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Novel Prospects of the Acidic Thermal Rearrangement of Spiro[cyclopropane-1,5′-isoxazolidines] to β-Lactams

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Dedicated to Professor Francesco De Sarlo on the occasion of his 65th birthday

Keywords: β-Lactams / β-Homoproline / Cycloaddition / Small ring systems / Spiro compounds

Monocyclic β-lactams were synthesized by a 1,3-cycloaddition/thermal rearrangement process in the presence of a protic acid, starting from methylenecyclopropane derivatives and acyclic nitrones. Five-membered cyclic nitrones failed to give carbapenam structures under the same conditions, affording exclusively the corresponding *N*-trifluoroacetyl β-amino acid derivatives in the presence of trifluoroacetic acid.

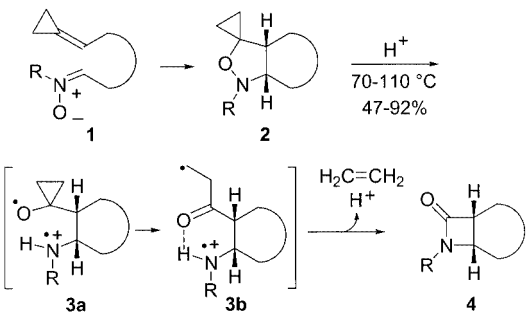
Introduction

The search for new versatile syntheses of β-lactam derivatives represents an important field of research because of the unique biological activity of these molecules. They are also increasingly being used as valuable intermediates in organic synthesis.[1]

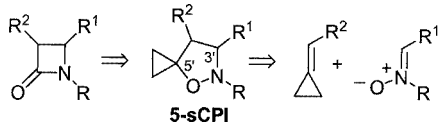
We have recently disclosed a new distinctive behavior of 3′,4′-*cis* ring-fused spiro[cyclopropane-1,5′-isoxazolidines] **2**, which are smoothly converted into azetidin-2-ones **4** in the presence of a protic acid at 70−110 °C. The process is believed to occur through the formation of a biradical cationic intermediate **3b**, which spontaneously decomposes to **4** and ethylene (Scheme 1).[2] The formation of azetidin-2-ones **4** complements the thoroughly studied thermal rearrangement of the same spiro-[cyclopropane-1,5′-isoxazolidines] to tetrahydropyridin-4-ones.[3]

Isoxazolidines **2** were easily obtained by intramolecular 1,3-dipolar cycloaddition (1,3-DC) of alkylidenecyclopropane nitrones **1**,[3,4] and the two-step process — 1,3-dipolar cycloaddition/acid-mediated thermal rearrangement (1,3-DC/ATR) — represents a general and useful strategy to synthesize 3,4-*cis*-fused bicyclic azetidin-2-ones **4**.[2]

To test the general scope of the two-step process towards different classes of β-lactams we studied the thermal behavior, under acidic conditions, of a variety of substituted spiro[cyclopropane-1,5′-isoxazolidines] (5-sCPI), prepared by intermolecular 1,3-DC reactions. In particular, the formation of monocyclic β-lactams was investigated starting from acyclic nitrones (Scheme 2).



Scheme 1



Scheme 2

Results and Discussion

C-(2-Chlorophenyl) *N*-methyl nitrone (**5**) reacts slowly with methylenecyclopropane (**6**) at 50 °C, in a sealed tube, to afford a 2.2:1 mixture of 4-oxa-5-azaspiro[2.4]heptane (5-sCPI) **7** and 5-oxa-6-azaspiro[2.4]heptane (4-SpI) **8** in a non-optimized 34% overall yield, along with 66% of unchanged nitrone **5** (Scheme 3).

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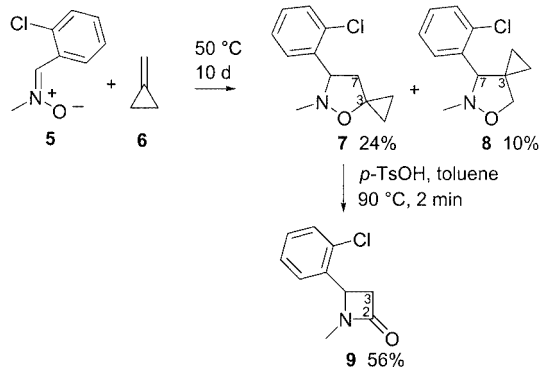
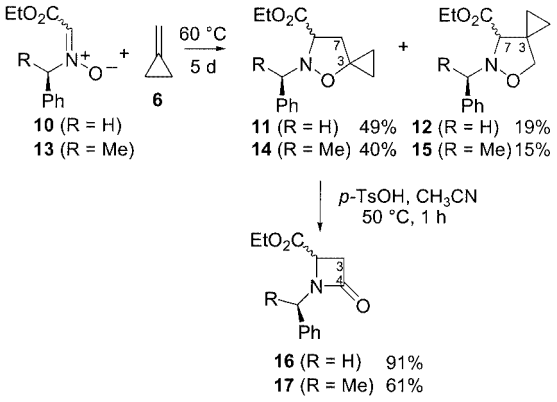


Scheme 3

The 5-sCPI **7** was transformed into 4-arylazetidinone **9** by heating in toluene in the presence of 1 equiv. of *p*-TsOH. The rearrangement is almost instantaneous at 90 °C, as the starting material **7** was completely converted after 2 min, and **9** was recovered in 56% yield after purification by chromatography on silica gel. Compound **9** was also obtained in the presence of TFA (2 equiv.) in 50% yield. The structure of **9** was assigned on the basis of its spectroscopic properties such as the IR absorption at 1747 cm^{-1}, attributed to the β-lactam carbonyl group, and the ^{13}C NMR resonance of C-2 at $\delta = 167.5$ ppm.

The cycloaddition of *C*-ethoxycarbonyl *N*-benzyl nitrone (**10**)[5] with **6** afforded a 2.6:1 mixture of the regioisomers **11** and **12** in 68% overall yield. The 5-sCPI **11** was easily converted into the *N*-benzyl monobactam **16** ($\nu_{CO(\beta\text{-lactam})} = 1763$ cm^{-1}; $\delta_{C\text{-}2} = 165.6$ ppm) in high yield (91%) (Scheme 4). The successful formation of **16** proved that the *N*-benzyl and alkoxycarbonyl moieties are compatible with the rearrangement of 5-sCPI under acidic conditions. The presence of the benzylic protecting group on the nitrogen atom is particularly significant as it lays the basis for the synthesis of *N*-unsubstituted monobactams and for the introduction of chiral auxiliaries to produce optically active β-lactams, for instance starting from nitrones derived from (*R*)- or (*S*)-*N*-(1-phenyl-ethyl)hydroxylamine.[6]



Scheme 4

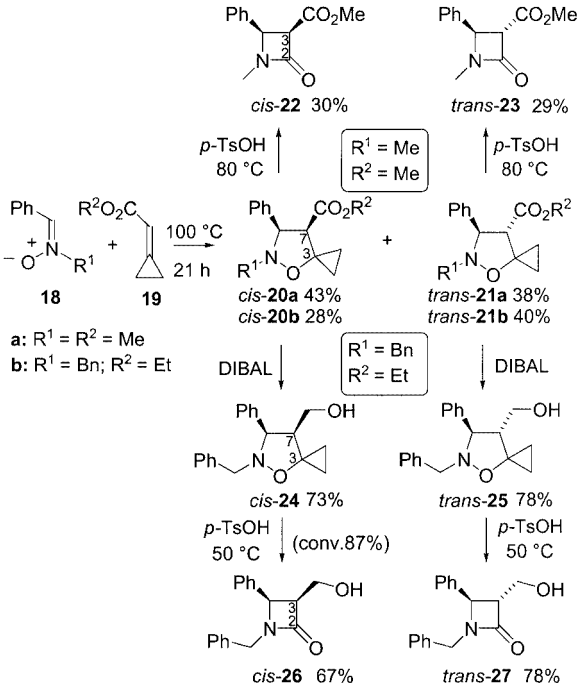
The regioisomeric ratio of the reaction of the chiral nitrone **13**[7,8] with **6** was again 2.6:1 in favor of 5-sCPI **14**. The adducts **14** and **15** were obtained as a mixture of two diastereomers in a 1:1 and 3.6:1 ratio, respectively. The low diastereoselectivity in the cycloaddition of acyclic *C*-alkoxycarbonyl nitrones with a chiral moiety bonded at the nitrogen atom has been observed previously.[9] Unfortunately, the two isoxazolidines **14** were not easily separable and only small amounts of the pure diastereomer **14a** was obtained after repeated chromatographic separations on silica gel. The equimolar mixture of the two diastereomers **14** afforded an inseparable 1:1 mixture of monobactams **17** (61% yield) by treatment with *p*-TsOH in CH_3CN at 50 °C for 1 h. Under the same reaction conditions, the sole diastereomer **14a** was converted into the single β-lactam **17a** in 50% yield. The absolute configuration of **14a** and **17a** has not been determined, but the formation of a single diastereomer from the rearrangement demonstrates that the conversion occurs without racemization of the ring carbon stereocenters. Although the formation of the simple β-lactams **17** has only limited synthetic value, it was useful to establish the applicability of the 1,3-DC/ATR approach to optically active azetidin-2-ones starting from chiral nitrones.

The use of methylenecyclopropane (**6**) as dipolarophile provides azetidin-2-one moieties unsubstituted at C-3, but 1-substituted methylenecyclopropane should give 3-substituted derivatives directly. To this end, the alkoxycarbonyl function was particularly appealing because it can be easily converted into other functional group and, at the same time, induces a complete regiocontrol in favor of the 5-sCPI in the 1,3-DC with nitrones.[3] Accordingly, we examined the β-lactam synthesis starting from [(alkoxycarbonyl)methylene]cyclopropanes **19** and the model nitrones **18** (Scheme 5).

