JOC*Note*

Stereoselective Addition of the Titanium Enolate of *N*-Acetyl (4*S*)-Isopropyl-1,3-thiazolidine-2-thione to Five-Membered *N*-Acyl Iminium Ions

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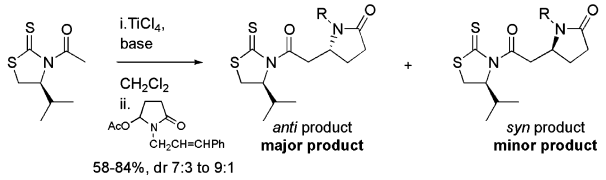

Addition of the chlorotitanium enolate of *N*-acetyl 4-isopropyl-1,3-thiazolidine-2-thione to five-membered, *N*-Substituted *N*-acyl iminium ions furnished the corresponding Mannich-type addition products with good diastereoselectivity and in good yields. The synthetic utility of the addition product **8** was demonstrated in a chemospecific *anti*-aldol reaction with cinnamaldehyde. By using this strategy, we constructed three contiguous chiral centers with high stereocontrol employing the same chiral auxiliary. X-Ray crystallographic analysis of addition product **2** and aldol product **14** revealed their absolute stereochemistry.

β-Aminocarbonyl functionalities are important constituents of many biologically active natural products and therapeutics. They are also useful building blocks for the syntheses of heterocyclic natural products and modified peptides with enhanced in vivo stability.[1] The Mannich reaction is one of the classical methods for the preparation of β-aminocarbonyl compounds.[2] Over the past few years, the addition of nucleophiles of silyl enol ethers, silyl keteneacetals, and enamines to preformed iminium salts has greatly expanded the versatility of this reaction.[3] Good diastereofacial selectivity has been demonstrated in the addition of nucleophiles to chiral cyclic imine and iminium ions.[4] Enolates derived from chiral ester surrogates such as *N*-acyl-oxazolidinones and particularly *N*-acyl-thiazolidinethiones have appeared to be promising nucleophiles for achieving high diastereoselection in the addition to prochiral cyclic imine and iminum ions.[5]

Highly diastereoselective alkylation of the tin(II) enolate of *N*-acetyl isopropyl thiazolidinethione (IPTT) was observed by Nagao's group when added to cyclic acyl imines.[5g−k] However, a lack of diastereoselectivity was observed when the same enolate was added to cyclic *N*-acyl iminium ions.[5c,g,h] Similarly to the acetate aldol reaction, the presence of a removable group on the *N*-acetyl group results in high enantioselectivities, albeit increasing the number of steps in the synthesis.[5g,6] Some diastereoselectivity was observed by Pilli when the titanium(IV) chloride of chiral *N*-acetyl oxazolidinone was alkylated with *N*-acylpiperidinium ions, but no selectivity was obtained with the corresponding five-membered analogues.[5c] In this paper, we describe our investigations on the addition of titanium(IV) enolates of *N*-acetyl IPTT to five-membered *N*-acyliminium ions. We are interested in these addition products because of their potential as intermediates for the synthesis of several *Stemona* and other alkaloids.[7]

A difference in stereoselectivity between *N*-acetyl and *N*-propionyl groups is observed in chiral auxiliary-based aldol and Mannich-type reactions. Although excellent diastereoselectivity is observed in propionate aldol reactions using chiral oxazolidinones, poor diastereoselectivity is observed in the acetate aldol reactions.[8] However, very good stereoselectivities have been observed in acetate aldol reactions using chiral oxazolidinethiones and thiazolidinethiones.[9] Several advantages of thiazolidinethione chiral auxiliaries have also been shown over their

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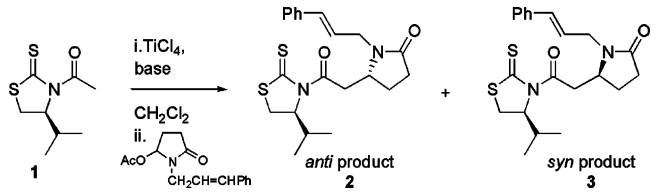
TABLE 1.



