12. Approaches to the Synthesis of Cytochalasans

Part 9[1])

A Versatile Concept Leading to All Structural Types of Cytochalasans

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(20.XI.89)

Starting from D-glutamic acid (**5**), the bicyclic compounds **4a** and **4b** were synthesized *via* **17** *(Schemes 1* and *2)*. The reaction leading to **4g** and **4h** with $LiCuPh_2$ was not successful. But treatment of the *N*-protected model lactams **19**, **21**, and **22** with $Li_2Cu(CN)Ph_2$ gave the amino ketones **24**, **26**, and **27**, respectively *(Scheme 3)*. The desired compound **23** was obtained from **20**. Conversion of the unprotected lactams **28**, **31**, and **32** gave the phenyl derivative **34** in excellent yields. Ester **35** was transformed to the α-amino-γ-oxo-acid derivative **36**. This conversion opens a novel access to this type of compounds.

Introduction. – The cytochalasans are a class of secondary microbial metabolites which exhibit a variety of interesting biological activities, *e.g.* against cancer cells. They also have become important tools in cell biology [2]. Their structures are characterized by a bicyclic hydrogenated isoindolinone moiety, and 11- to 14-membered macrocyclic ring that is fused to the bicyclic system, and by a variety of functional groups. The unique biological activities and the unusual structures represent an exciting and difficult challenge for chemical synthesis. As a result, several total syntheses have been carried out in the past few years [3]. We now wish to report a novel efficient approach to the total synthesis. It should allow the use of the same bicyclic moiety **4** for the construction of all types of cytochalasans. Attachment of suitable substituents at C(10), transformation of several functional groups, and connection with a subunit to produce the macrocyclic moiety would complete the synthesis.

To test this concept, cytochalasin B (**1**) was chosen as target molecule because we have already synthesized the subunit **2** which provides the macrocyclic moiety of the natural product [4] *(Scheme 1)*. We now describe the syntheses of **4a** and **4b** and reactions on model compounds establishing the best conditions for the introduction of a phenyl group at C(10), necessary for the buildup of the intermediate **3**.

Results. – D-Glutamic acid (**5**), which served as starting material, was converted to **6** by heating with H_2O. Treatment of the latter with $SOCl_2$ in MeOH yielded ester **7** in 86% overall yield. Subsequent reduction with $NaBH_4$ in i-PrOH led to alcohol **8** (58% yield). The OH group was protected by silylation with (*tert*-butyl)dimethylsilyl chloride and

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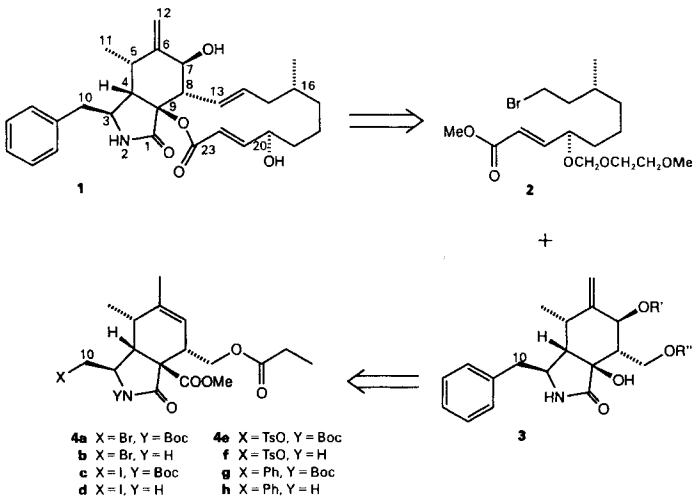
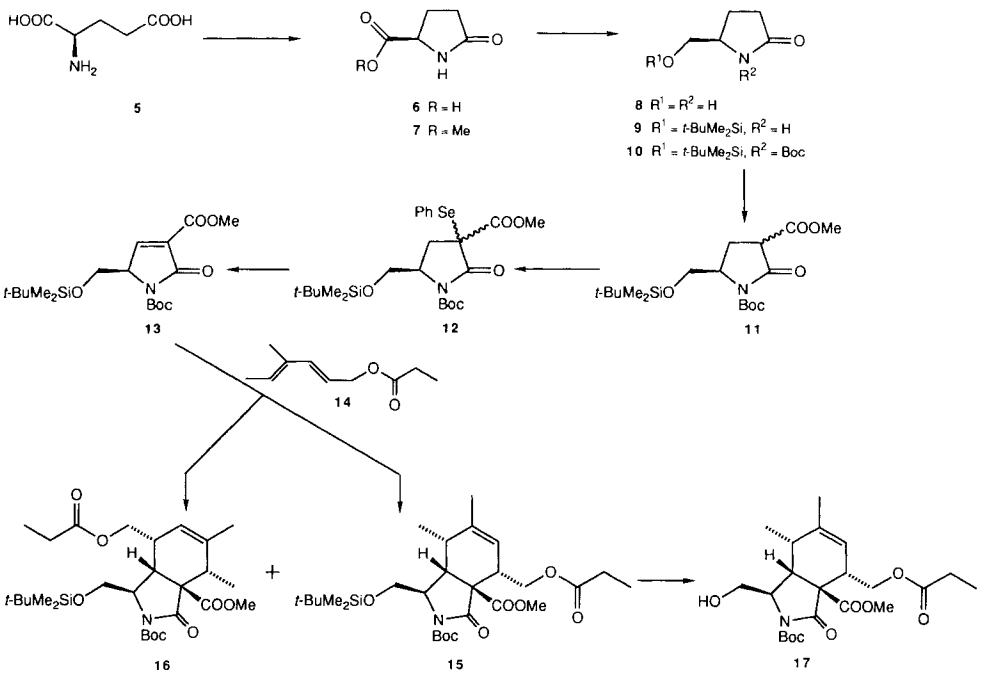
Scheme 1



imidazole in DMF to give **9** (99% yield) and the amide group by treatment with di(*tert*-butyl) dicarbonate (Boc_2O/4-(dimethylamino)pyridine (DMAP)/Et_3N in CH_2Cl_2 leading to **10** (84% yield). The introduction of methoxycarbonyl group into **10** was achieved by twofold deprotonation with lithium hexamethyldisilazide (LHMDS) and BuLi according to *Aebi* and *Seebach* [5] and subsequent treatment with methyl chloroformate, affording **11** in 97% yield. Twofold deprotonation of **11** with LHMDS and BuLi gave compound **12** as a mixture of diastereoisomers (89% yield) upon treatment with benzeneselenenyl chloride. The unsaturated γ-lactam **13** was obtained by reacting **12** with H_2O_2 in CH_2Cl_2 (95% yield). The diene **14** needed for the cycloaddition was prepared by the reaction of (*E,E*)-4-methylhexa-2,4-dien-1-ol [6] with propionic anhydride in the presence of Et_3N and DMAP (96% yield). Intermolecular [2 + 4] cycloaddition of olefin **13** and diene **14** at 140° in *o*-xylene gave the two regioisomers **15** (50%) and **16** (32%). The assignment of their structures and configuration was possible beyond any doubt by ^{1}H-NMR decoupling experiments as previously described in a similar case [7]. The desired isomer **15** was converted to compound **4a** in 40% yield by cleavage of the silyl ether with TsOH in MeOH (→**17**), followed by bromination with CBr_4/Ph_3P in CH_2Cl_2. Removal of the carbamate group with CF_3COOH in CH_2Cl_2 yielded **4b** in excellent yield (91%).

The next problem to be solved was the introduction of a Ph group at C(10). We first used lithium diphenylcuprate ($LiCuPh_2$) as nucleophile because of its high reactivity in displacement reactions at C-centers [8] and its relatively low reactivity towards esters. This cuprate has been successfully applied in the synthesis of Ph-substituted prolines [9] and Ph-substituted amino-acid derivatives [10]. However, all our attempts to prepare **4g** or **4h** from **4a** or **4b**, respectively, failed; only polar by-products could be isolated. We, therefore, changed the nucleophile using the higher-order dilithium diphenylcyanocuprate ($Li_2Cu(CN)Ph_2$). This cuprate is known to be more reactive, can be prepared

Scheme 2



more easily than $LiCuPh_2$, and allows to carry out substitution reactions under extremely mild conditions and with very high yields [11][12].

