A Convenient Synthesis of Functionalized α-Methylidenebutano-4-lactams

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A concise synthetic approach to functionalized α-methylidenebutanolactams has been developed. The synthetic strategy is based on the preliminary assembly of the lactam template equipped with appropriate functionalities. Subsequent installation of the methylidene by a metalation/alkylation/elimination sequence completed the elaboration of the racemic title compounds.

Introduction. – α-Alkylidene-γ-lactams **1** (*Fig.*) are the active constituents of many natural and synthetic compounds exhibiting pronounced biological properties [1][2]. In particular the α-methylidenebutano-4-lactams exhibit cytotoxicity [2] but with less toxic activity than the corresponding lactones [2g][3], rendering them promising compounds as potential anticancer [2a] and anti-inflammatory agents [2]. They are able to act as *Michael* acceptors in the reaction with thiol groups of bionucleophiles [2] or can readily form [2 + 2] cycloadducts with the DNA bases [4]. Additionally, they can be partners in ring-closing metathesis (RCM) reactions [5] and can serve as key building blocks for the synthesis of multifarious natural and/or bioactive compounds [6]. Paradoxically, these lactams, less common in nature [7] than their oxo analogues **2** (*Fig.*), have not elicited much synthetic efforts. Metal-promoted syntheses [1f][1h][1l][8] as well as radical [1g] or anionic methodologies [9] have been used with varying degrees of success, but most synthetic procedures leading to α-methylidenebutano-4-lactams utilize the base-promoted reaction of nitro alkanes with the acetates of *Baylis–Hillman* adducts [1j], with bromomethyl fumarates [1k] and functionalized acrylates [1i], followed by reductive or sonochemically induced [1r] cyclization. They can also be accessed by ring opening of *N*-tosylaziridines [1a] and from aldimines by exposure to β-functional crotyl-Zn reagents [1f] or In-promoted addition to (bromomethyl)acrylic acid derivatives [1b][1s]. The required methylidene unit can be incorporated early in the synthetic sequence or can be ultimately accessed by *Horner–Emmons* or *Peterson* olefination on preliminarily assembled phosphorylated [1i][1n][2g] or silylated lactams [1c]. All these methods are of procedural simplicity, but they can hardly accommodate additional functional groups and, particularly, carboxylic acid functions at C(3) of the lactam. This is rather worrying, since structurally sophisticated models, as *e.g.*, by **3** (*Fig.*), have been designed and developed for the treatment of immunopathy [10]. Furthermore, their formation is invariably accompanied by an undesirable isomerization leading to the corresponding

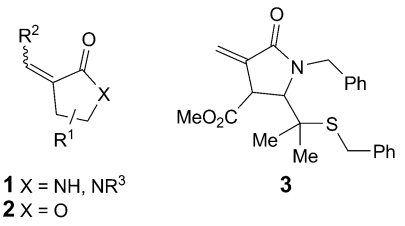

Figure. *α-Alkylidenebutano-4-lactams and -lactones* **1** *and* **2**, *respectively, and Biologically Active α-Methylidenebutano-4-lactam* **3**

endocyclic unsaturated analogs. As a consequence, for the construction of structurally diverse models the development of general synthetic methodologies providing molecular complexity in a highly efficient manner is an area of current interest.

In this context, we aimed to develop a synthetic approach to rapidly achieve molecular diversity, and, for this purpose, we targeted some exemplary functionalized and *C(3)*-disubstituted models **4** and **5** that fulfil the above-mentioned structural criteria. In particular, we speculated that the carboxylate function may serve as a handle or key branching point for alternative functionalization.

Results and Discussion. – The first facet of the synthesis, depicted in the *Scheme*, was the preliminary elaboration of the *C*-methylated keto diesters **6** and **7**. These precursors were readily assembled from keto esters **8** and **9**, respectively, by two sequential metalation/alkylation processes involving ethyl bromoacetate and MeI as alkylating agents. Compounds **6** and **7** were obtained in moderate yields, probably due to the steric congestion of the final compounds. Subsequent reductive amination reaction under forcing conditions by making use of $AcONH_4/NaBH_3CN$ in refluxing MeOH triggered the preliminary conversion of the keto diesters **6** and **7** to the primary amine **10**, followed by spontaneous intramolecular regioselective aminolysis leading to the lactam unit. The resulting lactams **11** and **12**, respectively, were obtained in satisfactory yields as almost equimolecular mixtures of easily separable diastereoisomers (*Table*). The *cis*-isomer was predominant by a small margin for **11** and the *trans*-isomer for **12**, probably due to the presence of the bulkier vicinal pentyl group. Although the ^{1}H- and ^{13}C-NMR chemical shifts were different for the diastereoisomers, stereochemical assignments were made on the basis of nuclear *Overhauser* effect (NOE). For the NOE experiments, the *singlet* resonance of Me–C(3) of either isomer was irradiated under identical conditions. For one isomer (*cis*-**11** and *cis*-**12**, resp.), the intensity of the signal of the H–C(2) was enhanced significantly, whereas this enhancement was reduced for the other isomer (*trans*-**11** and *trans*-**12**, resp.). These results are interpreted in terms of the spatial proximity of H–C(2) to the irradiated Me group, and the spectrum displaying the enhancement can be unambiguously assigned to the isomer having a *trans*-configuration for the two alkyl groups, *i.e.*, *cis*-**11** and *cis*-**12**. The ultimate installation of the exocyclic methylidene unit by a carbanionic process required the preliminary protection of the lactam N-atom. For this purpose, the isolated lactams *cis*- and *trans*-**11**, and *cis*- and *trans*-**12** were *N*-Boc-protected (Boc = (*tert*-

