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Rearrangement of oxazolidinethiones to thiazolidinediones or thiazinanediones and their application for the synthesis of chiral allylic ureas and α-methyl-β-amino acids

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ABSTRACT

A novel rearrangement has been found between oxazolidinethiones and acyl halides under N-acylation reaction conditions to afford *N*-substituted 2,4-thiazolidinediones and *N*-substituted 1,3-thiazinane-2,4-diones. These heterocycles were used for the synthesis of chiral allylic ureas and α-methyl-β-amino acids.

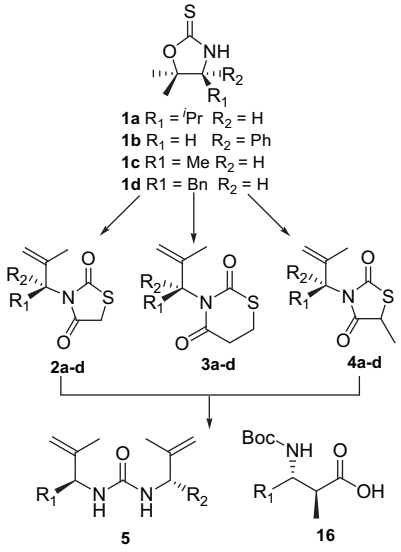
1. Introduction

Chiral oxazolidinethiones have been widely used as chiral auxiliaries in the asymmetric synthesis of complex natural products. The preparation and applications of chiral oxazolidinethiones in asymmetric synthesis have been covered in previous reviews.[1] A new series of reactions have been recently described employing chiral oxazolidinethiones such as the asymmetric intramolecular sulfur transfer reaction carried out on di-, tri-substituted α,β-unsaturated *N*-enoyl oxazolidinethiones, and β,β-disubstituted *N*-enoyl oxazolidinethiones to afford chiral β-sulfanyl carboxylic acid derivatives, β-sulfanyl alcohols,[2] 3-methylthioalcohols,[3] β,β-disubstituted β-sulfanyl carboxylic esters, and 1,3-hydroxythiols,[4] with high degrees of stereocontrol. Two tandem Michael-aldol reactions were described also, carried out on *N*-enoyl oxazolidinethiones to afford unusual heterotricyclic compounds[5] and 3-sulfanylpropanols[6] both with three consecutive chiral centers. Most significant, *N*-enoyl oxazolidinethiones can be arranged to *N*-substituted 1,3-thiazinane-2,4-diones with one or two new chiral centers.[7]

We had previously described an interesting reaction observed during the attempted attachment of oxazolidinethiones to bromoacetyl bromide, under *N*-acyl reaction conditions, to provide five-membered ring heterocycles of *N*-substituted 2,4-thiazolidinediones[8] type.

2. Results and discussion

We now report that the reaction described above proved to be successful for five- and six-membered rings' formation, giving good yields of 2,4-thiazolidinediones (**2a–d**), 1,3-thiazinane-2,4-diones (**3a–d**), and 5-methylthiazolidine-2,4-diones (**4a–d**) and their application to yield chiral ureas and α-methyl-β-amino acids, as shown in Scheme 1.



Scheme 1. Versatility of the oxazolidinethiones.

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Four chiral auxiliaries of oxazolidinethione (**1a–d**) type were easily prepared from their corresponding α-amino acids through a series of transformations described by Davies.[9] The condensation of their respective β-amino alcohols with CS_2 in an aqueous solution of Na_2CO_3 furnished compounds (**1a–d**) in good yields as shown in Figure 1. Furthermore, the physical and spectroscopic characterizations for compounds **1a–c** were completed. Compound **1d** had been previously described.[10]

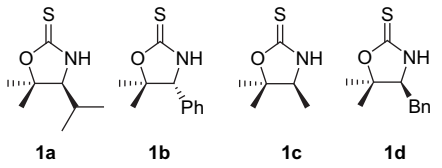
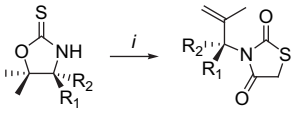


Figure 1. Oxazolidinethione derivatives from α-amino acids.

Oxazolidinethiones (**1a–d**) were treated with NaH in CH_2Cl_2 followed by dropwise addition of bromoacetyl bromide at 0 °C to afford the *N*-substituted 2,4-thiazolidinediones (**2a–d**) in moderate yields (40–67%). In all cases, the thiazolidinediones (**2a–d**) were dense liquids. The presence of disubstituted terminal olefins was confirmed by ^1H and ^{13}C NMR spectroscopy. Further, the presence of isopropyl group in oxazolidinethione **1a** has a significant influence on the reaction outcome. The thiazolidinedione **2a** was achieved with the best yield and it was easily purified, as shown in Scheme 2 and Table 1.



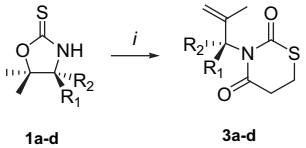
Scheme 2. (*i*) NaH, 0 °C, CH_2Cl_2, $BrCOCH_2Br$.

Table 1
Conversion of oxazolidinethiones to 2,4-thiazolidinediones

Entry	Product	R_1	R_2	Yield[a] (%)	$[\alpha]_D^{25}$ (*c*)[b]
1	**2a**	^{i}Pr	H	67.0	−45.9 (2.00)
2	**2b**	H	Ph	60.0	−14.8 (2.05)
3	**2c**	Me	H	40.0	+1.52 (1.42)
4	**2d**	Bn	H	48.0	−151.6 (0.96)

[a] Purified yield.
[b] Determined in $CHCl_3$ at 25 °C.

The methodology described above was successful for the achievement of the six-membered rings of 1,3-thiazinane-2,4-diones type too. Their synthesis was achieved through the reaction of oxazolidinethiones (**1a–d**) with NaH in CH_2Cl_2 followed by dropwise addition of 3-bromopropionyl chloride at 0 °C to afford the 1,3-thiazinane-2,4-diones (**3a–d**) in moderate yields (23–78%), Scheme 3. The oxazolidinethiones **1a** and **1b** gave the best results to produce five- and six-membered rings, as shown in Tables 1 and 2.



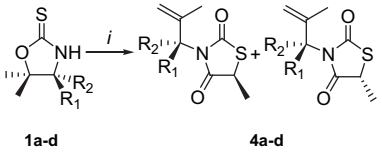
Scheme 3. (*i*) NaH, 0 °C, CH_2Cl_2, $BrCH_2CH_2COCl$.

Table 2
Conversion of oxazolidinethiones to 1,3-thiazinane-2,4-diones

Entry	Product	R_1	R_2	Yield[a] (%)	$[\alpha]_D^{25}$ (*c*)[b]
1	**3a**	^{i}Pr	H	70.0	−122.0 (1.08)
2	**3b**	H	Ph	78.0	−6.0 (0.9)
3	**3c**	Me	H	23.0	−89.5 (1.41)
4	**3d**	Bn	H	53.0	−162.1 (1.7)

[a] Purified yield.
[b] Determined in $CHCl_3$ at 25 °C.

5-Methyl-2,4-thiazolidinethiones (**4a–d**) were obtained as diastereomeric mixtures by reaction of oxazolidinethiones (**1a–d**) with an excess of racemic 2-bromopropionyl bromide under *N*-acyl reaction conditions. The diastereomeric mixture was formed because the structure of compounds (**4a–d**) has an asymmetric center at the C-5 position in the thiazolidine ring. We were however unable to separate these diastereomeric mixtures by column chromatography. A rapid analysis of the ^1H NMR spectra showed signals for a single diastereomer only, however, an analysis by HPLC showed that the diastereomeric ratios for compounds **4a–d** were 50/50 (Scheme 4, Table 3).



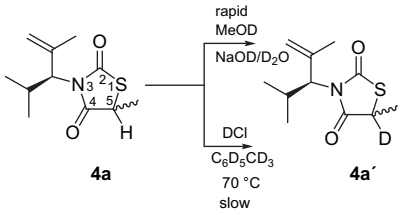
Scheme 4. (*i*) NaH, 0 °C, CH_2Cl_2, $BrCOCH_3CHBr$.

Table 3
Conversion of oxazolidinethiones to 5-methyl-2,4-thiazolidinediones

Entry	Product	R_1	R_2	Yield[a] (%)	$[\alpha]_D^{25}$ (*c*)[b]
1	**4a**	^{i}Pr	H	70.0	−33.4 (3.86) −33.1 (1.84)
2	**4b**	H	Ph	60.0	−33.9 (1.7)
3	**4c**	Me	H	50.0	−81.0 (1.2)
4	**4d**	Bn	H	67.0	−153.1 (2.0)

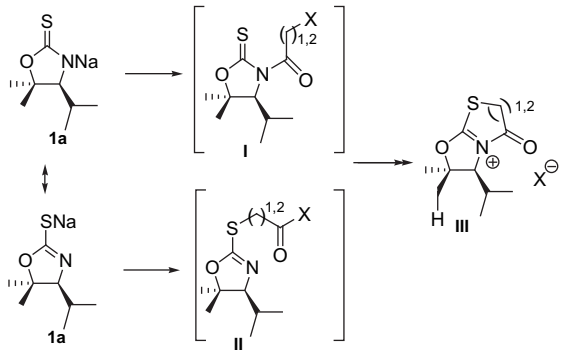
[a] Purified yield.
[b] Determined in $CHCl_3$ at 25 °C, value corresponding to mixture of diastereomers.

The reaction of oxazolidinethione **1a** with (*S*)-2-bromopropionyl bromide was explored under the same reaction conditions, which afforded compound **4a** again as a diastereomeric mixture. This result can be explained on the basis of an in situ racemization, because of basic reaction conditions employed. Interestingly, thiazolidinedione heterocycles have been the subject of extensive researches due to their important antidiabetic activity. These contain a stereogenic center at the C-5 position in the 2,4-thiazolidinethione ring and this stereogenic center has been claimed to undergo rapid racemization under physiological conditions.[11] In order to further characterize this peculiar behavior, compound **4a** was exposed under reaction conditions for isotopic exchange; first, **4a** was treated with a 40% solution of D_2O/NaOD in CH_3OD, this mixture provided a rapid exchange of α-hydrogen by deuterium at C-5: after 10 min, isotopic exchange was completed, giving **4a′**. In a second experiment, **4a** was treated with DCl in $C_6D_5CD_3$. By heating the mixture at 70 °C, completed deuteration was observed. In general compound **4a** showed a slow tautomeric equilibrium keto–enol, which can be catalyzed in basic or acid media, as shown in Scheme 5.



Scheme 5. Isotopic exchange reactions on compound **4a**.

The obtaining of five- and six-membered rings, in compounds **2**, **3**, and **4a–d** can be explained by previous formation of the α,β-bromoamide **I** or *S*-alkylated compound **II**, and both could give the immonium **III** by an intramolecular nucleophilic substitution reaction or an N-acylation reaction. The formation of the double bonds on heterocycles **2**, **3**, and **4a–d** could be presumably due to the presence of halides; the immonium **III** could loss an unusual acid hydrogen atom provoking the opening of bicycle **III**, as shown in Scheme 6.



Scheme 6. Possible course of the reaction from **1a** to **3a**.

