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Methyl 2-(Benzyloxycarbonylamino)-2-cyclopropylideneacetate: A Versatile Building Block for Cyclopropyl-Containing Amino Acids[‡]

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Dedicated to Professor Hans-Ulrich Reissig on the occasion of his 60th birthday

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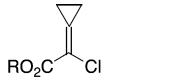
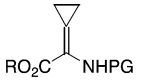
Methyl 2-(benzyloxycarbonylamino)-2-cyclopropylideneacetate (**2**) was prepared in nine steps starting from L-serine in an overall yield of 24 %. It has been demonstrated to be reasonably reactive in Michael additions of various nucleophiles (6 examples, 75–98 % yields) as well as Diels–Alder reactions, both leading to new cyclopropyl-containing amino acids in protected form. An application of **2** in the synthesis of methyl 4-*tert*-butoxycarbonylmethyl-5-oxo-4,7-diazaspiro-[2.5]octane-8-carboxylate (**15**), a precursor for geometrically constrained bicyclic peptidomimetics of type **16**, has also been proved.

Introduction

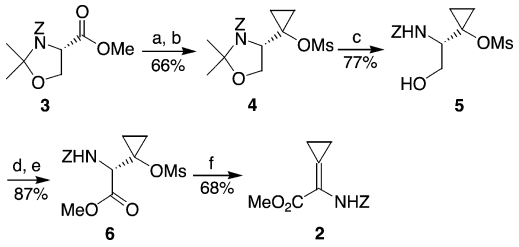
Naturally occurring cyclopropyl-containing amino acids and cyclopropyl analogues of other α- and β-amino acids have come to play an increasingly important role in the synthesis of various peptide mimics and other biologically active compounds.[1–3] Several such amino acids have been made accessible[4,5] from our previously developed alkyl 2-chloro-2-cyclopropylideneacetates **1**-R.[6,7] Although this type of multifunctional building block may be quite convenient, especially for the preparation of β-functionalized amino acids, a more convergent access to cyclopropyl-containing α-amino acids ought to be achievable from modified 2-cyclopropylideneacetates of type **2** already containing a protected amino group adjacent to the carboxylic acid functionality. Here we report a convenient preparation of methyl (2-benzyloxycarbonylamino)cyclopropylideneacetate (**2**) (Scheme 1) and some of its versatile transformations.



1-R (R = Me, Bn, *t*Bu)



2 (R = Me, PG = Z)



3 **4** **5** **6** **2**

Scheme 1. Synthesis of methyl 2-(benzyloxycarbonylamino)-2-cyclopropylideneacetate (**2**). Reagents and conditions: a) $MeTi(OiPr)_3$ (20 mol-%), EtMgBr THF/Et_2O 20 °C, 16 h; b) MsCl, Et_3N, CH_2Cl_2, 2 h; c) *p*TsOH, MeOH 20 °C, 14 h; d) $NaIO_4$, $RuCl_3 \cdot 3H_2O$ (2 mol-%) CCl_4/MeCN/H_2O 18 °C, 1 h; e) $SOCl_2$, MeOH, 20 °C, 20 h; f) KO*t*Bu, *t*BuOMe 0 °C, 2 h.

Results and Discussion

The Z-protected methyl oxazolidinecarboxylate **3** was prepared from L-Serine in 79 % yield according to a literature procedure.[8] Employing the Kulinkovich reductive cyclopropanation,[9,10] the ester functionality in **3** was converted to a cyclopropanol as previously reported by Taddei et al. in the context of an elegant enantioselective synthesis of the amino acid cleonine and some of its analogues.[11] Initial attempts to run this conversion on a multigram scale with titanium tetraisopropoxide either in catalytic (20 mol-%) or even stoichiometric amounts always left a large fraction of the starting material **3** unreacted. Using tetrahydrofuran instead of diethyl ether and changing the rate of addition of the ethylmagnesium bromide as well as the reaction temperature in the range from 0 to 70 °C, did not lead to a significant improvement of the yield. Only when

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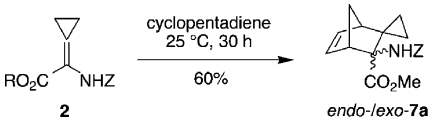
methyltitanium triisopropoxide (20 mol-%) was employed,[12] and the formed base- and acid-sensitive cyclopropanol was immediately protected as the mesylate **4**, could an overall yield of 66% be achieved after chromatographic purification of **4**.

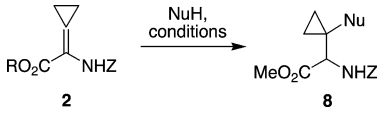
Cleavage of the oxazolidine moiety in **4** with *p*-toluenesulfonic acid furnished the *N*-protected amino alcohol **5** in 77% yield. Sharpless oxidation[13] of the hydroxymethyl group in **5** and esterification of the resulting carboxylic acid with methanol using thionyl chloride gave the precursor **6** of the protected dehydroamino acid **2** in 87% yield. The dehydromesylation of **6** required a stronger base than triethylamine, but it was achieved with potassium *tert*-butoxide in *tert*-butyl methyl ether to afford 2-(benzyloxycarbonylamino)-2-cyclopropylideneacetate (**2**) in 68% yield as a colorless solid.

To explore the various possibilities of converting the cyclopropyl-containing α,β-unsaturated α-amino acid ester **2** into cyclopropyl-containing saturated amino acid derivatives, **2** was first tested as a dienophile. As such it turned out to be less reactive than **1**-Me,[14] yet upon treatment with an excess of cyclopentadiene at 25 °C for 30 h, **2** gave the Diels–Alder adduct **7a** (4:1 mixture of diastereomers according to ^{1}H NMR) in 60% yield. However, **2** did not react with the less reactive 2,3-dimethylbutadiene and furan. In both cases, even after 10 d of stirring **2** at room temp. with an excess of either the diene, no reaction was observed. Attempts to carry out these Diels–Alder reactions at 60 °C revealed, that compound **2** itself is thermally unstable and completely disappears in an unidentified reaction within 14 h (Scheme 2). Pressurizing mixtures of **2** with either diene at 11 kbar and room temp. for 24 h did not help either.[15] The starting material **2** was completely consumed, but no cycloadducts could be isolated.



Scheme 2. Diels–Alder reaction of **2** with cyclopentadiene.

With respect to **2** being a Michael acceptor, various nucleophiles were found to smoothly undergo additions onto the double bond of **2** at ambient temperature (Scheme 3, Table 1) to yield the correspondingly 1′-substituted 2-(benzyloxycarbonylamino)cyclopropylacetates **8**. Thus, benzylamine and diethylamine gave the adducts **8a** and **8b** in 91 and 81% yield, respectively. Thiophenol can be added to **2** to produce **8c** in almost quantitative yield, when the reaction is carried out in the presence of a catalytic amount of triethylamine. The addition of benzyl alcohol onto **2** also proceeded well in the presence of a catalytic quantity of triethylamine, but was accompanied by partial transesterification, and furnished a 1:1 mixture of the methyl and benzyl esters **8e**-Me and **8e**-Bn, respectively, according to a ^{1}H NMR spectrum of the crude product. The two products **8e**-Me and **8e**-Bn could be isolated by column chromatography. The addition of (*R*)-(+)-1-phenylethylamine gave a 1:1 mixture of diastereomers (*R*,*S*)-**8f**/(*R*,*R*)-**8f**.



Scheme 3. Synthesis of 1′-substituted 2-(benzyloxycarbonylamino) cyclopropylacetates **8** by Michael additions of different nucleophiles to **2** (for details see Table 1).

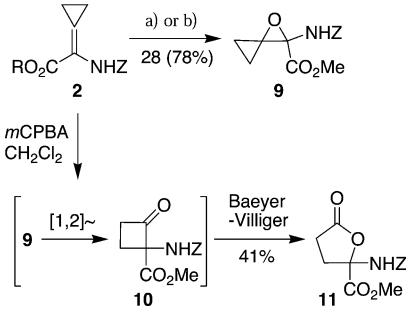
Table 1. Michael additions of various nucleophiles to methyl 2-(benzyloxycarbonylamino)-2-cyclopropylideneacetate (**2**).

NuH	Conditions	Product	% Yield[a]
$BnNH_2$	MeOH, 20 °C, 20 h	**8a**	91
Et_2NH	THF, 20 °C, 24 h	**8b**	81
PhSH	CH_2Cl_2, Et_3N (cat.) 20 °C, 22 h	**8c**	98
MeSH	MeSNa, THF (wet) 20 °C, 24 h	**8d**	75
BnOH	BnOH (neat), Et_3N (cat.)	**8e**-Me/**8e**-Bn (1:1)	80
(*R*)-PhCH(NH_2)Me	CH_2Cl_2, 20 °C, 24 h	(*R*,*S*)-**8f**/(*R*,*R*)-**8f** (1:1)	78

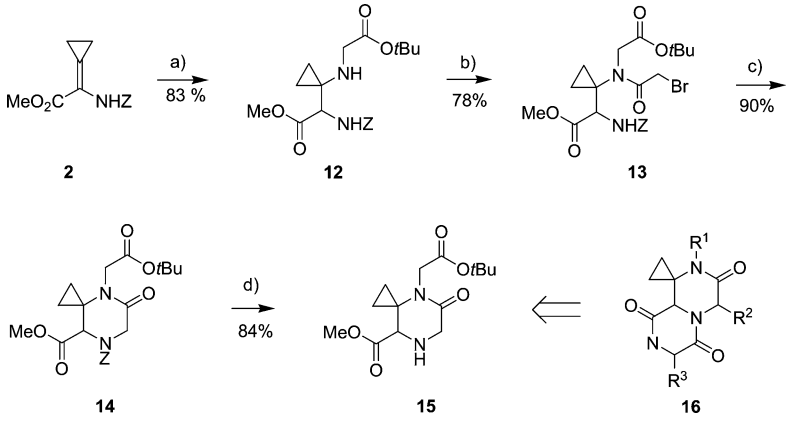
[a] Yield of isolated product.

