Pergamon

Tetrahedron 55 (1999) 13983–13998

TETRAHEDRON

Asymmetric Alkylation Mediated by Tricyclic Chiral Sultam Auxiliaries

Jing Lin, Wing Hong Chan[1]*, Albert W.M. Lee* and Wai Yeung Wong

Department of Chemistry, Hong Kong Baptist University, Kowloon Tong, Hong Kong

Received 21 June 1999; revised 13 September 1999; accepted 30 September 1999

Abstract: The use of enantiomerically pure sultams (+)-**1** and (-)-**1** as practical chiral auxiliaries for asymmetric alkylation reactions is described in full. Deprotonation of the *N*-acylated products derived from the auxiliaries with sodium hexamethyldisilazide followed by treatment with alkyl halides gave products with high diastereoselectivity. On treatment with excess racemic α-bromopropanoate or α-bromobutanoate, the enolates of the corresponding *N*-acyl sultam underwent highly diastereoselective alkylations to afford products with a complete absolute control of two contiguous chiral centres.

Keywords: Asymmetric alkylation; chiral sultams; kinetic resolution.

Introduction

In the rapidly expanding area of asymmetric synthesis, the development of more efficient chiral auxiliaries has continuously attracted the attention of many research groups.[1] Over the last two decades, a very large number of chiral auxiliaries have been devised and subsequently were used for asymmetric synthesis. Particularly useful in this regard have been Oppolzer's chiral sultams and Evans' chiral oxazolidinones, both readily accessible from naturally occurring compounds.[2-3] As a complementary approach, chiral auxiliaries based on rational chemical designs have also been developed which offer opportunities in terms of manipulation of structural properties and conformation rigidity necessary for optimizing a particular asymmetric process.[4] In this context, recently, we reported the preparation of tricyclic chiral sultams and their applications in asymmetric Diels-Alder reactions were demonstrated.[5] In order to define the general applicability of the auxiliaries in the arena of asymmetric synthesis, other types of reactions should be explored. In recognizing the fundamental importance of the asymmetric alkylation reaction of the α–carbon of carboxylic acid derivatives in modern synthetic organic chemistry,[6] we demonstrate here examples of the use of these chiral auxiliaries by reporting highly stereoselective alkylations of enolates derived from the *N*-propionoyl derivatives of chiral sultams (+)-**1** and (-)-**1**.

Results and Discussion

Acylsultams (-)-**2** and (+)-**2**, used as the substrates for conducting the asymmetric reactions, were obtained in 93% and 84% yield, from (+)-**1** and (-)-**1** respectively *via* successive treatment with BuLi and

[1] E-mail: whchan@hkbu.edu.hk

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00872-8

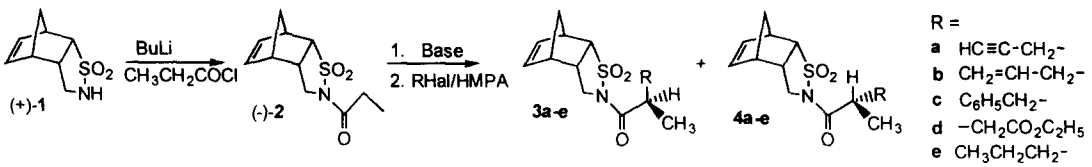
propanoyl chloride at -78°C. Deprotonation of **2** with either sodium or lithium hexamethyldisilazide (NaHMDS or LiHMDS) followed by alkylation with activated alkylating reagents such as allylic, benzylic, propargylic halides and ethyl bromoacetate in the presence of HMPA at -78 °C gave rise to good yields of products (Scheme 1). Results are summarized in Table 1. The temperature control of the alkylation reactions was absolutely essential. At -78 °C, satisfactory yields of the alkylation products were obtained invariantly. The yield of the products deteriorated at elevated temperature (Table 1, entries 2 and 8), presumably owing to the thermal instability of the enolates. The diastereoselectivity of the reactions was examined by 270 MHz ^{1}H NMR spectroscopic analysis. The crude mixture of the alkylation reaction was subjected to column chromatography separation affording a presumed diastereomeric mixture. In most of the cases, two distinct resolvable methyl doublets ascribed to the α–methyl group of the carbonyl carbon of the alkylated products of the ^{1}H NMR spectrum were used to assess the diastereomeric excess (de) of the reaction. ^{13}C NMR data of the crude mixture also indicated the presence of two structurally related compounds. To further show that the relationship between the two materials present in the crude reaction mixture is indeed diastereomeric, a 1:1 diastereomeric mixture of **3b**:**4b** was synthesized from an independent synthetic route as outlined in Scheme 2.

Table 1 Results for the asymmetric alkylation of (-)-**2** and (+)-**2** with alkyl halides

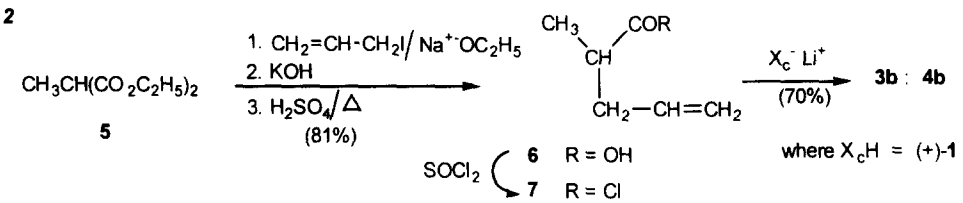
Entry	Substrate	Alkylating Agent	Base	Temp [°C]	Products [ratio]	Yield [%]	Absolute Configuration of the Chiral Centre Generated
1	(-)-**2**	$HC{\equiv}CCH_2Br$	LiHMDS	-78°	**3a**:**4a** (90:10)	67	R[a]
2	(+)-**2**	$HC{\equiv}CCH_2Br$	LiHMDS	-20°	–	decomposed	–
3	(+)-**2**	$HC{\equiv}CCH_2Br$	LiHMDS	-78°	***ent*-3a**:***ent*-4a** (88:12)	86	S
4	(-)-**2**	$CH_2{=}CHCH_2I$	NaHMDS	-78°	**3b**:**4b** (96:4)	78	R[a]
5	(-)-**2**	$CH_2{=}CHCH_2I$	LiHMDS	-78°	**3b**:**4b** (87:13)	78	R
6	(-)-**2**	$C_6H_5CH_2Br$	NaHMDS	-78°	**3c**:**4c** (63:37)	60	R
7	(+)-**2**	$C_6H_5CH_2Br$	NaHMDS	-78°	***ent*-3c**:***ent*-4c** (67:33)	45	S
8	(+)-**2**	$C_6H_5CH_2Br$	NaHMDS	-50°	***ent*-3c**:***ent*-4c** (50:50)	25	–
9	(+)-**2**	$C_6H_5CH_2I$	NaHMDS	-78°	***ent*-3c**:***ent*-4c** (84:16)	51	S
10	(-)-**2**	$BrCH_2COOC_2H_5$	NaHMDS	-78°	**3d**:**4d** (95:5)	74	R

a) Absolute configuration of the new chiral centre was determined by x-ray crystallographic analysis.

