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Stereoselective aldol additions of titanium enolates of *N*-acetyl-4-isopropyl-thiazolidinethione

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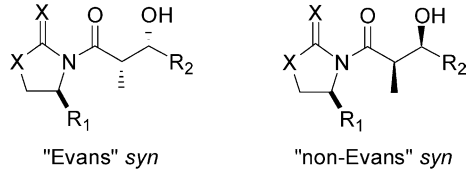
Abstract—The addition of chlorotitanium enolates of *N*-acetyl isopropyl thiazolidine-2-thione to aldehydes was investigated. The stereoselectivity of the aldol products was controlled by the number of equivalents of base added. The *syn* aldol product was obtained preferentially when 2 equiv of Lewis acid and 1 equiv of base were employed. The *anti* aldol product was obtained preferentially when 1 equiv of Lewis acid and 2 equiv of base were employed for unsaturated aldehydes. Unexpected results were found with hindered aldehydes when 2 equiv of base were employed.

1. Introduction

The aldol addition reaction is of paramount importance for the synthesis of polyketides and other families of natural products.[1] Powerful chiral auxiliaries for asymmetric aldol reactions have been developed in the last twenty-five years.[2] In particular, oxazolidinones developed by Evans, are valuable chiral auxiliaries for the syntheses of aldol products. Depending on reaction conditions, the 'Evans' *syn* and 'non-Evans' *syn* aldol products can be obtained.[3] However, poor diastereomeric ratios are observed for the acetate aldol reaction using chiral oxazolidinones.[4] Several methodologies have been investigated attempting to overcome this limitation. Studies have shown that addition of a temporary auxiliary group on the *alpha* carbon improves the diastereomeric excess. Unfortunately, this sequence solution adds additional steps to the synthetic route.[5] Efforts have also been directed at other potential methodologies (Scheme 1).

Excellent stereoselectivities have been observed for chiral auxiliary-based acetate aldol reaction using 1,3-oxazolidine-2-thiones and 1,3-thiazolidine-2-thiones.[6,7] Interestingly, thiazolidinethione chiral auxiliaries have also proved to have several advantages over its oxazolidinone analogs, e.g. they can be directly reduced to aldehydes, easily removed, and displaced by some nucleophiles.[8] However, highly stereoselective acetate aldol reactions employ either expensive metals or starting materials. Fujita–Nagao's chiral auxiliary, 4-alkyl thiazolidinethione, has been used successfully to obtain the acetate *syn* aldol product[9] when using tin(II) triflate as the Lewis acid.[6] In addition, a highly hindered oxazolidinethione derived from methyl valinate was used to obtain highly diastereoselective acetate *syn* product using titanium(IV) chloride, sparteine and *N*-methylpyrrolidinone.[10] Recently, a procedure to obtain the acetate *anti* aldol product with high diastereoselectivity has been reported.[11] In this procedure, a thiazolidinethione chiral auxiliary was prepared from *tert*-leucine and dichlorophenylborane was used as the Lewis acid. Although excellent diastereoselectivities have been achieved with these sulfur chiral auxiliaries, expensive starting materials and reagents are required. Herein, we report our investigations in the acetate aldol reaction using less expensive reagents and chiral auxiliaries (Scheme 2).

The Fujita–Nagao chiral auxiliary has been elegantly reintroduced by Crimmins.[8] Inexpensive reagents can be employed on the stereoselective aldol condensation of *N*-propionyl oxazolidinethiones and thiazolidinethiones. Interestingly, using the same chiral auxiliary, the 'Evans' *syn* or 'non-Evans' *syn* stereochemistry of the aldol product can be controlled by the nature and amount of Lewis acid and base employed. Based on these results, we decided to



Scheme 1.

Keywords: Aldol additions; Thiazolidinethiones; Chiral auxiliaries.
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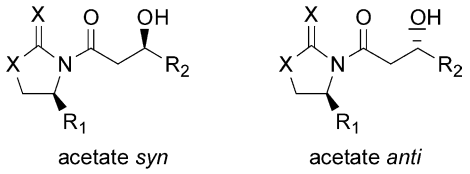


Scheme 2.

explore the synthetic utility of these conditions in the acetate aldol addition employing thiazolidinethiones.

2. Discussion and results

A highly coordinated Lewis acid transition state is formed when *N*-acyl thiazolidinethione is treated with one or 2 equiv of titanium(IV) chloride and 1 equiv of (−)-sparteine, followed by addition of an aldehyde.[8] A mixture with a high diastereomeric ratio of aldol acetate products was obtained using these conditions, Table 1.[12] The mixture of diastereomeric products was easily separated by silica gel column chromatography. The major product was the more polar *syn* aldol diastereomer. Good to modest yields and high diastereomeric ratios were obtained when using unsaturated aldehydes (entries 1–3) and also with *p*-bromobenzaldehyde and pivalaldehyde (entries 5 and 6). Less diastereoselectivity was obtained with saturated aldehydes (entries 7–9). The major *p*-bromobenzaldehyde aldol product was studied by X-ray crystallographic analysis to confirm its relative and absolute stereochemistry, Fig. 1.[13] The *syn* aldol product **5** showed characteristic ^{1}H NMR chemical shift signals for the *alpha*-protons at 3.8 ppm (dd, $J=17.6$, 2.7 Hz) for the less shielded proton and at 3.50 ppm (dd, $J=17.6$, 9.4 Hz) for the more shielded proton. The minor less polar *anti* product showed chemical shift signals for the *alpha*-protons at 3.79 (dd, $J=17.5$, 9.5 Hz) and 3.53 (dd, $J=17.5$, 3.1 Hz). These *alpha*-proton signals and coupling constants were useful to assign the stereochemistry of the aldol carbon of other products.

