187. Non-destructive Cleavage of *N*-Acylsultams Under Neutral Conditions: Preparation of Enantiomerically, Pure Fmoc-Protected α-Amino Acids

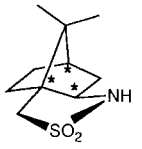
by **Wolfgang Oppolzer*** and **Philippe Lienard**

Département de Chimie Organique, Université de Genève, CH-1211 Genève 4

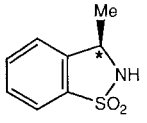
(2.X.92)

Heating diastereoisomerically pure *N*-acylsultams **3** or **4** with allyl alcohol/$Ti(OR)_4$ efficiently yields sultams **1** or **2** and allyl esters **5**. Esters **5** are hydrolyzed under nonbasic conditions in the presence of *Wilkinson*'s catalyst to give enantiomerically and diastereoisomerically pure carboxylic acids **7**. A series of [(fluoren-9-yl)methoxy]-carbonyl-(Fmoc)-protected amino acids **14** were thus prepared from *N*-[*N'*-(Fmoc)amino]acylsultams **12**.

Introduction. – Sultams **1** [1] and **2** [2] rank today among the most reliable and versatile chiral auxiliaries for asymmetric synthesis [3]. They are readily available in both antipodal forms[1]) and provide high π-facial discrimination in many reactions of their *N*-enoyl or 'enolate' derivatives **I** or **II**.

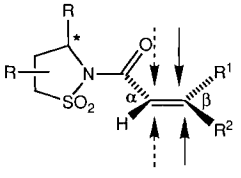


1



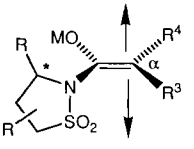
2

N-α,β-Enoyl Sultams



I

Sultams 'Enolates'



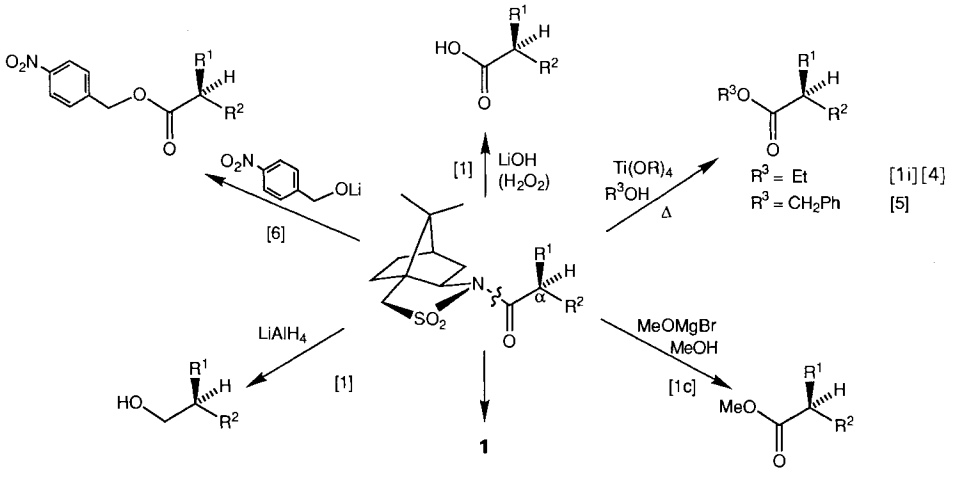
II

One advantage of using auxiliaries **1** and **2** is their mild removal from the asymmetric reaction products without loss of the induced chirality and with easy recovery of the chiral information.

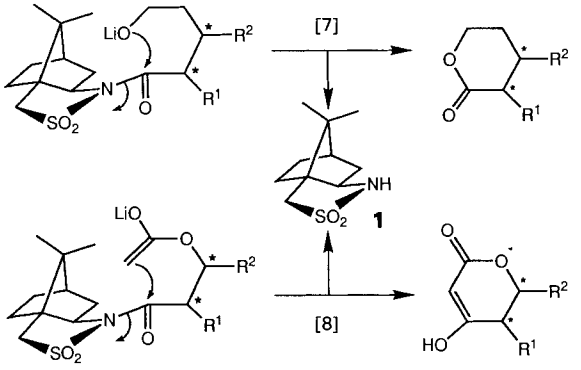
[1]) Sultam **1** and its antipode (up to multi-kg scale) and *N*-{*N'*-[bis(methylthio)methylidene]glycyl}bornane-10,2-sultam are distributed by: *NEWPORT, Synthesis Ireland Ltd.*, Dublin/Ireland.

These cleavage reactions can be carried out in a bimolecular (*Scheme 1*) [1] [2] [4–6] or intramolecular manner (*Scheme 2*) [7] [8].

Scheme 1

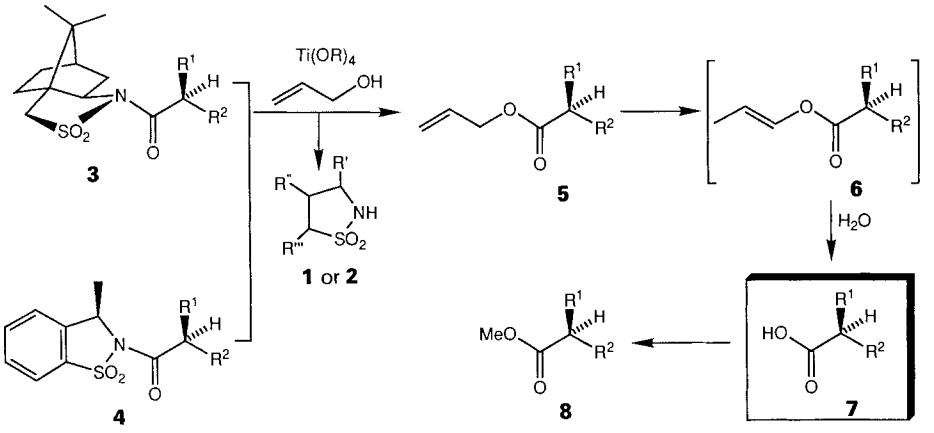


Scheme 2



For example, basic hydrolysis with LiOH (in the absence or presence of H_2O_2) is, so far, the method of choice for the conversion of acylsultams into synthetically important, enantiomerically pure carboxylic acids (*Scheme 1*) [1] [2]. However, those conditions are clearly incompatible with base-sensitive functionalities. We report here a solution to this problem based on the titanium-mediated 'alcoholysis' of acylsultams which has been shown to proceed under nonbasic reaction conditions and without epimerization at C(α) [1i] [4] [5]. It was intriguing to attempt such a 'transesterification' with allyl alcohol in view of the specific propensity of allyl esters to undergo neutral, transition-metal-catalyzed hydrolysis [9] (*Scheme 3*).

Scheme 3



Results. – Our first results are summarized in *Scheme 4* and *Table 1*. Stirring a solution of *N*-(acyl)bornane-10,2-sultam **3a** [10] in allyl alcohol containing Ti(i-PrO)$_4$ (1.5 mol-equiv.) and molecular sieves at 150° (using a closed *Carius* tube) for 3 h furnished

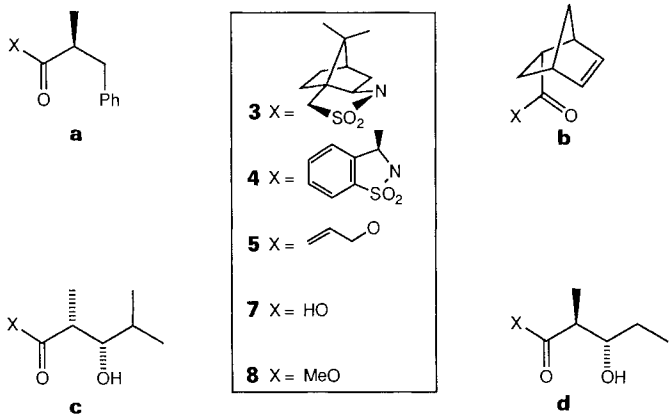


Table 1. *Conversion of* N-*Acylsultams into Carboxylic Acids by Ti(i-PrO)$_4$-Mediated Propenolysis (150°)/[RhCl(PPh$_3$)$_3$]-Catalyzed Hydrolysis:* **3** → **1** + **5** → **7** *and* **4** → **2** + **5** → **7**

Entry	Acyl-sultam	Sultam		Allyl ester		Carboxylic acid		
			Yield [%]		Yield [%]		Yield [%]	C(α)-epimer [%]
1	**3a**	**1**	88	**5a**	88	**7a**	89	⩽ 1.1[a])
2	**4a**	**2**	78	**5a**	86			
3	**3b**	**1**	88	**5b**	85	**7b**	78	⩽ 0.5[b])
4	**3c**	**1**	98	**5c**	88	**7c**	79	⩽ 0.9[b])
5	**4c**	**2**	75	**5c**	77			
6	**3d**	**1**	87	**5d**	88	**7d**	78	⩽ 1.5[b])

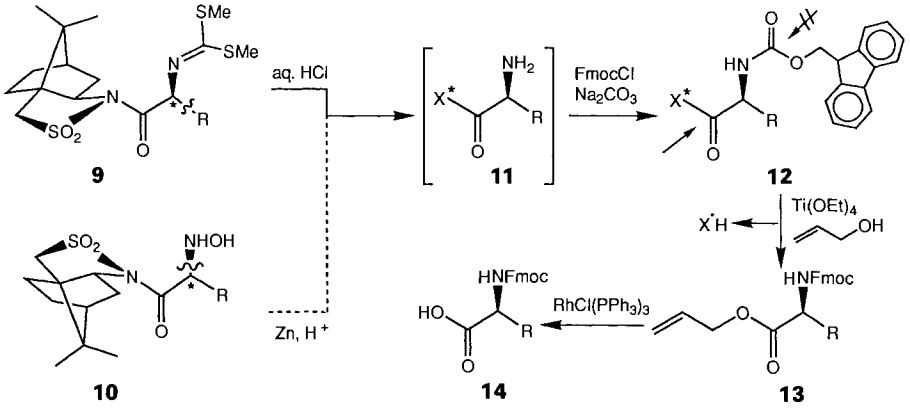
[a]) HPLC (chiral column). [b]) ^{1}H-NMR Analysis.

sultam **1** (88%) and allyl ester **5a** (88%; *Entry 1*). Using identical reaction conditions, *N*-(acyl)toluene-2,α-sultam **4a** [2c] was also 'transesterified' giving sultam **2** (78%) and the same allyl ester **5a** (86%; *Entry 2*).

