexahydropyrrolo[2,1-*b*][1,3]thiazole ring system.

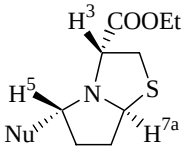



**Scheme 1**

**Nucleophilic substitutions of 10 with benzenethiol, NaCN or triethyl phosphite.** (c.f. entry a–c in Table 1) We have shown that the benzotriazolyl group easily undergoes nucleophilic substitutions allowing its transformation to other functionalities.[2,7] The results for the nucleophilic substitutions of **10** are summarized in Table 1.

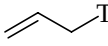
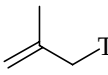
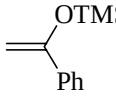
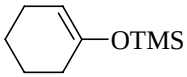
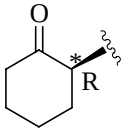
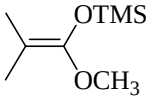
Reaction of **10** with benzenethiol in the presence of sodium hydride afforded the product **11** with 81% D.e. in 62% yield. Since compound **11** is labile on silica gel, it was isolated on neutral alumina column chromatography. For the major diastereoisomer in **11**, NOE experiment confirms the *cis*-orientation for H(3) (4.5 ppm, m) and H(5) (4.1 ppm, m) due to their positive NOE effect; thus the absolute configuration at 5-position is *S*.

The benzotriazolyl group was easily substituted by a cyano anion to afford **12** as a single enantiomer (>99% D.e.) in 61% yield. The NOE experiment also determined the *cis*-orientation of H(3) (4.47 ppm, dd) and H(5) (4.2 ppm, m) due to their positive NOE effect. Compound **13** was obtained as a single enantiomer in 56% yield by the treatment of **10** with triethyl phosphite in the presence of $ZnBr_2$. The Lewis acid, $ZnBr_2$, facilitates loss of the benzotriazolyl anion to form an iminium cation, which is then attacked by the P-nucleophile.




**11-16**

**Table 1.** Isolated yields and D. e. values for

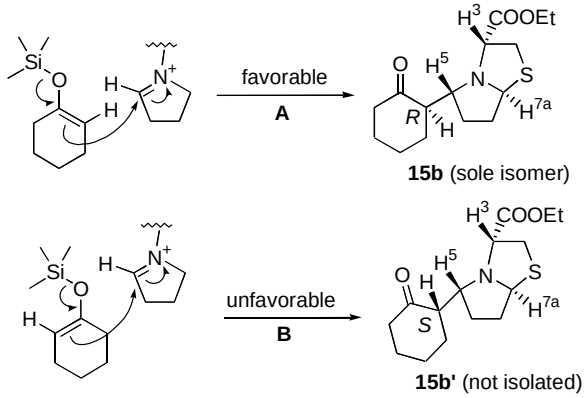
| Entry | Nucleophile (L.A.) | Product[a] | Nu | Yield (%) | D.e. (%)[b] |
|---|---|---|---|---|---|
| **a** | PhSH/NaH | **11** | PhS | 62 | 81 |
| **b** | NaCN | **12** | CN | 61 | >99 |
| **c** | $P(OEt)_3$ ($ZnBr_2$) | **13** | $PO(OEt)_2$ | 56 | >99 |
| **d** |  ($BF_3 \bullet Et_2O$) | **14a** | allyl | 72 | 54 |
| **e** |  ($BF_3 \bullet Et_2O$) | **14b** | $CH_2=C(CH_3)CH_2$ | 77 | 80 |
| **f** |  ($BF_3 \bullet Et_2O$) | **15a** | $PhCOCH_2$ | 77 | 50 |
| **g** |  • | **15b** |  | 76 | >99 |
| **h** |  • | **15c** | $C(CH_3)_2COOCH_3$ | 82 | >99 |
| **i** | PhZnCl | **16** | Ph | 65 | 60 |

[a] All of the products are supported by their $^1H$, $^{13}C$ NMR spectra and microanalyses results.
[b] The D.e. values were determined by the $^1H$ NMR spectra.

