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Diastereoselective Additions of Titanium Enolates from *N*-Glycolyl Thiazolidinethiones to Acetals

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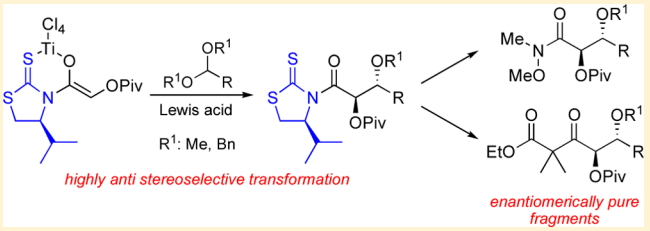
Supporting Information

ABSTRACT: The stereochemical outcome of the Lewis acid-mediated *glycolate* addition of the titanium enolates from protected *N*-hydroxyacetyl-4-isopropyl-1,3-thiazolidine-2-thiones to dimethyl and dibenzyl acetals depends on the hydroxyl protecting group. Particularly, the pivaloyl protected glycolate derivative provides the reluctant *anti* adducts in high yields and diastereomeric ratios, which can be isolated and further converted in enantiomerically pure form to β-methoxy or β-benzyloxy α-pivaloyloxy carbonyl fragments in a straightforward manner.



The ubiquitous presence of α,β-dihydroxy carbonyl motifs in the structure of natural products has stimulated the development of a plethora of synthetic methodologies. In this arena, one of the most successful approaches to install the two new oxygenated chiral centers relies on the aldol reaction of α-hydroxy carbonyl compounds, namely, the *glycolate* aldol reaction.[1] Thereby, a significant number of asymmetric catalytic procedures have been disclosed,[2,3] although stereoselective glycolate aldol reactions are still commonly carried out by using chiral auxiliary-based methodologies.[4−6] Of the various chiral auxiliary-based approaches reported to date, boron or titanium(IV) enolates of oxazolidinone and oxazolidinethione glycolate precursors are the most appropriate entries to the *syn* adducts,[7−9] whereas the more reluctant *anti* counterparts can be obtained with variable diastereoselectivity from the titanium(IV) enolates of oxazolidinethiones.[10,11] Moreover, Hulme has reported that boron enolates from a norephedrine-derived chiral auxiliary can afford both stereochemistries depending on the hydroxyl protecting group.[12] In spite of these accomplishments, there is a lack of methodologies directed to the synthesis of related α-hydroxy β-methoxy carbonyl moieties present in certain natural products like peloruside A (Figure 1).[13]

Therefore, these systems are usually prepared in a two-step process: (i) stereoselective glycolate aldol reaction and (ii) alkylation of the resultant aldol adduct. Taking into account that the second step is often troublesome and that the integration of a multistep sequence in a single step transformation increases the efficiency of a process, we envisaged that the stereoselective Lewis acid-mediated addition of the titanium enolates from chiral *N*-acyl 1,3-thiazolidine-2-thiones

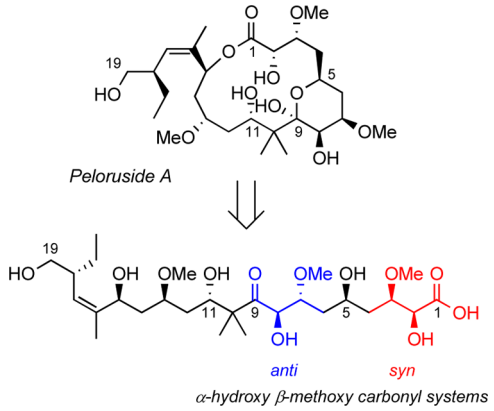


Figure 1. Seco-acid from peloruside A containing α-hydroxy β-methoxy carbonyl substructures.

to dimethyl acetals developed in our group[14] might be expanded to glycolic systems in order to gain access to the above-mentioned structural motifs in a straightforward and efficient manner.[15] We were also aware that similar additions to dibenzyl acetals[16] might afford double protected dihydroxy adducts capable to be immediately engaged in the synthesis of more complex structures. Herein, we disclose our studies on the Lewis acid-mediated addition of the titanium enolates from protected *N*-hydroxyacetyl-4-isopropyl-1,3-thiazolidine-2-thiones to dimethyl and dibenzyl acetals that provide the

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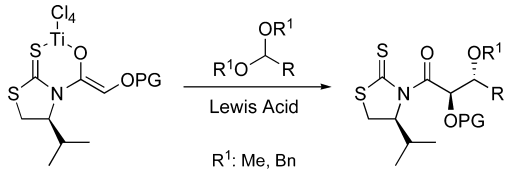
corresponding *anti* adducts in high yields and enantiomerically pure form (Scheme 1).

Scheme 1



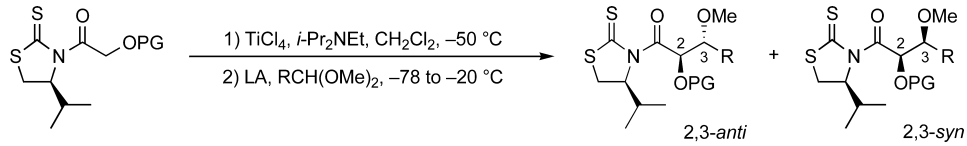
Application of experimental conditions optimized in former studies to the Lewis acid-mediated reactions of titanium enolates from valine-derived *N*-glycolyl thiazolidinethiones **1**–**5** and model dimethyl acetals revealed that their stereochemical outcome was highly dependent on the hydroxyl protecting group and, in a minor extent, on the aromatic or aliphatic character of the acetal. The additions of methyl ether and silyl protected glycolates **1** and **2** to dimethyl acetal of benzaldehyde and acetaldehyde (**a** and **b** respectively) illustrate this trend. Indeed, methyl ether protected glycolate **1** afforded *anti* adducts **6** but in variable diastereoselectivity: an excellent diastereomeric ratio favoring *anti* adduct **6a** for dimethyl acetal of benzaldehyde and a barely equimolar *anti*/*syn* mixture of adducts **6b** and **7b** for dimethyl acetal of acetaldehyde (see entries 1 and 6 in Table 1). In contrast, additions of silyl protected glycolate **2** to **a** and **b** furnished *syn* adducts **9a** and **9b** albeit in modest diastereomeric ratios (see entries 2 and 7 in Table 1). Aiming to improve these results, we assessed the influence of other silicon protecting groups and explored different experimental conditions, but we were unable to obtain pure *syn* adducts in a more efficient manner.[17] Finally, it was found that three ester protected glycolates **3**–**5** provided an excellent *anti* selection with both dimethyl acetals and delivered the corresponding *anti* adducts in high diastereomeric ratios (see entries 3–5 and 8–10 in Table 1).[18]