entry	$TiCl_4$	base	temp, time	dr (anti:syn)	yield
1	1 equiv	DIPEA, 1.2 equiv	−78 °C, 2 h	77:23	48%
2	2 equiv	DIPEA, 1.2 equiv	−78 °C, 2 h	74:26	66%
3	3 equiv	DIPEA, 1.2 equiv	−78 °C, 2 h	76:24	71%
4	2 equiv	(−)-sparteine, 1.2 equiv	−78 °C, 2 h	nd	30%
5	3 equiv	(−)-sparteine, 1.2 equiv	−78 °C, 2 h	70:30	61%
6	2 equiv	DIPEA, 1.2 equiv	−78 to 0 °C, 5 h	80:20	82%

oxazolidinone analogues, e.g., they can be directly reduced to aldehydes, easily removed, and displaced by some nucleophiles.[10,11] For these reasons, we are now interested in expanding their utility in Mannich-type additions.

A modest yield and good diastereoselectivity was obtained when the titanium(IV) enolate of *N*-acetyl IPTT[12] was reacted with *N*-cinammyl 5-acetoxypyrrolidinone,[13] employing 1 equiv of Lewis acid and 1 equiv of Hunig's base, Table 1. A slight improvement in yield was observed when the number of equivalents of Lewis acid was doubled and also when the reaction was allowed to warm to 0 °C before quenching. The diastereomeric products were separated on silica gel chromatography, and the major isomer was obtained as a solid. Single-crystal X-ray diffraction analysis of the major isomer revealed the stereochemistry of the newly created stereocenter.[14] The stereochemistry of the major diastereomer **2** corresponds to the *anti* product (where the isopropyl group on the chiral auxiliary and the heteroatom are on opposite sides). Interestingly and contrary to results obtained when employing tin(II) triflate,[5g,h] some good diastereoselectivity is observed when employing the less expensive titanium(IV) chloride.

The stereochemical outcome of the major diastereomer can be rationalized as being formed by a transition state in which the cyclic *N*-acyl iminium ion approaches the titanium(IV) enolate on the less hindered side, with the *N*-acyl group antiperiplanar to the enolate as illustrated

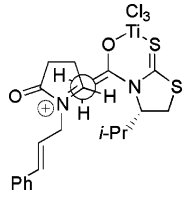
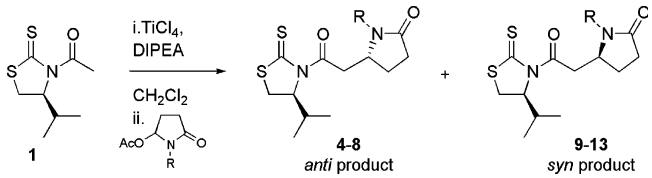


FIGURE 1. Open transition state.

TABLE 2. Alkylation of *N*-Acetyl IPTT with *N*-Substituted Cyclic *N*-Acyliminium Ion



entry	R	dr (anti:syn)	yield
1	−Ph	(**4**:**9**) 73:27	80%
2	*p*-$CH_2C_6H_4Br$	(**5**:**10**) 80:20	58%
3	$-CH_2Ph$	(**6**:**11**) 80:20	77%
4	$-(CH_2)_3CH_3$	(**7**:**12**) 78:22	75%
5	*trans*-$CH_2CH{=}CHPh$	(**2**:**3**) 80:20	82%
6	*trans*-$CH_2CH{=}CHCH_3$	(**8**:**13**) 88:12	84%

in Figure 1. This presumed transition state yields preferentially the *anti* product **2** (4′*S*,3*R* stereochemistries).

Addition of the titanium enolate of *N*-acetyl IPTT to other *N*-substituted 5-acetoxypyrrolidinones under the optimized reaction conditions is shown in Table 2. *N*-Substituents included aromatic, benzylic, allylic, and alkyl groups. Iminium addition products were obtained in a similar diastereomeric ratio in 58−84% yields. In all cases, chromatographic separation of the diastereomers was easy to monitor because of the yellow color of the addition products.

