Siloxycyclopropanes in Ugi Four-Component Reaction: A New Method for the Synthesis of Highly Substituted Pyrrolidinone Derivatives

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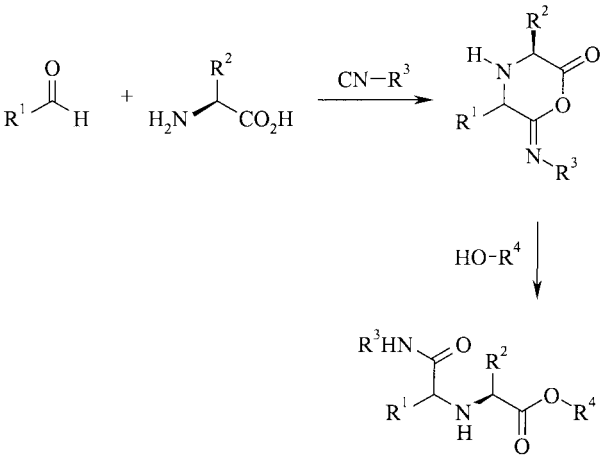
Abstract: Reaction of methyl trimethylsiloxycyclopropanecarboxylates **3** with amino acids, *tert*-butylisonitrile and methanol furnished amino diacid derivatives **2** as the result of an Ugi 5-center 4-component reaction. This one-pot reaction involves β-formyl esters such as **1** as intermediate, which are liberated in situ. Adducts **2** could be thermally cyclized to provide γ-lactams **4** in good yields. The multi component reaction was combined with this cyclization process to a fairly efficient one-pot procedure. Thus, cyclopropane derivative **3a** was converted into γ-lactam **4a** in good yield. Two of the γ-lactams **4** were reduced with lithium aluminum hydride to give pyrrolidine derivatives **5**. Based on an X-ray analysis of the major diastereomer of compound **5d**, the diastereoselectivity of the 4-component reaction is discussed.

Key words: amino acids, cyclopropanes, pyrrolidines, lactams, Ugi reaction

Introduction

The use of multi-component transformations is a very efficient strategy for the production of compound ensembles (libraries) of high diversity required in modern search for lead structures. Among these processes the Ugi four-component reaction (U-4CR) is one of the oldest, but most frequently employed schemes.[2,3] The combination of aldehyde, carboxylic acid, isonitrile and amine in a multistep process furnishes compounds with amino acid-like backbones in an intriguingly simple and flexible fashion. In 1996 Ugi and co-workers reported that α-amino acids may also be employed as amine component and that by use of methanol as solvent the U-4CR could be extended to an Ugi 5-center 4-component reaction (U5C-4CR) providing functionalized α-amino diacid derivatives (Scheme 1).[4] The configuration of the new stereogenic center generated at the former carbonyl carbon of the aldehyde component is controlled by the configuration of the amino acid used. The Ugi reaction has also been extended to functionalized α-amino acids,[5–7] anthranilic acid[8] as well as to γ- and δ-ketocarboxylic acids.[9,10] The latter compounds allow preparation of γ-lactams and δ-lactams in an efficient fashion.



Scheme 1

In numerous applications we could establish that methyl 2-siloxycyclopropanecarboxylates **A** (Figure 1) may serve as equivalents of γ-ketocarboxylates **B** which are smoothly liberated under certain conditions of ring cleavage.[11] This concept could be exploited in many one-pot reactions which are based on ring-opening of **A** and subsequent reactions without isolation of intermediate dicarbonyl components **B**. Of particular synthetic value are cyclopropane derivatives **A** which contain a hidden enone functionality (R^1 = alkenyl)[12] or aldehyde group (R^1 = H)[13] because the corresponding dicarbonyl compounds are often hardly accessible and occasionally very sensitive. Fascinated by the possibilities of the Ugi 5-center 4-component reaction we investigated the use of 2-siloxycyclopropanecarboxylates **A** as precursor in this process. We envisaged that **A** may directly be introduced as precursor of **B** since under protic conditions as employed for the U-5C-4CR, trimethylsiloxycyclopropanes **A** undergo smooth cleavage to furnish **B**. As particularly interesting aspect of this approach we considered the cyclization of the primary Ugi reaction products to highly functionalized pyrrolidinones which are interesting peptido mimetics.[14]

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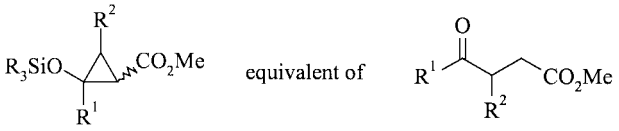


A B

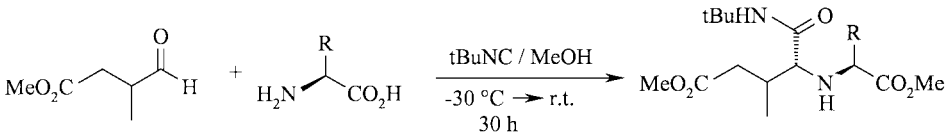
Figure 1 Methyl 2-siloxycyclopropanecarboxylates **A** as equivalents of γ-ketocarboxylates **B**

Results

In first orientating experiments we used the β-formyl ester **1**, which is easily available by ring-cleavage of siloxycyclopropane **3a**,[15] and combined this aldehyde with *tert*-butylisonitrile and phenylalanine or tryptophane in methanol as solvent (Scheme 2). The reaction temperature was allowed to rise from –30 °C to room temperature. After evaporation of the solvent the residue was purified by column chromatography providing the expected coupling products **2a** and **2b** in 82% and 71% yield, respectively, as mixture of the expected four diastereomers. Only the two major diastereomers are depicted in Scheme 2; the configurational assignment is based on an X-ray analysis of a subsequent product discussed below. Since chiral aldehyde **1** was used as a racemic mixture, pairs of diastereomers in a ratio of approximately 1:1 were obtained. As to be expected no kinetic resolution occurs under the conditions employed.[16]

Having demonstrated that β-formyl esters such as **1** smoothly react in this type of Ugi reaction we proceeded to our actual goal and used siloxycyclopropanes as direct precursor. Thus, reaction of methyl 3-methyl-2-trimethylsiloxycyclopropanecarboxylate (**3a**) with *tert*-butylisonitrile and alanine in methanol under similar conditions as above afforded the expected adduct **2c** in moderate yield (Scheme 3). Again, all four diastereomers were obtained. When siloxycyclopropane **3b** was employed as starting material the corresponding reactions with amino acids phenylalanine, alanine and isoleucine furnished the coupling products **2d**, **2e** and **2f** in good or moderate yields. In these examples only two diastereomers are observed since the in situ generated β-formyl ester is achiral. The diastereoselectivity induced by the stereogenic center of the amino acid is only moderate (ca 2:1 to 5:1, again only the major diastereomers are depicted in Scheme 3).

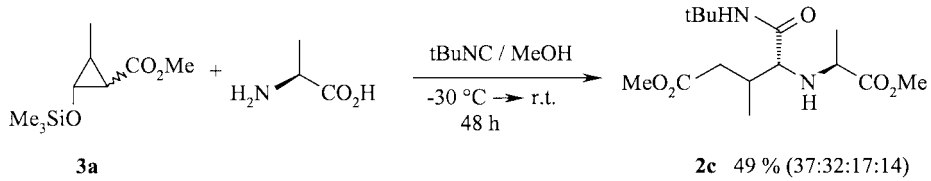
Primary adducts **2a–f** could efficiently be cyclized by heating in toluene for 3 hours providing the desired pyrrolidinone derivatives **4a–f** in good to excellent yields (Scheme 4). For compounds **4a–c**, derived from a chiral β-formyl ester, again four diastereomers were identified at this stage, with some deviations from the initially recorded ratios of isomers. Thus, under the rather harsh cyclization conditions isomerization at the stereogenic center α to the carbonyl group may to some extend have occurred. Likewise, the precursors **2d–f** were converted into the two diastereomers of **4d–f** with ratios similar to those of the starting materials.