These findings prove that the appropriate choice of the protecting group permits to access both to the *syn* and the *anti* stereochemistries, although the latter are obtained in a more stereocontrolled manner. In this context, we focused our attention on the pivaloyl glycolate **3**, since it was considered to be the most suitable substrate to prepare the reluctant *anti* adducts.

Thus, experimental conditions were carefully optimized for the addition of *O*-pivaloyl derivative **3** to dimethyl acetals **a** and **b**. Importantly, these studies uncovered that the enolization could be performed at 0 °C in 30 min and that the relatively low reactivity of the resultant titanium enolates could be overcome by using a substoichiometric amount of the acetal.[19] Then, these optimized procedures were successfully applied to a wide range of dimethyl acetals. Indeed, BF_3-mediated addition of **3** to dimethyl acetals of aromatic or α,β-unsaturated aldehydes provided the corresponding *anti* adducts in excellent diastereomeric ratios and good yields (entries 1–4 in Table 2), whereas dimethyl acetals from lineal as well as branched aliphatic aldehydes required a stronger Lewis acid as $SnCl_4$ to achieve similar results (see entries 5–8 in Table 2). Furthermore, other dimethyl acetals containing different functional groups also afforded the corresponding *anti* adducts in high yields and excellent diastereomeric ratios (see entries 9–10 in Table 2) with the exception of methyl 3,3-dimethoxypropanoate (**k**), which resulted completely unreactive (entry 11 in Table 2). This lack of reactivity was likely due to the electron-withdrawing character of the carboxylate group that prevents the formation of the necessary oxocarbenium intermediate.

The *anti* configuration of adducts **10** was initially established by ^{1}H NMR analysis of the $^3J_{2,3}$ coupling constants and was later secured by X-ray diffraction analysis of **10d** (see the Supporting Information),[20] which also confirmed the existence

Table 1. Preliminary Studies on the Influence of Protecting Group on the Lewis Acid-Mediated Addition of *N*-Glycolyl Thiazolidinethiones to Dimethyl Acetals



1 PG: Me; **2** PG: TBDPS; **3** PG: Piv; **4** PG: Bz; **5** PG: Ac

6 PG: Me; **8** PG: TBDPS; **10** PG: Piv; **12** PG: Bz; **14** PG: Ac

7 PG: Me; **9** PG: TBDPS; **11** PG: Piv; **13** PG: Bz; **15** PG: Ac

entry	glycolate	PG	LA	acetal	R	major adduct	dr[a] (*anti*/*syn*)	yield (%)[b]
1	**1**	Me	$BF_3{\cdot}Et_2O$	**a**	Ph	**6a**	95:5	66
2	**2**	TBDPS	$BF_3{\cdot}Et_2O$	**a**	Ph	**9a**	30:70	(80)
3	**3**	Piv	$BF_3{\cdot}Et_2O$	**a**	Ph	**10a**	93:7	57
4	**4**	Bz	$BF_3{\cdot}Et_2O$	**a**	Ph	**12a**	89:11	69
5	**5**	Ac	$BF_3{\cdot}Et_2O$	**a**	Ph	**14a**	95:5	30
6	**1**	Me	$SnCl_4$	**b**	Me	**6b**	60:40	(55)
7	**2**	TBDPS	$SnCl_4$	**b**	Me	**9b**	23:77	(71)
8	**3**	Piv	$SnCl_4$	**b**	Me	**10b**	92:8	70
9	**4**	Bz	$SnCl_4$	**b**	Me	**12b**	87:13	75
10	**5**	Ac	$SnCl_4$	**b**	Me	**14b**	95:5	50

[a]Established by ^{1}H NMR of the reaction mixture. [b]Isolated yield of 2,3-*anti* diastereomer after chromatographic purification. Overall yield in parentheses.

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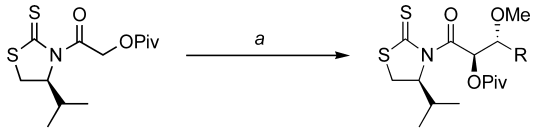
Table 2. Additions of *O*-Pivaloyl Derivative 3 to Dimethyl Acetals



3 10

entry	method[a]	acetal	R	dr[b]	yield (%)[c,d]
1	A	**a**	Ph	91:9	85
2	A	**c**	3-MeOPh	95:5	80
3	A	**d**	4-ClPh	93:7	67
4	A	**e**	(*E*)-PhCH=CMe	97:3	70
5	B	**b**	Me	94:6	77
6	B	**f**	*n*-Pr	95:5	82
7	B	**g**	*i*-Bu	95:5	75
8	B	**h**	*i*-Pr	97:3	75
9	B	**i**	CH_2CH_2OBn	>97:3	97
10	B	**j**	CH_2CH_2NPhth	>97:3	93
11	B	**k**	CH_2CO_2Me		