Isomerization/hydrolysis of allyl ester **5a** by heating a 0.03M solution in $EtOH/H_2O$ 9:1 under reflux in the presence of *Wilkinson*'s catalyst (0.11 mol-equiv.) [11] provided free carboxylic acid **7a** in 89% yield. Compound **7a** contained not more than 1.1% of its antipode as determined by HPLC analysis of the methyl ester **8a** (*Entry 1*). Similar propenolysis/hydrolysis of the *Diels-Alder* product **3b** [1a] afforded the sterically more encumbered carboxylic acid **7b** in good overall yield. Not more than 0.5% *exo*-isomer could be detected by ^{1}H-NMR analysis of **7b** (*Entry 3*). Using this two-step protocol, *syn*- and *anti-N*-(β-hydroxyacyl)sultams **3c** [12], **4c** [2c], and **3d** [13] underwent analogous conversion to β-hydroxy acids **5c** and **5d** with retention of their stereochemical integrity (^{1}H-NMR) and without competing *retro*-aldolization (*Entries 4–6*).

[(Fluoren-9-yl)methoxy]carbonyl (Fmoc)-protected amino acids **14** enjoy widespread popularity as building blocks in peptide synthesis [14]. After peptide coupling, this *N*-protecting group is routinely removed by mildly basic hydrolysis. *N*-Acylsultams **9** and **10** are attractive, mostly crystalline precursors for enantiomerically pure α-amino acids (*via* amine **11**). They are readily obtained by highly π-face selective alkylations (→**9**) [6] [15] or hydroxyaminations (→**10**) [16] of sultam-derived enolates **II**. Hence, the prospect of converting acylsultams **9** and **10** into Fmoc-amino acids **14** constitutes an interesting test case, to probe the compatibility of these neutral cleavage conditions with the base-labile *N*-Fmoc functionality (*Scheme 4*).

Scheme 4



a R = Me, **b** R = Me_2CHCH_2, **c** R = CH_2=$CHCH_2$, **d** R = (*E*)-$C_5H_{11}CH$=$CHCH_2$, **e** R = $PhCH_2$, **f** R = CH≡CCH_2

Starting with the diastereoisomerically pure alkylation products **9**, the bis(methylthio)methylidene group was exchanged by the Fmoc group without isolation of the free amine **11**. To accomplish selective acylsultam propenolysis with minimal cleavage of the protecting group, the 'transesterification' procedure was slightly modified. Thus, stirring a 0.01M solution of *N*-[*N'*-(Fmoc)amino]acylsultam **12a** in allyl alcohol in the presence of

Table 2. *Preparation of* N-*[(Fluoren-9-yl)methoxycarbonyl]amino Acids from* N-*Acylsultams by* $Ti(OEt)_4$*-Mediated Propenolysis (130°)/[*$RhCl(PPh_3)_3$*]-Catalyzed Hydrolysis:* **9** → **12** → **1** + **13** → **14**

Entry	{[Bis(methylthio)methylidene]amino}acylsultam **9**		(Fmoc-amino)-acylsultam **12** Yield [%]	Sultam **1** Yield [%]	Allyl ester **13** Yield [%]	Fmoc-amino acid **14**		
		R				Yield [%]	e.e. [%][a]	Configuration[b]
7	**a**	Me	90	100	95	67	98.8	*S*
8	**b**	Me_2CHCH_2	86	77	67	92	> 99	*S*
9	**c**	$CH_2{=}CHCH_2$	92	78	75	97	98.8	*S*
10	**d**	(*E*)-$C_5H_{11}CH{=}CHCH_2$	82	78	75	89	> 99	*S*
11	**e**	$PhCH_2$	75	98	73	86	98.1	*S*
12	**f**	$CH{\equiv}CCH_2$	89	74	80	–[c]	–[c]	–[c]

[a]) HPLC Comparison (*Chiracel OD*) with racemic sample. [b]) Based on the previously assigned configurations of **9** [6] [15]. [c]) Complex reaction mixture, **14f** not isolable.

$Ti(OEt)_4$ (5 mol-equiv.) at 130° (closed *Carius* tube) for 45 min yielded efficiently sultam **1** (100%) and allyl ester **13a** (95%; *Table 2, Entry 7*).

$[RhCl(PPh_3)_3]$-catalyzed hydrolysis of allyl ester **13a** furnished the *N*-protected alanine **14a** (67%; *Entry 7*). Compound **14a** proved to be 98.8% enantiomerically pure by HPLC comparison with the corresponding racemate using a chiral column (*Chiracel OD*). This three-step sequence **9** → **14** provided, furthermore, *N*-Fmoc derivatives of (*S*)-leucine, (*S*)-allylglycine, (*S*)-phenylalanine, and of the non-proteinogenic (*S*,*E*)-2-aminodec-4-enoic acid in virtually enantiomerically pure form (HPLC; *Entries 8–11*). The reaction conditions, thus, comply perfectly with the presence of a terminal or (*E*)-1,2-disubstituted C=C bond (*Entries 9* and *10*). However, a terminal acetylenic group seems to interfer with attempted Rh-catalyzed hydrolysis of **13f** (*Entry 12*).

Conclusion. – In summary, we have established a nonbasic two-step protocol for the overall non-destructive hydrolysis of *N*-acylsultams giving enantiomerically pure carboxylic acids containing various functionalities such as the base-sensitive *N*-Fmoc group. Further reactions bringing about non-destructive *N*-acylsultam cleavage with concomitant formation of a C–C or C–N bond are presently being explored in our laboratories.

Financial support of this work by the *Swiss National Science Foundation, Sandoz Pharma Ltd.*, Basel, and *Givaudan SA*, Vernier, is gratefully acknowledged. We thank Mr. *J. P. Saulnier*, Mr. *A. Pinto*, and Mrs. *C. Clément* for NMR and MS measurements.

Experimental Part

General. All reactions in an anh. medium were carried out under Ar with magnetic stirring, unless otherwise specified. Solvents were dried by distillation from drying agents as follows: Et_2O, THF, toluene (Na), CH_2Cl_2 (CaH_2). 'Workup' denotes extraction with an org. solvent, drying (Na_2SO_4), and evaporation *in vacuo*. Column flash chromatography (FC): SiO_2 (60, 0.04–0.06 mm, *Merck 9385*). GC: *Hewlett-Packard 5790 A*, integrator *HP 3390*, capillary column: *OV-1* (12 m × 0.2 mm), 10 psi H_2, 2 min 100°, 10°/min to 270°, unless otherwise specified, t_R in min (area %). HPLC: *Waters 501*; detector: UV 481 nm; integrator: *Waters 745*; 0.5 ml/min; *A: Chiracel OB* (hexane/i-PrOH 98:2); *B: Chiracel OD* (hexane/i-PrOH/HCO_2H 79:20:1), t_R in min (area %). M.p.: *Kofler* hot stage; uncorrected. $[\alpha]_D$: *Perkin-Elmer-241* polarimeter; in $CHCl_3$ at 20°, unless otherwise specified. IR: *Perkin-*

Elmer, FTIR 1600, in $CHCl_3$, unless otherwise specified. ^{1}H-NMR (*Bruker AMX 400*) at 400 MHz in $CDCl_3$, unless otherwise specified; standard $CHCl_3$ ($\delta = 7.27$ ppm), J in Hz. ^{13}C-NMR at 100 MHz in $CDCl_3$, unless otherwise specified. MS: *Varian CH-4* or *Finnigan 4023* at 70 eV, m/z (rel.-%). HR-MS: *VG 7070-E*.

Preparation of *N*-{2′-{*N*′-[Bis(methylthio)methylidene]amino}}acylsultams 9. – The preparation of **9a**, **9b**, **9c**, and **9e** has been previously described [15].