In order to optimize the reaction conditions and to establish the most suitable leaving group for the nucleophilic substitution, we first treated the Boc-protected γ-lactams **19**–**22** with $Li_2Cu(CN)Ph_2$. These model compounds were obtained from the fully protected lactam derivative **10** by treatment with TsOH in MeOH (→**18**; 57% yield), followed by bromination with CBr_4/Ph_3P in CH_2Cl_2 (→**19**; 95%), NaI treatment in acetone (**20**; 78% from **19**), tosylation (→**21**; 77% from **18**) and mesylation (→**22**; 97% from **18**). We later found that **19**–**22** could be prepared in higher yields from the unprotected lactams **28** and **31**–**33** (see below) by introduction of the Boc group in the last step. The reaction of compounds **19**–**22** with $Li_2Cu(CN)Ph_2$ in THF gave unexpected results *(cf. Table 1)*. Compounds **19**, **21**, and **22** failed to give the desired Ph-substituted product **23**. Instead, ring opening occurred[2]), yielding ketones **24**, **26**, and **27** in 15–38% yield. To our surprise, the iodo derivative **20** reacted differently. Upon treatment with $Li_2Cu(CN)Ph_2$, only traces (< 1% yield) of ketone **25** but satisfactory amounts (56% yield) of the desired Ph-substituted product **23** were obtained. This difference can be explained by the enhanced reactivity of the leaving group X [11][12], suppressing the competitive attack of the cuprate at the lactam carbonyl group.

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[2]) Recently, analogous ring-opening reactions of Boc-protected γ-lactams using *Grignard* reagents were reported [13–15].

Scheme 3

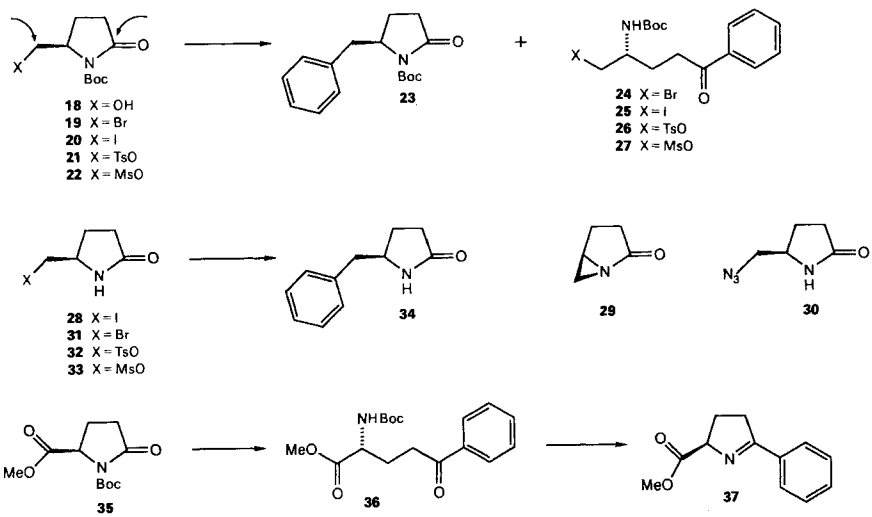

Table 1. *Reactivity of* **19–22** *towards* $Li_2Cu(CN)Ph_2$

Starting material	**19**	**20**	**21**	**22**
Substitution	0%	56%	0%	0%
Ring opening	38%	< 1%	30%	15%

In the course of our investigations, *Knapp* and *Levorse* reported [16] that the nucleophilic substitution of the I-atom in 5-(iodomethyl)pyrrolidin-2-one (**28**) with NaN_3 could greatly be accelerated by adding catalytical amounts of NaH prior to NaN_3. They concluded that NaH promoted ring closure of **28** to intermediary aziridine **29** which was subsequently opened by NaN_3 yielding azidolactam **30**. These findings prompted us to investigate whether a conversion of 5-substituted *N*-non-protected γ-lactams such as **28** and **31–33** with $Li_2Cu(CN)Ph_2$ could be achieved as well. These model compounds were obtained from the unprotected hydroxylactam **8** in the same way as **19–22** from **18** (see above and *Exper. Part*). The reaction of the γ-lactams **28** and **31–33** with $Li_2Cu(CN)Ph_2$ was carried out applying three different methods *(cf. Table 2)*. When no NaH was added prior to cuprate *(Method A)*, good-to-excellent yields of **34** were obtained with compounds **28**, **31**, or **32**. The high reactivity of tosylate **32** was unexpected (highest yield (96%) in shortest time), tosylates being usually approximately as reactive as bromides but less reactive than iodides towards higher-order cyanocuprates [11]. On the other hand, only traces of **34** were obtained, when mesylate **33** was treated with $Li_2Cu(CN)Ph_2$, a result in accordance with the findings of *Lipshutz et al.* [11] that mesylates are unsuitable for the reaction with cuprates. Evident acceleration of the reaction by adding 0.2 equiv. *(Method B)* or 1 equiv. *(Method C)* of NaH could only be observed for iodo compound **28**, but in contrast to the observations of *Knapp* and *Levorse* [16], lower yields were

Table 2. *Yields of* **34** *of the Reaction of* **28** *and* **31–33** *with* $Li_2Cu(CN)Ph_2$

Starting material	*Method A*[a])		*Method B*[b])		*Method C*[c])	
	Conditions	Yield [%]	Conditions	Yield [%]	Conditions	Yield [%]
28	6 h, r.t.	80	3 h, r.t.	65	1.5 h, r.t.	54
31	48 h, r.t.	83	24 h, r.t.	62	24 h, r.t.	67
32	4 h, r.t.	96	4 h, r.t.	78	4 h, r.t.	75
33	24 h, r.t.	3	24 h, r.t.	5	24 h, r.t.	3

[a]) 5 Equiv. of $Li_2Cu(CN)Ph_2$.
[b]) 5 Equiv. of $Li_2Cu(CN)Ph_2$, 0.2 equiv. of NaH.
[c]) 5 Equiv. of $Li_2Cu(CN)Ph_2$, 1 equiv. of NaH.

observed in all cases independently whether catalytic or equimolar amounts of NaH were added. All attempts to isolate the potential intermediate aziridine **29** by adding 1 equiv. of NaH but no cuprate failed. Therefore, we were unable to confirm the hypothesis of aziridine formation promoted by NaH on 5-(iodomethyl)pyrrolidin-2-one **28** which was postulated by *Knapp* and *Levorse* [16].

The results of the reaction of the model γ-lactams **19–22** and **28** and **31–33** with $Li_2Cu(CN)Ph_2$ should now enable us to introduce the Ph group at C(10) of **4b**, **4d**, or **4f** (→**4h**) using the conditions for the formation of **34** *(Method A)* or at C(10) of **4c** (→**4g**) using the conditions of the substitution **20**→**23**. Corresponding experiments are in progress.

Finally, we wish to report an application of the ring opening which we have observed in the case of the Boc-protected γ-lactams **19**, **21**, and **22**. If the substituent at C(5) of the pyrrolidinone is changed from CH_2X to COOR, lactam cleavage with a cuprate should yield a γ-oxo-α-amino-acid derivative[3]). Indeed, treatment of compound **35** (obtained from **7**, see *Exper. Part*) with $Li_2Cu(CN)Ph_2$ in THF gave **36** in 42% yield. To determine whether racemization had occurred on lactam cleavage, we conducted ^{1}H-NMR measurements using the chiral shift reagents (+)- or (−)-[Eu(tfc)$_3$]. However, no conclusion could be drawn due to line broadening, even at low concentrations of [Eu(tfc)$_3$]. Therefore, we decided to remove the *N*-protecting group and to convert the amino group into a chiral amide using *Mosher*'s acid chloride [17]. The Boc group was cleaved using CF_3COOH/CH_2Cl_2, but upon workup with weak base (sat. $NaHCO_3$ soln. or Et_3N), ring closure occurred immediately [15], yielding the optical active imine **37**[4]) which is unsuitable for the determination of the enantiomeric purity. At last, an enantiomeric purity (ee) of > 95% was established for **36** by ^{1}H-NMR spectroscopy, after addition of (+)- or (−)-1-(anthracen-9-yl)-2,2,2-trifluoroethanol[5]). Thus, no detectable racemization had taken place on opening of the γ-lactam. By the methodology described, a variety of other

[3]) After completation of our studies, *Nozoe et al.* reported that Boc-protected γ-lactams can be opened by *Grignard* reagents, yielding γ-oxo-α-amino-acid derivatives [13] [14].
[4]) *Mkairi* and *Hamelin* [18] have reported the synthesis of racemic imine **37**.
[5]) We thank Prof. Dr. *H. Fritz* and Dr. *M. Keller, Ciba-Geigy AG*, Basel, for conducting these ^{1}H-NMR experiments.