The cycloaddition was carried out at 100 °C and afforded a mixture of *cis*- and *trans*-5-sCPI (*cis*-**20**) (3-H,4-H: $J = 8.4-8.5$ Hz) and *trans*-**21** (3-H,4-H: $J = 7.3-7.7$ Hz). As expected, the cycloaddition regioselectivity was complete and in favor of the 5-sCPI adduct, although the diastereoselectivity was poor.

The separated isoxazolidines *cis*-**20a** and *trans*-**21a** yielded the corresponding monobactams *cis*-**22** (3-H,4-H: $J = 5.8$ Hz) and *trans*-**23** (3-H,4-H: $J = 2.2$ Hz),[10] albeit in poor yield (*cis*-**22**: 30%; *trans*-**23**: 29%), upon heating at 80 °C in the presence of 1 equiv. of *p*-TsOH. The *cis* and *trans* relative orientations of the substituents in 5-sCPI **20** and **21** are completely retained in the corresponding azetidinones **22** and **23**, which indirectly confirmed the assigned structures of cycloadducts **20** and **21**. Similar results were obtained starting from *N*-benzylisoxazolidines *cis*-**20b** and *trans*-**21b**.

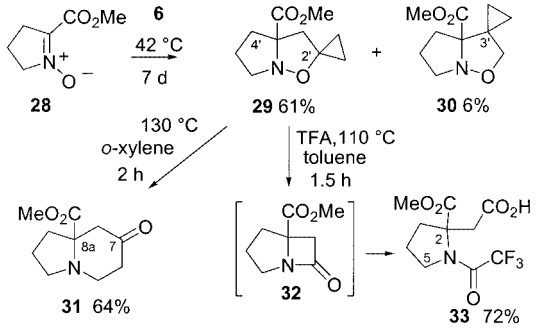
The poor yields of the oxoazetidinecarboxylates **22**, **23** can be attributed to the low stability of these monobactams under these reaction conditions. The stability of the products can be improved by reducing the alkoxycarbonyl group. Thus, treatment of isoxazolidines *cis*-**20b** and *trans*-**21b** with DIBAL resulted in the selective reduction of the



Scheme 5

ester moiety without affecting the isoxazolidine N−O bond (Scheme 5). The 3-(hydroxymethyl)azetidinones *cis*-**26** and *trans*-**27** could be obtained by the usual acidic treatment, from *cis*-**24** and *trans*-**25**, respectively, with much better yields (67−78%) than the oxidized analogues **22** and **23**.

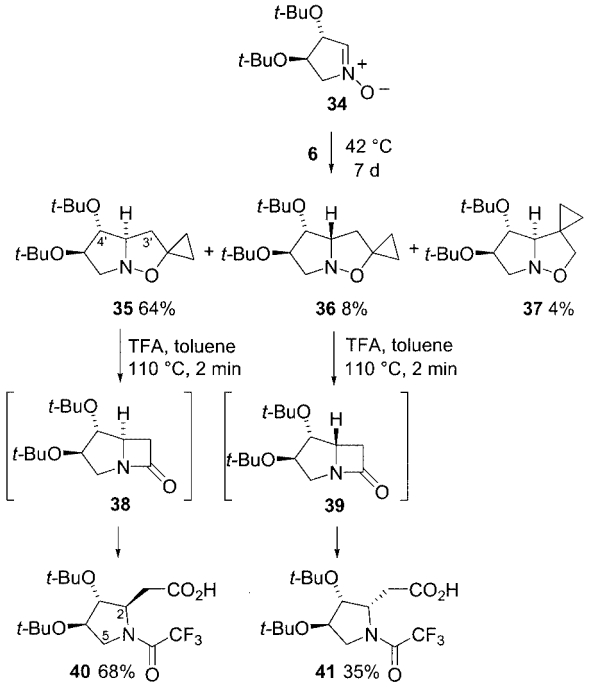
When the 1,3-DC/ATR sequence was applied to five-membered cyclic nitrones, the expected *N*-bridgehead bicyclic β-lactams failed to form. The cycloaddition of the pyrroline *N*-oxide **28**,[11] derived from methyl proline, with **6** was highly regioselective (10:1 regioisomeric ratio) and afforded the 2-spirofused pyrrolo[1,2-*b*]isoxazole **29** in 61% yield (Scheme 6).



Scheme 6

The tricyclic adduct **29** was selectively converted into indolizidinone **31** by heating at 130 °C under neutral conditions.[3] Treatment of **29** with *p*-TsOH at lower temperature (50−110 °C) afforded a complex mixture of non-β-lactam products. Rearrangement at 110 °C in the presence of 1 equiv. of TFA led to the *N*-trifluoroacetylated β-amino acid **33**. The structure of compound **33** was confirmed on the basis of its spectroscopic data. In particular, the ^{13}C NMR resonances at δ = 175.1 and 155.6 ppm, ascribed to the C=O moieties of the carboxylic acid and amide, respectively, and the presence of a four-bond coupling constant of 3.8 Hz between the fluorine atoms and C-5, confirm a covalent bond to the trifluoroacetyl moiety.

The application of the two-step process to an enantiopure nitrone, such as the pyrroline *N*-oxide **34** derived from (2*S*,3*S*)-tartaric acid,[12] was also investigated. The cycloaddition of **34** with **6** was highly regio- and diastereoselective and afforded the three isomeric adducts **35**, **36** and **37** in a 16:2:1 ratio after separation (76% overall yield) (Scheme 7).[13] Both the 5-sCPIs **35** and **36** gave the fragmentation process leading to *N*-trifluoroacetylated β-amino acids **40** (δ_{COOH} = 177.0 and δ_{CON} = 156.4 ppm; $^4J_{F,C\text{-}5}$ = 6.5 Hz) and **41** (δ_{COOH} = 176.8 and δ_{CON} = 153.6 ppm; $^4J_{F,C\text{-}5}$ = 3.2 Hz), respectively, upon heating in the presence of 1.5 equiv. of TFA at 110 °C for 2 min in toluene. It is worth noting that the acidic conditions for the rearrangement are sufficiently mild to maintain the *tert*-butyl protecting groups.



Scheme 7

As products **40** and **41** were obtained as single diastereomeric compounds, and with NMR spectroscopic data confirming the relative configuration of the parent isoxazolidines, this is further proof that the rearrangement of the isoxazoline ring followed by fragmentation occurs, as previously proposed,[2] without affecting the stereogenic centres present in the molecule.

The formation of β-homoprolines **33**, **40** and **41** probably occurs through the intermediate formation of carbapen-

ames **32**, **38** and **39**, respectively, which are unstable under the ATR reaction conditions and immediately undergo opening of the β-lactam ring followed by acylation of the nitrogen atom. An analogous reaction has previously been observed by Stoodley et al. for β-lactams fused to a five-membered ring in the presence of TFA at room temperature.[14] Despite the failure to form β-lactams in these cases, the β-amino acidic (β-homoproline type) structure in compounds **33**, **40** and **41** is nicely and conveniently achieved, and can be easily restored by hydrolysis of the trifluoroacetamide moiety and utilized for further synthetic purposes.

Conclusion

New prospects for the two-step 1,3-DC/ATR process in the synthesis of monocyclic β-lactams or β-homoprolines have been described. Appealing features of the approach include the ready availability of the starting materials (nitrones and methylenecyclopropanes) and the wide range of accessible products selectively substituted with various functionalities. The complete control of the stereogenic centres of the isoxazolidine precursors allows the application of this new strategy to the synthesis of more complex β-lactams or β-amino acids of biological interest.

Experimental Section

General Remarks: All the reactions requiring anhydrous conditions were carried out under nitrogen and the solvents were dried appropriately before use. R_f values refer to TLC on 0.25 mm silica gel plates (Merck F254). Melting points (m.p.) were determined with an RCH Kofler apparatus. Polarimetric measures were performed with a JASCO DIP-370 or a Perkin−Elmer 343 polarimeter. NMR spectra were recorded with Varian Gemini (^{1}H, 200 MHz), Bruker AVANCE 400 (^{1}H, 400 MHz), or Bruker DRX-500 (^{1}H, 500 MHz) instrument with $CDCl_3$ as solvent, unless otherwise specified. The NMR spectroscopic data are reported in δ (ppm) from TMS at 25 °C. IR spectra were recorded with a Perkin−Elmer 881 or a Perkin−Elmer Spectrum BX FT-IR System spectrophotometer in $CDCl_3$ solution. Mass spectra were recorded with a QMD 1000 Carlo Erba instrument by GC or direct inlet; relative percentages are shown in parentheses. Elemental analyses were performed with a Perkin−Elmer 2400 analyzer. Accurate mass spectra were recorded with a MAT 95S.

Intermolecular Cycloaddition of the Nitrones 5, 10, 28, and 34 with Methylenecyclopropane (6). General Procedure: Methylenecyclopropane (**6**) (9.0 mmol for **5**, **28**, **34**; 2.9 mmol for **10**) was added to a solution of the nitrone (**5**, **28**, **34**: 3.0 mmol; **10**: 1.2 mmol) in toluene (4 mL; 1 mL for **10**) and the mixture was heated in a sealed vial at 42−60 °C for 5−10 d (see Schemes 3, 4, 6 and 7). The solvent was then removed under reduced pressure and the crude products were purified by chromatography on silica gel to give the pure regioisomer adducts **7**−**8**, **11**−**12**, **29**−**30**, and **35**−**37**.