**Nucleophilic substitutions of 10 with allyl silanes or silyl enol ethers.** Nucleophilic substitutions of **10** with allyl silanes in the presence of $BF_3$ gave compounds **14a,b** in 72% and 77% yields, respectively (c.f. entry d,e in Table 1). The D.e. values for **14a,b** (54% and 80%, respectively) indicate that a larger stereohindered nucleophile gives a product with a higher D.e. value. Benzotriazolyl intermediate **10** reacted with silyl enol ethers in the presence of $BF_3$ to furnish hexahydropyrrolo[2,1-*b*][1,3]thiazoles **15a–c** in 77%, 76% and 82% yields, respectively (c.f. entry f–h in Table 1). The D.e. values for **15a–c** (50%, >99% and >99%, respectively) also indicate that among the silyl enol ethers, the larger stereohindered nucleophiles give higher D.e. values. NOE results confirm the *cis*-orientation between H(3) and H(5) in **15b,c** and in the major diastereoisomers of **14a,b** and **15a**.

For 15b, a new chiral center was formed at the $\alpha$-position of cyclohexanone, and both $^1H$, $^{13}C$ NMR spectra indicate 15b as a pure enantiomer. It is difficult to obtain direct experimental

evidences for its absolute configuration determination, since the oily product is not fit for X-ray analysis and the $\alpha$-H of cyclohexanone is overlapped with other protons. However, the absolute configuration at the 5-position in 15b indicates that the silyl enol ether attacks the iminium cation intermediate below the imine plane. We believe that route A is more favorable than route B, due to the larger repulsion between the cyclohexene and the iminium cation ring systems for route B. Thus attack A leads to enantiopure 15b; none of 15b′ was observed. Furthermore, the conformation in 15b is more stable than the conformation in 15b′ due to the larger gauche butane interaction in 15b′. Therefore, the new chiral center is believed to have *R*-configuration (c.f. Scheme 2).




**Scheme 2**

Our result (*anti* configuration between the 5-position and the new chiral center in 15b) is also consistent with the reported *anti* configuration of $\beta$-amino ketones *via* reactions of iminium cations with enamines.[8]

**Nucleophilic substitutions of 10 with PhZnCl.** (c.f. entry i in Table 1) In order to keep the ester group in 10, we used a weaker nucleophile, i.e., PhZnCl, obtained in situ by the treatment of phenylmagnesium bromide with ZnCl2. The nucleophilic substitutions of 10 with PhZnCl afforded the desired compound 16 in 65% yield with the major diastereoisomer having R-configuration at the 5-position. The D.e. value can be improved from 50% (using 1.5 equivalents of ZnCl2 based on PhMgBr) to 60% (using 4 equivalents of ZnCl2 based on PhMgBr). The reason is probably that the Lewis acid, ZnCl2, facilitates loss of the benzotriazolyl anion to form an iminium cation, which undergoes SN1 nucleophilic substitutions. Thus the addition of more ZnCl2 avoids SN2 nucleophilic substitutions leading to an inversion of the absolute configuration at the 5-position.

Compared to the configuration of Bt intermediate **10**, the absolute configurations at the 5-position remains unchanged in the major diastereoisomers of **11–16**. This result is consistent with our previous report on the nucleophilic substitution of oxygen analogue **1** with PhZnCl.[1]

Thus we believe that the nucleophilic substitutions of **10** should predominantly undergo $S_N1$ route instead of $S_N2$ route and that thermodynamic stability may play an important role on the determination of stereochemistry of final products.

In summary, we have developed a straightforward and efficient route to chiral hexahydropyrrolo[2,1-*b*][1,3]thiazoles **11–16** by the nucleophilic substitutions of ethyl (3*R*,5*S*,7a*S*)-5-(1*H*-1,2,3-benzotriazol-1-yl)hexahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylate **10** with a variety of nucleophiles, such as benzenethiol, NaCN, triethyl phosphite, allyl silanes, silyl enol ethers or an organozinc reagent. Compound **10** was readily obtained via the Mannich condensation of *L*-cysteine ethyl ester hydrochloride **8** with succindialdehyde **9** and benzotriazole.

