A Convenient New Synthesis of 3-Substituted β-Lactams Formally Derived from 1-(Aminomethyl)cyclopropanecarboxylic Acids[‡]

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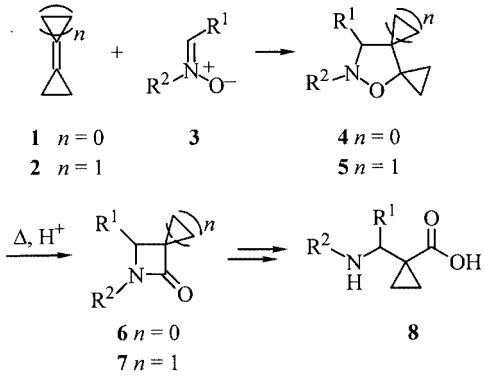
1,3-Dipolar cycloaddition of *N*-benzyl-*C*-(methoxycarbonyl)-nitrone (**3a**), *N*-benzyl-*C*-phenylnitrone (**3b**), *N*-benzyl-*C*-cyanonitrone (**3c**), *N*-(*p*-methoxybenzyl)-*C*-cyanonitrone (**3d**), *N*-phenyl- (**3e**) and *N*-(2-*p*yridyl)-*C*-methylnitrones (**3f**) to bicyclopropylidene (**2**) gave the corresponding cycloadducts **5a**−**f** in 100, 95, 94, 100, 93 and 71% yields, respectively. Treatment of these bisspirocyclopropanated isoxazolidines with trifluoroacetic acid in acetonitrile furnished the corresponding 3-spirocyclopropanated β-lactams **7a**−**f** in 78, 75, 75, 94, 96 and 96% yields, respectively. The structures of the cycloadduct **5b** and of the β-lactam **9a** were proved by X-ray crystal structure analyses. Thus, this new method furnishes compounds with a 5-azaspiro[2.3]hexan-4-one skeleton in 68−94% overall yield in two simple steps. β-Lactams **7a**, **7b**, and **7d** were converted into their *N*-acyl derivatives **9a**, **9b**, **9d** and **11** in 44, 28, 39 and 78% yields, respectively. Heating of the β-lactams **9b** and **11** with *tert*-butyl glycinate (**12**) or with *tert*-butyl (*S*)-phenylalaninate (**14**) in DMF led to ring-opening of the β-lactam moiety to give β-dipeptides **15**, **16** and **17** in 61, 84 and 79% yields, respectively, while β-lactam **9a** gave the amide **13** (51% yield). β-Lactams **7e** and **7f** turned out not to be transformable into such peptide products

Introduction

Since a number of β-lactams play an important role as powerful anti-infectants,[1] we were pleased to find that 1,3-dipolar cycloadducts **4** of nitrones **3** with methylenecyclopropanes **1** underwent facile and clean fragmentation upon treatment with trifluoroacetic acid to yield β-lactams **6**[2] (for a mechanistic interpretation of this transformation see ref.[2b]). As a logical extension of this method, we immediately conceived the possibility of subjecting the readily available 1,3-dipolar cycloadducts of nitrones **3** with bicyclopropylidene **2**,[3] the bisspirocyclopropanated isoxazolidines **5**, to these fragmentation conditions. By the same reaction mode, these compounds would lead to 2-spirocyclopropanated β-lactams **7** with variable substituents at the 3-position (Scheme 1). This would open up a convenient route to substituted 1-(aminomethyl)cyclopropanecarboxylic acids **8**, a subclass of the cyclopropyl-containing β-alanine analogues,[4] which have recently been reviewed exhaustively.[5] The parent 1-(aminomethyl)cyclopropanecarboxylic acid (**8**, $R^1 = R^2 = H$) has been used by Seebach et al. to build interesting oligo-β-peptides that form ribbon-type arrangements of eight-membered hydrogen-bonded



1 $n = 0$ **3** **4** $n = 0$
2 $n = 1$ **5** $n = 1$

6 $n = 0$ **8**
7 $n = 1$

Scheme 1. 1,3-Dipolar cycloadditions of nitrones **3** to methylenecyclopropane (**1**) and bicyclopropylidene (**2**), and subsequent possible transformations of the cycloadducts **4** and **5**

[‡] Cyclopropyl Building Blocks for Organic Synthesis, 102. For Part 101 see: A. de Meijere, R. R. Kostikov, A. I. Savchenko, S. I. Kozhushkov, *Eur. J. Org. Chem.* **2004**, in press. Part 100: M. Limbach, S. Dalai, A. de Meijere, *Adv. Synth. Catal.* **2004**, *346*, 760−766.

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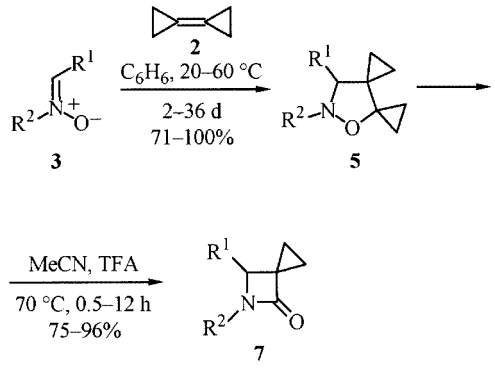
rings.[6a] Thus, a new general route to β-alanine analogues of type **8** would facilitate new studies towards β-peptide analogues incorporating these building blocks. Herein, we report our first successes along these avenues.

Results and Discussion

As could be expected from literature precedents,[7] 1,3-dipolar cycloadditions of *N*-benzyl-*C*-(methoxycarbonyl)-nitrone (**3a**),[8] *N*-benzyl-*C*-phenylnitrone (**3b**),[9] *N*-benzyl-*C*-cyanonitrone (**3c**),[10] *N*-(*p*-methoxybenzyl)-*C*-cyano-nitrone (**3d**), *N*-methyl-*C*-phenyl- (**3e**) and *N*-methyl-*C*-(2-pyridyl)nitrones (**3f**)[11] to bicyclopropylidene (**2**) in benzene at ambient or elevated temperature gave the corresponding cycloadducts **5a**−**f** in 100, 95, 94, 100, 93 and 71% yields, respectively (Scheme 2). As in previous cases, for those cycloadditions that were carried out at moderate temperatures in order to avoid the thermal rearrangement of the cycloadducts **5** at elevated temperature, very long reaction times were necessary (cf. ref.[7]).



3	R^1	R^2	5	%	7	%
a	CO_2Me	Bn	**a**	100	**a**	78
b	Ph	Bn	**b**	95	**b**	75
c	CN	Bn	**c**	94	**c**	75
d	CN	PMB	**d**	100	**d**	94
e	Ph	Me	**e**	93	**e**	96
f	2-Py	Me	**f**	71	**f**	96

PMB = CH_2–C$_6$H$_4$–OMe

Scheme 2. Preparation of cycloadducts **5a**−**f** from nitrones **3a**−**f** and bicyclopropylidene (**2**), and their conversion into β-lactams **7a**−**f**

The structures of **5a**−**f** were assigned on the basis of their NMR spectra. However, no signals for the benzylic CH_2 group or the nitrile and quaternary spirocyclopropane carbon atoms in position 4 were seen in the ^{13}C NMR spectra of **5c** and **5d** at room temperature under standard conditions; at 25 °C these signals are close to coalescence, due to a dynamic conformational exchange of the molecules with a rate close to the NMR time-scale. Upon raising the temperature, these signals became sharp only at 100 °C, and, after cooling, they returned to their initial broadened state (see Exp. Sect.). The structural features of one of the cycloadducts − 8-benzyl-9-phenyl-7-oxa-8-azadispiro-[2.0.2.3]nonane (**5b**) − were established by an X-ray crystal structure analysis (Figure 1).

