149. Asymmetric Induction on Copper(I) Chloride Catalyzed 1,4-Addition of Alkylmagnesium Chlorides to α,β-Disubstituted (*E*)-Enoylsultams and Subsequent Protonation

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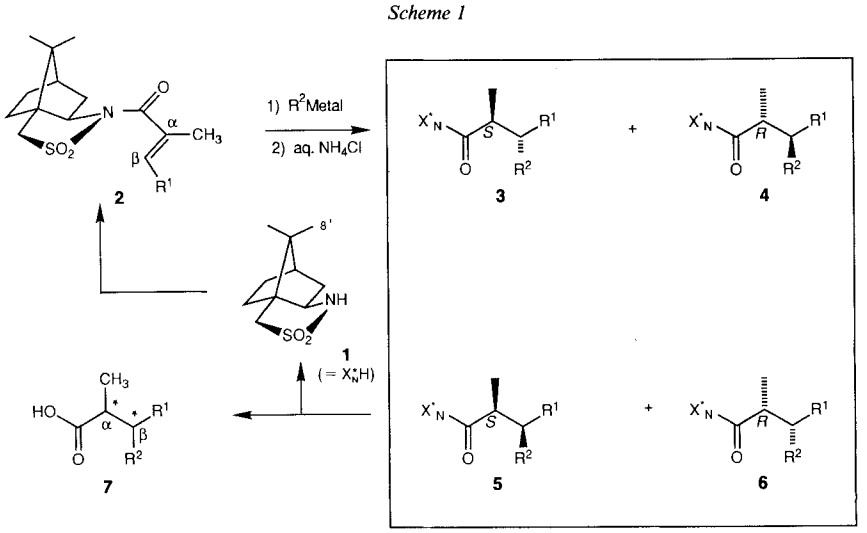
Successive treatment of conjugated *N*-enoylsultams **2** with alkyl *Grignard* reagents/CuCl and aq. NH_4Cl solution generated selectively two stereogenic centers at C(α) and C(β) providing, after flash chromatography and crystallization, acylsultams **5** in high purity. Mild cleavage afforded the recovered sultam auxiliary **1** and enantiomerically pure carboxylic acids **7**.

Introduction. – Recently, we described the selective generation of two contiguous stereogenic centers from α,β-disubstituted enoylsultams **2** *via* 1,4-addition/protonation, crystallization of the major product, and non-destructive cleavage of the sultam auxiliary **1** *(Scheme 1)* [1–3]. Interestingly, opposite topicity at *both* C(α) and C(β) was observed on employing either organomagnesium chlorides (→ **6**) [2], or *Gilman* reagents (R^2_2CuLi, R^2 = Me, Ph, vinyl → **5**) [3]. However, analogous transformations using Et_2CuLi or Bu_2CuLi proceeded less selectively. *E.g.*, successive treatment of *N*-tigloylsultam **2a** ($R^1 = CH_3$) with Bu_2CuLi/PBu_3 and aq. NH_4Cl solution furnished a mixture (R^2 = Bu, 77% yield) of isomers **3a** (3.3%), **4a** (2.0%), **5a** (27.2%), and **6a** (67.5%).

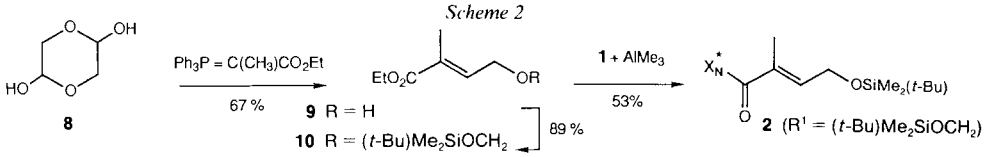
Scheme 1



We report here, as a complementary method, the CuCl-catalyzed conjugate addition of EtMgCl and BuMgCl to various enoylsultams **2**, followed by protonation of the non-isolated 'enolate' intermediates.

Results. – The starting *N*-enoyl derivatives **2** (R^1 = Me, Et, and Bu) are readily accessible by acylation of chirophore **1** with the corresponding enoyl chlorides in the presence of NaH [2] [3]. 4-Silyloxy-2-methylbut-2-enoyl-sultam (**2**; $R^1 = (t\text{-Bu})Me_2SiOCH_2$) was prepared by *Wittig* reaction of 2,5-dihydroxy-1,4-dioxane with [1-(ethoxycarbonyl)ethylidene]triphenylphosporane (**8** → **9**) followed by *O*-silylation (**9** → **10**) and Me_3Al-mediated *N*-acylation of sultam **1** with the resulting ethylester **10** *(Scheme 2)*.

Scheme 2

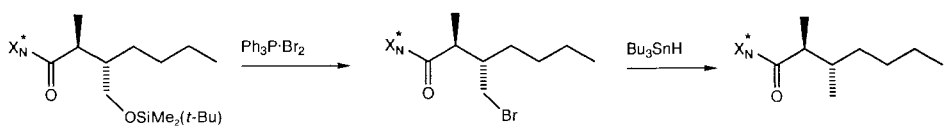


8 **2** ($R^1 = (t\text{-Bu})Me_2SiOCH_2$)

A solution of the corresponding enoylsultam **2** (in THF) was added to a slurry of alkylmagnesium chloride (2.5 mol-equiv.) and CuCl (0.2 mol-equiv.) in Et_2O/THF at −80°. The mixture was warmed to −40°, kept at this temperature for 16 h, and quenched at −80° by addition of sat. aq. NH_4Cl solution giving predominantly isomer **5**. The major product **5** could be routinely purified by flash chromatography and crystallization. Our results are summarized in *Scheme 1* and in the *Table*.