6-(2-Chlorophenyl)-5-methyl-4-oxa-5-azaspiro[2.4]heptane (7): Pale-yellow oil; 69% yield (calculated with respect to 34% conversion of **5**); R_f = 0.40 (ethyl acetate/petroleum ether, 1:30). ^{1}H NMR (200 MHz): δ = 0.59−0.82 (m, 2 H, cyclopropane), 0.99−1.09 (m, 2 H, cyclopropane), 2.27 (dd, J = 12.1, 7.0 Hz, 1 H, 7-H_a), 2.81 (s, 3 H, NMe), 3.00 (dd, J = 12.1, 8.4 Hz, 1 H, 7-H_b), 4.46 (pseudo-t, J = 7.6 Hz, 1 H, 6-H), 7.19−7.41 (m, 3 H, Ar), 7.78 (dd, J = 7.7, 1.9 Hz, 1 H, Ar) ppm. ^{13}C NMR (50 MHz): δ = 10.5 (t, cyclopropane), 11.0 (t; cyclopropane), 43.6 (t, C-7), 44.8 (q, NMe), 62.1 (s, C-3), 69.4 (d, C-6), 127.2 (d, Ar), 128.2 (d, Ar), 128.3 (d, Ar), 129.2 (d, Ar), 133.0 (s, Ar), 138.7 (s, Ar) ppm. IR: $\tilde{\nu}$ = 2961 cm^{-1}, 2878, 1473, 1439, 1349. MS (EI): m/z (%) = 223 (19) [M$^+$], 194 (37), 180 (14), 166 (23), 154 (39), 152 (83), 140 (24), 138 (86), 132 (58), 112 (15), 103 (54), 84 (100). $C_{12}H_{14}ClNO$ (223.7): calcd. C 64.43, H 6.31, N 6.26; found C 64.37, H 6.63, N 6.29.

7-(2-Chlorophenyl)-6-methyl-5-oxa-6-azaspiro[2.4]heptane (8): Yellow oil; 31% yield (calculated with respect to 34% conversion of **5**); R_f = 0.26 (ethyl acetate/petroleum ether, 1:30). ^{1}H NMR (200 MHz): δ = 0.28−0.31 (m, 1 H, cyclopropane), 0.36−0.52 (m, 1 H, cyclopropane), 0.81−1.00 (m, 2 H, cyclopropane), 2.80 (s, 3 H, NMe), 3.98 (d, J = 7.7 Hz, 1 H, 4-H_a), 4.13 (d, J = 7.7 Hz, 1 H, 4-H_b), 4.36 (s, 1 H, 7-H), 7.21−7.38 (m, 3 H, Ar), 7.68 (dd, J = 7.7, 1.8 Hz, 1 H, Ar) ppm. ^{13}C NMR (50 MHz): δ = 8.5 (t, cyclopropane), 11.5 (t, cyclopropane), 31.7 (s, C-3), 44.3 (q, NMe), 72.7 (d, C-7), 74.4 (t, C-4), 127.0 (d, Ar), 128.5 (d, Ar), 129.1 (d, Ar), 130.4 (d, Ar), 133.9 (s, Ar), 135.9 (s, Ar) ppm. IR: $\tilde{\nu}$ = 2962 cm^{-1}, 2929, 1663, 1609, 1363, 1264, 1036. MS (EI): m/z (%) = 223 (15) [M$^+$], 194 (15), 188 (8), 152 (25), 142 (100), 128 (41), 115 (33), 112 (16). $C_{12}H_{14}ClNO$ (223.7): calcd. C 64.43, H 6.31, N 6.26; found C 64.62, H 5.95, N 5.93.

Ethyl 5-(Phenylmethyl)-4-oxa-5-azaspiro[2.4]heptane-6-carboxylate (11): Yellow oil; 49% yield; R_f = 0.29 (ethyl acetate/petroleum ether, 1:15). ^{1}H NMR (200 MHz): δ = 0.69−0.70 (m, 2 H, cyclopropane), 0.99−1.00 (m, 2 H, cyclopropane), 1.24 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.61 (A part of an ABX system, J = 12.6, 6.2 Hz, 1 H, 7-H_a), 2.63 (B part of an ABX system, J = 12.2, 6.2 Hz, 1 H, 7-H_b), 3.83 (dd, X part of an ABX system, J = 8.6, 6.0 Hz, 1 H, 6-H), 4.13 (A part of an AB system, J = 12.1 Hz, 1 H, NC*H*H), 4.16 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.22 (B part of an AB system, J = 13.2 Hz, 1 H, NC*H*H), 7.26−7.43 (m, 5 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 9.6 (t, cyclopropane), 11.1 (t, cyclopropane), 14.1 (q, OCH_2CH_3), 38.0 (t, C-7), 61.2 (t, NCH_2), 62.4 (t, OCH_2), 62.4 (s, C-3), 67.5 (d, C-6), 127.5 (d, Ph), 128.3 (d, 2C, Ph), 129.2 (d, 2C, Ph), 136.6 (s, Ph), 171.0 (s, CO) ppm. IR: $\tilde{\nu}$ = 3670 cm^{-1}, 3454, 3032, 2985, 2875, 1740, 1496, 1454, 1375, 1346, 1273, 1201, 1037, 1014. MS (EI): m/z (%) = 261 (2) [M$^+$], 232 (1), 217 (1), 188 (35), 170 (2), 132 (15), 126 (2), 91 (100), 67 (5), 65 (37), 57 (25). $C_{15}H_{19}NO_3$ (261.3): calcd. C 68.94, H 7.33, N 5.36; found C 69.02, H 7.28, N 5.30.

Ethyl 6-(Phenylmethyl)-5-oxa-6-azaspiro[2.4]heptane-7-carboxylate (12): Colorless oil; 19% yield; R_f = 0.16 (ethyl acetate/petroleum ether, 1:15). ^{1}H NMR (200 MHz): δ = 0.64−0.72 (m, 1 H, cyclopropane), 0.76−0.88 (m, 3 H, cyclopropane), 1.20 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 3.41 (s, 1 H, 7-H), 3.81 (A part of an AB system, J = 7.3 Hz, 1 H, 4-H_a), 4.05 (B part of an AB system, J = 7.3 Hz, 1 H, 4-H_b), 4.06 (A part of an AB system, J = 11.8 Hz, 1 H, NC*H*H), 4.10 (q, J = 7.1 Hz, 2 H, OCH_2), 4.22 (B part of an AB system, J = 12.6 Hz, 1 H, NC*H*H), 7.25−7.41 (m, 5 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 6.7 (t, cyclopropane), 13.3 (t, cyclopropane), 14.2 (q, OCH_2CH_3), 28.4 (s, C-3), 60.9 (t, NCH_2), 61.8 (t, OCH_2), 72.0 (d, C-7), 73.5 (t, C-4), 127.6 (d, Ph), 128.2 (d, Ph), 128.3 (d, Ph), 129.1 (d, Ph), 129.3 (d, Ph), 136.2 (s, Ph), 169.7 (s, CO) ppm. IR: $\tilde{\nu}$ = 3067 cm^{-1}, 3032, 2938, 2872, 1742, 1497, 1455, 1372, 1340, 1275, 1184, 1030. MS (EI): m/z (%) = 261 (7) [M$^+$], 188 (100), 170 (12), 104 (23), 91 (100), 89 (44), 77 (32), 65 (100), 53 (25), 51 (37). $C_{15}H_{19}NO_3$ (261.3): calcd. C 68.94, H 7.33, N 5.36; found C 68.73, H 7.42, N 5.29.

Methyl Dihydro-3′*H*-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole]-3a′(4′*H*)-carboxylate (29): Yellow oil; 61% yield; R_f = 0.15 (ethyl acetate/petroleum ether, 1:2). ^{1}H NMR (500 MHz): δ = 0.60−0.67 (m, 1 H, cyclopropane), 0.71−0.77 (m, 1 H, cyclopropane), 0.91−0.98 (m, 1 H, cyclopropane), 1.00−1.08 (m, 1 H, cyclopropane), 1.86−1.94 (m, 1 H, 5′-H_a), 2.03−2.18 (m, 2 H, 4′-H_a, 5′-H_b), 2.26 (A part of an AB system, J = 15.0 Hz, 1 H, 3′-H_a), 2.32−2.39 (m, 1 H, 4′-H_b), 2.94 (B part of an AB system, J = 15.0 Hz, 1 H, 3′-H_b), 3.26 (ddd, J = 12.5, 8.5, 6.5 Hz, 1 H, 6′-H_a), 3.39 (ddd, J = 12.0, 5.5, 1.0 Hz, 1 H, 6′-H_b), 3.77 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (50 MHz): δ = 9.1 (t, cyclopropane), 9.7 (t, cyclopropane), 24.5, 36.3, 45.6 (t, C-3′, C-4′, C-5′), 52.6 (q, CO_2*Me*), 57.4 (t, C-6′), 62.3 (s, C-3a′), 78.2 (s, C-2′), 174.3 (s, *C*O_2Me) ppm. IR: $\tilde{\nu}$ = 3081 cm^{-1}, 2978, 1728, 1437, 1287, 1262, 1193, 1109. MS (EI): *m*/*z* (%) = 197 (4) [M$^+$], 182 (1), 138 (32), 126 (10), 110 (44), 96 (31), 82 (100). $C_{10}H_{15}NO_3$ (197.2): calcd. C 60.90, H 7.67, N 7.10; found C 60.47, H 7.75, N 6.80.