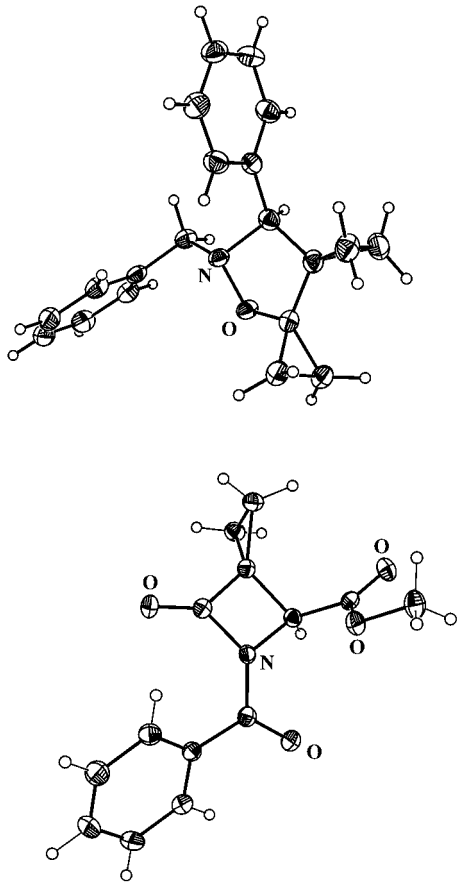
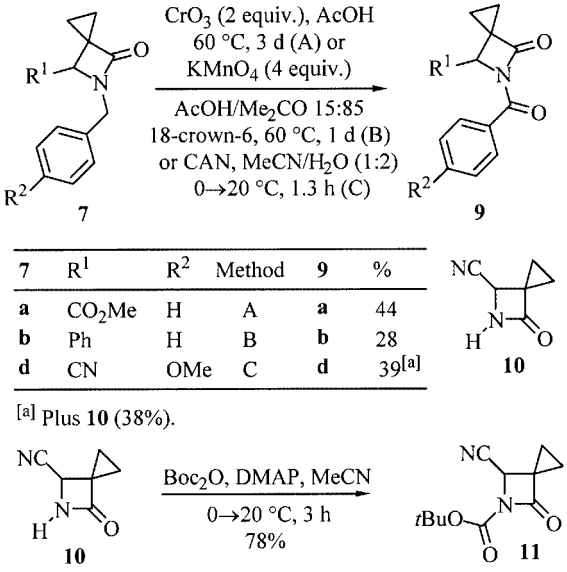


Figure 1. Crystal structures of 8-benzyl-9-phenyl-7-oxa-8-azadispiro[2.0.2.3]nonane (**5b**) and methyl 5-benzoyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (**9a**)[12]

Treatment of compounds **5a**−**f** with trifluoroacetic acid (TFA) in acetonitrile at 70 °C indeed furnished the corresponding 3-spirocyclopropanated β-lactams **7a**−**f** in 78, 75, 75, 94, 96 and 96% yields, respectively, after purification by column chromatography (Scheme 2). Thus, the overall yields of this new approach to compounds with a 5-azaspiro[2.3]hexan-4-one skeleton in two simple steps range from 68−94% (cf. ref.[13]).

An interesting application of the readily available spirocyclopropanated β-lactams **7a**−**f** would be their conversion into small oligopeptides in which the cyclopropanated β-alanines derived from **7a**−**f** would act as a conformational lock.[6] Nucleophilic ring opening of these β-lactams **7** with an appropriately protected glycine derivative should directly lead to simple dipeptides. Such transformations are known, however, to require an additional acyl substituent on the nitrogen.[14] In the present case, the preparation of such activated β-lactams might be achieved by two routes. The first

one would be by *N*-debenzylation of β-lactams **7a**–**d** followed by *N*-acylation. Unfortunately, attempted debenzylation of these compounds by hydrogenation under palladium catalysis led to hydrogenolytic opening of the N–C(R^1) bond of the lactam ring. In the case of **7b**, this bond is also benzylic, and its cleavage is facilitated by ring strain.[15] Attempted debenzylations of **7c** under Birch conditions (sodium in ammonia),[16a] or of **7d** by buffered sodium persulfate,[16b] only led to decomposition of the starting material or no reaction, respectively. However, the alternative approach, in which the benzylic methylene is oxidized to a carbonyl group, turned out to be more successful (Scheme 3). This type of oxidation was achieved for compounds **7a**,**b** with chromium trioxide in acetic acid (method A)[17a] or potassium permanganate in an acetic acid/acetone mixture (method B),[17b] which furnished the corresponding *N*-benzoyl-β-lactams **9a**,**b** in 44 and 28% yields, respectively. The structure of the *N*-benzoyl-β-lactam **9a** was rigorously proved by an X-ray crystal structure analysis (Figure 1).



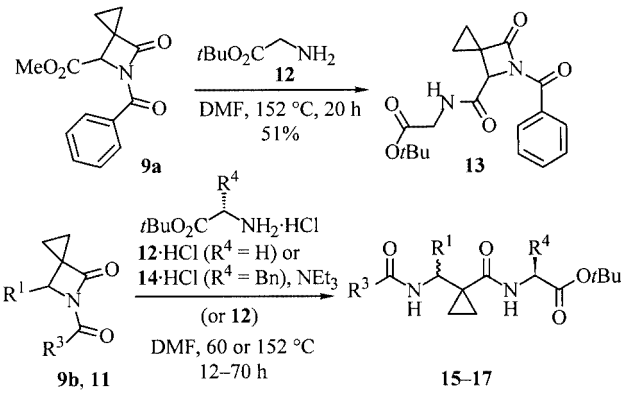
7	R^1	R^2	Method	9	%
a	CO_2Me	H	A	**a**	44
b	Ph	H	B	**b**	28
d	CN	OMe	C	**d**	39[a]

[a] Plus **10** (38%).

Scheme 3. Oxidation of the benzylic methylene group in β-lactams **7a**,**b**,**d**

The methylene group in the more labile *p*-methoxybenzyl group of the β-lactam **7d** can be oxidized using cerium ammonium nitrate (CAN) in aqueous acetonitrile (method C, cf. ref.[17c]). However, this oxidation was accompanied by oxidative *N*-deprotection of **7d**, giving *N*-(*p*-methoxybenzoyl)-β-lactam **9d** and *N*-deprotected β-lactam **10** in almost equal yields (39 and 38%, respectively). The latter was *tert*-butoxycarbonyl protected using an established procedure[17d] (Scheme 3).

The β-lactams **9a**, **9b** and **11** did not react with *tert*-butyl glycinate (**12**) in DMF at ambient temperature. Upon heating of **9a** with **12** in DMF under reflux (152 °C), the ester group was transformed into a *tert*-butoxycarbonylmethylenamido group to give the new lactam **13** (Scheme 4) without ring opening, even after prolonged heating with an excess of **12**. However, the β-lactams **9b** and **11** reacted with **12** in the desired manner under these conditions to give the corresponding β-dipeptides **15** and **16** in 61 and 84% yields, respectively (Scheme 4), as pure colorless solids, after column chromatography (**15**) or without any additional purification (**16**).



Starting Material	R^1	R^3	Product	R^4	%
9b	Ph	Ph	**15**	H	61
11	CN	O*t*Bu	**16**	H	84
11	CN	O*t*Bu	**17**	Bn	81

Scheme 4. Reactions of *N*-acylated β-lactams **9a**,**b** and **11** with *tert*-butyl glycinate (**12**) and *tert*-butyl (*S*)-phenylalaninate (**14**)

Under the same conditions, a 1.1:1 mixture of the diastereomeric dipeptides (2*S*,2′*S*)-**17** and (2*S*,2′*R*)-**17** was obtained from the β-lactam **11** and *tert*-butyl (*S*)-phenylalaninate (**14**). These diastereomeric dipeptides (2*S*,2′*S*)-**17** and (2*S*,2′*R*)-**17** could easily be separated by column chromatography (see Exp. Sect.), and the structure of the latter was established by an X-ray crystal structure analysis (Figure 2). The absolute configuration of the dipeptide (2*S*,2′*R*)-**17** was assigned on the basis of the known (*S*)-configuration of the *tert*-butyl (*S*)-phenylalaninate (**14**) used in the synthesis of **17**.

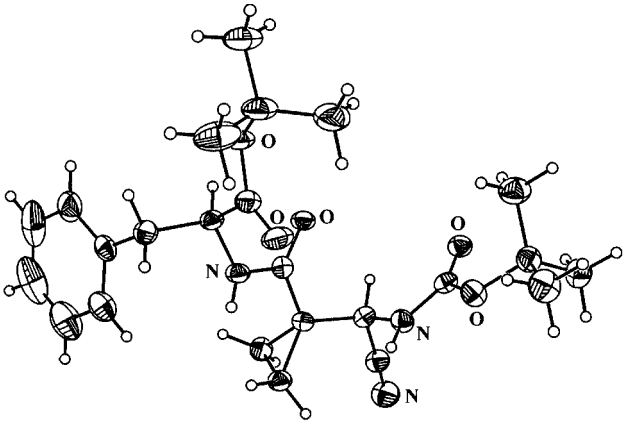


Figure 2. Crystal structure of *tert*-butyl (2*S*,2′*R*)-2-{[1-(*tert*-butoxycarbonylaminocyanomethyl)cyclopropylcarbonyl]amino}-3-phenylpropionate [(2*S*,2′*R*)-**17**][12]

In summary, a new, original and simple two step approach to cyclopropanated β-alanines in their β-lactam form has been developed. In addition, the potential use of these β-lactams in the construction of simple dipeptides incorporating cyclopropanated β-alanines by ring opening with protected amino acids has been demonstrated.