N-{2′-{N′-[*Bis(methylthio)methylidene]amino*}*dec-4-enoyl*}*bornane-10,2-sultam* (**9d**). A 1.6M soln. of BuLi in hexane (562 µl, 0.9 mmol) was added to a soln. of *N*-{*N*′-[bis(methylthio)methylidene]glycyl}bornane-10,2-sultam [15][1]) (300 mg, 0.797 mmol) in THF (4.1 ml) at −78°. The mixture was stirred at −78° for 1 h, and a soln. of (*E*)-1-iododoct-2-ene [17] (588 mg, 2.47 mmol) in HMPA (721 µl) was added dropwise at −78°. Stirring at −78° for 2 h, addition of a sat. aq. soln. of NH_4Cl, extraction with CH_2Cl_2, drying, evaporation, and FC of the residue (hexane/Et_2O 4:1→3:2) furnished pure (> 99% by GC) **9d** (359 mg, 93%, colorless oil). GC (2 min 150°, 10°/min→270°): 20.34 (99). ^{1}H-NMR: 0.87 (*t*, *J* = 7, 3 H); 0.97 (*s*, 3 H); 1.18 (*s*, 3 H); 1.05–1.43 (8 H); 1.8–2.1 (7 H); 2.43 (*s*, 3 H); 2.55 (*s*, 3 H); 2.57 (*m*, 1 H); 2.65 (*m*, 1 H); 3.42 (*d*, *J* = 14, 1 H); 3.50 (*d*, *J* = 14, 1 H); 3.92 (*dd*, *J* = 6.2, 5.1, 1 H); 5.02 (*t*, *J* = 6, 1 H); 5.39–5.55 (2 H). ^{13}C-NMR: 14.0 (*q*); 14.8 (*q*); 15.3 (*q*); 19.9 (*q*); 20.8 (*q*); 22.5 (*t*); 26.4 (*t*); 29.0 (*t*); 31.4 (*t*); 32.6 (*t*); 32.8 (*t*); 37.9 (*t*); 38.4 (*t*); 44.6 (*d*); 47.7 (*s*); 48.4 (*s*); 53.1 (*t*); 65.0 (*d*); 65.3 (*d*); 124.6 (*d*); 134.3 (*d*); 161.7 (*s*); 171.2 (*s*).

N-{2′-{N′-[*Bis(methylthio)methylidene]amino*}*pent-4-ynoyl*}*bornane-10,2-sultam* (**9f**). Following the procedure, described for the preparation of **9d**, *N*-{*N*′-[bis(methylthio)methylidene]glycyl}bornane-10,2-sultam [15][1]) (300 mg, 0.796 mmol) was deprotonated with BuLi (0.9 mmol) in THF at −78°, and a soln. of propargyl bromide (184 µl, 2.47 mmol) in HMPA (721 µl) was added dropwise. Stirring the mixture at −78° for 4 h, workup, FC, and crystallization (EtOH) furnished **9f** (170 mg, 51%). M.p.: 112–113°. ^{1}H-NMR: 0.97 (*s*, 3 H); 1.20 (*s*, 3 H); 1.3–1.5 (2 H); 1.8–2.2 (5 H); 2.44 (*s*, 3 H); 2.56 (*s*, 3 H); 2.75–2.9 (2 H); 3.44 (*d*, *J* = 14, 1 H); 3.51 (*d*, *J* = 14, 1 H); 3.95 (*m*, 1 H); 5.1 (*t*, *J* = 6, 1 H); 7.3 (*s*, 1 H).

Preparation of Diastereoisomerically Pure *N*-{2′-[(Fluoren-9-yl)methoxycarbonyl]amino}acylsultams 12. – *General Procedure*. A 1N aq. soln. of HCl (10 mol-equiv.) was added to a 0.1–0.2M soln. of **9** in THF, and the soln. was stirred at r.t. for 24 h. Evaporation of the THF, washing of the aq. residue with Et_2O, and evaporation of the H_2O gave a residue which was dissolved in THF (0.1–0.2 ml/mmol). Addition of a 10% aq. soln. of Na_2CO_3 (10 ml/mmol), followed by dropwise addition of a 0.4M soln. of (fluoren-9-yl)methyl chloroformate in THF (1.3 mol-equiv.), stirring of the mixture at r.t. for 3 h, addition of a sat. aq. soln. of NH_4Cl, workup (CH_2Cl_2), and FC (hexane/AcOEt 4:1) gave the corresponding acylsultam **12**.

(2R,2′S)-N-{N′-[(*Fluoren-9-yl)methoxycarbonyl]alanyl*}*bornane-10,2-sultam* (**12a**). Following the *General Procedure*, **9a** (200 mg, 0.512 mmol) was converted to **12a** (234 mg, 90%, oil). $[\alpha]_D = -63$, $[\alpha]_{578} = -65.3$, $[\alpha]_{546} = -74.3$, $[\alpha]_{436} = -125.4$, $[\alpha]_{365} = -198.4$ ($c = 1$). IR: 3016.0, 1722.8, 1504.1, 1450,4, 1342.2, 1234.2, 1137.4. ^{1}H-NMR (CD_3OD): 1.00 (*s*, 3 H); 1.14 (*s*, 3 H); 1.40 (*d*, *J* = 7.3, 3 H); 1.28–1.48 (2 H); 1.81–2.09 (5 H); 3.59 (*d*, *J* = 14, 1 H); 3.68 (*d*, *J* = 14, 1 H); 3.92 (br. *t*, *J* = 6.1, 1 H); 4.19–4.37 (3 H); 4.80 (*m*, 1 H); 7.30 (br. *t*, *J* = 7.3, 2 H); 7.38 (br. *t*, *J* = 7.5, 2 H); 7.56–7.65 (2 H); 7.75 (*d*, *J* = 7.3, 2 H). ^{13}C-NMR (CD_3OD): 18.6 (*q*); 20.1 (*q*); 21.3 (*q*); 27.3 (*t*); 33.5 (*t*); 39.3 (*t*); 46.1 (*d*); 51.9 (*d*); 53.5 (*t*); 66.2 (*d*); 68.1 (*t*); 120.9 (*d*); 126.2 (*d*); 126.3 (*d*); 128.1 (*d*); 128.2 (*d*); 128.7 (*d*); 142.5 (*s*); 145.1 (*s*); 145.3 (*s*); 157.9 (*s*); 174.1 (*s*). MS: 312 (2, $[C_{28}H_{32}N_2O_5S - C_{14}H_{12}O]^{+\cdot}$), 266 (15), 242 (100), 196 (21), 178 (96), 165 (80), 135 (52).

(2R,2′S)-N-{N′-[(*Fluoren-9-yl)methoxycarbonyl]leucyl*}*bornane-10,2-sultam* (**12b**). Following the *General Procedure*, **9b** (68 mg, 0.157 mmol) was converted to **12b** (75 mg, 86%). M.p. 98–102°. $[\alpha]_D = -62.6$, $[\alpha]_{578} = -65$, $[\alpha]_{546} = -73.6$, $[\alpha]_{436} = -123.6$, $[\alpha]_{365} = -193.6$ ($c = 1.5$). IR: 3019.2, 2962.0, 1725.0, 1697.0, 1510,1, 1450.3, 1341.0, 1232.1, 1221.4, 1167.4, 1137.7, 1067.0. ^{1}H-NMR (CD_3OD): 0.92 (*d*, *J* = 4.4, 3 H); 0.94 (*d*, *J* = 4.4, 3 H); 0.99 (*s*, 3 H); 1.14 (*s*, 3 H); 1.27–2.05 (10 H); 3.56 (*d*, *J* = 14.0, 1 H); 3.66 (*d*, *J* = 14.0, 1 H); 3.90 (br. *t*, *J* = 6.0, 1 H); 4.20 (*t*, *J* = 7.0, 1 H); 4.31–4.34 (2 H); 4.90 (*m*, 1 H); 7.29 (*t*, *J* = 7.3, 2 H); 7.37 (br. *t*, *J* = 7.5, 2 H); 7.66 (br. *t*, *J* = 5, 2 H); 7.78 (*d*, *J* = 8.0, 2 H). ^{13}C-NMR (CD_3OD): 20.1 (*q*), 21.2 (*q*); 21.4 (*q*); 23.8 (*q*); 26.2 (*d*); 27.3 (*t*); 33.5 (*t*); 39.3 (*t*); 42.1 (*t*); 46.1 (*d*); 53.5 (*t*); 54.8 (*d*); 66.2 (*d*); 67.9 (*t*); 120.8 (*d*); 126.3 (*d*); 128.1 (*d*); 128.2 (*d*); 128.7 (*d*); 142.5 (*s*); 145.4 (*s*); 158.3 (*s*); 174.4 (*s*). MS: 531 (10, $[C_{31}H_{38}N_2O_5S - 19]^+$), 298 (100), 242 (20), 196 (30), 178 (78), 165 (95), 151 (10), 135 (67), 112 (15), 93 (18).

(2R,2′S)-N-{2′-*Allyl*-N′-[(*fluoren-9-yl)methoxycarbonyl]glycyl*}*bornane-10,2-sultam* (**12c**). Following the *General Procedure*, **9c** (150 mg, 0.360 mmol) was converted to **12c** (177 mg, 92%, colorless oil). $[\alpha]_D = -52.7$, $[\alpha]_{578} = -55.2$, $[\alpha]_{546} = -62.7$, $[\alpha]_{436} = -106.2$, $[\alpha]_{365} = -169.6$ ($c = 0.8$). IR: 2960.9, 1723.2, 1504.1, 1450.3, 1342.5, 1233.7, 1167.3, 1137.2, 991.4. ^{1}H-NMR (CD_3OD): 0.99 (*s*, 3 H); 1.14 (*s*, 3 H); 1.22–1.58 (3 H); 1.83–2.10 (5 H); 2.40 (*m*, 1 H); 2.64 (*m*, 1 H); 3.58 (*d*, *J* = 13.9, 1 H); 3.69 (*d*, *J* = 13.9, 1 H); 3.92 (*t*, *J* = 6.2, 1 H); 4.21 (*m*, 1 H); 4.29–4.32 (2 H); 5.06–5.15 (2 H); 5.77 (*m*, 1 H); 7.29 (*t*, *J* = 7.3, 2 H); 7.37 (br. *t*, *J* = 7.5, 2 H); 7.61–7.68

(2 H); 7.78 (*d*, *J* = 7.7, 2 H). ^{13}C-NMR (CD_3OD): 20.0 (*q*); 21.4 (*q*); 27.5 (*t*); 33.5 (*t*); 38.2 (*t*); 39.3 (*t*); 46.0 (*d*); 48.3 (*d*); 53.6 (*t*); 55.7 (*d*); 66.3 (*d*); 68.1 (*t*); 119.1 (*t*); 120.9 (*d*); 126.3 (*d*); 128.2 (*d*); 128.7 (*d*); 134.0 (*d*); 142.5 (*s*); 145.1 (*s*); 145.3 (*s*); 158.0 (*s*); 172.6 (*s*). MS: 534 (0.5, $C_{30}H_{34}N_2O_5S^{+\cdot}$), 493 (6), 449 (5), 338 (55), 297 (100), 271 (22), 242 (10), 196 (25), 178 (99), 165 (92), 135 (58), 109 (12), 93 (22), 79 (16), 70 (20).