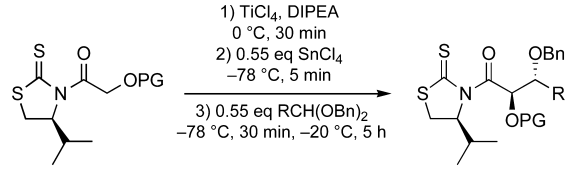
[a]Method A: (i) $TiCl_4$, DIPEA, 30 min, 0 °C; (ii) 1.1 equiv of $BF_3{\cdot}OEt_2$, −78 °C, 5 min; (iii) 0.55 equiv of $RCH(OMe)_2$, −78 °C, 2.5 h. Method B: (i) $TiCl_4$, DIPEA, 30 min, 0 °C; (ii) 0.55 equiv of $SnCl_4$, −78 °C, 5 min; (iii) 0.55 equiv of $RCH(OMe)_2$, −78 °C, 30 min, −20 °C, 5 h. [b]Established by ^1H NMR or HPLC analyses of the reaction mixtures. [c]Yield based on the consumption of the acetal. [d]Isolated yield after chromatographic purification.

of two intramolecular C−H···X (X = O, S) hydrogen bonds as occurs in other adducts.[21]

The high levels of stereocontrol achieved in the reaction of pivaloyl-protected *N*-glycolyl thiazolidinethione **3** and dimethyl acetals led us to assess similar transformations with dibenzyl acetals, aiming to obtain *anti* dihydroxy adducts with two different protecting groups. In this scenario, the Lewis acid of choice was $SnCl_4$ since $BF_3{\cdot}OEt_2$ was too weak even for the most reactive dibenzyl acetals from conjugated aldehydes.[16] Thus, application of the optimized conditions to glycolate **3** and dibenzyl acetals **l**−**p** provided the corresponding *anti* adducts in high yields and excellent diastereomeric ratios (see entries 1−5 in Table 3). Furthermore, the stereochemical induction imparted by ester protected glycolate derivatives **4** and **5** was also tested with dibenzyl acetal **p** containing a phtalimido group. Remarkably, a single diastereomer was observed in all the reaction mixtures, and the corresponding *anti* adducts **16**−**18** were easily isolated, although the yield for acetyl-protected glycolate **5** was significantly low (compare entries 5−7 in Table 3). All these results prove that the Lewis acid-mediated addition of the titanium enolates from ester protected glycolates **3**−**5** to dimethyl and dibenzyl acetals is a powerful tool to prepare the corresponding *anti* adducts in a highly efficient manner.

Irrespective of the results themselves, one of the most appealing features of the thiazolidinethione-based methodologies is the easy removal of the chiral auxiliary.[22] In accordance to these expectations, treatment of enantiomerically pure adduct **10i** with the lithium enolate from ethyl isobutyrate gave keto ester **19** in 80% yield (Scheme 2), which may be considered as a model for the synthesis of C5−C11 fragment of peloruside A shown in Figure 1.[23] Moreover, chiral auxiliary was removed under very mild conditions from benzyl adduct **16o** to give enantiomerically pure Weinreb amide **20** in which

Table 3. Additions to Dibenzyl Acetals



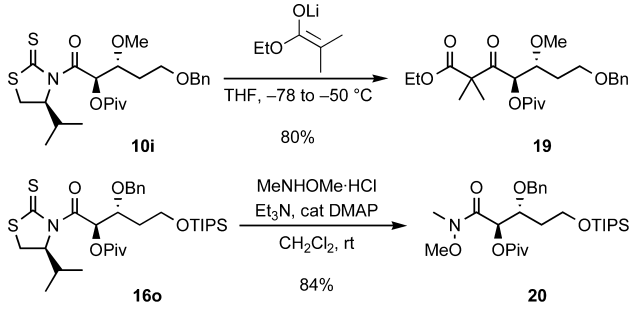
3 PG: Piv
4 PG: Bz
5 PG: Ac

16 PG: Piv
17 PG: Bz
18 PG: Ac

entry	glycolate	acetal	R	dr[a]	yield (%)[b,c]
1	**3**	**l**	Ph	>97:3	88
2	**3**	**m**	Me	89:11	(96)
3	**3**	**n**	*n*-Pr	92:8	70[d]
4	**3**	**o**	CH_2CH_2OTIPS	90:10	72
5	**3**	**p**	CH_2CH_2NPhth	>97:3	87
6	**4**	**p**	CH_2CH_2NPhth	>97:3	82
7	**5**	**p**	CH_2CH_2NPhth	>97:3	54

[a]Established by ^1H NMR or HPLC of the reaction mixtures. [b]Yield based on the consumption of the acetal. [c]Isolated yield. In parentheses, overall yield. [d]Isolated as the corresponding methyl ester (see reference 14).

Scheme 2



the alcohols at C2, C3, and C6 are protected with orthogonal protecting groups (Scheme 2).

In summary, highly stereoselective Lewis acid-mediated additions of titanium enolates from *N*-hydroxylacetyl-4-isopropyl-1,3-thiazolidine-2-thiones to a wide range of dimethyl and dibenzyl acetals have been developed. The choice of the protecting group has proved crucial for achieving highly stereocontrolled transformations. Thereby, ester-protected glycolates and especially pivaloyl-protected glycolate provide a highly stereoselective and straightforward access to the corresponding *anti* adducts, which can be easily isolated and further converted in enantiomerically pure *β*-methoxy or *β*-benzyloxy *α*-pivaloyloxy carbonyl fragments capable of being immediately used in the synthesis of natural products.