## Experimental Section

**General Procedures.** Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. $^1$H NMR (300 MHz), $^{13}$C NMR (75 MHz) and NOE spectra were recorded on a Gemini 300 NMR spectrometer in $CDCl_3$ (with TMS for $^1$H and chloroform-*d* for $^{13}$C as the internal reference). HRMS were measured on an AEI-30 mass spectrometer. Elemental analyses were performed on a Carlo Erba-1106 instrument. Optical rotation values were measured by a Perkin-Elmer 341 polarimeter with the use of the sodium D line. Column chromatography was performed on silica gel (200–425 mesh), unless otherwise stated. All of the reactions were carried out under $N_2$.

**General procedure for the preparation of Bt intermediates**

A mixture of 2,5-dimethoxytetrahydrofuran (0.66 g, 5.1 mmol) and HCl aqueous solution (0.1 M, 20 mL) was heated to 100 °C for 45 mins, then cooled to room temperature. $CH_2Cl_2$ (40 mL), benzotriazole (0.61 g, 5.1 mmol) and *L*-cysteine ethyl ester hydrochloride (**8**, 0.93 g, 5 mmol) were successively added and stirred at room temperature for 24 h. The reaction mixture was washed with saturated $Na_2CO_3$ solution and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic phase was washed with brine and dried over anhydrous $Na_2SO_4$. After removal of the solvent in vacuo, the residue was purified by neutral alumina (80–200 mesh) column chromatography with hexanes/EtOAc (1:1) as an eluent to give **10**.

**Ethyl (3*R*,5*S*,7a*S*)-5-(1*H*-1,2,3-benzotriazol-1-yl)hexahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylate (10).** Colorless prisms (from hexanes/$Et_2O$); yield, 88%; mp 57.5–58.0 °C; $[\alpha]^{25}_D$ = –32.6 (*c* 1.93, $CHCl_3$); $^1$H NMR δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 5.94 (dd, *J* = 7.6, 4.9 Hz, 1H, BtC*H*N), 5.36 (d, *J* = 4.4 Hz, 1H, NC*H*S), 4.31 (dd, *J* = 7.1, 2.9 Hz, 1H, NC*H*COOEt), 4.03–3.94 (m, 2H), 3.53–3.40 (m, 2H), 2.80–2.72 (m, 2H), 2.37–2.31 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR δ 170.2, 146.9, 131.5, 127.2, 124.0, 119.9, 112.0, 80.6, 72.8, 68.1, 61.3, 35.2, 30.4, 29.6, 13.7. Anal. Calcd for $C_{15}H_{18}N_4O_2S$: C, 56.58; H, 5.70; N, 17.60. Found: C, 56.94; H, 5.60; N, 17.69.

**Procedure for the reaction of 10 with benzenethiol**

To a solution of benzenethiol (0.33 g, 3.0 mmol) in dry THF (20 mL), NaH (60% in mineral oil, 0.10 g, 4 mmol) was added, and the mixture was stirred at 25 °C for 30 mins. One drop of methanol was added to quench excess NaH and then Bt intermediate **10** (0.64 g, 2 mmol) was added. The mixture was stirred at 25 °C for 24 h. After removal of THF in vacuo, 10% aqueous $Na_2CO_3$ was added to the residue and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine and dried over anhydrous $Na_2SO_4$. After removal of the solvent in vacuo, the residue was purified by neutral alumina (80–200 mesh) column chromatography with hexanes/EtOAc (2:1) as an eluent to give **11**.