*(2R,2′S)-*N*-{(E)-2′-{N′-[(Fluoren-9-yl)methoxycarbonyl]amino}dec-4′-enoyl}bornane-10,2-sultam* (**12d**). Following the *General Procedure*, **9d** (236 mg, 0.485 mmol) was converted to **12d** (240 mg, 82%, colorless oil). $[\alpha]_D = -40.7$, $[\alpha]_{578} = -41.5$, $[\alpha]_{546} = -47.5$, $[\alpha]_{436} = -82.5$, $[\alpha]_{365} = -134.3$ (*c* = 0.7). IR: 3020.0, 2961.5, 1722.2, 1602.2, 1503.0, 1450.4, 1341.9, 1222.0, 1136.9, 1111.7. ^{1}H-NMR (CD_3OD): 0.85 (*t*, *J* = 6.8, 3 H); 0.99 (*s*, 3 H); 1.15 (*s*, 3 H); 1.20–1.50 (8 H); 1.81–2.20 (7 H); 2.35 (*m*, 1 H); 2.57 (*m*, 1 H); 3.57 (*d*, *J* = 14.0, 1 H); 3.69 (*d*, *J* = 14.0, 1 H); 3.91 (br. *t*, *J* = 6.0, 1 H); 4.17–4.34 (3 H); 5.37 (*ddd*, *J* = 15.0, 7.0, 5.0, 1 H); 5.53 (*dt*, *J* = 15.0, 6.6, 1 H); 7.29 (*td*, *J* = 7.3, 1.1, 2 H); 7.37 (*t*, *J* = 7.3, 2 H); 7.64–7.67 (2 H); 7.78 (*d*, *J* = 7.3, 2 H). ^{13}C-NMR (CD_3OD): 14.3 (*q*); 20.1 (*q*); 21.4 (*q*); 23.5 (*t*); 27.3 (*t*); 30.1 (*t*); 32.4 (*t*); 33.5 (*t*); 37.2 (*t*); 39.4 (*t*); 46.1 (*d*); 53.6 (*t*); 56.1 (*d*); 66.3 (*d*); 68.1 (*t*); 120.9 (*d*); 125.0 (*d*); 126.3 (*d*); 128.2 (*d*); 128.8 (*d*); 136.1 (*d*); 142.6 (*s*); 145.2 (*s*); 157.9 (*s*); 172.8 (*s*). MS: 365 (10, $[C_{35}H_{44}N_2O_5S - C_{15}H_{13}NO_2]^{+\cdot}$), 294 (50), 196 (40), 165 (100), 151 (52), 135 (42), 107 (15), 93 (19).

*(2R,2′S)-*N*-{N′-[(Fluoren-9-yl)methoxycarbonyl]phenylalanyl}bornane-10,2-sultam* (**12e**). Following the *General Procedure*, **9e** (300 mg, 0.643 mmol) was converted to **12e** which was crystallized from hexane/Et_2O (283 mg, 75%). M.p. 87–90°. $[\alpha]_D = -51.6$, $[\alpha]_{578} = -53.6$, $[\alpha]_{546} = -59.8$, $[\alpha]_{436} = -95.4$, $[\alpha]_{365} = -142.8$ (*c* = 1). IR: 3683.3, 3620.3, 3020.7, 2975.1, 1699.5, 1521.6, 1422.8, 1334.0, 1223.7, 1046.1, 847.9. ^{1}H-NMR: 0.97 (*s*, 3 H); 1.09 (*s*, 3 H); 1.35–1.45 (2 H); 1.83–2.10 (5 H); 2.88 (*m*, 1 H); 3.42 (*d*, *J* = 14, 1 H); 3.48 (*d*, *J* = 14, 1 H); 3.81 (*m*, 1 H); 4.13–4.32 (3 H); 5.20–5.32 (2 H); 7.18–7.28 (7 H); 7.35 (br. *t*, *J* = 7.5, 2 H); 7.51 (*dd*, *J* = 13.6, 7.3, 2 H); 7.71 (*d*, *J* = 7.7, 2 H). ^{13}C-NMR: 19.8 (*q*); 20.7 (*q*); 26.4 (*t*); 32.8 (*t*); 38.2 (*t*); 39.3 (*t*); 44.6 (*d*); 47.0 (*d*); 47.7 (*s*); 48.7 (*s*); 52.8 (*t*); 55.4 (*d*); 64.9 (*d*); 67.0 (*t*); 119.8 (*d*); 125.2 (*d*); 126.9 (*d*); 127.1 (*d*); 127.5 (*d*); 128.4 (*d*); 129.6 (*d*); 135.5 (*d*); 141.2 (*s*); 143.8 (*s*); 143.9 (*s*); 155.2 (*s*); 171.2 (*s*). MS: 345 (1, $[C_{34}H_{36}N_2O_5S - C_{15}H_{13}NO_2]^{+\cdot}$), 179 (40), 178 (100), 165 (15), 131 (14), 128 (5), 120 (20), 91 (28).

*(2R,2′S)-*N*-{2′-{N′-[(Fluoren-9-yl)methoxycarbonyl]amino}pent-4′-ynoyl}bornane-10,2-sultam* (**12f**). Following the *General Procedure*, **9f** (170 mg, 0.410 mmol) was converted to **12f** (195 mg, 89%). $[\alpha]_D = -29.0$, $[\alpha]_{578} = -30.3$, $[\alpha]_{546} = -34.6$, $[\alpha]_{436} = -82.8$, $[\alpha]_{365} = -97.2$ (*c* = 1.4). IR: 3428, 3307, 2970, 2875, 1703, 1505, 1447, 1384, 1350, 1228, 1137, 1111, 843. ^{1}H-NMR (CD_3OD): 1.00 (*s*, 3 H); 1.16 (*s*, 3 H); 1.35 (*dt*, *J* = 11, 4.4, 1 H); 1.47 (*dt*, *J* = 9.6, 2.6, 1 H); 1.84 (*t*, *J* = 3.7, 1 H); 1.85–2.14 (4 H); 2.41 (br. *s*, 1 H); 2.7–2.9 (2 H); 3.6 (*d*, *J* = 14, 1 H); 3.7 (*d*, *J* = 14, 1 H); 3.95 (*dd*, *J* = 7.5, 5.1, 1 H); 4.23 (*t*, *J* = 7, 1 H); 4.33 (*d*, *J* = 7, 2 H); 4.97 (*m*, 1 H); 7.31 (*t*, *J* = 7.4, 2 H); 7.38 (*t*, *J* = 7.4, 2 H); 7.67 (br. *t*, *J* = 5.9, 2 H); 7.79 (*d*, *J* = 7.4, 2 H). ^{13}C-NMR (CD_3OD): 20.1 (*q*); 21.2 (*q*); 24.1 (*t*); 27.4 (*t*); 33.4 (*t*); 39.2 (*t*); 46.1 (*d*); 49.4 (*d*); 53.7 (*t*); 54.8 (*d*); 66.3 (*t*); 68.3 (*d*); 73.3 (*s*); 120.9 (*d*); 126.3 (*d*); 128.2 (*d*); 128.8 (*d*); 142.5 (*s*); 145.5 (*s*).

Non-destructive, Titanium-Mediated 'Transesterification' of *N*-Acylsultams with Allyl Alcohol. – *General Procedure A.* A 0.02M soln. of acylsultam **3a–d**, **4a**, and **4c** in propenol containing Ti(i-PrO)$_4$ (1.5 mol-equiv.) and molecular sieves (4 Å; 250 mg/mmol) was stirred in a closed *Carius* tube at 150° for the time indicated. Addition of a sat. aq. soln. of NH_4Cl, workup, and FC furnished sultam **1** or **2** and the corresponding allyl ester.

General Procedure B. A 0.01M soln. of **12** in propenol containing Ti(EtO)$_4$ (5 mol-equiv.) was stirred in a closed *Carius* tube at 130° for the time indicated. Addition of a sat. aq. soln. of NH_4Cl, workup, and FC furnished sultam **1** and the corresponding allyl ester **13**.