More sterically encumbered chiral amines, such as (*S*)-(–)-*N*,α-dimethylbenzylamine and (*R*)-(+)-*N*-benzyl-1-phenylethylamine did not undergo addition onto **2** within 48 h at ambient temperature.

The relatively low yield in the Diels–Alder reaction of **2** with cyclopentadiene (see above) probably was caused by partial oxidation of **2**. Control experiments proved that **2** undergoes oxidation to the reasonably stable and therefore isolable oxaspiropentanecarboxylate **9** upon standing in air. Such spontaneous reactions of other strained alkenes with ground-state triplet oxygen to give epoxides, hydroperoxides and other products have previously been discussed along with possible mechanisms.[16] The attack of triplet oxygen onto the double bond of **2** initially leads to a capto-datively substituted and thereby well stabilized[17] radical, and this should significantly lower the activation energy for the attack. The oxaspiropentane derivative **9** could be specifically synthesized in 78% yield by epoxidation of **2** with H_2O_2



Scheme 4. Epoxidation of **2** and further transformation of the oxaspiropentanecarboxylate **9**. Reagents and conditions: a) CH_2Cl_2, air, room temp. 48 h; b) 0.5 mol-% MTO, 12 mol-% pyridine, 1.5 equiv. 30% aq. H_2O_2, CH_2Cl_2, room temp. 6 h.



Scheme 5. Synthesis of the 3-spirocyclopropanated 5-oxopiperazine-2-carboxylate **15** from **2**. Reagents and conditions: a) H_2N-Glu-O*t*Bu, K_2CO_3, MeCN, 20 °C, 3 d; b) $BrCH_2COCl$, aq. $NaHCO_3$, 1,2-dichlorethane, 20 °C, 1 h; c) Cs_2CO_3, nBu_4NI, THF, 20 °C, 5 h; d) Pd/C, H_2, MeOH, 20 °C, 2 h.

in the presence of methyltrioxorhenium/pyridine (Scheme 4).[18] Attempted epoxidation of **2** with an excess of *m*-chloroperbenzoic acid (*m*CPBA) without a buffer in dichloromethane led to the γ-lactone derivative **11**, which arises by acid-catalyzed rearrangement of **9**[19] and subsequent Baeyer–Villiger oxidation of the oxocyclobutanecarboxylate, which apparently proceeds regioselectevely. The aminolactone **11**, which was isolated in 41% yield, had previously been obtained as a side product in small quantities.[20]

Another favorable use of the α,β-dehydroamino acid ester **2** would be in the synthesis of octahydro[2*H*]pyrazino-[1,2-*a*]pyrazine derivatives of type **16**, a class of geometrically constrained peptidomimetics.[21] The approach to such compounds from **2** would start with the transformation to 3-spirocyclopropanated 5-oxopiperazine-2-carboxylates of type **15**, some of which were synthesized[21] from **1**-Me in four steps in overall yields of ca. 20%. The route to **12** starting from **2** ought to be more efficient.

The Michael addition of *tert*-butyl glycinate to **2** could be brought about in acetonitrile in the presence of potassium carbonate at room temperature, but required three days to afford the product **11** in 83% yield. Comparable Michael additions onto the more reactive methyl 2-chloro-2-cyclopropylideneacetate (**1**-Me) proceed more rapidly.[22]

The amino group of the glycine moiety in the adduct **12** could be acylated under Schotten–Baumann conditions with bromoacetyl chloride to furnish **13** selectively in 78% yield. The latter underwent ring closure in 90% yield by intramolecular alkylation of the carbamate moiety upon treatment with cesium carbonate in the presence of tetra-*n*-butylammonium iodide for an in situ Finkelstein reaction. Hydrogenolytic removal of the Z group in **14** gave the six-membered dipeptide mimic **15** in 84% yield. Thus, the 3-spirocyclopropanated 5-oxopiperazine-2-carboxylate **15** was synthesized in four steps starting from **2** in 49% overall yield (Scheme 5).

Conclusions

The novel cyclopropyl-containing α,β-unsaturated α-amino acid derivative **2** has some obvious advantages over previously developed alkyl 2-chloro-2-cyclopropylideneacetates **1**-R, especially in the synthesis of various cyclopropyl-containing α-amino acids and conformationally restricted peptidomimetics.

Experimental Section

General Remarks: All reagents were used as purchased from commercial suppliers without further purification. All reactions in non-aqueous solvents were carried out using standard Schlenk techniques under an atmosphere of dry nitrogen. Solvents were purified and dried according to conventional methods prior to use. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AM 250 (250 MHz for ^{1}H and 62.9 MHz for ^{13}C), Varian UNITY-300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) or Inova-500 (125.7 MHz for ^{13}C) instrument. Chemical shifts δ are given in ppm relative to residual resonances of solvents (^{1}H: 7.26 ppm for $CHCl_3$, 2.50 ppm for [D_5]-DMSO; ^{13}C: 77.0 ppm for $CDCl_3$, 39.52 for [D_6]DMSO) or tetramethylsilane (^{1}H: 0.00 ppm; ^{13}C: 0.0 ppm), coupling constants *J* are given in Hertz. The multiplicities of ^{13}C signals were determined by the DEPT or the APT technique. IR: Bruker IFS 66 (FT-IR) spectrometer, measured as KBr pellets or oils between KBr plates. MS: EI-MS: Finnigan MAT 95, 70 eV. ESI-MS: Finnigan LCQ. High resolution mass spectrometry (HRMS): APEX IV 7T FTICR, Bruker Daltonic. Chromatography: separations were carried out on Merck Silica 60 (0.063–0.200 mm, 70–230 mesh ASTM). TLC: Macherey–Nagel, TLC plates Alugram® Sil G/UV254. Detection under UV-light at 254 nm, development with MOPS reagent (10% molybdophosphoric acid, solution in ethanol). Melting points: Büchi 540 capillary melting point apparatus, uncorrected values. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen.

1-(3′-Benzyloxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)cyclopropyl Mesylate (4): To a solution of the oxazolidine-4-carboxylate **3**

(15.0 g, 51.2 mmol)[13] in anhydrous THF (100 mL) kept under nitrogen was added dropwise with magnetic stirring at 20 °C first $MeTi(OiPr)_3$ (2.46 mL, 10.2 mmol), then slowly freshly prepared EtMgBr (30.6 mL of a 3.35 M solution in Et_2O, 102.4 mmol). The mixture was stirred at room temp. for 16 h, then the reaction was quenched by addition of a saturated solution of NH_4Cl (25 mL) at 0 °C, and the mixture was stirred with access of air to the flask at room temp., until the precipitate had turned colorless (ca. 30 min). The suspension was diluted with ethyl acetate (100 mL) and filtered through a pad of Celite. The filtrate was dried with anhydrous Na_2SO_4 and concentrated to give the crude cyclopropanol as a light-yellow oil, which was used in the next step without further purification. A small sample was purified by flash chromatography on silica gel (gradient pentane/diethyl ether, 2:1 to 2:1, R_f = 0.57, Et_2O) for characterization purposes. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 7.40–7.34 (m, 5 H, Ph), 5.20 (s, 2 H, CH_2Ph), 3.82 (m, 2 H, CH_2OH), 3.71–3.63 (m, 1 H, CH), 3.03 (br. s, 4 H, CH_3, OH), 1.50–1.41 (m, 1 H, *c*Pr-H), 1.36–1.25 (m, 1 H, *c*Pr-H), 1.10–0.93 (m, 2 H, *c*Pr-H) ppm. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C, APT): δ = 153.5 (–, C_{quat}, C=O), 136.2 (–, C_{ipso}), 128.3 (+, 2 C, Ph-CH), 127.9 (+, 1 C, Ph-CH), 127.8 (+, 2 C, Ph-CH), 94.7 [–, C_{quat}, $C(CH_3)_3$], 66.9 (–, *c*Pr-C), 66.2 (–, CH_2), 62.6 (+, CH), 56.6 (–, CH_2), 26.1 (+, CH_3), 24.0 (+, CH_3), 13.4 (–, CH_2, *c*Pr), 10.8 (–, CH_2, *c*Pr) ppm. IR (film): $\tilde{\nu}$ = 3435 (br), 2984, 1702, 1407, 1348, 1258, 1064, 840, 699 cm^{-1}. MS (ESI): *m/z* (%) = 604.8 (89) $[2M + Na]^+$, 314.1 (100) $[M + Na]^+$. HRMS (ESI) calcd. for $C_{16}H_{21}NO_4Na^+$ $[M + Na]^+$: 314.13628; found 314.13622.

