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Employing lactams for the unprecedented enantiopure synthesis of non-natural amino acid derivatives

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ABSTRACT

The enantiopure non-natural amino acids[1] have been synthesized by insitu generation of iminium and iminium triflates from lactams using triflic anhydride in pyridine buffered media. These molecules with remote chiral centers may be useful in synthesis of natural product particularly *Kopsia* derived alkaloids.

1. Introduction

Thiazoline is one of the most common heterocycle found in many bioactive natural products of peptide origin.[2] This substructure offers conformational rigidity and caters as a recognition site for DNA, RNA, and protein binding.[3] The β-turn structure is formed by intramolecular hydrogen bonding in a tripeptide substructure at the protein surface, and is well recognized ligand by various receptors.[4] The low molecular-weight compounds, especially those incorporating thiazoline mimic the β-turn substructure of natural polypeptide ligands to overcome the pharmacokinetic disadvantages of peptide ligands.[5] These molecules are of current interest due to their presence in numerous interesting natural products and in catalyst designing.[6] The thiazoline has an advantage of electrophilic addition at exomethine position followed by quenching with various alkyl halides and subsequent reduction to substituted 2-methyl thiazolidine. These 2-methyl thiazolidines can provide 2-alkyl substituted aldehydes and carboxylic acids on cleavage with mercuric chloride[7] and on acidic hydrolysis,[8] respectively. (Fig. 1) Even though numerous methodologies are available for the synthesis of thiazolines[6b,9] but high yields of substituted thiazolines are sometimes not obtained, especially with acid-sensitive or racemization prone substrates. There are reports that at low temperature in a buffered medium with excess pyridine, iminium, and imino triflates can be generated and reacted with amino thiols to allow efficient access to thiazolines without any racemization. Pioneering studies by Ghosez and others[10] have demonstrated that iminium (**2**) and imino triflates (**3**) can be generated by the treatment of tertiary or secondary amides with triflic anhydride (Tf_2O). Chaerette and Chua[9h,11] reasoned that subsequent addition of amino thiols to such highly electrophilic species may lead to the formation of thiazoline under tolerable conditions to most of the functional groups and chiral centers (Fig. 2).

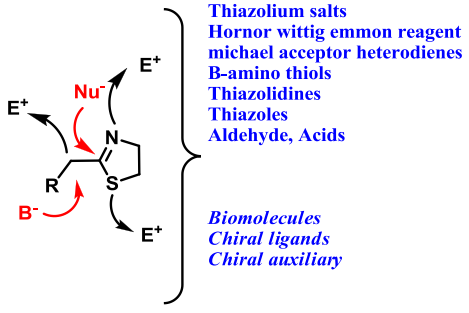

Fig. 1. Reactivity and synthetic application of 2-thiazoline.

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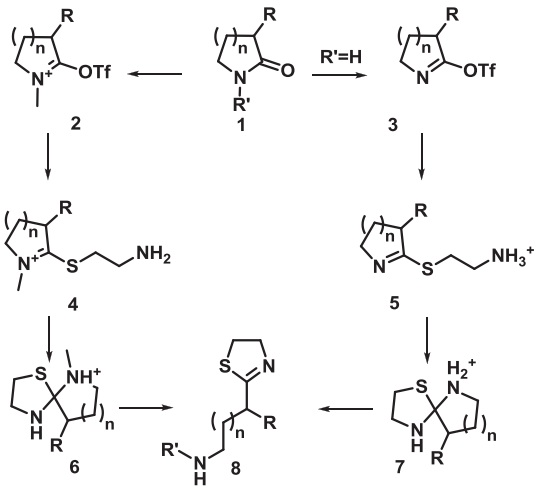


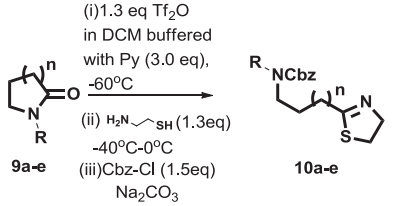
Fig. 2. Schematic representation of iminium and iminium triflates reacting with amino thiols resulting to respective thiazoline.

2. Result and discussion

In view of the importance of substrates bearing remote chiral center in the synthesis of natural products, it appeared of interest to explore the possibility of generating iminium and iminium triflates from different hither to unexplored cyclic amides (lactams). The optimal conditions involved an initial activation of the lactam by the slow addition of Tf_2O to the lactam to avoid the formation of *N*-triflylpyridinium triflates,[12] which are less reactive for O-sulfonylation of lactam due to the exotherm in anhydrous dichloromethane containing pyridine, which is present to neutralize any adventitious acid. Stronger bases than pyridine might form a conjugate acid that would be too weak to the addition of the amine on to the thioimidate or for the elimination of the amine residue.

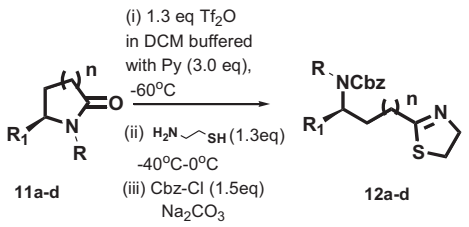
The methodology has been successfully extended to larger lactam ring viz. valero- and capro-lactam for the generation of the respective 4-(4,5-dihydrothiazol-2-yl) butan-1-amine (**10c**) and 5-(4,5-dihydrothiazol-2-yl) pentan-1-amine (**10e**) in 72% and 64% yield, respectively (Table 1). The reaction was found equally efficient for tertiary lactam (Table 2). It was a general observation that on continuing the reaction for longer time there was an increase in the yield. In view of the poor stability of the free amino derivatives, the amino group was protected as carbamate.

Table 1
The obtained after thiazolination mediated ring opening using triflic anhydride in the presence of pyridine



Compd	*n*	R	Time (h)	Yield (%)
10a	1	H	3.5	72
10b	1	CH_3	4.0	78
10c	2	H	3.5	64
10d	2	CH_3	4.0	67
10e	3	H	3.5	57
			5.0	68

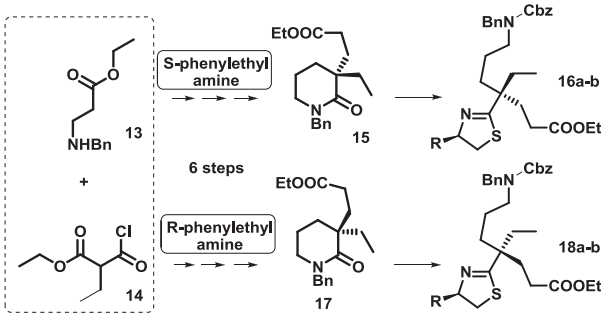
Table 2
The summarized results of the thiazolination employed on the derivatives of L-pyroglutamide



Compd	R	R_1	Tf_2O	Time (h)	Yield (%)
12a	CH_3	CH_3CO	1.3	2.5	65
12b	CH_3	$COOCH_3$	1.5	1.5	74
12c	H	CH_3CO	1.3	4.0	68
12d	H	$COOCH_3$	1.4	3.5	70

In this reaction there was no racemization at the C (α) of amidic center when thiazolination was carried out in (2*S*,4*S*)-methyl-4-methyl-5-oxopyrrolidine-2-carboxylate (**12a**–**d**). In order to generalize it we used (*R*)/(*S*)-ethyl 3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)propanoate (**15** and **17**) to give the respective thiazolinized product in quantitative with the retention of configuration (Table 3). The substrates **15** and **17** used in this reaction were synthesized using Desmaele's approach.[13]

