

ASYMMETRIC 1,4-ADDITIONS OF GILMAN REAGENTS TO α, β - DISUBSTITUTED (*E*)-ENOYLSULTAMS /
 "ENOLATE" PROTONATIONS.

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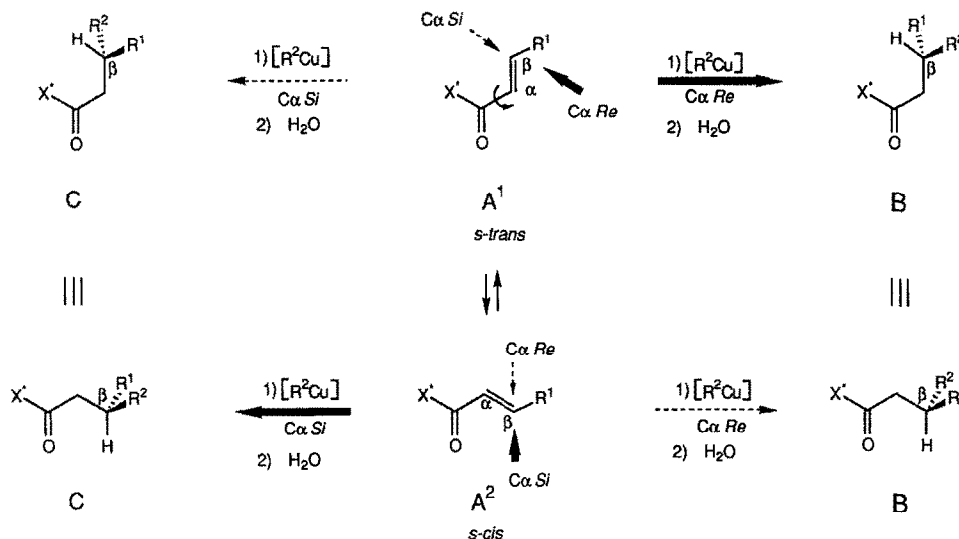
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Abstract: Successive treatment of (*E*)- α, β -disubstituted *N*-enoyl sultams **6** and **13** with organocopper reagents (Me_2CuLi , $(\text{CH}_2=\text{CH})_2\text{CuLi}$, Ph_2CuLi in the presence of PBU_3 or SCN^-) and aq. NH_4Cl gave products **7** and **14**, respectively, with good to excellent stereoface differentiation at $C\beta$ and $C\alpha$. Crystallization and mild saponification **7** \rightarrow **11** and **14** \rightarrow **15** furnished enantiomerically pure carboxylic acids containing two new stereogenic centers. The postulated reaction topology is supported via acetylation of the transient "enolate" (**22** \rightarrow **23**) and compared with that of the related organomagnesium- addition/protonation sequence.

Introduction.

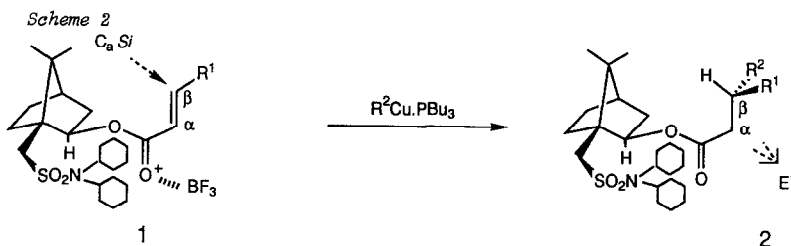
Since the pioneering work of Gilman¹ the conjugate addition of organocopper reagents to enones and enoates has become one of the more powerful carbon-carbon-bond-forming processes². Accordingly, asymmetric versions have attracted widespread attention during the last years. The most elegant concept, the use of chiral copper ligands has so far met encouraging but relatively limited success³. A further option is a non-destructive chirality transfer via covalently bound chiral auxiliary groups. These may be attached either to the organocopper⁴ or to the enoyl unit. The last approach has shown considerable potential in our^{5,6} and other laboratories^{6,7}.

Scheme 1



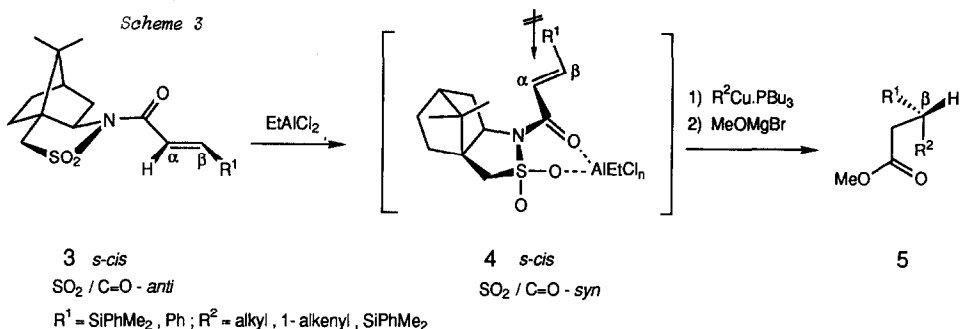
Thus, the chirophor X^* may be part of the acyl group directing the organocopper addition either to the top- or bottom face of the enoyl substrates **A** (Scheme 1). To control the developing stereogenic center at $C\beta \rightarrow B$ or **C** it is, furthermore, essential that one of the two conformers, *s-trans*- A^1 or *s-cis*- A^2 , predominates. Therefore, highly π -face-selective 1,4-additions of organocopper reagents to carboxylate esters **A**, $X^* = \text{OR}^*$ were observed only in the presence of a Lewis acid which, via C=O-coordination, favors the *s-trans* conformer of **A**⁸.

Thus, addition of PBu_3 -stabilized R^2Cu to BF_3 -coordinated *E*-enoates **1** gave, after aqueous work-up, β -substituted esters **2** in good yields and in 94 - 98% d.e. (Scheme 2) ^{5c,5e}.



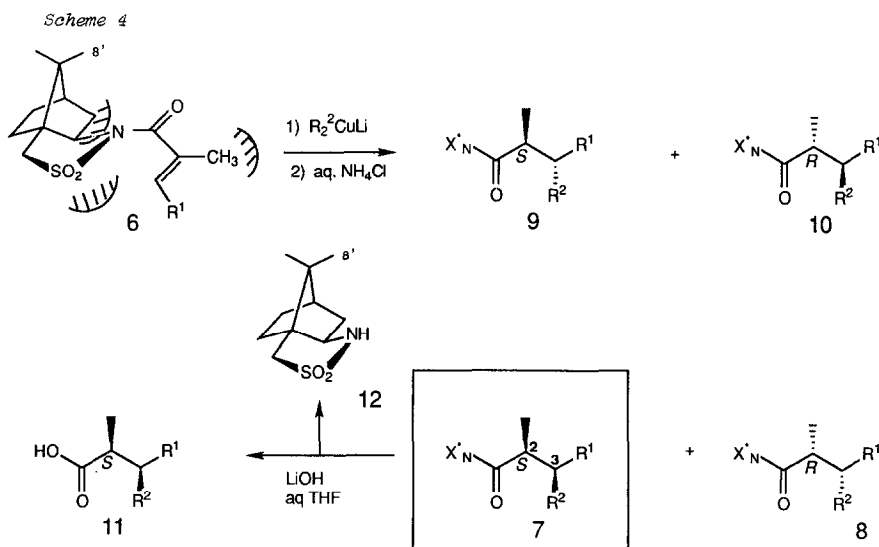
The topological bias of this readily available ester auxiliary ⁹ was also applied to asymmetric functionalizations of C_α by deprotonation of **2** followed by electrophilic attack ¹⁰.