To a solution of the crude cyclopropanol in anhydrous CH_2Cl_2 (300 mL) kept at 0 °C under nitrogen, was added triethylamine (40 mL, 29.2 g, 0.29 mol), then with stirring methanesulfonyl chloride (4.8 mL, 7.09 g, 62 mmol), and the mixture was stirred at room temp. for 2 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL), then washed with water (2 × 100 mL) and brine (100 mL). The solvent was evaporated, and the crude product was purified by column chromatography on silica gel (pentane/Et_2O, 1:1 to 1:2, R_f = 0.40, pentane/Et_2O, 1:2) to give 12.5 g (66% over two steps) of the pure mesylate **4** as a light-yellow oil, (3:2 ratio of rotamers A/B at 20 °C according to ^1H NMR). ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.27 (m, 5 H, Ph), 5.17 (s, 2 H, CH_2Ph), 4.39–4.23 (m, 2 H, CH_2O), 4.13–4.07 (m, 1 H, CH), 3.04 (s, 1.2 H, SCH_3, B), 2.89 (s, 1.8 H, SCH_3, A), 1.58 [s, 3 H, $C(CH_3)_2$], 1.54 [s, 3 H, $C(CH_3)_2$], 1.44–1.18 (m, 2 H, *c*Pr-H), 1.05–0.77 (m, 2 H, *c*Pr-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 153.8 (C_{quat}, C=O, B), 152.8 (C_{quat}, C=O, A) 135.9 (C_{quat}, C_{ipso}, A, B), 128.5 (2 C, Ph-CH, A, B), 128.2 (C, Ph-CH, A, B), 128.1 (2 C, Ph-CH, A, B), 95.0 [C_{quat}, $C(CH_3)_2$, A], 94.5 [C_{quat}, $C(CH_3)_2$, B], 68.0 (CH_2Ph, B), 67.6 (CH_2O, B), 67.5 (CH_2Ph, A), 67.1 (CH_2O, A), 66.9 (C_{quat}, *c*Pr-C, A), 66.0 (C_{quat}, *c*Pr-C, B), 60.5 (CH, B), 59.1 (CH, A), 39.2 (SO_2CH_3, A, B), 26.8 [$C(CH_3)_2$, B], 25.9 [$C(CH_3)_2$, A], 24.0 [$C(CH_3)_2$, B], 22.3 [$C(CH_3)_2$, A], 10.2 (CH_2, *c*Pr-C, A), 9.4 (CH_2, *c*Pr-C, B) ppm. MS (ESI): *m/z* (%) = 760.8 (3) $[2M + Na]^+$, 392.1 (100) $[M + Na]^+$. IR (film): $\tilde{\nu}$ = 3304 , 3055, 2950, 1736 (C=O), 1659 (C=O), 1457, 1436, 1419, 1341, 1213, 745 cm^{-1}. HRMS (ESI) calcd. for $C_{17}H_{23}NO_6SNa^+$ $[M + Na]^+$: 392.11383; found 392.11384. $C_{17}H_{23}NO_6S$ (369.44): calcd. C 55.27, H 6.28, N 3.79; found C 55.47, H 6.11, N 3.85.

1-(1′-Benzyloxycarbonylamino-2′-hydroxyethyl)cyclopropyl Mesylate (5): To a solution of **4** (5.25 g, 14.2 mmol) in methanol (42 mL), was added *p*-toluensulfonic acid (8.11 g, 42.7 mmol), and the mixture was stirred at 20 °C for 12 h. The solvent was evaporated under reduced pressure and ethyl acetate (200 mL) was added followed by water (30 mL). The organic layer was separated, washed with saturated $NaHCO_3$ solution (2 × 50 mL) and with brine (100 mL). After drying over Na_2SO_4 and evaporation of the solvent, column chromatography of the residue on silica gel (Et_2O, R_f = 0.32) gave compound **5** (3.62 g, 77%) as a yellow-orange oil. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.31 (m, 5 H, Ph), 5.87 (d, *J* = 8.8 Hz, 1 H, NH), 5.09 (s, 2 H, CH_2Ph), 3.82 (m, 2 H, CH_2OH), 3.71–3.63 (m, 1 H, CH), 3.03 (br. s, 4 H, CH_3, OH), 1.50–1.41 (m, 1 H, *c*Pr-H), 1.36–1.25 (m, 1 H, *c*Pr-H), 1.10–0.93 (m, 2 H, *c*Pr-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 156.7 (C_{quat}, C=O), 136.2 (C_{quat}, C_{ipso}), 128.5 (2 C, Ph-CH), 128.2 (C, Ph-CH), 128.0 (2 C, Ph-CH), 67.0 (CH_2Ph), 66.8 (CH_2OH), 62.4 (C_{quat}, *c*Pr-C), 57.4 (CH), 39.4 (CH_3), 11.7 (CH_2, *c*Pr-C), 10.4 (CH_2, *c*Pr-C) ppm. MS (ESI): *m/z* (%) = 680.8 (12) $[2M + Na]^+$, 352.1 (100) $[M + Na]^+$, 373.9 (100) $[M + HCOO]^-$, 327.9 (16) $[M – H]^-$. IR (film): $\tilde{\nu}$ = 3304 (OH), 3055, 2950, 1736 (C=O), 1659 (C=O), 1457, 1436, 1419, 1341, 1213, 745 cm^{-1}. $C_{14}H_{19}NO_6S$ (329.34): calcd. C 51.05, H 5.81, N 4.25; found C 51.36, H 5.71, N 4.11.

Methyl 2-(Benzyloxycarbonylamino)-2-[1-(methylsulfonyloxy)cyclopropyl]acetate (6): A 100 mL round-bottomed flask equipped with a magnetic stirring bar, was charged with **5** (3.08 g, 9.36 mmol), CCl_4 (20 mL), CH_3CN (20 mL), water (30 mL) and $NaIO_4$ (6.01 g, 28.09 mmol). To the resulting biphasic mixture was added $RuCl_3 \cdot 3H_2O$ (50 mg, 2 mol-%), and the entire mixture was stirred vigorously at room temp. for 1 h. Then CH_2Cl_2 (100 mL) was added, and the phases were separated. The upper aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated at reduced pressure. The resulting residue was diluted with Et_2O, filtered through a pad of Celite and concentrated to give the crude product (3.23 g, 97%), which was used in the next step without further purification. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 11.01 (br. s, 1 H, COOH), 7.34 (m, 5 H, Ph), 6.38 (d, *J* = 7.5 Hz, 1 H, NH), 5.12 (s, 2 H, CH_2Ph), 4.17 (d, *J* = 7.5 Hz, CH), 2.99 (s, 3 H, CH_3), 1.75–1.57 (m, 1 H, *c*Pr-H), 1.51–1.41 (m, 1 H, *c*Pr-H), 1.28–1.12 (m, 2 H, *c*Pr-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 172.8 (COOH), 156.3 (C=O), 135.9 (C_{quat}, C_{ipso}), 128.5 (2 C, Ph-CH), 128.3 (C, Ph-CH), 128.1 (2 C, Ph-CH), 67.4 (CH_2Ph), 65.9 (C_{quat}, *c*Pr-C), 59.6 (CH), 39.3 (CH_3), 13.2 (CH_2, *c*Pr-C), 11.6 (CH_2, *c*Pr-C) ppm. IR (film): $\tilde{\nu}$ = 3390 , 2977, 1723, 1520, 1345, 1170, 1059, 945 cm^{-1}. MS (ESI): *m/z* (%) = 366.1 (56) $[M + Na]^+$, 684.9 (100) $[2M – H]^-$. HRMS (ESI) calcd. for $C_{14}H_{17}NO_7SNa$ $[M + Na]^+$: 366.06179 found 366.06169.

To a solution of the crude acid (3.20 g, 9.33 mmol) in anhydrous MeOH (100 mL) was added dropwise with stirring thionyl chloride (1.22 g, 10.3 mmol), and the mixture was stirred at 20 °C for 20 h. The solvents were removed at reduced pressure, and the residue was purified by column chromatography on silica gel (diethyl ether/hexane, 2:1, R_f = 0.34) to give 3.0 g (90%) of desired methyl ester **6** as a colorless solid, m.p. 88–89 °C. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.35–7.27 (m, 5 H, Ph), 6.23 (d, *J* = 8.5 Hz, 1 H, NH), 5.12 (s, 2 H, CH_2), 4.15 (d, *J* = 8.5 Hz 1 H, CH), 3.80 (s, 3 H, CO_2CH_3), 2.99 (s, 3 H, SO_2CH_3), 1.61–1.44 (m, 2 H, *c*Pr-H), 1.25–1.10 (m, 2 H, *c*Pr-H) ppm. ^{13}C NMR (62.9 MHz, DEPT, $CDCl_3$, 25 °C): δ = 169.4 (–, C_{quat}, CO_2CH_3), 156.3 (–, $NHCO_2$), 136.0 (–, C_{quat}, C_{ipso}), 128.5 (+, CH, Ph-CH), 128.2 (+, 2 CH, Ph-CH), 128.1 (+, CH, Ph-CH), 67.2 (–, CH_2Ph), 66.0 (+, CH), 59.5 (–, C_{quat}, *c*Pr-C), 52.8 (+, CO_2CH_3), 39.3 (+, SO_2CH_3), 12.9 (–, CH_2, *c*Pr-C), 11.7 (–, CH_2, *c*Pr-C) ppm. MS (ESI): *m/z* (%) = 736.8 (3) $[2M + H]^+$, 380.1 (100) $[M + Na]^+$. IR (film): $\tilde{\nu}$ = 3327 (NH), 3026, 2950, 2857, 1734 (C=O), 1706 (C=O), 1652 (C=O), 1456, 1419, 1272, 1207, 1143, 1029, 735, 701 cm^{-1}. $C_{15}H_{19}NO_7S$ (357.39): calcd. C 50.41, H. 5.56, N 3.92; found C 50.29, H 5.30, N 4.05.