**Ethyl (3*R*,7a*S*)-5-(phenylsulfanyl)hexahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylate (11).** Obtained as a mixture of diastereoisomers with 81% D.e. value at the 5-position and NMR data are reported for its major stereoisomer (3*R*,5*S*,7a*S*); colorless oil; yield, 62%; $^1$H NMR δ 7.56 (d, *J* = 3.2 Hz, 2H), 7.32–7.16 (m, 3H), 5.07 (d, *J* = 4.9 Hz, 1H), 4.54–4.44 (m, 1H), 4.28–4.10 (m, 3H), 3.30–3.16 (m, 2H), 2.60–2.24 (m, 2H), 2.12–1.88 (m, 2H), 1.39 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR δ 171.0, 134.3, 132.7, 128.7, 127.9, 73.6, 73.2, 68.8, 61.3, 34.7, 31.0, 29.9, 14.1. Anal. Calcd for $C_{15}H_{19}NO_2S_2$: C, 58.22; H, 6.19; N, 4.53. Found: C, 58.23; H, 6.04; N, 4.87.

**Procedure for the reaction of 10 with NaCN**

A mixture of NaCN (0.1 g, 2.0 mmol) and **10** (0.48 g, 1.5 mmol) in DMSO (7 mL) was stirred at 25 °C for 20 h. The solution was diluted with EtOAc and washed with 5% $Na_2CO_3$, brine and dried over anhydrous $Na_2SO_4$. After removal of the solvent in vacuo, the residue was purified by silica gel column chromatography with hexanes/EtOAc (5:1) as an eluent to give **12**.

**Ethyl (3*R*,5*R*,7a*S*)-5-cyanohexahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylate (12).** Colorless oil; yield, 61%; $[\alpha]^{25}_D$ = –179 (*c* 1.83, $CHCl_3$); $^1$H NMR δ 5.06–5.03 (m, 1H), 4.47 (dd, *J* = 7.4, 4.0 Hz, 1H), 4.24–4.17 (m, 3H), 3.68 (dd, *J* = 11.4, 7.4 Hz, 1H), 3.38 (dd, *J* = 11.4, 4.0 Hz, 1H), 2.54–2.38 (m, 3H), 2.34–2.22 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR δ 170.8, 118.9, 72.8, 66.9, 61.6, 52.6, 37.1, 31.3, 30.8, 14.1. Anal. Calcd for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.24; N, 12.38. Found: C, 53.46; H, 5.92; N, 12.71.

**Procedure for the reaction of 10 with triethyl phosphite.** To a solution of **10** (0.64 g, 2.0 mmol) in dry $CH_2Cl_2$ (20 mL) at 0 °C, $ZnBr_2$ (0.89 g, 4.0 mmol) and triethyl phosphite (0.68 mL, 4.0 mmol) were sequentially added. The reaction mixture was stirred at 0 °C for 1 h and at room temperature overnight, and then quenched with 10% $Na_2CO_3$. After extraction with $CH_2Cl_2$, the combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. After removal of the solvent in vacuo, the desired product **13** was purified by column chromatography (silica gel) with hexanes/EtOAc (2:1) as an eluent.

**Ethyl (3*R*,5*S*,7a*S*)-5-(diethoxyphosphoryl)hexahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylate (13).** Colorless oil; yield, 56%; $[\alpha]^{25}_D$ = –74.6 (*c* 1.39, $CHCl_3$); $^1$H NMR δ 5.09 (d, *J* = 4.8 Hz, 1H), 4.66 (dd, *J* = 6.7, 2.3 Hz, 1H), 4.32–4.12 (m, 6H), 3.38–3.26 (m, 2H), 3.00 (dd,

*J* = 9.7, 5.9 Hz, 1H), 2.54–2.28 (m, 2H), 2.20–1.96 (m, 2H), 1.34 (t, *J* = 6.9 Hz, 3H), 1.32 (t, *J* = 6.6 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR δ 170.9, 75.1 (d, *J* = 17.8 Hz), 70.5 (d, *J* = 3.1 Hz), 63.4 (d, *J* = 6.9 Hz), 62.2 (d, *J* = 7.4 Hz), 61.2, 59.2 (d, *J* = 176.9 Hz), 34.4, 31.0 (d, *J* = 4.8 Hz), 24.5 (d, *J* = 2.3 Hz), 16.5 (d, *J* = 5.7 Hz), 16.4 (d, *J* = 5.7 Hz), 14.0. Anal. Calcd for $C_{13}H_{24}NO_5PS$: C, 46.28; H, 7.17. Found: C, 46.45; H, 7.31. HRMS Calcd for $C_{13}H_{24}NO_5PS$ 377.1112 (M), found 377.1113.