More recently, we have described the EtAlCl_2 -promoted conjugate additions of $\text{R}^2\text{Cu.PBu}_3$ to C_β substituted *E*-*N*-enoyl sultams **3** (Scheme 3) ^{5f,11}.



The observed diastereoface differentiation (88 to 96% d.e.) is consistent with an organocopper approach from the bottom face of **4** which features *s-cis*-disposed $\text{C}=\text{O}/\text{C}_\alpha, \text{C}_\beta$ -bonds, as well as a chelation of the SO_2 - and $\text{C}=\text{O}$ groups. Intrigued by the practical advantages which the sultam chirophor confers to substrates and products such as easy purification by crystallization, facile stereochemical analysis and mild non-destructive removal ^{6,12} (e.g. \rightarrow **5**) we explored the possibility of generating two stereogenic centers at C_β and C_α in one operation by subjecting *N*-enoyl sultams to an organocopper addition/protonation sequence.

π-Face-Selective Conjugate Additions of Gilman Reagents to α, β -Disubstituted (*E*)-*N*-Bornyl-10,2-sultams and Subsequent "Enolate" Protonations.



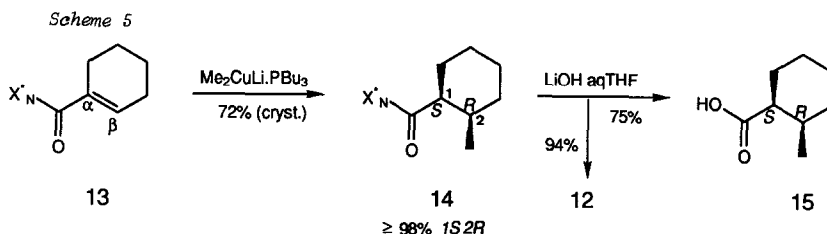
As an extension of a preliminary communication¹² this article describes in detail the 1,4-additions of Gilman reagents $(R^2)_2CuLi$ to enoyl sultams **6** followed by protonation of the non-isolated "enolates". The results of this tandem reaction, which does not require any additional Lewis acid, are summarized in the Schemes 4,5 and in the Table.

Table: Conjugate Additions of $(R^2)_2CuLi$ to α,β -Disubstituted (E)-Enoylsultams and Subsequent 'Enolate' Protonation: $6 \rightarrow 7 + 8 + 9 + 10$.

Series	Enoyl-sultam R^1	Organocopper-Reagent		Yield [%]	Ratio 7 / 8 / 9 / 10	7(crystallized)						
		R^2	Cu ^I -Salt			Yield [%]	Purity [%]	Configuration				
1	a	C ₂ H ₅	CH ₃	CuI	85	85	:15	:0	:0			
2	a	C ₂ H ₅	CH ₃	CuI.PBu ₃	94	91	:9	:0	:0	85	≥98	2S,3R
3	b	n-C ₄ H ₉	CH ₃	CuI.PBu ₃	78	89	:4.5	:2.7	:3.8	63	≥98	2S,3R
4	c	C ₆ H ₅	CH ₃	CuI.PBu ₃	67	90	:6	:(4)		54	≥98	2S,3S
5	d	CH ₃	C ₆ H ₅	CuSCN	60	83.4	:10.5	:0.4	:5.7	42	98.5	2S,3R
6	e	CH ₃	CH ₂ =CH	CuI.PBu ₃	72	86.3	:12.3	:0	:1.4	53	98.5	2S,3S

The starting enoylsultams were readily accessible by acylation of chirophor **12** with either NaH and enoyl chlorides (**6**), or with a methyl enoate/Me₃Al (**13**)^{13,14}.

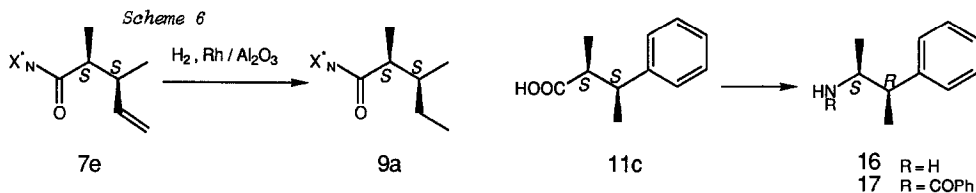
In view of the ubiquitous occurrence of methyl-substituted chiral centers in natural products we concentrated our efforts first on the conjugate additions of dimethylcopperlithium. The latter, prepared as usual², from MeLi (6 equiv) and CuI (3 equiv) added smoothly to enoylsultam **6a** in toluene/hexane at -80° to -40° to give, after protic quenching (sat aq. NH₄Cl/THF, -40°), an 85:15-mixture of **7a** and **8a** (entry 1, 85% yield)¹⁵. Comparison of entries 1 and 2 shows, however, the advantageous influence of a phosphine ligand on the yield and stereoselectivity of the overall conversion **6a** → **7a**. Thus, addition of MeLi (6 equiv) to a solution of CuI.PBu₃ (3 equiv) in toluene at -40° followed by the addition of enoylsultam **6a** (1 equiv in toluene) at -80°, stirring the mixture at -40° for 16h and quenching at -40° with an emulsion of sat. aq. NH₄Cl solution in THF afforded products **7a** + **8a** in 94% yield (entry 2). The crude reaction mixture, shown by capillary GC to contain **7a/8a** in a ratio of 91:9 gave, after flash chromatography (FC) and crystallization (hexane), the virtually pure 2S,3R- product **7a** in 85% yield (from **6a**). Similarly, enoyl sultams **6b** ($R^1 = n\text{-Bu}$) and **6c** ($R^1 = \text{Ph}$) when treated successively with dimethylcopperlithium (PBu₃) and aq. NH₄Cl provided mixtures of three to four of the possible stereoisomeric products **7** - **10** with isomer **7** predominating (entries 3,4). Analogous 1,4-addition of the phenyl (entry 5, using CuSCN¹⁶) and vinyl (entry 6) groups to **6d** - **6e** ($R^1 = \text{Me}$) and subsequent protonation showed the same sense of induction, although with a somewhat lower stereoselectivity. However, in all cases (entries 2-6), the major isomer **7** could be routinely isolated in almost pure form by FC and crystallization.