Following investigations from the Crimmins' group,[8] addition of *N*-propionate thiazolidinethione to aldehydes using 1 equiv of titanium(IV) chloride and 2 equiv of base generates an open transition state where the thiocarbonyl of the chiral auxiliary is not coordinated to the metal. According to this transition state, the major diastereomeric product is expected to be the *anti* aldol product. Applying this protocol, aldol acetate additions gave preferentially the *anti* products for unsaturated aldehydes (entries 1, 3 and 4), Table 2.[12] Contrary to our expectations, a high diastereomeric ratio favoring the *syn* products was observed for benzaldehyde and pivalaldehyde (entries 5 and 7). Interestingly, switching the Lewis acid to dichlorophenylborane,[11] the diastereomeric ratio for pivalaldehyde was completely reversed (entry 8). Also, the *anti* product was observed exclusively for the addition to cinnamaldehyde when using the boron acid (entry 2). Aldol reactions with saturated aldehydes showed only a slight preference for the *anti* product (entries 10 and 11). The diastereomeric ratio was improved when the thiazolidinethione derived from phenylalanine was employed (entry 12) (Fig. 2).

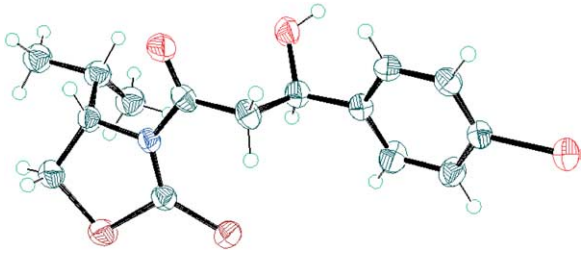
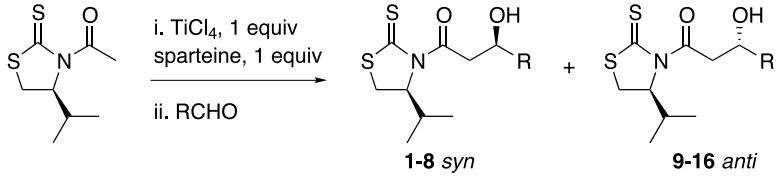


Figure 1. X-ray analysis of *syn* aldol product **5** (ORTEP drawing).

3. Conclusions

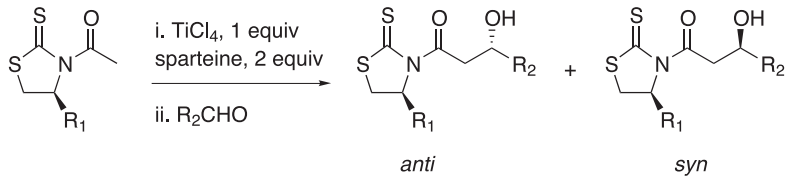
In summary, we have investigated the acetate aldol addition using inexpensive titanium(IV) chloride, sparteine and chiral thiazolidinethione derived from valine. The *syn* acetate aldol product was obtained in high diastereomeric ratio when using 2 equiv of Lewis acid and 1 equiv of base. The *anti* acetate aldol product was obtained preferentially when 1 equiv of Lewis acid and 2 equiv of base were employed for unsaturated aldehydes. In the case of hindered aldehydes, dichlorophenylborane was required to obtain the *anti* product. Further exploration of this phenomena is currently underway. The ease of separation of these

Table 1. Acetate *syn* aldol addition products



Entry	Aldehyde, R-CHO	Ratio *syn*/*anti*	Yield (%)
1	*t*-CH=CH–C_6H_5	92:8 (**1**:**10**)	73
2	–CH=$C(CH_3)_2$	91:9 (**2**:**11**)	60
3	–CH=CH–CH=CH–Br	96:4 (**3**:**12**)	94
4	–C_6H_5	85:15 (**4**:**13**)	69
5	*p*-C_6H_5-Br	95:5 (**5**:**14**)	50
6	–$C(CH_3)_3$	100:0 (**6**:**15**)	70
7	–$CH(C_6H_5)_2$	70:30 (**7**:**16**)	87
8	–CH_2CH_3	83:17 (**8**:**17**)	63
9	–$CH_2CH_2C_6H_5$	86:14 (**9**:**18**)	52