**General procedure for the reaction of 10 with allyl silanes and silyl enol ethers**

To a solution of **10** (0.64 g, 2.0 mmol) and allyl silanes (3 mmol) or silyl enol ethers (3 mmol) in dry $CH_2Cl_2$ (10 mL), was added $BF_3 \cdot Et_2O$ (0.36 mL, 3 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h and at 25 °C overnight. The mixture was quenched with 10% $Na_2CO_3$ and extracted with $CH_2Cl_2$. The combined organic layers were dried over anhydrous $Na_2SO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography (silica gel) with hexane/EtOAc (5 : 1) as eluent to afford **14a**,**b** or **15a**–**c**.

**Ethyl (3*R*,7a*S*)-5-allylhexahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylate (14a).** Obtained as a mixture of diastereoisomers with 54% D.e. value at the 5-position and NMR data are reported for its major stereoisomer (3*R*,5*R*,7a*S*); colorless oil; yield, 72%; $^1$H NMR δ 5.90–5.64 (m, 1H), 5.16–4.98 (m, 3H), 4.36–4.25 (m, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.37–3.16 (m, 2H), 2.82–2.68 (m, 1H), 2.44–1.92 (m, 5H), 1.68–1.54 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR δ 171.6, 135.2, 117.0, 75.3, 69.2, 63.1, 61.2, 40.2, 34.9, 30.0, 29.1, 14.1. Anal. Calcd for $C_{12}H_{19}NO_2S$: C, 59.72; H, 7.93; N, 5.80. Found: C, 59.49; H, 7.80; N, 6.12.

**Ethyl (3*R*,7a*S*)-5-(2-methyl-2-propenyl)hexahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylate (14b).** Obtained as a mixture of diastereoisomers with 80% D.e. value at the 5-position and NMR data are reported for its major stereoisomer (3*R*,5*R*,7a*S*); colorless oil; yield, 77%; $^1$H NMR δ 5.12 (d, *J* = 5.5 Hz, 1H), 4.78 (s, 1H), 4.73 (s, 1H), 4.30 (dd, *J* = 6.9, 2.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.33 (dd, *J* = 11.1, 6.9 Hz, 1H), 3.26 (dd, *J* = 11.1, 2.7 Hz, 1H), 2.92–2.80 (m, 1H), 2.46–2.26 (m, 2H), 2.22–1.98 (m, 3H), 1.74 (s, 3H), 1.70–1.52 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR δ 171.5, 142.9, 112.4, 75.3, 69.1, 61.6, 61.1, 44.3, 34.8, 29.9, 29.4, 22.9, 14.1. Anal. Calcd for $C_{13}H_{21}NO_2S$: C, 61.14; H, 8.29; N, 5.48. Found: C, 61.50; H, 8.53; N, 5.75.

**Ethyl (3*R*,7a*S*)-5-(2-oxo-2-phenylethyl)hexahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylate (15a).** Obtained as a mixture of diastereoisomers with 50% D.e. value at the 5-position and NMR data are reported for its major stereoisomer (3*R*,5*R*,7a*S*); colorless oil; yield, 77%; $^1$H NMR δ 7.75 (d, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 5.12 (d, *J* = 5.4 Hz, 1H), 4.41 (dd, *J* = 6.5, 2.0 Hz, 1H), 4.24–4.08 (m, 2H), 3.60–3.22 (m, 3H), 3.20–3.04 (m, 2H), 2.56–2.28 (m, 2H), 2.20–1.96 (m, 1H), 1.64–1.50 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR δ 199.0, 171.5, 137.0, 133.2, 128.6, 128.1, 74.7, 69.9, 61.2, 59.8, 45.6, 35.0, 30.5, 30.0, 14.1. Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.38. Found: C, 63.79; H, 6.53; N, 4.75.