Excellent stereoselection was again observed on subjecting 1-cyclohexenoylsultam **13** to the tandem C β -methylation/C α -protonation which gave the 1*S*,2*R* -isomer **14** as the sole product, obtained in ca. 100% purity (72% yield) after crystallization.

Stereochemical Assignment and Non-Destructive Hydrolysis of the Organocopper-Addition/Protonation Products.

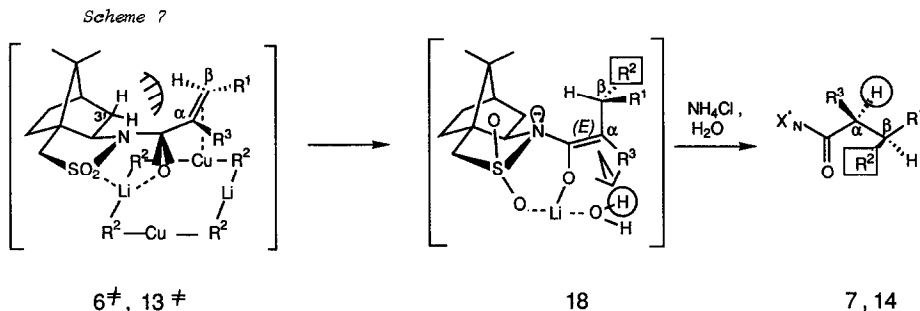
Direct determination of the product ratios **7/8/9/10** by GC (entries 1-4) or HPLC (entry 5) was based on comparison with samples obtained by acylation of sultam **12** with stereoisomer mixtures of the corresponding acyl chlorides. Olefinic products **7e/8e/9e/10e** (entry 6) were readily analyzed (GC) and assigned after subjecting the crude reaction mixture, as well as crystallized **7e**, to a Rh-catalyzed hydrogenation¹⁴ (eg. **7e** \rightarrow **9a**, Scheme 6).



Authentic samples of **8a**^{6,17}, **9a**¹⁸, **10a**¹⁴, **8b**¹⁷, **9b**¹⁸, **10b**^{14,17}, **10d**¹⁴, and the identity **7d** - **9c** allowed us to assign conveniently the minor products, as depicted in the Table, as well as the major products **7a**, **7b**. Mild saponification (LiOH, aq. THF, 65°) of the crystallized major products **7a**, **7b**, **7c**, **7e** and **14** furnished, without C α -epimerization, the corresponding, enantiomerically pure carboxylic acids **11a**, **11b**, **11c**, **11e** and **15**, respectively, (60-70%) together with recovered sultam auxiliary **12** (91-94%). The absolute configurations of **11a**, **11b** and **15** were determined by comparing their optical rotations with reference values. The unknown acid **11c**, when subjected to a Curtius degradation, gave amine **16** (Scheme 6); both **16** and its *N*-benzoyl derivative **17** showed chiroptic properties which agree with measurements reported in the literature.

Stereochemical Rationalization of the 1,4-Addition/Protonation Sequence: Dichotomy between Gilman- and Grignard Reagents.

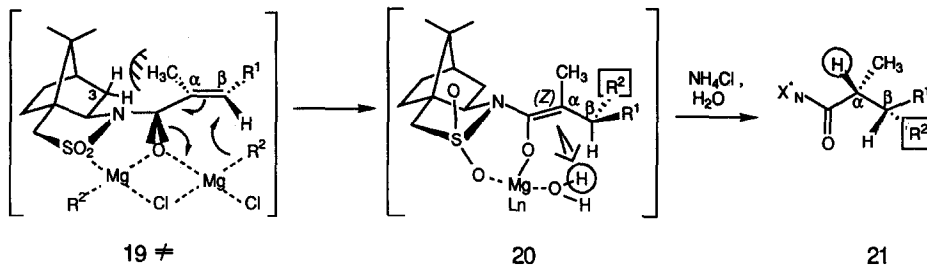
The stereodifferentiations described above are consistent with the transition state topologies depicted in the Scheme 7.



It thus appears that the α,β -disubstituted *E*-enoyl sultams **6** and **13** react with the Gilman reagents in a conformation where the carbonyl is *s-trans* to the C α ,C β -bond to avoid steric repulsion of the C α -substituent R³ with the C(3')H₂ group¹⁸. We assume, furthermore, that a planar, dimeric organocopper lithium cluster, as proposed for Me₂CuLi forms initially a π -complex **6**[#], **13**[#], featuring Li-chelated C=O and SO₂ groups and a coordination of copper (I) with the C-C bond from the bottom face opposite to the lone electron pair on the nitrogen atom^{20, 21}. Bond formation between C β and R² (e.g. via a Cu(III)-C β -intermediate), directed by the geometry of the π -complex **6**[#], **13**[#]²⁰, leads to O-lithium ketene-*N,O*-acetals **18**. This process obviously entails a "translation" of the reactive C=O/C α ,C β -*s-trans*-conformation of **6** and **13** into the *E*-configuration of "enolate" **18** (*vide infra*). **18** seems to adopt a conformation with the lone electron pair on a pyramidal nitrogen in the nodal plane of the C-C- π -system²².

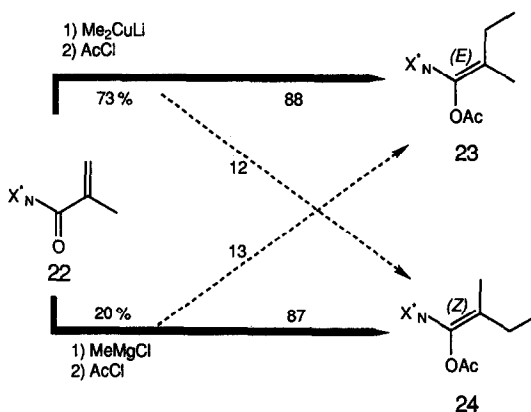
Moreover, chelation of the "enolate"- and the lower SO₂ oxygen atoms by Li, as well as association of the latter with H₂O complies plausibly with a protonation from the C(α)-Re (front) face of **18** (→ **7**, **14**). Comparison of Schemes 7 and 8 shows that 1,4-addition/protonations of (*E*)- Cα,Cβ- disubstituted enoylsultams **6** proceed with opposite overall topicities on Cβ and Cα depending on the deployment of a Gilman- (→**7**) or a Grignard ¹⁴(→ **21**) nucleophile.

Scheme 8



We attribute the stereochemistry of the transformation **6** → **21** to a chelation by Mg (C=O/SO₂ synperiplanar) and the operation of a cyclic transition state C=O...Mg...R²...Cβ which enforces the C=O/Cα,Cβ-*s-cis* conformation of **19**⁹ despite the Cα-methyl/bornane repulsion ¹⁴.

Scheme 9



This essential topological difference between conjugate additions of Gilman- versus Grignard reagents to Cα-substituted *N*-enoylsultams is visualized by acetylation of the transient "enolates" (Scheme 9). Thus, successive treatment of methacryloyl sultam **22** with, either Me₂CuLi and AcCl or, alternatively, with MeMgCl and AcCl gave predominantly (*E*)- or (*Z*)- *O*-acetyl- *N*,*O*-ketene acetal **23** or **24**, respectively ²³.