Both heterocycle types **2**, **3**, and **4**(**a**–**d**) can be transformed to the unexpected allylic ureas **5**(**a**, **b**, **d**) by treatment with KOH in THF/H_2O. The chiral ureas[12] **5**(**a**, **b**, **d**) were synthesized in good yields (70–80%) as crystalline solids, as shown in Figure 2. The chiral ureas derived from the heterocycles **2c**, **3c** or **4c** were not obtained because of their low yield.

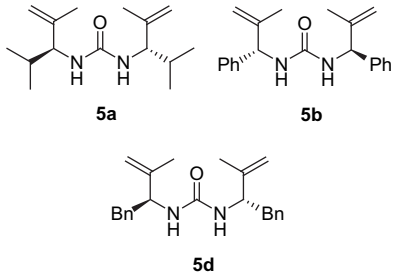


Figure 2. Chiral ureas bearing disubstituted terminal olefins.

The structure of compounds **5**(**a**, **b**, **d**) was established by ^{1}H NMR, ^{13}C NMR, and EM spectroscopy and confirmed by X-ray analysis[13] on compound **5d** as shown in Figure 3. This molecule approximates a C_2 symmetry in the solid state.

The obtaining of chiral symmetric ureas can be explained by in situ previous formation of the amine **I**, from the basic hydrolysis of **2a**, followed by a subsequent nucleophilic addition of **I** to **2a** to afford the non-detected 2-iminothiazolidin-4-one derivative[14] **II**, which could lead to urea **5a** by subsequent basic hydrolysis, as shown in Scheme 7.

Compounds **2a–d** and **4a–d** were hydroborated with 9-BBN, followed by an oxidation with peroxide to yield a diastereomeric

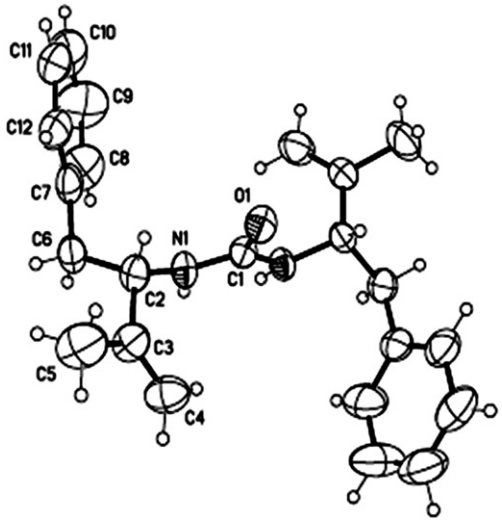
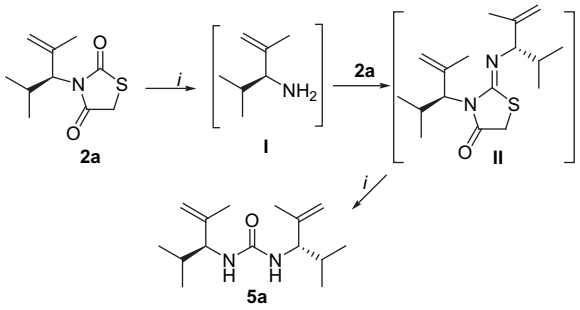
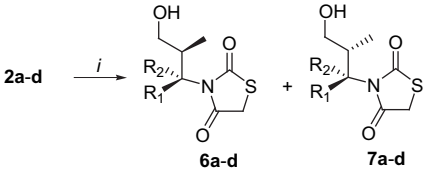


Figure 3. Molecular structure of the bis-allylurea **5d**.



Scheme 7. Possible course of the reaction from **2a** to **5a**. Reagents: (*i*) KOH, THF, H_2O.

mixture of *syn*- and *anti*-alcohols.[15] Compounds **2a–d** exposed to reaction conditions described above provided the *syn*-alcohols **6a–d** and *anti*-alcohols **7a–d** in 63–80% yield. Both alcohols **6a–d** and **7a–d** were separated by column chromatography on silica using hexane/ethyl acetate (8/2) as eluent and their diastereomeric ratios were determined by net weight of the diastereoisomers isolated. In all cases *syn*-alcohols were formed predominantly as shown in Scheme 8 and Table 4.



Scheme 8. Reagents: (*i*) 9-BBN, THF, rt, 24 h, EtOH, buffer of phosphates pH 7, peroxide, 24 h, Na_2SO_3.

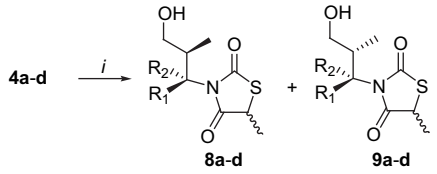
Table 4
Hydroboration–oxidation of compounds **2**(**a**–**d**)

Entry	Starting material	R_1	R_2	Yield[a] (%) **6**/**7**	*syn*/*anti* **6**/**7**
1	**2a**	^{i}Pr	H	80	60/40
2	**2b**	H	Ph	72	21/79[b]
3	**2c**	Me	H	63	73/27
4	**2d**	Bn	H	58	76/24

[a] Yields of diastereoisomer mixture.
[b] The major diastereoisomer is *syn*, compound **7b**.

When the diastereomeric mixtures of compounds **4a–d** were exposed to hydroboration–oxidation conditions, a mixture of *syn*-alcohols **8a–d** and *anti*-alcohols **9a–d** was obtained in 32–80%

yields. Both alcohols were isolated easily by column chromatography and their diastereomeric ratios were determined by net weight of the diastereomers. However, each *syn*- and *anti*-alcohol has a mixture of non-separable epimers because of the stereogenic center at C-5 of thiazolidinone ring, as detected by NMR and HPLC. Enhanced bulk on thiazolidinodione ring in compounds **4a–d** provided an increase of *syn*-selectivity in the hydroboration reaction, as shown in Scheme 9 and Table 5.



Scheme 9. Reagents: (*i*) 9-BBN, THF, rt, 24 h, EtOH, buffer of phosphates pH 7, peroxide, 24 h, Na_2SO_3.

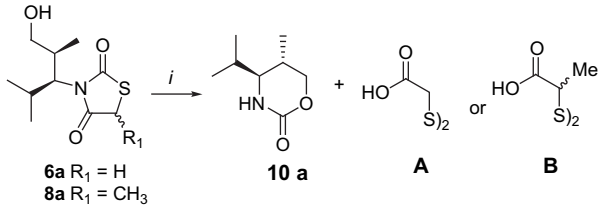
Table 5
Hydroboration–oxidation of compounds **4a–d**

Entry	Starting material	R_1	R_2	Yield[a] (%) **8**/**9**	*syn*/*anti* **8**/**9**
1	**4a**	^{i}Pr	H	77	80/20
2	**4b**	H	Ph	80	6/94[b]
3	**4c**	Me	H	32	80/20
4	**4d**	Bn	H	69	89/11

[a] Yields of diastereoisomer mixture.
[b] The major diastereoisomer is *syn*, compound **9b**.

The alcohols **6** (**a**, **b**, **d**) and **7** (**a**, **d**) were exposed under basic hydrolysis conditions with KOH in THF/H_2O to yield the heterocycles 1,3-oxazinones type **10** (**a**, **b**, **d**) and **11** (**a**, **d**) in moderate yields and the bis(carboxymethyl)disulfide **A**. The alcohols **8** (**a**, **b**, **d**) and **9** (**a**, **d**) were treated under the reaction conditions described above to yield 1,3-oxazinones type **10** (**a**, **b**, **d**) and **11** (**a**, **d**) too and the compound 2,2′-dithiobispropanoic acid **B**, as shown in Scheme 10.

The absolute and relative configurations of the 1,3-oxazinone **10a** were confirmed by X-ray analysis,[16] where its relative configuration is trans and absolute configurations at stereogenic centers (C-4, C-5) are *S* as shown in Figure 4. The achievement of the structure of compound **10a** by X-ray analysis allowed the assignment of the configurations for alcohols **6**, **7**, **8**, and **9**.



Scheme 10. Reagents: (*i*) KOH, THF/H_2O 3.0/1.0, rt, 4 h.

The α-alkyl-β-amino acids are constituents of biologically active natural products, as some peptides.[17] The asymmetric synthesis of α-methyl-β-amino acids bearing phenyl or methyl groups has been widely described.[18] However, the preparation of the derivates bearing isopropyl or benzyl group has not been reported to date. This work was focused on the preparation of these α-methyl β-amino acids through *N*-*tert*-butoxycarbonyl protection[19] of the 1,3-oxazinones **10** (**a**, **d**) and **11** (**a′**, **d′**) followed by ring opening with a catalytic amount of cesium carbonate in methanol at room temperature to give amino alcohols **14** (**a**, **d**) and **15** (**a′**, **d′**) in 95–97% yields. Their oxidation with $NaIO_4$ and a catalytic amount of $RuCl_3$ led to *N*-protected amino acids[20] **16** (**a**, **d**) and **17** (**a′**, **d′**) in 92–99% yields as shown in Scheme 11.

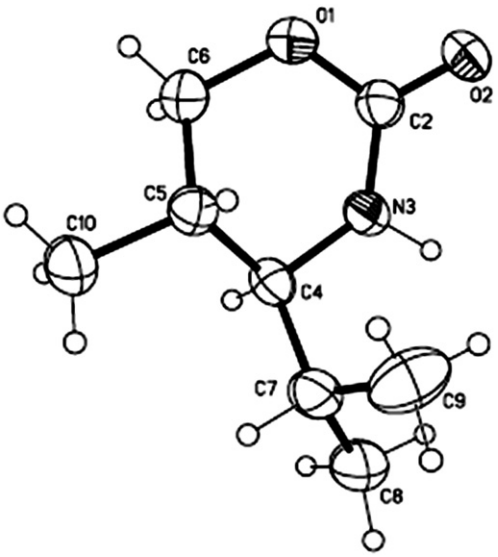
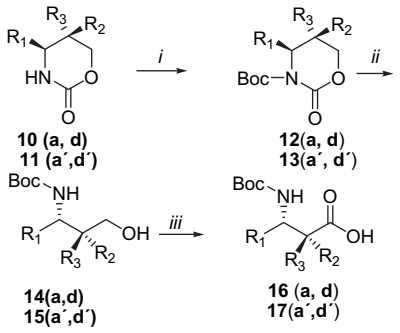


Figure 4. Molecular structure of the 1,3-oxazinones **10a**. The asymmetric unit of the crystal contains two molecules with almost identical conformations.



Scheme 11. Reagents and conditions: (*i*) *n*-BuLi, $(Boc)_2O$, THF, −78 °C, (*ii*) Cs_2CO_3, MeOH, rt, (*iii*) $NaIO_4$, $RuCl_3$, $CCl_4/CH_3CN/H_2O$ 1.0/1.0/1.2, rt.

In conclusion we have found a new reaction pathway that was carried out using oxazolidinethiones and acyl halides under N-acylation reaction conditions to provide *N*-substituted 2,4-thiazolidinedione and *N*-substituted 1,3-thiazinane-2,4-dione. This reaction featured an unexpected elimination reaction: one methyl group on oxazolidinethione was converted into a terminal olefin. These heterocycles were exposed to basic hydrolysis conditions to yield new chiral allylic ureas in good yields. The terminal olefins on the heterocycles were hydroborated with 9-BBN, followed by an oxidation with peroxide to yield a diastereomeric mixture of *syn*- and *anti*-alcohols. These alcohols were treated under basic hydrolysis conditions to provide 1,3-oxazinones, which were eventually employed for the synthesis of new α-methyl-β-amino acids and allylic ureas.