Methyl 2-(Benzyloxycarbonylamino)-2-cyclopropylideneacetate (2): Potassium *tert*-butoxide (1.04 g, 9.27 mmol) was added slowly at

0 °C under nitrogen to a solution of the mesylate **6** (2.76 g, 7.72 mmol) in anhydrous methyl *tert*-butyl ether (40 mL). The mixture was stirred at 0 °C for 2 h, then water (5 mL) and Et_2O (50 mL) were added. The aqueous phase was extracted with Et_2O (3 × 30 mL), and the combined organic phase was dried with anhydrous Na_2SO_4, filtered, and the solvents were removed at reduced pressure. The residue was purified by column chromatography (hexane/diethyl ether, 5:1, R_f = 0.18) to give 1.37 g (68%) of **2** as a colorless solid, m.p. 55–56 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.39–7.31 (m, 5 H, Ph), 6.92 (br. s, 1 H, NH), 5.14 (s, 2 H, CH_2), 3.80 (s, 3 H, CO_2CH_3), 1.52 (br. s, 4 H, *c*Pr-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 164.7 (C_{quat}, CO_2CH_3), 153.4 (C_{quat}, $NHCO_2$), 136.0 (C_{quat}, Ph), 128.5 (2 C, Ph-CH), 128.2 (C, Ph-CH), 128.1 (2 C, Ph-CH), 126.0 (C_{quat}, NHC=O), 116.6 (C_{quat}, *c*Pr-C), 66.9 (CH_2), 52.5 (CH_3, CO_2CH_3), 6.5 (*c*Pr-C), 6.0 (*c*Pr-C) ppm. MS (ESI): *m*/*z* (%) = 545.2 (100) $[2M + Na]^+$, 284.1 (22) $[M + Na]^+$. IR (film): $\tilde{\nu}$ = 3433 (NH), 3269 (NH), 3027, 2973, 1675 (C=O), 1641 (C=O), 1444, 1422, 1326, 1040, 755, 699, 612 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{15}NO_4Na^+$ $[M + Na]^+$: 284.08933; found 284.08942. $C_{14}H_{15}NO_4$ (261.3): calcd. C 64.36, H 5.79, N 5.36; found C 64.06, H 5.41, N 5.01.

***endo*-/*exo*-Methyl 3-{[(Benzyloxy)carbonyl]amino}spiro[bicyclo[2.2.1]-heptane-2,1′-cyclopropane]-5-ene-3-carboxylate (*endo*-/*exo*-7a):** A mixture of cyclopropylideneacetate **2** (118 mg, 0.45 mmol) and freshly distilled cyclopentadiene (60 mg, 0.90 mmol) was stirred under an atmosphere of nitrogen at 25 °C for 30 h. A small aliquot of the reaction mixture was evaporated and analyzed by ^{1}H NMR spectroscopy to prove the full consumption of **2**. After evaporation of the excess cyclopentadiene, the product was isolated by column chromatography on silica gel (hexane/ethyl acetate, 5:1, R_f = 0.26) to give 107 mg (60%) of a 4:1 mixture (according to ^{1}H NMR) of the diastereomeric cycloadducts *endo*-**7a** and *exo*-**7a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.42–7.31 (m, 5 H, Ph), 6.48–6.42 (dd, *J* = 5.7, 3.0 Hz, 0.2 H, CH=CH), 6.37–6.34 (dd, *J* = 5.7, 3.0 Hz, 0.8 H, CH=CH), 6.29–6.26 (dd, *J* = 5.7, 3.0 Hz, 0.2 H, CH=CH), 6.13–6.10 (dd, *J* = 5.7, 3.0 Hz, 0.8 H, CH=CH), 5.69 (br. s, 0.8 H, NH), 5.63 (br. s, 0.2 H, NH), 5.11 (d, *J* = 3.0 Hz, 0.4 H, $PhCH_2$), 5.06 (d, *J* = 3.0 Hz, 0.4 H, $PhCH_2$), 3.70 (s, 2.4 H, CH_3), 3.67 (s, 0.6 H, CH_3), 3.59 (s, 0.8 H), 3.40 (s, 0.2 H), 2.28 (d, *J* = 9.0 Hz, 0.8 H), 2.06 (s, 0.8 H), 2.01 (s, 0.8 H), 1.93 (d, *J* = 9.0 Hz, 0.2 H), 1.72 (d, *J* = 8.3 Hz, 0.8 H), 1.67 (d, *J* = 8.3 Hz, 0.2 H), 0.76–0.68 (m, 1 H, *c*Pr-H), 0.63–0.42 (m, 3 H, *c*Pr-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 172.9 (–, C_{quat}, CO_2Me), 171.6 (–, C_{quat}, CO_2Me), 155.1 (–, C_{quat}, CONH), 154.8 (–, C_{quat}, CONH), 138.4 (+, CH=CH), 136.3 (–, C_{quat}, C_{ipso}), 136.2 (+, CH=CH), 136.0 (–, C_{quat}, C_{ipso}), 128.5 (+, 2 CH, Ph), 128.2 (+, CH, Ph), 128.1 (+, 2 CH, Ph), 67.0 (–, C_{quat}, CNH), 66.9 (–, C_{quat}, CNH), 66.7 (+, CH_2, CH_2Ph), 66.5 (+, CH_2, CH_2Ph), 52.8 (+, CH), 52.5 (+, CH), 52.1 (+, CH_3), 51.6 (+, CH_3), 51.0 (+, CH), 50.6 (+, CH), 48.6 (–, C_{quat}, *c*Pr-C), 47.6 (–, C_{quat}, *c*Pr-C), 33.6 (–, CH_2), 33.0 (–, CH_2), 11.4 (–, CH_2, *c*Pr), 10.54 (–, *C*H_2, *c*Pr), 8.42 (–, *C*H_2, *c*Pr), 6.9 (–, CH_2, *c*Pr) ppm. IR (film): $\tilde{\nu}$ = 2953 , 1740, 1750, 1761, 1769, 1490, 1286, 1220, 1028, 1138 cm^{-1}. MS (ESI): *m*/*z* (%) = 676.9 (4) $[2M + Na]^+$, 350.4 (100) $[M + Na]^+$, 328.4 (3) $[M + H]^+$. HRMS (ESI) calcd. for $C_{19}H_{21}NO_4Na^+$ 350.13628 found 350.13624.

Methyl-2-(1-Benzylaminocyclopropyl)-2-(benzyloxycarbonylamino)-acetate (8a): To a solution of **2** (50 mg, 0.19 mmol) in anhydrous MeOH (1 mL) was added dropwise with stirring under an atmosphere of dry nitrogen a solution of benzylamine (20.5 mg, 0.19 mmol) in MeOH (1 mL). The mixture was stirred at 20 °C for 20 h, then the solvents were removed at reduced pressure. The crude product was purified by column chromatography on silica gel (pentane/diethyl ether, 4:1, R_f = 0.10) to give 64 mg (91%) of **8a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.30 (m, 5 H, Ph), 7.28–7.19 (m, 5 H, Ph), 5.74 (d, *J* = 8.3 Hz, 1 H, NH), 5.11 (s, 2 H, CH_2Ph), 4.24 (d, *J* = 8.7 Hz, 1 H, CH), 3.74 (br. s, 5 H, $NHCH_2$, CO_2CH_3), 1.63 (br. s, 1 H, CH_2NH), 0.91–0.80 (m, 2 H, CH_2-*c*Pr), 0.78–0.68 (m, 2 H, CH_2-*c*Pr) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT, 25 °C): δ = 171.8 (–, C_{quat}, CO_2CH_3), 156.1 (–, C_{quat}, $NHCO_2$), 140.2 (–,C_{quat}, C_{ipso}), 136.1 (–, C_{quat}, C_{ipso}), 128.5 (+, 2 C, Ar-CH), 128.3 (+, 2 C, Ar-CH), 128.1 (+, Ar-CH), 128.1 (+, 2 C, Ar-CH), 128.0 (+, 2 C, Ar-CH), 126.9 (+, Ar-CH), 67.0 (–, OCH_2Ph), 58.2 (+, CH), 52.3 (+, CO_2CH_3), 50.3 (–, NCH_2Ph), 41.6 (–, C_{quat}, *c*Pr-C), 13.5 (–, CH_2-*c*Pr), 13.2 (–, CH_2-*c*Pr) ppm. MS (ESI): *m*/*z* (%) = 758.8 (100) $[2M + Na]^+$, 391.2 (32) $[M + Na]^+$, 366.9 (82) $[M - H]^-$. IR (film): $\tilde{\nu}$ = 3352 , 3030, 1722, 1499, 1328, 1218, 1054, 699 cm^{-1}. $C_{21}H_{24}N_2O_4$ (368.43): calcd. C 68.46, H 6.57, N 7.60; found C 68.73, H 6.25, N 7.41.