To test the utility of these iminium addition products, *N*-acyl thiazolidinethione **8** was added to cinnamaldehyde employing the recently disclosed conditions for an *anti*-aldol reaction.[15] Aldol addition of *N*-acyl thiazolidinethione **8** to cinnamaldehyde in the presence of substoichiometric amounts (10%) of $MgBr_2{-}Et_2O$, TMSCl, and Et_3N in ethyl acetate gave exclusively one stereoisomer in 81% yield. The structure and stereochemistry of *anti*-

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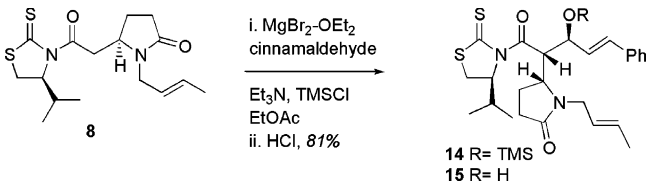
SCHEME 1. *anti*-Aldol Condensation of *N*-Acyl Thiazolidinethione 8 with Cinnamaldehyde.



aldol product **14** were verified by single-crystal X-ray diffraction analysis.[14] Gratifyingly, the aldol reaction proceeded uneventfully; no retro Mannich was observed, and the lactam ring was untouched. The free aldol product **15** was obtained in quantitative yield after acidic removal of the silyl group. By using this synthetic sequence, three contiguous chiral centers were constructed with high stereocontrol employing the same chiral auxiliary.In summary, we have studied the addition of titanium enolates of *N*-acetyl IPTT to *N*-substituted pyrrolidinonium formed in situ. Addition products were obtained in good yields and with good diastereoselectivity. No significant difference in diastereoselectivity was observed with different *N*-substituents in the iminium ion moiety. These iminium addition products were shown to be useful substrates for *anti*-aldol addition reactions.

Experimental Section

General Procedure for the Titanium Enolate Addition to Iminium Ions. The 5-acetoxy *N*-substituted pyrrolidinone was first prepared from the corresponding 5-hydroxy pyrrolidinone. To a solution of 5-hydroxy N-substituted pyrrolidinone (1.1 mmol) in dichloromethane (5 mL) was added acetic anhydride (0.5 mL, 2 mmol) and triethylamine (0.5 mL, 3.5 mmol). The reaction was quenched after 10 h by addition of water. The organic layer was washed with saturated $NaHCO_3$ (3 × 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, evaporated, and used without any further purification. A solution of $TiCl_4$ (1 M in CH_2Cl_2, 2.2 mL, 2.2 mmol) was added to a solution of *N*-acetyl-4-isopropylthiazolidinethione (223.6 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) cooled to −10 °C. The solution was stirred for 5 min and then cooled to −50 °C. The reaction mixture was treated with a solution of ethyldiisopropylamine (155 mg, 1.2 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 40 min and cooled to −78 °C. A solution of the 5-acetoxy N-substituted pyrrolidinone in CH_2Cl_2 (5 mL) was added to the reaction mixture. The reaction mixture was stirred and warmed to 0 °C for 6 h. The reaction was quenched by addition of saturated NH_4Cl and stirred for 15 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography.

5*R*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-(3-phenylprop-2-enyl)-pyrrolidin-2-one (2): R_f 0.35 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); mp 94−95 °C; $[\alpha]_D^{25}$ +290.7 (*c* 1.0, $CHCl_3$); IR 2965, 1685, 1373, 1161, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.21 (5H, m), 6.56 (1H, d, J = 16.0 Hz), 6.14 (1H, ddd, J = 16.0, 7.0, 6.0 Hz), 5.11 (1H, ddd, J = 8.0, 6.0, 1.1 Hz), 4.32 (1H, ddd, J = 15.5, 5.8, 1.4 Hz), 4.18 (1H, m), 3.95 (1H, dd, J = 17.5, 3.3 Hz), 3.88 (1H, dd, J = 15.5, 7.0 Hz), 3.38 (1H, dd, J = 11.5, 8.0 Hz), 3.20 (1H, dd, J = 17.4, 9.5 Hz), 2.99 (1H, dd, J = 11.6, 1.1 Hz), 2.61−2.26 (4H, m), 1.78 (1H, m), 1.04 (3H, d, J = 6.9 Hz), 0.96 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 202.9 (C), 174.6 (C), 170.3 (C), 136.2 (C), 132.8 (CH), 128.4 (2CH), 127.6 (CH), 126.3 (2CH), 124.0 (CH), 71.3 (CH), 54.7 (CH), 43.0 (CH_2), 42.1 (CH_2), 30.7 (CH), 30.2 (CH_2), 29.6 (CH_2), 24.4 (CH_2), 18.9 (CH_3), 17.5 (CH_3); HRMS (EI) exact mass calcd for $C_{21}H_{27}N_2O_2S_2$ [M + H]$^+$ 403.1514, found 403.1526.