Table 3
Results obtained with the lactam possessing chiral center at the α-C (**15** and **17** were synthesized using Desmaele's method)



	R	Tf_2O	Time (h)	Yield (%)
16a	H	1.3	7.0	64
16b	$COOCH_3$	1.5	6.0	72
18a	H	1.3	7.8	74
18b	$COOCH_3$	1.5	5.5	75

Since the thiazolination of lactam was equally facile similar to the case of amides, the comparison of amide and lactam reactivity toward the reaction conditions was made on (*R*)-*N*-methyl-pyroglutamide (**19**) (Fig. 3, Tables 4 and 5) as it possesses both lactam and simple amide functionalities within the same molecule. Thus the reaction of **19** with 1.3 equiv of Tf_2O and 1.0 equiv of amino thiol resulted in the formation of 5-(4,5-dihydrothiazol-2-yl)pyrrolidin-2-one (**20**) only as a single product indicating that the reaction preferably took place at amide than lactam. Whereas, the increase in the amount of Tf_2O to 2×1.3 equiv resulted in the thiazolination of both the amide and lactam to give (*R*)-1,3-bis(4,5-dihydrothiazol-2-yl)propan-1-amine (**21**, Table 4).When the experiment was carried out with the weinreb amide analogue *N*-methoxy-1-dimethyl-5-oxopyrrolidine-2-carboxamide (**22**) the terminal thiazolinization was superseded by the formation of open chain thiazoline counterpart as the isolated (*R*)-4-(4,5-dihydrothiazol-2-yl)-*N*-methoxy-*N*-methyl-2 (methylamino)-butanamide (**24**) was obtained as the major product, the ratio of the

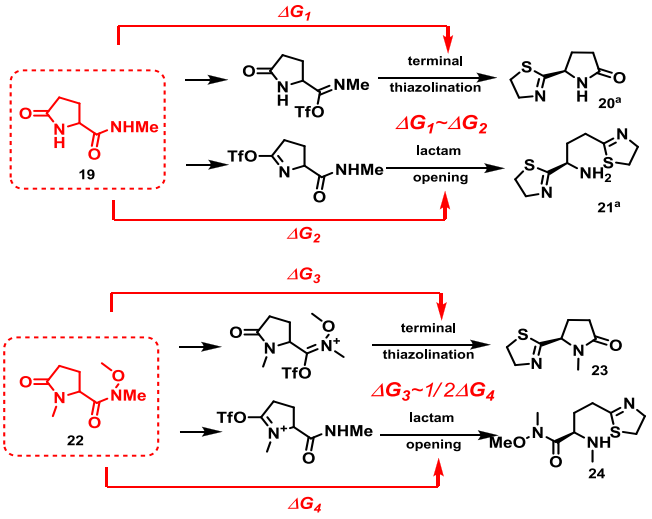


Fig. 3. Representation of the free energy for the two possibilities of thiazolination in the case of pyroglutamide (**19**) and its weinreb analogue (**22**). [a]Methyl ester cysteine hydrochloride was employed in place 2-amino ethanethiol resulted to the formation of the respective thiazolinized products (20.1 and 21.1) and showed similar reactivity (details are given in Supplementary data).

Table 4
Summary of the obtained results when pyroglutamide was subjected to the thiazolination

Tf_2O	Time (h)	Yield (%)[a]
Compd **20**		
1.3 equiv	1.5	34
	2.5	59
	3.5	65
Compd **21**		
3.0 equiv	2.0	40
	3.0	54
	4.0	68

[a] The yield shown are determined after the Cbz-protection due to the instability of the free amino products the NMR details of the protected products are denoted as **20[p]** and **21.1[p]** (details are given in Supplementary data).

Table 5
The amount of amide and lactam thiazolination and obtained when weinreb amide derivative of pyroglutamide was thiazolinized

Tf_2O	Time (h)	Yield (%)[a]	
		Compd **23**	Compd **24**
1.5	4.0	16	49
	5.0	21	58
	6.0	24	64

[a] Isolated yield.

two products (**24**:**23**) was 3:1 based on the isolated yields. This offers scope for the further investigation on the selectivity in the reactivity of amidic linkage.

In order to account for this selectivity the computational studies for the probable energetics of the two possible fates of thiazolination with pyroglutamide were performed and a comparison of the free energy change for the two possibilities of O-triflation (i) at lactam and (ii) at terminal amide was done using RHF 3-21G and RHF 6-31G basis set (Table 4 and Fig. 3). The optimization of the structure was accomplished and the relative values of free energy change were calculated on two hybrid basis set RHF 3-21G//RHF 6-31G and RHF 3-21G//Becke3LYP. Since, the free energy change G_1 and G_2 for the terminal and lactam, respectively, were almost equal, i.e., $\Delta G_2 \approx \Delta G_1$ therefore the possibility of thiazolination at the amidic linkage was nearly the same for thiazolination at lactam. Therefore, in the presence of 2.5 equiv of triflic anhydride dithazolinated product was obtained. Whereas, in the complementary case of weinreb amide analogue where $\Delta G_4 \approx 1/2\Delta G_3$ favored the formation of open chain thiazoline derivative.

The above described novel ring opening strategy could be implicated in the synthesis of molecules possessing remote chiral centers, which may be envisaged as crucial starting substrate for the total synthesis of natural product viz. alkaloids derived from the genus *Kopsia*.[14] The Desmaele's method of synthesizing lactam having substitutions at the third carbon center, which can be accomplished stereoselectively by an elegant incorporation of (*R*/*S*) α-methyl benzyl amine as a chiral auxiliary. A new application of Desmaele's method for generating stereoselectively *R*- and *S*-ethyl-7-(benzylamino)-4-(4,5-dihydrothiazol-2-yl)-4-ethyl heptanoate (**16a** and **18a**) from the corresponding *R*- and *S*-ethyl 3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)propanoate (**15** and **17**) via triflic anhydride mediated thiazolination has been explored (Table 4). The products **16a** and **18a** have an advantage that they possess easily transformable groups at three terminals, which can be explored in the generation of chemical libraries of non-natural amino acid derivatives of medicinal importance. To begin with the **16a** and **18a** were used to prepare 2-oxoazepanes (**25** and **26**, Fig. 4) possessing chiral center at C-5 as such scaffolds are of pharmaceutical importance.[15]

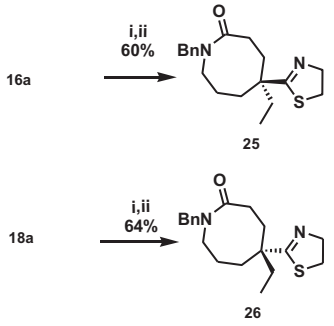


Fig. 4. Synthesis of 2-oxoazepane derivative by Lactamization. Reagent and conditions: (i) Pd (10% on activated charcoal), methanol, 2.5 h 94% (ii) $Al(Me)_3$ (1.5 equiv, 25% solution in hexane), benzene and DCM, 8 h, −10° to 0 °C.

Thus the presented novel method for the preparation of non-natural amino acids may be considered as an important tool in deriving molecules of targeted importance.