Scheme 1



Scheme 2

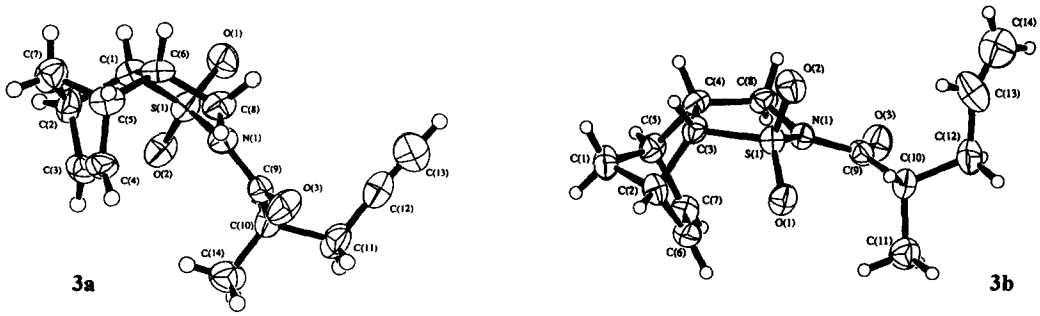


On treatment with thionyl chloride, racemic 2-methyl-4-pentenoic acid (**6**), prepared *via* alkylation of the substituted malonate **5** followed by decarboxylation, was converted into the corresponding acid chloride 7. The lithium salt of (+)-**1** was acylated with **7** affording a 1:1 diastereomeric mixture of **3b** and **4b** in 70% yield. On careful examination of its ^{1}H NMR spectrum, a 1:1 ratio of a pair of doublets at δ 1.11 and 1.13 is apparent. Except for the relative intensity of the signals, the ^{1}H NMR spectrum of the synthetic mixture is almost identical with that of the alkylation products of (-)-**2** with allyl iodide.

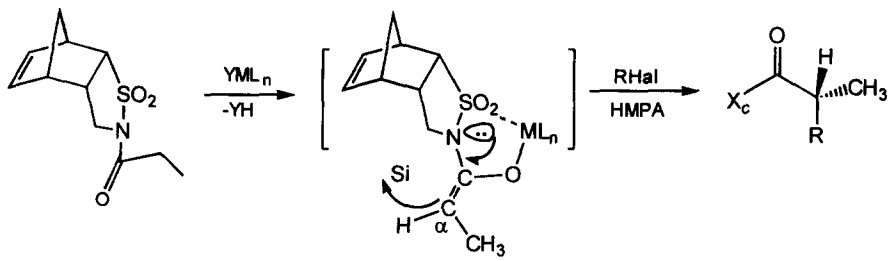
In all cases of the alkylation reaction except with benzylic halides, enantiopure materials could be obtained after a single recrystallisation,. The absolute configuration of the newly created chiral centre of the major diastereomers of the two reactions (Table 1, entries 1 and 4) was established unambiguously by x-ray crystallographic analysis and their structures are shown in Figure 1. The absolute configuration of the newly generated chiral centre of other alkylated products was established by inference. The sense of asymmetric induction by the influence of the chiral auxiliaries appears to be consistent with the model proposed by Oppolzer.[7] The diastereoselectivity bias observed may be attributed to the stereoelectronic effect exerted by the lone-pair of the sultam nitrogen atom. In the presence of 1 equiv. of LiHMDS or NaHMDS, a kinetically controlled metal chelated (Z)-enolate was generated. On steric consideration, both the top and bottom face of the π–system of the enolate are equally accessible to small alkylating reagents. The stereoelectronic influence of the lone-pair on the nitrogen atom plays a dominant role in directing the alkylation from its opposite face (i.e. the C(α)-*si* face) (Scheme 3). This model can also be used to rationalize the relatively poor diastereoselectivity observed in the alkylation reaction with benzylic halides (Table 1, entries 6 and 7). For fairly bulky alkylation reagents like benzylic halides, the stereoelectronic directing influence of the lone pair of the nitrogen atom is hampered by the steric hinderance associated with the C(α)-*si* face of the molecule. Furthermore, better diastereoselectivity in the alkylation reaction was observed from the use

of NaHMDS compared to the corresponding lithium salt (Table 2, entries 4 and 5), presumably due to the higher reactivity of the sodium enolates. Thus for most of the subsequent alkylations, NaHMDS was employed throughout. Taking advantage of the availability of both enantiomers, complementary results were obtained by using either (+)-**1** or (-)-**1** as chiral auxiliaries (Table 1, entries 1 and 3).

Figure 1 X-ray crystal structure of **3a** and **3b**

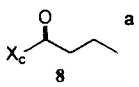
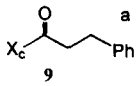
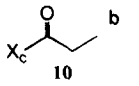
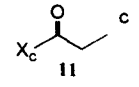


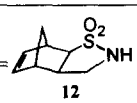
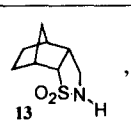
Scheme 3

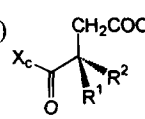


To further define the scope of using the synthetic chiral sultams for asymmetric alkylation, a more complete study was undertaken. Firstly, we were gratified to find out that excellent diastereoselectivity was observed from the reaction between the sodium enolate derived from **2** and non-activated halides as exemplified by propyl iodide (Table 2, entry 1). Secondly, other acyl substrates with longer carbon chains such as **10** and **11** underwent a similar reaction with a high degree of diastereoselectivity. In other words, the general applicability of the asymmetric reaction is evident. Thirdly, the exact structure of the chiral auxiliary plays a crucial role to effect the de of the asymmetric reaction. On that regard, in addition to chiral sultam **1**, two structurally related tricyclic sultams **12** and **13** were prepared and their use as chiral auxiliaries in asymmetric alkylation reactions was explored.[8] When **10** was subjected to an alkylation reaction with bromoacetate, much poorer reaction in terms of chemical yield and diastereoselectivity was observed (Table 2, entry 4). In accord with Oppolzer's model, in the transition state of the reaction, the stereoelectronic directing effect of the lone pair of the nitrogen is opposed by the repulsive interaction between the one carbon bridge C-H bond and the incoming alkylating agent at the top face of the molecule (Figure 2). To a greater extent, when saturated tricyclic sultam **13** was used as the auxiliary, no diastereoselectivity was

Table 2 Scope of the asymmetric alkylation promoted by tricyclic sultams

Entry	Substrate	Alkylating Agent	Base	Products [ratio]	Yield [%]	Absolute Configuration of the Chiral Centre Generated
1	(-)-**2**	$CH_3CH_2CH_2I$	NaHMDS	**3e**:**4e** (97:3)	43	R
2	 **8**	$BrCH_2COOEt$	NaHMDS	**14a**:**14b** (90:10)[d]	71	R
3	 **9**	$BrCH_2COOEt$	NaHMDS	**14c**:**14d** (94:6)[d]	66	R
4	 **10**	$BrCH_2COOEt$	NaHMDS	**14e**:**14f** (60:40)[d]	35	–
5	 **11**	$CH_2{=}CHCH_2I$	NaHMDS	**15a**:**15b** (1:1)[e]	78	
6	(-)-**2**	$CH_3{-}\underset{\displaystyle Br}{\underset{\vert}{CH}}{-}CO_2Et$	NaHMDS	**16**[f]	65	RR[g]
7	(-)-**2**	$CH_3CH_2\underset{\displaystyle Br}{\underset{\vert}{CH}}{-}CO_2Et$	NaHMDS	**17**[f]	67	RR
8	**9**	$CH_3{-}\underset{\displaystyle Br}{\underset{\vert}{CH}}{-}CO_2Et$	NaHMDS	**18**[f]	63	RR