Methyl 2-(Benzyloxycarbonylamino)-2-(1-diethylaminocyclopropyl)-acetate (8b): To a solution of **2** (50 mg, 0.19 mmol) in anhydrous THF (1 mL) was added dropwise with stirring under nitrogen a solution of diethylamine (15.4 mg, 0.21 mmol) in anhydrous THF (1 mL). The mixture was stirred at 20 °C for 24 h, and the solvents were removed at reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/diethyl ether, 4:1, R_f = 0.15) to give 52 mg (81%) of **8b** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.32 (m, 5 H, Ph), 5.55 (d, *J* = 8.7 Hz, 1 H, NH), 5.11 (s, 2 H, CH_2Ph), 4.13 (d, *J* = 9.0 Hz, 1 H, CH), 3.71 (s, 3 H, CO_2CH_3), 2.51 (q, *J* = 8.5 Hz, 4 H, NCH_2), 0.99 (t, *J* = 8.6 Hz, 6 H, NCH_2CH_3), 0.87–0.60 (m, 4 H, CH_2-*c*Pr) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT, 25 °C): δ = 172.0 (–, C_{quat}, CO_2CH_3), 155.7 (–, C_{quat}, $NHCO_2$), 136.3 (–,C_{quat}, C_{ipso}), 128.4 (+, 2 C, Ar-CH), 128.1 (+, 2 C, Ar-CH), 128.0 (+, Ar-CH), 67.1 (–, C_{quat}, *c*Pr-C), 66.9 (–, CH_2Ph), 58.0 (+, CO_2CH_3), 51.9 (+, CH), 46.3 (–, 2 C, NCH_2CH_3), 14.8 (+, 2 C, NCH_2CH_3), 14.5 (–, CH_2-*c*Pr), 10.8 (–, CH_2-*c*Pr) ppm. MS (ESI): *m*/*z* (%) = 757.2 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{18}H_{26}NaN_2O_4$ $[M + Na]^+$ 357.17848; found 357.17866. IR (film): $\tilde{\nu}$ = 3359 , 2968, 1725, 1506, 1202, 1055, 698 cm^{-1}. $C_{18}H_{26}N_2O_4$(334.22): calcd. C 64.65, H 7.84, N 8.38; found C 64.36, H 7.61, N 8.20.

Methyl 2-(Benzyloxycarbonylamino)-2-(1-phenylsulfanylcyclopropyl)-acetate (8c): To a solution of **2** (50 mg, 0.19 mmol) in anhydrous THF (1 mL) was added dropwise with stirring under nitrogen a solution of diethylamine (15.4 mg, 0.21 mmol) in anhydrous THF (1 mL). The mixture was stirred at 20 °C for 24 h, and the solvents were removed at reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/diethyl ether, 4:1, R_f = 0.15) to give 52 mg (81%) of **8c** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.37–7.32 (m, 5 H, Ph), 5.55 (d, *J* = 8.7 Hz, 1 H, NH), 5.11 (s, 2 H, CH_2Ph), 4.13 (d, *J* = 9.0 Hz, 1 H, CH), 3.71 (s, 3 H, CO_2CH_3), 2.51 (q, *J* = 8.5 Hz, 4 H, NCH_2), 0.99 (t, *J* = 8.6 Hz, 6 H, NCH_2CH_3), 0.87–0.60 (m, 4 H, CH_2-*c*Pr) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT, 25 °C): δ = 172.0 (–, C_{quat}, CO_2CH_3), 155.7 (–, C_{quat}, $NHCO_2$), 136.3 (–, C_{quat}, C_{ipso}), 128.4 (+, 2 C, Ar-CH), 128.1 (+, 2 C, Ar-CH), 128.0 (+, Ar-CH), 67.1 (–, C_{quat}, *c*Pr-C), 66.9 (–, CH_2Ph), 58.0 (+, CO_2CH_3), 51.9 (+, CH), 46.3 (–, 2 C, NCH_2CH_3), 14.8 (+, 2 C, NCH_2CH_3), 14.5 (–, CH_2-*c*Pr), 10.8 (–, *C*H_2-*c*Pr) ppm. MS (ESI): *m*/*z* (%) = 757.2 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{18}H_{26}NaN_2O_4$ $[M + Na]^+$ 357.17848; found 357.17866. IR (film): $\tilde{\nu}$ = 3359, 2968, 1725, 1506, 1202, 1055, 698 cm^{-1}. $C_{18}H_{26}N_2O_4$ (334.41): calcd. C 64.65, H 7.84, N 8.38; found C 64.36, H 7.61, N 8.20.

Methyl 2-(Benzyloxycarbonylamino)-2-(1-methylsulfanylcyclopropyl)acetate (8d): To a solution of **2** (100 mg, 0.38 mmol) in THF

(10 mL) was added with stirring one drop of triethylamine, then sodium methanethiolate (26.8 mg, 0.38 mmol). The mixture was stirred at 20 °C for 24 h, and the solvents were removed at reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/diethyl ether, 2:1, R_f = 0.29) to give 93 mg (75%) of **8d** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.28 (m, 5 H, Ph), 5.85 (d, J = 8.7 Hz, 1 H, NH), 5.12 (s, 2 H, CH_2Ph), 3.87 (d, J = 9.0 Hz, 1 H, CH), 3.76 (s, 3 H, CO_2CH_3), 2.05 (s, 3 H, SCH_3), 1.30–1.24 (m, 1 H, CH_2-*c*Pr), 1.18–1.03 (m, 2 H, CH_2-*c*Pr), 0.98–0.91 (m, 1 H, CH_2-*c*Pr) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT, 25 °C): δ = 171.1 (–, C_{quat}, CO_2CH_3), 155.9 (–, C_{quat}, $NHCO_2$), 136.1 (–,C_{quat}, C_{ipso}), 128.5 (+, 2 C, Ph-CH), 128.2 (+, Ph-CH), 128.1 (+, 2 C, Ph-CH), 67.1 (–, CH_2Ph), 60.5 (+, SCH_3), 52.4 (+, CO_2CH_3), 51.6 (+, CH), 33.0 (–, C_{quat}, *c*Pr-C), 17.0 (–, CH_2-*c*Pr), 15.6 (–, CH_2-*c*Pr) ppm. MS (EI): *m*/*z* (%) = 309 (3) $[M]^+$, 158 (36), 91 (100). IR (film): $\tilde{\nu}$ = 3362 , 2952, 1734, 1509, 1320, 1208, 1055 cm^{-1}. $C_{15}H_{19}NO_4S$ (309.38): calcd. C 58.23, H 6.19, N 4.53; found C 58.39, H 5.93, N 4.71.

Methyl 2-(Benzyloxycarbonylamino)-2-(1-benzyloxycyclopropyl)acetate (8e-Me) and

Benzyl 2-(Benzyloxycarbonylamino)-2-(1-benzyloxycyclopropyl)acetate (8e-Bn): To a solution of **2** (120 mg, 0.46 mmol) in anhydrous benzyl alcohol (1 mL) was added dropwise with stirring under nitrogen one drop of triethylamine. The mixture was stirred at 20 °C for 24 h, and the solvents were removed in vacuo at 60 °C. The crude product was analyzed by ^{1}H NMR spectroscopy and then purified by column chromatography on silica gel (pentane/diethyl ether, 2:1), to give 40 mg (20%) of the benzyl ester **8e**-Bn (R_f = 0.34), 78 mg of 1:1 mixture of **8e**-Bn and **8e**-Me and 32 mg (19%) of the methyl ester **8e**-Me (R_f = 0.28), total yield of of **8e**-Bn and **8e**-Me: 80%.

8e-Me: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 –7.31 (m, 5 H, Ph), 7.30–7.22 (m, 5 H), 5.71 (d, J = 5.9 Hz, 1 H, NH), 5.09 (dd, J = 5.6, 2.2 Hz, 2 H, CH_2), 4.83 (d, J = 11.5 Hz, 1 H, CH_2), 4.53 (d, J = 11.5 Hz, 1 H, CH_2), 3.80 (s, 3 H, CH_3), 1.49–1.39 (m, 1 H, CH), 0.76–0.71 (m, 2 H, *c*Pr-CH_2), 0.47–0.38 (m, 2 H, *c*Pr-CH_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 170.1 (–, C_{quat}, CO_2Me), 154.8 (–,C_{quat}, NCOO), 138.6 (–, C_{quat}, C_{ipso}), 135.9 (–, C_{quat}, C_{ipso}), 128.5 (+, 2 CH, Ph), 128.3 (+, CH, Ph), 128.3 (+, 2 CH, Ph), 128.1 (+, 2 CH, Ph), 127.3 (+, 2 CH, Ph), 127.2 (+, CH, Ph), 127.2 (+, 2 CH, Ph), 84.5 (–, C_{quat}, *t*Bu), 67.2 (–, CH_2Ph), 67.1 (–, C_{quat}, *c*Pr-C), 66.3 (–, CH_2Ph, Z), 52.8 (+, OCH_3), 19.3 (+, CH), 1.6 (–, *c*Pr-CH_2), 0.83 (–, *c*Pr-CH_2) ppm. IR (film): $\tilde{\nu}$ = 3344 , 2952, 1730, 1498, 1282, 1090, 1028, 736, 698 cm^{-1}. MS (ESI): *m*/*z* (%) = 760.8 (15) $[2M + Na]^+$, 392.3 (78) [M + Na]. $C_{21}H_{23}NO_5$ (369.41): calcd. C 68.28, H. 6.28, N 3.79; found C 68.48, H. 6.16, N 3.87.