Prop-2-enyl (2S)-2-Methyl-3-phenylpropionate (**5a**). Following the *General Procedure A*, **3a** (150 mg, 0.415 mmol) was 'transesterified' for 3 h. Workup and FC (hexane/Et_2O 98:2→3:2) furnished **1** (78.5 mg, 88%) and **5a** (74.4 mg, 88%). Under identical reaction conditions, **4a** (62 mg, 0.188 mmol) furnished **2** (27 mg, 78%) and **5a** (33 mg, 86%). $[\alpha]_D = +22.5$, $[\alpha]_{578} = +23.4$, $[\alpha]_{546} = +26.8$, $[\alpha]_{436} = +47.7$, $[\alpha]_{365} = +80.0$ (*c* = 2.4). GC: 5.48. IR: 3027, 3018, 2978, 2936, 2878, 1727, 1649, 1604, 1495, 1454, 1381, 1282, 1170, 1108, 1037, 982, 936. ^{1}H-NMR: 1.16 (*d*, *J* = 7.0, 3 H); 2.68 (*dd*, *J* = 13.1, 6.0, 1 H); 2.76 (*qdd*, *J* = 7.5, 7.0, 6.0, 1 H); 3.04 (*dd*, *J* = 13.1, 7.5, 1 H); 4.52–4.56 (2 H); 5.15 (*ddd*, *J* = 10.5, 3.0, 1.8, 1 H); 5.24 (*ddd*, *J* = 12.1, 3.0, 1.7, 1 H); 5.85 (*ddt*, *J* = 12.1, 10.5, 5.5, 1 H); 7.16–7.29 (5 H). ^{13}C-NMR: 16.7 (*q*); 39.6 (*t*); 41.4 (*d*); 64.9 (*t*); 117.9 (*t*); 126.3 (*d*); 128.3 (*d*); 128.9 (*d*); 132.2 (*d*); 139.3 (*s*); 175.7 (*s*). MS: 204 (3, $C_{13}H_{16}O_2^{+\cdot}$), 163 (13), 147 (2), 131 (2), 119 (11), 107 (49), 91 (100), 71 (8), 65 (15), 57 (45), 51 (9).

Prop-2-enyl endo-*(2S)-Bicyclo[2.2.1]hept-5-ene-2-carboxylate* (**5b**). Following the *General Procedure A*, **3b** (60 mg, 0.179 mmol) was 'transesterified' for 3 h. Workup and FC (hexane/Et_2O 98:2→3:2) furnished **1** (33.8 mg, 88%) and **5b** (27 mg, 85%). $[\alpha]_D = -98$, $[\alpha]_{578} = -102$, $[\alpha]_{546} = -117$, $[\alpha]_{436} = -205.8$, $[\alpha]_{365} = -337.2$ (*c* = 2.5). GC: 3.66. IR ($CHCl_3$): 3017.4, 2955.6, 2871.7, 1726.9, 1448.1, 1336.1, 1271.9, 1186.1, 1110.1, 1029.3, 993.7, 936.0. ^{1}H-NMR: 1.20–1.58 (3 H); 1.92 (*ddd*, *J* = 11.9, 9.4, 3.7, 1 H); 2.91 (br. *s*, 1 H); 2.98 (*m*, 1 H); 3.24 (br. *s*, 1 H);

4.48–4.59 (2 H); 5.22 (*ddd*, J = 10.4, 2.6, 1.4, 1 H); 5.31 (*ddd*, J = 17.0, 3.3, 1.4, 1 H); 5.85–5.95 (2 H); 6.20 (*dd*, J = 5.6, 3.2, 1 H). ^{13}C-NMR: 29.2 (*t*); 42.5 (*d*); 43.3 (*d*); 45.7 (*d*); 49.6 (*t*); 64.8 (*t*); 117.8 (*t*); 132.3 (*d*); 132.5 (*d*); 137.7 (*d*); 174.3 (*s*). MS: 178 (2, $C_{11}H_{14}O_2^{+\cdot}$), 113 (11), 91 (13), 66 (100), 55 (24). HR-MS: 178.0983 ($C_{11}H_{14}O_2^{+\cdot}$, calc. 178.0993).

*Prop-2-enyl (2*R*,3*S*)-3-Hydroxy-2,4-dimethylpentanoate* (**5c**). Following the *General Procedure A*, **3c** (100 mg, 0.291 mmol) was 'transesterified' for 2 h. Workup and FC (hexane/Et_2O 98:2→4:1) furnished **1** (61.5 mg, 98%) and **5c** (48 mg, 88%). Under identical reaction conditions, **4c** (50 mg, 0.16 mmol) furnished **2** (22 mg, 75%) and **5c** (23 mg, 77%). $[\alpha]_D$ = +5.6, $[\alpha]_{578}$ = +5.7, $[\alpha]_{546}$ = +6.5, $[\alpha]_{436}$ = +10.4, $[\alpha]_{365}$ = +15.1 (c = 0.9). IR: 2959.8, 2873.9, 1724.6, 1460.3, 1271.7, 1185.3, 1126.5, 980.8. ^{1}H-NMR: 0.88 (*d*, J = 7.0, 3 H); 1.02 (*d*, J = 6.2, 3 H); 1.20 (*d*, J = 7.0, 3 H); 1.70 (*m*, 1 H); 2.45 (*d*, J = 4.0, 1 H); 2.70 (*qd*, J = 7.0, 3.7, 1 H); 3.58 (*m*, 1 H); 4.57–4.63 (2 H); 5.25 (*ddd*, J = 10.3, 2.9, 1.1, 1 H); 5.33 (*ddd*, J = 17.3, 2.9, 1.5, 1 H); 5.93 (*ddt*, J = 17.3, 10.3, 5.6, 1 H). ^{13}C-NMR: 10.1 (*q*); 18.6 (*q*); 19.0 (*q*); 30.4 (*d*); 41.8 (*d*); 65.2 (*t*); 76.6 (*d*); 118.4 (*t*); 131.9 (*d*); 176.1 (*s*). MS: 143 (38, $[C_{10}H_{18}O_3 - C_3H_7]^{+\cdot}$), 114 (31), 101 (65), 85 (55), 69 (100), 56 (73).

*Prop-2-enyl (2*S*,3*S*)-3-Hydroxy-2-methylpentanoate* (**5d**). Following the *General Procedure A*, **3d** (78 mg, 0.237 mmol) was 'transesterified' for 2 h. Workup and FC (hexane/acetone 15:1→8:1) furnished **1** (44.4 mg, 87%) and **5d** (36 mg, 88%). $[\alpha]_D$ = +6.5, $[\alpha]_{578}$ = +6.5, $[\alpha]_{546}$ = +7, $[\alpha]_{436}$ = +12.5, $[\alpha]_{365}$ = +20.5 (c = 1). IR: 3695.0, 3531.1, 3026.8, 2964.8, 2937.5, 1710.1, 1648.8, 1599.7, 1452.6, 1381.8, 1174.7, 1114.8, 940.7, 935.0. ^{1}H-NMR: 0.99 (*t*, J = 7.3, 3 H); 1.23 (*d*, J = 7.4, 3 H); 1.40–1.63 (2 H); 2.52 (*d*, J = 7.0, 1 H); 2.57 (*dq*, J = 7.4, 6.6, 1 H); 3.61 (*m*, 1 H); 4.61–4.63 (2 H); 5.25 (*ddd*, J = 10.3, 2.7, 1.1, 1 H); 5.34 (*ddd*, J = 17.3, 2.7, 1.5, 1 H); 5.82 (*ddt*, J = 17.3, 10.3, 5.7, 1 H). ^{13}C-NMR: 9.8 (*q*); 14.4 (*q*); 27.6 (*t*); 44.9 (*d*); 65.1 (*t*); 74.6 (*d*); 118.4 (*t*); 131.9 (*d*); 175.7 (*s*).

*(2*S*)-*N*-[(Fluoren-9-yl)methoxycarbonyl]alanine Prop-2-enyl Ester* (**13a**). Following the *General Procedure B*, **12a** (30.5 mg, 0.06 mmol) was 'transesterified' for 45 min. Workup and FC (hexane/Et_2O 9:1→4:1) furnished **1** (14.2 mg, ~ 100%) and **13a** (20.1 mg, 95%). IR: 3435.8, 3028.8, 2928.5, 1714.2, 1500.1, 1451.1, 1362.3, 1336.7, 1228.3, 1074.9. ^{1}H-NMR: 1.46 (*d*, J = 7.3, 3 H); 4.23 (br. *t*, J = 7.2, 1 H); 4.35–4.47 (3 H); 4.61–4.70 (2 H); 5.23–5.39 (3 H); 5.92 (*m*, 1 H); 7.31 (*td*, J = 7.3, 1.0, 2 H); 7.40 (*t*, J = 7.3, 2 H); 7.58–7.60 (2 H); 7.76 (*d*, J = 7.7, 2 H). ^{13}C-NMR: 29.7 (*q*); 47.1 (*d*); 49.7 (*d*); 66.0 (*t*); 67.0 (*t*); 118.8 (*t*); 119.9 (*d*); 125.0 (*d*); 127.0 (*d*); 127.7 (*d*); 131.5 (*d*); 141.3 (*s*); 143.8 (*s*). MS: 351 (0.5, $C_{21}H_{21}NO_4^{+\cdot}$), 343 (0.4), 196 (10), 178 (100), 165 (30).