3. Conclusion

In conclusion we have successfully developed a methodology of thiazolination using lactam as starting material and extended this methodology in developing non-natural amino acids possessing remote chiral centers. In addition we have found a procedure for the selective thiazolination in the molecules possessing both lactam and amide, which can be explored further. The applications of this method toward the synthesis of Rhazinilam and Arbolocine are underway and will be reported in due course.

4. Experimental section

4.1. General information

In general, all reagents and solvents were of commercial quality and were used without further purification. IR spectra (ν_{max} in cm^{-1}) of the compounds were recorded on Perkin–Elmer's FT-IR

RX1 PC spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Supercon Magnet Avance DRX-300 spectrometers (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C) in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, J in Hz). Electro Spray Ionization Mass spectra (ESI-MS) were recorded on Thermo Lcq Advantage Max-IT, 6520 Accurate-mass Q-TOF LC/MS Agilant and JEOL, JMS T100LC Accu TOF. Elemental analyses were performed on Carlo Erba EA-1108 micro analyzer/ Vario EL-III C H N S analyzer. All compounds were analyzed of C, H, N and the results obtained were within ±0.4% of calculated values. The reaction progress was routinely monitored by thin layer chromatography (TLC) on pre-coated silica gel plates (Aldrich). Column chromatography was performed over Merck silica gel (100–200 mesh). All compounds were characterized by TLC, ^{1}H NMR and ^{13}C NMR, MS and HRMS. Elemental analyses data meet the criteria of ≥95% purity. All chemicals and solvents were procured from Sigma–Aldrich/Merck, India Ltd.

4.2. General experimental procedure for the thiazolination of secondary and tertiary lactams (Table 1, entry 1)

(a) Pyrrolidone (85 mg, 1 mmol), DCM (10 ml) and pyridine (235 μl, 3.0 mmol) are mixed in a dry 25 ml double necked R.B flask under nitrogen atmosphere. The resulting solution is cooled to −65 °C and then neat triflic anhydride (229 μl, 1.3 mmol) is added slowly to the solution. After completion of the addition of Tf_2O, the reaction mixture is allowed to warm up to −40 °C (approx.1.5 h) then gradually cooled to −60 °C and added 2-amino ethanethiol (130 mg, 1.7 mmol) followed by addition of another 235 μl (3.0 mmol) of pyridine and warmed the reaction mixture to −30 °C and is allowed to stir for another hour at the same temperature and then allowed to stir for 1.5 h at room temperature. After the optimum completion of the reaction (as per TLC), the reaction mixture is then filtered through silica bed (60–120 mesh) and eluted with diethyl ether. The ethereal filtrate is concentrated and purified using Flash chromatography to obtain thiazolinized product (**10a′**) as yellow colored oil. (In a general observation these products are sensitive to aqueous acid and are not stable enough at room temperature therefore protection of free amino terminal as carbamate is performed.)

(b) The ethereal filtrate was taken in a 25 ml R.B. flask and added TEA (187 μl, 1.3 mmol) at 0 °C, followed by the addition of benzyl chloroformate (186 μl, 1.5 mmol) or di-*tert*-butyl carbonate (344 μl, 1.5 mmol) and then allowed the reaction mixture to stir at room temperature for 10–14 h. After the completion of reaction in vacuo distillation is carried out a deep yellow colored crude product was obtained. The desired Cbz or Boc protected thiazolinized product was purified with flash chromatography on silica gel as light yellow colored oil in quantitative yield. (**10a**).

*4.2.1. 3-(4,5-Dihydrothiazol-2-yl)propan-1-amine (**10a′**).* The crude product obtained using the general procedure is purified using flash chromatography (15% EtOAc/hexane) to give the title compound **10a′** (41.0 mg, 78%) as light yellowish oil; R_f 0.26 (30% EtOAc/hexane); IR (neat) 3345, 2765, 2324, 1637, 1106 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (t, J=5.7 Hz, 2H, NCH_2), 3.36 (t, J=5.7 Hz, 2H, SCH_2), 2.69 (t, J=7.5 Hz, 2H, NH_2CH_2), 2.44 (dd, J=12.0 Hz, 4.3, 2H, αCH_2), 2.10 (s, 2H, NH_2), 2.04–1.58 (m, 2H, βCH_2); Due to instability of compound ^{13}C NMR was precluded; HRMS (ES) calcd for $C_6H_{12}N_2S$ (M^+) 144.0721 found 144.0754 m/z.

*4.2.2. Benzyl 3-(4,5-dihydrothiazol-2-yl)propylcarbamate (**10a**).* The crude product obtained using general procedure of carbamylation as using **10a′** as starting material is purified using flash chromatography (5% EtOAc/hexane) to give the title compound **10a** (57.0 mg, 72%) as light yellowish colored oil; R_f 0.76 (10% EtOAc/hexane); IR (neat) 1676.4, 1637.4 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.05 (m, 5H, ArH), 5.38 (s, 2H, benzyCH_2), 4.12–3.77 (m, 2H, NCH_2), 3.63–3.33 (m, 2H, SCH_2), 3.08 (q, J=7.6 Hz, 2H, NHCH_2), 2.64–2.23 (m, 2H, αCH_2), 1.76 (qd, J=7.9 Hz, 1.6, 2H, βCH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.67, 157.78, 137.09, 128.32, 128.32, 128.17, 128.17, 128.16, 66.69, 60.84, 41.22, 36.20, 28.84, 24.57; HRMS(ES) calcd for $C_{14}H_{18}N_2O_2S$ (M^+) 278.1089 found 278.1077 m/z.

*4.2.3. 3-(4,5-Dihydrothiazol-2-yl)-N-methylpropan-1-amine (**10b′**).* The crude product obtained using similar procedure (a) is purified using column chromatography (30% EtOAc/hexane) to give **10b** (64.0 mg, 80%) as yellowish oil; R_f 0.36 (30% EtOAc/hexane); IR (neat) 3254, 1640, 1213 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (dd, J=10.4, 3.8 Hz, 2H, NCH_2), 3.47 (dd, J=10.3, 3.8 Hz, 2H, SCH_2), 2.51 (dq, J=16.4, 7.7 Hz, 7H, NCH_3, NCH_2, αCH_2), 1.95–1.42 (m, 2H, βCH_2), 1.15 (s, 1H, NH); Due unstable nature of the compound ^{13}C NMR was precluded.; HRMS (ES) calcd for $C_7H_{14}N_2S$ (M^+) 158.0878, found 158.0874.

*4.2.4. Benzyl 3-(4,5-dihydrothiazol-2-yl)propyl(methyl)carbamate (**10b**).* The crude product obtained using general procedure is purified using column chromatography (5% EtOAc/hexane) to give the title compound **10b** (41.0 mg, 78%) as yellowish oil; R_f 0.54 (5% EtOAc/hexane); IR(neat) 1651, 1635, 935 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–6.91 (m, 5H, ArH), 5.36 (s, 2H, benzylCH_2), 4.05–3.74 (m, 2H, NCH_2), 3.76–3.38 (m, 3H, SCH_2, NHCHH), 3.23–2.92 (m, 4H, NHCHH, NCH_3), 2.61–2.12 (m, 2H, αCH_2), 1.84 (qd, J=7.9, 1.5 Hz, 2H, βCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.67, 156.07, 137.09, 128.32, 128.32, 128.17, 128.17, 128.16, 76.98, 67.05, 60.84, 49.53, 36.20, 34.62, 29.16, 21.08; ESI-MS: 293.4 (M^++1), Elemental analysis of $C_{15}H_{20}N_2O_2S$ calcd. C, 61.62; H, 6.89; N, 9.58 found C, 61.56; H, 6.79; N, 9.48.