butoxy)carbonyl), since we anticipated that deprotection of the resulting *N*-acyl carbamates at a later stage of the process would spare the latent functionalities within the lactam framework. This operation was easily performed under standard conditions to afford excellent yields of the desired *N*-Boc-protected lactams *cis*- and *trans*-**13**, and *cis*- and *trans*-**14** (*Scheme* and *Table*). For the creation of the methylidene unit, a metalation/electrophilic attack/elimination sequence precluding the use of paraformaldehyde was preferred. In this regard, compounds **13** and **14** were initially exposed to lithium hexamethyldisilazide (LHMDS) at low temperature, and the transient enolates were captured with iodomethyl methyl ether to afford excellent yields of the C(4)-substituted lactams *cis*- and *trans*-**15**, and *cis*- and *trans*-**16** (*Table*). At this stage, configurational considerations about the configuration at C(4) were not crucial for the outcome of the synthetic process, because conversion of the alkoxylated appendage to the mandatory methylidene moiety was planned behind in the sequence. The creation of the exocyclic unsaturated moiety was secured by treatment of the $MeOCH_2$-substituted precursors *cis*- and *trans*-**15**, and *cis*- and *trans*-**16** with 1,8-diazabicyclo[5.5.0]undec-7-ene (DBU) in toluene and, gratifyingly, this protocol afforded the methylidene compounds *cis*- and *trans*-**17**, and *cis*- and *trans*-**18**. With these compounds in hand, we were only one step away from the targeted compounds. Treatment of **17** and **18** with CF_3COOH (TFA) in CH_2Cl_2 for a short period triggered release of the *N*-Boc protection to provide the *N*-unsubstituted functionalized lactams *cis*- and *trans*-**4**, and *cis*- and *trans*-**5** in fairly good yields (*Table*).

Table. *Diastereoisomeric Ratio and Yields for the Synthesis of Compounds* **4**, **5**, *and* **11**–**18**

R	Compound	Yield [%] (*cis*/*trans* ratio)	Diastereo-isomer	Butano-4-lactams (Yield [%])			
Me	**11**	43 (56 : 44)	*cis*	**13** (71)	**15** (52)	**17** (74)	**4** (95)
			trans	**13** (75)	**15** (64)	**17** (57)	**4** (97)
C_5H_{11}	**12**	40 (40 : 60)	*cis*	**14** (79)	**16** (65)	**18** (70)	**5** (93)
			trans	**14** (75)	**16** (75)	**18** (65)	**5** (98)

Conclusions. – We have devised a concise and efficient method to synthesize functionalized α-methylidene-γ-butyrolactams. The notable advantages of this method are operational simplicity, mild reaction conditions, and ease of isolation of racemic *cis*- and *trans*-products. This simple protocol developed in this study paves the way for further biological studies, and we believe that this work provides a strong incentive for the elaboration of structurally modified models.

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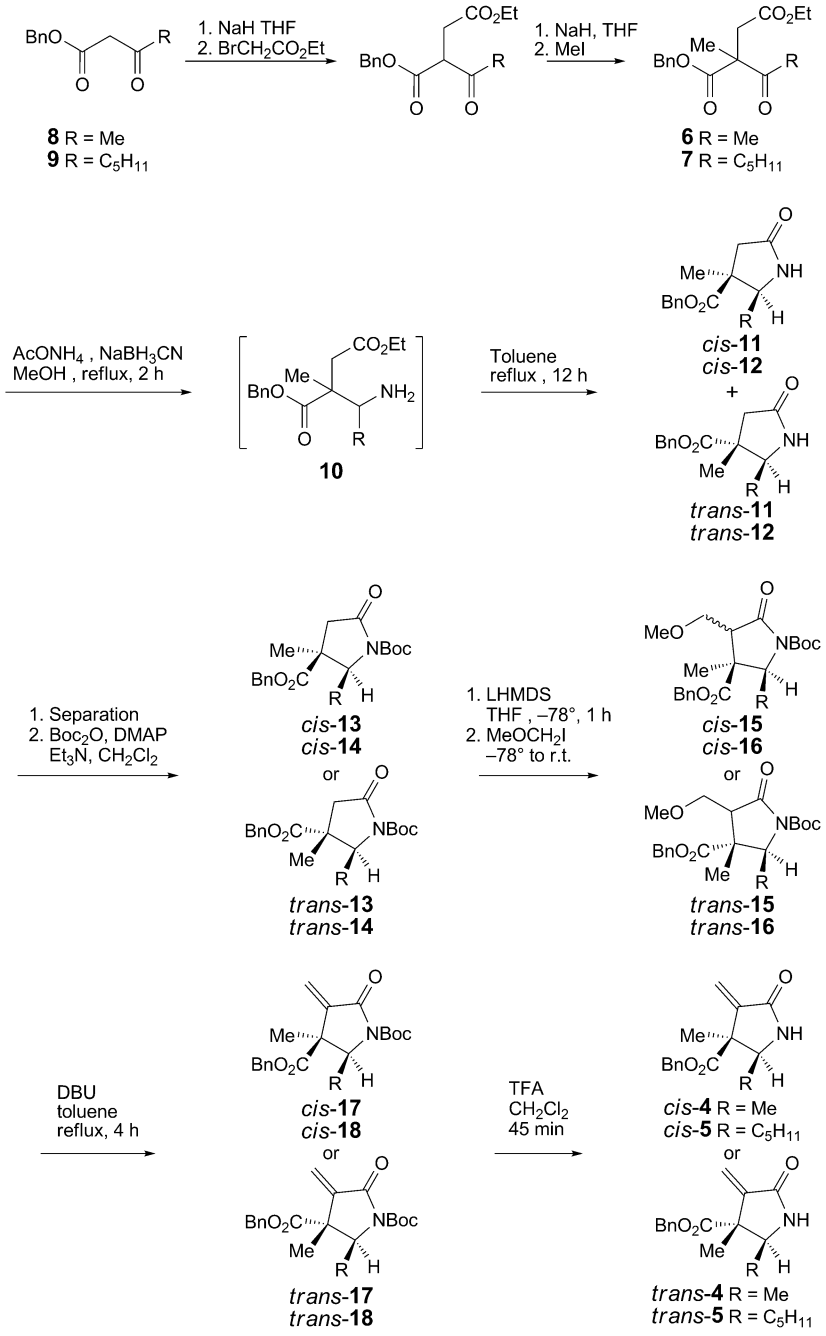
Experimental Part