Table 2. Acetate *anti* aldol addition products



Entry	Aldehyde, R-CHO	Auxiliary	Lewis Acid	Ratio anti:syn	Yield (%)
1	*t*-CH=CH–C_6H_5	R_1=i-Pr	$TiCl_4$	82:18 (**10**:**1**)	73
2	*t*-CH=CH–C_6H_5	R_1=i-Pr	$PhBCl_2$	100:0 (**10:1**)	61
3	–CH=$C(CH_3)_2$	R_1=i-Pr	$TiCl_4$	74:26 (**11**:**2**)	60
4	–CH=CH_2	R_1=i-Pr	$TiCl_4$	73:27 (**19**:**20**)	65
5	–C_6H_5	R_1=i-Pr	$TiCl_4$	7:93 (**13**:**4**)	69
6	*p*-C_6H_4-Br	R_1=i-Pr	$TiCl_4$	37:63 (**14**:**5**)	50
7	–$C(CH_3)_3$	R_1=i-Pr	$TiCl_4$	0:100 (**15**:**6**)	70
8	–$C(CH_3)_3$	R_1=i-Pr	$PhBCl_2$	100:0 (**15**:**6**)	54
9	–$CH(C_6H_5)_2$	R_1=i-Pr	$TiCl_4$	40:60 (**16**:**7**)	99
10	–CH_2CH_3	R_1=i-Pr	$TiCl_4$	67:33 (**17**:**8**)	63
11	–$CH_2CH_2C_6H_5$	R_1=i-Pr	$TiCl_4$	64:36 (**18**:**9**)	52
12	–$CH_2CH_2C_6H_5$	R_1=Bn	$TiCl_4$	86:14 (**21**:**22**)	81

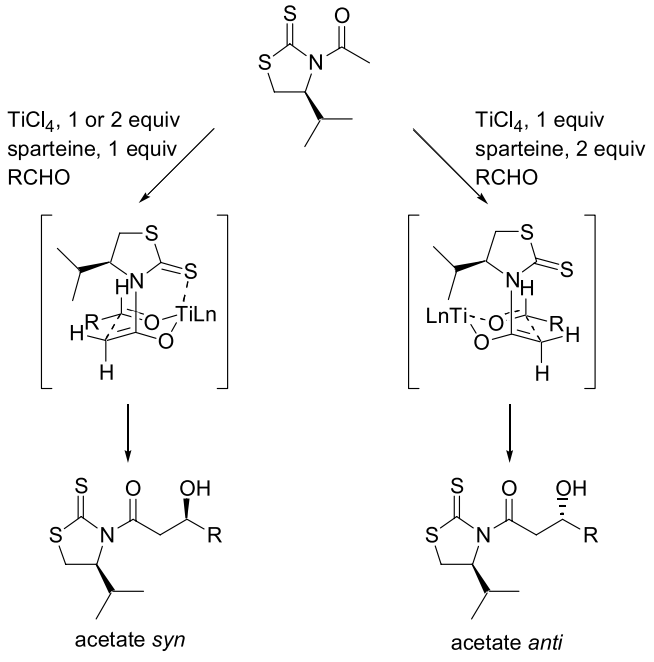


Figure 2. Suggested transition states for the titanium mediated acetate aldol reactions.

diastereomers and their advantages over their oxygen analogs make these sulfur chiral auxiliaries practical in synthesis of natural products.

4. Experimental

4.1. General procedures

General procedure. A solution of *N*-acetyl (4*S*)-isopropylthiazolidinethione (203 mg, 1.0 mmol) in freshly distilled dichloromethane (10 mL) at 0 °C, was treated dropwise with a solution of $TiCl_4$ (1.0 mL, 1 M solution in CH_2Cl_2, 1.0 mmol) under nitrogen atmosphere. The solution was stirred for 5 min and then cooled to −40 °C. A solution of (−)-sparteine (470 mg, 2.0 mmol) in dichloromethane (3 mL) was added via cannula. The reaction mixture was cooled to −78 °C and stirring continued for 35 min. A solution of aldehyde (hydrocinnamaldehyde, 135 mg, 1.0 mmoL) in dichloromethane (3 mL) was transferred via cannula to the reaction mixture, which was then stirred for 15 min at −78 °C. The reaction was quenched with the addition of 1 mL of a half-saturated NH_4Cl solution while stirring. Reaction mixture was warmed to rt and diluted with dichloromethane (20 mL) and washed with 50 mL of a half-saturated NH_4Cl solution. The organic layer was extracted with CH_2Cl_2 (2×20 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated. Separation of the two diastereomers was carried out by flash column chromatography using silica gel (3×15 cm) eluting with petroleum ether/EtOAc (75:25).

4.1.1. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-5-phenyl-pent-4-en-1-one (1). R_f 0.36 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D$=+351.7 (*c* 1.0, $CHCl_3$); IR 3445, 3024, 2965, 1689, 1468, 1363 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (2H, m), 7.37 (2H, m), 7.30 (1H, m), 6.73 (1H, dd, *J*=16.0, 1.1 Hz), 6.33 (1H, dd, *J*=16.0, 5.9 Hz), 5.22 (1H, m), 4.92 (1H, m), 3.79 (1H, dd, *J*=17.5, 3.1 Hz), 3.56 (1H, *J*=11.5, 8.0 Hz), 3.49 (1H, dd, *J*=17.5, 8.7 Hz), 3.08 (1H, dd, *J*=11.5, 1.0 Hz), 2.85 (1H, bs), 2.43 (1H, sext, *J*=6.7 Hz), 1.12 (3H, d, *J*=6.8 Hz), 1.05 (3H, d, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 172.5 (C), 136.6 (C), 130.7 (CH), 130.1 (CH), 128.7 (2CH), 127.9 (CH), 126.7 (2CH), 71.6 (CH), 68.9 (CH), 45.5 (CH_2), 31.0 (CH), 30.8 (CH_2), 19.2 (CH_3), 18.0 (CH_3). ES HRMS *m*/*z* $(M+Na)^+$ calcd 358.0911, obs 358.0925.