*4.2.5. Benzyl 4-(4,5-dihydrothiazol-2-yl)butylcarbamate (**10c**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **10c** (47.0 mg, 64%) yellowish oil; R_f 0.60 (5% EtOAc/hexane); IR (neat) 1655.8, 1637, 1243, 935 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–6.97 (m, 5H, ArH), 5.37 (s, 2H, benzylCH_2), 4.01 (t, J=5.8 Hz, 2H, NCH_2), 3.47 (t, J=5.8 Hz, 2H, SCH_2), 3.04 (t, J=7.5 Hz, 2H, NHCH_2), 2.44 (t, J=5.3 Hz, 2H, αCH_2), 1.87–1.37 (m, 4H, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.67, 157.78, 137.09, 128.31, 128.17, 76.98, 66.69, 60.84, 41.51, 36.20, 30.65, 28.92, 24.03.; HRMS(ES) calcd for $C_{15}H_{20}N_2O_2S$ (M^+), 292.1245, found 292.1223 m/z.

*4.2.6. Benzyl 4-(4,5-dihydrothiazol-2-yl)butyl(methyl)carbamate (**10d**).* The crude product obtained using general procedure is purified using flash chromatography (5% EtOAc/hexane) to give **10d** (40.0 mg, 70%) as yellowish oil; R_f 0.64 (5%EtOAc/hexane); IR(neat) 1654, 1635, 1212, 1195 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–6.83 (m, 5H, ArH), 5.35 (s, 2H, benzyCH_2), 4.00 (t, J=5.8 Hz, 2H, NCH_2), 3.73–3.52 (m, 2H, SCH_2), 3.43 (t, J=5.8 Hz, 2H, $NHCH_2$), 3.08 (s, 3H, NCH_3), 2.99–2.76 (m, 1H,), 2.42 (t, J=5.6 Hz, 2H, αCH_2), 1.82–1.11 (m, 4H, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.67, 156.07, 137.09, 128.31, 128.17, 76.98, 67.05, 60.84, 50.93, 36.20, 34.62, 30.65, 26.35, 23.91; HRMS (ES) calcd for $C_{16}H_{22}N_2O_2S$(M^+) 306.4231 found 306.4228 m/z.

*4.2.7. Benzyl 5-(4,5-dihydrothiazol-2-yl)pentylcarbamate (**10e**).* The crude product obtained using general procedure for the insitu carbamylation is purified using flash chromatography (5% EtOAc/hexane) to give **10e** (45.0 mg, 57%) as dirty yellow oil; R_f 0.62 (5% EtOAc/hexane) IR (neat) 1658, 1627, 1245, 935 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–6.87 (m, 5H, ArH), 5.38 (s, 2H, benzylCH_2), 4.11 (dd, J=9.6, 3.4 Hz, 2H, NCH_2), 3.87 (s, 1H, NH), 3.62 (dd, J=9.6, 3.4 Hz, 2H, SCH_2), 3.07 (td, J=7.4, 3.1 Hz, 2H, NHCH_2), 2.35 (t, J=7.7 Hz, 2H, αCH_2), 1.98–1.06 (m, 6H, 3CH_2).^{13}C NMR (75 MHz, $CDCl_3$) δ 171.67, 157.78, 137.09, 128.31, 128.17, 76.98, 66.69, 60.84,

41.51, 36.20, 30.65, 29.49, 26.64, 25.73; HRMS(ES) calcd for $C_{16}H_{22}N_2O_2S$ (M^+), 306.1402, found 306.1421 *m/z*.

*4.2.8. (R)-5-(4,5-Dihydrothiazol-2-yl)-3-(methylamino)pentan-2-one (**12a′**).* The crude product obtained using general procedure is purified using column chromatography (5% EtOAc/hexane) to give the title compound **12a′** (70.0 mg, 72%) as yellowish oil; IR (neat) 3435, 2932, 1720, 1654, 1616 cm^{-1}; R_f 0.28 (8% EtOAc/hexane); $[\alpha]_D^{20}$ +12.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.00 (t, *J*=6.4 Hz, 2H, NCH_2), 3.41 (t, *J*=6.4 Hz, 2H, SCH_2), 2.85 (t, *J*=5.6 Hz, 1H, NHC*H*), 2.55 (s, 3H, NCH_3), 2.52–2.29 (m, 2H, αCH_2), 2.15 (s, 3H, CH_3), 2.11–1.80 (m, 2H, βCH_2); Due to the unstability of **12a′** ^{13}C NMR is precluded; HRMS (ES) calcd for $C_9H_{16}N_2OS$ (M^+), 200.0983, found 200.1234 *m/z*.

*4.2.9. (S)-tert-Butyl-1-(4,5-dihydrothiazol-2-yl)-4-oxopentan-3-yl(methyl)carbamate (**12a**).* The crude product obtained using general procedure for insitu carbamylation is purified using flash chromatography (5% EtOAc/hexane) to give **12a** (68.0 mg, 65%) as yellowish oil; R_f 0.58 (5% EtOAc/hexane); IR (neat) 2943, 2929, 1720, 1666, 1654, 1414, 1108 cm^{-1}; $[\alpha]_D^{20}$ +43.5 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (t, *J*=6.6 Hz, 1H, NC*H*), 3.88 (t, *J*=5.7 Hz, 2H, NCH_2), 3.37 (t, *J*=5.7 Hz, 2H, SCH_2), 3.09 (s, 3H, NCH_3), 2.59–2.29 (m, 2H, αCH_2), 2.28–1.84 (m, 5H, $COCH_3$, βCH_2), 1.51 (s, 9H. 3CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.71, 170.74, 156.80, 80.96, 76.98, 66.83, 64.76, 40.06, 32.66, 29.79, 28.41, 28.13, 25.83 ESI-MS 301.1 (M+H); Elemental analysis: calcd for $C_{14}H_{24}N_2O_3S$ C, 55.97; H, 8.05; N, 9.32; found C, 55.93; H, 8.01; N, 9.26; HRMS (ES) calcd 300.1508, found 300.1515.

*4.2.10. (R)-Ethyl-2-((benzyloxycarbonyl) (methyl)amino)-4-(4,5-dihydrothiazol-2-yl)butanoate (**12b**).* The crude product obtained using condition A is purified using flash chromatography (5% EtOAc/hexane) to give **12b** (50.0 mg, 74%) as yellowish oil; R_f 0.62 (5% EtOAc/hexane); $[\alpha]_D^{20}$ +16.5 (*c* 1.0, $CHCl_3$); IR (neat) 1735.3, 1640.4, 1615, 1323.8, 937.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76–6.63 (m, 5H, Ar*H*), 5.36 (s, 2H, benzylCH_2), 4.40–4.26 (m, 1H, NC*H*), 4.20 (q, *J*=6.0 Hz, 2H, OCH_2), 4.05 (t, *J*=6.8 Hz, 2H, NCH_2), 3.61 (t, *J*=6.8 Hz, 2H, SCH_2), 3.01 (s, 3H, NCH_3), 2.44–2.10 (m, 4H, CH_2CH_2), 1.37 (t, *J*=6.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.80, 170.74, 155.47, 136.99, 128.33, 128.20, 76.98, 67.42, 64.76, 61.80, 60.49, 40.06, 32.66, 29.79, 28.47, 14.70.; HRMS (ES) calcd for $C_{18}H_{24}N_2O_4S$ (M^+), 364.1456, found 364.1389 *m/z*.