Conclusion.

Starting from easily accessible (*E*)- Cα,Cβ-disubstituted enoyl sultams, 1,4-addition of methyl-, vinyl- and aryl- Gilman reagents ²⁴ and protonation, followed by non-destructive removal of the sultam auxiliary, provides enantiomerically pure carboxylic acids (or amines) containing two new stereogenic centers. This methodology complements the related 1,4-addition/protonation using alkylmagnesium nucleophiles ^{14,18}. The latter proceeds either with inverse, or, in the presence of CuCl ¹⁸, identical π-face differentiation and allows efficient conjugate additions of alkyl groups whereas Gilman reagents are more suitable for methyl (vinyl and aryl) transfer. This work exemplifies once more the wide applicability of sultam **12** (and its enantiomer) as a chiral auxiliary ^{6,9,12}; its exploration is subject of further studies in our laboratory.

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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: Et₂O (Na); THF (Na); toluene (K). MeLi and PhLi (both 1.6 M in hexane) were purchased from Fluka. The concentration was determined by addition of a measured excess of aq. HCl and "back-titration" with 0.1 N aq. NaOH using phenolphthalein as indicator. Tetrakis[(tributylphosphine)copper(I)iodide] was prepared according to ref.²⁵. Temperatures are indicated in degrees Celsius. "Workup" denotes extraction with Et₂O, washing of the org. phase with sat. aq. NH₄Cl soln., drying (MgSO₄) and evaporation (rotary evaporator). Flash column chromatography (FC): SiO₂ (Merck 9385). GC: Hewlett-Packard 5790A, integrator HP 3390, capillary column (fused silica, 0.2 mm ID, 12 m), OV-1, 10 psi H₂. A: 160°, 10 min → 7.5°/min → 250°; B: 160°, 10 min → 10°/min → 250°, retention time in min (area%). HPLC: Waters ALC/GPC-244 (Li Chromorb, Si60 5 μm), retention time in min (area %). M.p.: Kofler hot stage; uncorrected. [α]_D: Perkin-Elmer-241 polarimeter; CHCl₃ unless otherwise specified. IR: Polaris/Mattson; CCl₄ unless otherwise specified. ¹H-NMR at 360 MHz, CDCl₃, unless otherwise specified; ¹³C-NMR at 50 MHz, CDCl₃, unless otherwise specified; standard tetramethylsilane (δ = 0 ppm); J in Hz. MS: m/z (rel. %).

Preparation of *N*-Enoyl Sultams. (2*R*)-Bornane-10,2-sultam **12**. Auxiliary **12**²⁶ was prepared from (1*S*)-(+)-camphor-10-sulfonylchloride following the procedure described for the preparation of its antipode²⁷.

N-[(*E*)-2-Methyl-2-pentenyl]bornane-10,2-sultam **6a**. Prepared according to ref.¹⁴.

N-[(*E*)-2-Methyl-2-heptenyl]bornane-10,2-sultam **6b**. Prepared according to ref.¹⁴.

N-[(*E*)-2-Methyl-3-phenyl-2-propenyl]bornane-10,2-sultam **6c**. Following the procedure described previously¹³ for the preparation of *N*-[(*E*)-2-hexenyl]bornane-10,2-sultam, (*E*)- α -methyl-cinnamic acid (2.72 g, 18 mmol) was converted (oxalyl chloride) into its acid chloride which served to acylate sultam **12** (3.9 g, 18 mmol) to give, after crystallization (hexane), **6c** (5.0 g, 77%). GC (B): 20.91. M.p. 125-6°. IR: 3010, 2970, 2890, 1675, 1335, 1270, 1165, 1110, 1060, 990. ¹H-NMR: 1.03 (s, 3H), 1.33 (s, 3H), 1.35 - 1.52 (2H), 1.57 (s, 3H), 1.86 - 2.14 (3H), 2.13 (d, *J* = 1.8, 2H), 3.42 (d, *J* = 14, 1H), 3.53 (d, *J* = 14, 1H), 4.13 (dd, *J* = 5, 7, 1H), 7.22 - 7.45 (5H). ¹³C-NMR: 172.58 (s), 138.59 (d), 135.39 (s), 131.49 (s), 129.41 (d), 128.29 (d), 128.18 (d), 65.35 (d), 53.38 (t), 47.93 (s), 47.66 (s), 45.14 (d), 38.23 (t), 33.04 (t), 26.45 (t), 21.31 (q), 19.81 (q), 14.70 (q). MS: 359 (12, C₂₀H₂₅NO₃S⁺), 145 (100), 117 (27), 91 (8). HR-MS: 359.1555 (C₂₀H₂₅NO₃S⁺, calc. 359.1555).

N-[(*E*)-2-Methyl-2-butenyl]bornane-10,2-sultam **6d**. Prepared according to ref.¹³.

N-[1-Cyclohexenyl]bornane-10,2-sultam **13**. A 2 M solution of trimethyl aluminium in hexane (9.9 ml, 19.8 mmol) was added slowly at r.t. to a solution of sultam **12** (3.88 g, 18.1 mmol) in toluene (50 ml). After stirring the mixture for 15 min, methyl 1-cyclohexene-1-carboxylate (3.7 ml, 27.0 mmol) was added and the resulting mixture was heated at 90° for 3 d. Workup, FC (hexane/EtOAc 4:1) and crystallization from hexane gave **13** (4.07 g, 70 %). GC (A): 18.91. M.p. 129-30°. IR: 2980, 2940, 2890, 1680, 1340, 1280, 1240, 1150, 540. ¹H-NMR: 0.93 (s, 3H), 1.18 (s, 3H), 1.28 - 1.44 (2H), 1.52 - 1.77 (5H), 1.83 - 2.50 (8H), 3.37 (d, *J* = 13.5, 1H), 3.47 (d, *J* = 13.5, 1H), 4.02 (dd, *J* = 7.5, 4.5, 1H), 6.56 (m, 1H). ¹³C-NMR: 171.51 (s), 139.63 (d), 133.19 (s), 65.21 (d), 53.44 (t), 47.80 (s), 47.61 (s), 45.12 (d), 38.16 (t), 33.08 (t), 26.46 (t), 25.17 (t), 24.19 (t), 21.72 (t), 21.28 (t), 21.22 (q), 19.83 (q). MS: 323 (6, C₁₇H₂₅NO₃S⁺), 244 (2), 231 (3), 216 (3), 149 (4), 135 (18), 109 (100), 79 (72), 53 (62). HR-MS: 323.1543 (C₁₇H₂₅NO₃S⁺, calc. 323.1555).