3. Experimental

3.1. General remarks

All ^1H and ^{13}C spectra were recorded in $CDCl_3$ using two NMR spectrometers operating at 400 or 300, and 100 or 75 MHz,

respectively. Chemical shifts are reported in parts per million (δ scale), and coupling constants (J values) are listed in hertz (Hz). Tetramethylsilane (TMS) and $CHCl_3$ were used as the internal standards (δ=0 ppm) and (δ=77.0 ppm). Infrared spectra were recorded on a Nicolet 380 FT-IR spectrometer. Melting points were recorded on a Barnsted Electrothermal apparatus and are uncorrected. Optical activities were measured at 589 nm using a digital polarimeter. Mass spectra were recorded on MStation JMS.

3.2. General procedure for the condensation reaction of β-amino alcohols with CS_2

To a flask were added (*S*)-3-amino-2,4-dimethylpentan-2-ol (1.0 g, 7.62 mmol), aqueous solution of Na_2CO_3 (100 mL), and CS_2 (2.32 g, 30.5 mmol). The mixture was allowed to stir at reflux temperature for 16 h, and then cooled to room temperature. After cooling, CS_2 (1.16 g, 15.2 mmol) was added and allowed to stir at reflux temperature for 4 h. The product was extracted with CH_2Cl_2 (50 mL×4), washed with brine (30 mL×2), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by column chromatography (10% ethyl acetate in hexane as eluent) to afford **1a** (1.06 g, 80% yield) as a white solid.

*3.2.1. (S)-4-Isopropyl-5,5-dimethyloxazolidine-2-thione (**1a**).* White solid, mp=110–111 °C, 80% yield, $[\alpha]_D^{25}$ −14.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (1H, br s, NH), 3.40 (1H, d, *J*=8.0 Hz, CHN), 1.90 (1H, m, $CHCH_3$), 1.60 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.00 (3H, d, *J*=6.6 Hz, CH_3CH), 0.90 (3H, d, *J*=6.6 Hz, CH_3CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.1 (C=S), 90.4 (C–O), 71.2 (C–N), 28.2 ($CHCH_3$), 28.0 (CH_3), 20.9 (CH_3), 19.9 ($2CH_3$); IR ν_{max}: 3177.6, 2964.1, 2935.0, 1717.5, 1518.6, 1391.4, 1210.7, 1139.6, 1023.8, 819.0 cm^{-1}. EI-HRMS: calculated for ($C_8H_{15}NOS$), 173.0874; found, 173.0875.

*3.2.2. (R)-5,5-Dimethyl-4-phenyloxazolidine-2-thione (**1b**).* White solid, mp=111–113 °C, 70% yield, $[\alpha]_D^{25}$ −94.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (1H, br s, NH). 7.40–7.36 (3H, m, Ph), 7.24–7.20 (2H, m, Ph), 4.76 (1H, s, CHN), 1.68 (3H, s, CH_3), 1.01 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.2 (C=S), 135.3 (C*i*), 129.1 (C*p*), 129.0 (C*m*), 126.5 (C*o*), 91.6 (C–O), 69.1 (C–N), 28.0 (CH_3), 23.3 (CH_3); IR ν_{max}: 3184.2, 2980.8, 1732.5, 1494.5, 1454.7, 1283.4, 1215.3, 1127.9, 746.1, 700.5 cm^{-1}. EI-HRMS: calculated for ($C_{11}H_{13}NOS$), 207.0718; found, 207.0715.

*3.2.3. (S)-4,5,5-Trimethyloxazolidine-2-thione (**1c**).* White solid, mp=100–101 °C, 65% yield, $[\alpha]_D^{25}$ −5.83 (*c* 1.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (1H, br s, NH), 3.82 (1H, q, *J*=6.8 Hz, CH), 1.52 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.23 (3H, d, *J*=7.2 Hz, CH_3CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.0 (C=S), 90.4 (C–O), 60.4 (C–N), 27.0 (CH_3), 21.1 (CH_3), 15.3 (CH_3); IR ν_{max}: 2980.0, 2939.1, 2872.8, 1748.5, 1681.2, 1324.9, 1180.6, 881.9 cm^{-1}. EI-HRMS: calculated for ($C_6H_{11}NOS$), 145.0561; found, 145.0565.

3.3. General procedure for the conversion of oxazolidinethiones to *N*-substituted 2,4-thiazolidinediones

To a solution of (*S*)-4-isopropyl-5,5-dimethyloxazolidine-2-thione **1a** (0.5 g, 2.88 mmol) in CH_2Cl_2 (30 mL) was added NaH (0.14 g, 5.76 mmol) at 0 °C under an argon atmosphere, followed by dropwise addition of bromoacetyl bromide (0.87 g, 4.32 mmol). The mixture was stirred at 0 °C for 4 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (15 mL). The product was extracted with CH_2Cl_2 (50 mL×2), washed first with a saturated solution of $NaHCO_3$ (20 mL×3) and then with brine (30 mL×2), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by column chromatography (2% ethyl acetate in hexane as eluent) to afford **2a** (0.41 g, 67% yield) as a colorless liquid.

*3.3.1. (S)-3-(2,4-Dimethylpent-1-en-3-yl)thiazolidine-2,4-dione (**2a**).* Colorless liquid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.13 (1H, s, d, *J*=0.8 Hz, CH=), 5.02 (1H, dq, *J*=1.6, 1.2 Hz, CH=), 4.22 (1H, d, *J*=11.6 Hz, CH–N), 3.91 (2H, s, CH_2), 2.85 (1H, m, $CH(CH_3)_2$), 1.74 (3H, s, CH_3), 0.93 (3H, d, *J*=6.4 Hz, CH_3), 0.83 (3H, d, *J*=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6 (2C=O), 140.3 (C=), 117.2 (CH_2=), 67.2 (CN), 33.3 (CH_2S), 25.4 ($CH(CH_3)_2$), 20.8 (CH_3) 20.6 (CH_3), 19.7 (CH_3); IR ν_{max}: 1753.1, 1676.5, 1370.9, 1318.3, 1181.4, 1165.7, 1113.2, 904.8 cm^{-1}. EIMS: calculated for ($C_{10}H_{15}NO_2S$), 213.08; found, 213.0 ($M^{+\bullet}$), 96.0 (100%).

*3.3.2. (S)-3-(2-Methyl-1-phenylallyl)thiazolidine-2,4-dione (**2b**).* Colorless liquid, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44–7.30 (5H, m, Ph), 5.82 (1H, s, CHN), 5.14 (1H, s, CH=), 4.75 (1H, s, CH=), 3.92 (2H, s, CH_2), 1.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.2 (2CO), 139.6 (C=), 135.8 (C*i*), 129.5 (C*m*), 128.3 (C*o*), 128.2 (C*p*), 115.3 (CH_2=), 63.0 (CHN), 33.3 (CH_2), 21.2 (CH_3); IR ν_{max}: 1754.6, 1677.8, 1378.6, 1330.4, 1153.9, 897.3, 724.4, 699.5, 669.5 cm^{-1}. EI-HRMS: calculated for ($C_{13}H_{13}NO_2S$), 247.0667; found, 247.0662.

*3.3.3. (S)-3-(3-Methylbut-3-en-2-yl)thiazolidine-2,4-dione (**2c**).* Colorless liquid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.02 (1H, s, CH=), 4.98 (1H, s, CH=), 4.80 (1H, q, CHN), 3.92 (2H, s, CH_2), 1.70 (3H, s, CH_3), 1.56 (3H, d, *J*=7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.2 (2CO), 141.3 (C=), 113.1 (CH_2=), 54.2 (CHN), 33.2 (CH_2), 20.4 (CH_3), 15.2 (CH_3); IR ν_{max}: 2919.8, 1753.7, 1674.1, 1377.7, 1332.7, 1144.6, 897.3, 749.4, 700.7 cm^{-1}. EI-HRMS: calculated for ($C_8H_{11}NO_2S$), 185.0511; found, 185.0510.

*3.3.4. (S)-3-(3-Methyl-1-phenylbut-3-en-2-yl)thiazolidine-2,4-dione (**2d**).* Colorless liquid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26–7.14 (5H, m, Ph), 5.12 (1H, s, CH=), 5.10 (1H, s, CH=), 5.00 (1H, dd, *J*=11.2, 5.2 Hz, CHN), 3.67 (2H, dd, *J*=17.2 Hz, CH_2S), 3.51(1H, dd, *J*=14.0, 11.2 Hz, CH_aH_b), 3.23 (1H, dd, *J*=14.0, 5.2 Hz, CH_bH_a), 1.77 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3 (2CO), 140.6 (C=), 137.3 (C*i*), 128.8 (C*m*), 128.5 (C*o*), 126.8 (C*p*), 114.0 (CH_2=), 60.0 (CH–N), 34.4 (CH_2), 33.0 (CH_2S), 21.0 (CH_3); IR ν_{max}: 2919.8, 1753.7, 1674.1, 1455.4, 1377.7, 1332.7, 1144.6, 897.3, 749.4, 700.7 cm^{-1}. EIMS: calculated for ($C_{14}H_{15}NO_2S$), 261.08; found, 261.0 ($M^{+\bullet}$), 144.0 (100%).

3.4. General procedure for the conversion of oxazolidinethiones to *N*-substituted 1,3-thiazinane-2,4-dione (3a)

To a solution of (*S*)-4-isopropyl-5,5-dimethyloxazolidine-2-thione **1a** (0.3 g, 1.73 mmol) in CH_2Cl_2 (30 mL) was added NaH (0.083 g, 3.46 mmol) at 0 °C under an argon atmosphere, followed by dropwise addition of 3-bromopropionyl chloride (0.44 g, 2.59 mmol). The mixture was stirred at 0 °C for 4 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (15 mL). The product was extracted with CH_2Cl_2 (50 mL×2), washed first with a saturated solution of $NaHCO_3$ (20 mL×3) and then with brine (30 mL×2), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by column chromatography (2% ethyl acetate in hexane as eluent) to afford **3a** (0.27 g, 70% yield) as a colorless liquid.

*3.4.1. (S)-3-(2,4-Dimethylpent-1-en-3-yl)-1,3-thiazinane-2,4-dione (**3a**).* Colorless liquid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.10 (1H, s, CH=), 5.07 (1H, s, CH=), 4.84 (1H, d, *J*=11.0 Hz, CHN), 3.05 (4H, m, $2CH_2$), 2.75 (1H, m, $CH(CH_3)_2$), 1.72 (3H, s, CH_3), 0.97 (3H, d, *J*=6.8 Hz, CH_3), 0.83 (3H, d, *J*=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7 (C=O), 169.0 (C=O), 140.5 (C=), 116.0 (CH_2=), 65.0 (CHN), 35.1 (CH_2S), 26.8 ($CH(CH_3)_2$), 22.0 (CH_2), 21.7 (CH_3), 21.3

(CH_3), 19.3 (CH_3); IR ν_{max}: 2967.7, 1711.6, 1644.3, 1334.8, 1284.1, 1219.6, 1156.6, 1112.5 cm^{-1}. EI-HRMS calculated for ($C_{11}H_{17}NO_2S$), 227.0980; found, 227.0984.