The product ratios **3**/**4**/**5**/**6** followed conveniently from capillary-GC comparison with independently prepared pure isomers **3**, **4**, and **6**, as well as with samples obtained by acylation of sultam **1** with mixtures of the corresponding acyl-chloride stereoisomers [2–4]. This comparison also allowed assignment of the absolute and relative configurations of products **5a–d**. The configuration of **5e** was established by correlation with **5a**: successive treatment of **5e** with $Ph_3P \cdot Br_2$ (→ **11**) and Bu_3SnH furnished **5a** *(Scheme 3)*.

Scheme 3



5e **11** **5a**

Moreover, **5b** showed no melting-point depression on admixture with an authentic sample [3] and provided, after mild cleavage, the carboxylic acid (2*S*,3*S*)-**7b** (R^1 = Me, R^2 = Et; *Scheme 1*) identified by comparison ([α], ^{1}H- and ^{13}C-NMR) with its known antipode [2]. Analogous, improved 'saponification' of **5a** with $LiOH/H_2O_2$/aq. THF (room temperature, < 16 h) afforded sultam auxiliary **1** and carboxylic acid (2*S*,3*S*)-**7a** (R^1 = Me, R^2 = Bu)[1]).

[1]) Hydrolyses **5**→**7** with LiOH/aq. THF usually required stirring at 65° for 16–120 h [2] [3]. For hydroperoxide-assisted saponifications, see [5].

Table. *CuCl-Catalyzed 1,4-Additions of* Grignard *Reagents to Enoylsultams Followed by Protonation:* **2**→**5**

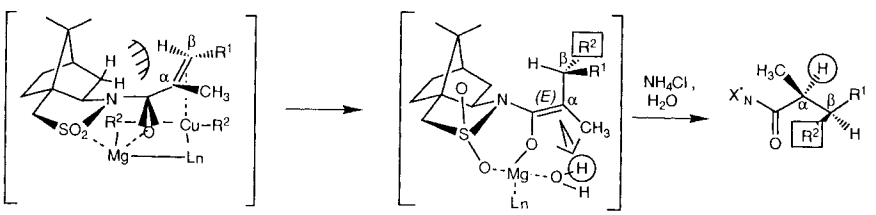
Entry	Enoyl-sultam **2** R^1	*Grignard* reagent R^2	Cu(I) Salt	Yield [%] **3**/**4**/**5**/**6**	Ratio **3**/**4**/**5**/**6**	Major product	Crystallized		
							Yield [%]	Purity [%]	Config-uration
1	Me	Bu	CuCl	90	2.1: 0 :86.3 :11.6	**5a**	67	97.7	(2*S*,3*S*)
2	Me	Bu	CuCN	72	2.5: 0 :83.7 :14.4	**5a**	–	–	(2*S*,3*S*)
3	Me	Et	CuCl	87	2.3: 85.4[a]):12.3	**5b**	66	98.6	(2*S*,3*S*)
4	Et	Bu	CuCl	88	0 : 0 :91.5 : 8.5	**5c**	71	99.8	(2*S*,3*S*)
5	Bu	Et	CuCl	71	0 : 0 :97.3 : 2.7	**5d**[b])	63	99	(2*S*,3*R*)
6	(*t*-Bu)Me_2SiOCH_2	Bu	CuCl	61	0 : 0 :97.0 : 3.0	**5e**	56	99.4	(2*S*,3*S*)
7	(*t*-Bu)Me_2SiOCH_2	Bu	None	–	–	**6e**[b])	83	> 99.8	(2*R*,3*R*)
8	Bu	Me	CuCl	74	10.5: 8.2:68.6 :12.7	**5g**	–	–	(2*S*,3*R*)
9	Me	Ph	CuCl	72	2.7: 3.2:72.5 :21.6[c])	**5h**	–	–	(2*S*,3*R*)

[a]) **4b**/**5b** not separable by GC.
[b]) Oil purified by flash chromatography.
[c]) Analyzed by GC and HPLC.

Examination of the *Table* reveals the following trends, possibilities, and limitations. CuCN was less efficient than CuCl in reversing the topicity of R^2MgCl additions/protonations (*cf. Entries 1* and *2*). Even in the presence of CuCl, isomers **6** were formed in small quantities which did not change on doubling the amount of CuCl but decreased on increasing the size of the resident group R^1 (*cf. Entries 3–6*). *Entries 4* and *5* exemplify the option to direct the developing configuration at C(β) in either sense by permutation of the resident (R^1) and transferred (R^2) substituents (without changing the induction at C(α)). As already mentioned, *both* centers C(α) and C(β) could be altered *via* addition of the *Grignard* reagents either in the presence or absence of CuCl (*Entries 6* and *7*). *Entry 6*, furthermore, demonstrates the highly selective generation of two 'acyclic' stereogenic centers flanked by chemodifferentiated C-atoms. On the other hand, only low π-face discriminations were observed when employing MeMgCl/CuCl or PhMgCl/CuCl (*Entries 8* and *9*). More selective formation of the same products **5g** or **5h**, however, has been accomplished by the use of Me_2CuLi/Bu_3P or Ph_2CuLi/Bu_3P [3]. From a practical standpoint, this indicates a complementary utility of alkylmagnesium chlorides/CuCl (alkyl transfer) *vs. Gilman* reagents (methyl, aryl, and vinyl transfer).

Rationalization. – The stereochemical dichotomy between 1,4-additions of *Grignard* reagents to enoylsultams **2** in the presence or absence of CuCl (followed by enolate protonation) can be explained as follows. Conjugate additions of reagents derived from organomagnesium halides and Cu(I) salts are well established but very poorly understood in structural and mechanistic terms [6]. Nevertheless, it appears that the enoylsultams **2** react with a (rapidly equilibrating) organocopper-magnesium species in a conformation where the C=O group is s-*trans* to the C(α)–C(β) bond (*vide infra*). We assume, furthermore, a chelation of the C=O and SO_2 groups by a Mg-atom and, initially, a coordination of a Cu-atom with the C=C bond from the bottom face, opposite to the lone pair on the N-atom (**2′**, *Scheme 4*). Subsequent transfer of R^2 from the Cu-atom to the lower face of C(β) leads to *O*-magnesium-ketene-*N*,*O*-acetals **12** which 'translates' the reactive C=O/C=C s-*trans*-conformation of **2** into the depicted (*E*)-configuration. Chelation of the 'enolate' O-atom and the lower SO_2 O-atom by Mg as well as association of the latter with H_2O are consistent with the observed protonation from the C(α)-*Re* (front) face of **12** (→ **5**).