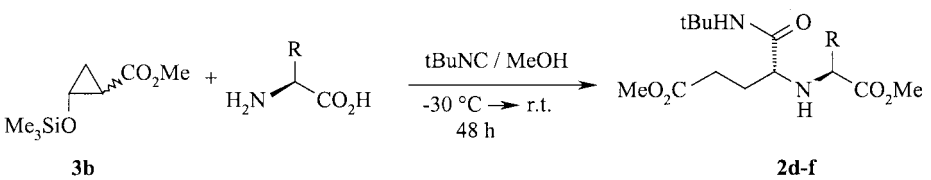
1 2a,b

a: R = Bn 82 % (42:39:10:9)
b: R = CH_2Indolyl 71 % (35:35:15:15)

Scheme 2



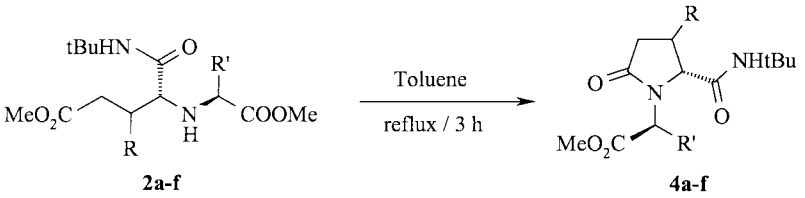
3a **2c** 49 % (37:32:17:14)



3b **2d-f**

d: R = Bn 81 % (83:17)
e: R = Me 46 % (67:33)
f: R = CHMeEt 81 % (74:26)

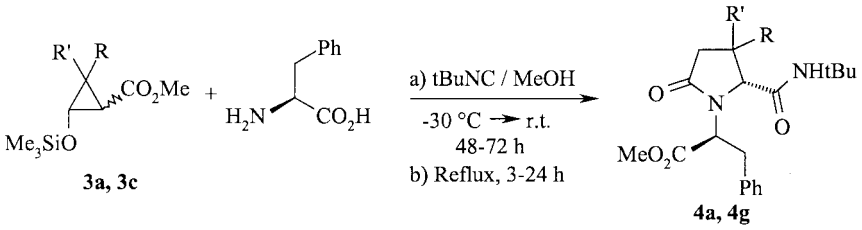
Scheme 3



2a-f **4a-f**

a: R = Me; R' = Bn	81 % (50:42:4:4)
b: R = Me; R' = CH_2Indolyl	69 % (52:42:3:3)
c: R = Me; R' = Me	71 % (34:22:22:22)
d: R = H; R' = Bn	98 % (90:10)
e: R = H; R' = Me	86 % (64:36)
f: R = H; R' = CHMeEt	82 % (79:21)

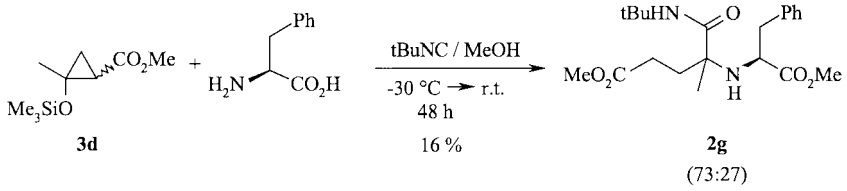
Scheme 4



3a, 3c **4a, 4g**

a: R = Me; R' = H	67 % (51:41:4:4)
g: R = R' = Me	16 % (53:47)

Scheme 5



3d **2g**
(73:27)

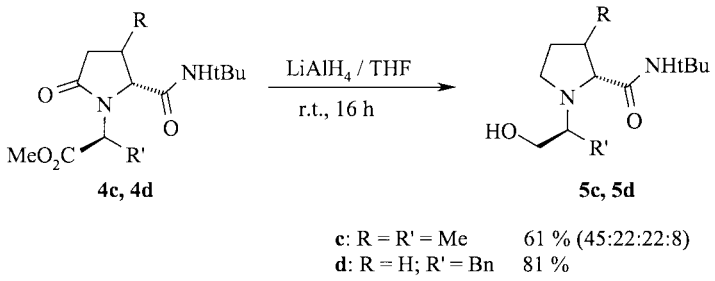
Scheme 6

With siloxycyclopropane **3a** and phenylalanine we attempted a one-pot protocol and successfully obtained the pyrrolidinone **4a** in 67% overall yield and almost identical ratio of diastereomers as observed in the two-step sequence (Scheme 5). The overall transformation **3a** to **4a** may be classified as 6-center 4-component reaction (6-C 4CR). Similarly, we introduced methyl 3,3-dimethyl-2-trimethylsiloxycyclopropanecarboxylate (**3c**) as precursor for an in situ generated β-dimethyl-substituted β-formyl ester. However, for this example the steric hinderance exhibited by the two methyl groups seems to hamper the Ugi reaction considerably. The expected pyrrolidinone derivative **4g** was isolated in only 16% yield and negligible diastereoselectivity.

For further exploration of scope and limitations of this modification of the Ugi reaction we introduced methyl 2-methyl-2-trimethylsiloxycyclopropanecarboxylate (**3d**). This cyclopropane derivative is equivalent to methyl levinulate, but its reaction with phenylalanine and *tert*-butylisonitrile in methanol was very inefficient under standard conditions (Scheme 6). Only 16% of the corresponding adduct **2g** containing a quarternary center were isolated. Thus, participation of γ-keto esters seems to be much less efficient compared to the related aldehydes.[17]

Structural Elucidation

The relative stereochemistry at the centers C-2 and C-3 in *cis*-**4a** and *trans*-**4a** as model compounds for 2,3-disubstituted pyrrolidinones **4** could be determined by means of 2D-NMR measurements (COSY, HSQC, HMBC, NOESY). The most significant signal in the ^{1}H NMR is the proton at position 2 in the pyrrolidinone ring. The 2-H signal in *cis*-**4a** appears at $\delta \approx 3$ as a doublet with J = 8.5 Hz whereas the corresponding signal for this proton in *trans*-**4a** is shifted slightly upfield and shows a coupling constant of 4 Hz. Further characteristics in the ^{1}H NMR spectra of phenylalanine or tryptophane derived pyrrolidinones **4** are the signals of the α-proton of the amino acid moiety (1'-H) as a doublet of doublet which gen-



Scheme 7

erally couple with 5 Hz to 6 Hz and 10 Hz to 11 Hz at δ = 3.9 to 4.4. In the ^{13}C NMR spectra, the chemical shifts for C-2 in *cis*-**4** are 3 to 5 ppm higher than the corresponding signals of the *trans*-**4** diastereomers whereas the chemical shifts for C-3 in *cis* compounds (δ ≈ 31–32) are very similar to those in *trans*-isomers (δ ≈ 33).

Reduction of pyrrolidinones **4c** and **4d** with lithium aluminum hydride furnished proline related amino alcohols **5c** and **5d** in good yields (Scheme 7). We were able to grow suitable crystals from the major diastereomer of **5d**, which could be analysed by an X-ray analysis (Figure 2). This unequivocally established the *R*-configuration of the major diastereomer at the pyrrolidine ring which is in accordance with the configuration of a product in a related example described by Kim et al.[6,18]