*3.4.2. (S)-3-(2-Methyl-1-phenylallyl)-1,3-thiazinane-2,4-dione (**3b**).* Colorless liquid, ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.41 (2H, m, Ph), 7.33–7.26 (3H, m, Ph), 6.33 (1H, s, CHN), 5.05 (1H, s, CH=), 4.70 (1H, s, CH=), 3.05 (4H, m, $2CH_2$), 1.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2 (C=O), 168.3 (C=O), 141.2 (C=), 137.2 (C*i*), 130.0 (C*m*), 128.0 (C*o*), 127.6 (C*p*), 114.0 (CH_2=), 62.6 (CHN), 35.0 (CH_2–S), 22.0 (CH_2), 21.4 (CH_3); IR ν_{max}: 2921.4, 1711.7, 1649.6, 1335.3, 1287.3, 1219.7, 1145.6 cm^{-1}. EIMS: calculated for ($C_{14}H_{15}NO_2S$), 261.08; found, 261.0 ($M^{+\cdot}$), 233.0 (100%).

*3.4.3. (S)-3-(3-Methylbut-3-en-2-yl)-1,3-thiazinane-2,4-dione (**3c**).* Colorless liquid, ^1H NMR ($CDCl_3$, 400 MHz): δ 5.32 (1H, q, *J*=6.4 Hz, CHN), 5.00 (1H, s, CH=), 4.90 (1H, s, CH=), 3.05 (4H, m, $2CH_2$), 1.68 (3H, s, CH_3), 1.52 (3H, d, *J*=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2 (C=O), 168.3 (C=O), 143.1 (C=), 111.3 (CH_2=), 54.0 (CHN), 35.0 (CH_2), 22.0 (CH_2), 20.1 (CH_3), 16.1 (CH_3); IR ν_{max}: 2938.6, 1709.2, 1643.6, 1222.5, 1162.6, 896.3 cm^{-1}. EIMS: calculated for ($C_9H_{13}NO_2S$), 199.07; found, 199.0 ($M^{+\cdot}$), 171.0 (100%).

*3.4.4. (S)-3-(3-Methyl-1-phenylbut-3-en-2-yl)-1,3-thiazinane-2,4-dione (**3d**).* White solid, mp=78–79 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29–7.15 (5H, m, Ph), 5.62 (1H, m, CHN), 5.00 (2H, s, CH_2=), 3.40 (1H, dd, *J*=13.4, 11.0 Hz, CH_aH_b), 3.25 (1H, dd, *J*=13.4, 6.0 Hz, CH_bH_a), 2.80–2.50 (4H, m, $2CH_2$), 1.74 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4 (C=O), 168.6 (C=O), 142.6 (C=), 138.2 (C*i*), 129.0 (C*m*), 128.3 (C*o*), 126.5 (C*p*), 111.4 (CH_2=), 58.5 (CHN), 35.5 (CH_2), 34.6 (CH_2), 21.7 (CH_2), 21.1 (CH_3); IR ν_{max}: 2937.6, 1709.5, 1643.1, 1222.7, 1135.2, 884.9, 748.8, 701.1 cm^{-1}. FAB-HRMS: calculated for ($C_{15}H_{17}NO_2S$) 276.1058 (M+H); found, 276.1067 (M+H).

3.5. General procedure for the conversion of oxazolidinethiones to *N*-substituted 2,4-thiazolidinediones

To a solution of (*S*)-4-isopropyl-5,5-dimethyloxazolidine-2-thione **1a** (0.4 g, 2.30 mmol) in CH_2Cl_2 (30 mL) was added NaH (83 mg, 3.46 mmol) at 0 °C under an argon atmosphere, followed by dropwise addition of 2-bromopropanoyl bromide (0.59 g, 2.77 mmol). The mixture was stirred at 0 °C for 4 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (15 mL). The product was extracted with CH_2Cl_2 (50 mL×2), washed first with a saturated solution of $NaHCO_3$ (20 mL×3) and then with brine (30 mL×2), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by column chromatography (2% ethyl acetate in hexane as eluent) to afford **4a** (0.36 g, 70% yield) as a diastereomeric mixture.

*3.5.1. 3-[(S)-2,4-Dimethylpent-1-en-3-yl]-5-methylthiazolidine-2,4-dione (**4a**).* Liquid, ^1H NMR ($CDCl_3$, 300 MHz): δ 5.11 (1H, s, HC=), 5.01 (1H, s, HC=), 4.20 (1H, d, *J*=11.2 Hz, CHN), 4.12 (1H, dq, *J*=5.0, 7.2 Hz, CH–S), 2.84 (1H, m, CH), 1.74 (3H, s, CH_3), 1.66 (3H, dd, *J*=7.2, 1.6 Hz, CH_3), 0.94 (3H, d, *J*=6.8 Hz, CH_3), 0.82 (3H, dd, *J*=6.4, 1.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 175.8 (2C=O), 140.5, 140.4 (C=), 117.1, 117.0 (C=), 67.0, 66.8 (CN) 43.0, 42.8 (CS), 25.4, 25.3 (CH_3) 20.8, 20.7 (CH_3), 20.5 (CH_3) 19.5, 19.4 (CH_3); IR ν_{max}: 2926.1, 1752.2, 1685.6, 1330.5, 1183.0, 1118.86, 911.8 cm^{-1}.

*3.5.2. 3-[((S)-2-Methyl-1-phenylallyl)]-5-methylthiazolidine-2,4-dione (**4b**).* Liquid, ^1H NMR ($CDCl_3$, 300 MHz): δ 7.70–7.13 (5H, m, Ph) 5.79 (1H, s, CH–N), 5.13 (1H, s, CH=), 4.73 (1H, s, CH=), 4.15 (1H, q, *J*=7.2 Hz, CHS), 1.78 (3H, s, CH_3), 1.65 (3H, d, *J*=7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.1 (C=O), 170.5 (C=O), 139.9 (C=), 135.9, 129.4, 128.3 (Ph), 115.2 (CH_2), 63.0 (CHN), 43.1 (CS), 21.0 (CH_3), 19.2 (CH_3); IR ν_{max} 2979.7, 1751.5, 1670.1, 1375.4, 1325.1, 1166.3, 740.2, 700.7 cm^{-1}. EI-HRMS: calculated for ($C_{14}H_{15}NO_2S$), 261.0824; found, 261.0830.

*3.5.3. 3-[(S)-3-Methylbut-3-en-2-yl]-5-methyl thiazolidine-2,4-dione (**4c**).* Liquid, ^1H NMR ($CDCl_3$, 400 MHz): δ 5.01 (1H, s, CH=), 4.96 (1H, s, CH=), 4.80 (1H, q, *J*=7.0 Hz, CH–N), 4.10 (1H, q, *J*=7.2 Hz, CHS), 1.70 (3H, s, CH_3), 1.67 (3H, d, *J*=7.0 Hz, CH_3), 1.56 (3H, d, *J*=7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.2 (C=O), 170.4 (C=O), 141.4, 141.3 (C=), 112.8 (CH_2), 54.0 (CHN), 43.1, 42.9 (CS), 20.4 (CH_3), 19.2, 19.1 (CH_3), 15.2, 15.1 (CH_3); IR ν_{max} 2979.9, 1748.8, 1667.2, 1448.7, 1376.7, 1328.7, 1180.8, 882.5 cm^{-1}. EI-HRMS: calculated for ($C_9H_{13}NO_2S$), 199.0667; found, 199.0665.

*3.5.4. 3-[(S)-3-Methyl-1-phenylbut-3-en-2-yl]-5-methyl thiazolidine-2,4-dione (**4d**).* Liquid, ^1H NMR ($CDCl_3$, 400 MHz): δ 7.27–7.13 (5H, m, Ph) 5.10 (1H, s, CH=), 5.08 (1H, s, CH=), 5.00 (1H, m, CHN), 3.93 (1H, q, *J*=7.3 Hz, CHS), 3.50 (1H, dd, *J*=14.0, 9.6 Hz, CH_aH_b), 3.21 (1H, dd, *J*=14.0, 5.0 Hz, CH_bH_a), 1.76 (3H, s, CH_3), 1.46 (3H, d, *J*=7.2 Hz, CH_3), 1.21 (3H, d, *J*=7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.2 (C=O), 170.8 (C=O), 140.6 (C=), 137.2, 128.9, 128.8, 128.4, 128.3, 126.7, 126.6 (Ph), 113.6, 113.4 (=CH_2), 59.4, 59.3 (CHN), 43.0, 42.6 (C–S), 34.5, 34.3 (CH_2), 21.0 (CH_3), 19.1 (CH_3), 19.0 (CH_3); IR ν_{max}: 2931.1, 1705.3, 1673.5, 1449.0, 1329.4, 1147.0, 738.9, 700.1 cm^{-1}. EIMS: calculated for ($C_{15}H_{17}NO_2S$), 275.098; found, 275, 144, 129, 91.

3.6. General procedure for basic hydrolysis of *N*-substituted 2,4-thiazolidinediones or *N*-substituted 1,3-thiazinane-2,4-dione

To a flask were added **3a** (0.15 g, 0.66 mmol), THF (9 mL), H_2O (3 mL), and KOH (0.15 g, 2.63 mmol). The mixture was allowed to stir at room temperature for 4 h. The THF was removed under reduced pressure. The product was extracted with CH_2Cl_2 (40 mL×2), washed first with a saturated solution of $NaHCO_3$ (20 mL×3) and then with brine (30 mL×2), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was recrystallized with ethanol (three drops) in hexane.

*3.6.1. 1,3-Bis((S)-2,4-dimethylpent-1-en-3-yl)urea (**5a**).* Crystalline solid, mp=224–225 °C, 80% yield, $[\alpha]_D^{25}$ +55.8 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.90 (1H, s, CH=), 4.85 (1H, s, CH=), 4.55 (1H, d, *J*=6.8 Hz, NH), 3.72 (1H, m, CHN), 1.77 (1H, m, $CH(CH_3)_2$), 1.68 (3H, s, CH_3), 0.92 (3H, d, *J*=6.8 Hz, CH_3), 0.90 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.8 (C=O), 142.2 (C=), 112.4 (CH_2=), 62.6 (CHN), 29.8 (CH_3), 20.1 (CH_3), 18.6 (CH), 18.4 (CH_3); IR ν_{max}: 3329.3, 2962.3, 1625.5, 1560.8, 1313.6, 891.4 cm^{-1}. EI-HRMS: calculated for ($C_{15}H_{28}N_2O$), 252.2202; found, 252.2189.

*3.6.2. 1,3-Bis((S)-2-methyl-1-phenylallyl)urea (**5b**).* White solid, mp=216–218 °C, 70% yield, $[\alpha]_D^{25}$ −85.5 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.20 (5H, m, Ph), 5.18 (1H, d, *J*=6.6 Hz, CHN), 5.01 (1H, s, CH=), 4.90 (1H, s, CH=), 4.81 (1H, d, *J*=7.0 Hz, NH), 1.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.0 (C=O), 145.0 (C=), 140.5 (C*i*), 128.6 (C*m*), 127.5 (C*p*), 127.0 (C*o*), 119.0 (CH_2=), 60.1 (CHN), 19.8 (CH_3); IR ν_{max}: 3317.1, 1624.3, 1556.6,1492.6, 1271.6, 901.1, 698.6 cm^{-1}. EI-HRMS: calculated for ($C_{21}H_{24}N_2O$), 320.1889; found, 320.1897.