Conjugate Additions of Gilman Reagents to (*E*)- α,β -Disubstituted Enoyl Sultams and Subsequent "Enolate"-Protonation. **General procedure.** A 1.5 - 2 M solution of alkylolithium (6 mol-equiv.) in hexane was slowly added to a ca. 0.3 M solution of Tetrakis[(tributylphosphine)copper(I)iodide] [unless otherwise specified] (3 mol-equiv.) in toluene at -40°; stirring was continued for 30 min at -40°, followed by cooling to -80°. At this temperature a 0.1 - 0.2 M solution of the enoyl sultam (1 mol-equiv.) in toluene was added and stirring continued for 30 min warming up to -40°, stirring (16 h), followed by addition of an emulsion THF/sat. aq. NH₄Cl and workup gave a crude product mixture which was analysed by GC and purified by flash chromatography and crystallization.

N-[(2*S*,3*R*)-2,3-Dimethylpentanoyl]bornane-10,2-sultam **7a**. Using the general procedure, addition of MeLi (0.38 ml, 0.62 mmol) to CuI.PBu₃ (121 mg, 0.31 mmol), followed by the addition of the enoyl sultam **6a** (34.2 mg, 0.11 mmol), aq. quenching and workup gave a mixture of stereoisomers; GC (A): 15.24 (91), 15.40 (9). FC (hexane/EtOAc 10:1, 34 mg, 94%) and crystallization from hexane furnished **7a** (30.6 mg, 85%). GC (A): 15.24 (100). M.p. 72-3°. IR: 2970, 1700, 1340, 1210, 1140, 500. ¹H-NMR: 0.80 (d, *J* = 7.5, 3H), 0.84 (t, *J* = 7, 3H), 0.92 (s, 3H), 1.03 (d, *J* = 6.5, 3H), 1.12 (s, 3H); 1.17 - 1.41 (4H); 1.74 - 1.90 (4H), 1.95 - 2.07 (2H), 2.96 (dq, *J* = 6.5, 1H), 3.41 (d, *J* = 13.5, 1H), 3.47 (d, *J* = 13.5, 1H); 3.88 (dd, *J* = 7, 5, 1H). ¹³C-NMR: 176.41 (s), 65.26 (d), 53.14 (t), 48.03 (s), 47.63 (s), 44.58 (d), 44.32 (d), 38.59 (t), 38.11 (d), 32.82 (t), 27.33 (t), 26.44 (t), 20.66 (q), 19.87 (q), 14.76 (q), 12.32 (q), 11.35 (q). MS: 312 (0.8, C₁₇H₂₉NO₃S⁺ - 15), 271 (8), 152 (5), 135 (20), 113 (42), 107 (10), 93 (15), 85 (100), 55 (34). HR-MS: 271.1230 (C₁₇H₂₉NO₃S⁺ - C₄H₈, calc. 271.1231).

Following the same procedure as above but using copper(I)-iodide (488 mg, 2.57 mmol) instead of the tributylphosphine-complex, MeLi (2.25 ml, 1.6 M in hexane, 5.14 mmol) and the enoyl sultam **6a** were added. Aq. quenching and workup gave a mixture of stereoisomers; GC (A): 15.24 (85), 15.40 (15). FC (hexane/EtOAc 8:1) gave the same mixture of stereoisomers (265 mg, 85%).

N-[(2*S*,3*R*)-2,3-Dimethylheptanoyl]bornane-10,2-sultam **7b**. Using the general procedure, addition of MeLi (14.1 ml, 22.6 mmol) to CuI.PBu₃ (4.44 g, 11.3 mmol), then addition of the enoyl sultam **6b** (1.28 g, 3.77 mmol), aq. quenching and workup gave a mixture of stereoisomers; GC (A): 18.27 (74.1), 18.40 (3.7), 18.51 (2.7), 18.77 (3.8). FC (hexane/EtOAc 6:1, 1.04 g, 78%) and crystallization from hexane furnished **7b** (844 mg, 63%). GC (A): 18.27 (100). M.p. 78-9°. IR: 2980, 2930, 2880, 1690, 1460, 1340, 1260, 1210, 1140, 540. ¹H-NMR: 0.75 (d, *J* = 7, 3H), 0.77 (t, *J* = 7, 3H), 0.88 (s, 3H), 0.99 (d, *J* = 6.5, 3H), 1.08 (s, 3H); 1.11 - 1.38 (8H); 1.72 - 1.90 (4H), 1.91 - 2.60 (2H), 2.90 (dq, *J* = 7, 1H), 3.39 (d, *J* = 13.5, 1H), 3.46 (d, *J* = 13.5, 1H); 3.86 (dd, *J* = 7.5, 5, 1H). ¹³C-NMR: 176.42 (s), 65.25 (d), 53.15 (t), 48.03 (s), 47.63 (s), 44.83 (d), 44.61 (d), 38.58 (t), 36.69 (d), 34.50 (t), 32.83 (t), 29.06 (t), 26.44 (t), 22.81 (t), 20.66 (q), 19.85 (q), 15.25 (q), 13.96 (q), 12.42 (q). MS: 340 (0.9, C₁₉H₃₃NO₃S⁺ - CH₃), 271 (18), 152 (7), 135 (25), 113 (41), 93 (10), 83 (7), 71 (90), 57 (100). HR-MS: 340.1923 (C₁₉H₃₃NO₃S⁺ - CH₃, calc. 340.1946).

N-[(1*S*,2*R*)-2-Methyl-1-cyclohexanoyl]bornane-10,2-sultam **14**. Using the general procedure, addition of MeLi (47 ml, 75.6 mmol) to the CuI.PBu₃ (14.8 g, 37.8 mmol), then addition of the enoyl sultam **13** (4.07 g, 12.6 mmol), aq. quenching and workup gave a crude mixture containing one stereoisomer; GC (A): 19.26 (84) (no other peaks between 17.00 and 21.00). FC (hexane/EtOAc 8:1, 3.33 g, 78%) and crystallization from hexane furnished **14** (3.07 g, 72%). GC (A): 19.26 (100). M.p. 190-1°. IR: 2970, 2890, 1695, 1340, 1220, 1140, 550. ¹H-NMR: 0.83 (d, *J* = 7.5, 3H), 0.92 (s, 3H), 1.10 (s, 3H); 1.22 - 1.42 (5H); 1.42 - 1.60 (5H), 1.65 - 1.80 (2H), 1.81 - 1.90 (2H), 1.91 - 2.10 (1H), 2.27 (m, 1H), 3.09 (dq, *J* = 4, 8, 1H), 3.41 (d, *J* = 14, 1H), 3.48 (d, *J* = 14, 1H); 3.88 (dd, *J* = 7.5, 5, 1H). Selective decoupling at 2.27 ppm caused the doublet of quartets at 3.09 ppm to collapse into a quartet (*J* = 8 Hz). Following the Karplus-curve the angle between the two methine protons approximates to 60°. ¹³C-NMR: 174.88 (s), 65.04 (d), 53.12 (t), 48.08 (s), 47.67 (s), 46.67 (d), 44.56 (d), 38.67 (t), 32.72 (t), 31.82 (t), 31.65 (d), 26.50 (t), 24.08 (t), 22.75 (t), 21.11 (t), 20.62 (q), 19.86 (q), 14.73 (q). MS: 339 (10, C₁₈H₂₉NO₃S⁺), 324 (0.8), 284 (4), 270 (7), 257 (6), 216 (11), 152 (7), 125 (9), 107 (6), 97 (100), 55 (87). HR-MS: 339.1863 (C₁₈H₂₉NO₃S⁺, calc. 339.1868).