1. *General. Abbreviations:* Boc: (*tert*-butoxy)carbonyl; DBU: 1,8-diazabicyclo[5.5.0]undec-7-ene; DMAP: 4-(dimethylamino)pyridine; LHMDS: lithium hexamethyldisilazide. All solvents were dried and distilled according to standard procedures. Glassware was dried in oven and assembled under dry Ar.

Scheme. *Synthesis of Functionalized α-Methylidenebutano-4-lactams*



The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Flash column chromatography (FCC): *Merck* silica gel *60* (SiO_2; 40–63 μm; 230–400 mesh *ASTM*) was used. M.p.: *Reichert-Thermopan* apparatus; uncorrected. NMR Spectra: *Bruker AM 300* (300 and 75 MHz, for ^1H and ^{13}C, resp.), $CDCl_3$ as solvent, TMS as internal standard. Elemental analyses: *Carlo-Erba CHNS-11110* equipment.

2. *Synthesis of Keto Diesters* **6** *and* **7**. *General Procedure.* A soln. of **8** or **9** (30 mmol) in THF (10 ml) was added dropwise to a suspension of NaH (35 mmol) in THF (80 ml) at 0° under Ar. The mixture was stirred at r.t. for 1 h. Then, $BrCH_2COOEt$ (33 mmol) was added dropwise, and the mixture was stirred at r.t. for an additional h. Aq. sat. NH_4Cl soln. (30 ml) was added, THF was evaporated under reduced pressure, and the remaining aq. layer was extracted with AcOEt (3 × 50 ml). The combined org. layers were washed with brine (10 ml) and dried ($MgSO_4$). After concentration under reduced pressure, the oily residue was purified by FCC (SiO_2; AcOEt/hexanes 20:80) to give the crude intermediate keto esters, which were methylated with MeI following the same procedure but upon heating the mixture to reflux for 4 h.

1-Benzyl 4-Ethyl 2-Acetyl-2-methylbutanedioate (**6**). Yield: 40% over the two steps from **8**. Oil. ^1H-NMR: 1.16 (*t*, *J* = 7.1, 3 H); 1.47 (*s*, 3 H); 2.14 (*s*, 3 H); 2.82 (*d*, *J* = 16.6, 1 H); 2.93 (*d*, *J* = 16.6), 1 H; 4.03 (*q*, *J* = 7.1, 2 H); 5.09–5.18 (*m*, 2 H); 7.24–7.35 (*m*, 5 H). ^{13}C-NMR: 14.0 (Me); 20.2 (Me); 26.2 (Me); 39.9 (CH_2); 57.5 (C); 60.7 (CH_2); 67.4 (CH_2); 128.3 (2 CH); 128.4 (CH); 128.6 (2 CH); 135.2 (C); 170.7 (CO); 171.6 (CO), 204.2 (CO). Anal. calc. for $C_{16}H_{20}O_5$ (292.33): C 65.74, H 6.90; found: C 65.48, H 7.02.

1-Benzyl 4-Ethyl 2-Hexanoyl-2-methylbutanedioate (**7**). Yield: 41% over the two steps from **9**. Oil. ^1H-NMR: 0.82 (*t*, *J* = 7.1, 3 H); 1.09–1.24 (*m*, 7 H); 1.41–1.50 (*m*, 2 H); 1.47 (*s*, 3 H); 2.37–2.49 (*m*, 2 H); 2.82 (*d*, *J* = 16.6, 1 H); 2.92 (*d*, *J* = 16.6, 1 H); 4.04 (*q*, *J* = 7.1, 2 H); 5.14 (*s*, 2 H); 7.25–7.36 (*m*, 5 H). ^{13}C-NMR: 13.9 (Me); 14.0 (Me); 20.1 (Me); 22.4 (CH_2); 23.2 (CH_2); 31.1 (CH_2); 38.2 (CH_2); 40.0 (CH_2); 57.4 (C); 60.7 (CH_2); 67.3 (CH_2); 128.4 (2 CH); 128.5 (CH); 128.6 (2 CH); 135.2 (C); 170.7 (CO); 171.7 (CO); 206.3 (CO). Anal. calc. for $C_{20}H_{28}O_5$ (348.44): C 68.94, H 8.10; found: C 68.80, H 8.14.