5*S*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-(3-phenylprop-2-enyl)-pyrrolidin-2-one (3): R_f 0.41 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); $[\alpha]_D^{25}$ +152.2 (*c* 1.0, $CHCl_3$); IR 2965, 1686, 1256, 1038, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41−7.19 (5H, m), 6.52 (1H, d, J = 15.8 Hz), 6.11 (1H, dd, J = 15.8, 6.0 Hz), 5.12 (1H, t, J = 7.0 Hz), 4.30 (1H, dd, J = 15.5, 6.3 Hz), 4.15 (1H, m), 3.89 (1H, dd, J = 15.8, 7.0 Hz), 3.76 (1H, dd, J = 17.7, 4.1 Hz), 3.48 (1H, dd, J = 17.7, 8.5 Hz), 3.30 (1H, dd, J = 11.7, 8.2 Hz), 2.95 (1H, dd, J = 11.4, 0.6 Hz), 2.63−2.23 (4H, m), 1.79 (1H, m), 1.05 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 175.0 (C), 170.9 (C), 136.5 (C), 132.9 (CH), 128.7 (2CH), 127.9 (CH), 126.5 (2CH), 124.4 (CH), 71.5 (CH), 54.7 (CH), 43.4 (CH_2), 42.9 (CH_2), 30.9 (CH), 30.3 (CH_2), 29.8 (CH_2), 25.3 (CH_2), 19.2 (CH_3), 17.8 (CH_3); HRMS (EI) exact mass calcd for $C_{21}H_{26}N_2O_2S_2Na$ [M + Na]$^+$ 425.1333, found 425.1353.

5*R*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-(phenyl)-pyrrolidin-2-one (4): R_f 0.34 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); $[\alpha]_D^{25}$ +311.5 (*c* 1.0, $CHCl_3$); IR 2966, 1694, 1376, 1169, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43−7.35 (4H, m), 7.23 (1H, m), 5.03 (1H, t, J = 7.1 Hz), 4.75 (1H, m), 3.63 (1H, dd, J = 17.5, 3.5 Hz), 3.43 (1H, dd, J = 11.2, 7.9 Hz), 3.35 (1H, dd, J = 17.5, 9.2 Hz), 2.98 (1H, dd, J = 11.6, 0.9 Hz), 2.72−2.41 (3H, m), 2.25 (1H, sext, J = 6.6 Hz), 1.86 (1H, m), 1.00 (3H, d, J = 6.8 Hz), 0.92 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 202.3 (C), 174.2 (C), 170.6 (C), 137.1 (C), 129.3 (2CH), 126.4 (CH), 124.6 (2CH), 71.4 (CH), 56.9 (CH), 42.4 (CH_2), 30.8 (CH), 30.8 (CH_2), 30.4 (CH_2), 24.7 (CH_2), 19.1 (CH_3), 17.6 (CH_3); HRMS (EI) exact mass calcd for $C_{18}H_{23}N_2O_2S_2$ [M + H]$^+$ 363.1201, found 363.1211.

5*R*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-(*p*-bromobenzyl)-pyrrolidin-2-one (5): R_f 0.37 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); $[\alpha]_D^{25}$ +256.7 (*c* 1.0, $CHCl_3$); IR 2965, 1683, 1488, 1258, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (2H, d, J = 8.3 Hz), 7.13 (2H, d, J = 8.3 Hz), 5.05 (1H, t, J = 7.0 Hz), 4.66 (1H, d, J = 15.4 Hz), 4.22 (1H, d, J = 15.4 Hz), 4.01 (1H, m), 3.76 (1H, dd, J = 17.5, 3.5 Hz), 3.46 (1H, dd, J = 11.3, 7.9 Hz), 3.07 (1H, dd, J = 17.3, 9.4 Hz), 3.00 (1H, d, J = 11.6 Hz), 2.63−2.19 (4H, m), 1.85−1.70 (1H, m), 1.02 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 175.3 (C), 170.3 (C), 136.1 (C), 131.9 (2CH), 129.7 (2CH), 121.5 (C), 71.4 (CH), 54.8 (CH), 44.3 (CH_2), 42.2 (CH_2), 30.9 (CH), 30.5 (CH_2), 29.7 (CH_2), 24.6 (CH_2), 19.1 (CH_3), 17.7 (CH_3); HRMS (EI) exact mass calcd for $C_{19}H_{24}BrN_2O_2S_2$ [M + H]$^+$ 455.0463, found 455.0466.