*4.2.11. (S)-Benzyl 1-(4,5-dihydrothiazol-2-yl)-4-oxopentan-3-ylcarbamate (**12c**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give **12c** (82.0 mg, 68%) as greenish yellow oil; R_f 0.65 (5% EtOAc/hexane); IR (neat) 1705, 1632, 1609, 1321, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J*=8.5 Hz, 5H, Ar*H*), 5.39 (s, 2H, benzylCH_2), 4.72–4.24 (m, 1H, NHC*H*), 4.20–3.76 (m, 3H, NCH_2, NH), 3.76–3.21 (m, 2H, SCH_2), 2.67–1.62 (m, 7H, $\alpha CH_2\beta CH2$, $COCH_3$); ^{13}C NMR (75 MHz, CDCl3) δ 207.17, 170.74, 159.05, 136.99, 128.33, 128.33, 128.21, 128.21, 128.18, 67.06, 64.76, 58.07, 40.06, 28.43, 28.32, 27.13; HRMS (ES) calcd for $C_{16}H_{20}N_2O_3S$ (M^+) 320.4066, found 320.4054 *m/z*.

*4.2.12. (R)-Ethyl 2-amino-4-(4,5-dihydrothiazol-2-yl)butanoate (**12d′**).* The crude product obtained using condition A is purified using flash chromatography (30% EtOAc/hexane) to give **12d′** (41.0 mg, 68%) as yellowish oil; R_f 0.14 (35% EtOAc/hexane); $[\alpha]_D^{20}$ +11.1 (*c* 1.0, $CHCl_3$); IR(neat) 3440, 1735, 1640, 1356 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, *J*=6.0 Hz, 2H, OCH_2), 4.06–3.85 (m, 2H, NCH_2), 3.71–3.37 (m, 3H, NH_2, NH_2CH), 2.57–2.32 (m, 2H, SCH_2), 2.14 (ddd, *J*=15.4, 8.9, 6.3 Hz, 2H, αCH_2), 1.38 (t, *J*=6.0 Hz, 3H, CH_3); Unstable for longer time therefore ^{13}C NMR were precluded; ESI-MS:217.2 (M+1), 201.2 ($M-NH_2$); HRMS (ES) calcd for $C_9H_{16}N_2O_2S$ (M^+) 216.0932, found 216.0940 *m/z*.

*4.2.13. (R)-Ethyl 2-(benzyloxycarbonylamino)-4-(4,5-dihydrothiazol-2-yl)butanoate (**12d**).* The crude product obtained using general procedure of insitu carbamoylation is purified using flash chromatography (5% EtOAc/hexane) to give **12d** (35.0 mg, 70%) as yellowish oil; R_f 0.56 (8% EtOAc/hexane); $[\alpha]_D^{19}$ −37.2 (*c* 1.0, $CHCl_3$); IR (neat) 3230, 2926, 1645, 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–6.84 (m, 5H, Ar*H*), 5.40 (s, 2H, benzylCH_2), 4.88–4.63 (m, 1H, NHC*H*), 4.16 (q, *J*=5.9 Hz, 2H, OCH_2), 3.77–3.49 (m, 2H, NCH_2), 3.48–3.26 (m, 2H, SCH_2), 2.55–2.17 (m, 4H, $\alpha CH_2\beta CH_2$), 1.36 (t, *J*=6.0 Hz, 3H, CH_3), 0.94 (s, 1H, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.12, 170.73, 159.04, 136.99, 128.33, 128.20, 76.97, 67.05, 64.76, 61.79, 52.79, 40.06, 30.10, 28.42, 14.69; HRMS (ES) calcd for $C_{17}H_{22}N_2O_4S$ (M^+): 186.1494, found 186.1488 *m/z*.

*4.2.14. (S)-Ethyl-7-(benzylamino)-4-(4,5-dihydrothiazol-2-yl)-4-ethylheptanoate (**16a′**).* The crude product obtained using condition A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **16a′** (41.0 mg, 72%) yellowish oil; R_f 0.74 (14% EtOAc/hexane); $[\alpha]_D^{20}$ +65 (*c* 1.0, $CHCl_3$); IR (neat) 3434, 1752, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 5H, Ar*H*), 4.35–3.82 (m, 2H, benzylCH_2), 3.55 (dd, *J*=9.5, 3.4 Hz, 4H, OCH_2, NCH_2), 2.62 (td, *J*=7.4, 2.9 Hz, 4H, SCH_2, αCH_2), 2.44–2.00 (m, 6H, βCH_2, alkyl*H*), 1.86 (td, *J*=6.7, 4.0 Hz, 2H, alkyl*H*), 1.82–1.44 (m, 2H, alkyl*H*), 1.37 (t, *J*=5.9 Hz, 3H, $COOCH_2CH_3$), 1.01 (t, *J*=6.6 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.42, 171.87, 140.76, 128.30, 127.52, 126.58, 76.98, 65.11, 61.18, 52.12, 50.49, 49.15, 41.45, 40.13, 38.15, 36.51, 30.56, 23.96, 14.70, 8.20; HRMS (ES) calcd for $C_{21}H_{32}N_2O_2S$ (M^+), 376.2184, found 376.2491 *m/z*.

*4.2.15. (S)-Ethyl-7-(benzyl(benzyloxycarbonyl)amino)-4-(4,5-dihydrothiazol-2-yl)-4-ethylheptanoate (**16a**).* The crude product obtained using general procedure is purified using flash chromatography (5% EtOAc/hexane) to give **16a** (35.0 mg, 64%) as yellowish oil; R_f 0.78 (5% EtOAc/hexane); $[\alpha]_D^{20}$ +132.7 (*c* 1.0, $CHCl_3$); IR (neat) 1735, 1685, 1647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (dd, *J*=8.7 Hz, 2.7, 10H, Ar*H*), 5.41 (s, 2H, benzylCH_2), 4.70 (s, 1H, benzylC*H*H), 4.31 (s, 1H, benzylCH*H*), 4.16 (q, *J*=5.9 Hz, 2H, $COCH_2CH_3$), 3.88–3.63 (m, 2H, NCH_2), 3.45 (ddd, *J*=12.7, 8.2, 3.0 Hz, 3H, SCH_2, $N_{Cbz}CH$*H*), 3.15 (t, *J*=4.5 Hz, 2H, $COCH_2$), 2.47–1.97 (m, 4H), 1.94–1.46 (m, 3H), 1.39 (dd, *J*=7.4, 4.4 Hz, 3H), 1.00 (t, *J*=6.6 Hz, 3H, $COOCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.42, 171.87, 155.86, 137.78, 136.99, 128.62, 128.47, 128.33, 128.20, 127.51, 76.98, 67.42, 65.11, 61.18, 50.49, 48.41, 47.60, 42.43, 40.13, 38.15, 36.51, 30.56, 21.81, 14.70, 8.20; HRMS (ES) calcd for $C_{29}H_{38}N_2O_4S$ (M^+), 510.2552, found 510.2561 *m/z*.