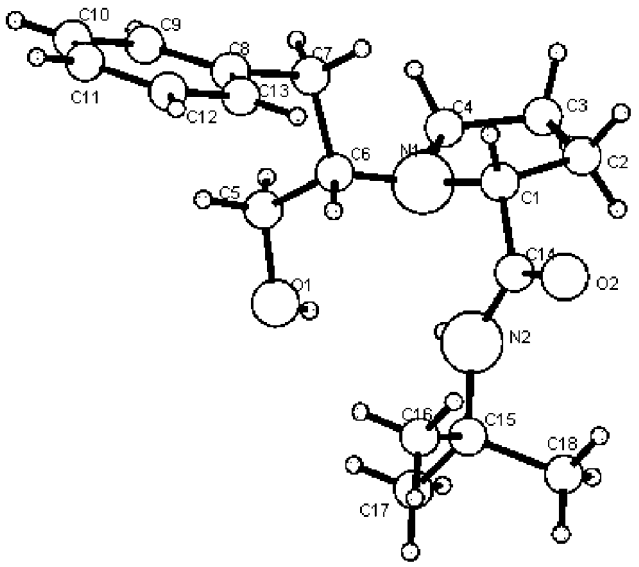
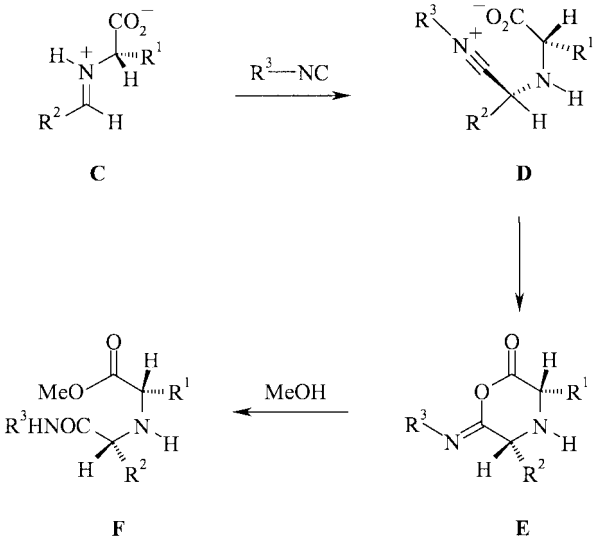


Figure 2 Structure of compound **5d** as determined by X-ray crystallography

Discussion of the Stereochemistry

The examples presented here demonstrate that the Ugi 5-center 4-component reaction of in situ liberated β-formyl esters proceeds with moderate to good diastereoselectivity. In series *b* (precursor **3b**) – where the interpretation is not complicated by an additional stereogenic center of the aldehyde component – alanine induces moderate selectivity at the newly formed stereogenic center (ca 65:35) whereas isoleucine and phenylalanine provide higher ratios of diastereomers (ca 75:25 and 85:15). For series *a* (precursor **3a**) the stereogenic center in the β-formyl ester makes the analysis more complex, however, the diastereoselectivity of the process may be simplified by adding the percentage values of the two major and those of the two minor diastereomers. We assume that both enantiomers of the intermediate aldehyde **1** react with approximately the same rate and that no kinetic resolution took place.[16] Alanine again shows only low selectivity in the range as observed in series *b*, but phenylalanine and tryptophane gave rather high ratios in favour of one diastereomer (with respect to the new stereogenic center).

The X-ray analysis obtained from a product derived from the major diastereomer of **4d** revealed *R*-configuration at C-2 in the pyrrolidine ring (Figure 2). On this basis we suggest that the preferred attack of the isonitrile to the intermediate iminium ion **C** formed from the aldehyde and the amino acid proceeds from the front side giving a nitrilium ion **D** as depicted in Scheme 8. Cyclization provides intermediate **E**, which is ring-opened by methanol to furnish the isolated product **F**. The front side attack is more favoured and hence the diastereoselectivity higher if substituent R^1 is larger. If R^2 also contains a stereogenic center in α-position, as in intermediates derived from



Scheme 8

Table 1 Synthesis of Iminodicarboxylic Derivatives **2a**–**g** (General Procedure 1)

Substrate	Amount g (mmol)	Amino Acid	Amount g (mmol)	Time (h)	Product[a]	Yield (Ratio) g (%)	Appearance	IR[b] ν (cm^{-1})
1	0.650 (5.00)	Phe	0.825 (5.00)	30	**2a**	(42:39:10.9) 1.62 (82)	resin	3390 (N−H), 3100–2860 (=CH, C−H), 1735 (C=O, ester), 1670 (C=O, amide)
1	0.285 (2.20)	Trp	0.449 (2.20)	30	**2b**	(35:35:15:15) 0.673 (71)	foam	3425 (N−H), 3070–2850 (=CH, C−H), 1735 (C=O, ester), 1655 (C=O, amide)
3a	0.405 (2.00)	Ala	0.178 (2.00)	48	**2c**	(37:32:17:14) 0.31 (49)	oil	3325–3310 (N–H), 2970–2835 (=CH, C–H), 1745 (C=O, ester), 1685 (C=O, amide)
3b	0.413 (2.00)	Phe	0.330 (2.00)	48	**2d**	(83:17) 0.636 (81)	oil	3450, 3340 (N–H), 3100–2880 (=CH, C–H) 1740 (C=O, ester), 1675 (C=O, amide)
3b	0.345 (2.00)	Ala	0.178 (2.00)	48	**2e**	(67:33) 0.279 (46)	resin	3320–3315 (N–H), 2965–2840 (=CH, C–H)), 1735 (C=O, ester), 1675 (C=O, amide)
3b	0.345 (2.00)	Ile	0.262 (2.00)	72	**2f**	(74:26) 0.557 (81)	oil	3330 (N–H) 2965–2875 (=CH, C–H), 1740 (C=O, ester), 1670 (C=O, amide)
3d	0.292 (1.45)	Phe	0.239 (1.45)	72	**2g**	(73:27) 0.072 (16)	resin	3450, 3355 (N–H), 3090–2815 (=CH, C–H), 1745, 1740 (C=O, ester), 1760 (C=O, amide)

[a] Satisfactory microanalyses obtained: C ±0.37, H ±0.25, N ±0.31; exception: **2a** (C –0.53) and **2c** (N –0.65).
[b] Oils and resins as film or in CCl_4, foams as KBR pellets.

Table 2 Synthesis of Lactams **4a**–**f** (General Procedure 2)

Substrate **2**	Amount g (mmol)		Yield of Product **4**[a] (Ratio)	g(%)	Appear-ance	IR[b] ν (cm^{-1})
2a	0.453 (1.15)	**4a**	(50:42:4:4)[c]	0.337 (81)	foam	3400, 3335 (N–H), 3100–2920 (=CH, C–H), 1735 (C=O, ester), 1705 (C=O, lactam), 1675 (C=O, amide)
2b	0.402 (0.93)	**4b**	(52:42:3:3)[d]	0.258 (69)	foam	3390, 3360, 3330 (N–H), 3050–2960 (=CH, C–H), 1730 (C=O, ester), 1680 (C=O, br, lactam, amide)
2c	0.175 (0.55)	**4c**	(34:22:22:22)	0.111 (71)	resin	3325 (N–H), 2970–2935 (C-H), 1745 (C=O, ester), 1710 (C=O, lactam), 1675 (C=O, amide)
2d	0.520 (1.37)	**4d**	(90:10)	0.461 (96)[e]	resin	3305 (N–H), 3100–2820 (=CH, C–H), 1735 (C=O, ester), 1715 (C=O, lactam), 1690 (C=O, amide)
2e	0.170 (0.56)	**4e**	(64:36)	0.130 (86)	oil	3365–3025 (N–H), 2970–2930 (C–H), 1740 (C=O, ester), 1710 (C=O, lactam), 1675 (C=O, amide)
2f	0.550 (1.60)	**4f**	(85:15)	0.406 (82)	resin	3330 (N–H), 1735 (C=O, ester), 1710 (C=O, lactam), 1680 (C=O, amide)

[a] Satisfactory microanalyses obtained: C ±0.34, H ±0.27, N ±0.26; exception: **4c** (N –0.46).
[b] Oils and resins as film or in CCl_4, foams as KBR pellets.
[c] *cis*-**4a**/*trans*-**4a** = 54:46.
[d] *cis*-**4b**/*trans*-**4b** = 55:45.
[e] After chromatography 182 mg of major diastereomer of **4d** was isolated in isomerically pure form; $[\alpha]_D^{23}$ –65.5 (*c* = 1.0, $CHCl_3$).