α-amino-γ-oxo-acid derivatives may now be accesible using other cuprates than $Li_2Cu(CN)Ph_2$.

Financial support of these investigations by the *Swiss National Science Foundation* is gratefully acknowledged.

Experimental Part

General. Water- and air-sensitive reactions were carried out under Ar. THF was freshly distilled over Na-K alloy; i-PrOH was distilled over Mg and stored over molecular sieves (4 Å); acetone was dried by distilling over B_2O_3 [19]; CH_2Cl_2, DMF, MeOH, *o*-xylene (all abs. grade), and CuCN were used as received. PhLi (*ca.* 2M in cyclohexane/Et_2O 7:3) was purchased from *Fluka* and BuLi (*ca.* 1.6M in hexane) from *Aldrich*. Both were titrated by the method of *Watson* and *Eastham* [20]. All org. extracts were dried (Na_2SO_4) and evaporated below 50°. TLC: silica gel *60 F_{254} (Merck)*. Column chromatography (CC): silica gel (60–200 μm or 35–70 μm, *Chemische Fabrik Uetikon*). M.p.: *Kofler* block; corrected. $[\alpha]_D$: *Perkin-Elmer-141* polarimeter. IR spectra (cm^{-1}): *Perkin-Elmer-781* IR spectrometer. NMR[5]): *Varian-EM-360* (^1H, 60 MHz), *Varian-EM-390* (^1H, 90 MHz), and *Varian-VXR-400* spectrometer (^1H, 400 MHz; ^{13}C, 101 MHz, correlation of the signals by BB and APT experiments); 360-MHz ^1H-NMR were recorded by *Sandoz*, Basel; $CDCl_3$ as solvent; chemical shifts in ppm rel. to internal TMS. MS (*m/z* (%)): *VG-70-250* spectrometer (CI with NH_3), *Hewlett Packard 5790 A/5970 A* (GLC/MS).

Methyl (2R)-5-Oxopyrrolidine-2-carboxylate (**7**) [22]. A soln. of 40.86 g (277.7 mmol) of **5** in H_2O (160 ml) was heated under reflux for 63 h; the solvent was then evaporated at 70°. The residue was dried by dissolving 3 times in 120 ml of abs. MeOH and evaporating at 60°. The colorless **6** was dissolved in 460 ml of abs. MeOH, and 1.30 ml (17.9 mmol) of $SOCl_2$ were added (pH 0). The mixture was stirred at r.t. for 48 h. The pH was corrected to 7 by addition of a sat. $NaHCO_3$ soln. The solvent was evaporated and the residue dried by dissolving it in 50 ml of abs. MeOH and evaporating at 40°. The residue was extracted with hot CH_2Cl_2 (3 × 200 ml). Removal of the solvent afforded 34.30 g (86%) of **7** as colorless oil that was pure on TLC. $[\alpha]_D^{20} = -8.7$ (*c* = 1.13, EtOH). IR ($CHCl_3$): 3440 (NH), 1740 (C=O, ester), 1700 (C=O, lactam). ^1H-NMR (90 MHz): 2.15–2.60 (*m*, $CH_2(3)$, $CH_2(4)$); 3.75 (*s*, MeO); 4.20–4.35 (*m*, H–C(2)); 7.20 (br. *s*, NH).

(5R)-5-(Hydroxymethyl)pyrrolidin-2-one (**8**). To a soln. of 5.02 g (35.1 mmol) of **7** in 50 ml of abs. i-PrOH, 2.70 g (71.4 mmol) of $NaBH_4$ were added. After 20 h at r.t., AcOH (13 ml) was slowly added and the mixture stirred for 1 h. Then, H_2O (9 ml) was added and the mixture stirred for 1 h at r.t. The pH value was adjusted to 7 by adding 2N NaOH, and the solvents were evaporated at 70°. The residue was extracted with hot AcOEt (6 × 100 ml) and after evaporation a colorless solid was obtained. Recrystallization from acetone yielded 2.33 g (58%) of **8** as colorless crystals. M.p. 85.5–87.5° (after 3 recrystallizations from acetone). $[\alpha]_D^{20} = -30.9$ (*c* = 1.10, EtOH) ([23]: $[\alpha]_D = +29$ (*c* = 5, EtOH) for enantiomer). IR ($CHCl_3$): 3440, 3350 (NH, OH), 1690 (C=O). ^1H-NMR (90 MHz): 1.70–2.45 (*m*, $CH_2(3)$, $CH_2(4)$); 3.30–3.90 (*m*, H–C(5), CH_2–C(5)); 4.25 (*s*, OH); 7.30 (br. *s*, NH).

(5R)-5-{[(tert-Butyl)dimethylsilyloxy]methyl}pyrrolidin-2-one (**9**). To a soln. of 8.37 g (72.7 mmol) of **8** and 12.4 g (182 mmol) of imidazole in 20 ml of DMF, 13.2 g (87.6 mmol) of (*tert*-butyl)dimethylsilyl chloride were added. After 24 h at r.t., 200 ml of Et_2O were added. The soln. was washed with H_2O and brine, dried, and evaporated at r.t. CC (AcOEt) yielded 16.49 g (99%) of **9** as a pale yellow oil. $[\alpha]_D^{20} = -4.3$ (*c* = 2.14, EtOH). IR (film): 3230 (NH), 1700 (C=O). ^1H-NMR (60 MHz): 0.0 (*s*, Me_2Si); 0.85 (*s*, *t*-BuSi); 1.45–2.50 (*m*,$CH_2(3)$, $CH_2(4)$); 3.35–3.90 (*m*, H–C(5), CH_2–C(5)); 6.30 (br. *s*, NH).

tert-*Butyl (2R)-2-{[(tert-Butyl)dimethylsilyloxy]methyl}-5-oxopyrrolidine-1-carboxylate* (**10**). To a soln. of 16.5 g (71.9 mmol) of **9** in 90 ml of CH_2Cl_2, 31.57 g (144.7 mmol) of $(Boc)_2O$, 8.84 g (72.4 mmol) of DMAP, and 10.3 ml (73.9 mmol) of Et_3N were added at r.t. After 24 h at r.t., 200 ml of Et_2O were added, and the mixture was washed with 10% citric acid, sat. $NaHCO_3$ soln. and brine, dried, and evaporated at r.t. CC (CH_2Cl_2/AcOEt 15:1) yielded 19.80 g (84%) of **10** as a yellow oil. $[\alpha]_D^{20} = +58.6$ (*c* = 1.03, $CHCl_3$) ([24]: $[\alpha]_D = -61$ (*c* = 1.1, $CHCl_3$) for enantiomer). IR (film): 1760 (C=O, Boc), 1720 (C=O, lactam). ^1H-NMR (60 MHz): 0.0 (*s*, Me_2Si); 0.90 (*s*, *t*-BuSi); 1.50 (*s*, *t*-BuO); 1.70–2.80 (*m*, $CH_2(3)$, $CH_2(4)$); 3.50–4.20 (*m*, H–C(2), CH_2–C(2)).

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[5]) Although cytochalasin nomenclature [21] was used in the *General Part* for all bicyclic compounds and for cytochalasin B, numbering according to IUPAC nomenclature is used for the NMR spectra.