Methyl Dihydrospiro[cyclopropane-1,3′-pyrrolo[1,2-*b*]isoxazole]-3a′(4′*H*)-carboxylate (30): Colorless oil; 6% yield; R_f = 0.33 (diethyl ether/pentane, 3:1). ^{1}H NMR (200 MHz): δ = 0.55−0.90 (m, 4 H, cyclopropane), 1.60−2.10 (m, 3 H, 4′-H_a, 5′-H), 2.10−2.35 (m, 1 H, 4′-H_b), 3.27 (m, 2 H, 6′-H), 3.75 (s, 3 H, CO_2Me), 3.84 (part A of an AB system, J = 8.4 Hz, 1 H, 2′-H_a), 3.90 (part B of an AB system, J = 8.0 Hz, 1 H, 2′-H_b) ppm. ^{13}C NMR (50 MHz): δ = 9.1 (t, cyclopropane), 9.7 (t, cyclopropane), 23.9, 32.6 (t, C-4′, C-5′), 34.1 (s, C-3′), 52.4 (q, CO_2*Me*), 56.7 (t, C-6′), 74.0 (t, C-2′), 79.2 (s, C-3a′), 173.2 (s,*C*O_2Me) ppm. IR: $\tilde{\nu}$ = 3081 cm^{-1}, 2956, 1725, 1431, 1270, 1165, 1113. MS (EI): *m*/*z* (%) = 197 (0.2) [M$^+$], 138 (100), 96 (4), 84 (70), 82 (8).

(3a′*R*,4′*R*,5′*R*)-4′,5′-Di-*tert*-butoxytetrahydro-3′*H*-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole] (35): White solid; 64% yield; R_f = 0.52 (ethyl acetate/petroleum ether, 1:2); m.p. 45−47 °C. $[\alpha]_D^{22}$ = −19.8 (*c* = 0.8, $CHCl_3$). ^{1}H NMR (200 MHz): δ = 0.50−0.63 (m, 1 H, cyclopropane), 0.67−0.95 (m, 2 H, cyclopropane), 0.96−1.08 (m, 1 H, cyclopropane), 1.17 (s, 18 H, C*Me*$_3$), 2.21 (dd, J = 12.1, 6.0 Hz, 1 H, 3′-H_a), 2.58 (dd, J = 12.1, 9.2 Hz, 1 H, 3′-H_b), 3.11 (t, J = 9.5 Hz, 1 H, 6′-H_a), 3.40 (dd, J = 9.5, 5.9 Hz, 1 H, 6′-H_b), 3.58−3.65 (m, 1 H, 3a′-H), 3.80−3.90 (m, 1 H, 4′-H), 3.96 (dt, J = 9.5, 6.2 Hz, 1 H, 5′-H) ppm. ^{13}C NMR (50 MHz): δ = 6.6 (t, cyclopropane), 12.6 (t, cyclopropane), 28.5 (q, 3C; C*Me*$_3$), 28.8 (q, 3C, C*Me*$_3$), 40.3 (t, C-3′), 58.7 (t, C-6′), 61.8 (s, C-2′), 70.3 (d, C-3a′), 73.7 (s, *C*Me$_3$), 73.8 (s, *C*Me$_3$), 75.8, 81.5 (d, C-4′, C-5′) ppm. IR: $\tilde{\nu}$ = 3081 cm^{-1}, 2979, 1599, 1451, 1389, 1187, 1083. MS (EI): *m*/*z* (%) = 283 (1) [M$^+$], 226 (15), 200 (3), 170 (14), 154 (3), 142 (10), 112 (14), 84 (36), 57 (100). $C_{16}H_{29}NO_3$ (283.4): calcd. C 67.81, H 10.31, N 4.94; found C 67.99, H 10.44, N 5.02.

(3a′*S*,4′*R*,5′*R*)-4′,5′-Di-*tert*-butoxytetrahydro-3′*H*-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole] (36): Colorless oil; 8% yield; R_f = 0.38 (diethyl ether/pentane, 2:1). $[\alpha]_D^{23}$ = −71.1 (*c* = 1.6, EtOH). ^{1}H NMR (200 MHz): δ = 0.54−0.63 (m, 1 H, cyclopropane), 0.70−0.80 (m, 1 H, cyclopropane), 0.84−1.05 (m, 2 H, cyclopropane), 1.18 (s, 18 H, C*Me*$_3$), 2.13 (m, 1 H, 3′-H_a), 2.62 (dm, J = 12.1 Hz, 1 H, 3′-H_b), 2.92 (dd, J = 13.9, 9.5 Hz, 1 H, 6′-H_a), 3.45 (dd, J = 13.9, 7.0 Hz, 1 H, 6′-H_b), 3.86−3.98 (m, 2 H, 3a′-H, 4′-H), 4.06−4.24 (m, 1 H, 5′-H) ppm. ^{13}C NMR (50 MHz): δ = 9.6 (t, cyclopropane), 10.1 (t, cyclopropane), 28.5 (q, 6C, C*Me*$_3$), 36.0 (t, C-3′), 59.5 (t, C-6′), 62.9 (s, C-2′), 66.5 (d, C-3a′), 73.5 (s, *C*Me$_3$), 73.8 (s, *C*Me$_3$), 74.2, 76.7 (d, C-4′, C-5′) ppm. IR: $\tilde{\nu}$ = 2977 cm^{-1}, 1390, 1365, 1192, 1117, 1011. MS (EI): *m*/*z* (%) = 283 (2) [M$^+$], 226 (4), 170 (8), 142 (18), 126 (16), 112 (54), 83 (23), 57 (100). $C_{16}H_{29}NO_3$ (283.4): calcd. C 67.81, H 10.31, N 4.94; found C 67.79, H 10.72, N 5.00.

(3a′*R*,4′*R*,5′*R*)-4′,5′-Di-*tert*-butoxytetrahydrospiro[cyclopropane-1,3′-pyrrolo[1,2-*b*]isoxazole] (37): Colorless oil; 4% yield; R_f = 0.22 (diethyl ether/pentane, 2:1). ^{1}H NMR (200 MHz): δ = 0.63−0.88 (m, 3 H, cyclopropane), 0.98−1.04 (m, 1 H, cyclopropane), 1.15 (s, 9 H, C*Me*$_3$), 1.18 (s, 9 H, C*Me*$_3$), 3.03 (dd, J = 12.1, 5.5 Hz, 1 H, 6′-H_a), 3.25 (d, J = 2.6 Hz, 1 H, 3a′-H), 3.51 (A part of an AB system, J = 7.3 Hz, 1 H, 2′-H_a), 3.56 (dd, J = 11.7, 5.5 Hz, 1 H, 6′-H_b), 3.78 (t, J = 2.7 Hz, 1 H, 4′-H), 3.87 (dt, J = 5.5, 2.9 Hz, 1 H, 5′-H), 4.17 (B part of an AB system, J = 7.3 Hz, 1 H, 2′-H_b) ppm. ^{13}C NMR (50 MHz): δ = 7.4 (t, cyclopropane), 13.3 (t, cyclopropane), 15.3 (s, C-3′), 28.6 (q, 3C, C*Me*$_3$), 28.7 (q, 3C, C*Me*$_3$), 61.8 (t; C-6′), 65.8 (d, C-3a′), 73.3 (t, C-2′), 73.7 (s, *C*Me$_3$), 74.2 (s, *C*Me$_3$), 75.8, 80.7 (d, C-4′, C-5′) ppm. IR: $\tilde{\nu}$ = 2979 cm^{-1}, 1392, 1369, 1253, 1189, 1105. MS (EI): *m*/*z* (%) = 283 (1) [M$^+$], 228 (25), 172 (80), 170 (71), 154 (62), 142 (33), 57 (88), 56 (100). $C_{16}H_{29}NO_3$ (283.4): calcd. C 67.81, H 10.31, N 4.94; found C 67.56, H 10.30, N 5.38.

Intermolecular Cycloaddition of the Nitrone 13 with Methylenecyclopropane (6): According to the General Procedure, compounds **14** and **15** were obtained from nitrone **13** (129 mg, 0.58 mmol) and an excess of **6**. The two 5-sCPIs **14a** and **14b** were obtained in 40% yield as a 1:1 mixture of diastereoisomers and the two 4-SpIs **15a** and **15b** in 15% yield as a 3.6:1 mixture of diastereoisomers. The two 5-sCPIs were further separated by HPLC (**15a**: R_t = 24; **15b**: R_t = 37; CH_2Cl_2/hexane, 5% →30% CH_2Cl_2 in 25 min) whereas the 4-SpIs were characterized as a mixture.