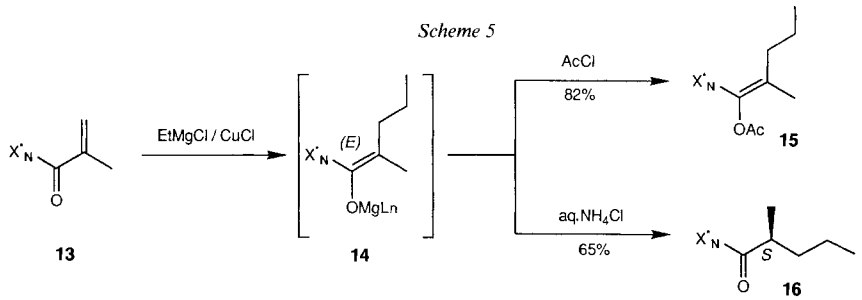
Scheme 4



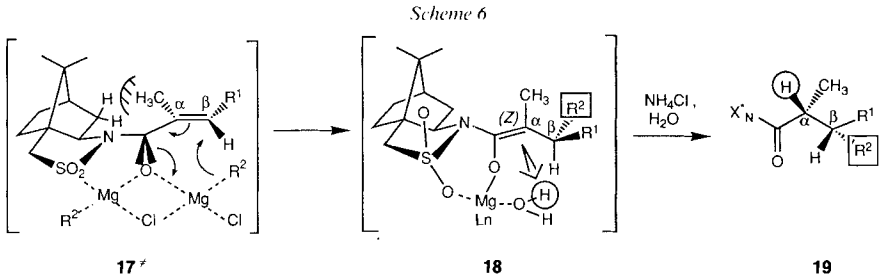
2′ **12** **5**

In agreement with this postulate, treatment of methacryloyl-sultam **13** with EtMgCl/CuCl, followed by *O*-acylation (AcCl) or protonation (aq. NH_4Cl solution) afforded (*E*)-*O*-acetyl-ketene-*N*,*O*-acetal **15** [7] or the (2*S*)-methylpentanoyl derivative **16**, respectively, with high selectivities (*Scheme 5*).

Scheme 5



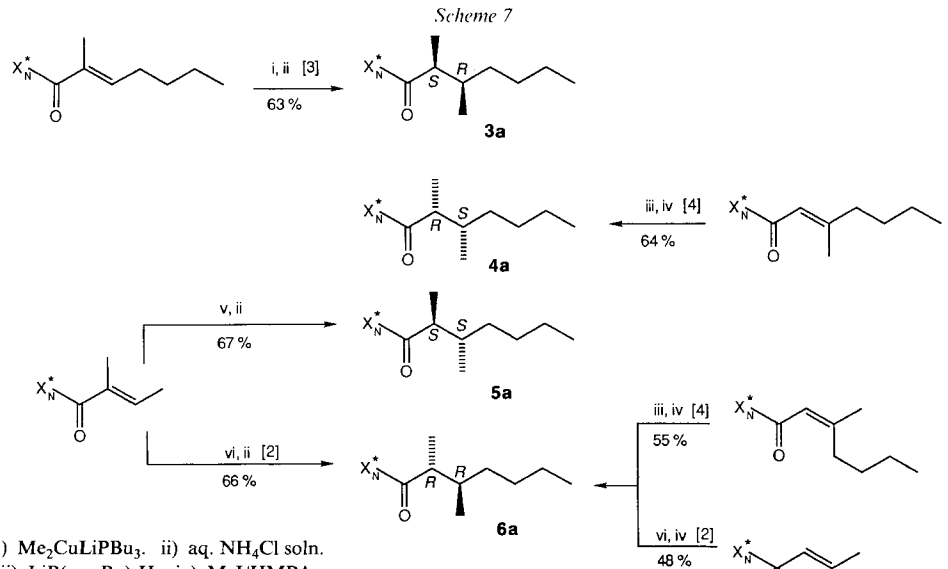
Scheme 6



The opposite topicity observed with *Grignard* reagents in the *absence* of CuCl can again be attributed to a C=O/SO_2 chelation by Mg *but* a C=O/C=C s-*cis*-conformation of **17**$^{\neq}$ enforced by a cyclic transition state C=O··Mg··R^2··C(β) *(Scheme 6)* [2].

Conclusion. – Comparison with related work shows the complementary nature of the presented method, as highlighted by the selective preparation of each possible isomer **3a**, **4a**, **5a**, and **6a** from *N*-enoyl derivatives of the *same* sultam auxiliary **1** *(Scheme 7)*.

Scheme 7



i) $Me_2CuLiPBu_3$. ii) aq. NH_4Cl soln.
iii) LiB(*sec*-Bu)$_3$H. iv) MeI/HMPA.
v) BuMgCl/CuCl. vi) BuMgCl.

The ready availability of sultam **1** as well as of its enantiomer, thus, offers a plethora of possibilities to generate two adjacent stereogenic centers in a diastereo- and enantioselective manner [1].