3. *Synthesis of Lactams* **11** *and* **12**. Ammonium acetate ($AcONH_4$; 15.4 g, 200 mmol) and $NaBH_3CN$ (0.80 g, 12.6 mmol) were added to a soln. of **6** or **7** (20 mmol) in MeOH (70 ml), and the mixture was heated to reflux for 2 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in toluene (60 ml). After boiling for 12 h, toluene was evaporated under reduced pressure, and the residue was dissolved in Et_2O (50 ml). The Et_2O layer was washed with aq. sat. $NaHCO_3$ soln. (2 × 30 ml) and brine (20 ml), and then dried ($MgSO_4$). After evaporation of the solvent, the oily residue was submitted to FCC (SiO_2; AcOEt/hexanes 90:10) to afford the separated *cis* and *trans* diastereoisomers of lactams **11** and **12**.

*Benzyl (2*RS*,3*RS*)-2,3-Dimethyl-5-oxopyrrolidine-3-carboxylate* (*cis*-**11**). White solid. M.p. 92–93°. ^1H-NMR: 1.19 (*d*, *J* = 6.6, 3 H); 1.27 (*s*, 3 H); 2.20 (*d*, *J* = 16.8, 1 H); 2.95 (*d*, *J* = 16.8, 1 H); 4.00–4.11 (*m*, 1 H); 5.14 (*s*, 2 H); 7.20–7.40 (*m*, 5 H). ^{13}C-NMR: 15.7 (Me); 18.6 (Me); 42.3 (CH_2); 48.6 (C); 54.9 (CH); 67.0 (CH_2); 128.0 (2 CH); 128.4 (CH); 128.7 (2 CH); 135.5 (C); 174.6 (CO); 175.8 (CO). Anal. calc. for $C_{14}H_{17}NO_3$ (247.29): C 68.00, H 6.93, N 5.66; found: C 67.85, H 7.04, N 5.37.

*Benzyl (2*RS*,3*SR*)-2,3-Dimethyl-5-oxopyrrolidine-3-carboxylate* (*trans*-**11**). White solid. M.p. .84–85°. ^1H-NMR: 1.02 (*d*, *J* = 6.4, 3 H); 1.40 (*s*, 3 H); 2.10 (*d*, *J* = 17.0, 1 H); 3.01 (*d*, *J* = 17.0, 1 H); 3.50–3.56 (*m*, 1 H); 5.07–5.17 (*m*, 2 H); 7.20–7.40 (*m*, 5 H). ^{13}C-NMR: 17.7 (Me); 23.9 (Me); 40.3 (CH_2); 49.3 (C); 58.7 (CH); 66.8 (CH_2); 128.2 (2 CH); 128.4 (CH); 128.6 (2 CH); 135.4 (C); 173.3 (CO); 176.3 (CO). Anal. calc. for $C_{14}H_{17}NO_3$ (247.29): C 68.00, H 6.93, N 5.66; found: C 67.96, H 6.69, N 5.71.

*Benzyl (2*RS*,3*RS*)-3-Methyl-5-oxo-2-pentylpyrrolidine-3-carboxylate* (*cis*-**12**). Oil. ^1H-NMR: 0.83 (*t*, *J* = 6.3, 3 H); 1.10–1.60 (*m*, 11 H); 2.16 (*d*, *J* = 16.6, 1 H); 2.92 (*d*, *J* = 16.6, 1 H); 3.86 (*dd*, *J* = 4.4, 9.0, 1 H); 5.13 (*s*, 2 H); 7.20–7.34 (*m*, 5 H); 7.52 (br. *s*, 1 H). ^{13}C-NMR: 14.0 (Me); 18.3 (Me); 22.3 (CH_2); 26.2 (CH_2); 30.3 (CH_2); 31.6 (CH_2); 43.1 (CH_2); 48.4 (C); 59.9 (CH); 67.0 (CH_2); 128.0 (2 CH); 128.4 (CH); 128.6 (2 CH); 135.6 (C); 174.7 (CO); 175.7 (CO). Anal. calc. for $C_{18}H_{25}NO_3$ (303.40): C 71.26, H 8.31, N 4,62; found: C 71.39, H 8.09, N 4.88.

*Benzyl (2*RS*,3*SR*)-3-Methyl-5-oxo-2-pentylpyrrolidine-3-carboxylate* (*trans*-**12**). Oil. ^1H-NMR: 0.80 (*t*, *J* = 6.8, 3 H); 1.10–1.30 (*m*, 8 H); 1.40 (*s*, 3 H); 2.09 (*d*, *J* = 17.0, 1 H); 2.99 (*d*, *J* = 17.0, 1 H); 3.30–3.34 (*m*, 1 H); 5.12 (*s*, 2 H); 7.20–7.35 (*m*, 5 H); 7.66 (br. *s*, 1 H). ^{13}C-NMR: 14.0 (Me); 22.3 (CH_2); 24.3

(Me); 25.9 (CH_2); 31.4 (CH_2); 31.8 (CH_2); 40.6 (CH_2); 49.2 (C); 63.5 (CH); 66.8 (CH_2); 128.4 (2 CH); 128.5 (CH); 128.6 (2 CH); 135.4 (C); 173.3 (CO); 176.5 (CO). Anal. calc. for $C_{18}H_{25}NO_3$ (303.40): C 71.26, H 8.31, N 4.62; found: C 71.14, H 8.58, N 4.87.

4. *Synthesis of* N-*Protected Lactams* **13** *and* **14**. A soln. of **11** or **12** (4 mmol), Boc_2O (0.95 g, 4.4 mmol), DMAP (0.49 g, 4 mmol), and Et_3N (0.56 ml, 4 mmol) in CH_2Cl_2 (30 ml) was stirred at r.t. for 12 h. The solvent was evaporated under reduced pressure, and the residue was purified by FCC (SiO_2; AcOEt/hexanes 40:60).