*(2*S*)-*N*-[(Fluoren-9-yl)methoxycarbonyl]leucine Prop-2-enyl Ester* (**13b**). Following the *General Procedure B*, **12b** (27 mg, 0.049 mmol) was 'transesterified' for 1.25 h. Workup and FC (hexane/Et_2O 9:1→4:1) furnished **1** (8.1 mg, 77%) and **13b** (12.9 mg, 67%). $[\alpha]_D$ = −5.4, $[\alpha]_{578}$ = −5.7, $[\alpha]_{546}$ = −6.4, $[\alpha]_{436}$ = −10.2; $[\alpha]_{365}$ = −15 (c = 0.7). IR: 3440.9, 3027.9, 2928.5, 1715.0, 1500.4, 1450.1, 1365.2, 1346.7, 1075.3. ^{1}H-NMR: 0.95 (*d*, J = 6.2, 3 H); 0.96 (*d*, J = 5.9, 3 H); 1.50–1.75 (3 H); 4.23 (br. *t*, J = 7.1, 1 H); 4.36–4.46 (3 H); 4.64 (br. *d*, J = 5.5, 2 H); 5.15 (br. *d*, J = 8.4, 1 H); 5.24–5.35 (2 H); 5.90 (*m*, 1 H); 7.31 (br. *t*, J = 7.5, 2 H); 7.40 (br. *t*, J = 7.5, 2 H); 7.38–7.62 (2 H); 7.76 (*d*, J = 7.3, 2 H). ^{13}C-NMR: 21.8 (*q*); 22.9 (*q*); 24.8 (*d*); 41.8 (*t*); 47.2 (*d*); 52.5 (*d*); 65.9 (*t*); 67.0 (*t*); 118.8 (*t*); 120.0 (*d*); 125.1 (*d*); 127.0 (*d*); 127.7 (*d*); 131.6 (*d*); 141.3 (*s*); 143.7 (*s*); 143.9 (*s*); 156.0 (*s*); 172.8 (*s*).

*(2*S*)-2-Allyl-*N*-[(fluoren-9-yl)methoxycarbonyl]glycine Prop-2-enyl Ester* (**13c**). Following the *General Procedure B*, **12c** (32 mg, 0.06 mmol) was 'transesterified' for 1 h. Workup and FC (hexane/Et_2O 4:1→3:2) furnished **1** (10 mg, 78%) and **13c** (17 mg, 75%). $[\alpha]_D$ = +2.4, $[\alpha]_{578}$ = +1.9, $[\alpha]_{546}$ = +2.4, $[\alpha]_{436}$ = +5.2, $[\alpha]_{365}$ = +8.9 (c = 1). IR: 3434.3, 3022.2, 2929.2, 1721.1, 1508.5, 1450.1, 1338.6, 1234.9, 1107.0, 989.6, 926.8. ^{1}H-NMR: 2.50–2.66 (2 H); 4.23 (*t*, J = 7.2, 1 H); 4.39 (br. *d*, J = 7.3, 2 H); 4.50 (*m*, 1 H); 4.61–4.70 (2 H); 5.13–5.37 (5 H); 5.71 (*m*, 1 H); 5.81 (*m*, 1 H); 7.31 (br. *t*, J = 7.3, 2 H); 7.40 (*t*, J = 7.3, 2 H); 7.58–7.60 (2 H); 7.76 (*d*, J = 7.3, 2 H). ^{13}C-NMR: 36.7 (*t*); 47.1 (*d*); 53.3 (*d*); 66.0 (*t*); 67.0 (*t*); 119.0 (*t*); 119.5 (*t*); 119.9 (*d*); 125.0 (*d*); 127.0 (*d*); 127.7 (*d*); 131.5 (*d*); 131.9 (*d*); 141.3 (*s*); 143.7 (*s*); 143.8 (*s*); 155.7 (*s*), 171.4 (*s*). MS: 377 (0.5, $C_{23}H_{23}NO_4^{+\cdot}$), 322 (0.6), 196 (12), 178 (100), 165 (50), 69 (10).

*Prop-2-enyl (2*S*,E)-2-{*N*-[(fluoren-9-yl)methoxycarbonyl]amino}dec-4-enoate* (**13d**). Following the *General Procedure B*, **12d** (36.2 mg, 0.06 mmol) was 'transesterified' for 1 h. Workup and FC (hexane/Et_2O 4:1→3:2) furnished **1** (10 mg, 78%) and **13d** (20 mg, 75%). M.p. 54–55°. $[\alpha]_D$ = +7.9, $[\alpha]_{578}$ = +8.2, $[\alpha]_{546}$ = +9.5, $[\alpha]_{436}$ = +17.8, $[\alpha]_{365}$ = +28.4 (c = 2). IR: 3437.3, 3020.1, 2928.8, 2855.9, 1720.7, 1509.1, 1450.3, 1381.5, 1339.1, 1220.0, 1105.3, 1056.9, 974.5. ^{1}H-NMR: 0.88 (*t*, J = 7.0, 3 H); 1.19–1.38 (6 H); 1.97–2.04 (2 H); 2.47–2.54 (2 H); 4.23 (br. *t*, J = 7.2, 1 H); 4.39 (br. *d*, J = 7.3, 2 H); 4.50 (*m*, 1 H); 4.59–4.70 (2 H); 5.25–5.36 (3 H); 5.55 (*dt*, J = 15.0, 6.8, 1 H); 5.91 (*m*, 1 H); 7.31 (br. *t*, J = 7.2, 2 H); 7.40 (*t*, J = 7.3, 2 H); 7.58–7.61 (2 H); 7.77 (*d*, J = 7.3, 2 H). ^{13}C-NMR: 14.0 (*q*); 22.4 (*t*); 28.9 (*t*); 31.3 (*t*); 32.5 (*t*); 35.6 (*t*); 47.2 (*d*); 53.6 (*d*); 65.9 (*t*); 67.0 (*t*); 118.8 (*t*); 119.9 (*d*); 122.9 (*d*); 125.1 (*d*); 127.0 (*d*); 127.7 (*d*); 131.6 (*d*); 136.0 (*d*); 141.3 (*s*); 143.8 (*s*); 143.9 (*s*); 155.7 (*s*); 171.6 (*s*). MS: 362 (0.14, $[C_{28}H_{33}NO_4 - C_4H_5O_2]^{+\cdot}$), 179 (36), 178 (100), 165 (7), 81 (5), 69 (10), 57 (11), 55 (14).

(2S)-N-[(Fluoren-9-yl)methoxycarbonyl]phenylalanine Prop-2-enyl Ester (**13e**). Following the *General Procedure B*, **12e** (20 mg, 0.034 mmol) was 'transesterified' for 1 h. Workup and FC (hexane/Et_2O 4:1→3:1) furnished **1** (7.2 mg, 98%) and **13e** (10.6 mg, 73%). M.p. 92–95° (hexane/Et_2O). $[\alpha]_D = +15.9$, $[\alpha]_{578} = +16.9$, $[\alpha]_{546} = +19.2$, $[\alpha]_{436} = +34.7$, $[\alpha]_{365} = +56.7$ ($c = 0.8$). IR: 3439.0, 3009.8, 1720.2, 1505.0, 1448.9, 1336.8, 1190.6, 1078.6, 1052.7, 988.0, 936.3. ^{1}H-NMR: 3.08–3.20 (2 H); 4.20 (*t*, *J* = 7, 1 H); 4.34 (*dd*, *J* = 10.6, 6.9, 1 H); 4.44 (*dd*, *J* = 10.6, 6.9, 1 H); 4.62 (br. *d*, *J* = 5.5, 2 H); 4.70 (*m*, 1 H); 5.20–5.36 (3 H); 5.87 (*m*, 1 H); 7.10 (br. *d*, *J* = 6.2, 2 H); 7.22–7.35 (5 H); 7.40 (br. *t*, *J* = 7.5, 2 H); 7.56 (br. *t*, *J* = 6.4, 2 H); 7.77 (*d*, *J* = 7.7, 2 H). ^{13}C-NMR: 38.3 (*t*); 47.2 (*d*); 54.8 (*d*); 66.1 (*t*); 67.0 (*t*); 119.1 (*t*); 119.9 (*d*); 125.0 (*d*); 125.1 (*d*); 127.0 (*d*); 127.2 (*d*); 127.7 (*d*); 128.6 (*d*); 129.4 (*d*); 131.3 (*d*); 135.6 (*d*); 141.3 (*s*); 143.7 (*s*); 143.8 (*s*); 155.5 (*s*); 171.2 (*s*). MS: 427 (0.2, $C_{27}H_{25}NO_4^{+\cdot}$), 179 (31), 178 (100), 166 (5), 165 (12), 120 (3), 92 (3), 91 (17).

Prop-2-enyl (2S)-2-{N-[(Fluoren-9-yl)methoxycarbonyl]amino}pent-4-ynoate (**13f**). Following the *General Procedure B*, **12f** (32 mg, 0.06 mmol) was 'transesterified' for 1 h. Workup and FC (hexane/acetone 9:1→4:1) furnished **1** (9.6 mg, 74%) and **13f** (18 mg, 80%). $[\alpha]_D = +26.0$, $[\alpha]_{578} = +27.1$, $[\alpha]_{546} = +30.8$, $[\alpha]_{436} = +52.8$, $[\alpha]_{365} = +82.1$ ($c = 1.7$). IR: 3431, 3308, 3011, 1721, 1509, 1450, 1338, 1224, 1198, 1062, 794, 666. ^{1}H-NMR: 2.08 (br. *s*, 1 H); 2.77–2.87 (2 H); 4.25 (*t*, *J* = 7.4, 1 H); 4.4 (*d*, *J* = 7.4, 2 H); 4.58 (*m*, 1 H); 4.65–4.75 (2 H); 5.28 (*m*, 1 H); 5.37 (*m*, 1 H); 5.67 (*d*, *J* = 8.5, 1 H); 5.39 (*m*, 1 H); 7.32 (br. *t*, *J* = 7.4, 2 H); 7.41 (*t*, *J* = 7.4, 2 H); 7.61 (*d*, *J* = 7.4, 2 H); 7.77 (*d*, *J* = 7.4, 2 H). ^{13}C-NMR: 22.8 (*t*); 47.1 (*d*); 52.4 (*d*); 66.4 (*t*); 67.3 (*t*); 71.9 (*s*); 78.2 (*d*); 119.0 (*t*); 120.0 (*d*); 125.1 (*d*); 127.1 (*d*); 127.8 (*d*); 131.3 (*d*); 141.3 (*s*); 143.7 (*s*); 143.8 (*s*); 155.6 (*s*); 170.0 (*s*).