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Experimental Part

General. All reactions were carried out under Ar with magnetic stirring, unless otherwise specified. Solvents were dried by distillation from drying agents as follows: Et_2O (Na), THF (Na), toluene (K). EtMgCl and PhMgCl (both 2M in Et_2O and THF, resp.) were purchased from *Aldrich.* The 1M soln. of BuMgCl in Et_2O was prepared from BuCl and Mg powder (*Merck,* 0.1–0.3 mm). The concentration was determined by addition of a measured excess of aq. HCl and 'back-titration' with 0.1N aq. NaOH using phenolphthalein as indicator. CuCl was purchased from *Fluka* and used without further purification. 'Workup' denotes extraction with Et_2O, washing of the org. phase with sat. aq. NH_4Cl soln., drying ($MgSO_4$), and evaporation. Flash column chromatography (FC): SiO_2 *(Merck 9385)*. GC: *Hewlett-Packard 5790A,* integrator *HP 3390,* capillary column (fused silica, 0.2 mm i.d., 12 m), *OV-1,* 10 psi H_2; *A:* 160°, 10 min → 7.5°/min → 250°; *B:* 160°, 10 min → 10°/min → 250°; t_R in min (area %). M.p.: *Kofler* hot stage; uncorrected. $[\alpha]_D$: *Perkin-Elmer-241* polarimeter; in $CHCl_3$, unless otherwise specified. IR: *Polaris/Mattson Instruments;* in CCl_4, unless otherwise specified. ^{1}H-NMR at 360 MHz, unless otherwise specified; ^{13}C-NMR at 50 MHz, unless otherwise specified; standard TMS (= 0 ppm); *J* in Hz. MS: *m/z* (rel.-%).

Preparation of *N*-Enoylsultams. – Enoylsultams **2** (R^1 = Me, Et, and Bu) as well as **13** were prepared as described in [2] [8] and **2** with R^1 = (*t*-Bu)Me_2SiOCH_2 from *2,5-dihydroxy-1,4-dioxane* (**8**) as follows.

*Ethyl (*E*)-4-Hydroxy-2-methylbut-2-enoate* (**9**). Heating a soln. of *2,5-dihydroxy-1,4-dioxane* (**8**; 800 mg, 13.8 mmol) and [1-(ethoxycarbonyl)ethylidene]triphenylphosphorane (5 g, 13.8 mmol) in CH_2Cl_2 (50 ml) under reflux for 4 h, addition of Et_2O (50 ml), filtration through SiO_2, evaporation, and distillation (150°/2.2 Torr) gave **9** (1.3 g, 67%). IR: 3620, 3600–3200, 2980, 2920, 1720, 1260, 1130, 1040, 920. ^{1}H-NMR: 1.21 (*t*, *J* = 7, 3 H); 1.76 (*q*, *J* = 1.7, 3 H); 2.76 (br. *s*, 1 H); 4.15 (*q*, *J* = 7, 2 H); 4.31 (*dd*, *J* = 1, 6, 2 H); 6.79 (*tq*, *J* = 1.7, 7, 1 H). ^{13}C-NMR: 167.81 (*s*); 140.31 (*d*); 128.29 (*s*); 60.72 (*t*); 59.49 (*t*); 14.08 (*q*); 12.51 (*q*). MS: 145 (12, $[M + 1]^+$), 144 (6, $C_7H_{12}O_3^{+\cdot}$), 115 (66), 98 (42), 87 (66), 71 (57), 69 (100). HR-MS: 144.0792 ($C_7H_{12}O_3^{+\cdot}$, calc. 144.0786).

*Ethyl (*E*)-4-[(*tert*-Butyl)dimethylsilyloxy]-2-methylbut-2-enoate* (**10**). A soln. of **9** (1.31 g, 9.3 mmol), (*t*-Bu)Me_2SiCl (1.82 g, 12.1 mmol) and imidazole (885 mg, 13 mmol) in DMF (10 ml) was stirred for 16 h at r.t., poured into H_2O, extracted with hexane, dried ($MgSO_4$), and evaporated. FC (hexane/AcOEt 8:1) gave **10** (2.15 g, 89%) as a colourless oil. IR: 2970, 2950, 2900, 2870, 1710, 1660, 1250, 1140, 1120, 1060, 840. ^{1}H-NMR: 0.03 (*s*, 6 H); 0.86 (*s*, 9 H); 1.25 (*t*, *J* = 7, 3 H); 1.78 (*q*, *J* = 1.5, 3 H); 4.19 (*q*, *J* = 7, 2 H); 4.34 (*dd*, *J* = 1, 5.5, 2 H); 6.77 (*tq*, *J* = 1.5, 5.5, 1 H). ^{13}C-NMR: 167.67 (*s*); 141.29 (*d*); 127.28 (*s*); 60.57 (*t*); 60.50 (*t*); 25.84 (*q*); 18.30 (*s*); 14.23 (*q*); 12.62 (*q*); 5.30 (*q*). MS: 258 (2.5, $C_{13}H_{26}O_3Si^{+\cdot}$), 257 (12), 215 (60), 159 (27), 143 (18), 103 (48), 97 (48), 85 (60), 75 (100), 73 (83), 57 (63). HR-MS: 258.1614 ($C_{13}H_{26}O_3Si^{+\cdot}$, calc. 258.1651).