*1-(*tert*-Butyl) 3-Methyl (5* R*)-5-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-2-oxopyrrolidine-1,3-dicarboxylate* (**11**). A soln. of 6.63 ml (31.8 mmol) of hexamethyldisilazane (HMDS) in 40 ml of abs. THF was cooled to −78°, then 19.4 ml (31.8 mmol) of BuLi (1.64 M) were added. After 5 min, a soln. of 9.50 g (28.8 mmol) of **10** in 15 ml of abs. THF was added dropwise and the mixture stirred for 50 min, followed by addition of 18.3 ml (30.0 mmol) of BuLi (1.64 M). The mixture was stirred for 10 min, then 9.4 ml (122 mmol) of $ClCOOCH_3$ were added. After 30 min, the mixture was diluted with 300 ml of Et_2O, washed with 10% citric acid, sat. $NaHCO_3$ soln. and brine, dried, and evaporated to yield 10.83 g (97%) of **11** as a yellow oil that was pure according to TLC and ^{1}H-NMR. IR (film): 1765 (C=O, Boc), 1740 (C=O, ester), 1720 (C=O, lactam). ^{1}H-NMR (60 MHz): 0.0 (*s*, Me_2Si); 0.85 (*s*, *t*-BuSi); 1.45 (*s*, *t*-BuO); 2.00–2.85 (*m*, CH_2(4)); 3.30–4.40 (*m*, H–C(3), H–C(5), CH_2–C(5)); 3.70 (*s*, MeO).

*1-(*tert*-Butyl) 3-Methyl (5*R*)-5-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-2-oxo-3-(phenylseleno)pyrrolidine-1,3-dicarboxylate* (**12**). A soln. of 6.41 ml (30.7 mmol) of HMDS in 30 ml of abs. THF was cooled to −78°, then 18.9 ml (30.8 mmol) of BuLi (1.63 M) were added. After 5 min, a soln. of 10.77 g (27.8 mmol) of **11** in 15 ml of abs. THF was added dropwise and the mixture stirred for 50 min, followed by addition of 18.0 ml (29.4 mmol) of BuLi (1.63 M). The mixture was stirred for 10 min, then 14.90 g (77.8 mmol) of PhSeCl in 30 ml of abs. THF were added. After 4 h, the mixture was diluted with 300 ml of Et_2O, washed with 10% citric acid, sat. $NaHCO_3$ soln. and brine, dried, and evaporated. The crude product was purified by CC (pentane/AcOEt 4:1): 13.44 g (89%) of **12** (red oil) as a mixture of the two diastereoisomers. ^{1}H-NMR (60 MHz): 0.0 (*s*, Me_2Si); 0.80 (*s*, *t*-BuSi); 1.50 (*s*, *t*-BuO); 1.80–3.70 (*m*, CH_2(4), H–C(5), CH_2–C(5)); 3.65 (*s*, MeO); 7.00–7.80 (*m*, 5 arom. H).

*1-(*tert*-Butyl) 3-Methyl (5*R*)-5-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-2,5-dihydro-2-oxo-1*H*-pyrrole-1,3-dicarboxylate* (**13**). To a soln. of 3.00 g (5.53 mmol) of **12** in 40 ml of CH_2Cl_2, 3 ml (14 mmol) of H_2O_2 (15%) were added at 0°. The mixture was stirred vigorously for 10 min, diluted with 150 ml of Et_2O, washed with H_2O and brine, dried, and evaporated at r.t. to yield 2.03 g (95%) of **13** as a colorless oil which was pure (TLC, ^{1}H-NMR). It was immediately used for the preparation of **15** and **16**. ^{1}H-NMR (60 MHz): 0.0 (*s*, Me_2Si); 0.80 (*s*, *t*-BuSi); 1.50 (*s*, *t*-BuO); 3.80 (*s*, MeO); 3.60–4.70 (*m*, H–C(5), CH_2–C(5)); 7.90 (*d*, *J* = 2, H–C(4)).

*(2*E*,4*E*)-4-Methylhexa-2,4-dienyl Propionate* (**14**). To a soln. of 4.50 g (40.1 mmol) of (2*E*,4*E*)-4-methylhexa-2,4-dien-1-ol [6] in 20 ml of Et_2O, 6.7 ml (48 mmol) of Et_3N and 100 mg (0.82 mmol) of DMAP were added. The mixture was cooled to 0°, followed by dropwise addition of 6.2 ml (48 mmol) of propionic anhydride. After 40 min, the mixture was diluted with 200 ml of Et_2O, washed with 10% citric acid, H_2O, sat. $NaHCO_3$ soln. and brine, dried, and evaporated. The crude product was purified by CC (petroleum ether/AcOEt 4:1): 6.50 g (96%) of **14** as a colorless oil. ^{1}H-NMR (60 MHz): 1.10 (*t*, *J* = 7, CH_3CH_2COO); 1.70 (*d*, *J* = 4, CH_3(6)); 1.75 (*s*, CH_3–C(4)); 2.35 (*q*, *J* = 7, CH_3CH_2COO); 4.65 (*d*, *J* = 7, CH_2(1)); 5.35–5.95 (*m*, H–C(2), H–C(5)); 6.35 (*d*, *J* = 15, H–C(3)).

*2-(*tert*-Butyl) 3a-Methyl (1*R*,3a*S*,4*S*,7*S*,7a*R*)-1-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-2,3,3a,4,7,7a-hexahydro-6,7-dimethyl-3-oxo-4[(propanoyloxy)methyl]-1*H*-isoindole-2,3a-dicarboxylate* (**15**) *and 2-(*tert*-Butyl) 3a-Methyl (1*R*,3a*R*,4*S*,7*R*,7a*R*)-1-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-2,3,3a,4,7,7a-hexahydro-4,5-dimethyl-3-oxo-7-[(propanoyloxy)methyl]-1*H*-isoindole-2,3a-dicarboxylate* (**16**). To a soln. of 2.03 g (5.27 mmol) of **13** in 30 ml of *o*-xylene, 2.93 g (17.4 mmol) of **14** were added. The mixture was heated at 150° for 100 min, then the solvent evaporated, and the residue purified by CC (petroleum ether/Et_2O 2:1): 1.46 g (50%) of **15** and 0.93 g (32%) of **16** as colorless oils.

15: $[\alpha]_D^{20} = +48.3$ (*c* = 1.03, EtOH). IR (film): 1790, 1740, 1720. ^{1}H-NMR (360 MHz): 0.0 (*s*, Me_2Si); 0.85 (*s*, *t*-BuSi); 1.09 (*t*, *J* = 7, CH_3CH_2COO); 1.18 (*d*, *J* = 7, Me–C(7)); 1.47 (*s*, *t*-BuO); 1.73 (*s*, Me–C(6)); 2.27 (*q*, *J* = 7, CH_3CH_2COO); 2.49 (*m*, H–C(7)); 2.71 (*dd*, *J* = 5, 3, H–C(7a)); 2.92 (*m*, H–C(4)); 3.61–3.66 (*m*, H–C(1), CH_2–C(1)); 3.75 (*s*, MeO); 4.47 (*d*, *J* = 7, CH_2–C(4)); 5.46 (*s*, H–C(5)). CI-MS: 554 (1, $[M + H]^+$), 454 (100), 396 (8), 380 (38), 322 (23).

16: $[\alpha]_D^{20} = +78.2$ (*c* = 1.09, EtOH). IR (film): 1790, 1745, 1720. ^{1}H-NMR (360 MHz): 0.0 (*s*, Me_2Si); 0.85 (*s*, *t*-BuSi); 1.12 (*t*, *J* = 7, CH_3CH_2COO); 1.30 (*d*, *J* = 7, Me–C(4)); 1.46 (*s*, *t*-BuO); 1.70 (*s*, CH_3–C(5)); 2.32 (*q*, *J* = 7, CH_3CH_2COO); 2.59 (*m*, H–C(7)); 2.85 (*q*, *J* = 7, H–C(4)); 2.91 (*dd*, *J* = 5, 3, H–C(7a)); 3.58–3.70 (*m*, H–C(1), CH_2–C(1)); 3.74 (*s*, MeO); 4.17 (*dd*, *J* = 11, 7, 1 H, CH_2–C(7)); 4.25 (*dd*, *J* = 11, 8, 1 H, CH_2–C(7)); 5.52 (*s*, H–C(6)). CI-MS: 554 (1, $[M + H]^+$), 454 (100), 396 (10), 380 (4), 322 (5).