Table 3 ^{1}H NMR Data of Compounds **2**

Product	^{1}H NMR (300 MHz, $CDCl_3$/TMS); δ, *J* (Hz)
2a[a]	7.35–7.21 (m, 5 H, C_6H_5), 7.05–6.85, 6.45 (m, br s, 0.81 H, 0.19 H, NH), 3.79–1.82 (m, 12 H with 8 s at δ = 3.73, 3.71, 3.69, 3.67, 3.65, 3.64, 3.60, 3.57, OCH_3, NH, aliphat CH), 1.35–0.74 (m, 14 H, *t*-C_4H_9, CH_3, aliphat CH)
2b[a]	8.70–8.35 (m, 1 H, NH), 7.70–6.75 (m, 6 H, arom CH, NH), 4.18–3.40, 3.30–1.65 (2 m, 7 H, 6 H, OCH_3, NH, aliphat CH, CH_2), 1.50–0.80 (m, 11.9 H with 3 s at δ = 1.33, 1.31, 1.28, *t*-C_4H_9, CH_3, aliphat CH), 0.68 (d, *J* = 7, 1.1 H, CH_3)
2c	6.90–6.73 (m, 1 H, NH), 4.32–4.03, 4.01–3.90, 3.87–1.81 (3 m, 12 H, CH, CH_2, CHN, NH, OCH_3), 1.45–0.82 (m, 15 H with 3 s at δ = 1.25, 1.24, 1.23, CH_3, *t*-C_4H_9)
2d (major)	7.38–7.16 (m, 5 H, C_6H_5), 6.97 (br s, 1 H, NH), 3.68, 3.64 (2 s, 6 H, 2 OCH_3), 3.45 (dd, *J* = 6.2, 7.6, 1 H, CH), 3.06 (dd, *J* = 6, 13.6, 1 H, CH), 2.97–2.81, 2.19, 1.93–1.69 (m, m_c, m, 2 H, 2 H, 3 H, CH_2, CH, NH), 1.31 (s, 9 H, *t*-C_4H_9)
2d[b] (minor)	6.52 (s, 1 H, NH), 3.67, 3.63 (2 s, 6 H, 2 OCH_3), 3.33–3.28, 2.70–2.58 (2 m, 1 H, 1 H, aliphat CH), 2.45 (t, *J* = 7.5, 2 H, CH_2), 1.30 (s, 9 H, *t*-C_4H_9)
2e (major)	7.03 (s, 1 H, NH), 3.72, 3.68 (2 s, 6 H, OCH_3), 3.33 (q, *J* = 6.9, 1 H, CH), 3.06 (dd, *J* = 5.8, 6.7, 1 H, CH), 2.50–2.38 (m, 2 H, CH_2), 2.03–1.85 (m, 3 H, CH_2, NH), 1.34 (s, 9 H, *t*-C_4H_9), 1.30 (d, *J* = 7.1, 3 H, CH_3)
2e[b] (minor)	7.09 (s, 1 H, NH), 3.71, 3.68 (2 s, 6 H, OCH_3), 3.20 (q, *J* = 7.1, 1 H, CH), 2.87 (dd, *J* = 5.4, 7.2, 1 H, CH), 1.35 (s, 9 H, *t*-C_4H_9), 1.28 (d, *J* = 6.9, 3 H, CH_3)
2f (major)	6.77 (br s, 1 H, NH), 3.70, 3.68 (2 s, 6 H, OCH_3), 3.09 (d, *J* = 5.6, 1 H, CH), 3.01 (t, *J* = 6.0, 1 H, CH), 2.45, 2.44 (2 t, *J* = 7.2, 7.5, 2 H, CH_2), 1.94 (m_c, 2 H, CH, CH_2), 1.83–1.69 (m, 3 H, CH_2, NH), 1.54–1.40, 1.25–1.11 (2 m, 1 H each, CH_2), 1.33 (s, 9 H, *t*-C_4H_9), 0.90 (t, *J* = 7.4, 3 H, CH_3), 0.89 (d, *J* = 6.8, 3 H, CH_3)
2f (minor)	7.30 (br s, 1 H, NH), 3.71, 3.69 (2 s, 6 H, OCH_3), 3.00 (d, *J* = 5.3, 1 H, CH), 2.80 (dd, *J* = 6.9, 7.0, 1 H, CH), 2.47 (br t, *J* = 7.4, 2 H, CH_2), 2.10–1.87, 1.71–1.63, 1.52–1.43 (3 m, 4 H, 1 H, 1 H, CH, CH_2, NH), 1.35 (s, 9 H, *t*-C_4H_9), 1.30–1.12 (m, 1 H, CH_2), 0.96 (d, *J* = 6.8, 3 H, CH_3), 0.91 (t, *J* = 7.2, 3 H, CH_3)
2g (major)	7.33–7.11 (m, 5 H, C_6H_5), 6.91 (br s, 1 H, NH), 3.67, 3.63 (2 s, 6 H, 2 OCH_3), 3.41 (dd, *J* = 6.3, 7.5, 1 H, CH), 2.89–2.75 (m, 2 H, CH_2), 2.41–1.73 (m, 5 H, CH_2, NH), 1.29 (s, 3 H, CH_3), 1.18 (s, 9 H, *t*-C_4H_9)
2g[b] (minor)	3.68, 3.62 (2 s, 6 H, 2 OCH_3), 3.53 (dd, *J* = 5.7, 8, 1 H, CH), 2.97 (dd, *J* = 5.6, 13.4, 1 H, CH_2), 1.11 (s, 3 H, CH3)

[a] Recorded on a 200 MHz spectrometer.
[b] Missing signals are hidden by the signals of the major isomer.

aldehyde **1**, no clear effect of this additional chiral unit is recorded. The diastereoselectivities of series *a* and *b* are rather similar and mainly dependent on the size of the amino acid substituent R^1.[19]

Conclusion

We could demonstrate in this study that methyl 2-siloxycyclopropanecarboxylates **A** may serve as equivalent of β-formyl esters **B** in the Ugi 5-center 4-component reaction. The primary products **2** are interesting in themselves, since compounds of this type or derivatives thereof may have biological activity. The four functional groups in **2** provide many possibilities for further transformations – as an example the cyclization to pyrrolidine derivatives **4** has been performed. If executed in a one-pot sequence the overall process may be classified as a 6-center 4-component reaction. Since precursor cyclopropanes **A** are easily available in many structural variations, this new modification of the Ugi reaction as presented here should allow preparation of highly diverse libraries of compounds **2** or **4** as well as of other products. The diastereoselectivity of the reactions is moderate to good depending on the amino acid employed and deserves further investigations.

All reactions were performed under argon in flame-dried flasks, and the components were added by means of syringes. All solvents were dried by standard methods. IR spectra were measured with a Perkin Elmer spectrometer IR-325 or Nicolet 205. ^{1}H and ^{13}C NMR spectra were recorded on Bruker instruments (AC 200, AC 300 or DXR 500) in $CDCl_3$ solution. The chemical shifts are given in relative to the TMS or to the $CDCl_3$ signal (δ_H = 7.27, δ_C = 77.0). Missing signals of minor isomers are hidden by signals of major isomers, or they could not be unambiguously identified due to low intensity. Neutral alumina (activity III, Fa. Merck) was used for column chromatography. Melting points (uncorrected) were measured with an apparatus from Büchi (SMP-20). Optical rotations were determined in a 1 mL cell with a pathlength of 10 cm using a Perkin-Elmer 241 polarimeter (Na D-line). The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and the concentrations are given in g/100 mL. Amino acids were commercially available and were used as received.

Siloxycyclopropanes **3a–d**,[20] and the formyl ester **1**[15] were prepared by literature known methods.