*N-{(*E*)-4-[(*tert*-Butyl)dimethylsilyloxy]-2-methylbut-2-enoyl}bornane-10,2-sultam* (**2**; R^1 = (*t*-Bu)-Me_2SiOCH_2). A 2M soln. of $AlMe_3$ in hexane (5.2 ml, 10.3 mmol) was added slowly at r.t. to a soln. of **1** (2.21 g, 10.3 mmol) in toluene (50 ml). After stirring the mixture for 15 min, **10** (2.15 mg, 8.3 mmol) was added and the mixture heated at 90° for 2 d. Workup, FC (hexane/AcOEt 4:1) and crystallization from hexane gave **2** (R^1 = (*t*-Bu)Me_2SiOCH_2; 2.33 g, 53%). GC (*A*): 22.40. M.p. 66–67°. IR: 2980, 2950, 2850, 1680, 1470, 1350, 1290, 1260, 1130, 1080, 840, 550. ^{1}H-NMR: 0.06 (*s*, 3 H); 0.07 (*s*, 3 H); 0.88 (*s*, 9 H); 0.98 (*s*, 3 H); 1.23 (*s*, 3 H); 1.39 (*m*, 2 H); 1.86 (*q*, *J* = 1.5, 3 H); 1.85–2.08 (5 H); 3.39 (*d*, *J* = 14, 1 H); 3.51 (*d*, *J* = 14, 1 H); 4.05 (*dd*, *J* = 5, 7.5, 1 H); 4.40 (*t*, *J* = 1, 1 H); 4.42 (*d*, *J* = 1, 1 H); 6.32 (*tq*, *J* = 1.5, 6, 1 H). ^{13}C-NMR: 171.86 (*s*); 141.24 (*d*); 130.02 (*s*); 65.30 (*d*); 60.19 (*t*); 53.45 (*t*); 47.93 (*s*); 47.67 (*s*); 45.16 (*d*); 36.18 (*t*); 33.14 (*t*); 26.49 (*t*); 25.84 (*q*); 21.21 (*q*); 19.86 (*q*); 18.31 (*s*); 13.29 (*q*); 5.32 (*q*); 5.26 (*q*). MS: 412 (1, $C_{21}H_{37}NO_4SSi^{+\cdot} - CH_3$), 370 (34), 272 (28), 208 (99), 155 (68), 127 (97), 73 (100). HR-MS: 370.1498 ($C_{17}H_{28}NO_4SSi^+$, calc. 370.1508).

Copper(I) Chloride Catalyzed Conjugate Additions of *Grignard* Reagents to α,β-Disubstituted (*E*)-Enoylsultams and Subsequent 'Enolate' Protonation. – *General Procedure.* At −80°, 1–2M alkylmagnesium chloride (2.5 mol-equiv.) in Et_2O was added dropwise to a slurry of CuCl in THF (0.02 mmol/ml, 0.2 mol-equiv.). The mixture

was stirred for 15 min (→turbid). Slow addition of enoylsultam **2** (1.0 mol-equiv.) in THF, stirring at −80° for 1 h, warming up to −40°, stirring at −40° for 16 h followed by addition of sat. aq. NH_4Cl soln. at −80° and workup gave a crude product mixture which was analyzed by GC and purified as indicated below.

N-[(2S,3S)-2,3-Dimethylheptanoyl]bornane-10,2-sultam (**5a**; R^1 = Me, R^2 = Bu). Using the *General Procedure*, **2** [8] (R^1 = Me; 214 mg, 0.72 mmol) and BuMgCl/CuCl gave a mixture of stereoisomers. GC (*A*): 18.47 (2.1), 18.77 (86.3), 19.00 (11.6). FC (hexane/AcOEt 15:1, 230 mg, 90%) and crystallization from pentane furnished **5b** (171 mg, 67%). GC (*A*): 18.55 (2.3), 18.85 (97.7). M.p. 58–59°. IR: 2970, 2930, 2880, 1700, 1410, 1340, 1210, 1130, 1060, 550. ^{1}H-NMR: 0.86 (*t*, *J* = 7, 3 H); 0.92 (*d*, *J* = 7, 3 H); 0.96 (*s*, 3 H); 1.11 (*d*, *J* = 6.5, 3 H); 1.16 (*s*, 3 H); 1.20–1.48 (8 H); 1.76–1.98 (4 H); 1.99–2.14 (2 H); 2.92 (*quint.*, *J* = 7, 1 H); 3.43 (*d*, *J* = 13.8, 1 H); 3.51 (*d*, *J* = 13.8, 1 H); 3.89 (*dd*, *J* = 2, 6.5, 1 H). ^{13}C-NMR: 176.40 (*s*); 65.27 (*d*); 53.16 (*t*); 48.00 (*s*); 47.62 (*s*); 45.17 (*d*); 44.62 (*d*); 38.53 (*t*); 37.26 (*d*); 32.88 (*t*); 32.15 (*t*); 28.76 (*t*); 26.40 (*t*); 22.81 (*t*); 20.71 (*q*); 19.87 (*q*); 17.20 (*q*); 13.99 (*q*); 13.59 (*q*). MS: 355 (0.1, $C_{19}H_{33}NO_3S^{+\cdot}$), 340 (0.15), 271 (83), 135 (50), 113 (62), 71 (90), 57 (100). HR-MS: 340.1964 ($C_{18}H_{30}NO_3S^{+\cdot}$, calc. 340.1946).

CuCN Catalysis. Using the *General Procedure*, addition of BuMgCl (1.87 mmol, 2.5 mol-equiv.) to CuCN (13.5 mg, 0.15 mmol) and then addition of **2** (R^1 = Me; 223 mg, 0.75 mmol) gave, after 16 h at −40°, protonation and workup, a mixture of stereoisomers. GC (*A*): 18.63 (2.5), 19.05 (80.7), 19.22 (14.0).