*2-(*tert*-Butyl) 3a-Methyl (1*R*,3a*S*,4*S*,7*S*,7a*R*)-1-(Bromomethyl)-2,3,3a,4,7,7a-hexahydro-6,7-dimethyl-3-oxo-4-[(propanoyloxy)methyl]-1*H*-isoindole-2,3a-dicarboxylate* (**4a**). To a soln. of 969 mg (1.75 mmol) of **15** in 20 ml of MeOH, 47 mg (0.25 mmol) of TsOH were added. The mixture was stirred for 8 h at r.t., diluted with 200 ml of Et_2O, washed with sat. $NaHCO_3$ soln. and H_2O, dried, and evaporated. To the crude **17** in 20 ml of CH_2Cl_2, 925 mg (3.53 mmol) of Ph_3P and 1171 mg (3.53 mmol) of CBr_4 were added. The mixture was stirred for 30 min at r.t., diluted with Et_2O, washed with H_2O and brine, dried, and evaporated. After CC (pentane/Et_2O 1:1), 353 mg (40%) of **4a** were obtained as colorless oil. IR (film): 1790, 1740. ^{1}H-NMR (400 MHz): 1.12 (*t*, *J* = 7, CH_3CH_2COO); 1.27 (*d*, *J* = 7, Me–C(7)); 1.53 (*s*, *t*-BuO); 1.76 (*s*, Me–C(6)); 2.30 (*q*, *J* = 7, CH_3CH_2COO); 2.56 (*m*, H–C(7));

2.68 (*dd*, J = 5, 3, H–C(7a)); 2.97 (*m*, H–C(4)); 3.47, 3.76 (2*m*, H–C(1), CH_2–C(1)); 3.81 (*s*, MeO); 4.51 (*m*, CH_2–C(4)); 5.50 (*s*, H–C(5)). CI-MS: 521, 519 (7, $[M + NH_4]^+$); 421, 419 (27); 404, 402 (100); 324 (30); 250 (15).

*Methyl (1*R*,3a*S*,4*S*,7*S*,7a*S*)-1-(Bromomethyl)-2,3,3a,4,7,7a-hexahydro-6,7-dimethyl-3-oxo-4-[(propanoyloxy)methyl]-1*H*-isoindole-3a-carboxylate* (**4b**). A soln. of 219 mg (0.43 mmol) of **4a** in 8 ml CH_2Cl_2 was treated with 0.20 ml (2.6 mmol) of CF_3COOH and stirred at r.t. for 35 min. The soln. was diluted with Et_2O, washed with sat. $NaHCO_3$ soln., H_2O and brine, dried, and evaporated. After CC (petroleum ether/AcOEt 1:1), 160 mg (91%) of **4b** were obtained. ^{1}H-NMR (60 MHz): 0.85–1.20 (*m*, Me–C(7), CH_3CH_2COO); 1.75 (*s*, Me–C(6)); 2.10–3.10 (*m*, CH_3CH_2COO, H–C(7a), H–C(4), H–C(7)); 3.20–3.60 (*m*, H–C(1), CH_2–C(1)); 3.75 (*s*, MeO); 4.25–4.45 (*m*, CH_2–C(4)); 5.45 (*s*, H–C(5)); 6.70 (*s*, NH).

tert-*Butyl (2*R*)-2-(Hydroxymethyl)-5-oxopyrrolidine-1-carboxylate* (**18**). To a soln. of 5.01 g (15.20 mmol) of **10** in 130 ml of abs. MeOH, 271 mg (1.42 mmol) of TsOH were added. The mixture was stirred at r.t. for 6 h, treated with 150 ml of 8% $NaHCO_3$ soln., extracted with CH_2Cl_2 (4 × 200 ml), dried, and evaporated. After CC (AcOEt/pentane 3:1), 1.88 g (57%) of crude **18** (colorless solid) was obtained that was used without further purification. IR (KBr): 3440 (OH), 1780 (C=O, Boc), 1690 (C=O, lactam). ^{1}H-NMR (90 MHz): 1.55 (*s*, *t*-BuO); 1.95–2.95 (*m*, CH_2(3), CH_2(4)); 3.25 (*s*, OH); 3.60–3.95 (*m*, CH_2–C(2)); 4.10–4.30 (*m*, H–C(2)).

tert-*Butyl (2*R*)-2-(Bromomethyl)-5-oxopyrrolidine-1-carboxylate* (**19**). To a soln. of 1.13 g (5.25 mmol) of **18** in 80 ml of abs. CH_2Cl_2, 4.84 g (18.5 mmol) of Ph_3P and 6.09 g (18.4 mmol) of CBr_4 were added. After 1 h at r.t., 400 ml of Et_2O were added, the org. layer was washed with H_2O and brine, dried, and evaporated at r.t. CC (pentane/AcOEt 3:1) yielded 1.39 g (95%) of **19** which crystallized spontaneously. An anal. sample was recrystallized from Et_2O/pentane. M.p. 66–67°. $[\alpha]_D^{20}$ = +71.8 (c = 1.50, EtOH). IR (CCl_4): 1760 (C=O, Boc), 1715 (C=O, lactam). ^{1}H-NMR (400 MHz): 1.55 (*s*, *t*-BuO); 2.02–2.09 (*m*, H–C(3)); 2.16–2.27 (*m*, H–C(3)); 2.42–2.50 (*m*, H–C(4)); 2.67–2.76 (*m*, H–C(4)); 3.59–3.67 (*m*, CH_2–C(2)); 4.39–4.44 (*m*, H–C(2)). CI-MS: 297, 295 (2, $[M + NH_4]^+$); 197, 195 (56); 180, 178 (100). Anal. calc. for $C_{10}H_{16}BrNO_3$ (278.15): C 43.18, H 5.80, N 5.04; found: C 43.09, H 6.13, N 5.00.

tert-*Butyl (2*R*)-2-(Iodomethyl)-5-oxopyrrolidine-1-carboxylate* (**20**). To a soln. of 2.154 g (14.37 mmol) of NaI in 10 ml of abs. acetone, 200 mg (0.72 mmol) of **19** were added. The mixture was heated under reflux for 2 h, then 60 ml of H_2O (containing 1 crystal of $Na_2S_2O_3$) were added. The product was extracted with CH_2Cl_2 (3 × 50 ml), dried, and evaporated at r.t. Recrystallization from pentane yielded 182 mg (78%) of **20**. M.p. 78–80°. $[\alpha]_D^{20}$ = +68.4 (c = 1.14, EtOH). IR (KBr): 1740 (C=O, Boc), 1720 (C=O, lactam). ^{1}H-NMR (90 MHz): 1.50 (*s*, *t*-BuO); 1.95–2.95 (*m*, CH_2(3), CH_2(4)); 3.30–3.55 (*m*, CH_2–C(2)); 4.15–4.35 (*m*, H–C(2)). FAB-MS: 326 (22, $[M + H]^+$), 270 (100), 226 (14), 57 (72).

tert-*Butyl (2*R*)-2-{[(4-Methylphenyl)sulfonyloxy]methyl}-2-oxopyrrolidine-1-carboxylate* (**21**). A soln. of 200 mg (0.93 mmol) of **18** in 1 ml of abs. pyridine was treated with 276 mg (1.45 mmol) of TsCl. After 2.5 h at r.t., 5 ml of H_2O were added, and the soln. was stirred for 5 min. Then, 50 ml of CH_2Cl_2 were added, and the org. layer was washed with 10% citric acid and 8% $NaHCO_3$ soln. The org. layer was dried and evaporated to yield a colorless oil that was purified by CC (AcOEt/pentane 1:1): 263 mg (77%) of **21** as colorless solid. An anal. sample was recrystallized from CH_2Cl_2/pentane. M.p. 104.5–105.5°. $[\alpha]_D^{20}$ = +43.2 (c = 0.93, EtOH). IR (KBr): 1780 (C=O, Boc), 1705 (C=O, lactam). ^{1}H-NMR (90 MHz): 1.45 (*s*, *t*-BuO); 2.00–2.90 (*m*, CH_2(3), CH_2(4)); 2.45 (*s*, Me–C(4')); 4.15–4.35 (*m*, H–C(2), CH_2–C(2)); 7.35 (*d*, J = 8, 2 arom.H); 7.80 (*d*, J = 8, 2 arom. H). FAB-MS: 370 (5, $M + H]^+$), 314 (65), 270 (100), 98 (65), 57 (81).