3-Benzyl 1-tert-*Butyl (2*RS,*3*RS*)-2,3-Dimethyl-5-oxopyrrolidine-1,3-dicarboxylate* (*cis*-**13**). Oil. ^{1}H-NMR: 1.25 (*d*, *J* = 6.6, 3 H); 1.29 (*s*, 3 H); 1.48 (*s*, 9 H); 2.42 (*d*, *J* = 17.3, 1 H); 2.99 (*d*, *J* = 17.3, 1 H); 4.51 (*q*, *J* = 6.6, 1 H); 5.09–5.20 (*m*, 2 H); 7.29–7.34 (*m*, 5 H). ^{13}C-NMR: 15.5 (Me); 19.0 (Me); 28.0 (3 Me); 41.4 (CH_2); 45.8 (C); 59.2 (CH); 67.4 (CH_2); 83.0 (C); 128.0 (2 CH); 128.4 (CH); 128.7 (2 CH); 135.3 (C); 146.4 (C); 171.6 (CO); 174.7 (CO). Anal. calc. for $C_{19}H_{25}NO_5$ (347.41): C 65.69, H 7.25, N 4.03; found: C 65.77, H 7.45, N 3.78.

3-Benzyl 1-tert-*Butyl (2*RS,*3*SR*)-2,3-Dimethyl-5-oxopyrrolidine-1,3-dicarboxylate* (*trans*-**13**). White solid. M.p. 67–68°. ^{1}H-NMR: 1.11 (*d*, *J* = 6.4, 3 H); 1.42 (*s*, 3 H); 1.49 (*s*, 9 H); 2.23 (*d*, *J* = 17.6, 1 H); 3.23 (*d*, *J* = 17.6, 1 H); 3,99 (*q*, *J* = 6.4, 1 H); 5.09–5.19 (*m*, 2 H); 7.25–7.40 (*m*, 5 H). ^{13}C-NMR: 16.2 (Me); 24.3 (Me); 28.0 (3 Me); 40.8 (CH_2); 46.2 (C); 61.5 (CH); 67.2 (CH_2); 83.2 (C); 128.4 (2 CH); 128.6 (CH); 128.7 (2 CH); 135.1 (C); 146.6 (C); 171.4 (CO); 172,5 (CO). Anal. calc. for $C_{19}H_{25}NO_5$ (347.41): C 65.69, H 7.25, N 4.03; found: C 65.94, H 7.37, N 4.24.

3-Benzyl 1-tert-*Butyl (2*RS,*3*RS*)-3-Methyl-5-oxo-2-pentylpyrrolidine-1,3-dicarboxylate* (*cis*-**14**). Oil. ^{1}H-NMR: 0.83 (*t*, *J* = 6.5, 3 H); 1.20–1.70 (*m*, 11 H); 1.42 (*s*, 9 H); 2.40 (*d*, *J* = 17.3, 1 H); 2.92 (*d*, *J* = 17.3, 1 H); 4.43 (*t*, *J* = 6.2, 1 H); 5.03–5.15 (*m*, 2 H); 7.23–7.31 (*m*, 5 H). ^{13}C-NMR: 13.9 (Me); 18.8 (Me); 22.5 (CH_2); 26.0 (CH_2); 27.9 (3 Me); 31.0 (CH_2); 32.0 (CH_2); 41.8 (CH_2); 46.7 (C); 62.8 (CH); 67.4 (CH_2); 82.8 (C); 128.0 (2 CH); 128.4 (CH); 128.6 (2 CH); 135.3 (C); 149.6 (C); 171.9 (CO); 174.8 (CO). Anal. calc. for $C_{23}H_{33}NO_5$ (403.52): C 68.46, H 8.24, N 3.47, found: C 68.54, H 7.94, N 3.32.

3-Benzyl 1-tert-*Butyl (2*RS,*3*SR*)-3-Methyl-5-oxo-2-pentylpyrrolidine-1,3-dicarboxylate* (*trans*-**14**). Oil. ^{1}H-NMR: 0.79 (*t*, *J* = 6.9, 3 H); 1.10–1.55 (*m*, 8 H); 1.41 (*s*, 3 H); 1.48 (*s*, 9 H); 2.21 (*d*, *J* = 17.6, 1 H); 3.22 (*d*, *J* = 17.6, 1 H); 3.97 (*t*, *J* = 5.6, 1 H); 5.09–5.18 (*m*, 2 H); 7.20–7.40 (*m*, 5 H). ^{13}C-NMR: 13.9 (Me); 22.4 (Me); 24.9 (CH_2); 25.5 (CH_2); 28.0 (3 Me); 31.8 (CH_2); 31.9 (CH_2); 41.6 (CH_2); 46.5 (C); 65.4 (CH); 67.2 (CH_2); 82.8 (C); 128.5 (2 CH); 128.6 (CH); 128.7 (2 CH); 135.3 (C); 149.6 (C); 171.9 (CO); 174.8 (CO). Anal. calc. for $C_{23}H_{33}NO_5$ (403.52): C 68.46, H 8.24, N 3.47; found: C 68.68, H 8.01, N 3.59.