**Ethyl (3*R*,5*R*,7a*S*)-5-[(1*R*)-2-oxocyclohexyl]hexahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylate (15b).** Colorless oil; yield, 76%; $[\alpha]^{25}_D = -103$ (*c* 1.67, $CHCl_3$); $^1$H NMR δ 5.02 (d, *J* = 4.7 Hz, 1H), 4.37 (t, *J* = 4.0 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.25 (d, *J* = 4.3 Hz, 2H),

3.22–3.10 (m, 1H), 2.50–2.20 (m, 6H), 2.20–1.80 (m, 3H), 1.80–1.40 (m, 4H), 1.26 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR δ 213.0, 171.2, 75.1, 72.0, 62.4, 60.9, 57.2, 42.6, 34.9, 30.8, 30.2, 28.3, 28.0, 25.0, 14.0. Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.79; N, 4.71. Found: C, 60.81; H, 8.05; N, 4.88.

**Ethyl(3*R*,5*R*,7a*S*)-5-[(1-methoxycarbonyl-1-methyl)ethyl]hexahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylate (15c).** Colorless oil; yield, 82%; $[\alpha]^{25}_D$ = −113 (*c* 2.18, $CHCl_3$); $^1$H NMR δ 5.06 (d, *J* = 4.3 Hz, 1H), 4.35 (dd, *J* = 5.5, 3.0 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.67 (s, 3H), 3.30–3.18 (m, 2H), 3.14 (d, *J* = 7.2 Hz, 1H), 2.34–2.16 (m, 2H), 2.16–1.98 (m, 1H), 1.60–1.50 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.20 (s, 3H), 1.13 (s, 3H); $^{13}$C NMR δ 177.9, 171.5, 75.7, 72.9, 70.2, 61.2, 51.9, 48.3, 35.2, 32.0, 25.0, 21.8, 20.9, 14.3. Anal. Calcd for $C_{14}H_{23}NO_4S$: C, 55.79; H, 7.69; N, 4.65. Found: C, 56.04; H, 7.97; N, 4.73.

**Procedure for the reaction of 10 with PhZnCl**

To a solution of PhMgBr (1.0 M in THF; 2.0 mL, 2.0 mmol) at 0 °C, $ZnCl_2$ (0.5 M in $Et_2O$; 16.0 mL, 8.0 mmol) was added dropwise. After stirring for 30 min, a solution of **10** (0.48 g, 1.5 mmol) in dry THF (10 mL) was added dropwise. The reaction mixture was stirred at 25 °C overnight. The mixture was quenched with 10% $Na_2CO_3$ and extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine and dried over anhydrous $Na_2SO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography (silica gel) with hexanes/EtOAc (5 : 1) as an eluent to afford **16**.

**Ethyl (3*R*,7a*S*)-5-phenylhexahydropyrrolo[2,1-*b*][1,3]thiazole-3-carboxylate (16).** Obtained as a mixture of diastereoisomers with 60% D.e. value at the 5-position and NMR data are reported for its major stereoisomer (3*R*,5*R*,7a*S*); colorless oil; yield, 65%; $^1$H NMR δ 7.50–7.10 (m, 5H), 5.26 (d, *J* = 5.3 Hz, 1H), 4.08–3.90 (m, 2H), 3.67 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.56 (t, *J* = 10.5 Hz, 1H), 3.14 (dd, *J* = 10.8, 7.5 Hz, 1H), 3.04 (dd, *J* = 10.5, 6.3 Hz, 1H), 2.74–2.44 (m, 2H), 2.16–2.04 (m, 1H), 1.86–1.72 (m, 1H), 0.83 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR δ 168.6, 144.2, 128.0, 127.3, 126.9, 77.2, 69.5, 62.4, 61.0, 34.7, 32.9, 30.1, 13.4. GC-MS (EI): 277 ($M^+$), 204 (b), 177, 144, 128, 117, 91, 77, 54. Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05. Found: C, 64.82; H, 7.11; N, 5.40.

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