tert-*Butyl (2*R*)-2-[(Methylsulfonyloxy)methyl]-2-oxopyrrolidine-1-carboxylate* (**22**). To a soln. of 758 mg (3.52 mmol) of **18** in 50 ml of abs. CH_2Cl_2, 1.39 ml (9.97 mmol) of Et_3N and 0.58 ml (7.46 mmol) of methanesulfonyl chloride (MsCl) were added at 0°. After 1 h, the mixture was quenched with 50 ml of sat. $NaHCO_3$ soln., extracted with CH_2Cl_2 (5 × 100 ml), dried, and evaporated. After CC (AcOEt/pentane 2:1), 1.00 g (97%) of **22** were obtained as a colorless oil that solidified upon standing. An anal. sample was recrystallized from AcOEt/pentane. M.p. 80.5–82°. $[\alpha]_D^{20}$ = +64.4 (c = 1.00, EtOH). IR (KBr): 1745 (C=O, Boc), 1710 (C=O, lactam). ^{1}H-NMR (90 MHz): 1.55 (*s*, *t*-BuO); 2.05–2.75 (*m*, CH_2(3), CH_2(4)); 3.05 (*s*, $MeSO_2$); 4.30–4.65 (*m*, H–C(2), CH_2–C(2)). FAB-MS: 294 (9, $[M + H]^+$), 238 (100), 194 (99), 57 (82).

General Procedure for the Reaction of the γ-Lactams **19**–**22** *with* $Li_2Cu(CN)Ph_2$. A suspension of CuCN in 1 ml of abs. THF was cooled to −78°, then PhLi was added. Subsequent warming to 0° for 3 min led to a clear soln. which was recooled to −78°, followed by dropwise addition of 0.18 mmol of **19**, **20**, **21**, or **22** in 1.5 ml of THF. The mixture was stirred at −78°, warmed to r.t., and quenched by either adding 5 ml of sat. NH_4Cl/conc. NH_4OH soln. 9:1 for **19**, **20**, and **21** or by injecting (syringe) the mixture into 5 ml of sat. NH_4Cl/conc. NH_4OH soln. 9:1 for **22**. Then, 100 ml of Et_2O were added, the org. phase washed twice with H_2O, dried, and evaporated.

tert-*Butyl* N-*[(1*R*)-1-(Bromomethyl)-4-oxo-4-phenylbutyl]carbamate* (**24**). The cuprate was prepared from 81 mg (0.90 mmol) of CuCN and 0.90 ml (1.80 mmol) of PhLi (2M). After adding 50 mg (0.18 mmol) of **19**, the

mixture was stirred for 2.5 h at −78°, yielding 24 mg (38%) of **24** as colorless crystals after CC (pentane/Et_2O 2:1). An anal. sample was recrystallized from Et_2O/pentane. M.p. 122–123°. $[\alpha]_D^{20} = +5.4$ ($c = 0.57$, EtOH). IR (CCl_4): 3450 (NH), 1725 (C=O, Boc), 1695 (C=O, ketone). ^{1}H-NMR (90 MHz): 1.45 (*s*, *t*-BuO); 2.05 (*td*, $J = 8$, 4, CH_2(2)); 3.05 (*t*, $J = 8$, CH_2(3)); 3.55 (*d*, $J = 5$, CH_2Br); 3.90 (*m*, H–C(1)); 4.75 (*m*, NH); 7.45–7.60 (*m*, 3 arom. H); 7.90–8.05 (*m*, 2 arom. H). ^{13}C-NMR (101 MHz): 27.8 (C(2)); 28.5 ((CH_3)$_3$C); 35.2 (C(3)); 38.5 (CH_2Br); 50.6 (C(1)); 79.9 ((CH_3)$_3C$); 128.3, 128.8 (C_m, C_o); 133.4 (C_p); 137.0 (C_{ipso}); 155.6 (*t*-BuO*C*O); 199.5 (C(4)). FAB-MS: 358, 356 (8, $[M + H]^+$), 302, 300 (20); 258, 256 (22); 105 (45); 57 (100).

tert-*Butyl* *(5*R*-2-Oxo-5-(phenylmethyl)pyrrolidine-1-carboxylate* (**23**) *and* tert-*Butyl* N-*[(1*R*)-1-(Iodomethyl)-4-oxo-4-phenylbutyl]carbamate* (**25**). As for **24**, from 40 mg (0.45 mmol) of CuCN, 0.45 ml (0.90 mmol) of PhLi (2M), and 59 mg (0.18 mmol) of **20** (1.5 h at −78°): 28 mg (56%) of **23** as a colorless oil and traces (< 1 mg (1%)) of **25**.

23: $[\alpha]_D^{20} = +48.5$ ($c = 1.50$, $CHCl_3$). IR ($CHCl_3$): 1755 (C=O, Boc), 1715 (C=O, lactam). ^{1}H-NMR (400 MHz): 1.59 (*s*, *t*-BuO); 1.78–1.84 (*m*, H–C(4)); 1.91–2.01 (*m*, H–C(4)); 2.30–2.34 (*m*, CH_2–C(5)); 2.71–2.77 (*m*, H–C(3)); 3.12–3.16 (*m*, H–C(3)); 4.35–4.40 (*m*, H–C(5)); 7.18–7.34 (*m*, 5 arom. H). ^{13}C-NMR (101 MHz): 21.6 (C(4)); 28.1 ((CH_3)$_3$C); 31.1 (C(3)); 39.5 (C(6)); 59.0 (C(5)); 83.0 ((CH_3)$_3C$); 126.9 (C_p); 128.7, 129.4 (C_m, C_o); 137.1 (C_{ipso}); 149.9 (*t*-BuO*C*O); 174.4 (C(2)). FAB-MS: 276 (10, $[M + H]^+$), 220 (100), 176 (9), 84 (18), 57 (56).

25: FAB-MS: 404 (14, $[M + H]^+$), 348 (29), 304 (28), 105 (37), 57 (100).

tert-*Butyl* N-{*(1*R*)-1-{[(4-Methylphenyl)sulfonyloxy]methyl}-4-oxo-4-phenylbutyl}carbamate* (**26**). As for **24**, from 66 mg (0.18 mmol) of **21** (1.25 h at −78°): 24 mg (30%) of **26** as colorless crystals after CC (Et_2O/pentane 2:1). M.p. 113–114° (crystallized from CH_2Cl_2/pentane). $[\alpha]_D^{20} = +18.8$ ($c = 0.86$, $CHCl_3$). IR (CCl_4): 3450 (NH), 1720 (C=O, Boc), 1690 (C=O, ketone). ^{1}H-NMR (400 MHz): 1.36 (*s*, *t*-BuO); 1.90–1.93 (*m*, CH_2(2)); 2.42 (*s*, Me–C(4″)); 3.00 (*t*, $J = 7$, CH_2(3)); 3.84–3.90 (*m*, H–C(1)); 4.02–4.12 (*m*, CH_2OTs); 4.68–4.71 (br. *d*, NH); 7.34 (*d*, $J = 8$, H–C(3″), H–C(5″)); 7.43–7.47 (*m*, H–C(3′), H–C(5′)); 7.54–7.58 (*m*, H–C(4′)); 7.79 (*d*, $J = 8$, H–C(2″), H–C(6″)); 7.90–7.92 (*m*, H–C(2′), H–C(6′)). ^{13}C-NMR (101 MHz): 21.6 (CH_3–C(4″)); 25.5 (C(2)); 28.2 ((CH_3)$_3$C); 34.7 (C(3)); 49.3 (C(1)); 71.6 (CH_2OTs); 79.8 ((CH_3)$_3C$); 128.0, 128.6, 130.0 (C(2′), C(3′), C(5′), C(6′), C(2″), C(3″), C(5″), C(6″)); 132.5 (C(1″)); 133.2 (C(4′)); 136.7 (C(1′)); 145.1 (C(4″)); 155.3 (*t*-BuO*C*O); 199.1 (C(4)). FAB-MS: 448 (7, $[M + H]^+$), 392 (27), 348 (63), 105 (45), 57 (100).