4.1.2. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-5-methyl-hex-4-en-1-one (2). R_f 0.45 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D$=+431.4 (*c* 1.0, $CHCl_3$); IR 3437, 2967, 2932, 1689, 1468, 1256, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.25 (1H, d, quint, *J*=8.6, 1.3 Hz), 5.16 (1H, td, *J*=7.0, 1.1 Hz), 4.90 (1H, td, *J*=8.8, 3.0 Hz), 3.54 (1H, dd, *J*=17.7, 3.0 Hz), 3.53 (1H, dd,

J=11.5, 8.0 Hz), 3.31 (1H, dd, J=17.7, 8.9 Hz), 3.04 (1H, dd, J=11.5, 1.0 Hz), 2.65 (1H, bs), 2.38 (1H, sext, J=6.7 Hz), 1.74 (3H, d, J=1.3 Hz), 1.72 (3H, d, J=1.3 Hz), 1.08 (3H, d, J=6.9 Hz), 0.99 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 172.9 (C), 136.2 (C), 125.7 (CH), 71.6 (CH) 65.3 (CH), 45.8 (CH_2), 31.0 (CH), 30.8 (CH_2), 25.9 (CH_3), 19.2 (CH_3), 18.5 (CH_3), 17.9 (CH_3). ES HRMS m/z $(M-H_2O)^+$ calcd 270.0986, obs 270.0985.

4.1.3. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-7-bromo-hepta-4,6-diene-1-one (3). R_f 0.32 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D$=+292.2 (c 1.0, $CHCl_3$); IR 3437, 3058, 1690, 1470, 1168 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.72 (1H, dd, J=13.3, 11.0 Hz), 6.35 (1H, d, J=13.3 Hz), 6.26 (1H, ddd, J=15.3, 11.0, 1.2 Hz), 5.80 (1H, dd, J=15.3, 5.6 Hz), 5.17 (1H, t, J=6.8 Hz), 4.70 (1H, m), 3.69 (1H, dd, J=17.8, 3.1 Hz), 3.53 (1H, dd, J=11.5, 7.9 Hz), 3.29 (1H, dd, J=17.6, 8.6 Hz), 3.05 (1H, d, J=11.5 Hz), 2.97 (1H, bs), 2.36 (1H, sext., J=6.8 Hz), 1.07 (3H, d, J=6.7 Hz), 0.99 (3H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 203.0 (C), 172.2 (C), 136.6 (CH), 134.6 (CH), 127.8 (CH), 109.5 (CH), 71.3 (CH), 67.9 (CH), 45.0 (CH_2), 31.0 (CH), 30.7 (CH_2), 19.0 (CH_3), 17.8 (CH_3).

4.1.4. 1-[(4*S*)-4-Isopropyl-2-thioxo-thiazolidine-3-yl]-(3*R*)-hydroxy-4-phenyl-propanone (4). R_f 0.45 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D$=+386.7 (c 1.0, $CHCl_3$); IR 3476, 2965, 1682, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–7.37 (4H, m), 7.32 (1H, m), 5.30 (1H, dd, J=9.3, 2.8 Hz), 5.16 (1H, t, J=7.0 Hz), 3.82 (1H, ddd, J=17.5, 2.7, 0.8 Hz), 3.63 (1H, dd, J=17.5, 9.3 Hz), 3.51 (1H, ddd, J=11.6, 8.0, 0.6 Hz), 3.22 (1H, t, J=3.2 Hz), 3.05 (1H, d, J=11.6 Hz), 2.40 (1H, sext, J=6.7 Hz), 1.10 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 172.7 (C), 142.6 (C), 128.7 (2CH), 127.9 (CH), 125.9 (2CH), 71.6 (CH), 70.3 (CH), 47.0 (CH_2), 31.0 (CH), 30.9 (CH_2), 19.2 (CH_3), 18.0 (CH_3). ES HRMS m/z $(M+Na)^+$ calcd 332.0755, obs 332.0754.

4.1.5. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-4-(*p*-bromophenyl)-propan-1-one (5). R_f 0.40 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D$=+317.7 (c 1.0, $CHCl_3$); mp 100–102 °C; IR 3468, 2955, 1686, 1359, 1300, 1243, 1219, 1157, 1008 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50 (2H, d, J=8.5 Hz), 7.29 (2H, d, J=8.5 Hz), 5.27 (1H, dd, J=9.4, 2.7 Hz), 5.16 (1H, dd, J=7.6, 6.6 Hz), 3.82 (1H, dd, J=17.6, 2.7 Hz), 3.51 (1H, ddd, J=11.5, 7.8, 1.5 Hz), 3.50 (1H, ddd, J=17.6, 9.4 Hz), 3.05 (1H, dd, J=11.5, 1.1 Hz), 2.73 (1H, bs), 2.38 (1H, sext, J=6.7 Hz), 1.08 (3H, d, J=6.8 Hz), 1.00 (3H, d, J=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 172.3 (C), 141.5 (C), 131.6 (2CH), 127.6 (2CH), 121.5 (C), 71.5 (CH), 69.6 (CH), 46.8 (CH_2), 30.9 and 30.7 (CH and CH_2), 19.1 (CH_3), 17.8 (CH_3). ES HRMS m/z $(M-H_2O+H)^+$ calcd 369.9935, obs 369.9930.