■ EXPERIMENTAL SECTION

General Methods. All reactions were conducted in oven-dried glassware with distilled and anhydrous solvents under an atmosphere of N_2. Thin-layer chromatography was carried out on silica gel 60 F_{254} plates. Specific rotations were determined at 20 °C. IR spectra were obtained as thin films on NaCl plates or KBr discs. ^1H NMR spectra were recorded in $CDCl_3$ and reported as δ ppm downfield from internal TMS (δ 0). ^{13}C NMR spectra were also recorded in $CDCl_3$ and referenced to solvent residual peak for $CDCl_3$ (δ 77). High resolution mass spectra (HRMS) were obtained by using ESI−TOF techniques.

Preparation of Glycolate 3. A mixture of glycolic acid (1.52 g, 20 mmol) and pivaloyl chloride (4.4 mL, 36 mmol) was stirred at room

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temperature for 48 h. Then, the volatiles were removed, obtaining 2.73 g of *O*-pivaloylglycolic acid, which were used in the next step without further purification.

A mixture of this acid, (*S*)-4-isopropyl-1,3-thiazolidine-2-thione (1.612 g, 10 mmol), EDC (2.6 mL, 15 mmol), and DMAP (60 mg, 0.5 mmol) in CH_2Cl_2 (15 mL) was stirred at 0 °C for 15 min and was allowed to reach room temperature for 3 h under a N_2 atmosphere. It was partitioned with Et_2O and 0.5 M HCl; the organic layer was washed with 0.5 M NaOH, H_2O, and brine, dried, and concentrated. The resulting residue was purified through flash chromatography (from 50:50 to 70:30 CH_2Cl_2/hexanes) to afford 2.62 g (8.6 mmol, 86%) of (*S*)-4-isopropyl-*N*-(pivaloyloxyacetyl)-1,3-thiazolidine-2-thione, **3**, as a yellow oil: R_f (CH_2Cl_2/hexanes 70:30) 0.50; $[\alpha]_D$ +232.8 (*c* 1.00, $CHCl_3$); IR (film) ν 2965, 2874, 1740, 1714, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 2H), 5.11 (ddd, *J* = 8.2, 5.9, 1.2 Hz, 1H), 3.63 (dd, *J* = 11.6, 8.2 Hz, 1H), 3.09 (dd, *J* = 11.6, 1.2 Hz, 1H), 2.43−2.32 (m, 1H), 1.27 (s, 9H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 202.5, 177.9, 168.1, 71.4, 65.0, 38.7, 31.4, 30.7, 27.1, 19.0, 17.5; HRMS *m*/*z* calcd for $[M + H]^+$ $C_{13}H_{22}NO_3S_2$ 304.1036, found 304.1037; *m*/*z* calcd for $[M + Na]^+$ $C_{13}H_{21}NNaO_3S_2$ 326.0855, found 326.0859.

Experimental Procedure for Method A. Neat $TiCl_4$ (0.12 mL, 1.1 mmol) is added dropwise to a solution of **3** (303 mg, 1.0 mmol) in CH_2Cl_2 (8 mL), at 0 °C. The orange suspension is stirred for 5 min at 0 °C, and a solution of *i*-Pr_2NEt (0.19 mL, 1.1 mmol) in CH_2Cl_2 (1.5 mL) is added. The dark brown enolate solution is stirred for 30 min at 0 °C and cooled at −78 °C. Then, recently distilled $BF_3{\cdot}OEt_2$ (140 μL, 1.1 mmol) and dimethyl acetal (0.55 mmol) are added, and the resulting mixture is stirred for 2.5 h at −78 °C.

The reaction is quenched by the addition of saturated NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts are dried and concentrated. The residue is analyzed by HPLC or ^1H NMR and purified through flash column chromatography with deactivated silica gel (2.5% Et_3N) using CH_2Cl_2 or 90:10 hexanes/EtOAc mixtures as solvents to afford the *anti* adduct as a pure diastereomer.