N-[(2S,3S)-2,3-Dimethylpentanoyl]bornane-10,2-sultam (**5b**; R^1 = Me, R^2 = Et). Using the *General Procedure*, **2** [8] (R^1 = Me; 462 mg, 1.55 mmol) and EtMgCl/CuCl gave a mixture of stereoisomers. GC (*A*): 15.99 (2.3), 16.33 (85.4), 16.40 (12.3). FC (hexane/AcOEt 19:1, 439 mg, 87%), and crystallization from hexane gave **5b** (323 mg, 66%). GC (*A*): 15.95 (1.4), 16.32 (98.6). M.p. 95°, no depression on admixture with an authentic sample [3]. IR: 2970, 2880, 1700, 1420, 1340, 1210, 1130, 550. ^{1}H-NMR: 0.85 (*t*, *J* = 7, 3 H); 0.9–1.1 (1 H); 0.92 (*d*, *J* = 7, 3 H); 0.96 (*s*, 3 H); 1.11 (*d*, *J* = 7, 3 H); 1.15 (*s*, 3 H); 1.30–1.45 (2 H); 1.45–1.56 (1 H); 1.75 (*m*, 1 H); 1.84–1.96 (3 H); 1.96–2.13 (2 H); 2.92 (*quint.*, *J* = 7, 1 H); 3.44 (*d*, *J* = 13.5, 1 H); 3.52 (*d*, *J* = 13.5, 1 H); 3.90 (*t*, *J* = 6.5, 1 H). ^{13}C-NMR: 176.45 (*s*); 65.27 (*d*); 53.16 (*t*); 48.01 (*s*); 47.62 (*s*); 44.91 (*d*); 44.62 (*d*); 38.80 (*d*); 38.54 (*t*); 32.85 (*t*); 26.40 (*t*); 25.10 (*t*); 20.67 (*q*); 19.88 (*q*); 16.68 (*q*); 13.63 (*q*); 10.95 (*q*). MS: 327 (0.2, $C_{17}H_{29}NO_3S^{+\cdot}$), 312 (0.5), 271 (38), 135 (31), 113 (32), 85 (100). HR-MS: 312.1697 ($C_{16}H_{26}NO_3S^{+\cdot}$, calc. 312.1634).

N-[(2S,3S)-3-Ethyl-2-methylheptanoyl]bornane-10,2-sultam (**5c**; R^1 = Et, R^2 = Bu). Using the *General Procedure*, **2** [2] (R^1 = Et; 251.6 mg, 0.81 mmol) and BuMgCl/CuCl gave a mixture of stereoisomers. GC (*A*): 19.64 (91.5), 19.91 (8.5). FC (hexane/AcOEt 8:1, 263 mg, 88%) and crystallization from hexane furnished **5c** (212 mg, 71%). GC (*A*): 19.75 (99.8), 19.98 (0.2). M.p. 87–88°. IR: 2970, 2930, 2880, 1700, 1340, 1260, 1210, 1140, 550. ^{1}H-NMR: 0.87 (*t*, *J* = 7.5, 3 H); 0.89 (*t*, *J* = 7.5, 3 H); 0.97 (*s*, 3 H); 1.08 (*d*, *J* = 6.5, 3 H); 1.17 (*s*, 3 H); 1.13–1.46 (10 H); 1.75 (*m*, 1 H); 1.84–1.96 (3 H); 1.98–2.12 (2 H); 3.10 (*quint.*, *J* = 6.5, 1 H); 3.42 (*d*, *J* = 14, 1 H); 3.49 (*d*, *J* = 14, 1 H); 3.90 (*dd*, *J* = 5, 7.5, 1 H). ^{13}C-NMR: 176.71 (*s*); 65.29 (*d*); 53.13 (*t*); 47.97 (*s*); 47.62 (*s*); 44.60 (*d*); 42.52 (*d*); 42.22 (*d*); 38.57 (*t*); 32.83 (*t*); 28.41 (*t*); 28.21 (*t*); 26.41 (*t*); 23.68 (*t*); 22.99 (*t*); 20.64 (*q*); 19.85 (*q*); 14.02 (*q*); 12.69 (*q*); 10.80 (*q*). MS: 369 (0.4, $C_{20}H_{35}NO_3S^{+\cdot}$), 354 (2), 340 (1), 271 (100), 155 (20), 135 (83), 85 (48), 71 (68), 57 (59). HR-MS: 354.2104 ($C_{20}H_{35}NO_3S^{+\cdot} - CH_3$, calc. 354.2105).

N-[(2S,3R)-3-Ethyl-2-methylheptanoyl]bornane-10,2-sultam (**5d**; R^1 = Bu, R^2 = Et). Using the *General Procedure*, **2** [2] (R^1 = Bu; 73.4 mg, 0.22 mmol) and EtMgCl/CuCl gave a mixture of stereoisomers. GC (*A*): 19.56 (97.3), 19.89 (2.7). FC (hexane/AcOEt 8:1) furnished **5d** (50.4 mg, 63%). GC (*A*): 19.66 (99), 20.03 (1). Oil. IR: 2970, 2940, 2880, 1700, 1340, 1260, 1210, 1140, 910, 730, 540. ^{1}H-NMR: 0.83 (*t*, *J* = 7.5, 3 H); 0.87 (*t*, *J* = 7, 3 H); 0.97 (*s*, 3 H); 1.09 (*d*, *J* = 7, 3 H); 1.17 (*s*, 3 H); 1.20–1.50 (10 H); 1.75 (*m*, 1 H); 1.84–1.98 (3 H); 1.99–2.11 (2 H); 3.08 (*quint.*, *J* = 7, 1 H); 3.42 (*d*, *J* = 14, 1 H); 3.51 (*d*, *J* = 14, 1 H); 3.91 (*dd*, *J* = 5.2, 7.5, 1 H). ^{13}C-NMR: 176.79 (*s*); 65.30 (*d*); 53.16 (*t*); 48.01 (*s*); 47.62 (*s*); 44.64 (*d*); 42.57 (*d*); 42.45 (*d*); 38.53 (*t*); 32.84 (*t*); 30.44 (*t*); 28.63 (*t*); 26.44 (*t*); 23.04 (*t*); 21.67 (*t*); 20.66 (*q*); 19.85 (*q*); 13.96 (*q*); 13.03 (*q*); 10.14 (*q*). MS: 369 (0.8, $C_{20}H_{35}NO_3S^{+\cdot}$), 354 (2.5), 340 (2), 271 (100), 155 (35), 135 (70), 85 (49), 71 (92), 57 (78). HR-MS: 271.1243 ($C_{13}H_{21}NO_3S^{+\cdot}$, calc. 271.1244).