N-[(2*S*,3*S*)-2-Methyl-3-phenyl-butanoyl]bornane-10,2-sultam **7c**. Using the general procedure, addition of MeLi (48.7 ml, 78 mmol) to the CuI.PBu₃ (15.3 g, 39 mmol), then addition of the enoyl sultam **6c** (4.65 g, 13 mmol), aq. quenching and workup gave a mixture of stereoisomers; GC (B): 19.27 (90), 19.72 (6), 20.23 (4). FC (hexane/EtOAc 6:1, 3.29 g, 67%) and crystallization from hexane furnished **7c** (2.65 g, 54%). GC (B): 19.27 (100). M.p. 108-10°. IR: 3030, 2980, 2880, 1690, 1340, 1210, 1140, 550. ¹H-NMR: 0.38 (s, 3H), 0.70 (s, 3H), 1.14 (d, *J* = 7, 3H), 1.16 (d, *J* = 7.5, 3H), 1.05 - 1.25 (3H), 1.48 - 1.54 (1H), 1.64 - 1.73 (3H), 2.97 (dq, *J* = 7.5, 10, 1H), 3.20 (dq, *J* = 7, 10, 1H), 3.22 (d, *J* = 14, 1H), 3.27 (d, *J* = 14, 1H), 3.65 (dd, *J* = 8, 5, 1H), 7.05 - 7.13 (1H), 7.14 - 7.24 (4H). ¹³C-NMR: 175.39 (s), 144.50 (s), 128.16 (d), 127.94 (d), 126.38 (d), 65.09 (d), 53.16 (t), 47.83 (s), 47.39 (s), 46.69 (d), 44.55 (d), 43.85 (d), 38.23 (t), 32.84 (t), 26.41 (t), 20.64 (q), 19.79 (q), 18.58 (q), 15.09 (q). MS: 375 (5, C₂₁H₂₉NO₃S⁺), 296 (2), 271 (12), 161 (18), 133 (77), 105 (100), 91 (76), 79 (25), 55 (24). HR-MS: 375.1870 (C₂₁H₂₉NO₃S⁺, calc. 375.1868).

N-[(2*S*,3*R*)-2-Methyl-3-phenyl-butanoyl]bornane-10,2-sultam **7d**. Using the general procedure, addition of PhLi (2.1 ml, 4.2 mmol) to copper(I)thiocyanate (257 mg, 2.1 mmol), then addition of the enoyl sultam **6d** (209 mg, 0.7 mmol), aq. quenching and workup gave a mixture of stereoisomers. HPLC (hexane/EtOAc 4:1): 6.00 (0.4), 6.29 (10.4), 6.66 (82.4), 7.29 (5.7). FC (hexane/EtOAc 8:1, 158 mg, 60%) and crystallization from hexane furnished **7d** (110 mg, 42%). GC (B): 20.23 (100). HPLC (hexane/EtOAc 4:1): 6.29 (1.5), 6.66 (98.5). M.p. 209-10°. IR: 3030, 2980, 2880, 1690, 1340, 1210, 1160, 550. ¹H-NMR: 0.85 (d, *J* = 6.5, 3H), 0.88 (s, 3H), 1.11 (s, 3H), 1.17 (d, *J* = 7, 3H), 1.23 - 1.37 (2H), 1.77 - 1.90 (3H), 2.00 - 2.10 (2H), 2.87 (dq, *J* = 6.5, 10, 1H), 3.23 (dq, *J* = 7, 10, 1H), 3.40 (d, *J* = 13.5, 1H), 3.50 (d, *J* = 13.5, 1H); 3.88 (dd, *J* = 6, 1H), 7.14 - 7.29 (5H). ¹³C-NMR: 176.23 (s), 144.35 (s), 128.46 (d), 127.68 (d), 126.55 (d), 65.46 (d), 53.27 (t), 48.18 (s), 47.73 (s), 46.42 (d), 45.26 (d), 44.74 (d), 38.58 (t), 33.01 (t), 26.45 (t), 20.88 (q), 20.46 (q), 19.96 (q), 16.19 (q). MS: 375 (1, C₂₁H₂₉NO₃S⁺), 296 (2), 271 (12), 161 (18), 133 (77), 105 (100), 91 (76), 79 (25), 55 (24). HR-MS: 375.1863 (C₂₁H₂₉NO₃S⁺, calc. 375.1868).

N-[(2*S*,3*S*)-2,3-Dimethyl-4-pentenoyl]bornane-10,2-sultam **7e**. Using the general procedure, addition of vinylolithium²⁸ (9.4 ml, 20.6 mmol, 2.2 M in THF) to the CuI.PBu₃ (4.03 g, 10.3 mmol), then addition of the enoyl sultam **6d** (1.02 g, 3.43 mmol), aq. quenching and workup gave a mixture of stereoisomers. GC (A): 15.84 (88) [the different stereoisomers could not be separated, except via reduction of the alkene (see ref.¹⁴) to **9a**]; GC (A): 15.53 (1.4), 15.86 (86.3), 16.24 (12.3). FC (hexane/EtOAc 8:1, 801 mg, 72%) and crystallization from pentane furnished **7e** (590 mg, 53%). GC (A): 15.65 (100) [reduced to **9a**]; GC: 15.79 (98.5), 16.06 (1.5)]. M.p. 117-8°. IR: 2980, 1690, 1320, 1210, 1140, 550. ¹H-NMR: 0.95 (s, 3H), 1.01 (d, *J* = 7, 3H), 1.08 (d, *J* = 6.5, 3H), 1.16 (s, 3H), 1.30 - 1.43 (2H), 1.83 - 1.96 (3H), 2.04 - 2.10 (2H), 2.50 (dq, *J* = 7, 8, 1H), 2.95 (dq, *J* = 6.5, 8, 1H), 3.44 (d, *J* = 14, 1H), 3.52 (d, *J* = 14, 1H), 3.91 (dd, *J* = 7, 5, 1H), 5.03 (m, 2H), 5.62 - 5.73 (1H). ¹³C-NMR: 175.80 (s), 140.56 (d), 115.34 (t), 65.34 (d), 53.19 (t), 48.09 (s), 47.67 (s), 44.72 (d), 44.66 (d), 42.67 (t), 38.58 (d), 32.93 (t), 26.42 (t), 20.82 (q), 19.89 (q), 18.40 (q), 14.37 (q). MS: 325 (2.3, C₁₇H₂₇NO₃S⁺), 310

(4), 218 (2), 152 (3), 135 (13), 111 (23), 93 (11), 83 (88), 69 (22), 55 (100). - HR-MS: 325.1716 ($C_{17}H_{27}NO_3S^+$, calc. 325.1711).