Experimental Procedure for Method B. Neat $TiCl_4$ (0.12 mL, 1.1 mmol) is added dropwise to a solution of **3** (303 mg, 1.0 mmol) in CH_2Cl_2 (8 mL), at 0 °C. The orange suspension is stirred for 5 min at 0 °C, and a solution of *i*-Pr_2NEt (0.19 mL, 1.1 mmol) in CH_2Cl_2 (1.5 mL) is added. The dark brown solution is stirred for 30 min at 0 °C and cooled at −78 °C. Then, a 1 M $SnCl_4$ solution (0.55 mL, 0.55 mmol) and dimethyl acetal (0.55 mmol) are added, and the resulting mixture is stirred for 30 min at −78 °C and 5 h at −20 °C. Quenching and purification of the reaction mixture is the same as in Method A.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-3-phenyl-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (10a). Yellow solid (197 mg, 85%): mp 142−143 °C; R_f (hexanes/CH_2Cl_2 50:50) 0.40; $[\alpha]_D$ +210.7 (*c* 1.15, $CHCl_3$); IR (KBr) ν 2962, 1728, 1707, 1368, 1178, 1149 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48−7.27 (m, 5H), 7.14 (d, *J* = 7.6 Hz, 1H), 5.29 (ddd, *J* = 8.2, 6.0, 1.2 Hz, 1H), 4.64 (d, *J* = 7.6 Hz, 1H), 3.60 (dd, *J* = 11.4, 8.2 Hz, 1H), 3.20 (s, 3H), 3.01 (dd, *J* = 11.4, 1.2 Hz, 1H), 2.38−2.27 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.08 (s, 9H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 202.6, 177.5, 170.3, 137.5, 128.5, 128.2, 128.1, 83.9, 73.0, 71.7, 56.9, 38.3, 30.6, 30.3, 26.8, 18.9, 17.5; HRMS *m*/*z* calcd for $[M + H]^+$ $C_{21}H_{30}NO_4S_2$ 424.1611, found 424.1625.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-2-pivaloyloxybutanoyl]-1,3-thiazolidine-2-thione (10b). Yellow oil (152 mg, 77%): R_f (CH_2Cl_2) 0.35; $[\alpha]_D$ +216.1 (*c* 0.65, $CHCl_3$); IR (film) ν 2967, 2932, 1730, 1702, 1363, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, *J* = 3.7 Hz, 1H), 5.23 (ddd, *J* = 8.2, 6.4, 1.1 Hz, 1H), 4.06 (qd, *J* = 6.4, 3.7 Hz, 1H), 3.65 (dd, *J* = 11.5, 8.2 Hz, 1H), 3.38 (s, 3H), 3.03 (dd, *J* = 11.5, 1.1 Hz, 1H), 2.29−2.22 (m, 1H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.25 (s, 9H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 202.4, 178.1, 169.4, 75.3, 73.5, 71.5, 56.9, 38.7, 30.9, 30.5, 26.9, 18.9, 17.6, 14.2; HRMS *m*/*z* calcd for $[M + H]^+$ $C_{16}H_{28}NO_4S_2$ 362.1454, found 362.1468.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-3-(3-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (10c). Yellow solid (198 mg, 80%): mp 85−88 °C; R_f (CH_2Cl_2) 0.55; $[\alpha]_D$ +247.4 (*c* 0.9, $CHCl_3$); IR (KBr) ν 3005, 2968, 2868, 1735, 1698, 1486, 1145, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.22 (m, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.14 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.02 (dt, *J* = 7.6, 1.5 Hz, 1H), 6.86 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 5.30 (ddd, *J* = 8.3, 5.9, 1.1 Hz, 1H), 4.61 (d, *J* = 7.6 Hz, 1H), 3.82 (s, 3H), 3.60 (dd, *J* = 11.4, 8.4 Hz, 1H), 3.20 (s, 3H), 3.02 (dd, *J* = 11.4, 1.1 Hz, 1H), 2.39−2.27 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.10 (s, 9H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.6, 177.5, 170.3, 159.6, 139.2, 129.0, 120.7, 114.5, 113.0, 83.9, 72.9, 71.7, 56.9, 55.2, 38.3, 30.5, 30.3, 26.8, 19.0, 17.5; HRMS *m*/*z* calcd for $[M + H]^+$ $C_{22}H_{32}NO_5S_2$ 454.1716, found 454.1714; calcd for $[M + Na]^+$ $C_{22}H_{31}NNaO_5S_2$ 476.1536, found 476.1539.

(*S*)-*N*-[(2*R*,3*S*)-3-(4-Chlorophenyl)-3-methoxy-2-pivaloyloxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (10d). Yellow solid (167 mg, 67%): mp 100−103 °C; R_f (hexanes/EtOAc 90:10) 0.30; $[\alpha]_D$ +124.4 (*c* 1.3, $CHCl_3$); IR (KBr) ν 2961, 2872, 1730, 1704, 1477, 1372, 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.32 (m, 4H), 7.09 (d, *J* = 7.6 Hz, 1H), 5.27 (ddd, *J* = 8.2, 6.1, 1.1 Hz, 1H), 4.64 (d, *J* = 7.6 Hz, 1H), 3.61 (dd, *J* = 11.4, 8.2 Hz, 1H), 3.20 (s, 3H), 3.02 (dd, *J* = 11.4, 1.1 Hz, 1H), 2.36−2.26 (m, 1H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.10 (s, 9H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.8, 177.5, 169.9, 136.0, 134.4, 129.6, 128.4, 81.3, 72.8, 71.7, 57.0, 38.4, 30.5 (×2), 26.8, 18.9, 17.5; HRMS *m*/*z* calcd for $[M + H]^+$ $C_{21}H_{29}ClNO_4S_2$ 458.1221, found 458.1225; calcd for $[M + Na]^+$ $C_{21}H_{28}ClNNaO_4S_2$ 480.1040, found 480.1052.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*,4*E*)-3-methoxy-4-methyl-5-phenyl-2-pivaloyloxy-4-pentenoyl]-1,3-thiazolidine-2-thione (10e). Yellow oil (177 mg, 70%): R_f (hexanes/EtOAc 90:10) 0.35; $[\alpha]_D$ +222.0 (*c* 2.1, $CHCl_3$); IR (film) ν 2966, 2874, 1732, 1700, 1364, 1176, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.19 (m, 5H), 7.18 (d, *J* = 7.5 Hz, 1H), 6.55 (br s, 1H), 5.31 (ddd, *J* = 8.5, 5.7, 1.1 Hz, 1H), 4.26 (d, *J* = 7.5 Hz, 1H), 3.57 (dd, *J* = 11.5, 8.5 Hz, 1H), 3.25 (s, 3H), 2.99 (dd, *J* = 11.5, 1.1 Hz, 1H), 2.32−2.22 (m, 1H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.10 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.5, 177.6, 170.3, 136.8, 134.5, 131.4, 128.9, 128.1, 126.8, 87.5, 71.6, 70.8, 56.3, 38.4, 30.5, 29.9, 26.9, 18.8, 17.1, 13.2; HRMS *m*/*z* calcd for $[M + Na]^+$ $C_{24}H_{33}NNaO_4S_2$ 486.1744, found 486.1742.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-2-pivaloyloxyhexanoyl]-1,3-thiazolidine-2-thione (10f). Yellow solid (174 mg, 82%): mp 51−53 °C; R_f (hexanes/EtOAc 90:10) 0.55; $[\alpha]_D$ +236.3 (*c* 1.2, $CHCl_3$); IR (KBr) ν 2966, 2873, 1731, 1700, 1362, 1182, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 4.3 Hz, 1H), 5.26 (ddd, *J* = 8.4, 6.0, 1.3 Hz, 1H), 3.91−3.87 (m, 1H), 3.62 (dd, *J* = 11.5, 8.4 Hz, 1H), 3.42 (s, 3H), 3.02 (dd, *J* = 11.5, 1.3 Hz, 1H), 2.31−2.23 (m, 1H), 1.75−1.66 (m, 1H), 1.60−1.46 (m, 2H), 1.40−1.32 (m, 1H), 1.24 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.5, 178.1, 169.7, 79.2, 72.7, 71.6, 58.2, 38.6, 32.1, 30.5 (×2), 27.0, 18.9, 18.8, 17.3, 14.1; HRMS *m*/*z* calcd for $[M + Na]^+$ $C_{18}H_{31}NNaO_4S_2$ 412.1587, found 412.1589.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-5-methyl-2-pivaloyloxyhexanoyl]-1,3-thiazolidine-2-thione (10g). Yellow solid (165 mg, 75%): mp 56−58 °C; R_f (CH_2Cl_2) 0.65; $[\alpha]_D$ +244.9 (*c* 0.8, $CHCl_3$); IR (KBr) ν 2959, 2871, 1731, 1702, 1363, 1179, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 3.7 Hz, 1H), 5.27 (ddd, *J* = 8.4, 5.9, 1.2 Hz, 1H), 4.03 (ddd, *J* = 9.9, 3.7, 2.7 Hz, 1H), 3.63 (dd, *J* = 11.5, 8.4 Hz, 1H), 3.44 (s, 3H), 3.02 (dd, *J* = 11.5, 1.3 Hz, 1H), 2.30−2.21 (m, 1H), 1.85−1.70 (m, 3H), 1.25 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.5, 178.2, 169.3, 77.3, 72.8, 71.6, 58.1, 38.9, 38.7, 30.6, 30.4, 27.0, 24.4, 23.7, 21.7, 19.0, 17.3; HRMS *m*/*z* calcd for $[M + H]^+$ $C_{19}H_{34}NO_4S_2$ 404.1924, found 404.1928; calcd for $[M + Na]^+$ $C_{19}H_{33}NNaO_4S_2$ 426.1743, found 426.1747.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-4-methyl-2-pivaloyloxypentanoyl]-1,3-thiazolidine-2-thione (10h). Yellow solid (160 mg, 75%): mp 88−90 °C; R_f (CH_2Cl_2) 0.40; $[\alpha]_D$ +168.6 (*c* 1.4, $CHCl_3$); IR (KBr) ν 2964, 2873, 1722, 1697, 1364, 1180, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 7.0 Hz, 1H), 5.23