5. *Synthesis of Methoxymethylated Lactams* **15** *and* **16**. LHMDS (3.85 ml, 1M soln. in THF, 3.9 mmol) was added dropwise to a soln. of **13** or **14** (3.5 mmol) in THF at −78° under Ar. The mixture was stirred at −78° for 1 h, then 1.5 equiv. of $MeOCH_2I$ (0.45 ml, 5.25 mmol) was added. The mixture was stirred at −78° for 1 h, and then the reaction was quenched with aq. sat. NH_4Cl soln. (10 ml). The temp. was raised to r.t., and the mixture was extracted with AcOEt (3 × 20 ml). The combined extracts were washed with brine (10 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the residue was purified by FCC (SiO_2; AcOEt/hexanes 30:70).

3-Benzyl 1-tert-*Butyl (2*RS,*3*RS*)-4-(Methoxymethyl)-2,3-dimethyl-5-oxopyrrolidine-1,3-dicarboxylate* (*cis*-**15**). Oil. ^{1}H-NMR: 1.11 (*d*, *J* = 6.6, 3 H); 1.24 (*s*, 3 H); 1.31 (*s*, 9 H); 2.61 (*dd*, *J* = 3.9, 6.5, 1 H); 3.05 (*s*, 3 H); 3.39 (*dd*, *J* = 6.5, 10.0, 1 H); 3.60 (*dd*, *J* = 3.9, 10.0, 1 H); 4.14 (*q*, *J* = 6.6, 1 H); 4.89–5.05 (*m*, 2 H); 7.15–7.20 (*m*, 5 H). ^{13}C-NMR: 15.4 (Me); 18.2 (Me); 27.8 (3 Me); 48.1 (C); 51.3 (CH); 57.8 (CH); 59.1 (Me); 66.8 (CH_2); 68.7 (CH_2); 82.6 (C); 127.9 (2 CH); 128.2 (CH); 128.5 (2 CH); 135.4 (C); 149.5 (C); 171.0 (C); 173.3 (C). Anal. calc. for $C_{21}H_{29}NO_6$ (391.47): C 64.43, H 7.47, N 3.58; found: C 64.25, H 7.69, N 3.61.

3-Benzyl 1-tert-*Butyl (2*RS,*3*SR*)-4-(Methoxymethyl)-2,3-dimethyl-5-oxopyrrolidine-1,3-dicarboxylate* (*trans*-**15**). Oil. ^{1}H-NMR: 1.19 (*d*, *J* = 6.4, 3 H); 1.40 (*s*, 3 H); 1.47 (*s*, 9 H); 2.66 (*dd*, *J* = 5.1, 7.8, 1 H); 3.11 (*s*, 3 H); 3.34 (*dd*, *J* = 7.8, 10.0, 1 H); 3.70–3.80 (*m*, 2 H); 5.07–5.19 (*m*, 2 H); 7.25–7.30 (*m*, 5 H). ^{13}C-NMR: 14.4 (Me); 21.4 (Me); 28.0 (3 Me); 49.9 (C); 52.6 (CH); 58.9 (Me); 60.5 (CH); 66.5 (CH_2); 69.5 (CH_2); 82.9 (C); 128.3 (2 CH); 128.4 (CH); 128.5 (2 CH); 135.2 (C); 150.0 (C); 171.5 (CO); 172.2 (CO). Anal. calc. for $C_{21}H_{29}NO_6$ (391.47): C 64.43, H 7.47, N 3.58; found: C 64.57, H 7.73, N 3.39.

3-Benzyl 1-tert-*Butyl (2*RS,*3*RS*)-4-(Methoxymethyl)-3-methyl-5-oxo-2-pentylpyrrolidine-1,3-dicarboxylate* (*cis*-**16**). Oil. ^{1}H-NMR: 0.70–0.90 (*m*, 3 H); 1.10–1.80 (*m*, 20 H); 2.72–2.76 (*m*, 1 H); 3.16 (*s*, 3 H); 3.44 (*dd*, *J* = 6.7, 10.2, 1 H); 3.70 (*dd*, *J* = 4.1, 10.2, 1 H); 4.17 (*t*, *J* = 6.1, 1 H); 5.05–5.11 (*m*, 2 H); 7.26–7.29 (*m*, 5 H). ^{13}C-NMR: 13.9 (Me); 18.0 (Me); 22.4 (CH_2); 26.1 (CH_2); 27.9 (3 Me); 31.1 (CH_2); 32.0 (CH_2); 49.3 (C); 51.7 (CH); 59.0 (Me); 61.4 (CH); 67.0 (CH_2); 68.9 (CH_2); 82.7 (C); 128.1 (2 CH); 128.3 (CH); 128.6 (2 CH); 135.3 (C); 149.9 (C); 171.6 (CO); 173.6 (CO). Anal. calc. for $C_{25}H_{37}NO_6$ (447.58): C 67.09, H 8.33, N 3.13; found: C 67.38, H 8.24, N 3.02.

3-Benzyl 1-tert-*Butyl (2*RS,*3*SR*)-4-(Methoxymethyl)-3-methyl-5-oxo-2-pentylpyrrolidine-1,3-dicarboxylate* (*trans*-**16**). Oil. ^{1}H-NMR: 0.79–0.84 (*m*, 3 H); 1.00–1.55 (*m*, 11 H); 1.50 (*s*, 9 H); 2.65 (*dd*, *J* = 5.0, 7.6, 1 H); 3.14 (*s*, 3 H); 3.33 (*dd*, *J* = 7.6, 10.0, 1 H); 3.67–3.70 (*m*, 1 H); 3.75 (*dd*, *J* = 5.0, 10.0, 1 H); 5.10–5.19 (*m*, 2 H); 7.25–7.32 (*m*, 5 H). ^{13}C-NMR: 14.0 (Me); 22.4 (CH_2); 23.1 (Me); 26.5 (CH_2); 28.0 (3 Me); 30.6 (CH_2); 32.0 (CH_2); 49.9 (C); 53.4 (CH); 58.9 (Me); 65.0 (CH); 66.6 (CH_2); 69.5 (CH_2); 83.0 (C); 128.4 (2 CH); 128.5 (CH); 128.6 (2 CH); 135.2 (C); 150.3 (C); 171.9 (CO); 172.1 (CO). Anal. calc. for $C_{25}H_{37}NO_6$ (447.58): C 67.09, H 8.33, N 3.13; found: C 67.14, H 8.50, N 3.03.