N-{(2S,3S)-3-{[(tert-Butyl)dimethylsilyloxy]methyl}-2-methylheptanoyl}bornane-10,2-sultam (**5e**; R^1 = (*t*-Bu)Me_2SiOCH_2, R^2 = Bu). Following the *General Procedure*, **2** (R^1 = (*t*-Bu)Me_2SiOCH_2; 1.11 g, 2.6 mmol) and BuMgCl (6.5 mmol, 1M in Et_2O)/CuCl (52 mg, 0.52 mmol) in Et_2O/THF gave a mixture of stereoisomers. GC (*A*): 24.69 (3), 24.77 (97). FC (hexane/AcOEt 8:1, 773, 61%) and crystallization from pentane furnished **5e** (710 mg, 56%). GC (*A*): 24.69 (0.6), 24.77 (99.4). M.p. 124–125°. IR: 2970, 2930, 2850, 1700, 1460, 1330, 1260, 1210, 1100, 840, 540. ^{1}H-NMR: 0.03 (*s*, 6 H); 0.89 (*s*, 9 H); 0.90 (*m*, 3 H); 0.97 (*s*, 3 H); 1.13 (*d*, *J* = 6.5, 3 H); 1.18 (*s*, 3 H); 1.21–1.45 (8 H); 1.84–2.00 (4 H); 2.00–2.14 (2 H); 3.20 (*quint.*, *J* = 6.5, 1 H); 3.42 (*d*, *J* = 14, 1 H); 3.51 (*d*, *J* = 14, 1 H); 3.57 (*d*, *J* = 6.5, 2 H); 3.90 (*dd*, *J* = 7.5, 5.5, 1 H). ^{13}C-NMR: 176.28 (*s*); 65.24 (*d*); 63.63 (*t*); 53.13 (*t*); 48.08 (*s*); 47.68 (*s*); 44.70 (*d*); 43.84 (*d*); 40.88 (*d*); 38.63 (*t*); 32.87 (*t*); 28.78 (*t*); 26.45 (*t*); 26.20 (*t*); 25.86 (*q*); 23.04 (*t*); 20.89 (*q*); 19.85 (*q*); 18.19 (*s*); 14.03 (*q*); 12.81 (*q*); 5.57 (*q*); 5.46 (*q*). MS: 470 (2, $C_{25}H_{47}NO_4SSi^{+\cdot} - CH_3$), 428

(56), 271 (33), 230 (18), 208 (77), 135 (74), 107 (65), 73 (100), 55 (75). HR-MS: 470.2730 ($C_{24}H_{44}NO_4SSi^+$, calc. 470.2700).

Sultam **5a** *from* **5e** *by Bromination* [9] *and Reduction* [10]. Stirring a soln. of $Ph_3P \cdot Br_2$ (53.2 mg, 0.126 mmol) and **5e** (55.6 mg, 0.115 mmol) in CH_2Cl_2 (2 ml) at r.t. for 1 h, quenching with 1N aq. NaOH, extraction with Et_2O, drying of the extracts ($MgSO_4$), filtration through silica gel, and evaporation afforded crude bromide **11** (24 mg, 48%; ^{1}H-NMR: loss of the silyl group). Crude **11** (24 mg) was stirred with Bu_3SnH (29 µl, 0.11 mmol) in toluene (1.3 ml) for 16 h. Quenching with 2N aq. HCl, workup, and FC (hexane/AcOEt 8:1) afforded **5a** (9.6 mg, 23.5% from **5e**). M.p. 60°, no depression on admixture of **5a**, prepared from **2** (R^1 = Me) as described above. ^{1}H- and ^{13}C-NMR of both samples were identical.

N-{*(2R,3R)-3-*{*(*tert*-Butyl)dimethylsilyloxy]methyl*}*-2-methylheptanoyl*}*bornane-10,2-sultam* (**6e**; R^1 = (*t*-Bu)Me_2SiOCH_2, R^2 = Bu). Following the *General Procedure* described previously for the additions of *Grignard* reagents to enoylsultams [2], BuMgCl (1.25 mmol, 1M in Et_2O) was added to **2** (R^1 = (*t*-Bu)Me_2SiOCH_2; 214 mg, 0.5 mmol) in toluene. Workup and FC (hexane/AcOEt 6:1) gave **6e** (201 mg, 83%). GC (*A*): 24.69. Oil. IR: 2970, 2930, 2850, 1700, 1440, 1340, 1260, 1200, 1120, 840, 540. ^{1}H-NMR: 0.02 (*s*, 6 H); 0.88 (*s*, 9 H); 0.89 (*t*, *J* = 6, 3 H); 0.96 (*s*, 3 H); 1.16 (*s*, 3 H); 1.21 (*d*, *J* = 7, 3 H); 1.24–1.46 (7 H); 1.56 (*m*, 1 H); 1.84–2.00 (4 H); 2.07 (*d*, *J* = 6.5, 2 H); 3.14 (*quint.*, *J* = 7.2, 1 H); 3.45 (*d*, *J* = 13.5, 1 H); 3.52 (*d*, *J* = 13.5, 1 H); 3.57 (*d*, *J* = 6, 2 H); 3.90 (*t*, *J* = 6.5, 1 H). ^{13}C-NMR: 176.15 (*s*); 65.02 (*d*); 63.60 (*t*); 53.15 (*t*); 48.19 (*s*); 47.71 (*s*); 44.58 (*d*); 41.75 (*d*); 40.73 (*d*); 38.49 (*t*); 32.83 (*t*); 28.57 (*t*); 26.67 (*t*); 26.44 (*t*); 25.93 (*q*); 23.14 (*t*); 20.83 (*q*); 19.89 (*q*); 18.25 (*s*); 15.84 (*q*); 14.09 (*q*); 5.46 (*q*). MS: 470 (4, $C_{25}H_{47}NO_4SSi^+ - CH_3$), 428 (48), 271 (18), 230 (10), 208 (52), 135 (31), 107 (27), 73 (100), 55 (62). HR-MS: 470.2672 ($C_{24}H_{44}NO_4SSi^+$, calc. 470.2700).