4.1.6. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-4,4-dimethyl-pentan-1-one (6). R_f 0.42 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D$=+454.5 (c 1.0, $CHCl_3$); IR 3524, 2961, 1686, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.16 (1H, t, J=7.0 Hz), 3.83 (1H, ddd, J=10.4, 3.9, 1.8 Hz), 3.62 (1H, dd, J=17.7, 2.0 Hz), 3.53 (1H, dd, J=11.4, 8.0 Hz), 3.15 (1H, dd, J=17.7, 10.5 Hz), 3.03 (1H, dd, J=11.5, 1.0 Hz), 2.67 (1H, J=3.8 Hz), 2.38 (1H, sext, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=7.0 Hz), 0.95 (9H, s); ^{13}C NMR ($CDCl_3$) δ 203.4 (C), 174.2 (C), 75.4 (CH), 71.7 (CH), 41.2 (CH_2), 34.7 (C), 31.1 (CH), 30.8 (CH_2), 26.0 ($3CH_3$), 19.3 (CH_3), 18.0 (CH_3).

4.1.7. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-4,4-diphenyl-butan-1-one (7). R_f 0.30 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D$=+271.0 (c 1.0, $CHCl_3$); IR 3548, 3022, 2965, 1688, 1457, 1163 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.15 (10H, m), 5.10 (1H, t, J=6.7 Hz), 4.96 (1H, td, J=9.0, 2.4 Hz), 4.00 (1H, d, J=8.7 Hz), 3.48 (1H, dd, J=11.4, 7.9 Hz), 3.45 (1H, dd, J=17.6, 2.6 Hz), 3.29 (1H, dd, J=17.6, 9.2 Hz), 2.99 (1H, dd, J=11.4, 1.0 Hz), 2.67 (1H, bs), 2.33 (1H, sext, J=6.7 Hz), 1.02 (3H, d, J=6.7 Hz), 0.94 (3H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 203.0 (C), 172.8 (C), 141.9 (C), 141.2 (C), 128.9 (2CH), 128.8 (2CH), 128.7 (2CH), 128.4 (2CH), 126.8 (2CH), 71.6 (CH), 70.4 (CH), 57.6 (CH), 44.2 (CH_2), 31.0 (CH_3), 30.7 (CH_2), 19.2 (CH_3), 17.9 (CH_3). ES HRMS m/z $(M+H)^+$ calcd 400.1405, obs 400.1413.

4.1.8. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-pentan-1-one (8). R_f 0.42 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D$=+470.1 (c 1.0, $CHCl_3$); IR 3456, 2964, 2876, 1689, 1466, 1165, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.17 (1H, t, J=6.8 Hz), 4.07 (1H, m), 3.65 (1H, dd, J=17.8, 2.3 Hz), 3.53 (1H, dd, J=11.5, 7.8 Hz), 3.12 (1H, dd, J=17.8, 9.5 Hz), 3.04 (1H, d, J=11.5 Hz), 2.69 (1H, bs), 2.37 (1H, sext, J=6.8 Hz), 1.68–1.47 (2H, m), 1.07 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=6.7 Hz), 0.98 (3H, t, J=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 173.4 (C), 71.5 (CH), 69.4 (CH), 45.2 (CH_2), 31.0 (CH), 30.7 (CH_2), 29.4 (CH_2), 19.2 (CH_3), 18.0 (CH_3), 10.1 (CH_3).

4.1.9. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-5-phenyl-pentan-1-one (9). R_f 0.42 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D$=+321.7 (c 1.0, $CHCl_3$); IR 3519, 3023, 2961, 1686, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38–7.17 (5H, m), 5.17 (1H, m), 4.15 (1H, m), 3.67 (1H, dd, J=17.8, 2.5 Hz), 3.53 (1H, dd, J=11.5, 8.0 Hz), 3.18 (1H, dd, J=17.8, 9.2 Hz), 3.04 (1H, dd, J=11.5, 1.0 Hz), 2.97–2.68 (3H, m), 2.37 (1H, sext, J=6.7 Hz), 1.98–1.75 (2H, m), 1.08 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 173.1 (C), 141.8 (C), 128.5 (2CH), 128.4 (2CH), 125.9 (CH), 71.4 (CH), 67.2 (CH), 45.6 (CH_2), 37.9 (CH_2), 31.8 (CH_2), 30.9 (CH), 30.6 (CH_2), 19.1 (CH_3), 17.8 (CH_3). ES HRMS m/z $(M+Na)^+$ calcd 360.1068, obs 360.1060.