5*R*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-benzyl-pyrrolidin-2-one (6): R_f 0.37 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); $[\alpha]_D^{25}$ +320.1 (*c* 1.0, $CHCl_3$); IR 2967, 1681, 1167, 1093, 1039, cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.18 (5H, m), 5.04 (1H, ddd, J = 7.1, 6.1, 0.9 Hz), 4.79 (1H, d, J = 15.3 Hz), 4.21 (1H, d, J = 15.3 Hz), 4.02 (1H, m), 3.77 (1H, dd, J = 17.4, 3.4 Hz), 3.44 (1H, dd, J = 11.5, 8.1 Hz), 3.09 (1H, dd, J = 17.3, 9.4 Hz), 2.99 (1H, dd, J = 11.5, 0.9 Hz), 2.61−2.19 (4H, m), 1.82−1.68 (1H, m), 1.02 (3H, d, J = 6.9 Hz), 0.92 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 202.9 (C), 175.2 (C), 170.5 (C), 136.8 (C), 128.7 (2CH), 127.9 (2CH), 127.5 (CH), 71.4 (CH), 54.6 (CH), 44.7 (CH_2), 42.1 (CH_2), 30.9 (CH), 30.5 (CH_2), 29.8 (CH_2), 24.7 (CH_2), 19.1 (CH_3), 17.7 (CH_3); HRMS (EI) exact mass calcd for $C_{19}H_{25}N_2O_2S_2$ [M + H]$^+$ 377.1357, found 377.1358.

5*R*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-butyl-pyrrolidin-2-one (7): R_f 0.33 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); $[\alpha]_D^{25}$ +268.5 (*c* 1.0, $CHCl_3$); IR 2962, 2873, 1685, 1373, 1168, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.16 (1H, t, J = 7.1 Hz), 4.15 (1H, m), 3.89 (1H, dd, J = 17.1, 3.4 Hz), 3.61 (1H, m), 3.55 (1H, dd, J = 11.6, 8.0 Hz), 3.09 (1H, dd, J = 17.1, 9.9 Hz), 3.07 (1H, dd, J = 11.5, 0.9 Hz), 2.92 (1H, dd, J = 11.6, 1.1 Hz), 2.52−2.21 (4H, m), 1.79−1.67 (1H, m), 1.63−1.40 (2H, m), 1.40−1.21 (2H, m), 1.08 (3H, d, J = 7.0 Hz), 0.99 (3H, d, J = 7.0 Hz), 0.93 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 174.7 (C), 170.7 (C), 71.5 (CH), 54.4 (CH), 42.0 (CH_2), 40.4 (CH_2), 30.9 (CH), 30.6 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 24.6 (CH_2), 20.1 (CH_2), 19.1 (CH_3), 17.7 (CH_3), 13.8 (CH_3); HRMS (EI) exact mass calcd for $C_{16}H_{27}N_2O_2S_2$ [M + H$^+$] 343.1514, found 343.1514.

5*R*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-(but-2-enyl)-pyrrolidin-2-one (8): R_f 0.32 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); $[\alpha]_D^{25}$ +298.4 (*c* 1.0, $CHCl_3$);

IR (film) 2965, 1733, 1687, 1374, 1375, 1257 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.64 (1H, m), 5.36 (1H, m), 5.14 (1H, t, J = 6.8 Hz), 4.12 (2H, m), 3.88 (1H, dd, J = 17.5, 3.3 Hz), 3.57 (1H, dd, J = 15.2, 7.2 Hz), 3.53 (1H, dd, J = 11.6, 8.1 Hz), 3.10 (1H, dd, J = 17.5, 9.8 Hz), 3.05 (1H, dd, J = 11.6, 0.8 Hz), 2.51−2.22 (4H, m), 1.76−1.65 (4H, m), 1.07 (3H, d, J = 6.9 Hz), 0.97 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 174.8 (C), 170.9 (C), 129.5 (CH), 125.5 (CH), 71.5 (CH), 54.7 (CH), 43.0 (CH_2), 42.3 (CH_2), 31.0 (CH), 30.7 (CH_2), 29.9 (CH_2), 24.8 (CH_2), 19.2 (CH_3), 17.9 ($2CH_3$); HRMS (EI) exact mass calcd for $C_{16}H_{25}N_2O_2S_2$ [M + H]$^+$ 341.1357, found 341.1373.