Experimental Section

General: NMR spectra were recorded on Bruker AM 250 (250 MHz for ^{1}H and 62.9 MHz for ^{13}C NMR), Varian Mercury 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C NMR), Unity 300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C NMR) or Inova 600 (150 MHz for ^{13}C NMR) instruments in $CDCl_3$ unless otherwise specified. Multiplicities were determined by DEPT (Distortionless Enhancement by Polarization Transfer) or APT (Attached Proton Test) measurements. Chemical shifts refer to $\delta_{TMS} = 0.00$ according to the chemical shifts of residual $CHCl_3$ signals. IR: Bruker IFS 66 (FT-IR) spectrophotometer, measured as KBr pellets or oils between KBr plates. MS (EI, 70 eV): Finnigan MAT 95 spectrometer. High resolution mass data (HRMS) were obtained by preselected-ion peak matching at R 10000 to be within ± 2 ppm of the exact mass. M.p.: Büchi 510 capillary melting point apparatus, uncorrected values. TLC: Macherey−Nagel precoated sheets, 0.25 mm Sil G/UV$_{254}$. Column chromatography: Merck silica gel, grade 60, 230−400 mesh. Starting materials: bicyclopropylidene (**2**),[18] *N*-benzyl-*C*-(methoxycarbonyl)nitrone (**3a**),[8] *N*-benzyl-*C*-phenylnitrone (**3b**),[9] *N*-benzyl-*C*-cyanonitrone (**3c**),[10] *N*-phenyl- (**3e**) and *N*-(2-pyridyl)-*C*-methylnitrones (**3f**),[11] and *tert*-butyl glycinate (**12**)[19] were prepared according to published procedures. All operations in anhydrous solvents were performed under an argon atmosphere in flame-dried glassware. Diethyl ether was dried by distillation from sodium benzophenone ketyl, DMF and triethylamine from calcium hydride, CH_2Cl_2 and acetonitrile from P_2O_5. *m*CPBA was enriched according to a published procedure.[20] All other chemicals were used as commercially available. Organic extracts were dried over $MgSO_4$ or Na_2SO_4 (for **13**, **15**−**17**).

***N*-(*p*-Methoxybenzyl)-*C*-cyanonitrone (3d):** Chloroacetonitrile (22.6 g, 18.9 mL, 0.30 mol) and K_2CO_3 (55.3 g, 0.40 mol) were added to a vigorously stirred solution of *p*-methoxybenzylamine (27.4 g, 26.1 mL, 0.20 mol) in acetonitrile (2 L). After additional stirring for 12 h at 60 °C, the suspension was filtered through a pad of Celite, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (R_f = 0.20, 660 g of silica gel, 7.5 × 20 cm column, hexane/Et$_2$O, 1:2) to give 28.0 g (80%) of (4-methoxybenzylamino)acetonitrile as a dark oil. This oil (28.0 g, 0.160 mol) was dissolved in anhydrous CH_2Cl_2 (760 mL), and *m*-CPBA (60.7 g, 0.352 mol) was added in small portions at 0 °C. After additional stirring for 30 min at 0 °C and for 1 h at ambient temperature, a 10% aq. solution of $Na_2S_2O_3$ (300 mL) and sat. aq. $NaHCO_3$ solution (300 mL) were added, and the mixture was stirred for an additional 1 h. The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL); the combined organic layers were washed with brine (2 × 200 mL), dried, and concentrated under reduced pressure. Nitrone **3d** (30.4 g, 100%, 1:4 mixture of *E*- and *Z*-isomers) was obtained as a yellow solid and used without purification. An analytical sample was obtained by column chromatography (R_f = 0.24, 20 g of silica gel, 2 × 13 cm column, hexane/Et$_2$O, 1:3) and had m.p. 74−75 °C. IR (KBr): $\tilde{\nu}$ = 3102 cm^{-1}, 2994, 2964, 2937, 2838, 2222, 1616, 1587, 1544, 1520, 1462, 1414. ^{1}H NMR (250 MHz): δ = 3.82 (s, 3 H, OCH_3, *E*-isomer), 3.84 (s, 3 H, OCH_3, *Z*-isomer), 4.94 (s, 2 H, CH_2, *Z*), 5.24 (s, 2 H, CH_2, *E*), 6.53 (s, 1 H, =CH, *Z*), 6.62 (s, 1 H, =CH, *E*), 6.90−6.99 (m, 4 H, Ar−H, *Z*- and *E*-isomers), 7.29−7.33 (m, 2 H, Ar−H, *Z*), 7.44−7.48 (m, 2 H, Ar−H, *E*) ppm. ^{13}C NMR (50.3 MHz): δ = 55.3 (CH_3, *E*), 55.4 (CH_3, *Z*), 69.4 (CH_2, *E*), 71.1 (CH_2, *Z*), 106.8 (CH, *Z*), 107.0 (CH, *E*), 112.1 (C, *Z*), 114.3 (2 CH, *E*), 114.8 (2 CH, *Z*), 115.3 (C, *E*), 122.4 (C, *Z*), 123.5 (C, *E*), 131.0 (2 CH, *E*), 131.5 (2 CH, *Z*), 160.7 (C, *E*), 161.0 (C, *Z*) ppm. MS (EI): *m*/*z* (%) = 190 (2) [M$^+$], 121 (100), 77 (12), 51 (8). $C_{10}H_{10}N_2O_2$ (190.2): calcd. C 63.14, H 5.30, N 14.73; found C 62.88, H 5.49, N 14.93.

Cycloaddition of Nitrones 3c−f to Bicyclopropylidene (2). General Procedure (GP) 1: A solution of the respective nitrone (5 mmol) and bicyclopropylidene (**2**) (0.85 g, 1.0 mL, 10.6 mmol) in benzene (3 mL) was stirred in a hermetically closed tube at the indicated temperature for the indicated time. After cooling to ambient temperature, the solution was concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel.

Methyl 8-Benzyl-7-oxa-8-azadispiro[2.0.2.3]nonane-9-carboxylate (5a): Column chromatography (R_f = 0.14, 115 g of silica gel, 4.5 × 15 cm column, hexane/Et$_2$O, 5:1) of the residue obtained from nitrone **3a** (1.0 g, 5.18 mmol) and bicyclopropylidene (**2**) (832 mg, 0.97 mL, 10.4 mmol) according to GP1 (45 °C, 2 d) gave the cycloadduct **5a** (1.40 g, 100%) as a yellow oil. IR (film): $\tilde{\nu}$ = 3064 cm^{-1}, 3031, 3006, 2953, 1766, 1456, 1437. ^{1}H NMR (250 MHz): δ = 0.27−0.36 (m, 2 H, *c*Pr−H), 0.40−0.46 (m, 1 H, *c*Pr−H), 0.61−0.78 (m, 3 H, *c*Pr−H), 0.91−0.94 (m, 2 H, *c*Pr−H), 3.65 (s, 3 H, OCH_3), 3.68 (s, 1 H, CH), 4.14 (d, J = 12.5 Hz, 1 H, CH_2), 4.37 (d, J = 12.5 Hz, 1 H, CH_2), 7.23−7.41 (m, 5 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 5.5 (CH_2), 6.8 (CH_2), 8.6 (CH_2), 10.7 (CH_2), 30.0 (C), 52.1 (CH_3), 62.8 (CH_2), 66.4 (C), 72.7 (CH), 127.7 (CH), 128.4 (2 CH), 129.4 (2 CH), 136.0 (C), 170.6 (C) ppm. MS (EI): *m*/*z* (%) = 273 (10) [M$^+$], 214 (90), 105 (19), 91 (100). $C_{16}H_{19}NO_3$ (273.3): calcd. C 70.31, H 7.01, N 5.12; found C 70.10, H 6.80, N 5.01.