4.1.10. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-5-phenyl-pent-4-en-1-one (10). R_f 0.48 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D$=+301.5 (c 1.0, $CHCl_3$); IR 3458, 3014, 2966, 1686, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (2H, m), 7.32 (2H, m), 7.24 (1H, m), 6.67 (1H, d, J=15.8 Hz), 6.27 (1H, dd, J=15.8, 5.9 Hz), 5.19 (1H, m), 4.78 (1H, m), 3.73 (1H, dd, J=17.4, 8.8 Hz), 3.52 (1H, J=11.5, 8.0 Hz), 3.48 (1H, dd, J=17.4, 3.5 Hz), 3.34 (1H, bs), 3.04 (1H, dd, J=11.5, 1.0 Hz), 2.37 (1H, sext, J=6.7 Hz), 1.07 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 172.9 (C), 136.7 (C), 130.9 (CH), 130.2 (CH), 128.7 (2CH), 127.9 (CH), 126.7 (2CH), 71.6 (CH), 69.4 (CH), 45.3 (CH_2), 30.9 (CH), 30.8 (CH_2),

19.3 (CH_3), 18.0 (CH_3). ES HRMS *m/z* $(M+Na)^+$ calcd 358.0911, obs 358.0925.

4.1.11. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-5-methyl-hex-4-en-1-one (11). R_f 0.53 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D=+257.3$ (*c* 1.0, $CHCl_3$); IR 3436, 2966, 2875, 1686, 1468, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.25 (1H, d, quint, $J=8.7$, 1.4 Hz), 5.18 (1H, td, $J=7.2$, 1.0 Hz), 4.81 (1H, td, $J=8.8$, 3.4 Hz), 3.57 (1H, dd, $J=17.4$, 8.8 Hz), 3.53 (1H, dd, $J=11.5$, 8.0 Hz), 3.31 (1H, dd, $J=17.4$, 3.4 Hz), 3.13 (1H, bs), 3.05 (1H, dd, $J=11.5$, 0.8 Hz), 2.37 (1H, sext, $J=6.7$ Hz), 1.73 (3H, d, $J=1.2$ Hz), 1.70 (3H, d, $J=1.2$ Hz), 1.07 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 173.4 (C), 136.1 (C), 125.9 (CH), 71.5 (CH) 65.6 (CH), 45.6 (CH_2), 30.9 (CH), 30.7 (CH_2), 25.9 (CH_3), 19.3 (CH_3), 18.5 (CH_3), 17.9 (CH_3). ES HRMS *m/z* $(M-H_2O+H)^+$ calcd 270.0992, obs 270.0986.

4.1.12. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-7-bromo-hepta-4,6-diene-1-one (12). R_f 0.42 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+312.8$ (*c* 1.0, $CHCl_3$); IR 3436, 2965, 2874, 1685, 1468, 1163, 979 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74 (1H, dd, $J=13.5$, 10.9 Hz), 6.38 (1H, d, $J=13.5$ Hz), 6.28 (1H, dd, $J=15.2$, 10.9 Hz), 5.82 (1H, dd, $J=15.2$, 5.5 Hz), 5.21 (1H, m), 4.65 (1H, m), 3.66 (1H, dd, $J=17.4$, 8.9 Hz), 3.56 (1H, dd, $J=11.6$, 8.0 Hz), 3.41 (1H, dd, $J=17.46$, 3.3 Hz), 3.08 (1H, d, $J=11.5$ Hz), 2.66 (1H, bs), 2.38 (1H, sext., $J=6.9$ Hz), 1.10 (3H, d, $J=6.8$ Hz), 1.01 (3H, d, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 172.8 (C), 136.8 (CH), 134.9 (CH), 128.1 (CH), 109.7 (CH), 71.5 (CH), 68.5 (CH), 44.9 (CH_2), 30.9 (CH), 30.8 (CH_2), 19.3 (CH_3), 18.0 (CH_3).

4.1.13. 1-[(4*S*)-4-Isopropyl-2-thioxo-thiazolidine-3-yl]-(3*S*)-hydroxy-4-phenyl-propanone (13). R_f 0.23 (4:1, petroleum ether/ethyl acetate); $[\alpha]_D=+279.2$ (*c* 1.0, $CHCl_3$); mp 88–95 C; IR 3494, 2965, 1689, 1279, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41–7.26 (4H, m), 5.17 (2H, m), 3.84 (1H, dd, $J=17.4$, 9.5 Hz), 3.58 (1H, dd, $J=17.4$, 3.1 Hz), 3.58 (1H, m), 3.49 (1H, dd, $J=11.5$, 8.0 Hz), 3.03 (1H, dd, $J=11.5$, 1.0 Hz), 2.36 (1H, sext, $J=6.8$ Hz), 1.06 (3H, d, $J=6.9$ Hz), 0.99 (3H, d, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 173.1 (C), 142.6 (C), 128.7 (2CH), 127.9 (CH), 126.1 (2CH), 71.6 (CH), 70.9 (CH), 46.9 (CH_2), 30.9 (CH), 30.8 (CH_2), 19.2 (CH_3), 18.0 (CH_3). ES HRMS *m/z* $(M-H_2O+H)^+$ calcd 292.0830, obs 292.0824.