tert-*Butyl* N-{*(1*R*)-1-[(Methylsulfonyloxy)methyl]-4-oxo-4-phenylbutyl}carbamate* (**27**). As for **24**, from 54 mg (0.18 mmol) of **22** (1 h at −78°): 10 mg (15%) of **27** as colourless crystals after CC (Et_2O/pentane 10:1). M.p. 102.5–104° (crystallized from CH_2Cl_2/pentane). $[\alpha]_D^{20} = +21.3$ ($c = 0.32$, $CHCl_3$). IR ($CHCl_3$): 3440 (NH), 1710 (C=O, Boc), 1685 (C=O, ketone). ^{1}H-NMR (400 MHz): 1.39 (*s*, *t*-BuO); 1.98–2.06 (*m*, CH_2(2)); 3.05 (*s*, $MeSO_2$); 3.00–3.17 (*m*, CH_2(3)); 3.93–3.99 (*m*, H–C(1)); 4.23–4.33 (*m*, CH_2OMs); 4.74–4.78 (br. *d*, NH); 7.41–7.49 (*m*, 2 H_m); 7.55–7.60 (*m*, H_p); 7.94–7.97 (*m*, 2 H_o). ^{13}C-NMR (101 MHz): 25.4 (C(2)); 28.3 ((CH_3)$_3$C); 34.8 (C(3)); 37.5 ($MeSO_2$); 49.7 (C(1)); 71.2 (CH_2OMs); 80.0 ((CH_3)$_3C$); 128.0, 128.7 (C_m, C_o); 133.3 (C_p); 136.7 (C_{ipso}); 155.5 (*t*-BuO*C*O); 199.2 (C(4)). FAB-MS: 372 (13, $[M + H]^+$), 316 (34), 272 (58), 105 (41), 57 (100).

*(5*R*)-5-(Bromomethyl)pyrrolidin-2-one* (**31**). To a soln. of 2.00 g (17.4 mmol) of **8** in 160 ml of abs. CH_2Cl_2, 10.48 g (39.95 mmol) of Ph_3P and 13.25 g (39.95 mmol) of CBr_4 were added. The mixture was stirred at r.t. for 1.5 h, the solvent evaporated, and the residue purified by CC (AcOEt/MeOH 40:1): 2.37 g (77%) of **31** as colorless crystals. An anal. sample was recrystallized from acetone/pentane. M.p. 66–76°. $[\alpha]_D^{20} = +26.7$ ($c = 1.08$, EtOH) ([23]: $[\alpha]_D = -33$ ($c = 5$, EtOH) for enantiomer). IR ($CHCl_3$): 3430 (NH), 1705 (C=O). ^{1}H-NMR (90 MHz): 1.75–2.65 (*m*, CH_2(3), CH_2(4)); 3.45 (*d*, $J = 6$, CH_2–C(5)); 3.85–4.25 (*m*, H–C(5)); 7.15 (br. *s*, NH). EI-MS: 179/177 (3, M^+), 84 (100). Anal. calc. for C_5H_8BrNO (178.03): C 33.73, H 4.53, N 7.87; found: C 33.71, H 4.65, N 7.80.

*(5*R*)-5-(Iodomethyl)pyrrolidin-2-one* (**28**). To a soln. of 500 mg (2.81 mmol) of **31** in 10 ml of abs. acetone, a soln. of 5.60 g (37.4 mmol) of NaI in 25 ml of abs. acetone was added. The mixture was heated under reflux for 2.5 h, then the solvent evaporated, and the residue extracted with 6 portions of 50 ml of abs. CH_2Cl_2. The org. extracts were evaporated, yielding a pale yellow solid that was recrystallized from acetone/pentane: 464 mg (73%) of **28** as colorless crystals. M.p. 79–81°. $[\alpha]_D^{20} = +60.5$ ($c = 0.97$, EtOH) ([22]: $[\alpha]_D = -55$ ($c = 1.24$, EtOH) for enantiomer). IR ($CHCl_3$): 3430 (NH), 1700 (C=O). ^{1}H-NMR (90 MHz): 1.65–2.55 (*m*, CH_2(3), CH_2(4)); 3.25 (*d*, $J = 6$, CH_2–C(5)); 3.60–4.00 (*m*, H–C(5)); 6.95 (br. *s*, NH). EI-MS: 225 (4, M^+), 127 (10), 98 (20), 84 (100).

*[(2*R*)-5-Oxopyrrolidin-2-yl]methyl 4-Methylbenzenesulfonate* (**32**). A soln. of 200 mg (1.74 mmol) of **8** in 1.5 ml of abs. pyridine was treated with 500 mg (2.62 mmol) of TsCl. After 2.5 h at r.t., 1 ml of H_2O was added and the soln. stirred for 30 min. Then, 10 ml of 2N HCl were added, followed by extraction with 8 portions of 30 ml of CH_2Cl_2. The org. layer was dried and evaporated to yield a slightly yellow solid that was recrystallized from CH_2Cl_2/hexane: 279 mg (60%) of **32** as colourless needles. M.p. 128.5–130° ([22]: 130.5°). $[\alpha]_D^{20} = -7.1$ ($c = 1.00$, EtOH). IR ($CHCl_3$): 3430 (NH), 1705 (C=O). ^{1}H-NMR (90 MHz): 1.65–2.40 (*m*, CH_2(3), CH_2(4)); 2.45 (*s*,

CH_3–C(4′)); 3.85–4.10 (*m*, H–C(2), CH_2–C(2)); 5.95 (br. *s*, NH); 7.40 (*d*, *J* = 8, 2 arom. H); 7.85 (*d*, *J* = 8, 2 arom. H). FAB-MS: 270 (100, $[M + H]^+$), 98 (63), 84 (16).

[(2R)-5-Oxopyrrolidin-2-yl]methyl Methanesulfonate (**33**). To a soln. of 500 mg (4.34 mmol) of **8** in 40 ml of abs. CH_2Cl_2, 1.21 ml (8.68 mmol) of Et_3N and 0.51 ml (6.56 mmol) of MsCl were added at 0°. The mixture was stirred for 1.5 h at 0°, then 0.1 ml of H_2O was added and the soln. stirred for 5 min. The soln. was evaporated completely and purified by CC (AcOEt/MeOH 10:1): 781 mg (93%) of **33** as a colorless solid. An anal. sample was recrystallized from AcOEt/pentane. M.p. 75.5–77.5°. $[\alpha]_D^{20} = -16.2$ (*c* = 1.02, EtOH). IR ($CHCl_3$): 3430 (NH), 1700 (C=O). ^{1}H-NMR (90 MHz): 1.75–2.55 (*m*, CH_2(3), CH_2(4)); 3.05 (*s*, $MeSO_2$); 3.85–4.30 (*m*, H–C(2), CH_2–C(2)); 7.30 (br. *s*, NH). CI-MS: 194 (100, $[M + H]^+$), 98 (11), 84 (25).

(5R)-5-(Phenylmethyl)pyrrolidin-2-one (**34**). *Method A* (no NaH). A suspension of 100 mg (1.12 mmol) of CuCN in 1.5 ml of abs. THF was cooled to −78°, then 1.16 ml (2.24 mmol) of PhLi (1.93M) were added. Subsequent warming to 0° for 3 min led to a clear soln. which was recooled to −78°, followed by dropwise addition of 0.22 mmol of a soln. of the γ-lactam (**28** and **31**–**33**) in 2 ml of abs. THF. The mixture was warmed to r.t. for 6 h (**28**), 48 h (**31**), 4 h (**32**), or 24 h (**33**), quenched by adding 5 ml of a sat. NH_4Cl/conc. NH_4OH soln. 9:1 and extracted with 5 portions of 10 ml of CH_2Cl_2. The org. extracts were dried and evaporated, and the residue was purified by CC (Et_2O/i-PrOH 10:1): **34** (31 mg (80%) from **28**, 32 mg (83%) from **31**, 37 mg (96%) from **32**, and 1 mg (3%) from **33**) as a colourless oil that solidified upon standing.