8-Benzyl-9-phenyl-7-oxa-8-azadispiro[2.0.2.3]nonane (5b): Column chromatography (R_f = 0.44, 165 g of silica gel, 5 × 17 cm column, hexane/Et$_2$O, 10:1) of the residue obtained from nitrone **3b** (3.76 g, 18.0 mmol) and bicyclopropylidene (**2**) (1.60 g, 1.87 mL, 20.0 mmol) according to GP1 (60 °C, 25 d) gave the cycloadduct **5b** (5.0 g, 95%) as a colorless solid, m.p. 70 °C. IR (KBr): $\tilde{\nu}$ = 3067 cm^{-1}, 2998, 2845, 1653, 1636, 1456, 1437. ^{1}H NMR (250 MHz): δ = 0.12−0.35 (m, 2 H, *c*Pr−H), 0.34−0.53 (m, 4 H, *c*Pr−H), 0.85−0.98 (m, 2 H, *c*Pr−H), 4.14 (s, 1 H, CH), 4.08 (m, 2 H, CH_2), 7.20−7.40 (m, 10 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 6.7 (CH_2), 7.3 (CH_2), 7.7 (CH_2), 8.6 (CH_2), 33.0 (C), 61.3 (CH_2), 66.5 (C), 76.3 (CH), 126.8 (CH), 127.6 (CH), 127.9 (2 CH), 128.1 (2 CH), 128.5 (4 CH), 137.7 (C), 138.1 (C) ppm. MS (EI): *m*/*z* (%) = 291 (10) [M$^+$], 262 (5), 235 (5), 129 (30), 115 (18), 91 (100). $C_{20}H_{21}NO$ (291.4): calcd. C 82.44, H 7.27, N 4.81; found C 82.19, H 6.97, N 4.76.

8-Benzyl-9-cyano-7-oxa-8-azadispiro[2.0.2.3]nonane (5c): Column chromatography (R_f = 0.20, 54 g of silica gel, 4 × 10 cm column, hexane/Et$_2$O, 2:1) of the residue obtained from the nitrone **3c** (1.46 g, 9.12 mmol) and bicyclopropylidene (**2**) (1.60 g, 1.9 mL, 20 mmol) according to GP1 (20 °C, 8 d) gave the cycloadduct **5c** (2.07 g, 94%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3066 cm^{-1}, 3031, 2959, 2863, 2246, 1497, 1454. ^{1}H NMR (300 MHz): δ = 0.30−0.49 (m, 2 H, *c*Pr−H), 0.51−0.60 (m, 2 H, *c*Pr−H), 0.80−0.97 (m, 4 H, *c*Pr−H), 3.78 (s, 1 H, CH), 4.11−4.26 (m, 2 H, CH_2), 7.20−7.37

(m, 5 H, Ar-H) ppm. ^{13}C NMR (50.3 MHz): δ = 7.3 (CH_2), 7.7 (CH_2), 8.2 (CH_2), 11.2 (CH_2), 62.5 (CH), 66.6 (C), 128.0 (CH), 128.6 (2 CH), 129.2 (2 CH), 135.0 (C), three carbon atom signals were not detectable at this temperature. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 7.0 (CH_2), 7.4 (CH_2), 7.7 (CH_2), 10.5 (CH_2), 30.6 (C), 60.8 (CH_2), 62.5 (CH), 66.2 (C), 116.1 (C), 127.6 (CH), 128.3 (2 CH), 128.8 (2 CH), 135.3 (C) ppm. MS (EI): *m*/*z* (%) = 239 (20) [M^+ − H], 214 (10), 211 (20), 105 (50), 91 (100). MS (DCI): *m*/*z* (%) = 481 (5) [2 M + H^+], 258 (8) [M + NH_4^+], 241 (100) [M + H^+]. $C_{15}H_{16}N_2O$ (240.3): calcd. C 74.97, H 6.71, N 11.66; found C 74.76, H 6.65, N 11.63.

9-Cyano-8-(4-methoxybenzyl)-7-oxa-8-azadispiro[2.0.2.3]nonane (5d): Column chromatography (R_f = 0.34, 55 g of silica gel, 3 × 17 cm column, hexane/Et_2O, 10:1) of the residue obtained from the nitrone **3d** (2.5 g, 13 mmol) and bicyclopropylidene (**2**) (2.10 g, 2.46 mL, 26.2 mmol) according to GP1 (20 °C, 8 d) gave the cycloadduct **5d** (3.50 g, 100%) as a colorless solid, m.p. 70−71 °C. IR (KBr): $\tilde{\nu}$ = 3075 cm^{-1}, 3010, 2934, 2868, 2838, 2246, 1611, 1585, 1512, 1468. ^{1}H NMR (250 MHz): δ = 0.36−0.70 (m, 4 H, *c*Pr−H), 0.82−1.04 (m, 4 H, *c*Pr−H), 3.80 (s, 3 H, OCH_3), 3.81 (s, 1 H, CH), 4.04−4.28 (m, 2 H, CH_2), 6.85−6.91 (m, 2 H, Ar-H), 7.30−7.37 (m, 2 H, Ar-H) ppm. ^{13}C NMR (50.3 MHz): δ = 7.2 (CH_2), 7.7 (CH_2), 8.2 (CH_2), 11.2 (CH_2), 55.2 (CH_3), 62.3 (CH), 66.5 (C), 114.0 (2 CH), 126.9 (C), 130.5 (2 CH), 159.4 (C), three carbon atom signals were not detectable at this temperature. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 6.9 (CH_2), 7.4 (CH_2), 7.7 (CH_2), 10.5 (CH_2), 30.5 (C), 55.2 (CH_3), 60.2 (CH_2), 62.3 (CH), 66.2 (C), 114.1 (2 CH), 116.2 (C), 127.3 (C), 130.1 (2 CH), 159.4 (C) ppm. MS (EI): *m*/*z* (%) = 270 (20) [M^+], 241 (8), 135 (25), 121 (100). $C_{16}H_{18}N_2O_2$ (270.3): calcd. C 71.09, H 6.71, N 10.36; found C 70.97, H 6.58, N 10.12.

8-Methyl-9-(pyridin-2-yl)-7-oxa-8-azadispiro[2.0.2.3]nonane (5f): Column chromatography (R_f = 0.20, 54 g of silica gel, 4 × 10 cm column, hexane/Et_2O, 2:1) of the residue obtained from the nitrone **3f** (3.0 g, 22.0 mmol) and bicyclopropylidene (**2**) (2.86 g, 3.35 mL, 36 mmol) according to GP1 (60 °C, 36 d) gave the cycloadduct **5f** (3.39 g, 71%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3073 cm^{-1}, 3001, 2956, 2871, 2777, 1590, 1570, 1472, 1434. ^{1}H NMR (250 MHz): δ = 0.03−0.18 (m, 2 H, *c*Pr−H), 0.33−0.42 (m, 2 H, *c*Pr−H), 0.58−0.62 (ddd, *J* = 10.0, 5.0, 5.0 Hz, 1 H, *c*Pr−H), 0.90−0.99 (m, 3 H, *c*Pr−H), 2.90 (s, 3 H, NCH_3), 4.07 (s, 1 H, CH), 7.17−7.20 (m, 1 H, Ar-H), 7.68−7.71 (m, 2 H, Ar-H), 8.44−8.47 (m, 1 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 5.9 (CH_2), 6.5 (CH_2), 9.0 (CH_2), 9.6 (CH_2), 33.1 (C), 45.7 (CH), 66.5 (C), 79.7 (CH_3), 122.5 (CH), 122.8 (CH), 136.8 (CH), 148.3 (CH), 159.3 (C) ppm. MS (EI): *m*/*z* (%) = 216 (2) [M^+], 201 (5), 187 (18), 159 (82), 145 (48), 130 (100), 119 (45), 92 (20), 78 (55), 42 (35). HRMS (EI) calcd. for $C_{13}H_{16}N_2O$ 216.1263 [M^+], found 216.1263. $C_{13}H_{16}N_2O$ (216.3): calcd. C 72.19, H 7.46; found C 72.45, H 7.79.

Preparation of β-Lactams 7a−f. General Procedure (GP) 2: Trifluoroacetic acid (TFA) was added to the solution of the respective isoxazolidine **5** in acetonitrile, and the resulting mixture was stirred at 70 °C for the indicated time. After cooling to ambient temperature, the mixture was filtered through a pad of Celite, concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel.