8e-Bn: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 10 H, Ph), 7.28–7.21 (m, 5 H, Ph), 5.71 (br. s, 1 H, NH), 5.29 (d, J = 12.8 Hz, 1 H, CH_2), 5.17 (d, J = 12.5 Hz, 1 H, CH_2), 5.08 (d, J = 2.2 Hz, 2 H, CH_2), 4.84 (d, J = 11.5 Hz, 1 H, CH_2), 4.54 (d, J = 11.8 Hz, 1 H, CH_2), 1.47–1.38 (m, 1 H, CH), 0.75–0.70 (m, 2 H, *c*Pr-H), 0.44–0.37 (m, 2 H, *c*Pr-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 169.4 (–, C_{quat}, CO_2Bn), 154.8 (–,C_{quat}, NHC=O), 138.6 (–, C_{quat}, C_{ipso}), 135.9 (–, C_{quat}, C_{ipso}), 135.5 (–, C_{quat}, C_{ipso}), 128.7 (+, CH, Ph), 128.5 (+, 2 CH, Ph), 128.5 (+, 2 CH, Ph), 128.3 (+, CH, Ph), 128.3 (+, 2 CH, Ph), 128.2 (+, 2 CH, Ph), 128.1 (+, 2 CH, Ph), 127.3 (+, 2 CH, Ph), 127.2 (+, CH, Ph), 84.4 (–, C_{quat}, *t*Bu), 67.6 (–, CH_2Ph), 67.1 (–, CH_2Ph), 63.4 (–, C_{quat}, *c*Pr-C), 66.4 (–, CH_2Ph), 19.3 (+, CH), 1.6 (–, CH_2, *c*Pr), 0.8 (–, CH_2, *c*Pr) ppm. IR (film): $\tilde{\nu}$ = 3348 , 3032, 1730, 1497, 1455, 1275, 1090, 1028, 736, 697 cm^{-1}. MS (ESI): *m*/*z* (%) = 912.9 (100) $[2M + Na]^+$, 468.4 (52) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{27}H_{27}NO_5Na^+$ $[M + Na]^+$: 468.17814. found 468.17824. $C_{27}H_{27}NO_5$ (445.51): calcd. C 72.79, H 6.11, N 3.14; found C 72.89, H 6.15, N 3.10.

Benzyl (Methoxycarbonyl)[1-(1-phenylethylamino)cyclopropyl]methylcarbamate [(*R*,*S*)-8f/(*R*,*R*)-8f]: To a solution of **2** (50 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (8 mL) was added dropwise with stirring under nitrogen a solution of (*R*)-(+)-1-phenylethylamine (23.0 mg, 0.19 mmol) in anhydrous THF (2 mL). The mixture was stirred at 20 °C for 24 h, and the solvents were removed at reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 4:1, R_f = 0.20) to give 56.6 mg (78%) of a 1:1 mixture of (*R*,*S*)-**8f**/(*R*,*R*)-**8f** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.38–7.17 (m, 10 H, Ph), 5.60 (d, J = 8.7 Hz, 0.5 H, NHZ), 5.42 (d, J = 8.7 Hz, 0.5 H, NHZ), 5.13 (m, 1 H, CH_2Ph), 5.10–5.02 (m, 1 H, CH_2Ph), 4.37 (d, J = 8.6 Hz, 0.5 H, CH), 4.11 (d, J = 9.4 Hz, 0.5 H, CH), 3.99 (q, J = 6.5 Hz, 0.5 H, CH), 3.89 (q, J = 6.5 Hz, 0.5 H, CH), 3.76 (s, 1.5 H, CO_2CH_3), 3.64 (s, 1.5 H, CO_2CH_3), 1.78 (s, 1 H, NH), 1.28 (d, J = 4.4 Hz, 1.5 H, CH_3), 1.26 (d, J = 4.9 Hz, 1.5 H, CH_3), 0.78–0.43 (m, 4 H, CH_2-*c*Pr) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT, 25 °C): δ = 171.8 (–, C_{quat}, CO_2CH_3), 171.5 (–, C_{quat}, CO_2CH_3), 156.1 (–, C_{quat}, $NHCO_2$), 156.0 (–, C_{quat}, $NHCO_2$), 146.8 (–,C_{quat}, C_{ipso}), 146.6 (–,C_{quat}, C_{ipso}), 136.2 (–,C_{quat}, C_{ipso}), 136.1 (–,C_{quat}, C_{ipso}), 128.5 (+, Ph-CH), 128.4 (+, 2 C, Ph-CH), 128.2 (+, 2 C, Ph-CH), 128.1 (+, 2 C, Ph-CH), 128.0 (+, Ph-CH), 127.0 (+, Ph-CH), 126.8 (+, Ph-CH), 126.6 (+, Ph-CH), 126.5 (+, Ph-CH), 67.0 (–, CH_2Ph), 66.9 (–, CH_2Ph), 58.8 (+, CO_2CH_3), 58.0 (+, CO_2CH_3), 54.9 (+, CH), 54.6 (+, CH), 52.2 (+, 2 C, CH), 40.1 (–, C_{quat}, *c*Pr-C), 39.9 (–, C_{quat}, *c*Pr-C), 25.0 (+, CH_3), 24.8 (+, CH_3), 13.4 (–, CH_2-*c*Pr), 12.3 (–, CH_2-*c*Pr), 12.1 (–, CH_2-*c*Pr), 11.9 (–, CH_2-*c*Pr) ppm. MS (ESI): *m*/*z* (%) = 383.2 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{22}H_{27}N_2O_4^+$ $[M + H]^+$: 383.1965. found 383.1960.

Methyl 1-(Benzyloxycarbonylamino)-1-(oxaspiropentane)acetate (9): In a 5 mL flask equipped with a magnetic stirring bar, **2** (73 mg, 0.28 mmol) and methyltrioxorhenium (0.36 mg, 0.0014 mmol, 0.5 mol-%) were dissolved in CH_2Cl_2 (1 mL). To this solution was first added with stirring pyridine (2.65 mg, 0.0336 mmol, 12 mol-%), then dropwise with a syringe 30% aq. H_2O_2 (0.48 mL, 0.42 mmol). The reaction was complete after 6 h at 20 °C. The mixture was diluted with CH_2Cl_2 (5 mL), treated with MnO_2 (catalytic quantity) to decompose the excess of H_2O_2, the solution dried with anhydrous Na_2SO_4 and concentrated to give a crude product, which was purified by column chromatography on silica gel deactivated with NEt_3 (hexane/ethyl acetate, 4:1, R_f = 0.34) to give 60.5 mg (78%) of **9** as colorless solid, m.p. 74–75 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 11.02 (s, 1 H, NH), 7.42–7.33 (m, 5 H, Ph), 5.21 (s, 2 H, CH_2Ph), 3.70 (s, 3 H, CO_2CH_3), 1.82–1.78 (m, 2 H, CH_2-*c*Pr), 1.71–1.68 (m, 2 H, CH_2-*c*Pr) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT, 25 °C): δ = 173.3 (–, C_{quat}, CO_2CH_3), 167.3 (–, C_{quat}, $NHCO_2$), 135.2 (–,C_{quat}, C_{ipso}), 128.5 (+, 4 C, Ph-CH), 128.4 (+, 2 C, Ph-CH), 67.4 (–, CH_2Ph), 66.7 (–, C_{quat}, C-1), 52.7 (+, CO_2CH_3), 27.3 (–, C_{quat}, C-5), 21.8 (–, CH_2-*c*Pr) ppm. MS (ESI): *m*/*z* (%) = 576.9 (100) $[2M + Na]^+$, 300.2 (6) $[M + Na]^+$, 575.1 (100) $[2M – 2H + Na]^-$, 276.2 (98) $[M – H]^-$. IR (film): $\tilde{\nu}$ = 3276 , 1781, 1717, 1506, 1216, 1027 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{15}NO_5Na^+$ $[M + Na]^+$: 300.08424. found 300.08425.

In a control experiment, a solution of **2** (50 mg, 0.19 mmol) in CH_2Cl_2 (1 mL) was stirred in the open air for 48 h. Evaporation of the solvent and purification of the residue by column chromatography on silica gel also gave **9** (15 mg, 28%), which was identical with the authentic sample prepared before.