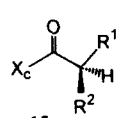
a) Chiral auxiliary X_cH = **1**, b) Chiral auxiliary X_cH =  **12**, c) Chiral auxiliary X_cH =  **13**,

d)  **14**

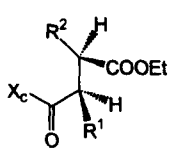
a $R^1 = C_2H_5$, $R^2 = H$
b $R^1 = H$, $R^2 = C_2H_5$
} X_cH = (+)-**1**

c $R^1 = PhCH_2$, $R^2 = H$
d $R^1 = H$, $R^2 = PhCH_2$
} X_cH = (+)-**1**

e $R^1 = CH_3$, $R^2 = H$
f $R^1 = H$, $R^2 = CH_3$
} X_cH = **12**

e)  **15**

a $R^1 = CH_3$, $R^2 = CH_2{=}CH{-}CH_2$
b R1 = $CH_2{=}CH{-}CH_2-$, $R^2 = CH_3$
X_cH = **13**

f) 

16 $R^1 = CH_3$, $R^2 = CH_3$
17 $R^1 = CH_3$, $R^2 = C_2H_5$
18 $R^1 = PhCH_2$, $R^2 = CH_3$
} X_cH = (+)-**1**

g) Absolute configuration of the new chiral centre was determined by x-ray crystallographic analysis.

observed for the alkylation reaction. Only a 1:1 diastereomeric mixture of products was obtained (Table 2, entry 5). By changing the C-C double bond to a C-C single bond in the chiral auxiliary, the diastereoselectivity bias of the reaction was much deteriorated. As indicated in the transition state, the preferred attack of the alkylating agent from the C(α)-*si* face originated from the stereoelectronic influence of the lone pair of the nitrogen atom is retarded by the nonbonding repulsion between the newly created methylene group and the incoming alkylating agent (Figure 2). Apparently, a small structural variation on the chiral auxiliary may induce a tremendous effect on the asymmetric reaction. We envisage that an outstanding chiral auxiliary may emerge from rational chemical design. In this context, as the chiral auxiliary, compound **1** was found to be superior to **12** and **13**. Furthermore, it is particularly worth noting that (-)-**2** can react with excess racemic α-bromopropanoate and α-bromobutanoate in a highly stereoselective manner. Among the four possible products, only one diastereoisomer was isolated. Under the experimental conditions, not only the absolute configuration of the α-carbon of the acyl group was completely controlled, but the stereochemical control was further extended to the β-carbon. The absolute configuration of the two adjacent stereogenic centres generated in one of the reactions was unambiguously established by x-ray study (Figure 3). The reasons(s) for the observed kinetic resolution of the racemic α-bromoalkanoate by the enolate is unclear. Some chelation between the carboethoxyl group and the enolate may exaggerate the activation energy difference of various transition states. As a result, excellent de was observed for this type of reaction.

Figure 2

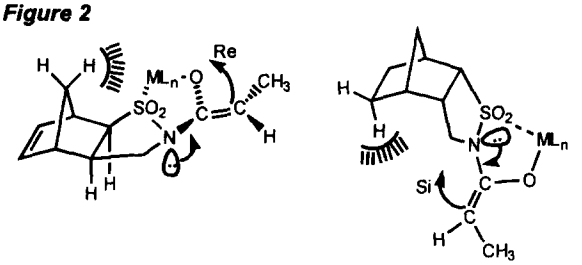
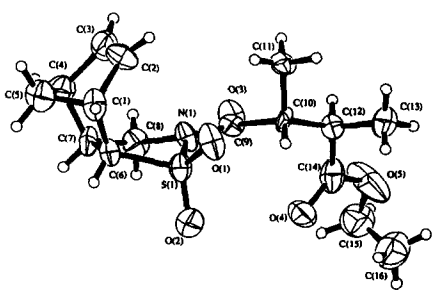
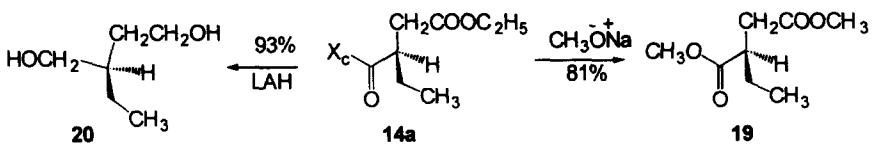


Figure 3 X-ray crystal structure of **16**



Finally, the recovery of the chiral auxiliaries could be achieved by the following two routes. Non-destructive cleavage of **14a** by treatment with sodium methoxide in methanol solution afforded the pure chiral auxiliary in over 90% yield together with the formation of the optically active diester **19** in 81% yield (Scheme 4). The optical integrity of the chiral auxiliary and the diester were confirmed by optical rotation measurements. **19** is a good starting material for the preparation of some important natural products.[9] Alternatively, LAH reduction of **14a** gave chiral diol **20** in 93% yield and recovered the auxiliary in 60% yield without losing the optical activities.

Scheme 4



In conclusion, based on rational chemical design, we have shown that some of the chiral sultams developed in our laboratory are effective chiral auxiliaries in promoting asymmetric alkylation of carboxylic acid derivatives. The general applicability of the reaction in preparing enantiopure materials has been demonstrated. Important chiral synthons **16-18** which possess two contiguous chiral centres were constructed in a highly effective manner. Their use in heterocycle synthesis is in progress.

Experimental

General Information. All reactions were carried out under N_2 with magnetic stirring unless otherwise specified. All chemicals used were of reagent grade and purchased from Aldrich chemical Company or Acros Organic. Solvents were dried with suitable agents and distilled by standard methods.

Melting points were determined with a MEL-TEMP II melting point apparatus and are reported in Celsius degrees (uncorrected). Optical rotation of new compounds was determined by Jasco Dip 1000 Digital Polarimeter. Low-resolution mass spectra (MS) were obtained at 50-70 eV by electron impact (EI) or fast atom bombardment (FAB) on a Finnigan MAT SSQ-710 Mass Spectrometer. NMR spectra in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard were measured with a JEOL EX 270 (270 MHz for ^1H and 67.8 MHz for ^{13}C) spectrometer. Elemental analysis was carried out at the Shanghai Institute of Organic Chemistry.

X-Ray Crystal Structure Determination of Compounds 3a, 3b and 16. Crystals of compounds **3a, 3b and 16** suitable for X-ray diffraction experiments were grown by slow evaporation of their respective solutions in hexane-CH_2Cl_2. Geometric and intensity data were collected using graphite-monodiromated M_o-K_α radiation (λ = 0.71073 Å) on the following diffractometers: Rigaku AFC7R (**3a**) and Mar Research image plate scanner (**3b** and **16**). For **3a**, data were collected using the ω-2θ scan technique with a scan rate of 16.0 °min^{-1} (in ω). For **3b** and **16**, 60 x 3° frames with an exposure time of 5 min per frame was used. The intensity data were corrected for Lorentz-polarization effects.

The structures were solved by a combination of direct methods (SHELXS86[10] for **3a**, SIR92[11] for **3b** and **16**) and Fourier-difference syntheses and refined on F by full-matrix least-squares analysis. The

absolute configuration of each structure has been established. All calculations were preformed on a Silicon Graphics workstation using TEXSAN software package and will be deposited at CCDC.

Acylation of Chiral Sultams

To a solution of chiral sultam in dry THF (5 ml/mmol) was added n-butyl lithium (1.1 eq., 1.6 M solution in hexane). After stirring at room temperature for 1 h, freshly distilled acid chloride (1.2 eq.) was added. The mixture was stirred at room temperature for 2 h. Water (0.5 ml) was introduced to quench the reaction. After removing THF, the residue was treated with H_2O and CH_2Cl_2. The organic layer was separated, dried and evaporated, the crude mixture was purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:3 or 1:4), to give the respective *N*-acylsultam.