Methyl 5-Benzyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (7a): Column chromatography (R_f = 0.21, 40 g of silica gel, 3 × 14 cm column, hexane/Et_2O, 1:1) of the residue obtained from the isoxazolidine **5a** (1.41 g, 5.16 mmol) and TFA (0.710 g, 0.480 mL, 6.22 mmol) in acetonitrile (32 mL) according to GP2 (12 h) gave the β-lactam **7a** (990 mg, 78%) as a yellow oil. IR (film): $\tilde{\nu}$ = 3065 cm^{-1}, 3029, 3003, 2953, 2849, 1756, 1729, 1455, 1436. ^{1}H NMR (250 MHz): δ = 0.84−0.92 (m, 1 H, *c*Pr−H), 1.06−1.16 (m, 1 H, *c*Pr−H), 1.18−1.29 (m, 2 H, *c*Pr−H), 3.71 (s, 3 H, OCH_3), 4.02 (s, 1 H, CH), 4.24 (d, *J* = 15.0 Hz, 1 H, CH_2), 4.91 (d, *J* = 15.0 Hz, 1 H, CH_2), 7.25−7.39 (m, 5 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 6.5 (CH_2), 8.0 (CH_2), 37.2 (C), 45.5 (CH_2), 52.1 (CH), 57.4 (CH_3), 127.7 (CH), 128.3 (2 CH), 128.7 (2 CH), 135.2 (C), 170.0 (C), 170.9 (C) ppm. MS (EI): *m*/*z* (%) = 245 (4) [M^+], 217 (20), 186 (30), 158 (40), 91 (100). $C_{14}H_{15}NO_3$ (245.3): calcd. C 68.56, H 6.16, N 5.71; found C 68.45, H 6.08, N 5.49.

5-Benzyl-6-phenyl-5-azaspiro[2.3]hexane-4-one (7b): Column chromatography (R_f = 0.15, 40 g of silica gel, 3 × 14 cm column, hexane/Et_2O, 3:1) of the residue obtained from the isoxazolidine **5b** (1.48 g, 5.08 mmol) and TFA (698 mg, 0.472 mL, 6.12 mmol) in acetonitrile (32 mL) according to GP2 (3 h) gave the β-lactam **7b** (1.0 g, 75%) as a colorless solid, m.p. 64−65 °C. IR (KBr): $\tilde{\nu}$ = 3029 cm^{-1}, 1745, 1653, 1559, 1494, 1456. ^{1}H NMR (250 MHz): δ = 0.37−0.43 (ddd, *J* = 10.0, 7.5, 5.0 Hz, 1 H, *c*Pr−H), 1.01−1.06 (ddd, *J* = 10.0, 7.5, 5.0 Hz, 1 H, *c*Pr−H), 1.09−1.18 (ddd, *J* = 10.0, 7.5, 5.0 Hz, 1 H, *c*Pr−H), 1.24−1.32 (ddd, *J* = 10.0, 7.5, 5.0 Hz, 1 H, *c*Pr−H), 3.85 (d, *J* = 15.0 Hz, 1 H, CH_2), 4.48 (s, 1 H, CH), 4.88 (d, *J* = 15.0 Hz, 1 H, CH_2), 7.15−7.21 (m, 4 H, Ar-H), 7.24−7.43 (m, 6 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 7.2 (CH_2), 8.2 (CH_2), 40.3 (C), 44.5 (CH_2), 61.4 (CH), 127.5 (CH), 127.6 (CH), 128.4 (4 CH), 128.6 (2 CH), 128.7 (2 CH), 135.8 (C), 136.3 (C), 172.4 (C) ppm. MS (EI): *m*/*z* (%) = 263 (36) [M^+], 172 (10), 130 (100), 129 (85), 115 (42), 91 (65). $C_{18}H_{17}NO$ (263.3): calcd. C 82.10, H 6.51, N 5.32; found C 82.0, H 6.25, N 5.12.

5-Benzyl-6-oxo-5-azaspiro[2.3]hexane-4-carbonitrile (7c): Column chromatography (R_f = 0.11, 41 g of silica gel, 3 × 12 cm column, hexane/Et_2O, 2:1) of the residue obtained from the isoxazolidine **5c** (627 mg, 2.61 mmol) and TFA (357 mg, 0.24 mL, 3.13 mmol) in acetonitrile (15 mL) according to GP2 (12 h) gave the β-lactam **7c** (415 mg, 75%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3065 cm^{-1}, 3032, 3009, 2923, 2243, 1772, 1496, 1456, 1382, 1355. ^{1}H NMR (300 MHz): δ = 1.17−1.29 (m, 2 H, *c*Pr−H), 1.32−1.44 (m, 2 H, *c*Pr−H), 4.14 (s, 1 H, CH), 4.25 (d, *J* = 15.1 Hz, 1 H, CH_2), 4.81 (d, *J* = 15.1 Hz, 1 H, CH_2), 7.27−7.42 (m, 5 H, Ar-H) ppm. ^{13}C NMR (75.5 MHz): δ = 8.2 (CH_2), 9.1 (CH_2), 38.3 (C), 46.0 (CH_2), 46.7 (CH), 115.6 (C), 128.3 (CH), 128.4 (2 CH), 129.0 (2 CH), 133.9 (C), 169.8 (C) ppm. MS (EI): *m*/*z* (%) = 212 (85) [M^+], 183 (32), 122 (32), 91 (100), 80 (45), 69 (50). $C_{13}H_{12}N_2O$ (212.25): calcd. C 73.56, H 5.70, N 13.20; found C 73.74, H 5.77, N 13.08.

5-(4-Methoxybenzyl)-6-oxo-5-azaspiro[2.3]hexane-4-carbonitrile (7d): Column chromatography (R_f = 0.10, 44 g of silica gel, 3 × 13 cm column, hexane/Et_2O, 1.5:1) of the residue obtained from the isoxazolidine **5d** (2.00 g, 7.40 mmol) and TFA (1.01 g, 0.68 mL, 8.88 mmol) in acetonitrile (45 mL) according to GP2 (12 h) gave the β-lactam **7d** (1.68 g, 94%) as a colorless solid, m.p. 54−56 °C. IR (KBr): $\tilde{\nu}$ = 3003 cm^{-1}, 2973, 2913, 2867, 2841, 2249, 1754, 1613, 1585, 1515. ^{1}H NMR (250 MHz): δ = 1.14−1.27 (m, 2 H, *c*Pr−H), 1.30−1.44 (m, 2 H, *c*Pr−H), 3.80 (s, 3 H, OCH_3), 4.10 (s, 1 H, CH), 4.18 (d, *J* = 15.0 Hz, 1 H, CH_2), 4.75 (d, *J* = 15.0 Hz, 1 H, CH_2), 6.84−6.93 (m, 2 H, Ar-H), 7.20−7.26 (m, 2 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 8.2 (CH_2), 9.0 (CH_2), 38.2 (C), 45.5 (CH_2), 46.4 (CH), 55.2 (CH_3), 114.3 (2 CH), 115.7 (C), 125.9 (C), 129.8 (2 CH), 159.5 (C), 169.6 (C) ppm. MS (EI): *m*/*z* (%) = 242 (40) [M^+], 213 (15), 121 (100). $C_{14}H_{14}N_2O_2$ (242.3): calcd. C 69.41, H 5.82, N 11.56; found C 69.14, H 5.61, N 11.37.

5-Methyl-6-phenyl-5-azaspiro[2.3]hexan-4-one (7e): Column chromatography (R_f = 0.66, 21 g of silica gel, 14 × 2.5 cm column, CH_2Cl_2/MeOH, 30:1) of the residue obtained from the isoxazolidine **5e** (150 mg, 697 μmol) and TFA (96 mg, 0.10 mL, 840 μmol) in acetonitrile (3 mL) according to GP2 (30 min) gave the β-lactam **7e** (125 mg, 96%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3001 cm^{-1}, 2902, 1751, 1456, 1386, 1172, 1039. ^1H NMR (250 MHz): δ = 0.42 (dt, J = 7.3, 2.6 Hz, 1 H, *c*Pr−H), 1.08−1.18 (m, 2 H, *c*Pr−H), 1.25−1.35 (m, 1 H, *c*Pr−H), 2.86 (s, 3 H, NCH_3), 4.63 (s, 1 H, CH), 7.20−7.37 (m, 2 H, Ar-H), 7.38−7.43 (m, 3 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 7.6 (CH_2), 8.6 (CH_2), 27.7 (NCH_3), 40.2 (C), 64.4 (CH), 127.3 (2 CH), 128.9 (3 CH), 135.1 (C), 175.2 (C) ppm. MS (EI): *m*/*z* (%) = 187 (59) [M^+], 158 (7), 129 (100), 118 (48), 115 (56). HRMS (EI) calcd. for $C_{12}H_{13}NO$ [M^+] 187.0997, found 187.0997.