Methyl 2-(Benzyloxycarbonylamido)-5-oxo-tetrahydrofuran-2-carboxylate (11): To a solution of **2** (150 mg, 0.57 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C 75% mCPBA (262 mg, 1.14 mmol). The mixture was stirred at room temp. for 2 h, and the solvent was removed under reduced pressure. The title compound (70 mg, 42%) was isolated by column chromatography on silica gel (hexane/ethyl acetate, 1:1, R_f = 0.24) as a colorless solid, m.p. 138 °C [lit.[20] 136 –138 °C] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.35 (s, 5 H, Ph), 6.56 (s, 1 H, NH), 5.12 (d, J = 3.1 Hz, 2 H, CH_2Ph), 3.85 (s, 3 H, CO_2CH_3), 3.07–2.90 (m, 1 H), 2.84–2.58 (m, 3 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$, APT, 25 °C): δ = 174.8 (–, C_{quat}, CO_2Me), 168.3 (–, C_{quat}, CO_2Me), 153.7 (–, C_{quat}, $NHCO_2$), 135.2 (–,C_{quat}, C_{ipso}), 128.5 (+, 2 C, Ph-CH), 128.4 (+, Ph-CH), 128.2 (+, 2 C, Ph-CH), 89.2 (–, CH_2), 67.5 (–, CH_2Ph), 54.1 (+, CO_2CH_3), 30.0 (–, C_{quat}), 28.5 (–, CH_2) ppm. MS (ESI): m/z (%) = 609.2 (80) [2M + Na]$^+$, 316.0 (100) [M + Na]$^+$. IR (film): $\tilde{\nu}$ = 3296 , 3061, 2954, 1798, 1781, 1703, 1544, 1355, 1311, 1202, 1052, 1009, 952, 754, 627 cm^{-1}. $C_{14}H_{15}NO_6$ (293.27): calcd. C 57.34, H 5.16, N 4.78; found C 57.34, H 5.16, N 4.78.

Methyl 2-(Benzyloxycarbonylamino)-2-[1-(*tert*-butoxycarbonylmethylamino)cyclopropyl]acetate (12): To a solution of **2** (2.56 g, 9.78 mmol) and glycine *tert*-butyl ester (1.18 g, 10.3 mmol) in acetonitrile (100 mL) was added K_2CO_3 (1.49 g, 10.8 mmol). The resulting suspension was stirred at room temperature for 3 d, then the solvent was removed at reduced pressure and the residue was purified by column chromatography (hexane/diethyl ether, 2:1 R_f = 0.13) to give 3.19 g (83%) of **12** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 5 H, Ph), 5.97 (d, J = 8.3 Hz, 1 H, NHC=O), 5.12 (s, 2 H, CH_2), 3.91 (d, J = 8.7 Hz, 1 H, CH), 3.76 (s, 3 H, CH_3), 3.30 (d, J = 7.5 Hz, 2 H, CH_2N), 1.83 (br. s, 1 H, NH), 1.44 (s, 9 H, *t*Bu), 0.92–0.67 (m, 4 H, *c*Pr-H) ppm. ^{13}H NMR (75.5 MHz, $CDCl_3$, APT): δ = 172.2 (–, C_{quat}, C=O), 171.8 (–, C_{quat}, C=O), 156.2 (–, C_{quat}, NHC=O), 136.3 (–, C_{quat}, C_{ipso}), 128.5 (+, 2 CH, Ph), 128.1 (+, CH, Ph), 128.1 (+, 2 CH, Ph), 81.4 (–, C_{quat}, *t*Bu), 67.0 (–, CH_2), 59.2 (+, CH), 52.4 (+, CH_3), 48.9 (–, $NHCH_2$), 41.6 (–, C_{quat}, *c*Pr-C), 28.0 (+, CH_3, *t*Bu), 14.2 (–, CH_2, *c*Pr), 12.7 (–, CH_2, *c*Pr) ppm. MS (ESI): m/z (%) = 806.8 (18) [2M + Na]$^+$, 415.1 (100) [M + Na]$^+$. IR (film): $\tilde{\nu}$ = 3327 (NH), 3062, 3028, 2929, 1734 (C=O), 1669 (C=O), 1454, 1410, 1347, 1195, 1029, 749, 699 cm^{-1}. $C_{20}H_{28}N_2O_6$ (392.45): calcd. C 61.21, H 7.19, N 7.14; found C 60.92, H 6.98, N 6.93.

Methyl 2-(Benzyloxycarbonylamino)-2-{1-[(2-bromoacetyl)-*tert*-butoxycarbonylmethylamino]cyclopropyl}acetate (13): To a solution of **12** (2.34 g, 5.96 mmol) in 1,2-dichloroethane (20 mL) was added at 20 °C first $NaHCO_3$ (1.60 g, 19.1 mmol) then bromoacetylchloride (1.21 g, 7.74 mmol). Water (12 mL) was added dropwise to this vigorously stirred mixture, which was kept stirring at 20 °C for 1 h. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried with Na_2SO_4 and the solvents were removed at reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1:1, R_f = 0.18) to afford 2.39 g (78%) of **13** as a colorless oil. ^{1}H NMR (300 MHz, [D6]DMSO, 35 °C) (2 rotamers): δ = 7.87 (t, J = 8.3 Hz, 1 H, NH), 7.41–7.29 (m, 5 H, Ph), 5.06 (d, J = 6.8 Hz, 2 H, CH_2), 4.53 (d, J = 8.7 Hz, 0.5 H, CH_2), 4.35 (d, J = 11.7 Hz, 0.5 H, CH_2), 4.12 (d, J = 11.7 Hz, 0.5 H, CH_2), 3.96 (d, J = 8.7 Hz, 0.5 H, CH_2), 3.93 (s, 1 H, CH), 3.66 (s, 2 H, CH_2), 3.26 (s, 3 H, CH_3), 1.36 (s, 9 H, *t*Bu), 1.30–1.08 (m, 2 H, *c*Pr-H), 1.08–0.95 (m, 2 H, *c*Pr-H) ppm. ^{13}C NMR (125.7 MHz, [D6]DMSO, 35 °C, APT): δ = 170.0 (–, C_{quat}, C=O), 169.8 (–, C_{quat}, C=O), 168.1 (–, 2 C_{quat}, C=O), 168.0 (–, 2 C_{quat}, C=O), 156.5 (–, C_{quat}, C=O), 156.3 (–, C_{quat}, C=O), 136.6 (–, C_{quat}, C_{ipso}), 136.5 (–, C_{quat}, C_{ipso}), 128.4 (+, 2 CH, Ph), 128.3 (+, 2 CH, Ph), 128.2 (+, 2 CH, Ph), 128.0 (+, CH, Ph), 127.9 (+, CH, Ph), 127.8 (+, 2 CH, Ph), 82.0 (–, 2 C_{quat}, *t*Bu), 80.7 (–, CH_2), 80.5 (–, CH_2), 66.1 (–, CH_2), 65.9 (–, CH_2), 65.7 (–, CH_2), 64.8 (–, CH_2), 59.5 (+, CH), 57.1 (+, CH), 52.3 (+, 2 C, CO_2CH_3), 51.4 (–, CH_2), 51.3 (–, CH_2), 41.8 (–, C_{quat}, *c*Pr), 41.4 (–, C_{quat}, *c*Pr), 27.5 (+, CH_3, *t*Bu), 17.4 (–, CH_2, *c*Pr), 15.0 (–, CH_2, *c*Pr), 11.5 (–, CH_2, *c*Pr), 10.2 (–, CH_2, *c*Pr) ppm. MS (ESI): m/z (%) = 1048.8 (58) [2M + Na]$^+$, 535.0 (100) [M + Na]$^+$. IR (film): $\tilde{\nu}$ = 3323 (NH), 2977, 2923, 1726 (C=O), 1670 (C=O), 1454, 1407, 1369, 1347, 1233, 1154, 843, 748, 701 cm^{-1}. $C_{22}H_{29}BrN_2O_7$ (513.38): calcd. C 51.47, H 5.69, N 5.46; found C 51.71, H 5.52, N 5.75.

Methyl 4-(*tert*-Butoxycarbonylmethyl)-5-oxo-7-(benzyloxycarbonyl)-4,7-diazapiro[2.5]octane-8-carboxylate (14): To a solution of **13** (1.90 g, 3.70 mmol) in THF (50 mL) was added nBu$_4$NI (2.05 g, 5.55 mmol) and Cs_2CO_3 (1.81 g, 5.55 mmol). The resulting suspension was stirred at 20 °C for 5 h, then the solvent was removed at reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1:1, R_f = 0.11) to afford 1.44 g (90%) of **14** as a colorless oil. The NMR spectra recorded at ambient temperature indicated two rotamers A:B in a ratio of 2:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H, Ph, A, B), 5.18 (d, J = 1.8 Hz, 1 H, CH_2, part of an AB system), 5.13 (dd, J = 51.4, 12.5 Hz, 1 H, CH_2, part of an AB system), 4.58 (dd, J = 22.7, 16.5 Hz, 1 H, CH_2, part of an AB system), 4.25–4.08 (m, 2 H, CH_2), 3.94–3.58 (m, 2 H, CH_2), 3.77 (s, 2 H, CH_3, A), 3.60 (s, 1 H, CH_3, B), 1.43, 1.44 (s, 9 H, *t*Bu, A, B), 1.38–1.11 (m, 2.6 H, CH_2, *c*Pr, A), 0.97–0.80 (m, 1.4 H, CH_2, *c*Pr, B) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$, APT): δ = 169.9 (–, C_{quat}, C=O), 169.7 (–, C_{quat}, C=O), 168.8 (–, C_{quat}, C=O), 168.3 (–, C_{quat}, C=O), 167.9 (–, 2 C_{quat}, C=O), 154.8 (–, C_{quat}, NCOO), 154.1 (–, C_{quat}, NCOO), 135.9 (–, C_{quat}, C_{ipso}), 135.9 (–, C_{quat}, C_{ipso}), 128.6 (+, CH, Ph), 128.6 (+, CH, Ph), 128.3 (+, CH, Ph), 128.1 (+, 2 CH, Ph), 82.2 (–, C_{quat}, *t*Bu), 68.0 (–, CH_2), 67.8 (–, CH_2), 62.8 (+, CH), 62.2 (+, CH), 52.7 (+, OCH_3), 52.6 (+, OCH_3), 47.5 (–, CH_2), 47.4 (–, CH_2), 46.0 (–, CH_2), 45.7 (–, CH_2), 41.4 (–, 2 C, *c*Pr-C), 28.0 (+, CH_3, *t*Bu), 13.8 (–, CH_2, *c*Pr), 13.2 (–, CH_2, *c*Pr), 9.9 (–, CH_2, *c*Pr), 9.8 (–, CH_2, *c*Pr) ppm. IR (film): $\tilde{\nu}$ = 2978 , 1745, 1407, 1367, 1227, 1155, 1105, 1016, 748, 699, 662 cm^{-1}. MS (ESI): m/z (%) = 887.1 (100) [2M + Na]$^+$, 455.3 (65) [M + Na]$^+$. $C_{22}H_{28}N_2O_7$ (432.47): C 61.10, H. 6.53, N 6.48; found C 61.44, H. 6.19, N 6.12.