Hydrogenation of the double bond with $H_2/Rh, Al_2O_3$, according to Ref ¹⁴ gave *N*-[(2*S*,3*S*)-2,3-dimethylpentanoyl]bornane-10,2-sultam **9a**. ¹H-NMR- and GC-comparison as well as mixed m.p. (94-5°) with a sample obtained by another route ¹⁸ proved the expected (2*S*,3*S*) configuration.

Preparations and GC-Analyses of Mixtures of *N*-[(2*R*,3*R*)- and (2*R*,3*S*)]-(2,3-Dialkylalkanoyl]bornane-10,2-sultams.

N-[(2,3-Dimethylpentanoyl)]bornane-10,2-sultam. Prepared and analysed according to ref. ¹⁴.

N-[(2,3-Dimethylheptanoyl)]bornane-10,2-sultam. Prepared and analysed according to ref. ¹⁴.

N-[(2-Methyl-3-phenyl-butanoyl)]bornane-10,2-sultams. A mixture of racemic (major) *syn*- and (minor) *anti*-2-methyl-3-phenyl-butyric acid was prepared according to ref. ²⁹. Following the procedure described above for the preparation of *N*-[(*E*)-2-methyl-3-phenyl-2-propenoyl]bornane-10,2-sultam **6c**, 2-methyl-3-phenylbutyric acid (620 mg, 3.5 mmol) was converted (oxalyl chloride) into its acid chloride which served to acylate sultam **12** (828 mg, 3.85 mmol) to give a mixture of stereoisomeric (2-methyl-3-phenyl-butanoyl)bornane-10,2-sultams (923 mg, 70%). GC (B): 19.27 (38.3), 19.72 (34), 20.23 (27.7).

Saponifications of *N*-Acyl Sultams **7**. General procedure. A 7 M aq. solution of LiOH·H₂O was added to a 0.35 M solution of the sultam **7** in THF and vigorously stirred at 65° for 3 - 5 d. Evaporation *in vacuo*, trituration of the residue with CH₂Cl₂ and evaporation of the dried extracts gave sultam **12**. Acidification of the CH₂Cl₂-insoluble residue with 2 N aq. HCl, saturation with NaCl, extraction with CH₂Cl₂ and evaporation of the dried (MgSO₄) extracts gave the crude acid **11** which was purified by distillation.

(2*S*,3*R*)-2,3-Dimethylpentanoic acid **11a**. Following the general procedure LiOH·H₂O (1.26 g, 30 mmol) and the sultam **7a** (980 mg, 3 mmol) were stirred for 5 d, workup and bulb-to-bulb distillation (bath 100°/15 torr) gave **11a** as an oil (190 mg, 60%). $[\alpha]_D^{25} = +24.5^\circ$; $[\alpha]_{578} = +25.7^\circ$; $[\alpha]_{546} = +29.5^\circ$; $[\alpha]_{436} = +53.2^\circ$; $[\alpha]_{365} = +90.2^\circ$ (neat, T = 25°); $[\alpha]_D = +30.5^\circ$; $[\alpha]_{578} = +31.9^\circ$; $[\alpha]_{546} = +36.7^\circ$; $[\alpha]_{436} = +66.2^\circ$; $[\alpha]_{365} = +112.1^\circ$ (c = 0.98, T = 20°), lit. ³⁰: $[\alpha]_D = +35.7^\circ$ (neat). [Extrapolated value from 10% e.e.]. GC-comparison-analysis of the methyl esters showed no epimerisation. IR: 3300 - 2500, 2980, 1710, 1460, 1300, 1210, 900. ¹H-NMR: 0.87 (d, J = 7, 3H), 0.89 (t, J = 7.5, 3H), 1.07 (d, J = 6.8, 3H), 1.22 (1H), 1.40 (1H), 1.81 (dq, J = 7, 6, 1H), 2.44 (dq, J = 6.8, 6, 1H). ¹³C-NMR: 183.45 (s), 43.66 (d), 36.78 (d), 27.39 (t), 15.04 (q), 11.73 (q), 11.60 (q). MS: 115 (22, C₇H₁₄O₂⁺ - CH₃), 101 (68), 97 (10), 85 (17), 74 (100), 57 (18). HR-MS: 115.0773 (C₇H₁₄O₂⁺ - CH₃, calc. 115.0759)

(2*S*,3*R*)-2,3-Dimethylheptanoic acid **11b**. Following the general procedure sultam **6b** (605 mg, 1.7 mmol) was heated with LiOH·H₂O (716 mg, 17 mmol) in THF/H₂O (1:1, 10 ml) for 16 h at 65°. Workup and bulb-to-bulb distillation (bath 150°, 0.4 Torr) gave sultam **12** (340 mg, 93%) and acid **11b** (distilled, 172 mg, 64%). $[\alpha]_D = +40.65^\circ$; $[\alpha]_{578} = +42.68^\circ$; $[\alpha]_{546} = +48.64^\circ$; $[\alpha]_{436} = +85.57^\circ$; $[\alpha]_{365} = +140.85^\circ$ (c = 1.64, CH₂Cl₂, T = 23°); authentic sample of enantiomer ¹⁷: $[\alpha]_D = -40.8^\circ$; $[\alpha]_{578} = -42.6^\circ$; $[\alpha]_{546} = -48.7^\circ$; $[\alpha]_{436} = -85.8^\circ$; $[\alpha]_{365} = -141.7^\circ$ (c = 1.7, CH₂Cl₂, T = 20°). IR: 3500 - 3000, 2980, 2940, 2880, 2870, 1710. ¹H-NMR: 0.86 (d, J = 7, 3H); 0.88 (t, J = 7, 3H); 1.08 (d, J = 7, 3H); 1.12 - 1.40 (6H); 1.88 (m, 1H); 2.44 (m, 1H).

(2*S*,3*S*)-2,3-Dimethyl-4-pentenoic acid **11c**. Acylsultam **7c** (459 mg, 1.41 mmol) was heated with LiOH·H₂O (592 mg, 14.1 mmol) in THF/H₂O (1:1, 8 ml) at 65° for 24 h. Workup and bulb-to-bulb distillation (135° (bath)/12 Torr) furnished the recovered auxiliary **12** (276 mg, 91%), as well as the acid **11c** (110 mg, 61%). $[\alpha]_D = -37.4^\circ$; $[\alpha]_{578} = -38.8^\circ$; $[\alpha]_{546} = -44.6^\circ$; $[\alpha]_{436} = -80.6^\circ$; $[\alpha]_{365} = -135.0^\circ$ (c = 1.18, CHCl₃, T = 21°). IR (film): 3300 - 2500 broad, 3080, 2980, 2960, 1710, 1445, 1420, 915. ¹H-NMR: 1.03 (d, J = 7, 3H); 1.06 (d, J = 7, 3H); 2.27 (m, 1H); 2.42 (m, 1H); 5.20 (m, 2H), 5.63 (m, 1H).