*3.6.3. 1,3-Bis((S)-3-methyl-1-phenylbut-3-en-2-yl)urea (**5d**).* White solid, mp=80–81 °C, 71% yield, $[\alpha]_D^{25}$ −21.3 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29–7.10 (5H, m, Ph), 4.80 (1H, s, CH=), 4.65 (1H, s, CH=), 4.51 (1H, d, *J*=7.2 Hz, NH), 4.20 (1H, m, CHN), 2.84 (1H, dd, *J*=14.0, 6.8 Hz, CH_aH_b), 2.75 (1H, dd, *J*=14.0, 7.4 Hz, CH_bH_a), 1.72 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.1 (C=O), 145.1 (C=), 137.3 (C*i*), 129.1 (C*m*), 128.3 (C*o*), 126.6 (C*p*), 112.2 (CH_2=),

57.0 (CHN), 29.6 (CH_2), 18.7 (CH_3); IR ν_{max}: 3340.8, 2922.3, 2853.2, 1747.2, 1682.8, 1638.5, 1551.3, 1328.7, 1064.3, 743.1, 699.3 cm^{-1}. FAB-HRMS: calculated for ($C_{23}H_{28}N_2O$) 349.2280 (M+H); found, 349.2272 (M+H).

*3.6.4. 3-[((2S,3S)-1-Hydroxy-2,4-dimethylpentan-3-yl)thiazolidine-2,4-dione (**6a**).* Liquid, 55% yield, $[\alpha]_D^{25}$ −7.0 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.03 (1H, s, CHS), 4.00 (1H, dd, *J*=9.6, 7.2 Hz, CHN), 3.87 (1H, s, CHS), 3.51 (2H, m, CH_2O), 2.52 (2H, m, 2CH), 1.01 (3H, d, *J*=6.6 Hz, CH_3), 0.96 (3H, d, *J*=7.0 Hz, CH_3), 0.85 (3H, d, *J*=6.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.6, 172.6, 65.0, 64.8, 64.7, 35.3, 35.2, 33.8, 32.2, 29.6, 27.6, 27.4, 20.7, 20.6, 19.8, 19.6, 15.4; IR ν_{max}: 3415.7, 2965.9, 2934.8, 2876.1, 1750.4, 1667.2, 1387.5, 1331.9, 1187.3, 1108.0, 897.9, 802.1 cm^{-1}; EIMS: calculated for ($C_{10}H_{17}NO_3S$), 231.09; found, 231 (2%), 188 (27%), 172 (36%), 158 (100), 118 (68%), 84 (30%).

*3.6.5. 3-[((2R,3S)-1-Hydroxy-2,4-dimethylpentan-3-yl)thiazolidine-2,4-dione (**7a**).* Liquid, 45% yield, $[\alpha]_D^{25}$ −5.5 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.97 (1H, s, CHS), 3.94 (1H, dd, *J*=10.0, 5.6 Hz, CHN), 3.81 (1H, s, CHS), 3.40 (1H, dd, *J*=12.0, 4.8 Hz, CH_aO), 3.20 (1H, m, CH_bO), 2.75 (1H, m, CH), 2.26 (1H, m, $CHCH_3$), 0.93 (3H, d, *J*=6.8 Hz, CH_3), 0.81 (3H, d, *J*=7.6 Hz, CH_3), 0.78 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.3, 172.6, 65.1, 63.6, 63.4, 37.0, 36.9, 33.6, 32.4, 29.6, 25.6, 25.4, 20.6, 20.5, 12.4, 12.2; IR ν_{max}: 3415.5, 2924.7, 1749.2, 1670.7, 1333.1, 1162.4, 703.3 cm^{-1}; EIMS: calculated for ($C_{10}H_{17}NO_3S$), 231.09; found, 231 (7%), 188 (27%), 172 (35%), 158 (100), 118 (68%), 84 (32%).

*3.6.6. 3-[(1S,2S)-3-Hydroxy-2-methyl-1-phenylpropyl]thiazolidine-2,4-dione (**6b**).* Colorless liquid, 15% yield, $[\alpha]_D^{25}$ −41.9 (*c* 1.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.55–7.53 (2H, m, Ph), 7.36–7.30 (3H, m, Ph), 5.16 (1H, d, *J*=11.6 Hz, CHN), 3.85 (2H, s, CH_2), 3.63 (2H, d, *J*=4.4 Hz, CH_2OH), 3.26 (1H, m, CH),1.78 (1H, br s, OH), 0.88 (3H, d, *J*=7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3 (C=O), 172.0 (C=O), 136.8 (C*i*), 129.5 (C_i), 128.5 (C_o), 128.4 (C_p), 65.6 (C–O), 61.5 (CN), 33.4 (CH), 33.2 (CS), 15.4 (CH_3); IR ν_{max}: 3416.0, 2929.1, 1748.9, 1655.5, 1328.8, 1170.7, 700.0 cm^{-1}. EI-HRMS: calculated for ($C_{13}H_{15}NO_3S$), 265.0773; found, 265.0761.

*3.6.7. 3-[(1S,2R)-3-Hydroxy-2-methyl-1-phenylpropyl]thiazolidine-2,4-dione (**7b**).* White solid 57% yield, mp=103 °C, $[\alpha]_D^{25}$ −22.3 (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.56–7.54 (2H, m, Ph), 7.33–7.31 (3H, m, Ph), 5.20 (1H, d, *J*=12.0 Hz, CHN), 3.86 (2H, s, CH_2), 3.53 (1H, dd, *J*=10.8, 2.8 Hz, CH_aH_b), 3.31 (1H, dd, *J*=10.4, 5.2 Hz, CH_bH_a), 3.24 (1H, m, CH), 1.63 (1H, br s, OH), 1.05 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0 (C=O), 171.7 (C=O), 137.1 (C*i*), 129.2 (C*m*), 128.6 (C*o*), 128.5 (C*p*), 64.6 (C–O), 61.2 (CN), 34.3 (CH), 33.1 (C–S), 14.5 (CH_3); IR ν_{max}: 3415.5, 2924.7, 1749.2, 1670.7, 1333.1, 1162.4, 703.3 cm^{-1}. EI-HRMS: calculated for ($C_{13}H_{15}NO_3S$), 265.0773; found 265.0776.

*3.6.8. 3-[((2S,3S)-4-Hydroxy-3-methylbutan-3-yl)thiazolidine-2,4-dione (**6c**).* Liquid 46% yield, $[\alpha]_D^{25}$ +6.40 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.39 (1H, dq, *J*=7.0, 9.2 Hz, CHN), 3.94 (2H, d, *J*=0.8 Hz, CH_2S), 3.62 (2H, d, *J*=4.8 Hz, CH_2O), 2.40 (1H, m, $CHCH_3$), 1.83 (1H, br s, OH), 1.49 (3H, d, *J*=6.8 Hz, CH_3), 0.90 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.1 (C=O), 64.8 (CH_2O), 53.1 (CHN), 37.8 (CH_2S), 33.2 (CH), 15.7 (CH_3), 14.1 (CH_3); IR ν_{max}: 3402.9, 2934.8, 2866.7, 1742.8, 1672.2, 1339.4, 1179.2, 872.6 cm^{-1}. EIMS: calculated for ($C_8H_{13}NO_3S$), 203.06; found, 203 (5%), 173 (40%), 144 (80%), 118 (100%), 116 (45%).

*3.6.9. 3-[((2S,3R)-4-Hydroxy-3-methylbutan-3-yl)thiazolidine-2,4-dione (**7c**).* Liquid, 17% yield, $[\alpha]_D^{25}$ +3.76 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.26 (1H, dq, *J*=10.7, 7.1 Hz, CHN), 3.92 (2H, s, CH_2S), 3.46 (2H, dd, *J*=4.0, 2.4 Hz, CH_2O), 2.38 (1H, m, $CHCH_3$), 1.71 (1H, br s, OH), 1.47 (3H, d, *J*=6.8 Hz, CH_3), 1.04 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3 (C=O), 65.6 (CH_2O), 53.4 (CHN), 37.0 (CH_2S), 33.4 ($CHCH_3$), 16.0 (CH_3), 14.8 (CH_3); IR ν_{max}: 3402.7, 2934.8, 2866.7, 1742.8, 1672.2, 1339.4, 1179.2, 873.0 cm^{-1}. EIMS: calculated for ($C_8H_{13}NO_3S$), 203.06; found, 203 (5%), 173 (39%), 144 (80%), 118 (100%), 116 (40%).

*3.6.10. 3-[(2S,3S)-4-Hydroxy-3-methyl-1-phenylbutan-2-yl]-thiazolidine-2,4-dione (**6d**).* Colorless liquid, 44% yield, $[\alpha]_D^{25}$ −51.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.10 (5H, m, Ph), 4.55 (1H, m, CHN), 3.74 (2H, m, CH_2S), 3.68 (1H, dd, *J*=11.2, 4.4 Hz, CHBn), 3.48 (1H, m, CHBn), 3.31(1H, m, CHO), 3.18 (1H, dd, *J*=14.0, 5.2 Hz, CHO), 2.50 (1H, m, $CHCH_3$), 0.94 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 172.0, 137.6, 128.7, 128.4, 126.6, 64.7, 59.2, 37.2, 35.0, 34.5, 33.2, 14.4; IR ν_{max}: 3414.1, 2928.4, 1676.0, 1343.6, 1152.7, 1030.6, 710.8 cm^{-1}. FABMS: calculated for ($C_{14}H_{17}NO_3S$), 279.09; found, 280 (15%), 154 (100), 136 (85%), 91 (55%), 57 (95%) 55 (90%), 43 (72%).

*3.6.11. 3-[(2S,3R)-4-Hydroxy-3-methyl-1-phenylbutan-2-yl]-thiazolidine-2,4-dione (**7d**).* Colorless liquid, 14% yield, $[\alpha]_D^{25}$ −60.2 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.05 (5H, m, Ph), 4.40 (1H, m CHN), 3.68 (1H, m, CH_aO), 3.49 (2H, d, *J*=4.0 Hz, CH_2S), 3.43 (1H, m, CH_bO), 3.31 (1H, m, CHBn), 0.88 (1H, dd, *J*=4.8, 14.0 Hz, CHBn), 2.50 (1H, m, $CHCH_3$), 1.17 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 172.1, 137.5, 128.7, 128.4, 126.7, 65.5, 59.5, 36.4, 34.8, 33.3, 24.6, 15.1; IR ν_{max}: 3414.1, 2928.4, 1676.0, 1343.6, 1152.7, 1030.6, 710.8 cm^{-1}. FABMS: calculated for ($C_{14}H_{17}NO_3S$), 279.09; found, 280 (15%), 154 (100), 136 (85%), 91 (55%), 57 (95%) 55 (90%), 43 (72%).

*3.6.12. 3-[(2S,3S)-1-Hydroxy-2,4-dimethylpentan-3-yl]-5-methyl-thiazolidine-2,4-dione (**8a**).* Liquid, 61.5% yield, $[\alpha]_D^{25}$ −10.33 (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.25 (1H, q, *J*=7.2 Hz, CH–S), 4.10 (1H, q, *J*=7.2, CHS), 3.97 (4H, m, CH_2O), 3.48 (2H, m, CHN), 2.57 (2H, m, $CH(CH_3)_2$), 2.51 (2H, m, $CHCH_3$), 1.67 (6H, d, *J*=6.8 Hz, CH_3), 1.00 (6H, d, *J*=6.8 Hz, CH_3), 0.96 (6H, d, *J*=7.2 Hz, CH_3), 0.84 (6H, d, *J*=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.6, 176.7 (C=O), 172.9, 172.3 (C=O), 65.0, 64.9 (CH_2O), 64.7, 64.6, 64.3 (CHN), 43.8 (CH_2S), 41.9 (CH), 35.5, 35.3, 35.2 ($CH(CH_3)_2$), 27.7, 27.5, 27.3, 27.1 (CH_3), 20.7 (CH_3), 19.8, 19.7, 19.6, 19.5, 19.4 (CH_3), 15.4 (CH_3); IR ν_{max}: 3414.1, 2930.0, 1745.3, 1658.7, 1330.5, 1100.5, 1027.2, 741.0 cm^{-1}. EI-HRMS: calculated for ($C_{11}H_{19}NO_3S$), 245.1086; found, 245.1088.