4.1.14. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-4-(*p*-bromophenyl)-propan-1-one (14). R_f 0.53 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D=+236.4$ (*c* 1.0, $CHCl_3$); mp 103–105 °C; IR 3415, 2964, 1698, 1343, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (2H, d, $J=8.5$ Hz), 7.27 (2H, d, $J=8.5$ Hz), 5.18 (1H, t, $J=7.0$ Hz), 5.11 (1H, dt, $J=9.5$, 3.4 Hz), 3.79 (1H, dd, $J=17.5$, 9.5 Hz), 3.68 (1H, d, $J=3.6$ Hz), 3.53 (1H, dd, $J=17.5$, 3.1 Hz), 3.51 (1H, dd, $J=11.6$, 8.0 Hz), 3.05 (1H, d, $J=11.6$ Hz), 2.35 (1H, sext, $J=6.8$ Hz), 1.06 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.3 (C), 172.9 (C), 141.6 (C), 131.8 (2CH), 127.8 (2CH), 121.7 (C), 71.5 (CH), 70.2 (CH), 46.8 (CH_2), 30.9 (CH), 30.8 (CH_2), 19.2 (CH_3), 18.0 (CH_3). ES HRMS *m/z* $(M-H_2O+H)^+$ calcd 369.9935, obs 369.9932.

4.1.15. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-4,4-dimethyl-pentan-1-one (15). R_f 0.59 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+302.3$ (*c* 1.0, $CHCl_3$); IR 3539, 2961, 1686, 1158, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (1H, t, $J=6.9$ Hz), 3.72 (1H, ddd, $J=10.5$, 4.8, 2.0 Hz), 3.53 (1H, dd, $J=16.7$, 10.5 Hz), 3.52 (1H, dd, $J=11.5$, 8.0 Hz), 3.31 (1H, dd, $J=16.7$, 2.0 Hz), 3.21 (1H, d, $J=4.9$ Hz), 3.04 (1H, dd, $J=11.5$, 1.1 Hz), 2.37 (1H, sext, $J=6.8$ Hz), 1.07 (3H, d, $J=6.7$ Hz), 0.99 (3H, d, $J=6.7$ Hz), 0.93 (9H, s); ^{13}C NMR ($CDCl_3$) δ 203.6 (C), 174.6 (C), 76.4 (CH), 71.7 (CH), 40.5 (CH_2), 34.9 (C), 30.9 (CH), 30.7 (CH_2), 26.0 ($3CH_3$), 19.3 (CH_3), 18.0 (CH_3). ES HRMS *m/z* $(M-H_2O+H)^+$ calcd 272.1143, obs 272.1151.

4.1.16. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-4,4-diphenyl-butan-1-one (16). R_f 0.30 (8:2, petroleum ether/ethyl acetate); $[\alpha]_D=+191.9$ (*c* 1.0, $CHCl_3$); IR 3567, 3018, 2968, 1684, 1362, 1217, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.11 (10H, m), 5.08 (1H, t, $J=7.1$ Hz), 4.87 (1H, m), 4.02 (1H, d, $J=8.7$ Hz), 3.61 (1H, dd, $J=17.2$, 9.4 Hz), 3.36 (1H, dd, $J=11.5$, 8.0 Hz), 3.24 (1H, dd, $J=17.2$, 2.8 Hz), 3.10 (1H, d, $J=4.0$ Hz), 2.92 (1H, dd, $J=11.5$, 1.0 Hz), 2.30 (1H, sext, $J=6.6$ Hz), 1.00 (3H, d, $J=6.7$ Hz), 0.93 (3H, d, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 173.1 (C), 141.9 (C), 141.2 (C), 128.9 (2CH), 128.8 (2CH), 128.6 (2CH), 128.5 (2CH), 126.9 (CH), 126.8 (CH), 71.5 (CH), 70.8 (CH), 57.9 (CH), 43.9 (CH_2), 30.8 (CH_3), 30.5 (CH_2), 19.2 (CH_3), 17.8 (CH_3).

4.1.17. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-pentan-1-one (17). R_f 0.42 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+313.3$ (*c* 1.0, $CHCl_3$); IR 3441, 2964, 2876, 1685, 1466, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.19 (1H, ddd, $J=7.7$, 6.3, 1.1 Hz), 3.97 (1H, m), 3.53 (1H, dd, $J=11.5$, 7.9 Hz), 3.46 (1H, dd, $J=17.5$, 9.1 Hz), 3.34 (1H, dd, $J=17.4$, 3.0 Hz), 3.25 (1H, bs), 3.05 (1H, d, $J=11.5$ Hz), 2.37 (1H, sext, $J=6.8$ Hz), 1.67–1.49 (2H, m), 1.07 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=6.8$ Hz), 0.98 (3H, t, $J=7.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.3 (C), 173.9 (C), 71.5 (CH), 69.9 (CH), 44.8 (CH_2), 30.9 (CH_2), 30.7 (CH), 29.6 (CH_2), 19.2 (CH_3), 17.8 (CH_3), 10.0 (CH_3). ES HRMS *m/z* $(M-H_2O+H)^+$ calcd 244.0830, obs 244.0822.

4.1.18. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-5-phenyl-pentan-1-one (18). R_f 0.44 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+197.6$ (*c* 1.0, $CHCl_3$); IR 3437, 3025, 2962, 1686, 1167 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–7.17 (5H, m), 5.18 (1H, m), 4.06 (1H, m), 3.53 (1H, dd, $J=17.8$, 9.4 Hz), 3.52 (1H, dd, $J=11.6$, 8.0 Hz), 3.33 (1H, dd, $J=17.6$, 2.7 Hz), 3.05 (1H, dd, $J=11.6$, 1.0 Hz), 2.90–2.68 (2H, m), 2.37 (1H, sext, $J=6.7$ Hz), 2.22 (1H, bs), 1.99–1.73 (2H, m), 1.08 (3H, d, $J=6.7$ Hz), 0.99 (3H, d, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 173.7 (C), 141.9 (C), 128.6 (2CH), 128.4 (2CH), 125.9 (CH), 71.4 (CH), 67.7 (CH), 45.3 (CH_2), 38.2 (CH_2), 31.8 (CH_2), 30.8 (CH), 30.7 (CH_2), 19.2 (CH_3), 17.9 (CH_3).