(-)-(1*R*, 2*S*, 6*S*, 7*S*)-*N*-Propionyl-3, 4,-thiazatricyclo [5. 2. 1. $0^{2,6}$]deca-8-ene- 3,3-dioxide [(-)-2]

93% of isolated yield was obtained. White solid, mp 113-115 °C, ^{1}H NMR ($CDCl_3$): δ 1.12 (t, J = 7.3 Hz, 3H), 1.42 (d, J = 8.9 Hz, 1H), 1.66 (d, J = 8.9 Hz, 1H), 2.52-2.74 (m, 2H) 3.15 (s, 2H), 3.47 (m, 1H), 3.54 (d, J = 6.1 Hz, 1H), 3.76 (m, 1H), 3.99 (dd, J = 3.8, 9.2 Hz, 1H), 6.26 (dd, J = 2.6, 5.7 Hz, 1H), 6.36 (dd, J = 2.7, 5.7 Hz, 1H); ^{13}C NMR: δ 8.34, 28.7, 37.5, 44.4, 46.7, 47.1, 50.3, 66, 133.9, 135.6, 171.7; MS *m/z* 242 (M^++1); Anal. Calcd. for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80. Found: C, 54.81; H, 6.20; N, 5.82. IR cm^{-1}: 3010, 2939, 1734, 1467, 1460, 1324, 1225, 1144, 1062, 997, 900, 807, 792, 736, 587; $[\alpha]_D$ = -39.04 (c 0.5, $CHCl_3$).

(+)-(1*S*, 2*R*, 6*R*, 7*R*)-*N*-Propionyl-3,4,-thiazatricyclo [5. 2. 1. $0^{2,6}$]deca-8-ene- 3,3-dioxide [(+)-2]

85% of isolated yield was obtained. White solid, mp 115-116 °C, $[\alpha]_D^{20}$ = + 38.78 (c 0.4, $CHCl_3$).

(-)-(1*R*, 2*S*, 6*S*, 7*S*)-*N*-Butanoyl-3,4,-thiazatricyclo[5.2.1.$0^{2,6}$]deca-8-ene-3,3-dioxide [(-)-8]

75% of isolated yield was obtained. White solid, mp 53-54 °C, ^{1}H NMR ($CDCl_3$): δ 0.94 (t, J = 7.0 Hz, 3H), 1.42 (d, J = 8.9 Hz, 1H), 1.6-1.7 (m, 3H), 2.49-2.68 (m, 2H), 3.14 (s, 2H), 3.48-3.56 (m , 2H), 3.75-3.79 (m, 1H), 4.0 (dd, J = 3.8, 8.9 Hz, 1H), 6.27 (m, 1H), 6.35 (m, 1H); ^{13}C NMR: δ 13.6, 17.8, 37.0, 37.4, 44.3, 46.7, 47.1, 50.3, 66.2, 133.9, 135.6, 170.9, IR cm^{-1}: 3012, 2970, 1687, 1473 1344, 1279, 1258, 1145, 1065, 793, 739, 562; MS *m/z* 256 (M^++1); Anal. Calcd. for $C_{12}H_{17}NO_3S$: C, 56.45; H, 6.72; N, 5.49. Found: C, 56.52; H, 6.58; N, 5.57; $[\alpha]_D^{22}$ = -36.9 (c 0.35, $CHCl_3$).

(+)-(1*S*, 2*R*, 6*R*, 7*R*)-*N*-Butanoyl-3,4,-thiazatricyclo [5.2.1.$0^{2,6}$] deca-8-ene-3,3-dioxide [(+)-8]

85% of isolated yield was obtained. Mp 54-55 °C, $[\alpha]_D^{21.5}$ = +35.1 (c 0.35, $CHCl_3$).

(-)-(1*S*, 2*R*, 6*R*, 7*R*)-*N*-(3'-Phenyl)propionyl-3,4,-thiazatricyclo[5.2.1.0^{2,6}]deca-8-ene- 3,3-dioxide (9)

82% of isolated yield was obtained. White solid, mp 68-70 °C, ^{1}H NMR ($CDCl_3$): δ 1.40 (d, J = 9.2 Hz, 1H), 1.63 (d, J = 9.2 Hz, 1H), 2.84-3.13 (m, 6H), 3.45-3.55 (m, 2H), 3.78 (m, 1H), 3.95 (m, 1H), 6.22 (d, 1H, J = 3.0 Hz), 6.27 (d, J = 3.0 Hz, 1H), 7.18-7.28 (m, 5H); ^{13}C NMR: 30.4, 36.8, 37.6, 44.4, 46.8, 47.1, 50.3, 66.0, 126.1, 128.3, 128.4, 133.8, 135.4, 140.2, 169.9; IR cm^{-1}: 3025, 2932, 2887, 1688, 1325, 1292, 1141, 1091, 1031, 900, 792, 757, 697, 579; MS *m/z* 318 (M^++1); Anal. Calcd. for $C_{17}H_{19}O_3NS$: C, 64.33; H, 6.03; N, 4.41. Found: C, 64.46; H, 5.94; N, 4.26; $[\alpha]_D^{20}$ = -7.2 (c 3.0, $CHCl_3$).

(+)-(1*S*, 2*S*, 6*S*, 7*R*)-*N*-Propionyl-3,4,-thiazatricyclo[5.2.1.0^{2,6}]deca-8-ene-3,3-dioxide (10)

93% of isolated yield was obtained. Mp 80-84 °C, ^{1}H NMR: δ 1.17 (t, J = 7.3 Hz, 3H), 1.61 (d, J = 10.0 Hz, 1H), 1.85 (d, J = 10.0 Hz, 1H), 2.64-2.90 (m, 4H), 3.33 (d, J = 8.4 Hz, 1H), 3.47 (s, 1H), 3.71 (dd, J = 3.0, 12.2 Hz, 1H), 3.85 (dd, J = 3.0, 8.9 Hz, 1H), 6.22 (m, 1H), 6.33 (m, 1H); ^{13}C NMR: δ 8.3, 28.7, 38.2, 43.4, 45.8, 46.4, 48.7, 65.1, 135.7, 140.4, 172.5; MS *m/z* 242 (M^++1); Anal. Calcd. for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80. Found: C, 54.95; H, 6.22; N, 5.87; $[\alpha]_D^{22}$ = +45.2 (c 1.0, $CHCl_3$).

(+)-(1*S*, 2*R*, 6*R*, 7*R*)-*N*-Propionyl-3,4,-thiazatricyclo[5.2.1.0^{2,6}]decane-3,3-dioxide (11)

71% of isolated yield was obtained. Mp 89-91 °C, ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.3 Hz, 3H), 1.49-1.63 (m, 4H), 2.14-2.17 (m, 1H), 2.49 (m, 1H), 2.65-2.84 (m, 4H), 3.48 (m, 1H), 3.6 (dd, J = 4.1, 10.8 Hz, 2H), 4.15 (d, J = 13.0 Hz, 1H); ^{13}C NMR: δ 8.3, 21.7, 22.3, 28.9, 36.4, 40.6, 40.8, 41.5, 42.5, 63.7, 172.2; MS *m/z* 244 (M^++1); Anal. Calcd. for $C_{11}H_{17}NO_3S$: C, 54.3; H, 7.04; N, 5.76. Found: C, 54.02; H, 7.28, N 5.43; $[\alpha]_D^{21}$ = 39.65 (c 0.4, $CHCl_3$).