*3.6.13. 3-[(2R,3S)-1-Hydroxy-2,4-dimethylpentan-3-yl]-5-methyl-thiazolidine-2,4-dione (**9a**).* Liquid, 15.5% yield, $[\alpha]_D^{25}$ −1.16 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.27 (1H, m, CHS), 4.09 (1H, m, CHS), 4.00 (2H, m, CHN), 3.46 (2H, m, CH_aO), 3.23 (2H, m, CH_bO), 2.81 (2H, m, $CH(CH_3)_2$), 2.33 (2H, m, $CHCH_3$), 1.68 (6H, d, *J*=7.2 Hz, CH_3), 0.99 (6H, d, *J*=6.8 Hz, CH_3), 0.88 (6H, d, *J*=7.2 Hz, CH_3), 0.85 (6H, d, *J*=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.6, 178.4 (C=O), 176.6, 176.2 (C=O), 65.0 (CH_2O), 63.5, 63.4, 62.7 (CHN), 43.4 (CH_2S), 42.1 (CH), 37.1, 37.0, 36.9, 36.8 ($CH(CH_3)_2$), 25.7, 25.5, 25.4, 25.2 (CH_3), 20.5, 20.2, 20.1, 20.0 (CH_3), 19.9, 19.8, 19.5, 19.4 (CH_3), 12.2, 12.1, 12.0 (CH_3); IR ν_{max}: 3414.1, 2930.0, 1745.3, 1658.7, 1330.5, 1100.5, 1027.2, 741.0 cm^{-1}. EI-HRMS: calculated for ($C_{11}H_{19}NO_3S$), 245.1086; found, 245.1088.

*3.6.14. 3-[(1S,2S)-3-Hydroxy-2-methyl-1-phenylpropyl]-5-methyl-thiazolidine-2,4-dione (**8b**).* Liquid, 5.0% yield, $[\alpha]_D^{25}$ −44.0 (*c*, 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.60–7.50 (2H, m, Ph), 7.40–7.30 (3H, m, Ph), 5.14 (1H, dd, *J*=11.7, 6.3 Hz, CHN), 4.08 (1H, dq, *J*=7.2, 2.8 Hz, CHS), 3.62 (2H, d, *J*=4.5 Hz, CH_2O), 3.23(1H, m, $CHCH_3$), 1.63 (3H, dd, *J*=7.2, 2,1 Hz, CH_3), 0.88 (3H, dd, *J*=6.9, 6.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.6 (C=O), 171.2 (C=O), 137.1

(C*i*), 129.5 (C, Ph), 128.4 (C, Ph), 65.6 (CH_2O), 61.5 (CHN), 43.1 (CHS), 33.5 ($CHCH_3$), 18.9 (CH_3), 15.4 (CH_3); IR ν_{max}: 3409.2, 2927.1, 1747.4, 1662.8, 1326.9, 1168.9, 701.0 cm^{-1}. EI-HRMS: calculated for ($C_{14}H_{17}NO_3S$), 279.0929; found, 279.0931.

*3.6.15. 3-[(1S,2R)-3-Hydroxy-2-methyl-1-phenylpropyl]-5-methylthiazolidine-2,4-dione (**9b**).* Liquid, 75% yield, $[\alpha]_D^{25}$ −43.0 (*c*, 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60–7.50 (2H, m, Ph), 7.38–7.30 (3H, m, Ph), 5.16 (1H, dd, *J*=11.6, 12.0 Hz, CHN), 4.11 (1H, m, CHS), 3.54 (1H, ddd, *J*=10.4, 5.6, 2.8 Hz, CH_aO), 3.34 (1H, ddd, *J*=10.4, 5.6, 2.8 Hz, CH_bO), 3.32 (1H, m, $CHCH_3$), 1.63 (3H, dd, *J*=7.6, 7.2 Hz, CH_3), 1.04 (3H, dd, *J*=6.8, 6.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.6 (C=O), 171.2 (C=O), 137.1 (C*i*), 129.2 (C, Ph), 128.4 (C, Ph), 64.7 (CH_2–O), 61.1 (CHN), 43.1 (CHS), 34.6 ($CHCH_3$), 19.2 (CH_3), 14.4 (CH_3); IR ν_{max}: 3412.8, 2952.2, 1747.2, 1667.2, 1327.5, 1163.4, 697.2 cm^{-1}. EI-HRMS: calculated for ($C_{14}H_{17}NO_3S$), 279.0929; found, 279.0930.

*3.6.16. 3-[(2S,3S)-4-Hydroxy-3-methylbutan-2-yl]-5-methylthiazolidine-2,4-dione (**8c**).* Liquid 65% yield, $[\alpha]_D^{25}$ +8.77 (*c* 1.23, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.31 (1H, m, CHN), 4.10 (1H, q, *J*=7.2 Hz, CHS), 3.60 (2H, d, *J*=4.8 Hz, CH_2O), 2.40 (1H, m, $CHCH_3$), 2.04 (1H, br s, OH), 1.70 (3H, d, *J*=6.8 Hz, CH_3), 1.50 (3H, d, *J*=7.2 Hz, CH_3), 0.88 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.0 (C=O), 171.5 (C=O), 64.8 (CH_2O), 53.0 (CHN), 43.1, 42.9 (CH_2S), 37.9, 37.7 ($CHCH_3$), 19.4, 19.2 (CH_3), 15.8, 15.7 (CH_3), 14.0 (CH_3); IR ν_{max}: 3410.1, 2931.0, 1746.3, 1653.7, 1329.5, 1108.5, 1027.2, 740.4 cm^{-1}. EIMS: calculated for ($C_9H_{15}NO_3S$); 217.08; found, 217 (5%), 199 (15%), 187 (30%), 158 (70%), 132 (100%), 130 (42%).

*3.6.17. 3-[(2S,3R)-4-Hydroxy-3-methylbutan-2-yl]-5-methylthiazolidine-2,4-dione (**9c**).* Liquid 6.5% yield, $[\alpha]_D^{25}$ −0.8 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.21 (1H, m, CHN), 4.16 (1H, dq, *J*=7.2, 1.0 Hz, CHS), 3.43 (2H, dd, *J*=4.2, 2.6 Hz, CH_2O), 2.40 (1H, m, $CHCH_3$), 1.69 (3H, dd, *J*=7.4, 3.4 Hz, CH_3), 1.46 (3H, d, *J*=6.8 Hz, CH_3), 1.03 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.3, 176.1 (C=O), 171.8, 171.7 (C=O), 65.6, 65.5 (CH_2O), 53.4, 53.3 (CHN), 43.2, 43.0 (CH_2S), 37.1, 36.9 ($CHCH_3$), 19.1, 19.0 (CH_3), 16.0, 15.9 (CH_3), 14.8 (CH_3); IR ν_{max}: 3412.0, 2931.0, 1746.3, 1653.7, 1329.5, 1108.5, 1027.2, 740.4 cm^{-1}. EIMS: calculated for ($C_9H_{15}NO_3S$); 217.08; found, 217 (3%), 199 (15%), 187 (30%), 158 (70%), 132 (100%), 130 (42%).

*3.6.18. 3-[(2S,3S)-4-Hydroxy-3-methyl-1-phenylbutan-2-yl]-5-methylthiazolidine-2,4-dione (**8d**).* Liquid 62% yield, $[\alpha]_D^{25}$ −49.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.27–7.13 (5H, m, Ph), 4.64 (1H, m, CHN), 3.94 (1H, m, CHS), 3.76 (1H, m, CH_aH_bO), 3.68 (1H, dd, *J*=11.2, 4.8 Hz, CH_bH_aO), 3.36 (1H, m, CH_aH_bPh), 3.17 (1H, dd, *J*=13.4, 5.0 Hz, CH_bH_aPh), 2.49 (1H, m, $CHCH_3$), 2.10 (1H, br s, OH), 1.55 (1H, d, *J*=6.8 Hz, CH_3), 1.28 (1H, d, *J*=7.2 Hz, CH_3), 1.0 (1H, d, *J*=7.2 Hz, CH_3), 0.95 (3H, d, *J*=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.0 (C=O), 171.8 (C=O), 137.6 (C*i*), 129.0, 128.9, 128.8 (Ph), 128.4, 128.35 (Ph), 126.6 (Ph), 64.9 (CH_2O), 59.1, 58.9, 57.4 (CHN), 43.4, 43.2, 41.9 (CHS), 37.6, 37.4, 37.1, (CH_2), 35.2, 35.1, 34.5 ($CHCH_3$), 19.2 (CH_3), 14.5, 14.3 (CH_3); IR ν_{max}: 3413.1, 2965.3, 2931.9, 1748.4, 1670.6, 1339.3, 1154.5, 979.2, 740.0, 701.2 cm^{-1}. EIMS: calculated for ($C_{15}H_{19}NO_3S$), 293.11; found, 293 (3%), 154 (100%), 136 (90%), 91 (60%), 55 (50%).

*3.6.19. 3-[(2S,3R)-4-Hydroxy-3-methyl-1-phenylbutan-2-yl]-5-methylthiazolidine-2,4-dione (**9d**).* Liquid 7.5%, yield, $[\alpha]_D^{25}$ −79.3 (*c*, 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.27–7.13 (5H, m, Ph), 4.36 (1H, m, CHN), 3.94 (1H, m, CHS), 3.49 (2H, s, CH_2O), 3.30 (1H, m, CH_aH_bPh), 3.11 (1H, dd, *J*=13.6, 4.8 Hz, CH_bH_aPh), 2.50 (1H, m, $CHCH_3$), 1.54 (1H, br s, OH), 1.18 (3H, d, *J*=6.8 Hz, CH_3), 0.99 (3H, d, *J*=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.3 (C=O), 137.5 (C*i*), 129.0 (Ph), 128.5, 128.4 (Ph), 126.7 (Ph), 65.5 (CH_2O), 59.0 (CHN), 43.5 (CHS), 36.7, 36.5 (CH_2), 35.1 ($CHCH_3$), 19.2 (CH_3), 15.0 (CH_3); IR ν_{max}: 3415.0, 2967.0, 2935.0, 1750.4, 1671.6, 1340.3, 1154.7, 979.1, 740.3, 703.2 cm^{-1}. EIMS: calculated for ($C_{15}H_{19}NO_3S$), 293.11; found, 293 (2%), 154 (100%), 136 (70%), 91 (43%), 55 (50%).