5-Methyl-6-(pyrid-2-yl)-5-azaspiro[2.3]hexan-4-one (7f): Column chromatography (R_f = 0.38, 21 g of silica gel, 14 × 2.5 cm column, CH_2Cl_2/MeOH, 20:1) of the residue obtained from the isoxazolidine **5f** (400 mg, 1.85 mmol) and TFA (254 mg, 0.20 mL, 2.22 mmol) in acetonitrile (5 mL) according to GP2 (40 min) gave the β-lactam **7f** (335 mg, 96%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3003 cm^{-1}, 2924, 1751, 1472, 1291. ^1H NMR (250 MHz): δ = 0.35 (ddd, J = 10.0, 7.5, 5.2 Hz, 1 H, *c*Pr−H), 1.03 (ddd, J = 10.2, 7.0, 5.1 Hz, 1 H, *c*Pr−H), 1.18 (ddd, J = 10.0, 7.5, 5.1 Hz, 1 H, *c*Pr−H), 1.26 (ddd, J = 10.2, 7.5, 5.2 Hz, 1 H, *c*Pr−H), 2.91 (s, 3 H, NCH_3), 4.72 (s, 1 H, CH), 7.21−7.27 (m, 1 H, Ar-H), 7.33 (d, J = 7.8 Hz, 1 H, Ar-H), 7.75 (dt, J = 7.7, 1.7 Hz, 1 H, Ar-H), 8.53−8.55 (m, 1 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 6.7 (CH_2), 8.2 (CH_2), 27.8 (NCH_3), 40.7 (C), 64.7 (CH), 120.6 (CH), 123.1 (CH), 137.1 (CH), 149.5 (CH), 157.4 (C), 173.0 (C) ppm. MS (EI): *m*/*z* (%) = 188 (9) [M^+], 159 (54), 145 (16), 130 (100), 119 (19), 78 (27). $C_{11}H_{12}N_2O$ (188.20): calcd. C 70.20, H 6.43; found C 70.31, H 6.56.

Methyl 5-Benzoyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (9a): Finely powdered CrO_3 (0.202 g, 0.202 mmol) was added in one portion to a stirred solution of β-lactam **7a** (247 mg, 1.01 mmol) in acetic acid (20 mL) at ambient temperature, and the resulting mixture was stirred at 60 °C for an additional 3 days. After cooling to room temperature and dilution with diethyl ether (20 mL), $NaHCO_3$ (15.0 g, 179 mmol) was added to the solution in several portions, and the reaction mixture was stirred until the carbon dioxide evolution ceased. The organic phase was washed with aq. sat. $NaHCO_3$ solution in 20 mL portions until the evolution of carbon dioxide ceased, then it was dried, and concentrated under reduced pressure. Column chromatography (R_f = 0.20, 42 g of silica gel, 3 × 13 cm column, hexane/Et_2O, 2:1) of the residue gave **9a** (113 mg, 44%) as a colorless solid, m.p. 92−93 °C. IR (KBr): $\tilde{\nu}$ = 3090 cm^{-1}, 3077, 2987, 2961, 1796, 1734, 1676, 1601, 1581, 1481, 1441. ^1H NMR (300 MHz): δ = 1.07−1.33 (m, 2 H, *c*Pr−H), 1.34−1.56 (m, 2 H, *c*Pr−H), 3.80 (s, 3 H, OCH_3), 4.80 (s, 1 H, CH), 7.44−7.49 (m, 2 H, Ar-H), 7.54−7.68 (m, 1 H, Ar-H), 8.06−8.15 (m, 2 H, Ar-H) ppm. ^{13}C NMR (50.3 MHz): δ = 9.6 (CH_2), 11.4 (CH_2), 34.4 (C), 52.6 (CH), 56.0 (CH_3), 128.1 (2 CH), 129.9 (2 CH), 131.2 (C), 133.3 (CH), 164.5 (C), 167.6 (C), 168.7 (C) ppm. MS (EI): *m*/*z* (%) = 259 (2) [M^+], 228 (5), 200 (97), 105 (100), 77 (45). The structure of this β-lactam **9a** was verified by X-ray crystal structure analysis. Some starting material **7a** (72 mg, 29%) was also recovered by column chromatography (R_f = 0.12).

5-Benzoyl-6-phenyl-5-azaspiro[2.3]hexane-4-one (9b): $KMnO_4$ (721 mg, 4.56 mmol) and 18-crown-6 (15.0 mg, 0.057 mmol, 5 mol %) were added to a stirred solution of β-lactam **7b** (0.300 g, 1.14 mmol) in a mixture of acetone/acetic acid 85:15 (30 mL). The solution was stirred at 60 °C for 24 h. After cooling to room temperature, the mixture was diluted with diethyl ether (30 mL), then an aq. sat. solution of $NaHCO_3$ (50 mL) was added in small portions under vigorous stirring, and the reaction mixture was stirred until the carbon dioxide evolution ceased. The organic phase was washed with brine (2 × 20 mL), dried, and concentrated under reduced pressure. Column chromatography (R_f = 0.26, 12 g of silica gel, 2 × 10 cm column, hexane/Et_2O, 3:1) of the residue gave **9b** (90.0 mg, 28%) as a colorless solid, m.p. 121−123 °C. IR (KBr): $\tilde{\nu}$ = 3065 cm^{-1}, 3010, 2950, 1800, 1675, 1653, 1448. ^1H NMR (250 MHz): δ = 0.66−0.76 (m, 1 H, *c*Pr−H), 1.28−1.39 (m, 2 H, *c*Pr−H), 1.43−1.53 (m, 1 H, *c*Pr−H), 5.35 (s, 1 H, CH), 7.29−7.43 (m, 5 H, Ar-H), 7.45−7.51 (m, 2 H, Ar-H), 7.55−7.62 (m, 1 H, Ar-H), 8.04−8.11 (m, 2 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 10.6 (CH_2), 11.7 (CH_2), 37.9 (C), 59.7 (CH), 126.9 (2 CH), 128.1 (2 CH), 128.5 (CH), 128.7 (2 CH), 129.9 (2 CH), 132.2 (C), 133.1 (CH), 136.4 (C), 164.8 (C), 170.4 (C) ppm. MS (EI): *m*/*z* (%) = 277 (36) [M^+], 249 (25), 129 (32), 105 (100), 77 (50). $C_{18}H_{15}NO_2$ (277.3): calcd. C 77.96, H 5.45, N 5.05; found C 77.69, H 5.35, N 4.82. Some starting material **7b** (200 mg, 67%) was also recovered by column chromatography (R_f = 0.11).