*4.2.16. (S)-Ethyl-7-(benzylamino)-4-(4,5-dihydrothiazol-2-yl)-4-ethylheptanoate (**16b**).* The crude product obtained using above mentioned general procedure is purified using column chromatography (5% EtOAc/hexane) to give **16b** (61.0 mg, 72%); R_f 0.72 (14% EtOAc/hexane); IR (neat) 1728, 1632, 1345, 917 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 7.30 (d, *J*=2.3 Hz, 5H, Ar*H*), 5.41 (d, *J*=2.8 Hz, 2H, OCH_2), 4.80–3.96 (m, 2H, NCH_2), 3.84 (s, 4H, benzylCH_2), 3.71–3.24 (m, 2H, SCH_2), 3.04 (dd, *J*=6.1, 4.5 Hz, 2H, NHCH_2), 2.65–1.22 (m, 4H, CH_2CH_2), 0.99 (t, *J* 6.5 Hz, 1H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.63, 174.41, 172.85, 155.86, 137.78, 136.99, 128.61, 128.47, 128.33, 128.20, 127.51, 74.04, 67.41, 61.17, 52.17, 50.67, 48.41, 47.59, 42.43, 38.15, 36.51, 35.23, 30.55, 21.80, 14.69, 8.20; HRMS (ES) calcd for $C_{21}H_{32}N_2O_2S$ (M^+) 376.2184, found 376.2176 *m/z*.

*4.2.17. (R)-Ethyl-7-(benzylamino)-4-(4,5-dihydrothiazol-2-yl)-4-ethylheptanoate (**18a′**).* The crude product obtained using condition

A is purified using column chromatography (5% EtOAc/hexane) to give the title compound **18a′** (54.0 mg, 80%) yellowish oil; R_f 0.52 (10% EtOAc/hexane); $[\alpha]_D^{20}$ −64.2 (*c* 1.0, $CHCl_3$); IR(neat) 3434, 1752, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–6.86 (m, 5H, Ar*H*), 4.46–3.90 (m, 4H, OCH_2, benzylCH_2), 3.90–3.65 (m, 2H, NCH_2), 3.60–3.28 (m, 2H, SCH_2), 2.92–2.23 (m, 4H, NHCH_2, COCH_2), 2.23–1.97 (m, 3H, $COCH_2CH_2$, $NHCH_2CHH$), 1.93–1.48 (m, 4H, $NH(CH_2)_2CH_2$, CH_2CH_3), 1.48–1.17 (m, 5H, $NHCH_2CHH$, OCH_2CH_3), 0.99 (t, *J*=6.6 Hz, 3H, CH_2CH_3); Due to the unstability of the compound ^{13}C NMR was precluded; HRMS(ES) calcd for $C_{21}H_{32}N_2O_2S$ (M^+), 376.2184, found 376.2171 *m*/*z*.

*4.2.18. (R)-Ethyl-7-(benzyl(benzyloxycarbonyl)amino)-4-(4,5-dihydrothiazol-2-yl)-4-ethylheptanoate (**18a**).* The crude product obtained using general procedure is purified using flash chromatography (5% EtOAc/hexane) to give **18a** (54.0 mg, 74%); R_f 0.78 (5% EtOAc/hexane); $[\alpha]_D^{20}$ −130.1 (*c* 1.0, $CHCl_3$); IR (neat) 1735, 1685, 1647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–6.87 (m, 10H, Ar*H*), 5.37 (s, 2H, benzylCH_2), 4.50 (d, *J*=32.6 Hz, 2H, benzylCH_2), 4.16 (q, *J*=6.0 Hz, 2H, OCH_2), 3.99–3.66 (m, 2H, NCH_2), 3.51 (ddd, *J*=7.1, 3.4, 2.2 Hz, 3H, SCH_2, NC*H*H), 3.19 (t, *J*=7.2 Hz, 1H, NCH*H*), 2.42–1.86 (m, 5H, COCH_2, αCH_2), 1.86–1.58 (m, 3H), 1.53–1.20 (m, 5H, $COOCH_2CH_3$, βCH_2), 1.02 (t, *J*=6.6 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.41, 171.87, 155.86, 137.78, 136.99, 128.62, 128.47, 128.33, 128.20, 127.51, 67.41, 65.11, 61.17, 50.48, 48.41, 47.59, 42.43, 40.12, 38.15, 36.51, 30.55, 21.80, 14.69, 8.20; HRMS (ES) calcd for $C_{29}H_{38}N_2O_4S$ (M^+), 510.2552, found 510.2421 *m*/*z*.

*4.2.19. (S)-Ethyl-7-(benzyl(benzyloxycarbonyl)amino)-4-(4,5-dihydrothiazol-2-yl)-4-ethylheptanoate (**18b**).* The crude product obtained using general procedure is purified using flash chromatography (5% EtOAc/hexane) to give **18b** (61.0 mg, 75%); R_f 0.78 (5% EtOAc/hexane); IR (neat) 1738, 1689, 1632, 935; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 10H, ArH), 5.42 (d, *J*=2.8 Hz, 3H, benzylCH_2, benzylC*H*H), 4.94–4.27 (m, 2H, NCH_2), 4.11 (t, *J*=5.9 Hz, 2H, OCH_2), 3.85 (s, 1H, benzylCH*H*), 3.73–3.26 (m, 2H, SCH_2), 3.08 (dd, *J*=6.4, 3.5 Hz, 2H, NCH_2), 2.11 (d, *J*=3.6 Hz, 4H, COCH2, αCH_2), 1.78–0.61 (m, 12H, alkylH); ^{13}C NMR (75 MHz, CDCl3) δ 184.63, 174.41, 172.85, 155.86, 137.78, 136.99, 128.61, 128.47, 128.33, 128.20, 127.51, 74.04, 67.41, 61.17, 52.17, 50.67, 48.41, 47.59, 42.43, 38.15, 36.51, 35.23, 30.55, 21.80, 14.69, 8.20; HRMS(ES) calcd for $C_{29}H_{38}N_2O_4S$ (M^+) 510.2552, found 510.2546 *m*/*z*.

*4.2.20. (R)-1,3-Bis(4,5-dihydrothiazol-2-yl)propan-1-amine (**20**).* The crude product obtained using general procedure is purified using column chromatography (25% EtOAc/hexane) to give the desired compound **20** (31.0 mg, 65%) as yellowish oil; R_f 0.18 (30% EtOAc/hexane); $[\alpha]_D^{20}$ (*c* 1.0) n.d.; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (t, *J*=3.4 Hz, 1H, αC*H*), 4.27 (t, *J*=7.0 Hz, 2H, NCH_2), 3.72 (t, *J*=6.2 Hz, 2H, NCH_2), 2.96 (dd, *J*=9.8, 4.1 Hz, 4H, 2SCH_2), 2.53–2.33 (m, 2H, δCH_2), 2.35–2.10 (m, 2H, βCH_2); Due to instability ^{13}C were precluded IR(neat) 3421, 1623, 1617, 1412, 1109 cm^{-1}; HRMS(ES) calcd for $C_9H_{15}N_3S_2$ (M+H) 229.0707, found 229.0013 *m*/*z*.