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(ddd, J = 8.3, 5.8, 1.1 Hz, 1H), 3.61 (dd, J = 11.4, 8.3 Hz, 1H), 3.57 (dd, J = 7.0, 4.4 Hz, 1H), 3.38 (s, 3H), 3.02 (dd, J = 11.4, 1.2 Hz, 1H), 2.37−2.28 (m, 1H), 2.08−1.99 (m, 1H), 1.21 (s, 9H), 1.07 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.8, 177.9, 170.6, 85.4, 71.7, 71.6, 60.2, 38.4, 30.7, 30.5, 30.2, 26.9, 19.9, 19.0, 17.6, 17.2; HRMS m/z calcd for $[M + H]^+$ $C_{18}H_{32}NO_4S_2$ 390.1767, found 390.1768; calcd for $[M + Na]^+$ $C_{18}H_{31}NNaO_4S_2$ 412.1587, found 412.1586.

(*S*)-*N*-[(2*R*,3*R*)-4-Benzyloxy-3-methoxy-2-pivaloyloxypentanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (10i). Yellow oil (256 mg, 97%): R_f (CH_2Cl_2) 0.55; $[\alpha]_D$ +187.8 (c 1.2, $CHCl_3$); IR (film) ν 3029, 2967, 2872, 1731, 1363, 1153 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 6.98 (d, J = 3.5 Hz, 1H), 5.25 (ddd, J = 8.4, 5.9, 1.3 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.16−4.12 (m, 1H), 3.61 (dd, J = 11.4, 8.4 Hz, 1H), 3.61−3.58 (m, 2H), 3.41 (s, 3H), 3.01 (dd, J = 11.4, 1.2 Hz, 1H), 2.29−2.20 (m, 1H), 1.98−1.88 (m, 2H), 1.22 (s, 9H), 1.00 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.5, 178.1, 169.3, 138.5, 128.3, 127.6, 127.5, 76.1, 72.8, 72.7, 71.6, 66.2, 58.3, 38.6, 30.6, 30.5, 30.2, 26.9, 19.0, 17.2; HRMS m/z calcd for $[M + H]^+$ $C_{24}H_{36}NO_5S_2$ 482.2029, found 482.2023; calcd for $[M + Na]^+$ $C_{24}H_{35}NNaO_5S_2$ 504.1849, found 504.1840.

(*S*)-*N*-[(2*R*,3*R*)-5-Amino-3-methoxy-*N*,*N*-phtaloyl-2-pivaloyloxypentanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (10j). Yellow solid (132 mg, 93%): mp 47−50 °C; R_f (CH_2Cl_2) 0.25; $[\alpha]_D$ +150.5 (c 1.0, $CHCl_3$); IR (KBr) ν 2965, 2932, 1772, 1713, 1467, 1364 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.82 (m, 2H), 7.72−7.70 (m, 2H), 6.98 (d, J = 3.5 Hz, 1H), 5.21 (ddd, J = 8.2, 6.2, 1.2 Hz, 1H), 4.04 (ddd, J = 9.3, 3.5, 2.7 Hz, 1H), 3.90−3.78 (m, 2H), 3.61 (dd, J = 11.5, 8.2 Hz, 1H), 3.48 (s, 3H), 3.00 (dd, J = 11.5, 1.0 Hz, 1H), 2.24−2.15 (m, 1H), 2.13−2.04 (m, 1H), 1.99−1.91 (m, 1H), 1.24 (s, 9H), 0.98 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.4, 178.2, 169.0, 168.2, 133.9, 132.2, 123.1, 76.8, 71.8, 71.5, 57.8, 38.7, 34.9, 30.8, 30.6, 28.4, 26.9, 18.9, 17.4; HRMS m/z calcd for $[M + H]^+$ $C_{25}H_{33}N_2O_6S_2$ 521.1775, found 521.1776; calcd for $[M + Na]^+$ $C_{25}H_{32}N_2NaO_6S_2$ 543.1594, found 543.1596.