Diastereoselective Alkylations of *N*-acylsultams

General method: To a solution of *N*-acylsultam (1.0 eq.) in dry THF (5 ml/mmol) was added NaHMDS (1.1 eq. in 2M THF solution) under N_2 at -78 °C. After stirring for 1 h, alkylating agents (2 eq.) and HMPA (2 eq.) in THF was added, then the mixture was stirred at -78 °C for 10-16 h. Slowly warming up to 0 °C, the reaction was quenched with water. The mixture was extracted with petroleum ether. The combined organic layers were dried and evaporated to dryness. The residue was purified by flash chromatography on silica gel, using 10% ethylacetate (EA)/petroleum ether (bp 60-80 °C) (PE) as an eluent.

(-)-(1*R*, 2*S*, 6*S*, 7*S*)-*N*-[(2'*R*)-2'-Methylpent-4'-ynoyl]-3,4,-thiazatricyclo[5.2.1.0^{2,6}]deca-8-ene-3,3-dioxide (3a)

Following the above procedure, the reaction was carried out for 10 h with 86% of chemical yield (isomeric ratio 2'*R*:2'*S* = 88:12). Recrystallisation from CH_2Cl_2 and hexane afforded the pure major isomer as white solids. Mp 145-149 °C, ^{1}H NMR ($CDCl_3$): δ 1.23 (d, J = 7.0 Hz, 3H), 1.43 (d, J = 8.9 Hz, 1H), 1.66 (d, J = 8.9 Hz, 1H), 1.98 (t, J = 2.7 Hz, 1H), 2.35-2.39 (m, 1H), 2.47-2.51 (m, 1H), 3.15-3.29 (m, 3H), 3.49-3.60 (m, 2H), 3.75-3.79 (m, 1H), 4.02 (dd, J = 3.8, 6.6 Hz, 1H), 6.26 (m, 1H), 6.36 (m, 1H); ^{13}C NMR: δ 16.98, 22.6, 37.3, 38.7, 44.5, 46.8, 47.1, 50.3, 66.2, 69.9, 81.3, 133.9, 135.6, 173.4;. MS *m/z* 279; Anal. Calcd. for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 59.44; H, 6.20; N, 5.02; $[\alpha]_D^{21.5}$ = -25.49 (c 1.0 $CHCl_3$).

(-)-(1*R*, 2*S*, 6*S*, 7*S*)-*N*-[(2'*R*)-2'-Methylpent-4'-enoyl]-3,4,-thiazatricyclo[5.2.1.0^{2,6}]deca-8-ene-3,3-dioxide (3b)

Following the above procedure the reaction was carried out at -78°C for 10 h with 78% of chemical yield (isomeric ratio 2'*R*:2'*S* = 96:4). Recrystallisation from CH_2Cl_2 and hexane afforded the pure major isomer as white solids. Mp 70-72 °C, ^{1}H NMR ($CDCl_3$): δ 1.09 (d, J = 6.8 Hz, 3H), 1.39 (d, J = 8.9 Hz, 1H), 1.63 (d, J = 8.9 Hz, 1H), 2.08-2.16 (m, 1H), 2.37-2.45 (m, 1H), 3.10-3.17 (m, 3H), 3.45-3.53 (m, 2H), 3.73-3.77 (m, 1H), 3.98 (dd, J = 4.1, 8.9 Hz, 1H), 4.97-5.06 (m, 2H), 5.62-5.75 (m, 1H), 6.23 (m, 1H), 6.33 (m, 1H); ^{13}C NMR: δ 16.98, 37.3, 37.7, 38.8, 44.4, 46.8, 47.1, 50.2, 66.3, 116.96, 133.9, 135.2, 135.6, 174.5; IR cm^{-1} : 3075, 3020, 2989, 2964, 2878, 1676, 1640, 1473, 1482, 1320, 1258, 1135, 1073, 1000, 895, 793, 747, 563; MS *m/z* 281; Anal. Calcd. for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.8; N, 4.98. Found: C, 59.99; H, 7.09; N, 4.83; $[\alpha]_D^{21}$ = -35.6 (c 0.9, $CHCl_3$).

(-)-(1*R*, 2*S*, 6*S*, 7*S*)-*N*-[(2'*R*)-2'-Methyl-3'-ethoxycarbonylpropionyl]-3,4,-thiazatricyclo [5.2.1.0^{2,6}]deca-8-ene-3,3-dioxide (3d)

Following the above procedure, the reaction was carried for 16 h with 74% of chemical yield (isomeric ratio 2'*R*:2'*S* = 95:5) . Recrystallisation from ether and hexane afforded the pure major isomer as white solids. Mp 65-67 °C, ^{1}H NMR: δ 1.17 (t, J = 6.5 Hz, 3H), 1.24 (d, J = 7.3 Hz, 3H), 1.43 (d, J = 9.2 Hz, 1H), 1.66 (d, J = 9.2 Hz, 1H), 2.36 (dd, J = 4.9, 17.0 Hz, 1H), 2.8-2.9 (m, 1H), 3.15 (s, 2H), 3.47-3.6 (m, 3H), 3.73-3.77 (m, 1H), 4.0-4.14 (m, 3H), 6.26 (dd, J= 3.0, 5.7 Hz, 1H), 6.38 (dd, J = 3.0, 5.7 Hz, 1H); ^{13}C NMR: δ 14.5, 17.7, 36.1, 37.6, 38.4, 44.9, 47.2, 47.5, 50.6, 61, 66.6, 134.2, 136.1, 171.8, 174.4; IR cm^{-1}: 3078, 3014, 2983, 2942, 1775, 1680, 1464, 1454, 1337, 1237, 1067, 1026, 945, 791, 741, 733, 693, 558; MS *m/z* 328 (M^++1); Anal. Calcd. for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.47; N, 4.28. Found: C, 54.75; H, 6.56; N, 4.15; $[\alpha]_D^{21}$ = -10.5 (c 1.06, $CHCl_3$).

(-)-(1*R*, 2*S*, 6*S*, 7*S*)-*N*-[(2'*R*)-2'-Methylpentanoyl]-3,4,-thiazatricyclo[5.2.1.0^{2,6}]deca-8-ene-3,3-dioxide (3e)

Following the above procedure, using 3 eq. of alkyl iodide, the reaction was carried out for 16 h with 43% of chemical yield (isomeric ratio 2'*R*:2'*S* = 97:3). Recrystallisation from ether and hexane afforded the pure major isomer as white solids. Mp 95-96 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 1.12 (d, J = 6.5 Hz, 3H), 1.25-1.43 (m, 3H), 1.59-1.72 (m, 3H), 3.04-3.13 (m, 3H), 3.48-3.56 (m, 2H), 3.8 (dd, J = 1.6, 12.4 Hz, 1H), 4.01 (dd, J = 4.1, 8.9 Hz, 1H), 6.26 (dd, J = 3.0, 5.9 Hz, 1H), 6.36 (dd, J = 3.0, 5.9 Hz, 1H); ^{13}C NMR: δ 13.9, 17.5, 20.4, 36.1, 37.1, 39, 44.4, 46.8, 47.1, 50.2, 66.3, 133.9, 135.6, 175.4; MS *m/z* 284 (M^++1); Anal. Calcd. for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.48; N, 4.95. Found: C, 59.51; H, 7.49; N, 5.01; $[\alpha]_D^{21}$ = -42.16 (c 0.9, $CHCl_3$).