4.1.19. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-pent-4-en-1-one (19). R_f 0.33 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+354.1$ (*c* 1.0, $CHCl_3$); IR 3436, 2965, 1685, 1364, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (1H, ddd, $J=17.2$, 10.5,

5.4 Hz), 5.34 (1H, dt, $J=17.2$, 1.5 Hz), 5.19 (1H, m), 5.16 (1H, m), 4.60 (1H, m), 3.64 (1H, dd, $J=17.4$, 8.9 Hz), 3.54 (1H, dd, $J=11.6$, 6.6 Hz), 3.40 (1H, dd, $J=17.4$, 3.4 Hz), 3.06 (1H, dd, $J=11.6$, 1.1 Hz), 2.83 (1H, bs), 2.37 (1H, m), 1.08 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 173.0 (C), 138.9 (CH), 115.6 (CH_2), 71.5 (CH), 69.4 (CH), 45.0 (CH_2), 30.9 (CH), 30.8 (CH_2), 19.2 (CH_3), 18.0 (CH_3).

4.1.20. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-pent-4-en-1-one (20). R_f 0.27 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+340.7$ (*c* 1.0, $CHCl_3$); IR 3442, 2964, 1691, 1363, 1168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (1H, ddd, $J=17.3$, 10.5, 5.3 Hz), 5.33 (1H, dt, $J=17.3$, 1.5 Hz), 5.17 (1H, m), 5.14 (1H, m), 4.67 (1H, m), 3.65 (1H, dd, $J=17.7$, 3.0 Hz), 3.54 (1H, dd, $J=11.6$, 8.0 Hz), 3.31 (1H, dd, $J=17.7$, 8.8 Hz), 3.04 (1H, dd, $J=11.6$, 1.0 Hz), 2.79 (1H, bs), 2.37 (1H, m), 1.07 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 172.5 (C), 138.9 (CH), 115.4 (CH_2), 71.5 (CH), 68.9 (CH), 45.2 (CH_2), 30.9 (CH), 30.8 (CH_2), 19.2 (CH_3), 17.9 (CH_3).

4.1.21. 1-[(4*S*)-Benzyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-5-phenyl-pentan-1-one (21). R_f 0.48 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+138.5$ (*c* 1.0, $CHCl_3$); IR 3547, 3026, 2927, 1685, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47–7.02 (10H, m), 5.39 (1H, m), 4.06 (1H, m), 3.51 (1H, dd, $J=17.5$, 9.1 Hz), 3.38 (1H, dd, $J=11.4$, 7.2 Hz), 3.31 (1H, dd, $J=17.5$, 2.4 Hz), 3.24 (1H, d, $J=3.0$ Hz), 3.21 (1H, dd, $J=13.5$, 4.1 Hz), 3.03 (1H, dd, $J=13.2$, 10.4 Hz), 2.89 (1H, d, $J=11.6$ Hz), 2.88–2.68 (2H, m), 1.98–1.72 (2H, m); ^{13}C NMR ($CDCl_3$) δ 201.6 (C), 173.8 (C), 141.9 (C), 136.5 (C), 129.6 (2CH), 129.1 (2CH), 128.7 (2CH), 128.5 (2CH), 127.4 (CH), 126.0 (CH), 68.3 (CH), 67.7 (CH), 45.7 (CH_2), 38.3 (CH_2), 37.0 (CH_2), 32.2 (CH), 31.8 (CH_2). ES HRMS *m/z* $(M+H)^+$ calcd 386.1248, obs 386.1242.

4.1.22. 1-[(4*S*)-Benzyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-5-phenyl-pentan-1-one (22). R_f 0.35 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+190.6$ (*c* 1.0, $CHCl_3$); IR 3554, 3025, 2927, 1689, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36–7.16 (10H, m), 5.38 (1H, m), 4.15 (1H, m), 3.67 (1H, dd, $J=17.8$, 2.3 Hz), 3.38 (1H, dd, $J=11.6$, 7.2 Hz), 3.20 (1H, dd, $J=13.1$, 4.1 Hz), 3.16 (1H, dd, $J=17.8$, 9.4 Hz), 3.03 (1H, dd, $J=13.1$, 10.3 Hz), 2.88 (1H, d, $J=11.6$ Hz), 2.85–2.67 (3H, m), 1.98–1.74 (2H, m); ^{13}C NMR ($CDCl_3$) δ 201.5 (C), 173.3 (C), 141.9 (C), 136.5 (C), 129.6 (2CH), 129.1 (2CH), 128.6 (2CH), 128.5 (2CH), 127.5 (CH), 126.0 (CH), 68.4 (CH), 67.2 (CH), 46.1 (CH_2), 38.0 (CH_2), 37.0 (CH_2), 32.2 (CH), 32.0 (CH_2). ES HRMS *m/z* $(M+Na)^+$ calcd 408.1068, obs 408.1087.

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