6. *Synthesis of α-Methylidenebutano-4-lactams* **17** *and* **18**. A soln. of **15** or **16** (5 mmol) and DBU (0.75 ml, 5 mmol) in toluene (30 ml) was heated at reflux for 4 h. After cooling, the solvent was evaporated under reduced pressure, and the residue was purified by FCC (SiO_2; AcOEt/hexanes 30 : 70).

3-Benzyl 1-tert-*Butyl (2*RS,*3*RS*)-2,3-Dimethyl-4-methylidene-5-oxopyrrolidine-1,3-dicarboxylate* (*cis*-**17**). Oil. ^{1}H-NMR: 1.08 (*d*, *J* = 6.6, 3 H); 1.33 (*s*, 3 H); 1.40 (*s*, 9 H); 4.52 (*q*, *J* = 6.6, 1 H); 4.93–5.03 (*m*, 2 H); 5.50 (*s*, 1 H); 6.24 (*s*, 1 H); 7.13–7.22 (*m*, 5 H). ^{13}C-NMR: 16.6 (Me); 17.4 (Me); 27.9 (3 Me); 50.0 (C); 57.5 (CH); 67.3 (CH_2); 82.9 (C); 121.9 (CH_2); 127.6 (2 CH); 128.2 (CH); 128.5 (2 CH); 135.2 (C); 142.9 (C); 149.8 (C); 164.6 (CO); 172.5 (CO). Anal. calc. for $C_{20}H_{25}NO_5$ (359.43): C 66.83, H 7.01, N 3.90; found: C 66.61, H 6.87, N 3.64.

3-Benzyl 1-tert-*Butyl (2*RS,*3*SR*)-2,3-Dimethyl-4-methylidene-5-oxopyrrolidine-1,3-dicarboxylate* (*trans*-**17**). ^{1}H-NMR: 1.06 (*d*, *J* = 6.4, 3 H); 1.14 (*s*, 3 H); 1.45 (*s*, 9 H); 3.90 (*q*, *J* = 6.4, 1 H); 5.09 (*s*, 2 H); 5.67 (*s*, 1 H); 6.27 (*s*, 1 H); 7.15–7.35 (*m*, 5 H). ^{13}C-NMR: 17.0 (Me); 25.4 (Me); 28.0 (3 Me); 50.4 (C); 60.2 (CH); 66.9 (CH_2); 83.2 (C); 122.6 (CH_2); 128.3 (2 CH); 128.4 (CH); 128.6 (2 CH); 135.1 (C); 142.5 (C); 150.1 (C); 164.8 (CO); 171.2 (CO). Anal. calc. for $C_{20}H_{25}NO_5$ (359.43): C 66.83, H 7.01, N 3.90; found: C 66.94, H 7.20, N 4.06.

3-Benzyl 1-tert-*Butyl (2*RS,*3*RS*)-3-Methyl-4-methylidene-5-oxo-2-pentylpyrrolidine-1,3-dicarboxylate* (*cis*-**18**). Oil. ^{1}H-NMR: 0.83 (*t*, *J* = 6.5, 3 H); 1.12–1.76 (*m*, 11 H); 1.46 (*s*, 9 H); 4.55 (*t*, *J* = 5.7, 1 H); 5.06 (*s*, 2 H); 5.53 (*s*, 1 H); 6.30 (*s*, 1 H); 7.21–7.31 (*m*, 5 H). ^{13}C-NMR: 13.9 (Me); 17.4 (Me); 22.4 (CH_2); 25.2 (CH_2); 27.9 (3 Me); 31.6 (CH_2); 31.9 (CH_2); 50.7 (C); 61.0 (CH); 67.5 (CH_2); 83.0 (C); 121.1 (CH_2); 127.7 (2 CH); 128.3 (CH); 128.6 (2 CH); 135.2 (C); 143.5 (C); 150.1 (C); 165.1 (CO); 172.8 (CO). Anal. calc. for $C_{24}H_{33}NO_5$ (415.53): C 69.37, H 8.00, N 3.37; found: C 69.26, H 7.73, N 3.16.

3-Benzyl 1-tert-*Butyl (2*RS,*3*SR*)-3-Methyl-4-methylidene-5-oxo-2-pentylpyrrolidine-1,3-dicarboxylate* (*trans*-**18**). Oil. ^{1}H-NMR: 0.79 (*t*, *J* = 6.7, 3 H); 0.99–1.54 (*m*, 8 H); 1.49 (*s*, 3 H); 1.51 (*s*, 9 H); 3.99 (*t*, *J* = 5.5, 1 H); 5.17 (*s*, 2 H); 5.76 (*s*, 1 H); 6.32 (*s*, 1 H); 7.33 (*s*, 5 H). ^{13}C-NMR: 13.9 (Me); 22.3 (CH_2); 24.6 (CH_2); 27.3 (Me); 28.0 (3 Me); 31.7 (CH_2); 32.4 (CH_2); 50.5 (C); 64.1 (CH); 67.1 (CH_2); 83.3 (C); 122.5 (CH_2); 128.5 (2 CH); 128.6 (CH); 128.7 (2 CH); 135.0 (C); 143.0 (C); 150.4 (C); 165.1 (CO); 171.5 (CO). Anal. calc. for $C_{24}H_{33}NO_5$ (415.53): C 69.37, H 8.00, N 3.37; found: C 69.51, H 7.82, N 3.60.