(+)-(1*S*, 2*R*, 6*R*, 7*R*)-*N*-[(2'*S*)-2'-Methylpent-4'-ynoyl]-3,4,-thiazatricyclo[5.2.1.0^{2,6}]deca-8-ene-3,3-dioxide (*ent*-3a)

Following the above procedure, the reaction was carried out for 10 h with 67% of chemical yield (isomeric ratio 2'*S*:2'*R* = 90:10). Recrystallisation from CH_2Cl_2 and hexane afforded the pure major isomer as white solids, Mp 130-134 °C, ^{1}H NMR ($CDCl_3$): δ 1.21 (d, J = 7.0 Hz, 3H), 1.38 (d, J = 8.9 Hz, 1H), 1.61 (d, J = 8.9 Hz, 1H), 1.95 (t, J = 2.7 Hz, 1H), 2.21-2.31 (m, 1H), 2.45-2.60 (m, 1H), 3.11 (m, 2H), 3.33-3.49 (m, 3H), 3.80-3.84 (m, 1H), 3.97 (dd, J = 3.8, 6.6 Hz, 1H), 6.23 (m, 1H), 6.32 (m, 1H); ^{13}C NMR: δ 17.1, 22.4, 37.5, 38, 44.4, 46.8, 47.0, 50.2, 66, 69.6, 81.5, 133.9, 135.5, 173.1; IR cm^{-1}: 3297, 3010, 2967, 2964, 1684, 1397, 1339, 1261, 1139, 751, 651, 558; $[\alpha]_D^{20}$ = 24.30 (c 0.75, $CHCl_3$).

(+)-(1*S*, 2*R*, 6*R*, 7*R*)-*N*-[(2'*S*)-2'-Methylpent-4'-enoyl]-3,4,-thiazatricyclo[5.2.1.0^{2,6}]deca-8-ene-3,3-dioxide (*ent*-3b)

Following the above procedure the reaction was carried out at -78° C for 10 h with 81% of chemical yield (isomeric ratio 2'*S*:2'*R* = 90:10). Viscous oil. ^{1}H NMR ($CDCl_3$): δ 1.12 (d, J = 6.5 Hz, 3H), 1.41 (d, J = 8.9 Hz, 1H), 1.64 (d, J = 8.9 Hz, 1H), 2.10-2.17 (m, 1H), 2.40-2.47 (m, 1H), 3.11-3.19 (m, 3H), 3.47-3.55 (m, 2H), 3.74-3.79 (m, 1H), 4.0 (dd, J = 4.1, 9.2 Hz, 1H), 4.99-5.07 (m, 2H), 5.67-5.77 (m, 1H), 6.25 (m, 1H), 6.34 (m, 1H); ^{13}C NMR: δ 16.98, 37.3, 37.8, 38.8, 44.4, 46.8, 47.1, 50.2, 66.3, 116.98, 133.9, 135.2, 135.6, 174.5; IR cm^{-1}: 3075, 3020, 2989, 2964, 2878, 1676, 1640, 1473, 1482, 1320, 1258, 1135, 1073, 1000, 895, 793, 747, 563; $[\alpha]_D^{20}$ = 38.50 (c 1.20, $CHCl_3$).

(1*S*, 2*R*, 6*R*, 7*R*)-*N*-[(2'*R*) and (2'*S*)-2'-Benzylpropionyl]-3,4,-thiazatricyclo[5.2.1.0^{2,6}]deca-8-ene-3,3-dioxide (*ent*-3c and *ent*-4c)

45% of isolated yield. Oil. ^{1}H NMR: δ 1.12 (two doublet, 3H, J = 6.5 Hz, ratio 1:2), 1.59 (d, J = 9.2 Hz, 1H), 1.77 (d, J = 9.2 Hz, 1H), 2.56-2.64 (m, 2H), 3.03-3.16 (m, 3H), 3.27-3.42 (m, 2H), 3.78-3.96 (m, 2H), 6.21 (d, J = 3.0 Hz, 1H), 6.26 (d, J = 3.0 Hz, 1H), 7.17-7.36 (m, 5H); ^{13}C NMR: δ 16.53 (17.77), 39.57, 40.70, 41.06, 42.57 (42.81), 45.66 (45.43), 47.94 (48.03), 48.99 (48.79), 50.71 (50.84), 128.64 (128.09), 128.70 (128.27), 129.13 (128.79), 130.21 (129.38), 134.50 (135.36), 137.50 (138.96), 174.14 (174.14) (The data in the parenthesis indicate the δ value of the other isomer); IR cm^{-1}: 3068, 3063, 2967, 2953, 1684, 1497, 1447, 1375, 1332, 1246, 1146, 1103, 744, 701, 565.

(-)-(1*R*, 2*S*, 6*S*, 7*S*)-*N*-[(2'*R*)-2'-Ethyl-3'-ethoxycarbonylpropionyl]-3,4,-thiazatricyclo[5.2.1.0^{2,6}]deca-8-ene- 3,3-dioxide [(-)-14a]

Following the above procedure, the reaction was carried out for 16 h, 71% of chemical yield was obtained (isomeric ratio 2'*R*:2'*S* = 90:10). Recrystallisation from Et_2O/hexane, afforded the pure major isomer as white solids. Mp 77-78 °C, ^{1}H NMR: δ 0.93 (t, J = 7.3 Hz, 3H), 1.22 (t, J = 7.3 Hz, 3H), 1.41-1.52 (m, 2H), 1.64-1.73 (m, 2H), 2.44 (dd, J = 4.6, 16.7 Hz, 1H), 2.77 (dd, J = 10.0, 16.7 Hz, 1H), 3.15 (m, 2H), 3.48-3.76 (m, 4H), 4.01-4.15 (m, 3H), 6.26 (dd, J = 3.2, 6.2 Hz, 1H), 6.38 (dd, J = 3.2, 6.2 Hz, 1H); ^{13}C NMR: δ 11.09, 14. 1, 25.1, 35.5, 37.1, 41.98, 44.7, 46.9, 47.1, 50.2, 60.6, 66.3, 133.8, 135.9, 171.6, 173.5; IR cm^{-1}: 3010, 2987, 2971, 1732, 1679, 1466, 1373, 1337, 1299, 1269, 1235, 1182, 1145, 898, 792, 732, 637, 572; Anal. Calcd. for $C_{16}H_{23}NO_5S$: C, 56.28; H, 6.80; N, 4.10. Found: C, 56.32; H, 6.84; N, 4.24; $[\alpha]_D^{22}$ = -11.27 (c 0.9, $CHCl_3$).

(+)-(*1R, 2S, 6S, 7S*)-*N*-[(2'*R*)-2'-Benzyl-3'-ethoxycarbonylpropionyl]-3,4,-thiazatricyclo[5.2.1.0^{2,6}]deca-8-ene-3,3-dioxide (14c)

Following the above procedure the reaction was carried out at -78 °C for 16 h with 79% of chemical yield. (isomers ratio *R*:*S* 94:6). Recrystallisation from ether and hexane to afford the pure predominant isomer. Mp 105-107 °C, ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.0 Hz, 3H), 1.42 (d, J = 9.2 Hz, 1H), 1.64 (d, J = 9.2 Hz, 1H), 2.29 (dd, J = 4.6, 17.0 Hz, 1H), 2.46 (m, 1H), 2.76 (m, 4H), 3.62 (m, 3H), 6.2 (m, 1H), 6.3 (m, 1H), 7.24-7.29 (m, 5H); ^{13}C NMR: 14.2, 35.2, 37.3, 37.5, 42.8, 44.7, 46.9, 47.2, 50.3, 60.7, 66.2, 126.6, 128.4, 129.3, 133.7, 135.6, 137.9, 171.3, 172.7; IR cm^{-1}: 3075, 2984, 2962, 1732, 1680, 1326, 1193, 1142, 1080, 1029, 900, 767, 736, 574; Anal. Calcd. for $C_{21}H_{25}O_5NS$: C, 62.51; H, 6.25; N, 3.47. Found: C, 62.33; H, 6.33; N, 3.33. MS *m/z* 463 (M^++1); $[\alpha]_D^{25}$ = +59.4 (c 0.5, $CHCl_3$).