Deprotection of β-Lactam 7d: A solution of CAN (6.63 g, 12.1 mmol) in water (85 mL) was added to a stirred solution of β-lactam **7d** (900 mg, 3.72 mmol) in acetonitrile (40 mL) at 0 °C. After an additional stirring for 20 minutes at the same temperature and for 1 h at ambient temperature, the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed successively with a 10% aq. Na_2SO_3 solution (2 × 50 mL), a 5% aq. $NaHCO_3$ solution (2 × 50 mL) and brine (50 mL), dried, and concentrated under reduced pressure. Column chromatography (hexane/Et_2O, 1:2, 75 g of silica gel, 3.5 × 16 cm column) of the residue gave **6-oxo-5-azaspiro[2.3]hexane-4-carbonitrile (10)** (172 mg, 38%) as a colorless solid, m.p. 72−73 °C, R_f = 0.15, and **5-(4-methoxybenzoyl)-6-oxo-5-azaspiro[2.3]hexane-4-carbonitrile (9d)** (371 mg, 39%) as a colorless solid, m.p. 109−110 °C, R_f = 0.38 (hexane/Et_2O, 1:4). **10**: IR (KBr): $\tilde{\nu}$ = 3250 cm^{-1}, 3097, 2720, 2249, 1763, 1331. ^1H NMR (250 MHz): δ = 1.26−1.37 (m, 2 H, *c*Pr−H), 1.41−1.48 (m, 2 H, *c*Pr−H), 4.44 (s, 1 H, CH), 6.40 (s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz): δ = 9.1 (CH_2), 9.8 (CH_2), 39.8 (C), 43.6 (CH), 116.9 (C), 171.5 (C) ppm. MS (EI): *m*/*z* (%) = 122 (12) [M^+], 79 (50), 52 (100). $C_6H_6N_2O$ (122.1); calcd. C 59.01, H 4.95, N 22.94; found C 59.20, H 5.08, N 22.81. **9d**: IR (KBr): $\tilde{\nu}$ = 3084 cm^{-1}, 3005, 2977, 2938, 2843, 2251, 1798, 1666, 1603, 1576, 1514. ^1H NMR (250 MHz): δ = 1.47−1.67 (m, 4 H, *c*Pr−H), 3.89 (s, 3 H, OCH_3), 4.92 (s, 1 H, CH), 6.95−7.01 (m, 2 H, Ar-H), 8.08−8.14 (m, 2 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 11.4 (CH_2), 12.2 (CH_2), 34.8 (C), 44.4 (CH), 55.5 (CH_3), 113.8 (2 CH), 115.4 (C), 122.2 (C), 132.6 (2 CH), 163.3 (C), 164.3 (C), 166.3 (C) ppm. MS (EI): *m*/*z* (%) = 256 (20) [M^+], 135 (100), 92 (9), 77 (9). $C_{14}H_{12}N_2O_3$ (256.3): calcd. C 65.62, H 4.72, N 10.93; found C 65.75, H 4.61, N 11.15.

***tert*-Butyl 4-Cyano-6-oxo-5-azaspiro[2.3]hexane-5-carboxylate (11):** Di-*tert*-butyl pyrocarbonate (Boc_2O, 873 mg, 4.00 mmol) and DMAP (24.0 mg, 0.196 mmol) were added in one portion to a stirred solution of β-lactam **10** (245 mg, 2.01 mmol) in anhydrous acetonitrile (30 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for an additional 3 h, diluted with dichloromethane (30 mL), washed successively with 10% aq. Na_2SO_3 solution (2 × 20 mL), aq. sat. $NaHCO_3$ solution (2 × 20 mL) and brine (2 × 20 mL), dried, and concentrated under reduced pressure. Column chromatography (R_f = 0.10, 12 g of silica gel, 2 × 10 cm

column, hexane/Et_2O, 2:1) furnished **11** (346 mg, 78%) as a colorless solid, m.p. 87 °C. IR (KBr): $\tilde{\nu}$ = 3012 cm^{-1}, 2992, 2250, 1823, 1717. ^1H NMR (300 MHz): δ = 1.35−1.46 (m, 2 H, *c*Pr−H), 1.48−1.64 (m, 2 H, *c*Pr−H), 1.56 (s, 9 H, 3 CH_3), 4.64 (s, 1 H, CH) ppm. ^{13}C NMR (50.3 MHz): δ = 10.6 (CH_2), 11.4 (CH_2), 28.0 (3 CH_3), 37.0 (C), 45.9 (CH), 85.1 (C), 115.0 (C), 145.7 (C), 166.6 (C) ppm. MS (EI): *m*/*z* (%) = 223 (1) [M + H^+], 167 (9), 149 (30), 57 (100). MS (DCI): *m*/*z* (%) = 684 (5) [3 M + NH_4^+], 462 (40) [2 M + NH_4^+], 257 (72) [M + NH_3 + NH_4^+], 240 (100) [M + NH_4^+]. $C_{11}H_{14}N_2O_3$ (222.2): calcd. C 59.45, H 6.35, N 12.61; found C 59.55, H 6.14, N 12.47.

Reaction of *N*-Acylated β-Lactams 9a,b, 11 with *tert*-Butyl Glycinate (12) and *tert*-Butyl (*S*)-Phenylalaninate (14). General Procedure (GP) 3: *tert*-Butyl amino ester **12** (or its hydrochloride in the presence of 1 equiv. of triethylamine) was added to a solution of the respective β-lactam **9a**,**b** or **11** in DMF, and the resulting mixture was stirred at 152 °C (if not otherwise specified) for the indicated time. After cooling to ambient temperature, diethyl ether (20 mL) was added, and the organic layer was washed with water (10 mL), brine (2 × 10 mL), and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel.

***tert*-Butyl [(5-Benzoyl-6-oxo-5-azaspiro[2.3]hexane-4-carbonyl)-amino]acetate (13):** Column chromatography (R_f = 0.10, 12 g of silica gel, 2 × 10 cm column, hexane/Et_2O, 1:1) of the residue obtained from the β-lactam **9a** (113 mg, 0.436 mmol) and glycinate **12** (171 mg, 1.31 mmol) in DMF (10 mL) according to GP3 (20 h) gave the glycinate **13** (80 mg, 51%) as a colorless solid, m.p. 112−115 °C. IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1} (br.), 2982, 2925, 2853, 1790, 1719, 1644, 1604, 1581, 1516, 1487. ^1H NMR (250 MHz): δ = 1.08−1.19 (m, 1 H, *c*Pr−H), 1.31−1.45 (m, 2 H, *c*Pr−H), 1.48 (s, 9 H, 3 CH_3), 1.58−1.66 (m, 1 H, *c*Pr−H), 4.27 (s, 2 H, CH_2), 5.03 (d, *J* = 7.4 Hz, 1 H, CH), 6.91 (d, *J* = 7.4 Hz, 1 H, NH), 7.39−7.47 (m, 2 H, Ar-H), 7.5−7.57 (m, 1 H, Ar-H), 7.75−7.81 (m, 2 H, Ar-H) ppm. ^{13}C NMR (150 MHz): δ = 13.3 (CH_2), 15.2 (CH_2), 27.2 (C), 28.0 (3 CH_3), 40.7 (CH_2), 53.4 (CH), 83.2 (C), 127.2 (2 CH), 128.7 (2 CH), 132.3 (CH), 132.5 (C), 165.9 (C), 167.8 (C), 174.7 (C), 177.4 (C) ppm. MS (DCI): *m*/*z* (%) = 734 (10) [2 M + NH_4^+], 376 (100) [M + NH_4^+]. $C_{19}H_{22}N_2O_5$ (358.39) calcd. C 63.67, H 6.19, N 7.82; found C 63.33, H 5.95, N 7.71.

***tert*-Butyl {[1-(Benzoylaminophenylmethyl)cyclopropylcarbonyl]-amino}acetate (15):** Column chromatography (R_f = 0.17, 15 g of silica gel, 2 × 10 cm column, hexane/Et_2O, 1:2) of the residue obtained from the β-lactam **9b** (243 mg, 0.877 mmol) and glycinate **12** (354 mg, 2.7 mmol) in DMF (35 mL) according to GP3 (12 h) gave **15** (217 mg, 61%) as a colorless solid, m.p. 133−134 °C. IR (KBr): $\tilde{\nu}$ = 3311 cm^{-1}, 3238, 3064, 2974, 1754, 1734, 1656, 1636. ^1H NMR (300 MHz): δ = 0.99−1.29 (m, 4 H, *c*Pr−H), 1.36 (s, 9 H, 3 CH_3), 3.71 (dd, *J* = 18.3, 5.0 Hz, 1 H, CH_2), 3.78 (dd, *J* = 18.3, 5.0 Hz, 1 H, CH_2), 4.76 (d, *J* = 8.7 Hz, 1 H, CH), 5.81 (t, *J* = 5.0 Hz, 1 H, NH), 7.12−7.27 (m, 3 H, Ar-H), 7.32−7.47 (m, 5 H, Ar-H), 7.85−7.89 (m, 2 H, Ar-H), 8.66 (d, *J* = 8.7 Hz, 1 H, NH) ppm. ^{13}C NMR (75.5 MHz): δ = 13.1 (CH_2), 14.1 (CH_2), 27.9 (3 CH_3), 29.5 (C), 41.8 (CH_2), 58.3 (CH), 82.5 (C), 126.5 (2 CH), 127.2 (2 CH), 127.4 (CH), 128.5 (4 CH), 131.5 (CH), 134.1 (C), 140.2 (C), 166.5 (C), 168.8 (C), 173.5 (C) ppm. MS (EI): *m*/*z* (%) = 408 (2) [M^+], 335 (10), 277 (85), 250 (15), 210 (15), 105 (100), 77 (30), 57 (22). MS (DCI): *m*/*z* (%) = 426 (55) [M + NH_4^+], 409 (100) [M + H^+]. $C_{24}H_{28}N_2O_4$ (408.5): calcd. C 70.57, H 6.91, N 6.86; found C 70.76, H 7.10, N 7.26.