*4.2.21. (R)-Benzyl 1,3-bis(4,5-dihydrothiazol-2-yl)propylcarbamate (**20^p**).* The crude product obtained using condition A is purified using column chromatography (15% EtOAc/hexane) to give the title compound **20^p** (41.0 mg, 62%) as yellowish oil; R_f 0.48 (EtOAc/hexane); $[\alpha]_D^{20}$ +8.4 (*c* 1.0, $CHCl_3$) (uncorrected); IR(neat) 3232, 2929, 1662, 1647, 1632, 1424 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–6.87 (m, 5H, Ar*H*), 5.35 (s, 2H, benzylCH_2), 4.80 (t, *J*=7.3 Hz, 1H, NC*H*), 3.97 (dd, *J*=10.3, 3.7 Hz, 2H, NCH_2), 3.68–3.26 (m, 4H, NCH_2, SCH_2), 2.88 (t, *J*=5.9 Hz, 2H, SCH_2), 2.70–2.25 (m, 3H, $N_{Cbz}CHCHH$, $N_{Cbz}CHCH_2CH_2$), 2.09 (dt, *J*=11.9, 5.9 Hz, 1H, $N_{Cbz}CHCHH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.73, 165.67, 159.04, 136.99, 128.33, 128.20, 76.97, 67.05, 64.78, 51.06, 40.05, 40.02, 30.49, 30.49, 28.42; HRMS(ES) calcd for $C_{17}H_{21}N_3O_2S_2$ (M+H), 364.10752, found 364.1065 *m*/*z*.

*4.2.22. (S)-Methyl 2((R)-5-oxopyrrolidin-2-yl)-4,5-dihydrothiazole-4-carboxylate (**20.1**).* The crude product obtained using general procedure is purified using flash chromatography (18% EtOAc/hexane) to give **20.1** (41.0 mg, 62%) as yellowish oil; R_f 0.52 (10% EtOAc/hexane); $[\alpha]_D^{24}$ +52.1 (*c* 1.0, $CHCl_3$); IR(neat) 3243, 2935, 2100, 1732, 1653, 1634, 1616, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (t, *J*=8.0 Hz, 1H, C*H*COOCH$_3$), 4.71–4.38 (m, 1H, αC*H*), 4.29–3.89 (m, 2H), 3.86 (s, 3H, OCH_3), 2.70 (tdd, *J*=9.7, 6.9, 4.2 Hz, 1H, SC*H*H), 2.54–2.38 (m, 2H, SCH*H*, COC*H*H), 2.38–2.08 (m, 3H, COCH*H*, COCHHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.84, 172.85, 170.74, 76.98, 75.57, 56.92, 52.17, 35.53, 31.08, 30.41; ESI-MS 229.4 (M+H); Elemental analysis calcd for $C_9H_{12}N_2O_3S$ C, 47.35; H, 5.30; N, 12.27; found C, 46.35; H, 5.40; N, 11.47; HRMS (ES) calcd for $C_9H_{12}N_2O_3S(M^+)$ 228.0569 found 228.0554.

*4.2.23. (R)-5-(4,5-Dihydrothiazol-2-yl)pyrrolidin-2-one (**21**).* The crude product obtained using general procedure is purified using column chromatography (5% EtOAc/hexane) to give **21** (48.0 mg, 68%) as yellowish oil; R_f 0.32 (10% EtOAc/hexane); $[\alpha]_D^{20}$ +29.2 (*c* 1.0, $CHCl_3$); IR (neat) 3233, 3009, 2903, 2121, 1632, 1616, 1509, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.56 (t, *J*=7.5 Hz, 1H, αC*H*), 4.01 (t, *J*=5.8 Hz, 2H, NCH_2), 3.60 (t, *J*=5.8 Hz, 2H, SCH_2), 2.87–2.54 (m, 1H, COC*H*H), 2.55–2.38 (m, 2H, COCH*H*, COCHHC*H*H), 2.38–2.04 (m, 1H, COCHHCH*H*), 1.63 (s, 1H, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.84, 163.74, 76.98, 64.80, 57.36, 40.02, 31.08, 30.41; HRMS (ES) calcd for $C_7H_{10}N_2OS$ (M^+) 170.05138, found 169.9901 *m*/*z*.

*4.2.24. (4S,4′S)-Dimethyl 2,2′-((R)-1-aminopropane-1,3-diyl)-bis(4,5-dihydrothiazole-4-carboxylate) (**21.1**).* The crude product obtained using general procedure is purified using column chromatography (5% EtOAc/hexane) to give **21.1** (37.0 mg, 62%) as yellowish oil; R_f 0.22 (10% EtOAc/hexane); $[\alpha]_D^{20}$ +19.2 (*c* 1.0, $CHCl_3$); IR (neat) 3435, 1717, 1709, 1632, 1609, 1435, 1215.4, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.08 (t, *J*=4.4 Hz, 1H, C*H*COOCH$_3$), 5.19 (dd, *J*=12.0, 8.0 Hz, 1H, C*H*COOCH$_3$), 4.82 (t, *J*=7.8 Hz, 1H, NH_2CH), 4.35 (t, *J*=3.3 Hz, 1H), 3.84 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.74–3.43 (m, 2H, SCH_2), 2.64–2.29 (m, 3H, SCH_2,), 2.22–1.99 (m, 2H, CH_2); HRMS (ES) calcd for $C_{13}H_{19}N_3O_4S_2$ (M^+) 345.0817 found 345.0831 *m*/*z*.

*4.2.25. (S)-Methyl 2-((R)-1-methyl-5-oxopyrrolidin-2-yl)-4,5-dihydrothiazole-4-carboxylate (**21^p**).* The crude product obtained using general procedure is purified using column chromatography (5% EtOAc/hexane) to give the title compound **21^p** (41.0 mg, 62%) yellowish oil; R_f 0.28 (10% EtOAc/hexane); $[\alpha]_D^{20}$ +65.2 (*c* 1.0, $CHCl_3$); IR(neat) 1750, 1743.2, 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.64 (t, *J*=9.2 Hz, 1H, NC*H*COOMe), 4.72–4.33 (m, 1H, NC*H*), 4.16 (dd, *J*=12.4, 9.2 Hz, 2H, SCH_2), 4.02–3.66 (m, 4H, OCH_3, COC*H*H), 2.88 (s, 3H, NCH_3), 2.62–1.92 (m, 3H, COC*H*H, $COCH_2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.53, 173.82, 172.85, 76.98, 75.57, 58.56, 52.17, 35.53, 29.90, 28.59, 28.08. HRMS (ES) calcd for $C_{10}H_{14}N_2O_3S$ (M^+), 242.2947, found 242.3045 *m*/*z*.

*4.2.26. (4S,4′S)-Dimethyl 2,2′-((R)-1-(benzyloxycarbonylamino)-propane-1,3-diyl)bis(4,5-dihydrothiazole-4-carboxylate) (**21.1^p**).* The crude product obtained using general procedure is purified using column chromatography (5% EtOAc/hexane) to give **21.1^p** (45.0 mg, 68%) as yellowish oil; R_f 0.52 (7% EtOAc/hexane); $[\alpha]_D^{20}$ +32.1 (*c* 1.0, $CHCl_3$); IR (neat) 3234, 2938, 1754, 1723, 1634, 1624, 1616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–6.86 (m, 5H, Ar*H*), 5.61–5.10 (m, 2H, benzylCH_2), 4.88 (t, *J*=8.0 Hz, 2H, NC*H*, NC*H*), 4.19–3.51 (m, 2H), 3.07–2.59 (m, 1H, C*H*), 2.56–2.31 (m, 1H), 2.15 (ddd, *J*=7.5, 6.1, 4.9 Hz, 1H), 0.97 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.95, 172.85, 169.58, 159.04, 136.99, 128.33, 128.20, 76.97, 75.56, 67.05, 52.17, 51.15,

51.15, 35.87, 35.53, 30.49, 28.32; HRMS (ES) calcd for $C_{21}H_{25}N_3O_6S_2$ (M^+), 479.1184, found 479.1162 *m*/*z*.