(1*S*, 2*S*, 6*S*, 7*R*)-*N*-[(2'*S*) and (2'*R*)-2'-Methyl-3'-ethoxycarbonylpropionyl]-3,4,-thiazatricyclo[5.2.1.0^{2,6}] deca-8-ene-3,3-dioxide (14e and 14f)

Following the above procedure the reaction was carried out at -78 °C for 16 h with 35% of chemical yield (isomeric ratio 2'*S*:2'*R* = 60:40). The diastereomeric mixture was obtained as an oil. ^{1}H NMR ($CDCl_3$): δ 1.20-1.30 (m, 6H), 1.55-1.64 (d, J = 10.0 Hz, 1H), 1.99 (d, J = 10.0 Hz, 1H), 2.35-2.43 (m, 2H), 2.83-2.93 (m, 2H), 3.26-3.55 (m, 2H), 3.82-3.84 (m, 2H), 3.94-4.01 (m, 1H), 4.07-4.22 (m, 2H), 6.21-6.23 (m, 1H), 6.30-6.37 (m, 1H); ^{13}C NMR: δ 14.02 (14.09), 17.5, 35.2 (38.13), 37.79, 40.09, 43.13 (43.37), 44.8 (45.73), 46.27 (49.69), 48.3 (48.81), 60.95 (65.03), 61.42, 135.83 (136.32), 140.07 (140.49), 168.18, 171.4. (The data in the parenthesis indicate the δ value of the other isomer); IR cm^{-1}: 3075, 2983, 2881, 1735, 1693, 1464, 1329, 1305, 1262, 1186, 1133, 1026, 1014, 818, 700, 564; MS *m/z* 328 (M^++1).

(1*S*, 2*R*, 6*R* 7*R*)-*N*-[(2'*S*) and (2'*R*)-2'-Methylpent-4'-enoyl]-3,4,-thiazatricyclo[5.2.1.0^{2,6}]decane-3,3-dioxide (15a and 15b)

78% of chemical yield was obtained (isomeric ratio 2'*R*:2'*S* = 1:1). Mp 75-78 °C. ^{1}H NMR ($CDCl_3$): δ 1.17 (dd, J = 3.0, 6.5 Hz, 3H), 1.47-1.60 (m, 5H), 2.14-2.22 (m, 2H), 2.47-2.52 (m, 2H), 2.78 (s, 2H), 3.31-3.50 (m, 2H), 3.60 (dd, J = 4.6, 11.1 Hz, 1H), 4.97-5.09 (m, 1H), 5.69-5.78 (m, 2H), 7.24 (m, 1H); ^{13}C NMR: 17.06 (17.13), 21.64 (21.69), 22.46, 36.12 (36.26), 37.67 (38.03), 38.38 (38.74), 40.61 (40.68), 40.92 (40.97), 41.64, 42.64 (42.95), 64.04 (64.08), 117.07 (117.14), 135.15 (135.26), 175.26 (175.30) (The data in the parenthesis indicate the δ value of the other isomer); MS *m/z* 283; Anal. Calcd. for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.47; N, 4.94. Found: C, 60.03; H, 7.84; N, 4.79.

(-)-(1*R*, 2*S*, 6*S*, 7*S*)-*N*-[(2'*R*), (3'*R*)-2'-Methyl-3'-ethoxycarbonylbutanoyl]-3,4,-thiazatricyclo[5.2.1.0^{2,6}] deca-8-ene-3,3-dioxide (16)

Following the above procedure, using 3 eq. of α-bromopropanoate, the reaction was carried out for 20 h, with 65% of chemical yield. The spectra showed that only one isomer has formed. White solid, Mp. 97-99 °C. ^{1}H NMR ($CDCl_3$): δ 1.14 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 7.3 Hz, 3H), 1.21 (t, J = 7.3 Hz, 3H), 1.42 (d, J = 9.2 Hz, 1H), 1.65 (d, J = 9.2 Hz, 1H), 2.77-2.84 (m, 1H), 3.13-3.22 (m, 3H), 3.48-3.56 (m, 2H), 3.72-3.76 (m, 1H), 4.0-4.13 (m, 3H), 6.26 (m, 1H), 6.4 (m, 1H); ^{13}C NMR δ 14.1, 14.4, 15, 37.2, 41.8, 42.2, 44.5, 46.8, 47.1, 50.2, 60.6, 66.2, 133.8, 135.7, 174.5, 175; IR cm^{-1}: 3075, 3014, 2984, 2939, 1728, 1682, 1458, 1390, 1329, 1258, 1188, 1147, 1055, 959, 795, 736, 566; MS *m/z* 342 (M^++1); Anal. Calcd. for $C_{16}H_{23}NO_5S$: C, 56.28; H, 6.8; N, 4.1. Found: C, 56.37; H, 6.84; N, 4.2; $[\alpha]_D^{21}$ = -9.07 (c 0.5, $CHCl_3$).

(-)-(1*R*, 2*S*, 6*S*, 7*S*)-*N*-[(2'*R*),(3'*R*)-2'-Methyl-3'-ethyl-3'-ethoxycarbonylpropionyl]-3,4,-thiazatricyclo[5. 2.1.0^{2,6}]deca-8-ene-3,3-dioxide (17)

Following the above procedure, using 3 eq. of α-bromobutanoate, the reaction was carried out at -78 °C for 16 h, with 67% of chemical yield. Recrystallisation from ether and hexane. White solid, mp 90-92 °C. ^{1}H

NMR ($CDCl_3$): δ 0.88 (t, J = 4.9 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.42 (d, J = 8.9 Hz, 1H), 1.64 (d, J = 8.9 Hz, 1H), 1.70-1.80 (m, 2H), 2.72 (dd, J = 4.1, 11.8 Hz, 1H), 3.12-3.29 (m, 3H), 3.47-3.54 (m, 2H), 3.7- 3.75 (m, 1H), 4.0-4.17 (m, 3H), 6.25 (d, J = 3.0 Hz, 1H), 6.37 (d, J = 3.0 Hz, 1H); ^{13}C NMR: δ 10.5, 14.2, 15.2, 21.7, 37.1, 39.8, 44.4, 46.8, 47.1, 48.8, 50.2, 60.4, 66.2, 133.8, 135.6, 174.1, 174.4; MS *m/z* 356 (M^++1); Anal. Calcd. For $C_{17}H_{25}O_5NS$: C, 57.44; H, 7.09; N, 3.94. Found: C, 57.11; H, 7.08; N, 3.78; $[\alpha]_D^{24}$ = -5.9 (c 0.35, $CHCl_3$).