Iminodicarboxylic Derivatives 2, General Procedure 1

To a solution of γ-keto ester **1** or cyclopropanecarboxylate **3** (1.0 equiv) in MeOH (10 mL/mmol), the appropriate amino acid (1.0 equiv) and *tert*-butylisonitrile (1.0 equiv) were added at –30 °C. The

Table 4 ^{13}C NMR Data of Primary Products **2**

Product	^{13}C NMR ($CDCl_3$, 75.5 MHz), δ
2a[a]	174.2, 174.0, 173.2, 173.0, 172.2, 171.7, 171.3, 171.0, 170.6 (9 s, *C*O_2Me, *C*ONH*t*-Bu), 137.5, 136.9, 136.8, 136.7, 129.4, 129.3, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 127.2, 127.0, 126.9 (4 s, 11 d, C_6H_5), 66.0, 65.8, 65.7, 65.6, 62.8, 62.3, 62.1, 59.3 (8 d, CHN), 52.0, 51.9, 51.8, 51.5, 51.4, 51.3, 50.8 (7 q, OCH_3), 50.8, 50.7, 50.2, 50.1 [4 s, *C*$(CH_3)_3$], 40.3, 39.1, 38.9, 38.0, 37.8, 37.7, 37.6, 37.5 (8 t, CH_2), 33.8, 33.7, 33.6, 33.1 (4 d, CH), 28.7, 28.6, 28.55, 28.5 [4 q, C(*C*$H_3)_3$], 16.0, 15.6, 15.2, 15.1 (4 q, CH_3)
2b[a]	175.5, 174.7, 173.3, 172.9, 171.9, 171.5, 171.2, 171.1 (8 s, *C*O_2Me, *C*ONH*t*-Bu), 136.5–110.6 (several s and d, indolyl-C), 66.1, 62.1, 61.5, 61.45, 61.4, 58.6, 52.9, 52.8 (8 d, CHN), 51.9-51.4 (several q, OCH_3), 50.7, 28.6, 28.56, 28.4 [s, 3 q, C$(CH_3)_3$], 37.8–37.5, 32.0–30.5 (several t, CH_2), 33.7, 33.65, 33.4, 28.4 (4 d, CH), 15.9, 15.6, 15.0 (3 q, CH_3)
2c	175.3, 175.0, 174.8, 173.8, 173.3, 173.1, 171.9, 171.7, 171.6, 171.5, 170.9, 170.7 (12 s, *C*O_2Me, *C*ONH*t*-Bu), 69.3, 68.2, 65.9, 65.8, 65.2, 64.8, 64.6, 64.5 (8 d, CHN), 52.6, 52.5, 51.9, 51.7, 51.6, 51.6, 51.5, 51.4 (8 q, OCH_3), 51.3, 51.0, 50.8, 50.6, 28.7, 28.6, 28.5, 28.4 [4 s, 4 q, C$(CH_3)_3$], 37.8, 37.7, 37.6, 37.3 (4 t, CH_2), 34.0, 33.7, 33.6, 33.3, (4 d, CH), 21.1, 20.0, 19.7, 17.9, 16.0, 15.5, 15.4, 15.3, 14.5, 14.1, 13.8, 13.4 (12 q, CH_3)
2d (major)	173.9, 173.6, 172.2 (3 s, *C*O_2Me, *C*ONH*t*-Bu), 136.8, 129.3, 129.1, 128.6 (s, 3 d, C_6H_5), 61.8, 61.6 (2 d, 2 CH), 51.8, 51.5 (2 q, 2 OCH_3), 50.5, 28.6 [s, q, C$(CH_3)_3$], 39.0, 30.0, 28.5 (3 t, 3 CH_2)
2d (minor)	174.8, 173.7, 171.9 (3 s, *C*O_2Me, *C*ONHBu-*t*), 137.5, 129.1, 128.6, 126.9 (s, 3 d, C_6H_5), 62.1, 61.9 (2 d, 2 CH), 51.9, 51.55 (2 q, 2 OCH_3), 50.0, 28.3 [s, q, C$(CH_3)_3$], 40.1, 30.5, 28.9 (3 t, 3 CH_2)
2e (major)	174.7, 173.7, 172.3 (3 s, *C*O_2Me, *C*ONH*t*-Bu), 60.6, 55.1 (2 d, CHN), 51.8, 51.5 (2 q, OCH_3), 50.5, 28.5 [s, q, C$(CH_3)_3$], 30.3, 28.5 (2 t, CH_2), 17.8 (q, CH_3)
2e (minor)	175.5, 173.6, 172.2 (3 s, *C*O_2Me, *C*ONH*t*-Bu), 61.9, 55.4 (2 d, CHN), 51.7, 51.3 (2 q, OCH_3), 50.3, 28.4 [s, q, C$(CH_3)_3$], 30.4, 28.6 (2 t, CH_2), 19.6 (q, CH_3)
2f (major)	174.6, 173.9, 172.5 (3 s, *C*O_2Me, *C*ONH*t*-Bu), 64.9, 62.2 (2 d, CHN), 51.7, 51.6 (2 q, OCH_3), 50.7, 28.6 [s, q, C$(CH_3)_3$], 38.1 (d, CH), 30.3[b] (t, CH_2), 25.4 (t, CH_2), 15.3 (q, CH_3), 11.5 (q, CH_3)
2f (minor)	174.9, 173.8, 172.3 (3 s, *C*O_2Me, *C*ONH*t*-Bu), 65.0, 62.4 (2 d, CHN), 51.6, 51.5 (2 q, OCH_3), 50.4, 28.7 [s, q, C$(CH_3)_3$], 38.4 (d, CH), 30.6, 28.9, 24.8 (3 t, 3 CH_2), 16.4, 11.6 (2 q, CH_3)
2g (major)	176.4, 173.7, 173.6 (3 s, *C*O_2Me, *C*ONH*t*-Bu), 137.0, 129.4, 128.6, 127.0 (s, 3 d, C_6H_5), 61.8 (s, CNH), 58.1 (d, CH), 52.0, 51.6 (2 q, OCH_3), 50.3, 28.5 [s, q, C$(CH_3)_3$], 41.8, 35.6, 29.7 (3 t, 3 CH_2), 21.4 (q, CH_3)
2g (minor)	175.8, 174.0 (2 s, *C*O_2Me, *C*ONH*t*-Bu), 136.9, 129.3 (s, d, C_6H_5), 61.5 (s, CNH), 57.2 (d, CH), 51.5 (q, OCH_3), 50.5, 28.6 [s, q, C$(CH_3)_3$], 41.2, 33.3, 28.7 (3 t, 3 CH_2), 22.9 (q, CH_3)

[a] Recorded on a 50.3 MHz spectrometer.
[b] Two C atoms.

resulting suspension was allowed to warm up to r.t. and stirred for the time indicated in Table 1. After removal of MeOH the residue was purified by column chromatography. The spectroscopic data are compiled in Tables 3 and 4.

Lactams 4, General Procedure 2

A solution of primary product **2** in toluene (3 mL/mmol) was stirred for 3 h (exception **2f**: 96 h) under reflux (Table 2). After evaporation of the solvent the residue was purified by column chromatography. The spectroscopic data are compiled in Tables 4 and 5.

Methyl 2-(2-*tert*-Butylcarbamoyl-3-methyl-5-oxopyrrolidin-1-yl)-3-phenylpropanoate (4a); One-pot Procedure

According to the general procedure 1, cyclopropanecarboxylate **3a** (0.404 g, 2.0 mmol), phenylalanine (0.330 g, 2.0 mmol), and *tert*-butylisonitrile (0.166 g, 2.0 mmol) in MeOH (20 mL) were stirred for 50 h at r.t. After removal of the solvent, the residue was dissolved in toluene (10 mL) and the solution was heated for 3 h. Column chromatography (hexane–EtOAc, 1:1) of the crude product yielded **4a** (0.483 g, 67%) as a mixture of 4 diastereomers (51:41:4:4). An amount of 56 mg of the major *cis* diastereomer could be separated; $[\alpha]_D^{23}$ –88.3 (*c* = 0.49, $CHCl_3$). The spectroscopic data are compiled in Tables 4 and 5.