Cleavage of Allyl Esters. – *General Procedure.* A 0.03M soln. of the allyl ester in EtOH/H_2O 9:1 was heated under reflux while adding portionwise $[RhCl(PPh_3)_3]$ (0.11 mol-equiv.). Stirring the mixture under reflux for the time indicated, filtration through *Celite* evaporation, and chromatography gave the free carboxylic acid.

(2S)-2-Methyl-3-phenylpropionic Acid (**7a**). Following the *General Procedure*, **5a** (18 mg, 0.088 mmol) was heated with $[RhCl(PPh_3)_3]$ in aq. EtOH for 5 h. Subsequent FC (hexane/Et_2O/AcOH 9:1:0.01) gave **7a** (12.8 mg, 89%). $[\alpha]_D = +25.5$, $[\alpha]_{578} = +26.5$, $[\alpha]_{546} = +30$, $[\alpha]_{436} = +51.8$, $[\alpha]_{365} = +85.9$ ($c = 1$) ([10]: $[\alpha]_D = +29.3$ ($c = 1.15$); [18]: $[\alpha]_D = +25.2$ ($c = 2.2$, EtOH)). ^{1}H-NMR: 1.17 (*d*, *J* = 7, 3 H); 2.67 (*d*, *J* = 13.2, 8.0, 1 H); 2.76 (*m*, 1 H); 3.08 (*dd*, *J* = 13.4, 6.4, 1 H); 7.17–7.30 (5 H).

For determination of its enantiomeric purity a sample was treated with an excess of CH_2N_2 in Et_2O and crude methyl ester **8a** was analyzed by HPLC: *A*: 14.23 (0.96), 15.24 (87.82). HPLC of racemic methyl ester: *A*: 14.31 (41.55), 15.56 (46.12).

endo-*(2S)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid* (**7b**). Following the *General Procedure*, **5b** (25 mg, 0.14 mmol) was heated with $[RhCl(PPh_3)_3]$ in aq. EtOH for 3 h. Subsequent FC (hexane/Et_2O/AcOH 9:1:0.01) gave **7b** (15 mg, 78%). $[\alpha]_D = -145.8$, $[\alpha]_{578} = -151$, $[\alpha]_{546} = -172.5$, $[\alpha]_{436} = -302$, $[\alpha]_{365} = -493.2$ ($c = 0.47$, EtOH 95%) ([19]: $[\alpha]_D = -147.14$ ($c = 0.49$, 95% EtOH)). ^{1}H-NMR: 1.27 (*m*, 1 H); 1.37–1.47 (2 H); 1.91 (*ddd*, *J* = 11.7, 9.6, 3.7, 1 H); 2.91 (br. *s*, 1 H); 2.99 (*dt*, *J* = 9.6, 4.0, 1 H); 3.23 (br. *s*, 1 H); 6.00 (*dd*, *J* = 5.5, 2.6, 1 H); 6.20 (*dd*, *J* = 5.5, 3.1, 1 H).

(2R,3S)-3-Hydroxy-2,4-dimethylpentanoic Acid (**7c**). Following the *General Procedure*, **5c** (17 mg, 0.091 mmol) was heated with $[RhCl(PPh_3)_3]$ in aq. EtOH for 3 h. Subsequent FC (hexane/AcOEt/AcOH 6:1:0.01) gave **7c** (10.5 mg, 79%). ^{1}H-NMR: 0.88 (*d*, *J* = 7, 3 H); 1.02 (*d*, *J* = 6.6, 3 H); 1.20 (*d*, *J* = 7, 3 H); 1.72 (*m*, 1 H); 2.72 (*m*, 1 H); 3.63 (*dd*, *J* = 8.2, 3.1, 1 H); 5.61 (br. *s*, 2 H).

A sample was treated with an excess of CH_2N_2 in Et_2O to give the methyl ester **8c**. $[\alpha]_D = +7.2$, $[\alpha]_{578} = +9.8$, $[\alpha]_{546} = +11.7$, $[\alpha]_{436} = +17.7$, $[\alpha]_{365} = +25.1$ ($c = 1.2$) ([12]: $[\alpha]_D = +7.5$ ($c = 0.9$)). ^{1}H-NMR: 0.86 (*d*, *J* = 7.0, 3 H); 0.99 (*d*, *J* = 7.0, 3 H); 1.16 (*d*, *J* = 7.0, 3 H); 1.66 (*m*, 1 H); 2.46 (br. *s*, 1 H); 2.65 (*dq*, *J* = 7.0, 4.0, 1 H); 3.55 (*dd*, *J* = 8.1, 4.1, 1 H); 3.68 (*s*, 3 H).

(2S,3S)-3-Hydroxy-2,4-dimethylpentanoic Acid (**7d**). Following the *General Procedure*, **5d** (11 mg, 0.063 mmol) was heated with $[RhCl(PPh_3)_3]$ in aq. EtOH for 3 h. Subsequent FC (hexane/AcOEt/AcOH 4:1:0.01) gave **7d** (6.5 mg, 78%, oil). ^{1}H-NMR: 0.99 (*t*, *J* = 7.3, 3 H); 1.24 (*d*, *J* = 7.0, 3 H); 1.49 (*m*, 1 H); 1.64 (*m*, 1 H); 2.57 (*dq*, *J* = 7.3, 7.0, 1 H); 3.63 (*m*, 1 H); 5.80 (br. *s*, 2 H).

A sample was treated with an excess of CH_2N_2 in Et_2O to give the methyl ester **8d**. $[\alpha]_D = +7.9$, $[\alpha]_{578} = +7.9$, $[\alpha]_{546} = +8.7$, $[\alpha]_{436} = +14.5$, $[\alpha]_{365} = +22.2$ ($c = 1$) ([13]: $[\alpha]_D = +7.2$ ($c = 0.9$)). ^{1}H-NMR: 0.98 (*t*, *J* = 7.3, 3 H); 1.21 (*d*, *J* = 7.3, 3 H); 1.45 (*m*, 1 H); 1.58 (*m*, 1 H); 2.52–2.58 (2 H); 3.59 (*m*, 1 H); 3.71 (*s*, 3 H).

(2S)-N-[(Fluoren-9-yl)methoxycarbonyl]alanine (**14a**). Following the *General Procedure*, **13a** (11 mg, 0.031 mmol) was heated with $[RhCl(PPh_3)_3]$ in aq. EtOH for 1 h. Subsequent FC (hexane/AcOEt/AcOH 4:1:0.01) gave **14a** (6.5 mg, 67%; colorless solid). ^{1}H-NMR (CD_3OD): 1.38 (*d*, *J* = 7.3, 3 H); 4.17 (*q*, *J* = 7.3, 1 H); 4.21 (*t*, *J* = 7.0, 1 H); 4.27–4.37 (2 H); 7.30 (*t*, *J* = 7.3, 2 H); 7.38 (*t*, *J* = 7.3, 2 H); 7.67 (*t*, *J* = 7.3, 2 H); 7.78 (*d*, *J* = 7.3, 2 H). HPLC: *B*: 20.77 (0.59), 33.67 (93.93). HPLC of racemic **14a**: *B*: 20.39 (41.58), 34.12 (40.78).

(2S)-N-[(Fluoren-9-yl)methoxycarbonyl]leucine (**14b**). Following the *General Procedure*, **13b** (10 mg, 0.026 mmol) was heated with $[RhCl(PPh_3)_3]$ in aq. EtOH for 2 h. Subsequent FC (hexane/AcOEt/AcOH 4:1:0.01) gave **14b** (8.2 mg, 91%; colorless solid). ^{1}H-NMR (CD_3OD): 0.91 (*d*, *J* = 6.2, 3 H); 0.95 (*d*, *J* = 6.6, 3 H); 1.58–1.72 (3 H); 4.16–4.22 (2 H); 4.30–4.42 (2 H); 7.29 (br. *t*, *J* = 7.5, 2 H); 7.37 (*t*, *J* = 7.3, 2 H); 7.66 (br. *t*, *J* = 7.1, 2 H); 7.78 (*d*, *J* = 7.3, 2 H). HPLC: *B*: 14.28 (100). HPLC of racemic **14b**: *B*: 16.18 (49.84), 18.10 (49.89).

(2S)-2-Allyl-N-[(Fluoren-9-yl)methoxycarbonyl]glycine (**14c**). Following the *General Procedure*, **13c** (14 mg, 0.037 mmol) was heated with $[RhCl(PPh_3)_3]$ in aq. EtOH for 2 h. Subsequent FC (hexane/AcOEt/AcOH 4:1:0.01) gave **14c** (12.1 mg, 97%; colorless solid). M.p. 126–130° (toluene). ^{1}H-NMR (CD_3OD): 2.40–2.47 (2 H); 2.56–2.62 (2 H); 4.19–4.23 (2 H); 4.32–4.33 (2 H); 5.03–5.18 (2 H); 5.80 (*m*, 1 H); 7.30 (*dt*, *J* = 7.5, 1.1, 2 H); 7.38 (br. *t*, *J* = 8, 2 H); 7.66 (*dd*, *J* = 7.3, 4.4, 2 H); 7.78 (*d J* = 7.3, 2 H). HPLC: *B*: 16.77 (0.56), 20.26 (96.75). HPLC of racemic **14c**: *B*: 16.71 (47.36), 20.23 (47.27).