*3.6.20. (4S,5S)-4-Isopropyl-5-methyltetrahydro-2H-1,3-oxazin-2-one (**10a**).* White crystalline solid, 77% yield, mp=108–109 °C, $[\alpha]_D^{25}$ −3.03 (*c* 1.12, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.44 (1H, br s, NH), 4.17 (1H, dd, *J*=10.8, 4.0 Hz, CH_aH_b), 3.88 (1H, dd, *J*=11.2, 9.6 Hz, CH_bH_a), 2.94 (1H, ddd, *J*=8.3, 3.7, 1.2 Hz, CHN), 1.98 (1H, m, $CHCH_3$), 1.90 (1H, m, $CH(CH_3)_2$), 1.00 (3H, d, *J*=6.6 Hz, CH_3), 0.99 (3H, d, *J*=6.6 Hz, CH_3), 0.91 (3H, d, *J*=6.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0 (C=O), 70.8 (C–O), 62.4 (C–N), 29.6 (CHN), 28.5 (CH), 19.4 (CH_3), 15.3 (CH_3), 13.7 (CH_3); IR ν_{max}: 3289.1, 2962.3, 2875.7, 1693.3, 1479.0, 1421.0, 1285.8, 1109.6, 1016.6, 766.8 cm^{-1}. EI-HRMS: calculated for ($C_8H_{15}N_1O_2$), 157.1103; found, 157.1100.

*3.6.21. (4S,5R)-4-Isopropyl-5-methyl tetrahydro-2H-1,3-oxazin-2-one (**11a′**).* White solid, 79.2% yield, mp=90–92 °C, $[\alpha]_D^{25}$ −1.75 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.41 (1H, br s, NH), 4.28 (1H, dd, *J*=11.0, 2.6 Hz, CH_aH_b), 4.13 (1H, dd, *J*=11.0, 2.6 Hz, CH_bH_a), 3.08 (1H, dd, *J*=10.0, 4.0 Hz, CHN), 2.08 (1H, m, $CHCH_3$), 1.60 (1H, m, $CH(CH_3)_2$), 1.05 (3H, d, *J*=6.8 Hz, CH_3), 1.01 (3H, d, *J*=6.4 Hz, CH_3), 0.94 (3H, d, *J*=6.8 Hz CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.7 (C=O), 72.8 (C–O), 61.0 (C–N), 29.3 (CH), 27.4 (CH), 19.0 (CH_3), 18.5 (CH_3), 9.5 (CH_3); IR ν_{max}: 3290.0, 2964.3, 2932.2, 1695.3, 1487.0, 1423.0, 1286.0, 1108.6, 1016.6, 766.2 cm^{-1}. EI-HRMS: calculated for ($C_8H_{15}N_1O_2$), 157.1103; found, 157.1100.

*3.6.22. (4S,5S)-4-Benzyl-5-methyltetrahydro-2H-1,3-oxazin-2-one (**10d**).* White solid, 60% yield, mp=124 °C, $[\alpha]_D^{25}$ −79.3 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.19 (5H, m, Ph), 5.00 (1H, br s, NH), 4.26 (1H, dd, *J*=3.0, 11.0 Hz, CH_aH_b), 4.14 (1H, dd, *J*=4.6, 11.0 Hz, CH_bH_a), 3.80 (1H, ddd, *J*=10.0, 5.0, 5.1 Hz, CHN), 2.85 (1H, dd, *J*=5.2, 13.2 Hz, CH_aH_bPh), 2.60 (1H, dd, *J*=9.6, 13.2 Hz, CH_bH_aPh), 2.17 (1H, m, CH), 1.16 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4 (C=O), 136.2 (C*i*), 129.2 (C*m*), 129.0 (C*o*), 127.1 (C*p*), 71.5 (CH_2–O), 55.3 (CHN), 38.2 (CH_2Ph), 28.8 (CH), 10.6 (CH_3); IR ν_{max}: 3242.8, 2922.7, 1703.8, 1422.8, 1117.6, 767.5, 731.3, 700.8 cm^{-1}; FAB-HRMS calculated for ($C_{12}H_{16}N_1O_2$), 206.1181; found, 206.1162.

*3.6.23. (4S,5R)-4-Benzyl-5-methyltetrahydro-2H-1,3-oxazin-2-one (**11d′**).* White solid, 60% yield, mp=126 °C, $[\alpha]_D^{25}$ −39.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.18 (5H, m, Ph), 5.60 (1H, br s, NH), 4.22 (1H, dd, *J*=4.0, 11.2 Hz, CH_aH_b), 3.91 (1H, t, *J*=11.0 Hz, CH_bH_a), 3.33 (1H, ddd, *J*=9.0, 4.0, 3.6 Hz, CHN), 3.09 (1H, dd, *J*=14.0, 3.6 Hz, CH_aH_bPh), 2.55 (1H, dd, *J*=13.6, 9.6 Hz, CH_bH_aPh), 1.92 (1H, m, CH), 1.09 (3H, d, *J*=6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5 (C=O), 135.7 (C*i*), 129.2 (C*m*), 129.0 (C*o*), 127.3 (C*p*), 70.7 (CH_2O), 58.0 (CHN), 40.7 (CH_2Ph), 31.1 (CH), 13.4 (CH_3); IR ν_{max}: 3243.8, 2924.6, 1704.8, 1420.8, 1117.6, 768.5, 733.3, 701.8 cm^{-1}; FAB-HRMS calculated for ($C_{12}H_{16}N_1O_2$), 206.1181; found, 206.1162.

*3.6.24. (4S,5S)-4-Isopropyl-5-methy-3-(tert-butylcarboxylate)-tetrahydro-2H-1,3-oxazin-2-one (**12a**).* Liquid, 80% yield, $[\alpha]_D^{25}$ +78.4 (*c* 1.39 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.18 (1H, dd, *J*=10.8, 5.6 Hz, CH_aH_bO), 3.80 (1H, dd, *J*=4.8, 2.4 Hz, CHN), 3.77 (1H, d, *J*=10.8 Hz, CH_aH_bO), 2.27 (1H, m, $CHCH_3$), 2.01 (1H, m, CH), 1.52 (9H, s, $3CH_3$), 1.10 (3H, d, *J*=6.8 Hz, CH_3), 0.96 (3H, d, *J*=6.8 Hz, CH_3), 0.95 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.7 (C=O), 151.9 (C=O), 83.1 (C), 70.4 (CH_2O), 64.5 (CHN), 30.0 (CH), 30.1 (CH), 28.0 ($3CH_3$), 19.1 (CH_3), 17.7 (CH_3); IR ν_{max}: 2966.4, 2928.6, 1762.3, 1720.4, 1366.9, 1298.8, 1156.6,

854.8 cm^{-1}. EIMS: calculated for ($C_{13}H_{23}NO_4$), 257.16; found, 257 (2.0%), 114 (100%), 70 (35%) 57 (55%).

*3.6.25. (4S,5R)-4-Isopropyl-5-methyl-3-(tert-butylcarboxylate)-tetrahydro-2H-1,3-oxazin-2-one (**13a′**).* Liquid, 60% yield, $[\alpha]_D^{25}$ +15.5 (*c* 0.6 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.27 (1H, ddd, *J*=11.2, 6.4, 1.2 Hz, CH_aH_bO), 4.07 (1H, dd, *J*=11.28 Hz, CH_aH_bO), 4.06 (1H, dd, *J*=4.4 Hz, CHN), 2.47 (1H, m, $CHCH_3$), 1.98 (1H, m, CH), 1.54 (9H, s, $3CH_3$), 1.10 (3H, d, *J*=6.8 Hz, CH_3), 1.05 (3H, d, *J*=6.8 Hz, CH_3), 0.95 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.6 (C=O), 149.01 (C=O), 83.5 (C), 70.3 (CH_2O), 61.4 (CHN), 32.0 (CH), 29.7 (CH), 28.0 ($3CH_3$), 27.4 (CH_3), 19.2 (CH_3), 13.3 (CH_3); IR ν_{max}: 2966.4, 2928.6, 1762.3, 1720.4, 1366.9, 1298.8, 1156.6, 854.8 cm^{-1}. EIMS: calculated for ($C_{13}H_{23}NO_4$), 257.16; found, 257 (2.0%), 114 (100%), 70 (35%) 57 (55%).

*3.6.26. (4S,5S)-4-Benzyl-5-methy-3-(tert-butylcarboxylate)tetrahydro-2H-1,3-oxazin-2-one (**12d**).* Liquid, 97% yield, $[\alpha]_D^{25}$ +27.9 (*c* 1.36 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.20 (5H, m, Ph), 4.28 (1H, dd, *J*=11.0, 4.6 Hz, CH_aH_bO), 4.13 (1H, ddd, *J*=9.2, 4.6, 4.4 Hz, CHN), 3.88 (1H, dd, *J*=11.2, 6.8 Hz, CH_aH_bO), 3.15 (1H, dd, *J*=13.6, 4.6 Hz, CH_aH_b), 2.75 (1H, dd, *J*=13.6, 9.2 Hz, CH_aH_b), 2.10 (1H, m, $CHCH_3$), 1.54 (9H, s, $3CH_3$), 0.90 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3 (C=O), 150.4 (C=O), 136.5 (C*i*), 129.4 (C*m*), 128.7 (C*o*), 127.0 (C*p*), 83.6 (C), 69.6 (CH_2O), 61.2 (CHN), 40.9 (CH_2), 30.8 ($CHCH_3$), 27.9 ($3CH_3$), 16.3(CH_3); IR ν_{max}: 2978.1, 2933.4, 1788.8, 1741.1, 1720.1, 1292.9, 1255.3, 1153.0, 1096.3, 701.0 cm^{-1}. EIMS: calculated for ($C_{17}H_{18}NO_4$), 305.37; found, 305 (1.0%), 249 (10%), 141 (40%), 114 (100%), 71 (90%) 57 (62%).

*3.6.27. (4S,5R)-4-Benzyl-5-methyl-3-(tert-butylcarboxylate)tetrahydro-2H-1,3-oxazin-2-one (**13d′**).* Liquid, 97% yield, $[\alpha]_D^{25}$ −8.9 (*c* 1.38 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.20 (5H, m, Ph), 4.55 (1H, ddd, *J*=10.9, 6.2, 1.2 Hz, CH_aH_bO), 4.14 (1H, dd, *J*=12.0, 11.2 Hz, CH_aH_bO), 2.93 (1H, dd, *J*=14.0, 4.8 Hz, CH_aH_b), 2.73 (1H, dd, *J*=14.0, 9.6 Hz, CH_aH_b), 2.52 (1H, m, $CHCH_3$), 1.26 (9H, s, $3CH_3$), 1.06 (3H, d, *J*=7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.0 (C=O), 148.7 (C=O), 137.1 (C*i*), 129.5 (C*m*), 128.6 (C*o*), 126.7 (C*p*), 83.4 (C), 70.4 (CH_2O), 58.1 (CHN), 34.6 (CH_2), 31.4 ($CHCH_3$), 27.6 ($3CH_3$), 13.4 (CH_3); IR ν_{max}: 2980.0, 2934.4, 1788.8, 1741.1, 1721.0, 1292.9, 1255.3, 1154.0, 1096.3, 701.0 cm^{-1}. EIMS: calculated for ($C_{17}H_{18}NO_4$), 305.37; found, 249 (10%), 141 (40%), 114 (100%), 71 (90%) 57 (55%).