Methyl 2-(2-*tert*-Butylcarbamoyl-3,3-dimethyl-5-oxopyrrolidin-1-yl)-3-phenylpropanoate (4g); One-pot Procedure

According to the general procedure 1, cyclopropanecarboxylate **3c** (0.648 g, 3.0 mmol), phenylalanine (0.495 g, 3.0 mmol), and *tert*-butylisonitrile (0.249 g, 3.0 mmol) in MeOH (30 mL) were stirred for 72 h at r.t. and subsequently 24 h under reflux. Column chromatography (hexane–EtOAc, 1:1 → 2:1) of the resulting crude product yielded **4g** (0.157 g, 16%, mixture of 2 diastereomers = 53:47) as a colourless resin.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major diastereomer) = 7.32–7.20 (m, 5 H, C_6H_5), 6.55 (br s, 1 H, NH), 5.02 (dd, *J* = 7, 10 Hz, 1 H, 1'-H), 3.68 (s, 3 H, OCH_3), 3.50 (s, 1 H, 2-H), 3.30 (dd, *J* = 7, 14.5 Hz, 1 H, 2'-H), 2.98 (dd, *J* = 10, 14.5 Hz, 1 H, 2'-H), 2.45 (d, *J* = 16.5 Hz, 1 H, 4-H), 1.98 (d, *J* = 16.5 Hz, 1 H, 4-H), 1.34 (s, 9 H, *t*-C_4H_9), 1.08, 0.80 (2 s, 3 H each, 3-CH_3);

δ (minor diastereomer) = 7.32–7.20 (m, 5 H, C_6H_5), 7.05 (br s, 1 H, NH), 4.12 (dd, *J* = 6.5, 10 Hz, 1 H, 1'-H), 3.82 (s, 3 H, OCH_3), 3.43 (dd, *J* = 10, 14 Hz, 1 H, 2'-H), 3.34 (dd, *J* = 6.5, 14 Hz, 1 H, 2'-H), 2.97 (s, 1 H, 2-H), 2.33 (d, *J* = 16.5 Hz, 1 H, 4-H), 2.03 (d, *J* = 16.5 Hz, 1 H, 4-H), 1.33 (s, 9 H, *t*-C_4H_9), 1.02, 0.75 (2 s, 3 H each, 3-CH_3).

Table 5 ^{1}H NMR Data of Lactams **4**

Product	^{1}H NMR (300 MHz, $CDCl_3$/TMS); δ, *J* (Hz)
4a[a] (*cis*)	7.42–7.08 (m, 6 H, C_6H_5, NH), 3.93 (dd, *J* = 6, 10, 1 H, 1'-H), 3.84 (s, 3 H, OCH_3), 3.41 (dd, *J* = 10, 14, 1 H, 2'-H), 3.30 (dd, *J* = 6, 14, 1 H, 2'-H), 2.98 (d, *J* = 8.5, 1 H, 2-H), 2.39 (dd, *J* = 7, 13.5, 1 H, 4-H), 2.32–2.19 (m, 2 H, 3-H, 4-H), 1.32 (s, 9 H, *t*-C_4H_9), 0.95 (d, *J* = 6.5, 3 H, 3-CH_3)
4a[a] (*trans*)	7.35 (s, 1 H, NH), 7.32–7.15 (m, 5 H, C_6H_5), 3.97 (dd, *J* = 5.5, 11, 1 H, 1'-H), 3.86 (s, 3 H, OCH_3), 3.47 (dd, *J* = 11, 14, 1 H, 2'-H), 3.36 (dd, *J* = 5.5, 14, 1 H, 2'-H), 2.73 (d, *J* = 4, 1 H, 2-H), 2.60 (dd, *J* = 9, 17, 1 H, 4-H), 2.25–2.18 (m, 1 H, 3-H), 1.86 (dd, *J* = 5, 17, 1 H, 4-H), 1.32 (s, 9 H, *t*-C_4H_9), 0.76 (d, *J* = 7, 3 H, 3-CH_3)
4a[b,c]	7.09, 6.55 (2 br s, 0.5 H each, NH), 3.71, 3.67 (2 s, 1.5 H each, OCH_3), 3.53 (d, *J* = 3, 0.5 H, 2-H), 2.68 (dd, *J* = 8.5, 17, 0.5 H, 2'-H), 2.38 (d, *J* = 7.5, 0.5 H, 2-H), 1.37, 1.36 (2 s, 4.5 H each, *t*-C_4H_9), 1.06, 0.86 (2 d, *J* = 6.5, 7, 1.5 H each, 3-CH_3)
4b[a] (*cis*)	8.16 (br s, 1 H, NH), 7.55–6.98 (m, 6 H, arom CH, NH), 4.11 (dd, *J* = 5, 11, 1 H, 1'-H), 3.86 (s, 3 H, OCH_3), 3.59 (dd, *J* = 11, 15, 1 H, 2'-H), 3.43 (dd, *J* = 5, 15, 1 H, 2'-H), 3.08 (d, *J* = 9, 1 H, 2-H), 2.33 (dd, *J* = 8.5, 16.5, 1 H, 4-H), 2.08 (dd, *J* = 11.5, 16.5, 1 H, 4-H), 2.03–1.92 (m, 1 H, 3-H), 1.26 (s, 9 H, *t*-C_4H_9), 0.88 (d, *J* = 7, 3 H, 3-CH_3)
4b[a] (*trans*)	8.55 (br s, 1 H, NH), 7.55–6.98 (m, 6 H, arom CH, NH), 4.09 (dd, *J* = 5, 11, 1 H, 1'-H), 3.87 (s, 3 H, OCH_3), 3.67 (dd, *J* = 11, 15, 1 H, 2'-H), 3.45 (dd, *J* = 5, 15, 1 H, 2'-H), 2.67 (d, *J* = 4, 1 H, 2-H), 2.55 (dd, *J* = 9, 17, 1 H, 4-H), 2.18–2.13 (m, 1 H, 3-H), 1.78 (dd, *J* = 5, 17, 1 H, 4-H), 1.28 (s, 9 H, *t*-C_4H_9), 0.50 (d, *J* = 7, 3 H, 3-CH_3)
4b[b,d]	8.60 (br s, 1 H, NH), 7.54, 7.51 (br s, 1 H, NH_{indol}), 3.80, 3.85 (2 s, 3 H, OCH_3), 0.89, 0.55 (2 d, *J* = 7 each, 3 H, 3-CH_3)
4c[a] (*cis*)	7.25 (s, 1 H, NH), 4.41 (q, *J* = 7.6, 1 H, 1'-H), 4.02 (d, *J* = 9, 1 H, 2-H), 3.77 (s, 3 H, OCH_3), 2.74–2.67 (m, 1 H, 3-H), 2.45 (dd, *J* = 8.5, 16.6, 1 H, 4-H), 2.23 (dd, *J* = 11.3, 16.6, 1 H, 4-H), 1.43 (d, *J* = 7.7, 3 H, 2'-H), 1.35 (s, 9 H, *t*-C_4H_9), 1.13 (d, *J* = 7, 3 H, 3-CH_3)
4c (*trans*)	6.80 (s, 1 H, NH), 4.07 (q, *J* = 7.2, 1 H, 1'-H), 3.77 (s, 3 H, OCH_3), 3.57 (d, *J* = 3.1, 1 H, 2-H), 2.67 (dd, *J* = 8.3, 16.8, 1 H, 4-H), 2.48–2.43 (m, 1 H, 3-H), 1.93 (dd, *J* = 3.7, 16.8, 1 H, 4-H), 1.42 (d, *J* = 7.2, 3 H, 2'-H), 1.34 (s, 9 H, *t*-C_4H_9), 1.22 (d, *J* = 7, 3 H, 3-CH_3)
4d[a] (major)	7.58 (s, 1 H, NH), 7.31–7.25, 7.14–7.12 (2 m, 3 H, 2 H, C_6H_5), 3.88–3.86 (m, 1 H, 1'-H), 3.86 (s, 3 H, OCH_3), 3.40 (dd, *J* = 11.4, 13.8, 1 H, 2'-H), 3.31 (dd, *J* = 5, 13.8, 1 H, 2'-H), 2.92 (q, *J* = 3.8, 1 H, 2-H), 2.41–2.34, 2.25–2.19, 2.03–1.88 (3 m, 1 H, 1 H, 2 H, 3-H, 4-H), 1.30 (s, 9 H, *t*-C_4H_9)
4d[b] (minor)	3.85 (s, 3 H, OCH_3), 1.29 (s, 9 H, *t*-C_4H_9)
4e	7.63, 6.87 (2 br s, 0.36 H, 0.64 H, NH), 4.18–4.03, 3.73–3.60 (2 m, 1 H each, CH), 3.79, 3.80 (2 s, 3 H each, OCH_3), 2.59–2.05 (m, 4 H, CH_2), 1.90–0.85 (m, 12 H, CH_3, with s at δ = 1.36, *t*-C_4H_9)
4f	6.81, 6.45 (2 br s, 0.85 H, 0.15 H, NH), 4.48 (dd, *J* = 3, 9, 0.15 H, 2-H), 4.11 (dd, *J* = 3, 9.5, 0.85 H, 2-H), 4.06 (d, *J* = 7.5, 1 H, 1'-H), 3.77, 3.72 (2 s, 2.55 H, 0.45 H, OCH_3), 2.69–2.51, 2.41–2.25, 2.21–1.95 (3 m, 1 H, 2 H, 2 H, 3-H, 4-H, 2'-H), 1.62–1.51 (m, 1 H, 3'-H), 1.37, 1.35 (2 s, 7.65 H, 1.35 H, *t*-C_4H_9), 1.19–1.02 (m, 1 H, 3'-H), 0.96 (d, *J* = 7, 1 H, 2'-CH_3), 0.88 (t, *J* = 7.5, 1 H, 4'-H)