(*S*)-*N*-[(2*R*,3*R*)-3-Benzyloxy-3-phenyl-2-pivaloyloxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (16l). Yellow oil (240 mg, 88%): R_f (hexanes/CH_2Cl_2 50:50) 0.15; $[\alpha]_D$ +159.2 (c 1.0, $CHCl_3$); IR (film) ν 3030, 2967, 2873, 1732, 1698, 1178, 1150 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.50 (m, 2H), 7.39−7.20 (m, 8H), 7.06 (d, J = 7.4 Hz, 1H), 5.20−5.16 (m, 1H), 4.93 (d, J = 7.4 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.28 (d, J = 11.7 Hz, 1H), 3.56 (dd, J = 11.4, 8.2 Hz, 1H), 2.97 (dd, J = 11.4, 0.6 Hz, 1H), 2.26−2.14 (m, 1H), 1.08 (s, 9H), 0.91 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.7, 177.6, 169.9, 137.7, 137.5, 128.6, 128.4, 128.2, 128.1, 127.5, 127.4, 81.6, 73.1, 71.7, 70.7, 38.4, 30.7, 30.5, 26.8, 19.0, 17.4; HRMS m/z calcd for $[M + H]^+$ $C_{27}H_{34}NO_4S_2$ 500.1924, found 500.1924; m/z calcd for $[M + Na]^+$ $C_{27}H_{33}NNaO_4S_2$ 522.1743, found 522.1745.

(*S*)-*N*-[(2*R*,3*R*)-3-Benzyloxy-2-pivaloyloxybutanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (16m). Yellow oil (230 mg, 96%, dr 89:11): R_f (CH_2Cl_2) 0.55; $[\alpha]_D$ +236.1 (c 1.15, $CHCl_3$); IR (film) ν 3029, 2968, 2873, 1730, 1702, 1364, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.31 (m, 5H), 6.82 (d, J = 3.4 Hz, 1H), 5.20 (ddd, J = 8.1, 6.3, 1.2 Hz, 1H), 4.66−4.59 (m, 2H), 4.32 (qd, J = 6.4, 3.4 Hz, 1H), 3.62 (dd, J = 11.5, 8.2 Hz, 1H), 3.01 (dd, J = 11.5, 1.2 Hz, 1H), 2.28−2.20 (m, 1H), 1.31 (d, J = 6.5 Hz, 3H), 1.25 (s, 9H), 0.99 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.5, 178.2, 169.2, 138.4, 128.3, 127.6, 127.5, 73.6, 73.3, 71.6, 70.8, 38.7, 31.0, 30.6, 27.0, 19.0, 17.5, 14.8; HRMS m/z calcd for $[M + H]^+$ $C_{22}H_{32}NO_4S_2$ 438.1767, found 438.1772; calcd for $[M + Na]^+$ $C_{22}H_{31}NNaO_4S_2$ 460.1587, found 460.1593.

(*S*)-*N*-[(2*R*,3*R*)-3-Benzyloxy-2-pivaloyloxy-5-triisopropylsilyloxypentanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (16o). Yellow oil (245 mg, 72%): R_f (CH_2Cl_2) 0.45; $[\alpha]_D$ +163.8 (c 2.3, $CHCl_3$); IR (film) ν 3031, 2962, 2866, 1731, 1700, 1463, 1153 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.22 (m, 5H), 6.96 (d, J = 3.1 Hz, 1H), 5.22 (ddd, J = 8.2, 6.2, 1.2 Hz, 1H), 4.80 (d, J = 11.4 Hz, 1H), 4.64−4.59 (m, 1H), 4.61 (d, J = 11.4 Hz, 1H), 3.90−3.77 (m, 2H), 3.63 (dd, J = 11.4, 8.2 Hz, 1H), 3.02 (dd, J = 11.4, 1.2 Hz, 1H), 2.28−2.19 (m, 1H), 2.00−1.92 (m, 1H), 1.88−1.79 (m, 1H), 1.24 (s, 9H), 1.07−1.03 (m, 21H), 1.00 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.4, 178.3, 168.9, 138.6, 128.2, 127.5, 127.5, 73.7, 72.9, 71.9, 71.6, 59.2, 38.6, 33.0, 30.9, 30.6, 26.9, 19.1, 18.0, 17.5, 11.9; HRMS m/z calcd for $[M + H]^+$ $C_{32}H_{54}NO_5S_2Si$ 624.3207, found 624.3212; m/z calcd for $[M + Na]^+$ $C_{32}H_{53}NNaO_5S_2Si$ 646.3027, found 646.3034.