(2S,E)-2-{N-[(Fluoren-9-yl)methoxycarbonyl]amino}dec-4-enoic Acid (**14d**). Following the *General Procedure*, **13d** (15 mg, 0.033 mmol) was heated with $[RhCl(PPh_3)_3]$ in aq. EtOH for 1 h. Subsequent FC (hexane/AcOEt/AcOH 4:1:0.01) gave **14d** (12 mg, 89%, colorless oil). $[\alpha]_D = +17.9$, $[\alpha]_{578} = +18.6$, $[\alpha]_{546} = +20.9$, $[\alpha]_{436} = +35.2$, $[\alpha]_{365} = +58.7$ (*c* = 1.2). IR: 3017.1, 2929.0, 1719.8, 1509.6, 1450.3, 1332.3, 1236.1, 1203.5, 1080.5, 1060.3, 969.7. ^{1}H-NMR (CD_3OD): 0.85 (br. *t*, *J* = 6.8, 3 H); 1.20–1.39 (6 H); 1.97 (*dd*, *J* = 13.6, 6.6, 2 H); 2.36 (*m*, 1 H); 2.52 (*m*, 1 H); 4.16 (*dd*, *J* = 8.6, 5.0, 1 H); 4.21 (*t*, *J* = 7.0, 1 H); 4.28–4.34 (2 H); 5.39 (*dt*, *J* = 15.0, 7, 1 H); 5.55 (*dt*, *J* = 15.0, 6.6, 1 H); 7.29 (*dd*, *J* = 7.3, 6.6, 2 H); 7.38 (br. *t*, *J* = 7.5, 2 H); 7.64–7.67 (2 H); 7.78 (*d*, *J* = 7.7, 2 H). ^{13}C-NMR: 14.3 (*q*); 23.5 (*t*); 30.1 (*t*); 32.4 (*t*); 33.5 (*t*); 36.1 (*t*); 48.4 (*d*); 55.7 (*d*); 68.1 (*t*); 120.9 (*d*); 125.9 (*d*); 126.3 (*d*); 128.2 (*d*); 128.8 (*d*); 135.6 (*d*); 142.6 (*s*); 145.2 (*s*); 145.3 (*s*); 158.5 (*s*); 175.5 (*s*). MS: 407 (0.2, $C_{25}H_{29}NO_4^{+\cdot}$), 196 (12), 179 (32), 178 (100), 166 (26), 165 (39), 69 (11). HPLC (*Chiracel OD*, hexane/i-PrOH/HCOOH 89:10:1): 37.46 (100). HPLC of racemic **14d** (*Chiracel OD*, hexane/i-PrOH/HCOOH 89:10:1): 28.26, (20.60), 37.40 (17.98).

(2S)-N-[(Fluoren-9-yl)methoxycarbonyl]phenylalanine (**14e**). Following the *General Procedure*, **13e** (13.1 mg, 0.03 mmol) was heated with $[RhCl(PPh_3)_3]$ in aq. EtOH for 1 h. Subsequent FC (hexane/AcOEt/AcOH 4:1:0.01) gave **14e** (10 mg, 86%; colorless solid). $[\alpha]_D = +11.4$ (*c* = 1, AcOEt) ([20]: $[\alpha]_D = +11.6$ (*c* = 1.2, AcOEt)). ^{1}H-NMR (CD_3OD): 2.93 (*dd*, *J* = 14.0, 9.6, 1 H); 3.20 (*dd*, *J* = 14.0, 4.8, 1 H); 4.14 (*t*, *J* = 7, 1 H); 4.20 (*dd*, *J* = 10.3, 7, 1 H); 4.28 (*dd*, *J* = 10.3, 7, 1 H); 4.40 (*dd*, *J* = 9.6, 4.8, 1 H); 7.15–7.30 (7 H); 7.37 (br. *t*, *J* = 7.5, 2 H); 7.58 (br. *d*, *J* = 7.7, 2 H); 7.77 (*d*, *J* = 7.7, 2 H). HPLC: *B*: 24.93 (0.94), 29.29 (98.72). HPLC of racemic **14e**: *B*: 24.79 (49.69), 28.73 (49.02).

REFERENCES

[1] a) W. Oppolzer, C. Chapuis, G. Bernardinelli, *Helv. Chim. Acta* **1984,** *67,* 1397; b) W. Oppolzer, *Tetrahedron* **1987,** *43,* 1969; *Erratum, ibid.* **1987,** *43,* 4057; c) W. Oppolzer, *Pure Appl. Chem.* **1988,** *60,* 39; d) D.P. Curran, B.H. Kim, J. Daugherty, T.A. Heffner, *Tetrahedron Lett.* **1988,** *29,* 3555; e) A.B. Smith III; K.J. Hale, L.M. Laakso, K. Chen. A. Riéra, *ibid.* **1989,** *30,* 6963; f) W. Oppolzer, *Pure Appl. Chem.* **1990,** *62,* 1241; g) D.M. Walba, C.A. Przybyla, C.B. Walker, Jr., *J. Am. Chem. Soc.* **1990,** *112,* 5624; h) D.P. Curran, W. Shen, J. Zhang, T.A. Heffner, *ibid.* **1990,** *112,* 6738; i) P. Garner, W.B. Ho, S.K. Grandhee, W.J. Youngs, V.O. Kennedy, *J. Org. Chem.* **1991,** *56,* 5893; j) H. Josien, A. Martin, G. Chassaing, *Tetrahedron Lett.* **1991,** *32,* 6547; k) V. Gouverneur, G. Dive, L. Ghosez, *Tetrahedron: Asymmetry* **1991,** *2,* 1173; l) W. Oppolzer, C. Starkemann, *Tetrahedron Lett.* **1992,** *33,* 2439; m) P.A. Zoretic, X. Weng, C.K. Biggers, M.S. Biggers, M.L. Caspar, D.G. Davis, *ibid.* **1992,** *33,* 2637.

[2] a) W. Oppolzer, M. Wills, C. Starkemann, G. Bernardinelli, *Tetrahedron Lett.* **1990,** *31,* 4117; b) W. Oppolzer, M. Wills, M.J. Kelly, M. Signer, J. Blagg, *ibid.* **1990,** *31,* 5015; c) W. Oppolzer, I. Rodriguez, C. Starkemann, E. Walther, *ibid.* **1990,** *31,* 5019.

[3] 'Asymmetric Synthesis', Ed. J.D. Morrison, Academic Press, New York, 1983–1985, Vol. 1–5.

[4] W. Oppolzer, P. Schneider, *Helv. Chim. Acta* **1986,** *69,* 1817.

[5] J. Vallgårda, U. Hacksell, *Tetrahedron Lett.* **1991,** *32,* 5625.

[6] W. Oppolzer, H. Bienaymé, A. Genevois-Borella, *J. Am. Chem. Soc.* **1991,** *113,* 9660.

[7] W. Oppolzer, D. Dupuis, G. Poli, T.M. Raynham, G. Bernardinelli, *Tetrahedron Lett.* **1988,** *29,* 5885.

[8] S. Brandänge, H. Leijonmarck, *Tetrahedron Lett.* **1992,** *33,* 3025.

[9] T.W. Greene, P.G.M. Wuts, 'Protective Groups in Organic Synthesis', 2nd edn., Wiley, New York, 1991, p. 248.

[10] W. Oppolzer, R. Moretti, S. Thomi, *Tetrahedron Lett.* **1989,** *30,* 5603.

[11] H. Kunz, H. Waldmann, *Helv. Chim. Acta* **1985,** *68,* 618.
[12] W. Oppolzer, J. Blagg, I. Rodriguez, E. Walther, *J. Am. Chem. Soc.* **1990,** *112,* 2767.
[13] W. Oppolzer, C. Starkemann, I. Rodriguez, G. Bernardinelli, *Tetrahedron Lett.* **1991,** *32,* 61.
[14] M. Bodanszky, 'Principles of Peptide Synthesis', Springer, Berlin, 1984; M. Bodanszky, 'The Practice of Peptide Synthesis', Springer, Berlin, 1984.
[15] W. Oppolzer, R. Moretti, S. Thomi, *Tetrahedron Lett.* **1989,** *30,* 6009.
[16] W. Oppolzer, O. Tamura, *Tetrahedron Lett.* **1990,** *31,* 991; W. Oppolzer, O. Tamura, J. Deerberg, *Helv. Chim. Acta* **1992,** *75,* 1965.
[17] T. Kanai, S. Irifune, Y. Ishii, M. Ogawa, *Synthesis* **1989,** 283.
[18] L. Guoqianq, M. Hjalmarsson, H.-E. Högberg, K. Jernstedt, T. Norin, *Acta Chem. Scand., Ser. B* **1984,** *38,* 795.
[19] W. Choy, L. A. Reed III, S. Masamune, *J. Org. Chem.* **1983,** *48,* 1137.
[20] L. A. Carpino, G. Y. Han, *J. Org. Chem.* **1972,** *37,* 3404.