Ethyl 5-[(1*R*)-1-Phenylethyl]-4-oxa-5-azaspiro[2.4]heptane-6-carboxylate (14). 14a: Colorless oil; 8% yield; R_f = 0.43 (ethyl acetate/petroleum ether, 1:4). $[\alpha]_D^{20}$ = +34.4 (*c* = 0.4 $CHCl_3$). ^{1}H NMR (200 MHz): δ = 0.86 (m, 2 H, cyclopropane), 0.60 (m, 2 H, cyclopropane), 1.30 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.42 (d, J = 6.6 Hz, 3 H, $NCHCH_3$), 2.42 (dd, J = 11.9, 9.0 Hz, 1 H, 7-H_a), 2.60 (dd, J = 11.9, 6.0 Hz, 1 H, 7-H_b), 3.91 (dd, J = 9.0, 5.7 Hz, 1 H, 6-H), 4.15 (q, J = 6.8 Hz, 1 H, $NCHCH_3$), 4.22 (q, J = 6.8 Hz, 2 H, OCH_2CH_3), 7.23−7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 9.2 (t, cyclopropane), 10.4 (t, cyclopropane), 13.9 (q, OCH_2CH_3), 21.0 (q, $NCHCH_3$), 38.5 (t, C-7), 60.9 (t, OCH_2CH_3), 61.7 (s, C-3), 65.0, 65.1 (d, C-6, $NCHCH_3$), 126.6 (d, Ph), 126.8 (d, Ph), 127.5 (d, Ph), 127.8 (d, Ph), 128.3 (d, Ph), 142.0 (s, Ph), 171.2 (s, CO) ppm. GC-MS: *m*/*z* (%) = 275 (3) [M$^+$], 246 (2), 202 (35), 105 (100), 98 (18), 79 (15), 77 (18). **14b:** Colorless oil; 8% yield; R_f = 0.52 (ethyl acetate/petroleum ether, 1:4). $[\alpha]_D^{20}$ = +41.9 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (200 MHz): δ = 0.69−0.73 (m, 2 H, cyclopropane), 1.04−1.05 (m, 2 H, cyclopropane), 1.16 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.47 (d, J = 6.6 Hz, 3 H, $NCHCH_3$), 2.47 (dd, J = 12.3, 8.6 Hz, 1 H, 7-H_a), 2.66 (dd, J = 12.5, 4.4 Hz, 1 H, 7-H_b), 3.78 (dd, J = 8.6, 4.4 Hz, 1 H, 6-H), 3.98−4.11 (m, 3 H, $NCHCH_3$, OCH_2CH_3), 7.31−7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 7.4 (t, cyclopropane), 12.0 (t, cyclopropane), 13.7 (q, OCH_2CH_3), 21.9 (q, $NCHCH_3$), 37.4 (t, C-7), 60.7 (t, OCH_2CH_3), 62.2 (s, C-3), 65.8, 66.1 (d, C-6, $NCHCH_3$), 127.0 (d, Ph), 127.4 (d, Ph), 127.7 (d, Ph), 127.9 (d, Ph), 128.1 (d, Ph), 142.0 (s, Ph), 171.3 (s, CO) ppm. GC-MS: *m*/*z* (%) = 275 (1) [M$^+$], 202 (24), 105 (100), 98 (22), 77 (100).

Ethyl 6-[(1*R*)-1-Phenylethyl]-5-oxa-6-azaspiro[2.4]heptane-7-carboxylate (15a and 15b): Colorless oil; 15% yield (major diastereoisomer/minor diastereoisomer = 3.6:1); R_f = 0.56 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (200 MHz): δ = 0.66−0.80 (m, 4 H major + 4 H minor, cyclopropane), 1.14 (t, J = 7.1 Hz, 3 H

major, OCH_2CH_3), 1.14 (t, J = 7.1 Hz, 3 H minor, OCH_2CH_3), 1.43 (d, J = 7.0 Hz, 3 H minor, $NCHCH_3$), 1.56 (d, J = 6.2 Hz, 3 H major, $NCHCH_3$), 3.29 (s, 1 H major, 7-H), 3.44 (s, 1 H minor, 7-H), 3.63 (d, J = 7.7 Hz, 1 H minor, 4-H_a), 3.83 (d, J = 7.3 Hz, 1 H major; 4-H_a), 3.94−4.24 (m, 5 H major + 5 H minor; 4-H_b, OCH_2CH_3, NCH_2CH_3), 7.23−7.34 (m, 5 H major + 5 H minor; Ph) ppm. ^{13}C NMR (50 MHz, major adduct): δ = 6.0 (t, cyclopropane), 13.9 (t, cyclopropane), 14.1 (q, OCH_2CH_3), 21.8 (q, $NCHCH_3$), 28.5 (t, C-3), 60.7 (t, OCH_2CH_3), 66.2, 71.5 (d, C-7, $NCHCH_3$), 73.2 (t, C-4), 127.7 (d, Ph), 127.8 (d, Ph), 127.9 (d, Ph), 128.3 (d, Ph), 128.6 (d, Ph), 142.2 (s, Ph), 170.4 (s, CO) ppm. IR: $\tilde{\nu}$ = 3066 cm^{-1}, 2982, 2936, 2872, 1740, 1602, 1493, 1373, 1281, 1182, 1028. GC-MS: m/z (%) = 275 (3) [M$^+$], 202 (100), 149 (36), 105 (100), 103 (50), 98 (100), 77 (80). $C_{16}H_{21}NO_3$ (275.3): calcd. C 69.79, H 7.69, N 5.09; found C 69.49, H 7.64, N 5.19.

Synthesis of β-Lactams 9, 16, 17. General Procedure: *p*-Toluensulfonic acid (1 equiv.) was added to a 0.04 M solution of the cycloadducts **7**, **11** or **14** (1:1 mixture of the two diastereoisomers or pure **14a**) (0.02−0.25 mmol) in CH_3CN and the mixture was heated at 50−90 °C for between 2 min and 1 h (cf. Schemes 3 and 4). The solvent was then removed under reduced pressure. Purification of the crude products by chromatography on silica gel afforded pure β-lactams **9**, **16** and **17** (1:1 mixture of the two diastereoisomers or pure **17a**).

4-(2-Chlorophenyl)-1-methylazetidin-2-one (9): Pale yellow oil; 56% yield; R_f = 0.28 (ethyl acetate/petroleum ether, 1:2). ^{1}H NMR (200 MHz): δ = 2.76 (dd, J = 14.4, 2.4 Hz, 1 H, 3-H_a), 2.87 (s, 3 H, NMe), 3.47 (dd, J = 14.4, 5.3 Hz, 1 H, 3-H_b), 4.97 (dd, J = 5.3, 2.4 Hz, 1 H, 4-H), 7.31−7.43 (m, 4 H, Ar) ppm. ^{13}C NMR (50 MHz): δ = 27.8 (q, NMe), 46.3 (t, C-3), 52.5 (d, C-4), 125.8 (d, Ar), 127.3 (d, Ar), 129.1 (d, Ar), 129.9 (d, Ar), 133.0 (s, Ar), 136.0 (s, Ar), 167.5 (s, C-2) ppm. IR: $\tilde{\nu}$ = 2961 cm^{-1}, 1747, 1446, 1386, 1053. MS (EI): m/z (%) = 195 (1) [M$^+$], 152 (22), 140 (31), 138 (100), 103 (54), 84 (61), 57 (35). $C_{10}H_{10}ClNO$ (195.6): calcd. C 61.39, H 5.15, N 7.16; found C 61.13, H 5.13, N 7.52.

Ethyl 4-Oxo-1-(phenylmethyl)-2-azetidinecarboxylate (16): Colorless oil; 91% yield; R_f = 0.30 (ethyl acetate/pentane, 1:4). ^{1}H NMR (200 MHz): δ = 1.23 (t, J = 7.2 Hz, 3 H, och_2ch_3), 3.01 (dm, J = 14.6 Hz, 1 H, 3-H_a), 3.20 (dd, J = 14.6, 5.5 Hz, 1 H, 3-H_b), 3.89−3.93 (m, 1 H, 2-H), 4.14 (q, J = 7.2 Hz, 2 H, och_2ch_3), 4.17 (A part of an AB system, J = 15.0 Hz, 1 H, NC*H*H), 4.74 (B part of an AB system, J = 15.0 Hz, 1 H, NC*H*H), 7.21−7.34 (m, 5 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 14.0 (q, och_2ch_3), 41.9 (t, C-3), 45.6 (d, C-2), 50.1 (t, NCH_2), 61.5 (t, och_2ch_3), 127.8 (d, Ph), 128.4 (d, 2C, Ph), 128.7 (d, 2C, Ph), 134.8 (s, Ph), 165.6 (s, C-4), 170.1 (s, *C*OCH_2) ppm. MS (EI): m/z (%) = 234 (1) [MH$^+$], 205 (90), 160 (100), 132 (100), 128 (7), 117 (16), 106 (52), 101 (31), 91 (100), 77 (29), 65 (99), 55 (46). IR: $\tilde{\nu}$ = 3671 cm^{-1}, 3488, 3034, 2962, 1755 br, 1496, 1441, 1392, 1353, 1294, 1218, 1087, 1049, 1029. $C_{13}H_{15}NO_3$ (233.3): calcd. C 66.94, H 6.48, N 6.00; found C 66.59, H 6.55, N 5.73.

Ethyl 4-Oxo-1-[(1*R*)-1-phenylethyl]-2-azetidinecarboxylate (17). 17a: Colorless oil; 50% yield; R_f = 0.21 (ethyl acetate/petroleum ether, 1:4). ^{1}H NMR (200 MHz): δ = 1.16 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.74 (d, J = 7.3 Hz, 3 H, $NCHCH_3$), 2.91 (A part of an ABX system, J = 14.3, 2.6 Hz, 1 H, 3-H_a), 3.11 (B part of an ABX system, J = 14.3, 5.5 Hz, 1 H, 3-H_b), 3.90 (dd, X part of an ABX system, J = 5.5, 2.6 Hz, 1 H, 2-H), 3.99 (A part of an ABX_3 system, J = 7.2 Hz, 1 H, $OCHHCH_3$), 4.01 (B part of an ABX_3 system, J = 6.8 Hz, 1 H, $OCHHCH_3$), 4.70 (q, J = 7.1 Hz, 1 H, $NCHCH_3$), 7.26−7.38 (m, 5 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 13.7 (q, OCH_2CH_3), 19.3 (q, $NCHCH_3$), 40.8 (t, C-3), 49.5 (d, C-2), 54.6 (d, $NCHCH_3$), 61.1 (t, OCH_2CH_3), 126.6 (d, 2C, Ph), 127.5 (d, Ph), 128.3 (d, 2C, Ph), 140.0 (s, Ph), 165.4 (s, C-4), 170.2 (s, *C*OCH_2CH_3) ppm. MS (EI): m/z (%) = 232 (12) [M$^+$ − Me], 174 (33), 159 (1), 146 (32), 142 (4), 120 (79), 105 (100), 77 (71), 73 (31). **17b:** Colorless oil, 61% yield. ^{1}H NMR (200 MHz, selection of signals of the ^{1}H NMR spectrum of the **17a** and **17b** mixture): δ = 1.25 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.59 (d, J = 7.0 Hz, 3 H, $NCHCH_3$), 2.93 (dd, J = 14.3, 2.7 Hz, 1 H, 3-H_a), 3.06 (dd, J = 14.3, 5.5 Hz, 1 H, 3-H_b), 3.82 (dd, J = 5.3, 2.7 Hz, 1 H, 2-H), 4.13 (A part of an ABX_3 system, J = 7.1 Hz, 1 H, $OCHHCH_3$), 4.15 (B part of an ABX_3 system, J = 7.0 Hz, 1 H, $OCHHCH_3$), 4.96 (q, J = 7.2 Hz, 1 H, $NCHCH_3$), 7.26−7.42 (m, 5 H, Ph) ppm.