(*S*)-*N*-[(2*R*,3*R*)-5-Amino-3-benzyloxy-*N*,*N*-ftaloyl-2-pivaloyloxypentanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (16p). Yellow solid (283 mg, 87%): mp 46−47 °C; R_f (CH_2Cl_2) 0.40; $[\alpha]_D$ +142.4 (c 0.95, $CHCl_3$); IR (KBr) ν 3030, 2966, 2933, 1772, 1713, 1467, 1363 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.79 (m, 2H), 7.69−7.67 (m, 2H), 7.36−7.21 (m, 5H), 7.03 (d, J = 3.1 Hz, 1H), 5.20 (ddd, J = 8.2, 6.1, 1.2 Hz, 1H), 4.78 (d, J = 11.3 Hz, 1H), 4.65 (d, J = 11.3 Hz, 1H), 4.33 (dt, J = 9.8, 2.9 Hz, 1H), 3.91−3.78 (m, 2H), 3.65 (dd, J = 11.5, 8.3 Hz, 1H), 3.00 (dd, J = 11.5, 1.3 Hz, 1H), 2.22−2.12 (m, 1H), 2.00−1.91 (m, 1H), 1.24 (s, 9H), 0.98 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.4, 178.2, 168.8, 168.2, 138.3, 133.8, 132.1, 128.2, 127.7, 127.5, 123.1, 75.1, 72.1, 71.5, 71.5, 38.7, 35.0, 30.9, 30.6, 28.5, 27.0, 18.9, 17.4; HRMS m/z calcd for $[M + H]^+$ $C_{31}H_{37}N_2O_6S_2$ 597.2088, found 597.2092; m/z calcd for $[M + Na]^+$ $C_{31}H_{36}N_2NaO_6S_2$ 619.1907, found 619.1911.

Synthesis of Keto Ester 19. Ethyl isobutyrate (475 μL, 3.5 mmol) was added to a freshly prepared 0.5 M solution of LDA in THF (7 mL, 3.5 mmol) at −78 °C. Stirring continued for 1 h, and a solution of **10i** (566 mg, 1.2 mmol) in THF (0.75 + 0.25 mL) was carefully added. The reaction mixture was stirred for 30 min at −78 °C and 3.5 h at −50 °C, quenched with saturated NH_4Cl, and partitioned with CH_2Cl_2 and water. The organic layer was dried and concentrated, and the resultant residue was purified by flash chromatography (hexanes/EtOAc 85:15), affording 410 mg (0.94 mmol, 80% yield) of ethyl (4*R*,5*R*)-7-benzyloxy-5-methoxy-2,2-dimethyl-3-oxo-4-pivaloyloxyheptanoate (**19**) as a colorless oil: R_f (hexanes/EtOAc 85:15) 0.55; $[\alpha]_D$ +49.0 (c 1.5, $CHCl_3$); IR (film) ν 3030, 2979, 2872, 1742, 1711, 1456, 1274, 1137 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 5.96 (d, J = 3.2 Hz, 1H), 4.53 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.20−4.01 (m, 2H), 3.89 (dt, J = 9.4, 3.2 Hz, 1H), 3.57−3.53 (m, 2H), 3.28 (s, 3H), 1.79−1.63 (m, 2H), 1.43 (s, 3H), 1.32 (s, 3H), 1.25−1.15 (m, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 205.4, 177.3, 172.5, 138.5, 128.3, 127.7, 127.5, 78.3, 75.4, 72.8, 66.5, 61.4, 57.5, 53.8, 40.0, 30.5, 27.1, 22.4, 21.6, 13.8; HRMS m/z calcd for $[M + H]^+$ $C_{24}H_{37}O_7$ 437.2542, found 437.2534.

Synthesis of Weinreb Amide 20. A solution of **16o** (67 mg, 107 μmol), MeONHMe·HCl (16 mg, 0.16 mmol), DMAP (15 mg, 107 μmol), and Et_3N (15 μL, 107 μmol) in CH_2Cl_2 (1 mL) was stirred for 16 h at rt. The reaction mixture was diluted in Et_2O and washed with 0.5 M HCl, 0.5 M NaOH, H_2O, and brine, dried and concentrated. The resultant colorless oil was filtered over silica gel (eluted with CH_2Cl_2/EtOAc 95:5), yielding 47 mg (90 μmol, 84%) of (2*R*,3*R*)-3-benzyloxy-*N*-methoxy-*N*-methyl-2-pivaloyloxy-5-triisopropylsilyloxypentanamide (**20**) as a colorless oil: R_f (CH_2Cl_2/EtOAc 95:5) 0.40; $[\alpha]_D$ +6.3 (c 1.2, $CHCl_3$); IR (film) ν 3031, 2942, 2866, 1733, 1684, 1463, 1159, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.25 (m, 5H), 5.55 (s, 1H), 4.64 (d, J = 11.5 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.17−4.13 (m, 1H), 3.86−3.76 (m, 2H), 3.74 (s, 3H), 3.17 (s, 3H), 1.88−1.84 (m, 2H), 1.27 (s, 9H), 1.09−1.01 (m, 21H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.5, 168.3, 138.3, 128.3, 127.8, 127.7, 74.5, 72.4, 71.6, 61.1, 59.1, 38.8, 33.9, 27.1, 18.0, 11.9; HRMS m/z calcd for $[M + H]^+$ $C_{28}H_{50}NO_6Si$ 524.3402, found 524.3412.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for adducts **10** and **16**, derivatives **19** and **20**, and data for X-ray crystal structure of

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adduct **10d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) Only two of the four possible isomers have been observed across all the reactions. These results are in accordance to our previous studies on the Lewis acid-mediated additions of titanium enolates to acetals, which established the absolute stereocontrol provided by the chiral auxiliary on the *R* configuration of the α-stereocenter in these processes. See reference 14 for further details.

(19) Importantly, 0.25−0.35 mmol of acyl thiazolidinethione **3** are commonly recovered after chromatographic purification of the reaction mixtures, whereas minor amounts of the chiral auxiliary are observed in these mixtures.

(20) Crystallographic data for **10d** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-885194. Copy of the data can be obtained free of charge on application to CCDC (e-mail: deposit@ccdc.cam.ac.uk).

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