7. N-*Boc Deprotection. Synthesis of the* N-*Unsubstituted Lactams* **4** *and* **5**. A soln. of **17** or **18** (2.8 mmol) and TFA (2 ml) in CH_2Cl_2 (15 ml) was stirred at r.t. for 45 min. Elimination of the solvents under vacuum furnished **4** or **5**. Compounds *trans*-**4** and *trans*-**5** were recrystallized from Et_2O/hexane.

*Benzyl (2*Rs,*3*RS*)-2,3-Dimethyl-4-methylidene-5-oxopyrrolidine-3-carboxylate* (*cis*-**4**). Oil. ^{1}H-NMR: 1.12 (*d*, *J* = 6.4, 3 H); 1.33 (*s*, 3 H); 4.25 (*q*, *J* = 6.4, 1 H); 5.03 (*s*, 2 H); 5.56 (*s*, 1 H); 6.11 (*s*, 1 H); 7.15–7.35 (*m*, 5 H); 8.38 (br. *s*, 1 H). ^{13}C-NMR: 16.5 (Me); 19.5 (Me); 51.4 (C); 54.3 (CH); 67.3 (CH_2); 119.6 (CH_2); 127.9 (2 CH); 128.3 (CH); 128.6 (2 CH); 135.5 (C); 143.9 (C); 169.8 (CO); 172.6 (CO). Anal. calc. for $C_{15}H_{17}NO_3$ (259.31): C 69.48, H 6.61, N 5.40; found: C 69.59, H 6.57, N 5.29.

*Benzyl (2*RS,*3*SR*)-2,3-Dimethyl-4-methylidene-5-oxopyrrolidine-3-carboxylate* (*trans*-**4**). White solid. M.p. 124–125°. ^{1}H-NMR: 1.10 (*d*, *J* = 6.4, 3 H); 1.46 (*s*, 3 H); 3.53 (*q*, *J* = 6.4, 1 H); 5.11 (*s*, 2 H); 5.31 (*s*, 1 H); 6.01 (*s*, 1 H); 7.10–7.35 (*m*, 5 H); 7.91 (br. *s*, 1 H). ^{13}C-NMR: 16.7 (Me); 22.6 (Me); 52.6 (C); 57.4 (CH); 66.7 (CH_2); 116.9 (CH_2); 128.0 (2 CH); 128.2 (CH); 128.5 (2 CH); 135.4 (C); 145.1 (C); 169.7

(CO); 172.0 (CO). Anal. calc. for $C_{15}H_{17}NO$ (259.31): C 69.48, H 6.61, N 5.40; found: C 69.48, H 6.84, N 5.12.

*Benzyl (2*RS,*3*RS*)-3-Methyl-4-methylidene-5-oxo-2-pentylpyrrolidine-3-carboxylate* (*cis*-**5**). Oil. ^{1}H-NMR: 0.80–0.94 (*m*, 3 H); 1.15–1.70 (*m*, 8 H); 1.42 (*s*, 3 H); 4.08–4.19 (*m*, 1 H); 5.18 (*s*, 2 H); 5.64 (*s*, 1 H); 6.17 (*s*, 1 H); 7.20–7.40 (*m*, 5 H); 8.47 (br. *s*, 1 H). ^{13}C-NMR: 13.3 (Me); 19.3 (Me); 21.8 (CH_2); 25.4 (CH_2); 30.3 (CH_2); 31.0 (CH_2); 51.0 (C); 58.9 (CH); 67.2 (CH_2); 119.9 (CH_2); 127.6 (2 CH); 128.1 (CH); 128.2 (2 × CH); 134.7 (C); 143.1 (C); 170.1 (CO); 172.0 (CO). Anal. calc. for $C_{19}H_{25}NO_3$ (315.42): C 72.35, H 7.99, N 4.44, found: C 72.20, H 8.15, N 4.57.

*Benzyl (2*RS,*3*SR*)-3-Methyl-4-methylidene-5-oxo-2-pentylpyrrolidine-3-carboxylate* (*trans*-**5**). White solid. M.p. 65–66°. ^{1}H-NMR: 0.86 (*t*, *J* = 6.0, 3 H); 1.10–1.60 (*m*, 8 H); 1.51 (*s*, 3 H); 3.40–3.54 (*m*, 1 H); 5.16 (*s*, 2 H); 5.52 (*s*, 1 H); 6.16 (*s*, 1 H); 7.25–7.40 (*m*, 5 H); 8.33 (br. *s*, 1 H). ^{13}C-NMR: 13.9 (Me); 22.3 (CH_2); 22.9 (Me); 26.3 (CH_2); 31.3 (CH_2); 31.5 (CH_2); 51.7 (C); 62.4 (CH); 66.8 (CH_2); 116.9 (CH_2); 128.2 (2 CH); 128.3 (CH); 128.5 (2 CH); 134.6 (C); 143.6 (C); 170.9 (CO); 171.0 (CO). Anal. calc. for $C_{19}H_{25}NO_3$ (315.42): C 72.35, H 7.99, N 4.44, found: C 72.49, H 8.14, N 4.67.

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