Methyl (6*R,7*R**)-5-Methyl-6-phenyl-4-oxa-5-azaspiro[2.4]heptane-7-carboxylate (*cis*-20a) and Methyl (6*R**,7*S**)-5-Methyl-6-phenyl-4-oxa-5-azaspiro[2.4]heptane-7-carboxylate (*trans*-21a):** In a Sovirel vial, the nitrone **18a** (405 mg, 3.00 mmol) was added to a solution of the ester **19a** (251 mg, 2.24 mmol) in toluene (0.50 mL) and the reaction mixture was heated in an oven at 100 °C for 21 h. Evaporation of the solvent under reduced pressure and purification of the crude product by chromatography on silica gel (ethyl acetate/petroleum ether, 1:7) afforded the two adducts *cis*-**20a** (237 mg, 43%) and *trans*-**21a** (210 mg, 38%). ***cis*-20a:** Yellow oil; R_f = 0.17. ^{1}H NMR (200 MHz): δ = 0.68−0.82 (m, 1 H, cyclopropane), 0.84−1.00 (m, 1 H, cyclopropane), 1.01−1.22 (m, 2 H, cyclopropane), 2.75 (s, 3 H, NMe), 3.28 (s, 3 H, OMe), 3.69 (d, J = 8.5 Hz, 1 H, 7-H), 4.29 (d, J = 8.5 Hz, 1 H, 6-H), 7.25−7.43 (m, 5 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 10.2 (t, cyclopropane), 11.3 (t, cyclopropane), 44.5 (q, NMe), 51.3 (q, OMe), 58.9 (d, C-7), 63.8 (s, C-3), 76.2 (d, C-6), 127.8 (d, 2C, Ph), 128.0 (d, Ph), 128.2 (d, 2C, Ph), 136.0 (s, Ph), 170.3 (s, CO) ppm. ***trans*-21a:** Pale yellow oil; R_f = 0.21. ^{1}H NMR (200 MHz): δ = 0.79−0.83 (m, 2 H, cyclopropane), 1.17−1.28 (m, 2 H, cyclopropane), 2.68 (s, 3 H, NMe), 3.36 (d, J = 7.7 Hz, 1 H, 7-H), 3.70 (s, 3 H, OMe), 4.22 (d, J = 7.7 Hz, 1 H, 6-H), 7.30−7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 7.2 (t, cyclopropane), 14.1 (t, cyclopropane), 43.3 (q, NMe), 51.8 (q, OMe), 61.2 (d, C-7), 64.4 (s, C-3), 77.2 (d, C-6), 127.8 (d, 2C,Ph), 128.2 (d, Ph), 128.6 (d, 2C, Ph), 138.0 (s, Ph), 171.5 (s, CO) ppm. IR: $\tilde{\nu}$ = 3034 cm^{-1}, 3003, 2955, 2879, 2780, 1737, 1604, 1494, 1455, 1437, 1346, 1330, 1285, 1248, 1192, 1172, 1021. MS (EI): m/z (%) = 247 (1) [M$^+$], 216 (5), 188 (5), 168 (34), 111 (6), 106 (35), 92 (100), 78 (79). $C_{14}H_{17}NO_3$ (247.3) calcd. C 68.00, H 6.93, N 5.66; found C 68.40, H 6.96, N 5.53.

Ethyl (6*R,7*R**)-6-Phenyl-5-(phenylmethyl)-4-oxa-5-azaspiro[2.4]-heptane-7-carboxylate (*cis*-20b) and Ethyl (6*R**,7*S**)-6-Phenyl-5-(phenylmethyl)-4-oxa-5-azaspiro[2.4]heptane-7-carboxylate (*trans*-21b):** According to the same procedure, the two adducts *cis*-**20b** (228 mg, 28%) and *trans*-**21b** (316 mg, 40%) were obtained from the nitrone **18b** (500 mg, 2.37 mmol) and the ester **19b** (388 mg, 3.08 mmol). ***cis*-20b:** Colorless oil; R_f = 0.21 (ethyl acetate/petroleum ether, 1:20). ^{1}H NMR (200 MHz): δ = 0.83 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.03−1.09 (m, 2 H, cyclopropane), 1.24−1.34 (m, 2 H, cyclopropane), 3.67 (A part of an ABX_3 system, J = 7.0 Hz, 1 H, $CHHCH_3$), 3.68 (A part of an ABX_3 system, J = 7.0 Hz, 1 H, $CHHCH_3$), 3.71 (d, J = 8.4 Hz, 1 H, 7-H), 4.01 (B part of an AB system, J = 14.3 Hz, 1 H, NC*H*H), 4.15 (B part of an AB system, J = 14.3 Hz, 1 H, NC*H*H), 4.56 (d, J = 8.4 Hz, 1 H, 6-H), 7.19−7.37 (m, 8 H, Ph), 7.44 (dd, J = 7.5, 1.7 Hz, 2 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 9.1 (t, cyclopropane), 11.7 (t, cyclopropane), 13.7 (q, OCH_2CH_3), 57.5 (d, C-7), 60.3, 60.7 (t, OCH_2CH_3, NCH_2), 63.9 (s, C-3), 72.9 (d, C-6), 127.2 (d, Ph), 127.8 (d, Ph), 128.0 (d, 2C, Ph), 128.1 (d, 2C, Ph), 128.2 (d, 2C, Ph),

128.8 (d, 2C, Ph), 137.0 (s, Ph), 169.6 (s, CO) ppm. IR: $\tilde{\nu}$ = 3631 cm^{-1}, 3031, 2855, 1740, 1496, 1455, 1372, 1182, 1030. MS (EI): *m/z* (%) = 338 (1) [MH^+], 195 (7), 132 (27), 116 (6), 104 (13), 92 (100), 78 (15). $C_{21}H_{23}NO_3$ (337.4): calcd. C 74.75, H 6.87, N 4.15; found C 74.30, H 7.08, N 4.60. ***trans*-21b:** White solid; R_f = 0.29 (ethyl acetate/petroleum ether, 1:20); m.p. 106−109 °C. ^{1}H NMR (200 MHz): δ = 0.74−0.85 (m, 2 H, cyclopropane), 0.88−1.14 (m, 2 H, cyclopropane), 1.24 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 3.35 (d, *J* = 7.3 Hz, 1 H, 7-H), 3.92 (A part of an AB system, *J* = 14.2 Hz, 1 H, NC*H*H), 4.04 (B part of an AB system, *J* = 13.9 Hz, 1 H, NC*H*H), 4.13−4.20 (m, 2 H, OCH_2CH_3), 4.52 (d, *J* = 7.3 Hz, 1 H, 6-H), 7.22−7.35 (m, 8 H, Ph), 7.48−7.51 (m, 2 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 7.9 (t, cyclopropane), 13.3 (t, cyclopropane), 14.3 (q, OCH_2CH_3), 60.1 (t, NCH_2), 60.9 (d, C-7), 61.1 (t, OCH_2), 64.8 (s, C-3), 74.6 (d, C-6), 127.0 (d, Ph), 127.9 (d, Ph), 128.0 (d, 2C, Ph), 128.1 (d, 2C, Ph), 128.5 (d, 2C, Ph), 128.8 (d, 2C, Ph), 137.8 (s, Ph), 139.2 (s, Ph), 171.2 (s, CO) ppm. IR: $\tilde{\nu}$ = 3690 cm^{-1}, 2928, 1731, 1603, 1496, 1455, 1180. MS (EI): *m/z* (%) = 338 (5) [MH^+], 309 (1), 265 (6), 195 (22), 147 (16), 131 (66), 107 (37), 92 (100), 78 (34). $C_{21}H_{23}NO_3$ (337.4): calcd. C 74.75, H 6.87, N 4.15; found C 74.82, H 6.74, N 4.40.

Methyl (3*R,4*R**)-1-Methyl-2-oxo-4-phenyl-3-azetidinecarboxylate (*cis*-22):** *p*-Toluenesulfonic acid (6 mg, 0.04 mmol) was added to a solution of the isoxazolidine *cis*-**20a** (6 mg, 0.03 mmol) in toluene (1 mL) and the reaction flask was placed in an oil bath at 80 °C. After heating for 2 h, the reaction mixture was allowed to reach room temp. and the solvent was then removed under reduced pressure. Purification of the crude product by chromatography on silica gel (ethyl acetate/petroleum ether, 1:2) gave the pure β-lactam *cis*-**22** (2 mg, 30%) as a colorless oil. R_f = 0.07. ^{1}H NMR (200 MHz): δ = 2.89 (s, 3 H, NMe), 3.23 (s, 3 H, OMe), 4.40 (d, *J* = 5.9 Hz, 1 H, 3-H), 4.86 (d, *J* = 5.9 Hz, 1 H, 4-H), 7.27−7.40 (m, 5 H, Ph) ppm.