[a] Recorded on a 500 MHz spectrometer.
[b] Missing signals are hidden by the signals of the major isomer.
[c] Overlapped with signals of both 4% diastereomers of **4a**.
[d] Overlapped with signals of both 3% diastereomers of **4b**.

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (major diastereomer) = 175.6, 171.7, 168.6 (3 s, *C*O_2Me, CON), 135.9, 128.8, 128.6, 127.1 (s, 3 d, C_6H_5), 70.5 (d, C-2), 55.4 (d, C-1'), 52.5 (q, OCH_3), 51.7, 28.6 [s, q, $C(CH_3)_3$], 44.4 (t, C-4), 37.3 (s, C-3), 34.5 (t, C-2'), 29.7, 23.9 (2 q, 3-CH_3); δ (minor diastereomer) = 174.7, 171.0, 168.5 (3 s, *C*O_2Me, CON), 136.7, 129.2, 128.8, 127.1 (s, 3 d, C_6H_5), 74.5 (d, C-2), 58.6 (d, C-1'), 52.8 (q, OCH_3), 51.1, 28.6 [s, q, $C(CH_3)_3$], 45.1 (t, C-4), 36.4 (s, C-3), 34.7 (t, C-2'), 29.7, 24.4 (2 q, 3-CH_3).

IR (neat): ν = 3330 (N–H), 3100–2940 (=C–H, C–H), 1730 (C=O, ester), 1700 (C=O, lactam), 1675 cm^{-1} (C=O, amide).

MS (EI, 70 eV): *m*/*z* (%) = 734 (M^+, 1), 276 (15), 274 (70), 214 (15), 91 (12), 57 (15), 41 (13), 32 (100), 26 (13).

Anal. Calcd for $C_{21}H_{30}N_2O_4$ (374.5): C, 67.36; H, 8.07; N, 7.48. Found C, 67.70; H, 8.56; N, 7.95.

2-(2-*tert*-Butylcarbamoylpyrrolidin-1-yl)-3-phenylpropan-1-ol (5d)

To a solution of the isomerically pure lactam **4d** (0.030 g, 0.086 mmol) in anhyd THF (2 mL) was added $LiAlH_4$ (0.026 g, 0.688 mmol) and the suspension was stirred for 16 h at r.t. Then the reaction mixture was carefully treated with H_2O (0.03 mL), aq 2 N NaOH solution (0.06 mL) and again with H_2O (0.03 mL). After extraction with EtOAc (3 × 5 mL) the combined organic phases were dried (Na_2SO_4) and concentrated to provide the crude product (0.030 g). Purification by colum chromatography (silica gel, EtOAc–MeOH, 95:5) afforded 0.021 g (81%) of **5d** as colorless crystals, mp 125–127 °C; $[\alpha]_D^{22}$ +37.6 (*c* = 0.34, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (s, 1 H, NH), 7.31–7.14 (m, 5 H, C_6H_5), 3.63–3.49 (m, 2 H, 1'-H), 3.33 (dd, *J* = 4, 9.7 Hz, 1 H, 2-H), 3.12–3.06, 3.01–2.93, 2.85–2.73 (3 m, 4 H, 5-H, 2'H, 3'-H), 2.55 (dd, *J* = 9.8, 13.4 Hz, 1 H, 3'-H), 2.14–1.67 (m, 5 H, 3-H, 4-H, OH), 1.31 (s, 9 H, *t*-C_4H_9).

Table 6 ^{13}C NMR Data of Lactams **4**[a]

Product	C-2 (d)	C-3 (d)	C-4 (t)	C-5 (s)	Other Signals
4a[b] (*cis*)	68.4	30.9	37.5	168.0	175.2 (s, *C*ONH*t*-Bu), 170.7 (s, *C*O_2Me), 136.9, 129.0, 128.8, 127.2 (s, 3 d, C_6H_5), 59.3 (d, C-1'), 52.9 (q, OCH_3), 51.6, 28.6 [s, q, $C(CH_3)_3$], 34.5 (t, C-2'), 15.6 (q, 3-CH_3)
4a[b] (*trans*)	71.8	33.1	37.8	170.6	175.1 (s, *C*ONH*t*-Bu), 171.0 (s, *C*O_2Me), 136.6, 129.3, 128.9, 127.2 (s, 3 d, C_6H_5), 58.8 (d, C-1'), 53.0 (q, OCH_3), 51.2, 28.5 [s, q, $C(CH_3)_3$], 34.2 (t, C-2'), 20.9 (q, 3-CH_3)
4a[c]	67.9 64.2	33.9 31.9	37.4 37.2	170.7 168.3	176.5, 176.1 (2 s, *C*ONH*t*-Bu), 172.5, 170.6 (2 s, *C*O_2Me), 135.9, 135.8, 129.3, 129.2, 128.7, 128.4, 127.1, 126.9 (2 s, 6 d, C_6H_5), 56.1, 55.6 (2 d, C-1'), 52.7, 52.5 (2 q, OCH_3), 51.7, 51.6, 28.5 [2 s, q, $C(CH_3)_3$], 34.6, 34.4 (2 t, C-2'), 20.6, 15.4 (2 q, 3-CH_3)
4b (*cis*)	68.2	30.7	37.6	168.3	175.4, 171.0 (2 s, *C*O_2Me, *C*ONH*t*-Bu), 136.2, 127.2, 122.4, 122.3, 119.5, 118.2, 111.4, 111.1 (2 s, 5 d, s, indolyl-C), 58.9 (d, C-1'), 52.9 (q, OCH_3), 51.6, 28.4 [s, q, $C(CH_3)_3$], 24.1 (t, C-2'), 15.5 (q, 3-CH_3)
4b (*trans*)	71.6	32.9	37.7	170.9	175.4, 171.2, (3 s, *C*O_2Me, *C*ONH*t*-Bu), 136.3, 127.2, 122.8, 122.3, 119.7, 118.3, 111.4, 110.7 (2 s, 5 d, s, indol-C), 58.5 (d, C-1'), 53.0 (q, OCH_3), 51.2, 28.6 [s, q, $C(CH_3)_3$], 23.8 (t, C-2'), 20.4 (q, 3-CH_3)
4c[b] (*cis*)	64.6	31.5	37.7	168.6	175.9 (s, *C*ONH*t*-Bu), 173.5 (s, *C*O_2Me), 52.8 (q, OCH_3), 51.7 (d, C-1'), 51.6, 28.6 [s, q, $C(CH_3)_3$], 15.8 (q, 3-CH_3), 14.2 (q, C-2')
4c[b] (*trans*)	69.4	33.3	37.7	170.6	175.0 (s, *C*ONH*t*-Bu), 171.6 (s, *C*O_2Me), 52.7 (q, OCH_3), 52.0 (d, C-1'), 51.4, 28.6 [s, q, $C(CH_3)_3$], 21.1 (q, 3-CH_3), 13.8 (q, C-2')
4d[b] (major)	64.5	25.2, t	29.3	170.7	175.9, 171.0 (2 s, *C*O_2Me, *C*ONH*t*-Bu), 136.9, 129.0, 128.9, 127.3 (s, 3 d, C_6H_5), 59.5 (d, C-1'), 53.1 (q, OCH_3), 51.4, 28.6 [s, q, $C(CH_3)_3$], 34.2 (t, C-2')
4d[b] (minor)	60.3	34.4, t	25.7	170.9	176.9, 172.2 (2 s, *C*O_2Me, *C*ONH*t*-Bu), 136.7 (s, C_6H_5), 56.3 (d, C-1'), 52.4 (q, OCH_3), 51.2, 28.3 [s, q, $C(CH_3)_3$]
4e (major)	61.9	29.4, t	25.7	171.2	175.8, 174.0 (2 s, *C*O_2Me, *C*ONH*t*-Bu), 52.7 (d, C-1'), 52.0 (q, OCH_3), 51.4, 28.7 [s, q, $C(CH_3)_3$], 14.1 (q, CH_3)
4e (minor)	60.7	29.3, t	25.0	171.5	176.9, 171.7 (2 s, *C*O_2Me, *C*ONH*t*-Bu), 51.9 (q, OCH_3), 51.7 (d, C-1'), 51.3, 28.8 [s, q, $C(CH_3)_3$], 14.15 (q, CH_3)
4f (major)	61.2	29.35, t	25.5	170.8	176.1, 171.2 (2 s, *C*O_2Me, *C*ONH*t*-Bu), 62.6 (d, C-1'), 52.2 (q, OCH_3), 51.4, 28.5 [s, q, $C(CH_3)_3$], 35.4 (d, C-2'), 24.8 (t, C-3'), 16.3, 11.2 (2 q, 2 CH_3)
4f (minor)	59.4	29.25, t	26.4	171.5	176.1, 171.3 (2 s, *C*O_2Me, *C*ONH*t*-Bu), 59.7 (d, C-1'), 52.1 (q, OCH_3), 51.4, 28.5 [s, q, $C(CH_3)_3$], 33.8 (d, C-2'), 26.0 (t, C-3'), 15.4, 10.9 (2 q, 2 CH_3)