Methyl 4-(*tert*-Butoxycarbonylmethyl)-5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylate (15): A solution of **14** (1.36 g, 3.14 mmol) in MeOH (50 mL) was added to a pre-hydrogenated suspension of Pd/C (1.01 g, 10%) in MeOH (20 mL) and the mixture was stirred at 20 °C for 2 h under an atmosphere of hydrogen. Then the suspension was filtered through a pad of Celite and the solids were washed with MeOH (100 mL). Evaporation of the solvents at reduced pressure gave **15** (788 mg, 84%) as a colorless viscous oil. ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 4.12 (d, J = 8.74 Hz, CH_2, B part of an AB system), 3.75 (s, 3 H, OCH_3), 3.68 (d, J = 7.76 Hz, 1 H, CH_2, B part of an AB system), 3.61 (d, J = 8.69 Hz, 1 H, CH_2, A part of an ABsystem), 3.58 (d, J = 7.96 Hz, 1 H, CH_2, A part of an AB system), 3.16 (s, 1 H, CH), 2.85–2.61 (br. s, 1 H, NH), 1.41 (s, 9 H, *t*Bu), 1.30–0.83 (m, 4 H, *c*Pr-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C, DEPT): δ = 173.0 (C_{quat}, C=O), 172.7 (C_{quat}, C=O), 168.1 (C_{quat}, NC=O), 81.9 (C_{quat}, *t*Bu), 62.6 (+, CH), 52.6 (+, OCH_3), 47.9 (–, CH_2), 45.4 (–, CH_2), 41.2 (C_{quat}, *c*Pr-C), 27.8 (+, *t*Bu), 15.2 (–, *c*Pr-C), 8.1 (–, *c*Pr-C) ppm. IR (film): $\tilde{\nu}$ = 3311 (NH), 3086, 3060, 3039, 3005, 2985, 2964, 2953, 2932, 2918, 2874, 1733 (C=O), 1663 (C=O), 1469, 1405, 1318, 1208, 1187, 1138, 989, 700 cm^{-1}. MS (ESI): m/z (%) = 597.3 (16) [2M + Na]$^+$, 321.4 (20) [M + Na]$^+$, 299.4 (100) [M + H]$^+$. $C_{14}H_{22}N_2O_5$ (298.33): calcd. C 56.36, H 7.43, N 9.39; found C 56.55, H 7.53, N 9.54.

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[1] F. Gnad, O. Reiser, *Chem. Rev.* **2003**, *103*, 1603–1624.
[2] F. Brackmann, A. de Meijere, *Chem. Rev.* **2007**, *107*, 4493–4537.
[3] F. Brackmann, A. de Meijere, *Chem. Rev.* **2007**, *107*, 4538–4583.
[4] a) L. Wessjohann, N. Krass, D. Yu, A. de Meijere, *Chem. Ber.* **1992**, *125*, 867–882; b) M. Es-Sayed, C. Gratkowski, N. Krass, A. de Meijere, *Synlett* **1992**, 962–964; c) M. Es-Sayed, C. Gratkowski, N. Krass, A. I. Meyers, A. de Meijere, *Tetrahedron Lett.* **1993**, *34*, 289–292; d) L. Wessjohann, K. Giller, B. Zuck, L. Skattebøl, A. de Meijere, *J. Org. Chem.* **1993**, *58*, 6442–6450; e) M. Tamm, M. Thutewohl, C. Ricker, M. T. Bes, A. de Meijere, *Eur. J. Org. Chem.* **1999**, 2017–2024; f) M. W. Nötzel, T. Labahn, M. Es-Sayed, A. de Meijere, *Eur. J. Org. Chem.* **2001**, *16*, 3025–3030.
[5] For reviews see: a) A. de Meijere, L. Wessjohann, *Synlett* **1990**, 20–32; b) A. de Meijere, S. I. Kozhushkov, L. Hadjiarapoglou, *Top. Curr. Chem.* **1999**, *207*, 149–227.
[6] a) T. Liese, G. Splettstösser, A. de Meijere, *Angew. Chem.* **1982**, *94*, 799; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 790; b) T. Liese, F. Seyed-Mahdavi, A. de Meijere, *Org. Synth.* **1990**, *69*, 148–153; c) L. Wessjohann, N. Krass, D. Yu, A. de Meijere, *Chem. Ber.* **1992**, *125*, 867–882.
[7] For an advanced synthesis of **1**-Me see: M. Limbach, S. Dalai, A. de Meijere, *Adv. Synth. Catal.* **2004**, *346*, 760–766.
[8] J. A. Marshall, S. Beaudoin, *J. Org. Chem.* **1996**, *61*, 581–586.
[9] a) O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevski, *Synthesis* **1991**, 234; b) O. G. Kulinkovich, D. A. Vasilevskii, A. I. Savchenko, S. V. Sviridov, *J. Org. Chem. USSR (Engl. Transl.)* **1991**, *27*, 1249–1251; *Zh. Org. Khim.* **1991**, *27*, 1428–1430; c) S. V. Sviridov, D. A. Vasilevskii, O. G. Kulinkovich, *J. Org. Chem. USSR (Engl. Transl.)* **1991**, *27*, 1251–1253; *Zh. Org. Khim.* **1991**, *27*, 1431–1433; d) For a theoretical study of the mechanism, see: Y.-D. Wu, Z.-X. Yu, *J. Am. Chem. Soc.* **2001**, *123*, 5777–5786.
[10] For a review, see: O. G. Kulinkovich, A. de Meijere, *Chem. Rev.* **2000**, *100*, 2789–2834.
[11] A. Esposito, P. P. Piras, M. Taddei, *Org. Lett.* **2001**, *3*, 3273–3275.
[12] The use of methyltitanium triisopropoxide was originally introduced in the reductive cyclopropanation of *N*,*N*-dialkylcarboxamides to give *N*,*N*-dialkylcyclopropylamines, see V. Chaplinski, H. Winsel, M. Kordes, A. de Meijere, *Synlett* **1997**, 111–114. It was later found to be superior to $Ti(OiPr)_4$ in the Kulinkovich reaction as well, see a) H. Winsel, V. Gazizova, O. Kulinkovich, V. Pavlov, A. de Meijere, *Synlett* **1999**, *12*, 1999–2003; b) J. C. Lee, M. J. Sung, J. K. Cha, *Tetrahedron Lett.* **2001**, *42*, 2059–2061.
[13] P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936–3938.
[14] A. de Meijere, S. Teichmann, F. Seyed-Mahdavi, S. Kohlstrunk, *Liebigs Ann.* **1996**, 1989–2000.
[15] The authors are grateful to Prof. Oliver Reiser, University of Regensburg, for carrying out these high-pressure experiments.
[16] P. D. Bartlett, R. Banavali, *J. Org. Chem.* **1991**, *56*, 6043–6050.
[17] H. G. Viehe, Z. Janousek, R. Merenyi, I. Stella, *Acc. Chem. Res.* **1985**, *18*, 148–154.
[18] J. Rudolph, K. L. Reddy, J. P. Chiang, K. B. Sharpless, *J. Am. Chem. Soc.* **1997**, *119*, 6189–6190.
[19] For Lewis acid-catalyzed rearrangements of oxaspiropentanes to cyclobutanones, see a) B. M. Trost, M. J. Bogdanovicz, *J. Am. Chem. Soc.* **1973**, *95*, 5321–5334; b) A. Lechevallier, F. Huet, J. M. Conia, *Tetrahedron* **1983**, *39*, 3329–3336; c) I. Kortmann, B. Westermann, *Synthesis* **1995**, *8*, 931–933.
[20] C. Mapelli, L. F. Elrod, E. M. Holt, C. H. Stammer, *Tetrahedron* **1989**, *45*, 4377–4382.
[21] V. N. Belov, C. Funke, T. Labahn, M. Es-Sayed, A. de Meijere, *Eur. J. Org. Chem.* **1999**, 1345–1356 and references cited therein.
[22] F. Seyed-Mahdavi, S. Teichmann, A. de Meijere, *Tetrahedron Lett.* **1986**, *27*, 6185–6188.

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