Methyl (3*R,4*S**)-1-Methyl-2-oxo-4-phenyl-3-azetidinecarboxylate (*trans*-23):** Under the same conditions, the isoxazolidine *trans*-**21a** (14 mg, 0.06 mmol) gave the β-lactam *trans*-**23** (4 mg, 29%) as a colorless oil. R_f = 0.23 (ethyl acetate/petroleum ether, 1:7). ^{1}H NMR (200 MHz): δ = 2.82 (s, 3 H, NMe), 3.80 (s, 3 H, OMe), 3.88 (m, 1 H, 3-H), 4.82 (d, *J* = 2.2 Hz, 1 H, 4-H), 7.30−7.43 (m, 5 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 27.2 (q, NMe), 52.4 (d, C-3), 58.6 (d, C-4), 63.4 (q, OMe), 126.1 (d, 2C, Ph), 128.7 (d, Ph), 128.8 (d, 2C, Ph), 135.7 (s, Ph), 162.0, 166.9 (s, C-2, CO_2Me) ppm. IR: $\tilde{\nu}$ = 3035 cm^{-1}, 2956, 1763, 1735, 1457, 1439, 1362, 1333, 1258, 1211, 1014. MS (EI): *m/z* (%) = 219 (1) [M^+], 190 (14), 161 (41), 131 (100), 118 (26), 103 (45), 91 (8), 77 (39), 51 (27).

(6*R,7*R**)-7-(Hydroxymethyl)-6-phenyl-5-(phenylmethyl)-4-oxa-5-azaspiro[2.4]heptane (*cis*-24):** A 1.5 M solution of DIBAL-H in toluene (0.4 mmol) was added dropwise under nitrogen to a solution of the adduct *cis*-**20b** (61 mg, 0.18 mmol) in CH_2Cl_2 (0.60 mL) cooled to 0 °C. The reaction mixture was stirred at low temperature for 2 h and then treated in turn with methanol and a saturated sodium potassium tartrate solution. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic extracts were dried with anhydrous Na_2SO_4. Evaporation of the solvent and purification by chromatography on silica gel gave the alcohol *cis*-**24** (39.5 mg, 74%) as a colorless oil. R_f = 0.14 (ethyl acetate/petroleum ether, 1:10). ^{1}H NMR (200 MHz): δ = 0.64−0.73 (m, 1 H, cyclopropane), 0.85−1.00 (m, 3 H, cyclopropane), 1.60 (br. s, 1 H, OH), 2.76 (q, *J* = 5.9 Hz, 1 H, 7-H), 3.41−3.50 (m, 2 H, CH_2O), 3.96 (A part of an AB system, *J* = 14.3 Hz, 1 H, NC*H*H), 4.11 (B part of an AB system, *J* = 14.7 Hz, 1 H, NC*H*H), 4.47 (d, *J* = 7.3 Hz, 1 H, 6-H), 7.23−7.43 (m, 8 H, Ph), 7.49−7.54 (m, 2 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 6.7 (t, cyclopropane), 10.6 (t, cyclopropane), 51.9 (d, C-7), 61.3 (t, NCH_2), 61.4 (t, OCH_2), 64.8 (s, C-3), 73.0 (d, C-6), 127.1 (d, Ph), 127.9 (d, Ph), 128.1 (d, 2C, Ph), 128.2 (d, 2C, Ph), 128.4 (d, 2C, Ph), 128.7 (d, 2C, Ph), 137.0 (s, Ph), 137.5 (s; Ph) ppm. IR: $\tilde{\nu}$ = 3621 cm^{-1}, 3066, 3031, 2928, 2890, 1603, 1496, 1454, 1029, 1016. MS (EI): *m/z* (%) = 295 (10) [M^+], 236 (19), 194 (21), 135 (14), 119 (35), 104 (79), 92 (100), 77 (45). $C_{19}H_{21}NO_2$ (295.4): calcd. C 77.26, H 7.17, N 4.74; found C 77.16, H 7.00, N 4.69.

(6*R,7*S**)-7-(Hydroxymethyl)-6-phenyl-5-(phenylmethyl)-4-oxa-5-azaspiro[2.4]heptane (*trans*-25):** Under the same conditions, the adduct *trans*-**21b** (78 mg, 0.23 mmol) afforded the alcohol *trans*-**25** (58 mg, 78%) as a white solid, which was recrystallized from diisopropyl ether. R_f = 0.28 (ethyl acetate/pentane, 1:5); m.p. 94−96 °C. ^{1}H NMR (200 MHz): δ = 0.57−0.67 (m, 1 H, cyclopropane), 0.88−1.15 (m, 3 H, cyclopropane), 1.52 (m, 1 H, OH), 2.59 (dt, *J* = 7.3, 5.1 Hz, 1 H, 7-H), 3.64−3.80 (m, 2 H, CH_2O), 3.80 (A part of an AB system, *J* = 14.6 Hz, 1 H, NC*H*H), 3.90 (d, *J* = 7.3 Hz, 1 H, 6-H), 3.99 (B part of an AB system, *J* = 14.6 Hz, 1 H, NC*H*H), 7.19−7.40 (m, 8 H, Ph), 7.51−7.55 (m, 2 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 6.0 (t; cyclopropane), 13.0 (t, cyclopropane), 57.4 (d, C-7), 60.0 (t, NCH_2), 62.4 (t, OCH_2), 64.2 (s, C-3), 74.8 (d, C-6), 126.9 (d, Ph), 127.9 (d, Ph), 128.0 (d, 2C, Ph), 128.1 (d, 2C, Ph), 128.4 (d, 2C, Ph), 128.7 (d, 2C, Ph), 137.8 (s, Ph), 139.9 (s, Ph) ppm. IR: $\tilde{\nu}$ = 3623 cm^{-1}, 3031, 2876, 2248, 1603, 1498, 1454, 1365, 1089, 1015. MS (EI): *m/z* = 295 (10) [M^+], 264 (3), 207 (24), 194 (35), 134 (23), 116 (42), 104 (86), 91 (100), 79 (46). $C_{19}H_{21}NO_2$ (295.4): calcd. C 77.26, H 7.17, N 4.74; found C 77.76, H 7.42, N 4.68.

(3*R,4*S**)-3-(Hydroxymethyl)-4-phenyl-1-(phenylmethyl)-2-azetidinone (*cis*-26):** *p*-Toluenesulfonic acid (14 mg, 0.08 mmol) was added to a solution of the isoxazolidine *cis*-**24** (23 mg, 0.08 mmol) in CH_3CN (2 mL) and the reaction flask was placed in an oil bath at 47 °C. After heating at 50 °C for 1.5 h, the reaction mixture was allowed to reach room temp. and the solvent was evaporated under reduced pressure. Purification of the crude product by chromatography on silica gel (ethyl acetate/petroleum ether, 1:1) gave the isoxazolidines *cis*-**24** (3 mg) and pure β-lactam *cis*-**26** (12 mg, 58%; 67% with respect to 87% of conversion of *cis*-**24**) as a colorless oil. R_f = 0.35. ^{1}H NMR (200 MHz): δ = 3.46−3.58 (m, 1 H, 3-H), 3.64−3.75 (m, 2 H, OCH_2), 3.93 (d, *J* = 14.8 Hz, 1 H, NC*H*H), 4.66 (d, *J* = 4.8 Hz, 1 H, 4-H), 4.91 (d, *J* = 14.8 Hz, 1 H, NC*H*H), 7.14−7.18 (m, 2 H, Ph), 7.23−7.35 (m, 5 H, Ph), 7.37−7.41 (m, 3 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 44.3 (t, NCH_2); 56.5 (d, C-3), 57.2 (t, OCH_2), 57.9 (d, C-4), 126.7 (d, 2C, Ph), 127.5 (d, 2C, Ph), 128.2 (d, 2C, Ph), 128.5 (d, 2C, Ph), 128.6 (d, 2C, Ph), 134.3 (s, Ph), 134.9 (s, Ph), 167.7 (s, C-2) ppm. IR: $\tilde{\nu}$ = 3608 cm^{-1}, 3033, 2925, 1742, 1456, 1029. MS (EI): *m/z* (%) = 267 (0.2) [M^+], 194 (10), 134 (89), 105 (47), 91 (100), 78 (53). $C_{17}H_{17}NO_2$ (267.3): calcd. C 76.38, H 6.41, N 5.24; found C 76.14, H 6.72, N 5.16.

(3*R,4*R**)-3-(Hydroxymethyl)-4-phenyl-1-(phenylmethyl)-2-azetidinone (*trans*-27):** Under the same conditions, the isoxazolidine *trans*-**25** (10 mg, 0.03 mmol) gave the β-lactam *trans*-**27** (7 mg, 78%) as a colorless oil. R_f = 0.20 (ethyl acetate/petroleum ether, 1:1). ^{1}H NMR (200 MHz): δ = 3.25 (m, 1 H, 3-H), 3.82 (d, *J* = 15.4 Hz, 1 H, NC*H*H), 3.91 (A part of an ABX system, *J* = 12.1, 4.0 Hz, 1 H, OC*H*H), 4.06 (B part of an ABX system, *J* = 12.1, 4.8 Hz, 1 H, OC*H*H), 4.46 (d, *J* = 2.2 Hz, 1 H, 4-H), 4.87 (d, *J* = 15.0 Hz, 1 H, NC*H*H), 7.16−7.46 (m, 10 H, Ph) ppm. ^{13}C NMR (50 MHz): δ = 44.3 (t, NCH_2), 56.7 (d, C-3), 58.5 (t, OCH_2), 62.0 (d, C-4), 126.3 (d, Ph), 127.3 (d, Ph), 127.9 (d, 2C, Ph), 128.1 (d, 2C, Ph), 128.3 (d, 2C, Ph), 128.6 (d, 2C, Ph), 135.0 (s, Ph), 137.0 (s, Ph),

168.2 (s, CO) ppm. IR: $\tilde{\nu}$ = 3617 cm^{-1}, 3444, 3033, 2925, 2879, 1738, 1497, 1456, 1029. MS (EI): *m/z* (%) = 267 (0.3) [M^+], 134 (41), 132 (82), 116 (18), 105 (33), 92 (83), 90 (100), 78 (30), 76 (38). $C_{17}H_{17}NO_2$ (267.3): calcd. C 76.38, H 6.41, N 5.24; found C 75.89, H 6.52, N 5.68.