*4.2.27. (R)-5-(4,5-Dihydrothiazol-2-yl)-1-methylpyrrolidin-2-one (**23.1**).* The crude product obtained using general procedure is purified using flash chromatography (5% EtOAc/hexane) to give **23.1** (21.0 mg, 60%) yellowish oil; R_f 0.42 (10% EtOAc/hexane); $[\alpha]_D^{20}$ +22.2 (1.0, $CHCl_3$) (uncorrected); IR(neat) cm^{-1}:1756.4, 1627.9; ^1H NMR (300 MHz, $CDCl_3$) δ 4.29–4.11 (m, 1H, αC*H*), 3.97 (t, *J*=5.8 Hz, 2H, NCH_2), 3.53 (t, *J*=5.8 Hz, 2H, SCH_2), 2.95 (s, 3H, NCH_3), 2.63–2.27 (m, 3H, COCH_2, $COCH_2CH$H), 2.27–1.99 (m, 1H, $COCH_2CH$*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.53, 163.70, 76.98, 64.80, 58.07, 40.02, 29.90, 28.59, 28.08; HRMS (ES) calcd for $C_8H_{12}N_2OS$ (M^+), 184.2586, found 184.2491 *m*/*z*.

*4.2.28. (R)-Benzyl 4-(4,5-dihydrothiazol-2-yl)-1-(methoxy-(methyl) amino)-1-oxobutan-2-yl(methyl)carbamate (**24**).* The crude product obtained using general procedure is purified using column chromatography (5% EtOAc/hexane) to give **24** (41.0 mg, 62%) as yellowish oil; $[\alpha]_D^{20}$ +53.1 (*c* 1.0, $CHCl_3$); IR (neat) 2958, 2874.2, 1667.3, 1653, 1465, 1414, 1175.5, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59–6.92 (m, 5H, Ar*H*), 5.31 (s, 2H, benzylCH_2), 4.44 (t, *J*=7.5 Hz, 1H, NC*H*), 3.99–3.68 (m, 5H, NCH_3, NCH_2), 3.39 (t, *J*=5.8 Hz, 2H, SCH_2), 3.28 (s, 3H, OCH_3), 3.01 (s, 3H, NCH_3), 2.47 (t, *J*=5.5 Hz, 2H, αCH_2), 2.28–1.94 (m, 2H, βCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.27, 170.74, 155.47, 136.99, 128.33, 128.20, 76.98, 67.42, 64.76, 57.58, 56.85, 40.06, 32.96, 32.66, 29.79, 28.68; ESI-MS 380.3 (M+H); HRMS (ES) calcd for $C_{18}H_{25}N_3O_4S$(M^+) 379.1566 found 379.1557 *m*/*z*.

4.3. Detailed procedure for the synthesis of oxepane rings

A dry, 50-ml, two-necked, round-bottomed flask equipped with a reflux condenser fitted with a nitrogen inlet at its top, a rubber septum, and a magnetic stirring bar is charged with 10 ml of benzene (Ref. 16) and flushed briefly with nitrogen, after which 2.2 ml (0.57 mmol) of a 25% solution of trimethylaluminum in hexane is injected through the septum into the flask. The solution is stirred and cooled in an ice–salt bath at −10° to −15°, 255 mg (0.549 mmol), dissolved in 1 ml DCM of debenzylated **16a** (Ref. 16) is added slowly with a syringe. Twenty minutes after the addition is completed, the cooling bath is removed, and the contents of the flask are allowed to stir and warm slowly to room temperature over a 45 min period. The resulting solution is allowed to stir for 22 h at room temperature, and hydrolyzed by slow and cautious addition of 0.85 ml (0.55 mmol) of 0.67 M hydrochloric acid. The upper organic layer is separated, and the aqueous layer is extracted with three 25 ml portions of ethyl acetate. The organic extracts are combined, washed with brine solution, dried with anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude thus obtained was purified by flash chromatography (EtOAc/hexane 5:95) afforded **25** in 178.3 mg (75%).

*4.3.1. (S)-1-Benzyl-5-(4,5-dihydrothiazol-2-yl)-5-ethylazocan-2-one (**25**).* The crude product obtained using procedure mentioned in Section 4.3 is purified using flash chromatography (5% EtOAc/hexane) to give **25** (178.3 mg, 60%) as glassy yellow solid; mp 78 °C; R_f 0.54 (15% EtOAc/hexane); IR (neat) 1680, 1635, 1342, 935 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–6.94 (m, 5H, Ar*H*), 4.46 (s, 2H, benzylCH_2), 3.92 (dd, *J*=9.6, 3.5 Hz, 2H, NCH_2), 3.69–3.33 (m, 3H, SCH_2, NC*H*H), 3.33–2.99 (m, 1H, NCH*H*), 2.85 (td, *J*=5.6, 1.2 Hz, 2H, COCH_2), 2.10–1.12 (m, 8H, $NCH_2CH_2CH_2$, CH_2CH_3, $COCH_2CH_2$), 0.99 (t, *J*=6.5 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.79, 171.87, 137.78, 128.61, 128.49, 127.51, 65.11, 48.84, 47.16, 40.12, 39.07, 36.51, 33.72, 20.96, 8.20; HRMS (ES) calcd for $C_{19}H_{26}N_2OS$ 330.1766 found 330.1772 *m*/*z*.

*4.3.2. (R)-1-Benzyl-5-(4,5-dihydrothiazol-2-yl)-5-ethylazocan-2-one (**26**).* The crude product obtained using procedure mentioned in Section 4.3 and purified using flash chromatography (5% EtOAc/hexane) to give **26** (44.0 mg, 64%) as yellowish oil; R_f 0.54 (15% EtOAc/hexane); IR (neat) 1679, 1639, 1339, 935 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (dt, *J*=1.4, 0.7 Hz, 5H, Ar*H*), 4.66–4.33 (m, 2H, benzylCH_2), 4.30–3.79 (m, 2H, NCH_2), 3.79–3.10 (m, 4H, SCH_2, NCH_2), 2.89 (dd, *J*=8.5, 3.2 Hz, 2H, COCH_2), 2.28–1.26 (m, 8H, $NCH_2CH_2CH_2$, CH_2CH_3, $COCH_2CH_2$), 1.18–0.50 (m, 3H, CH_3); ^{13}C NMR values corroborates with the proton spectra of 25; HRMS (ES) calcd for $C_{19}H_{26}N_2OS$ 330.1766 found 330.1762 *m*/*z*.

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Supplementary data

Spectral details of all compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.11.047.

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16. The hydrogenation was carried out using Pd/C (10 mol %,) in dried methanol in Parr assembly the selective hydrogenation of Cbz was obtained within 30–40 min on longer duration of hydrogen atmosphere causes the complete removal of both Cbz and benzyl group.