[a] 75.5 MHz, $CDCl_3$, δ.
[b] Recorded on a 126 MHz spectrometer.
[c] Overlapped with signals of both 4% diastereomers of **4a**.

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 174.4 (s, *C*ONH*t*-Bu), 139.0, 129.1, 128.6, 126.3 (s, 3 d, C_6H_5), 65.0 (d, C-2), 63.5 (d, C-2'), 62.0 (t, C-1'), 50.3, 28.6 [s, 3 q, $C(CH_3)_3$], 46.0 (t, C-3'), 32.7, 31.0 (2 t, C-3, C-4).

IR (KBr): ν = 3300 (br, O−H, N−H), 2990–2930 (C−H), 1695 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{28}N_2O_2$ (304.4): C, 70.99; H, 9.27; N, 9.24. Found C, 70.51; H, 9.08; N, 8.96.

2-(2-*tert*-Butylcarbamoyl-3-methylpyrrolidin-1-yl)-1-propanol (5c)

According to the procedure described above, a mixture of lactam **4c** (0.200 g, 0.704 mmol) and $LiAlH_4$ (0.191 g, 6.20 mmol) in anhyd THF (15 mL) was stirred for 18 h. Workup and purification of the crude product (0.252 g) by chromatography (silica gel, EtOAc–MeOH, 95:5) yielded 0.028 g (16%) of isomerically pure compound **5c** and 0.077 g (45%) of **5c** as a mixture of four diastereomers (30:30:30:10).

The isolated pure diastereomer of **5c**

$[\alpha]_D^{23}$ +67.0 (*c* = 0.42, $CHCl_3$).

^1H NMR (270 MHz, $CDCl_3$): δ = 7.35 (s, 1 H, NH), 3.39 (d, *J* = 8 Hz, 2 H, 1'-H), 3.25–3.00, 2.85–2.76 (2 m, 2 H, 3 H, 3-H, 5-H, 2'-H, OH), 2.63 (d, *J* = 9 Hz, 1 H, 2-H), 2.20–2.03, 1.95–1.78 (2 m, 1 H each, 4-H), 1.35 (s, 9 H, *t*-C_4H_9), 1.05, 0.87 (2 d, *J* = 7 Hz, 3 H each, 3-CH_3, 3'-H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.9 (s, *C*ONH*t*-Bu), 72.7 (d, C-2), 65.1 (t, C-1'), 56.4 (d, C-2'), 50.3, 28.7 [s, 3 q, $C(CH_3)_3$]), 43.2 (t, C-5), 38.9 (d, C-3), 32.4 (t, C-4), 20.1, 10.0 (2 q, 3-CH_3, C-3').

NMR signals of the other 3 diastereomers (* Signal has double intensity).

^1H NMR (270 MHz, $CDCl_3$): δ = 7.30, 7.25 (2 br s, 0.7 H, 0.3 H, NH), 3.43, 3.41, 3.40 (3 d, *J* = 8 Hz each, 2 H, 1'-H), 3.20–2.20 (m, 7 H, 2-H, 3-H, 4-H, 5-H, 2'-H, OH), 1.98–1.83 (m, 1 H, 4-H), 1.35

(s, 9 H, *t*-C_4H_9), 1.08, 0.95, 0.93, 0.89, 0.88, 0.875 (6 d, *J* = 7 Hz each, 6 H, 3-CH_3, 3'-H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.5*, 172.1 (2 s, *C*ONH*t*-Bu), 71.2, 68.4* (2 d, C-1'), 65.0, 62.6, 61.6 (3 t, C-2), 58.9, 56.9, 56.4 (3 d, C-2'), 50.5, 50.2, 50.0, 28.7*, 28.6 [3 s, 2 q, $C(CH_3)_3$], 44.5, 43.2, 39.5 (3 t, C-5), 36.0, 33.3* (2 d, C-3), 32.1*, 29.9 (2 t, C-4), 20.5, 15.7*, 14.4, 10.4*, 10.0, 9.95 (6 q, 3-CH_3, C-3').

IR (KBr): ν = 3350 (br, O–H, N–H), 2990–2900 (C–H), 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{26}N_2O_2$ (242.4): C, 64.43; H, 10.81; N, 11.61. Found C, 63.98; H, 10.68; N, 11.96.

X-Ray Crystal Structure Analysis of the Pyrrolidine 5d

Crystals of **5d** suitable for X-ray analysis were obtained by recrystallization from hexane–EtOAc.

$C_{18}H_{28}N_2O_2$, M_r = 304.4; T = 153(2) K; crystal size: 0.92 × 0.62 × 0.5 mm; orthorhombic, space group $P2_12_12_1$, a = 6.3389(6), b = 9.4044(9), c = 30.300(3) Å; V = 1806.3(3) $Å^3$; Z = 4; D_c = 1.119 Mg/m^3; F(000) = 664; μ (Mo-K) = 0.073 mm^{-1}. Φ range for data collection: 2.27–30.03°; index ranges: $-8 \le h \le 8$, $-13 \le k \le 13$, $-42 \le l \le 42$; reflections collected/unique: 21156/5258 (R_{int} = 0.0204); final *R* [I>2σ(I)]: *R*1 = 0.0547, *wR*2 = 0.1451; *R* (all data): *R*1 = 0.0633, *wR*2 = 0.1518. For structure solution and refinement, the programs SHELXS97 and SHELXL97 were used.[21] Atomic coordinates and further crystallographic details have been deposited at the Cambridge Crystallographic Data Centre, deposition number CCDC 162256, and copies of this data can be obtained in application to CCDC, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK (fax: +44 1223-336033; E-mail: deposit@ccdc.cam.ac.uk).

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