Methyl 7-Oxohexahydro-8a(1*H*)-indolizidinecarboxylate (31): The cycloadduct **29** (59 mg, 0.30 mmol) was dissolved in *o*-xylene (15 mL) and the solution was heated at 130 °C for 2 h. After cooling the reaction mixture to room temp., the solvent was removed by filtration through a short pad of silica gel, eluting in turn with petroleum ether and ethyl acetate. Purification of the crude product by chromatography on silica gel (ethyl acetate/petroleum ether, 1:3) afforded the ketone **31** (38 mg, 64%) as a yellow oil. R_f = 0.35 (ethyl acetate/petroleum ether, 1:1). ^1H NMR (500 MHz): δ = 1.74 (ddd, *J* = 12.7, 9.6, 8.2 Hz, 1 H, 1-H_a), 1.91−2.09 (m, 2 H, 1-H_b, 2-H_a), 2.26−2.37 (m, 3 H, 2-H_b, 6-H_a, 8-H_a), 2.50 (ddd, *J* = 16.0, 9.9, 7.4 Hz, 1 H, 6-H_b), 2.79 (dd, *J* = 14.8, 1.7 Hz, 1 H, 8-H_b), 2.85−3.93 (m, 2 H, 3-H_a, 5-H_a), 3.07 (dt, *J* = 8.6, 5.3 Hz, 1 H, 3-H_b), 3.18 (ddd, *J* = 12.2, 7.3, 2.7 Hz, 1 H, 5-H_b), 3.68 (s, 3 H, OMe) ppm. ^{13}C NMR (50 MHz): δ = 22.4, 36.3, 38.2, 44.8 (t, C-1, C-2, C-6, C-8), 48.1, 50.9 (t, C-3, C-5), 51.8 (q, OMe), 69.3 (s, C-8a), 173.0 (s, *C*O_2Me), 207.2 (s, C-7) ppm. IR: $\tilde{\nu}$ = 2954 cm^{-1}, 2836, 1725, 1435, 1339, 1218, 1196. MS (EI): *m/z* (%) = 138 (100), 136 (4), 96 (89), 84 (10).

Synthesis of β-Amino Acids 33, 40 and 41. General Procedure: TFA (1 equiv. for **29**, 1.5 equiv. for **35** and **36**) was added to a 0.04 M solution of the cycloadduct **29**, **35** or **36** (0.51−0.70 mmol) in toluene and the mixture was heated at 110 °C for between 2 min and 1.5 h (cf. Schemes 6 and 7). The reaction mixture was filtered through a short pad of silica gel eluting initially with petroleum ether to remove the high-boiling solvent, then with ethyl acetate to recover the product. Purification of the crude products by chromatography on silica gel afforded pure β-amino acids **33**, **40** and **41**.

[2-(Methoxycarbonyl)-1-(trifluoroacetyl)-2-pyrrolidinyl]acetic Acid (33): Colorless oil; 72% yield; R_f = 0.61 (ethyl acetate/petroleum ether, 3:1). ^1H NMR (500 MHz): δ = 1.98−2.18 (m, 2 H, 4-H), 2.23 (ddd, *J* = 13.3, 7.1, 4.3 Hz, 1 H, 3-H_a), 2.47 (ddd, *J* = 13.5, 9.6, 7.5 Hz, 1 H, 3-H_b), 3.19 (A part of an AB system, *J* = 16.3 Hz, 1 H, C*H*HCO_2H), 3.38 (B part of an AB system, *J* = 16.3 Hz, 1 H, C*H*HCO_2H), 3.75 (s, 3 H, OMe), 3.70−3.89 (m, 1 H, 5-H_a), 3.91−4.00 (m, 1 H, 5-H_b) ppm. ^{13}C NMR (50 MHz): δ = 23.8 (t, C-4), 34.9 (t, C-3), 36.4 (t, *C*H_2CO_2H), 48.4 (tq, $J_{C,F}$ = 3.8 Hz, C-5), 53.0 (q, OMe), 67.8 (s, C-2), 115.8 (q, $J_{C,F}$ = 285.3 Hz, *C*F_3), 155.6 (q, $J_{C,F}$ = 37.9 Hz, CF_3*C*O), 171.5 (s, *C*O_2Me), 175.1 (s, *C*O_2H) ppm. IR: $\tilde{\nu}$ = 3683 cm^{-1}, 3509, 2958, 1745, 1716, 1693, 1453, 1267, 1234, 1215, 1155. MS (EI): *m/z* (%) = 224 (35) [M^+ − CO_2Me], 223 (19), 206 (88), 178 (100), 83 (53), 69 (16), 59 (2). $C_{10}H_{12}F_3NO_5$ (283.2): calcd. C 42.41, H 4.27, N 4.95; found C 42.72, H 4.16, N 4.17.

[(2*R*,3*R*,4*R*)-3,4-Di-*tert*-Butoxy-1-(trifluoroacetyl)pyrrolidinyl]-acetic Acid (40): Colorless oil; 68% yield; R_f = 0.52 (ethyl acetate/petroleum ether, 1:1). $[\alpha]_D^{23}$ = −8.1 (*c* = 0.7, EtOH). ^1H NMR (400 MHz, CD_3OD): δ = 1.25 (s, 9 H, CMe_3), 1.27 (s, 9 H, CMe_3), 2.87 (A part of an ABX system, *J* = 16.2, 4.4 Hz, 1 H, C*H*HCO_2H), 2.96 (B part of an ABX system, *J* = 16.2, 10.4 Hz, 1 H, C*H*HCO_2H), 3.61 (d, *J* = 11.3 Hz, 1 H, 5-H_a), 3.95 (dd, *J* = 11.3, 4.4 Hz, 1 H, 5-H_b), 4.05 (s, 1 H, 3-H), 4.08−4.12 (m, 1 H, 4-H), 4.26 (X part of an ABX system, dd, *J* = 10.4, 4.4 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125 MHz): δ = 28.6 (q, 3C, C*Me*$_3$), 28.8 (q, 3C, C*Me*$_3$), 34.4 (t, *C*H_2CO), 54.1 (tq, $J_{C,F}$ = 6.5 Hz, C-5), 63.9 (d, C-2), 75.2 (s, *C*Me_3), 75.4 (s, *C*Me_3), 76.7, 77.2 (d, C-3, C-4), 116.6 (q, $J_{C,F}$ = 286.1 Hz, *C*F_3), 156.4 (q, $J_{C,F}$ = 36.7 Hz, CF_3*C*O), 177.0 (s, CO_2H) ppm. IR: $\tilde{\nu}$ = 2982 cm^{-1}, 1740, 1710, 1680, 1366, 1240, 1149, 1077. GC-MS: *m/z* (%) = 240 (2), 222 (30), 214 (10), 196 (4), 156 (3), 102 (9), 57 (100). HRMS (EI): calcd. for $C_{16}H_{26}F_3NO_5$ [M^+] 392.16607; found 392.16605.

[(2*S*,3*R*,4*R*)-3,4-Di-*tert*-Butoxy-1-(trifluoroacetyl)pyrrolidinyl]acetic Acid (41): Pale yellow oil; 35% yield; R_f = 0.27 (diethyl ether/pentane, 1:1). ^1H NMR (500 MHz): δ = 1.18 (s, 9 H, C*Me*$_3$), 1.20 (s, 9 H, C*Me*$_3$), 2.82−2.87 (m, 2 H, *C*H_2CO_2H), 3.48 (dm, *J* = 12.9 Hz, 1 H, 5-H_a), 3.75 (dd, *J* = 11.9, 4.8 Hz, 1 H, 5-H_b), 3.94 (q, *J* = 4.1 Hz, 1 H, 4-H), 3.93 (dd, *J* = 6.1, 4.0 Hz, 1 H, 3-H), 4.49 (q, *J* = 6.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz): δ = 28.2 (q, 3C, C*Me*$_3$), 28.3 (q, 3C, C*Me*$_3$), 31.6 (t, *C*H_2CO_2H), 51.7 (qt, $J_{C,F}$ = 3.2 Hz, C-5), 57.3 (d, C-2), 73.5 (s, *C*Me_3), 74.3 (s, *C*Me_3), 74.6, 74.9 (d, C-3, C-4), 116.0 (q, $J_{C,F}$ = 287.5 Hz, *C*F_3), 156.3 (q, $J_{C,F}$ = 36.6 Hz, CF_3*C*O), 176.8 (s, CO_2H) ppm. IR: $\tilde{\nu}$ = 3514 cm^{-1}, 2979, 1745, 1711, 1688, 1366, 1235, 1189, 1152, 1085. GC-MS: *m/z* (%) = 369 (1) [M^+], 255 (25), 240 (29), 213 (55), 195 (47), 178 (14), 100 (54), 83 (82), 56 (100). $C_{16}H_{26}F_3NO_5$ (369.4): calcd. C 52.03, H 7.09, N 3.79; found C 52.48, H 7.13, N 4.04.

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