***tert*-Butyl {[1-(*tert*-Butoxycarbonylaminocyanomethyl)cyclopropyl-carbonyl]amino}acetate (16):** The colorless solid (0.20 g, 84%) obtained from β-lactam **11** (150 mg, 0.67 mmol), *tert*-butyl glycinate hydrochloride (**12**·HCl) (195 mg, 1.16 mmol) and triethylamine (118 mg, 162 μL, 1.16 mmol) in DMF (16 mL) according to GP3 (12 h) after evaporation of the solvent was essentially pure acetate **16**. An analytical sample was obtained by column chromatography (R_f = 0.70, 20 g of silica gel, 2 × 16 cm column, Et_2O) and had m.p. 86−88 °C. IR (KBr): $\tilde{\nu}$ = 3311 cm^{-1}, 3096, 2989, 2939, 1751, 1688, 1638, 1550, 1511. ^1H NMR (300 MHz): δ = 1.08−1.16 (m, 1 H, *c*Pr−H), 1.17−1.28 (m, 2 H, *c*Pr−H), 1.30−1.37 (m, 1 H, *c*Pr−H), 1.44 (s, 9 H, 3 CH_3), 1.47 (s, 9 H, 3 CH_3), 3.87 (dd, *J* = 18.4, 4.4 Hz, 1 H, CH_2), 3.94 (dd, *J* = 18.4, 4.4 Hz, 1 H, CH_2), 4.24 (d, *J* = 9.2 Hz, 1 H, CH), 5.83 (br. t, *J* = 4.4 Hz, 1 H, NH), 6.20 (br. d, *J* = 9.2 Hz, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz): δ = 13.2 (CH_2), 14.8 (CH_2), 27.9 (C), 28.0 (3 CH_3), 28.2 (3 CH_3), 41.9 (CH_2), 47.0 (CH), 81.2 (C), 82.8 (C), 117.4 (C), 168.8 (2 C), 171.2 (C) ppm. MS (EI): *m*/*z* (%) = 353 (2) [M^+], 297 (15), 224 (28), 197 (42), 57 (100). MS (DCI): *m*/*z* (%) = 724 (10) [2 M + NH_4^+], 707 (18) [2 M + H^+], 371 (85) [M + NH_4^+], 354 (100) [M + H^+]. $C_{17}H_{27}N_3O_5$ (353.41): calcd. C 57.77, H 7.70, N 11.89; found C 57.49, H 7.58, N 11.81.

***tert*-Butyl (2*S*,2′*S*)-2-{[1-(*tert*-Butoxycarbonylaminocyanomethyl)-cyclopropylcarbonyl]amino}-3-phenylpropionate [(2*S*,2′*S*)-17] and *tert*-Butyl (2*S*,2′*R*)-2-{[1-(*tert*-Butoxycarbonylaminocyanomethyl)-cyclopropylcarbonyl]amino}-3-phenylpropionate [(2*S*,2′*R*)-17]:** Column chromatography (44 g of silica gel, 3 × 13 cm column, hexane/Et_2O, 1:1) of the residue obtained from the β-lactam **11** (184 mg, 0.83 mmol), *tert*-butyl (*S*)-phenylalaninate hydrochloride (**14**·HCl) (428 mg, 1.66 mmol) and Et_3N (168 mg, 230 μL, 1.66 mmol) in DMF (33 mL) according to GP3 (60 °C, 12 h) gave (2*S*,2′*S*)-**17** (155 mg, 42%) and (2*S*,2′*R*)-**17** (143 mg, 39%) as colorless solids.

The diastereoisomer (2*S*,2′*S*)-**17**: R_f = 0.34, m.p. 101−102 °C, $[\alpha]_D^{20}$ = +53.4 (*c* = 0.5 in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3438 cm^{-1}, 3426, 3090, 2981, 2935, 2247, 1738, 1719, 1650, 1540, 1524, 1370. ^1H NMR (250 MHz): δ = 1.00−1.22 (m, 4 H, *c*Pr−H), 1.41 (s, 9 H, 3 CH_3), 1.43 (s, 9 H, 3 CH_3), 3.06 (dd, *J* = 15, 5 Hz, 1 H, CH_2), 3.15 (dd, *J* = 15, 5 Hz, 1 H, CH_2), 4.18 (d, *J* = 8.7 Hz, 1 H, CH), 4.65 (dd, *J* = 12.5, 5 Hz, 1 H, CH), 5.71 (br. d, *J* = 8.7 Hz, 1 H, NH), 6.12 (br. d, *J* = 7.6 Hz, 1 H, NH), 7.11−7.14 (m, 2 H, Ar-H), 7.23−7.29 (m, 3 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 13.2 (CH_2), 14.7 (CH_2), 27.9 (3 CH_3), 28.2 (3 CH_3), 37.4 (CH_2), 46.9 (CH), 53.4 (CH), 81.1 (C), 82.7 (C), 117.3 (C), 127.1 (CH), 128.4 (2 CH), 129.4 (2 CH), 135.6 (C), 170.2 (C), 170.7 (C) ppm; two carbon atom signals were not detectable at this temperature. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 12.5 (CH_2), 13.9 (CH_2), 27.5 (C), 27.7 (3 CH_3), 28.0 (3 CH_3), 37.4 (CH_2), 47.1 (CH), 53.5 (CH), 81.1 (C), 82.5 (C), 117.0 (C), 126.9 (CH), 128.2 (2 CH), 129.1 (2 CH), 135.7 (C), 154.3 (C), 169.8 (C), 170.2 (C) ppm. MS (EI): *m*/*z* (%) = 443 (9) [M^+], 387 (10), 331 (28), 314 (30), 286 (22), 242 (10), 148 (100), 120 (85), 91 (15), 57 (40). $C_{24}H_{33}N_3O_5$ (443.5): calcd. C 64.99, H 7.50, N 9.47; found C 64.76, H 7.76, N 9.60. The diastereoisomer (2*S*,2′*R*)-**17**: R_f = 0.27, m.p. 142−143 °C, $[\alpha]_D^{20}$ = +22.5 (*c* = 0.16 in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3374 cm^{-1}, 3281, 3036, 2970, 2250, 1739, 1690, 1649, 1535, 1369. ^1H NMR (250 MHz): δ = 0.99−1.26 (m, 4 H, *c*Pr−H),), 1.43 (s, 9 H, 3 CH_3), 1.46 (s, 9 H, 3 CH_3), 3.04 (dd, *J* = 12.5, 5 Hz, 1 H, CH_2), 3.12 (dd, *J* = 12.5, 7.5 Hz, 1 H, CH_2), 4.10 (d, *J* = 10 Hz, 1 H, CH), 4.71 (dd, *J* = 12.5, 5 Hz, 1 H, CH), 5.67 (br. d, *J* = 10 Hz, 1 H, NH), 6.15 (br. d, *J* = 12.5 Hz, 1 H, NH), 7.06−7.10 (m, 2 H, Ar-H), 7.24−7.31 (m, 3 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz): δ = 13.3 (CH_2), 14.7 (CH_2), 27.9 (3 CH_3), 28.2 (3 CH_3), 37.7 (CH_2), 47.1 (CH), 53.3

(CH), 81.1 (C), 83.0 (C), 117.5 (C), 127.1 (CH), 128.4 (2 CH), 129.4 (2 CH), 135.8 (C), 170.2 (C), 170.3 (C) ppm, two carbon atom signals were not detectable at this temperature. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 12.5 (CH_2), 13.9 (CH_2), 27.6 (C), 27.7 (3 CH_3), 28.0 (3 CH_3), 37.7 (CH_2), 47.1 (CH), 53.4 (CH), 81.1 (C), 82.7 (C), 117.0 (C), 126.8 (CH), 128.2 (2 CH), 129.1 (2 CH), 135.8 (C), 154.3 (C), 169.9 (C), 170.1 (C) ppm. MS (EI): *m/z* (%) = 443 (38), 387 (35), 331 (75), 314 (65), 286 (68), 240 (25), 184 (22), 148 (100), 120 (55), 57 (50). $C_{24}H_{33}N_3O_5$ (443.5): calcd. C 64.99, H 7.50, N 9.47; found C 64.77, H 7.62, N 9.42.

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