(1*S*,2*R*)-2-Methyl-1-cyclohexanecarboxylic acid **11d**. Following the general procedure LiOH·H₂O (3.70 g, 88 mmol) and the sultam **14** (3.01 g, 8.8 mmol) were stirred for 4 d, workup and bulb-to-bulb distillation (bath 95°/1.5 Torr) gave **11d** as an oil (937 mg, 75%). $[\alpha]_D = -8.0^\circ$; $[\alpha]_{578} = -8.24^\circ$; $[\alpha]_{546} = -8.97^\circ$; $[\alpha]_{436} = -11.3^\circ$; $[\alpha]_{365} = -8.8^\circ$ (c = 6.02, EtOH, T = 21.5°), lit. ³¹: $[\alpha]_D = +7.6^\circ$ (94% e.e. for the antipode (c = 5.95, EtOH, T = 21.5°). IR: 3300 - 2500, 2930, 2880, 2660, 1710, 1450, 1420, 1260, 940. ¹H-NMR: 0.97 (d, J = 7, 3H), 1.22 - 1.45 (2H), 1.45 - 1.78 (6H), 2.20 (m, 1H), 2.56 (m, 1H). ¹³C-NMR: 182.14 (s), 45.83 (d), 31.72 (t), 30.98 (d), 24.35 (t), 23.64 (t), 21.42 (t), 15.13 (q). MS: 142 (14, C₈H₁₄O₂⁺), 124 (67), 96 (46), 87 (44), 82 (73), 73 (77), 55 (100). HR-MS: 142.0996 (C₈H₁₄O₂⁺, calc. 142.0994)

(2*S*,3*S*)-2-Methyl-3-phenylbutanoic acid **11e**. Following the general procedure LiOH·H₂O (2.94 g 70 mmol) and the sultam **7c** (2.65 g, 7 mmol) were stirred for 5 d, workup and bulb-to-bulb distillation (bath 120 - 125°/0.5 Torr) gave **11e** as an oil (832 mg, 67%). $[\alpha]_D = +53.1^\circ$; $[\alpha]_{578} = +55.7^\circ$; $[\alpha]_{546} = +64.0^\circ$; $[\alpha]_{436} = +116.2^\circ$; $[\alpha]_{365} = +200.1^\circ$ (c = 1.17, T = 21.5°). IR: 3300 - 2500, 3020, 2980, 1710, 1480, 1290, 1240, 1230, 1220, 910. ¹H-NMR: 1.16 (d, J = 7, 3H), 1.27 (d, J = 7.5, 3H), 2.71 (dq, J = 7, 1H), 3.16 (dq, J = 7.5, 1H), 7.20 (s, 3H). ¹³C-NMR: 182.10 (s), 144.55 (s), 128.28 (d), 127.37 (d), 126.41 (d), 46.30 (d), 41.63 (d), 16.91 (q), 13.37 (q). MS: 178 (10, C₁₁H₁₄O₂⁺), 149 (7), 105 (100), 91 (8), 77 (9). HR-MS: 178.1004 (C₁₁H₁₄O₂⁺, calc. 178.0904)

(2*S*,3*R*)-2-amino-3-phenylbutane **16**. To a solution of (2*S*,3*S*)-2-methyl-3-phenylbutanoic acid **11c** (832 mg, 4.7 mmol) and triethylamine (0.65 ml, 4.7 mmol) in benzene (30 ml) at 0° was added diphenylphosphoryl azide (DPPA) ³² (1.01 ml, 4.7 mmol) in benzene (20 ml). The mixture was stirred for 1 h at r.t. and heated at reflux for 16 h. After evaporation of the solvent an IR of an aliquot confirmed the formation of the isocyanate. To the residue was slowly added conc. HCl (20 ml) and stirring continued (2 h) at r.t. Washing with Et₂O, treatment with aq. NH₃ (24%), workup and bulb-to-bulb distillation (bath 95°/3 Torr) gave **16** as an oil (388 mg, 56%). [α]_D²⁵ = +44.9°; [α]_D¹⁸ = +47.1°; [α]_D¹⁵ = +54.6°; [α]_D¹² = +103.3°; [α]_D¹⁰ = +186.9° (neat, T = 25°), lit.³³: [α]_D²⁵ = 41.2° (neat, T = 25°). IR: 3380, 3030, 2980, 1660, 1610, 1490, 1450, 1360, 700. ¹H-NMR: 1.16 (d, J = 6, 3H), 1.28 (d, J = 7, 3H), 1.24 - 1.35 (2H), 2.52 (dq, J = 7, 1H), 3.04 (dq, J = 6, 8, 1H), 7.21 - 7.38 (5H). ¹³C-NMR: 145.01 (s), 128.40 (d), 127.72 (d), 126.28 (d), 52.39 (d), 48.46 (d), 21.23 (q), 18.54 (q). MS: 148 (11, C₁₀H₁₅N⁺-1), 134 (22), 121 (14), 105 (21), 91 (26), 86 (63), 84 (100), 77 (24), 70 (59). HR-MS: 148.1119 (C₁₀H₁₄N⁺, calc. 148.1127)

N-Benzoyl-(2*S*,3*R*)-2-amino-3-phenylbutane **17**. To a solution of (2*S*,3*R*)-2-amino-3-phenylbutane **16** (135 mg, 0.9 mmol) in CH₂Cl₂ (2 ml) was first added pyridine (0.7 ml, 9 mmol) followed by benzoylchloride (0.1 ml, 0.9 mmol). After stirring (1 h at r.t.), the mixture was poured onto ice, acidified with 2 N HCl and worked up. FC (hexane/EtOAc 4:1) and crystallization (hexane/Et₂O) gave pure **17** (216 mg, 95%). M.p. 141°, Lit.³³: 141°. [α]_D²⁵ = -20.5°; [α]_D¹⁸ = -21.6°; [α]_D¹⁵ = -25.4°; [α]_D¹² = -52.9°; [α]_D¹⁰ = +109.7° (c = 10, T = 25°). Lit.³³: [α]_D²⁵ = -19.5 (c = 10, T = 25°). IR: 3450, 3350, 3080, 3020, 2980, 2940, 2880, 1670, 1510, 1480, 1450, 710. ¹H-NMR: 1.21 (d, J = 6.5, 3H), 1.37 (d, J = 7.5, 3H), 3.00 (dq, J = 6.5, 1H), 4.44 (m, 1H), 5.88 (d (br.), J = 8, 1H), 7.22 - 7.48 (8H), 7.57 - 7.65 (2H). ¹³C-NMR: 166.80 (s), 142.83 (s), 134.92 (s), 131.25 (d), 128.49 (d), 127.94 (d), 126.76 (d), 126.72 (d), 50.05 (d), 44.78 (d), 18.93 (q), 17.58 (q). MS: 253 (8, C₁₇H₁₉NO⁺), 148 (52), 105 (100), 77 (31). HR-MS: 253.1469 (C₁₇H₁₉NO⁺, calc. 253.1466).

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