N-*[(2S,3R)-2,3-Dimethylheptanoyl]bornane-10,2-sultam* (**5g**; R^1 = Bu, R^2 = Me) *and Isomers*. Using the *General Procedure*, **2** [2] (R^1 = Bu; 34 mg, 0.1 mmol) and MeMgCl (0.245 mmol)/CuCl in Et_2O/THF gave, after FC, a mixture of stereoisomers (25 mg, 74%). GC (*A*): 18.56 (68.6), 18.72 (12.7), 18.84 (10.5), 19.08 (8.2).

N-*[(2S,3R)-2-Methyl-3-phenylbutanoyl]bornane-10,2-sultam* (**5h**; R^1 = Me, R^2 = Ph) *and Isomers*. Using the *General Procedure*, **2** [8] (R^1 = Me; 274 mg, 0.83 mmol) and PhMgCl (2.08 mmol)/CuCl (16.5 mg) in Et_2O/THF gave, after FC, a mixture of stereoisomers (223 mg, 72%). GC (*B*): 19.29 (2.4), 19.74 (3.0), 20.28 (94.5). HPLC (hexane/AcOEt 4:1): 7.31 (20.1), 7.85 (67.5) *cf.* [3].

N-*[(2S)-Methylpentanoyl]bornane-10,2-sultam* (**16**). Using the *General Procedure*, **13** (168 mg, 0.59 mmol) and EtMgBr/CuCl in Et_2O/THF (−80°, 1 h) gave a mixture of stereoisomers. GC (*A*): 13.01 (96.6), 13.13 (3.4). FC (hexane/AcOEt 4:1, 141 mg, 76%), and crystallization from hexane gave **16** (121 mg, 65%) [4]. GC (*A*): 13.01 (98.2), 13.13 (1.8). M.p. 122–123°. IR: 2970, 2940, 2880, 1695, 1340, 1265, 1130, 550. ^{1}H-NMR: 0.92 (*t*, *J* = 7, 3 H); 0.98 (*s*, 3 H); 1.16 (*d*, *J* = 6.5, 3 H); 1.18 (*s*, 3 H); 1.26–1.50 (5 H); 1.68–1.80 (1 H); 1.84–1.95 (3 H); 2.08 (*m*, 2 H); 3.13 (*m*, 1 H); 3.43 (*d*, *J* = 14, 1 H); 3.51 (*d*, *J* = 14, 1 H); 3.90 (*t*, *J* = 6, 1 H). ^{13}C-NMR: 176.66 (*s*); 65.25 (*d*); 53.16 (*t*); 48.14 (*s*); 47.67 (*s*); 44.66 (*d*); 39.62 (*d*); 38.58 (*t*); 37.56 (*t*); 32.87 (*t*); 26.44 (*t*); 20.77 (*q*); 20.20 (*t*); 19.89 (*q*); 16.60 (*q*); 13.95 (*q*). MS: 313 (0.2, $C_{16}H_{27}NO_3S^+$), 298 (0.5), 284 (0.3), 271 (28), 152 (10), 135 (18), 99 (50), 71 (100). HR-MS: 271.1242 ($C_{13}H_{21}NO_3S^+$, calc. 271.1240).

Saponification of *N*-Acylsultams 5. – *(2S,3S)-2,3-Dimethylheptanoic Acid* (**7a**; R^1 = Me, R^2 = Bu). At 0°, 30% aq. H_2O_2 soln. (2.04 mmol) and $LiOH \cdot H_2O$ (59 mg, 1.42 mmol) were added to a soln. of **5a** (252 mg, 0.71 mmol) in THF/H_2O 3:1 (7 ml). The mixture was stirred at 0° for 2 h and at r.t. for 16 h, acidified with HCl, saturated with NaCl, and extracted with CH_2Cl_2. Evaporation of the dried ($MgSO_4$) extracts and FC gave recovered **1** (133 mg, 87%) and, after bulb-to-bulb distillation at 135° (bath)/0.25 Torr, **7a** (83 mg, 74%). $[\alpha]_D$ = +7.90; $[\alpha]_{578}$ = +8.35; $[\alpha]_{546}$ = +9.56; $[\alpha]_{436}$ = +18.71; $[\alpha]_{365}$ = +34.61 (*c* = 0.99, $CHCl_3$, 20°). ^{1}H-NMR: 0.90 (*t*, *J* = 6.5, 3 H); 0.95 (*d*, *J* = 6.5, 3 H); 1.14 (*d*, *J* = 7, 3 H); 1.05–1.52 (6 H); 1.78 (*m*, 1 H); 2.39 (*quint.*, *J* = 7, 1 H). ^{13}C-NMR: 183.23 (*s*); 44.69 (*d*); 35.70 (*d*); 32.83 (*t*); 29.16 (*t*); 22.84 (*t*); 17.11 (*q*); 14.01 (*q*); 13.55 (*q*).

(2S,3S)-2,3-Dimethylpentanoic Acid (**7b**; R^1 = Me, R^2 = Et). As for **7a**, with 30% aq. H_2O_2 soln. (25.6 mmol), $LiOH \cdot H_2O$ (540 mg, 12.8 mmol), and **5b** (2.11 g, 6.4 mmol) in THF/H_2O 3:1 (60 ml): gave recovered **1** (991 mg, 72%) and, after bulb-to-bulb distillation at 130° (bath)/17 Torr, **7b** (407 mg, 49%). $[\alpha]_D$ = +19.7; $[\alpha]_{578}$ = +20.7; $[\alpha]_{546}$ = +23.8; $[\alpha]_{436}$ = +42.51; $[\alpha]_{365}$ = +71.51 (*c* = 0.96, CH_2Cl_2, 20°); [2]: for the enantiomer of **7b**, $[\alpha]_D$ = −20.2 (*c* = 1.04, CH_2Cl_2, 20°). ^{1}H- and ^{13}C-NMR: identical to those of the enantiomer [2].

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