5*S*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-phenyl-pyrrolidin-2-one (9): R_f 0.41 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); $[\alpha]_D^{25}$ +170.4 (*c* 1.0, $CHCl_3$); IR 2968, 1693, 1597, 1497, 1372, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42−7.32 (4H, m), 7.23 (1H, m), 4.93 (1H, ddd, J = 7.6, 6.2, 1.0 Hz), 4.71 (1H, m), 3.55 (2H, m), 3.33 (1H, dd, J = 11.6, 7.9 Hz), 2.94 (1H, dd, J = 11.5, 1.0 Hz), 2.76−2.46 (3H, m), 2.27 (1H, sext, J = 6.7 Hz), 1.93 (1H, m), 1.01 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 203.0 (C), 174.3 (C), 170.9 (C), 137.2 (C), 129.3 (2CH), 126.6 (CH), 125.0 (2CH), 71.4 (CH), 57.2 (CH), 42.2 (CH_2), 30.9 (CH_2), 30.8 (CH), 30.5 (CH_2), 25.0 (CH_2), 19.1 (CH_3), 17.8 (CH_3); HRMS (EI) exact mass calcd for $C_{18}H_{23}N_2O_2S_2$ [M]$^+$ 363.1201, found 363.1195.

5*S*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-(*p*-bromobenzyl)-pyrrolidin-2-one (10): R_f 0.46 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); $[\alpha]_D^{25}$ +112.8 (*c* 1.0, $CHCl_3$); IR 2965, 1683, 1488, 1172, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (2H, d, J = 8.2 Hz), 7.09 (2H, d, J = 8.2 Hz), 5.02 (1H, t, J = 6.9 Hz), 4.62 (1H, d, J = 15.0 Hz), 4.25 (1H, d, J = 15.5 Hz), 4.00 (1H, m), 3.61 (1H, dd, J = 17.6, 4.5 Hz), 3.39 (1H, dd, J = 11.7, 8.1 Hz), 3.34 (1H, dd, J = 17.6, 8.1 Hz), 2.98 (1H, d, J = 11.5 Hz), 2.62−2.21 (4H, m), 1.81 (1H, m), 1.02 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 175.5 (C), 170.6 (C), 136.2 (C), 131.9 (2CH), 129.5 (2CH), 121.5 (C), 71.4 (CH), 54.7 (CH), 44.6 (CH_2), 42.9 (CH_2), 31.0 (CH), 30.4 (CH_2), 29.8 (CH_2), 25.3 (CH_2), 19.2 (CH_3), 17.8 (CH_3); HRMS (EI) exact mass calcd for $C_{19}H_{24}BrN_2O_2S_2$ [M + H]$^+$ 455.0463, found 455.0447.

5*S*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-benzyl-pyrrolidin-2-one (11): R_f 0.42 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); $[\alpha]_D^{25}$ +119.0 (*c* 1.0, $CHCl_3$); IR 3017, 2969, 1685, 1216, 1174 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.18 (5H, m), 5.04 (1H, t, J = 7.0 Hz), 4.74 (1H, d, J = 15.4 Hz), 4.27 (1H, d, J = 15.4 Hz), 4.02 (1H, m), 3.59 (1H, dd, J = 17.9, 4.4 Hz), 3.41 (1H, dd, J = 11.6, 8.1 Hz), 3.38 (1H, dd, J = 17.9, 8.4 Hz), 2.97 (1H, d, J = 11.6 Hz), 2.65−2.21 (4H, m), 1.82 (1H, m), 1.04 (3H, d, J = 6.9 Hz), 0.95 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 202.9 (C), 175.4 (C), 170.7 (C), 136.9 (C), 128.8 (2CH), 127.7 (2CH), 127.6 (CH), 71.4 (CH), 54.6 (CH), 45.0 (CH_2), 42.7 (CH_2), 30.9 (CH), 30.4 (CH_2), 29.9 (CH_2), 25.3 (CH_2), 19.2 (CH_3), 17.8 (CH_3); HRMS (EI) exact mass calcd for $C_{19}H_{25}N_2O_2S_2$ [M + H]$^+$ 377.1357, found 377.1349.