(-)-(*1R, 2S, 6S, 7S*)-*N*-[(2'*R*),(3'*R*)-2'-Benzyl-3'-methyl-3'-ethoxycarbonylpropionyl]-3,4,-thiazatricyclo [5.2.1.$0^{2,6}$]deca-8-ene-3,3-dioxide (18)

Following the above procedure, using 3 eq. of α-bromopropanoate, the reaction was carried out at -78 °C for 20 h. The product was obtained as an oil in 63% yield. ^1H NMR: δ 1.15 (d, J = 7.3 Hz, 3H), 1.26-1.33 (m, 4H), 1.52 (m, 1H), 2.81 (m, 2H), 3.03 (m, 3H), 3.35 (m, 2H), 3.73-3.9 (m, 3H), 4.17-4.19 (m, 2H), 5.77-5.83 (m, 2H), 7.22- 7.26 (m, 5H); ^{13}C NMR: 13.4, 14.3, 34.01, 37.2, 40.3, 44.3, 46.7, 47.0, 48.3, 50.1, 60.8, 65.8, 126.3, 128.1, 129.5, 133.5, 135.1, 138.8, 171.3, 173.9. Anal. Calcd. for $C_{22}H_{27}O_5NS$: C, 63.29; H, 6.52; N, 3.35. Found: C, 62.97; H, 6.65; N, 3.40; MS *m/z* 418 (m^++1); $[\alpha]_D^{25}$ = -24.4 (c 0.8, $CHCl_3$).

(2*R*)-Diethyl-2-ethyl-1,4-succinate (19)

Under nitrogen atmosphere, a solution of **14a** (90 mg, 2.6 mmol) in dry CH_3OH (3 ml) was added to a stirred CH_3ONa/CH_3OH solution (0.3 ml, 1 mol solution) at 0 °C. Then the mixture was slowly warmed up to room temperature and was stirred for 3 h. The reaction was quenched by ethylacetate and water solution. The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The resulting residue was purified by column chromatography on silica gel eluting with PE-EA (10% EA/PE to 50% EA/PE) to give the recovered sultam (45 mg, 92%) and diester **19** (37 mg, 81% yield). $[\alpha]_D^{22.5}$ = +12.5 (c 0.75, $CHCl_3$), Lit. $[\alpha]_D^{22}$ = +13 (c 1.23, $CHCl_3$). The NMR spectra were identical with those reported in the literature.[9]

(2*R*)-2-Ethylbutane-1,4-diol (20)

A solution of **14a** (300 mg, 0.88 mmol) in dry THF/Et_2O (1:3, 6 ml) was added to a stirred suspension of $LiAlH_4$ (170 mg, 5 eq.) in diethyl ether (10 ml) at 0 °C. The mixture was stirred overnight at room temperature then 4 h at 60 °C. The reaction was quenched by adding saturated aqueous ammonium chloride solution. The mixture was filtered and dried over $MgSO_4$. The solvent was removed. The residue was purified by flash chromatography on silica gel (20% EA/PE to 50% EA/PE), the recovered sultam (95 mg, 60% yield) and **20** (96 mg, 93% yield) were obtained. The diol **20** was isolated as an oil. $[\alpha]_D^{17.4}$ = +14.13 (c 1.5, $CHCl_3$). The ^1H and ^{13}C NMR spectral data of **20** were identical with those reported.[12]

(*1S, 2R, 6R, 7R*)-*N*-[(2'*S*) and (2'*R*)-2'-Methylpent-4'enoyl]-3,4-thiazatricyclo[5.2.1.$0^{2,6}$]deca-8-ene-3,3-dioxide (3b and 4b)

The acid chloride 7 required for the preparation of a 1:1 mixture of **3b** and **4b** was prepared as below. At room temperature to thionyl chloride (5 ml, 10 eq.), the acid **6** (1 g, 8.7 mmol)[13] was added. The mixture was heated to 50-60 °C for 2 h and then subjected to fractional distillation. The acid chloride **7** was collected in the 134-138 °C boiling fraction as colorless oils (0.99 g, 86% yield). A 1:1 mixture of **3b** and **4b** was obtained in 70% yield by treating **7** with the lithium salt of (+)-**1** using the method B described above in the acylation of chiral sultam. ^{1}H NMR ($CDCl_3$): 1.12 (dd, J = 2.7, 6.8 Hz, 3H), 1.40 (d, J = 8.4 Hz, 1H), 1.64 (d, J = 8.4 Hz, 1H), 2.03-2.15 (m, 1H), 2.40-2.46 (m, 1H), 3.13-3.24 (m, 3H), 3.46-3.56 (m, 2H), 3.72-3.78 (m, 1H), 3.97-4.02 (dd, J = 4.3, 9.2 Hz, 1H), 5.01-5.07 (m, 2H), 5.67-5.74 (m, 1H), 6.22 (m, 1H), 6.34 (m, 1H); ^{13}C NMR: 16.9, 37.1 (37.2), 37.7 (37.74), 38.2 (38.7), 44.4 (44.6), 46.7 (46.8), 47.0, 50.2, 66.2, 116.7 (116.9), 133.8, 135.2 (135.3), 135.6 (135.7), 174.5 (The data in the parenthesis indicate the δ value of the other isomer).

Acknowledgement

Financial support from the Faculty Research Committee of the Hong Kong Baptist University (FRG/98-99/II-11) is gratefully acknowledged.

References

1. "*Chiral Auxiliaries and Ligands in Asymmetric Synthesis*", Seyden Penne, J., Eds., John Wiley & Sons Inc.: New York, 1995.
2. Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767-2772 and references therein.
3. Evans, D.A.; Ennis, M.D.; Mathre, D.J. *J. Am. Chem. Soc.* **1982**, *104*, 1737- 1739.
4. For recent examples, see: (a) Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117-4120; (b) Sudo, A.; Saigo, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2153-2156. (c) Yamamoto, Y.; Kin, H.; Suzuki, I.; Asao, N. *Tetrahedron Lett.* **1996**, *37*, 1863-1866; (d) Ghosh, A.K.; Cho, H.; Onishi, M. *Tetrahedron: Asymmetry* **1997**, *8*, 821-824.
5. Chan, W.H.; Lee, A.W.M.; Jiang, L.S.; Mak, T.C.W. *Tetrahedron: Asymmetry* **1997**, *8*, 2501-2504.
6. For recent examples, see: (a) Davies, S.G.; Doisneau, G. J-M.; Prodger, J.C.; Sangance, H.J. *Tetrahedron Lett.* **1994**, *35*, 2373-2376; (b) Palomo, C.; Oiarbide, M.; Gonzalez, A.; Garcia, J.M.; Berree, F. *Tetrahedron Lett.* **1996**, *37*, 4565-4568; (c) Myers, A.G.; Yang, B.H.; Chen, H.; McKinstry, L.; Kopecky, D.J.; Gleason, J.L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

7. Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603-5606.
8. Jiang, L.S.; Chan, W.H.; Lee, A.W.M.; Wong, W.Y. submitted to *J. Chem. Soc. Perkin Trans. 1* for publication.
9. Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K-I. *J. Org. Chem.* **1997**, *62*, 5830-5837.
10. Sheldrick, G.M. "*Crystallographic Computing 3*", Sheldrick, G.M.; Kruger, C.; Goddard, R. Eds., Oxford University Press: Oxford, 1985, pp. 175-189.
11. Altomare, A.; Purla, M.C.; Camalli, M.; Cascarano, M.; Giacvazzo, C.; Guagliardi, A.; Polidori, G. *J. Appl. Cryst.* **1992**, *25*, 310.
12. Lee, N.; Kim, Y-W.; Cheng, K.; Kim, K.H.; Jew, S-S.; Kim, D-K. *Tetrahedron Lett.* **1996**, *37*, 2429.
13. William, C.A. *J. Org. Chem.* **1953**, *18*, 842.