Method B (0.2 equiv. of NaH). At 0°, 2 mg (0.05 mmol) of a NaH dispersion (55% in oil) were washed with 1 ml of hexane, then 1 ml of abs. THF was added. A soln. of 0.22 mmol of the γ-lactam (**28** and **31**–**33**) in 2 ml of abs. THF was added dropwise. After evolution of H_2 had ceased, a soln. of $Li_2Cu(CN)Ph_2$, prepared from 100 mg (1.12 mmol) of CuCN and 1.16 ml (2.24 mmol) of PhLi (1.93M) in abs. THF as described in *Method A* was added at 0°. The mixture was warmed to r.t. for 3 h (**28**), 24 h (**31**), 4 h (**32**), or 24 h (**33**), quenched, and worked up as described in *Method A*: **34** (25 mg (65%) from **28**, 24 mg (62%) from **31**, 30 mg (78%) from **32**, and 2 mg (5%) from **33**) as a colorless oil that solidified upon standing.

Method C (1 equiv. of NaH). As in *Method B*, with 10 mg (0.23 mmol) of a NaH dispersion (washing with hexane (3 × 1 ml). The mixture was warmed to r.t. for 1.5 h (**28**), 24 h (**31**), 4 h (**32**), or 24 h (for **33**), quenched, and worked up as described in *Method A*: **34** (21 mg (54%) from **28**, 26 mg (67%) from **31**, 29 mg (75%) from **32**, and 1 mg (3%) from **33**) as a colorless oil that solidified upon standing.

34: M.p. 56–58° (crystallized from Et_2O/pentane). $[\alpha]_D^{20} = +39.9$ (*c* = 1.07, EtOH) ([25]: $[\alpha]_D = +39.6$ (*c* = 1.19, EtOH)). IR ($CHCl_3$): 3430 (NH), 1695 (C=O). ^{1}H-NMR (400 MHz): 1.80–1.92 (*m*, H–C(4)); 2.20–2.36 (*m*, CH_2(3), H–C(4)); 2.70–2.86 (*m*, CH_2–C(5)); 3.85–3.92 (*m*, H–C(5)); 6.02 (br. *s*, NH); 7.17–7.34 (*m*, 5 arom. H). ^{13}C-NMR (101 MHz): 26.9 (C(4)); 30.1 (C(3)); 43.0 (C(6)); 55.7 (C(5)); 126.9 (C_p); 128.8, 129.0 (C_m, C_o); 137.5 (C_{ipso}); 177.9 (C(2)). FAB-MS: 176 (100, $[M + H]^+$), 91 (12), 84 (26). Anal. calc. for $C_{11}H_{13}NO$ (175.23): C 75.40, H 7.48, N 7.99; found: C 75.13, H 7.53, N 7.83.

1-(tert-Butyl) 2-Methyl (2R)-5-Oxopyrrolidine-1,2-dicarboxylate (**35**). To a soln. of 1.51 g (10.6 mmol) of **7** in 20 ml of CH_2Cl_2, 4.69 g (21.5 mmol) of $(Boc)_2O$, followed by 1.32 g (10.8 mmol) of DMAP and 1.50 ml (10.8 mmol) of Et_3N were added. After 5 h at r.t., 300 ml of Et_2O were added, and the mixture was washed with 10% citric acid, sat. $NaHCO_3$ soln., and brine, dried, and evaporated. CC (Et_2O) yielded 2.10 g (82%) of **35** as colorless crystals. An anal. sample was recrystallized from Et_2O/pentane. M.p. 69–70.5°. $[\alpha]_D^{20} = +40.7$ (*c* = 1.36, EtOH). IR (KBr): 1760 (C=O, Boc), 1740 (C=O, ester), 1705 (C=O, lactam). ^{1}H-NMR (90 MHz): 1.50 (*s*, *t*-BuO); 1.95–2.80 (*m*, CH_2(3), CH_2(4)); 3.80 (*s*, MeO); 4.55–4.70 (*m*, H–C(5)). FAB-MS: 244 (22, $[M + H]^+$), 188 (48), 144 (100), 84 (17), 57 (37).

Methyl (2R)-2-{[(tert-Butyloxy)carbonyl]amino}-5-oxo-5-phenylpentanoate (**36**). A suspension of 700 mg (7.82 mmol) of CuCN in 10 ml of abs. THF was cooled to − 78°, then 7.9 ml (15.6 mmol) of PhLi (1.98M) were added. Subsequent warming to 0° led to a clear soln. to which a soln. of 500 mg (2.06 mmol) of **35** in 15 ml of THF was added dropwise. The mixture was stirred for 30 min at 0° and quenched by adding 40 ml of a sat. NH_4Cl/conc. NH_4OH soln. 9:1. Then, 300 ml of Et_2O were added, and the mixture was washed with H_2O (2 × 100 ml). The org. extract was dried and evaporated to yield a yellow oil that was purified by CC (pentane/Et_2O 4:3) yielding 279 mg (42%) of **36** as colorless crystals. An anal. sample was recrystallized from Et_2O/pentane. M.p. 98.5–100°. $[\alpha]_D^{20} = -14.8$ (*c* = 1.13, $CHCl_3$). IR (CCl_4): 3440 (NH), 1745 (C=O, ester), 1720 (C=O, Boc), 1690 (C=O, ketone). ^{1}H-NMR (400 MHz): 1.42 (*s*, *t*-BuO); 2.04–2.14 (*m*, H–C(3)); 2.27–2.36 (*m*, H–C(3)); 3.00–3.18 (*m*, CH_2(4)); 3.75 (*s*, MeO); 4.36–4.42 (*m*, H–C(2)); 5.12–5.16 (br. *d*, NH); 7.43–7.48 (*m*, 2 H_m); 7.55–7.59 (*m*, H_p); 7.94–7.97 (*m*, 2 H_o). ^{13}C-NMR (101 MHz): 27.0 (C(3)); 28.3 ($(CH_3)_3C$); 34.5 (C(4)); 52.4 (MeO); 53.1 (C(2)); 80.0 ($(CH_3)_3C$); 128.0, 128.6 (C_m, C_o); 133.2 (C_p); 136.7 (C_{ipso}); 155.5 (*t*-BuOCO); 172.9 (C(1)); 198.9 (C(5)). FAB-MS: 322 (29, $[M + H]^+$), 266 (64), 222 (12), 204 (100), 162 (27), 105 (22), 57 (89). Anal. calc. for $C_{17}H_{23}NO_5$ (321.37): C 63.54, H 7.21, N 4.36; found: C 63.66, H 7.17, N 4.18.

Methyl (2R)-3,4-Dihydro-5-phenyl-2H-pyrrole-2-carboxylate (**37**) [18]. To a soln. of 100 mg (0.31 mmol) of **36** in 1 ml of CH_2Cl_2, 1.00 ml (13.1 mmol) of CF_3COOH was added at 0°. The mixture was stirred for 30 min, quenched with 20 ml of sat. $NaHCO_3$ soln., extracted with CH_2Cl_2 (5 × 10 ml), dried, and evaporated. After CC (Et_2O/pentane 10:3), 56 mg (89%) of **37** were obtained as a colorless oil. $[\alpha]_D^{20} = -109.5$ ($c = 1.01$, $CHCl_3$). IR (film): 1740 (C=O). ^{1}H-NMR (400 MHz): 2.22–2.41 (*m*, CH_2(3)); 2.95–3.04 (*m*, H–C(4)); 3.13–3.22 (*m*, H–C(4)); 3.79 (*s*, MeO); 4.90–4.95 (*m*, H–C(2)); 7.39–7.48 (*m*, 2 H_m, H_p); 7.87–7.90 (*m*, 2 H_o). CI-MS: 204 (100, $[M + H]^+$), 144 (15).

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