5*S*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-butyl-pyrrolidin-2-one (12): R_f 0.33 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); $[\alpha]_D^{25}$ +132.5 (*c* 1.0, $CHCl_3$); IR 2962, 2873, 1686, 1372, 1256, 1167 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.19 (1H, ddd, J = 7.7, 6.3, 1.1 Hz), 4.07 (1H, m), 3.65 (1H, dd, J = 17.5, 3.6 Hz), 3.56 (1H, m), 3.53 (1H, dd, J = 11.5, 2.1 Hz), 3.45 (1H, dd, J = 17.5, 9.3 Hz), 3.06 (1H, dd, J = 11.6, 1.2 Hz), 2.87 (1H, m), 2.57−2.25 (4H, m), 1.78 (1H, m), 1.61−1.20 (4H, m), 1.08 (3H, d, J = 7.0 Hz), 0.99 (3H, d, J = 7.0 Hz), 0.92 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 174.8 (C), 171.0 (C), 71.5 (CH), 54.4 (CH), 42.2 (CH_2), 40.5 (CH_2), 30.9 (CH), 30.5 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 25.1 (CH_2), 20.2 (CH_2), 19.2 (CH_3), 17.9 (CH_3), 13.9 (CH_3); HRMS (EI) exact mass calcd for $C_{16}H_{27}N_2O_2S_2$ [M + H]$^+$ 343.1514, found 343.1528.

5*S*-[2-(4*S*-Isopropyl-2-thioxo-thiazolidin-3-yl)-2-oxo-ethyl]-1-(but-2-enyl)-pyrrolidin-2-one (13): R_f 0.42 ($CHCl_3$−ethyl acetate−petroleum ether, 4:2:1); $[\alpha]_D^{25}$ +168.2 (*c* 1.0, $CHCl_3$); IR 2964, 2876, 1682, 1373, 1039 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.61 (1H, m), 5.36 (1H, m), 5.19 (1H, t, J = 7.2 Hz), 4.07 (2H, m), 3.66 (1H, ddd, J = 17.6, 3.7, 1.2 Hz), 3.60−3.49 (2H, m), 3.44 (1H, ddd, J = 17.6, 9.3, 1.1 Hz), 3.05 (1H, d, J = 11.6 Hz), 2.55−2.23 (4H, m), 1.82−1.72 (4H, m), 1.07 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 203.0 (C), 174.7 (C), 171.0 (C), 129.1 (CH), 125.6 (CH), 71.4 (CH), 54.5 (CH), 42.9 (CH_2), 42.4 (CH_2), 30.9 (CH), 30.5 (CH_2), 29.8 (CH_2), 25.0 (CH_2), 19.2 (CH_3), 17.8 ($2CH_3$); HRMS (EI) exact mass calcd for $C_{16}H_{25}N_2O_2S_2$ [M]$^+$ 341.1357, found 341.1374.