*3.6.28. (2S,3S)-2,4-Dimethyl-3-[N-(tert-butoxy carbonyl)amino]pentan-1-ol (**14a**).* Liquid, 95% yield, $[\alpha]_D^{25}$ −4.1 (*c* 0.70 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.53 (1H, d, *J*=10.0 Hz, NH), 3.73 (1H, dd, *J*=12.0, 3.0 Hz, CH_aH_bO), 3.44 (1H, dd, *J*=12.0, 2.0 Hz, CH_bH_aO), 3.38 (1H, ddd, *J*=10.0, 9.6, 4.0 Hz, CHN), 3.15 (1H, br s, OH), 2.00 (1H, m, $CHCH_3$), 1.45 (9H, s, $3CH_3$), 1.43 (1H, m, $CH(CH_3)_2$), 1.03 (3H, d, *J*=7.2 Hz, CH_3), 0.93 (3H, d, *J*=7.2 Hz, CH_3), 0.81 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.7 (C=O), 79.6 (C), 65.0 (CH_2O), 56.2 (CHN), 38.0 (CH), 28.3 ($3CH_3$), 27.5 (CH), 20.6 (CH_3), 15.1 (CH_3), 15.0 (CH_3); IR ν_{max}: 3329.9, 2965.9, 2929.6, 1677.4, 1532.6, 1366.2, 1170.9 cm^{-1}. FAB-HRMS calculated for ($C_{12}H_{16}N_1O_3$), 232.1913; found, 232.1923.

*3.6.29. (2R,3S)-2,4-Dimethyl-3-[N-(tert-butoxy carbonyl)amino]pentan-1-ol (**15a′**).* White solid, mp=76 °C, 95% yield, $[\alpha]_D^{25}$ −6.6 (*c* 0.5 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.42 (1H, d, *J*=8.0 Hz, NH), 4.13 (1H, br, OH), 3.45 (1H, ddd, *J*=10.0, 9.8, 2.8 Hz, CHN), 3.41 (1H, dd, *J*=12.4, 4.8 Hz, CH_aH_bO), 3.21 (1H, dd, *J*=11.6, 10.4 Hz, CH_bH_aO), 2.03 (1H, m, $CHCH_3$), 1.58 (1H, m, CH), 1.45 (9H, s, $3CH_3$), 1.00 (3H, d, *J*=6.8 Hz, CH_3), 0.94 (3H, d, *J*=6.4 Hz, CH_3), 0.63 (3H, d, *J*=7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.7 (C=O), 79.8 (C), 65.0 (CH_2O), 55.6 (CHN), 36.1 (CH), 30.0 (CH), 28.2 ($3CH_3$), 20.6 (CH_3), 19.6 (CH_3), 9.0 (CH_3); IR ν_{max}: 3329.9, 2965.9, 2929.6, 1677.4, 1532.6, 1366.2, 1170.9 cm^{-1}. FAB-HRMS calculated for ($C_{12}H_{16}N_1O_3$), 232.1913; found, 232.1923.

*3.6.30. (2S,3S)-2-Methyl-4-phenyl-3-[N-(tert-butoxy carbonyl)amino]-butan-1-ol (**14d**).* White solid, mp=76 °C, 95% yield, $[\alpha]_D^{25}$ +3.35 (*c* 0.92 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.18 (5H, m, Ph), 4.64 (1H, d, *J*=9.2 Hz, NH), 3.83 (1H, m, CHN), 3.78 (1H, d, *J*=12.0 Hz, CH_aH_bO), 3.46 (1H, d, *J*=11.6 Hz, CH_bH_aO), 3.00 (1H, dd, *J*=4.8, 14.0 Hz, CH_aH_b), 2.86 (1H, br s, OH), 2.71 (1H, dd, *J*=8.0, 14.0, CH_bH_a), 1.54 (1H, m, $CHCH_3$), 1.36 (9H, s, $3CH_3$), 1.15 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.8 (C=O), 138.0 (C*i*), 129.1 (C*m*), 128.5 (C*o*), 126.4 (C*p*), 79.6 (C), 64.6 (CH_2O), 53.1 (CHN), 39.0 (CH_2), 38.3 ($CHCH_3$), 28.3 ($3CH_3$), 15.1 (CH_3); IR ν_{max}: 3365.6, 2974.9, 2930.6, 1685.3, 1506.9, 1365.7, 1250.0, 1169.3, 1042.8 cm^{-1}. EI-HRMS: calculated for ($C_{16}H_{25}N0_3$) [M^+−$OC(CH_3)_3$], 206.1181; found, 206.1178.

*3.6.31. (2R,3S)-2-Methyl-4-phenyl-3-[N-(tert-butoxy carbonyl)amino]-butan-1-ol (**15d′**).* White solid, mp=116 °C, 99% yield, $[\alpha]_D^{25}$ −18.5 (*c* 1.94, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.22 (5H, m, Ph), 6.13 (1H, d, *J*=9.2 Hz, NH), 5.36 (1H, d, *J*=9.6 Hz, NH), 4.00 (1H, m, CHN), 2.84 (1H, m, $CHCH_3$), 2.68 (2H, m, CH_2), 1.40 (9H, s, $3CH_3$), 1.26 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.7 (C=O), 156.0 (C=O), 137.8 (C*i*), 129.3 (C*m*), 128.4 (C*o*), 126.5 (C*p*), 79.4 (C), 54.1 (CHN), 40.8 ($CHCH_3$), 40.2 (CH_2), 28.3 ($3CH_3$), 15.1 (CH_3); IR ν_{max}: 3089.4, 2977.6, 2931.8, 1704.5, 1497.1, 1394.1, 1367.3, 1166.0, 700.1 cm^{-1}. EI-HRMS: calculated for ($C_{16}H_{25}N0_3$) [M^+−$OC(CH_3)_3$], 206.1181; found, 206.1178.

*3.6.32. (2S,3S)-2,4-Dimethyl-3-[N-(tert-butoxy carbonyl)amino]pentanoic acid (**16a**).* White solid, mp=89 °C, 97% yield, $[\alpha]_D^{25}$ −29.4 (*c* 0.9 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.95 (1H, br, OH), 5.82 (1H, d, *J*=10.4 Hz, NH), 5.21 (1H, d, *J*=10.4 Hz, NH), 3.40 (1H, m, CHN), 2.82 (1H, m, $CHCH_3$), 1.74 (1H, m, $CH(CH_3)_2$), 1.44 (9H, s, $3CH_3$), 1.26 (3H, d, *J*=7.2 Hz, CH_3), 0.96 (3H, d, *J*=6.8 Hz, CH_3), 0.93 (3H, d, *J*=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.3 (C=O), 156.4 (C=O), 79.0 (C), 58.4 (CHN), 40.5 ($CHCH_3$), 32.0 ($CH(CH_3)_2$), 28.4 ($3CH_3$), 20.0 (CH_3), 19.3 (CH_3), 15.6 (CH_3); IR ν_{max}: 3313.1, 2964.4, 2926.5, 1709.0, 1392.0, 1367.4, 1169.9 cm^{-1}. FAB-HRMS calculated for ($C_{12}H_{24}N0_4$), 246.1705; found, 246.1690.

*3.6.33. (2R,3S)-2,4-Dimethyl-3-[N-(tert-butoxy carbonyl)amino]pentanoic acid (**17a′**).* Liquid, 96% yield, $[\alpha]_D^{25}$ +3.7 (*c* 0.9 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.22 (1H, br, OH), 5.83 (1H, d, *J*=10.0 Hz, NH), 4.50 (1H, d, *J*=10.8 Hz, NH), 3.80 (1H, m, CHN), 3.67 (1H, m, $CHCH_3$), 1.77 (1H, m, $CH(CH_3)_2$), 1.43 (9H, s, $3CH_3$), 1.17 (3H, d, *J*=7.2 Hz, CH_3), 0.95 (3H, d, *J*=6.4 Hz, CH_3), 0.90 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.0 (C=O), 156.0 (C=O), 79.3 (C), 57.1 (CHN), 42.5 ($CHCH_3$), 30.2 ($CH(CH_3)_2$), 28.3 ($3CH_3$), 20.2 (CH_3), 16.9 (CH_3), 12.9 (CH_3); IR ν_{max}: 3313.1, 2964.4, 2926.5, 1709.0, 1392.0, 1367.4, 1169.9 cm^{-1}. FAB-HRMS calculated for ($C_{12}H_{24}N0_4$), 246.1705; found, 246.1690.

*3.6.34. (2S,3S)-2-Methyl-4-phenyl-3-[N-(tert-butoxy carbonyl)amino]-butanoic acid (**16d**).* White solid, mp=116 °C, 99% yield, $[\alpha]_D^{25}$ −18.5 (*c* 1.94, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.22 (5H, m, Ph), 6.13 (1H, d, *J*=9.2 Hz, NH), 5.36 (1H, d, *J*=9.6 Hz, NH), 4.00 (1H, m, CHN), 2.84 (1H, m, $CHCH_3$), 2.68 (2H, m, CH_2), 1.40 (9H, s, $3CH_3$), 1.26 (3H, d, *J*=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.7 (C=O), 156.0 (C=O), 137.8 (C*i*), 129.3 (C*m*), 128.4 (C*o*), 126.5 (C*p*), 79.4 (C), 54.1 (CHN), 40.8 ($CHCH_3$), 40.2 (CH_2), 28.3 ($3CH_3$), 15.1 (CH_3); IR ν_{max}: 3089.4, 2977.6, 2931.8, 1704.5, 1497.1, 1394.1, 1367.3, 1166.0, 700.1 cm^{-1}. EI-HRMS: calculated for ($C_{16}H_{23}N0_4$) [M^+−$OC(CH_3)_3$], 220.0974; found, 220.0970.

*3.6.35. (2R,3S)-2-Methyl-4-phenyl-3-[N-(tert-butoxy carbonyl)amino]-butanoic acid (**17d′**).* White solid, mp=156 °C, 92% yield, $[\alpha]_D^{25}$ −32.7

(*c* 1.88, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.92–7.19 (5H, m, Ph), 6.22 (1H, d, *J*=8.8 Hz, NH), 4.81 (1H, d, *J*=9.2 Hz, NH), 4.12 (1H, m, CHN), 2.87 (1H, m, $CHCH_3$), 2.71 (2H, m, CH_2), 1.34 (9H, s, $3CH_3$), 1.26 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.8 (C=O), 155.3 (C=O), 137.7 (C*i*), 129.3 (C*m*), 128.3 (C*o*), 126.4 (C*p*), 79.4 (C), 53.4 (CHN), 43.1 ($CHCH_3$), 37.8 (CH_2), 28.0 ($3CH_3$), 13.3 (CH_3); IR ν_{max}: 3316.1, 2977.8, 2931.8, 1704.9, 1647.6, 1393.9, 1167.1, 699.6 cm^{-1}. EI-HRMS: calculated for ($C_{16}H_{23}N0_4$) [$M^+-OC(CH_3)_3$], 220.0974; found, 220.0970.

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References and notes

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13. *Crystal data for* ***5d***: $C_{23}H_{28}N_2O$, *M*=348.47, colorless prism, 0.60×0.40×0.38 mm^3, space group $P6_4$, cell parameters *a*=*b*=11.737 (3), *c*=13.573(8) Å *Z*=3, *Ź*=1/2, D_c=1.072 g cm^{-3}. 6350 reflections collected on a Siemens P4 diffractometer at room temperature, with the Mo Kα radiation (λ=0.71073 Å) in the range 2θ=4–50°, of which 979 are unique (R_{int}=0.0386). 124 variables refined: R_1=0.0608 [601 data with $I>2\sigma(I)$] and wR_2=0.1849 [all data].[21] Absolute configuration was determined assigned as (*S*,*S*) from synthetic route, which uses a commercial chiral starting material, and measured Friedel pairs were merged. CCDC-745170 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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