1-(4(*S*)-Isopropyl-2-thioxo-thiazolidin-3-yl)-3(*R*)-trimethylsilanyloxy-2(*R*)-(1-but-2-enyl-5-oxo-pyrrolidin-2(*S*)-yl)-5-phenyl-pent-4-en-1-one (14). To a solution of the addition product **8** (340.5 mg, 1 mmol) in EtOAc (2.5 mL) was added $MgBr_2{\cdot}OEt_2$ (26 mg, 0.1 mmol), followed by cinnamaldehyde (140 μL, 1.1 mmol), Et_3N (0.280 μl, 2.0 mmol), and freshly distilled TMSCl (0.190 μL, 1.5 mmol). The reaction mixture was stirred at room temperature for 24 h. The resulting suspension was filtered through a small plug of silica gel (2 × 2 cm) eluting the TMS ether **14** with Et_2O: 440 mg (81% yield); R_f 0.23 (ethyl acetate−petroleum ether, 3:7); mp 92−93 °C; $[\alpha]_D^{25}$ +270.7 (*c* 1.0, $CHCl_3$); IR 3355, 2964, 2356, 2336, 1682, 1252, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42−7.19 (5H, m), 6.54 (1H, d, J = 15.9 Hz), 6.09 (1H, dd, J = 15.9, 7.1 Hz), 5.65 (1H, m), 5.41 (1H, m), 5.33 (1H, dd, J = 7.4, 4.4 Hz), 4.94 (1H, t, J = 6.8 Hz), 4.69 (1H, t, J = 7.3 Hz), 4.26−4.18 (2H, m), 3.40 (1H, dd, J = 15.3, 7.1 Hz), 3.32 (1H, dd, J = 11.4, 7.6 Hz), 2.99 (1H, dd, J = 11.4, 0.6 Hz), 2.57−2.29 (4H, m), 2.19−2.04 (1H, m), 1.66 (3H, dd, J = 6.4, 1.0 Hz), 1.07 (3H, d, J = 6.7 Hz), 0.99 (3H, d, J = 7.0 Hz), 0.12 (9H, s); ^{13}C NMR ($CDCl_3$) δ 204.0 (C), 175.2 (C), 172.8 (C), 136.3 (C), 131.7 (CH), 129.7 (CH), 129.2 (CH), 128.9 (2CH), 128.2 (CH), 126.7 (2CH), 125.4 (CH), 73.3 (CH), 72.6 (CH), 56.2 (CH), 51.4 (CH), 43.0 (CH_2), 31.4 (CH_2), 31.2 (CH), 30.5 (CH_2), 20.8 (CH_2), 19.3 (CH_3), 18.1 (CH_3), 17.9 (CH_3), 0.66 ($3CH_3$).

1-(4(*S*)-Isopropyl-2-thioxo-thiazolidin-3-yl)-3(*R*)-hydroxy-2(*R*)-(1-but-2-enyl-5-oxo-pyrrolidin-2(*S*)-yl)-5-phenyl-pent-4-en-1-one (15). The free alcohol was obtained by treating the TMS ether **14** in THF (20 mL) with 1 N HCl solution (4 mL) for 1 h. The reaction mixture was diluted with Et_2O and water. The organic layer was washed with saturated $NaHCO_3$ and brine. The aldol product **15** was purified by silica gel column chromatography eluting with ethyl acetate−petroleum ether (7:3): 382 mg (quantitative yield); R_f 0.4 (ethyl acetate−petroleum ether, 7:3); $[\alpha]_D^{25}$ +239.8 (*c* 1.0, $CHCl_3$); IR 3019, 2969, 1674, 1215, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41−7.23 (5H, m), 6.62 (1H, dd, J = 16.0, 1.9 Hz), 6.16 (1H, dd, J = 16.0, 3.9 Hz), 6.16 (1H, dd, J = 16.0, 3.9 Hz), 5.68 (1H, m), 5.43 (1H, m), 5.20 (1H, dd, J = 6.6, 3.3 Hz), 4.88 (1H, ddd, J = 7.3, 6.2, 0.9 Hz), 4.63 (1H, m), 4.41 (1H, ddd, J = 9.0, 6.6, 2.8 Hz), 4.24 (1H, ddt, J = 15.2, 6.1, 1.2 Hz), 3.49 (1H, dd, J = 15.1, 6.4 Hz), 3.28 (1H, m), 2.95 (1H, dd, J = 11.5, 7.7 Hz), 2.83 (1H, dd, J = 11.5, 1.0 Hz), 2.70 (1H, dd, J = 16.9, 8.8 Hz), 2.44−2.10 (3H, m), 1.71 (3H, dd, J = 6.4, 1.3 Hz), 1.62 (1H, bs), 1.02 (3H, d, J = 6.8 Hz), 0.96 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 204.1 (C), 175.7 (C), 174.3 (C), 136.2 (C), 130.0 (CH), 129.8 (CH), 129.5 (CH), 129.0 (2CH), 128.2 (CH), 126.5 (2CH), 125.3 (CH), 72.1 (CH), 70.5 (CH), 57.2 (CH), 49.4 (CH), 43.2 (CH_2), 31.1 (CH), 31.0 (CH_2), 30.2 (CH_2), 21.9 (CH_2), 19.3 (CH_3), 18.0 (CH_3), 17.9 (CH_3); HRMS (EI) exact mass calcd for $C_{25}H_{33}N_2O_3S_2$ [M + H]$^+$ 473.1933, found 473.1936.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **2**−**14**, ORTEP drawings for compounds **2** and **14**, and crystallographic data in CIF format for compounds **2** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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