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Synthesis of spirocyclopropyl γ-lactams by tandem intramolecular azetidine ring-opening/closing cascade reaction: synthetic and mechanistic aspects

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ABSTRACT

The scope and limitations of a novel intramolecular azetidine ring-opening/closing cascade reaction affording spirocyclopropyl γ-lactams from azetidines in high regio- and stereoselectivity is reported. The key step of the process is a S_N2-type ring-opening of TMSOTf-activated azetidine rings by silyl ketene acetals generated by treatment with TMSOTf and TEA. This study is a very rare example of nucleophilic ring-opening of azetidines that does not require formation of quaternary azetidinium salts by N-alkylation or the use of *N*-electron-withdrawing groups. Application of this process to 2-azetidinone system led to a complete change in reactivity and provide 6-aza-bicyclo[3.2.0]heptane derivatives via an unprecedented Mukaiyama aldol-like reaction involving an ester acceptor and a silyl imidate.

1. Introduction

Spirocyclopropyl compounds have stimulated the imagination of theoretical, synthetic, and medicinal chemists because of their appealing structures and their pharmacological interests. The spirocyclopropyl scaffold is indeed a useful tool for the design of constrained bioactive molecules projecting pharmacophores into the appropriate protein binding pockets. The 5-azaspiro[2.4]heptane skeleton, combining a cyclopropane moiety and a pyrrolidine moiety via a spiro carbon, is a structural motif present in various biologically active molecules including anti-autoimmune and antibacterial agents (Fig. 1).[1,2] The addition of the 5-azaspiro[2.4]heptane motif to various classes of well-known antibiotics, such as carbapenem or fluoroquinolone derivatives, has been found to be beneficial both in terms of antibacterial activity and pharmacokinetic profiles.[1a–h] Spirocyclopropyl γ-lactams have also been used as key intermediates in the synthesis of cyclopropyl amino acids.[3] Despite recent progress in the area,[4] the efficient stereoselective synthesis of such constrained small ring systems remains a challenge. In connection with our work on novel class of iminosugars,[5] we have recently reported the synthesis of α-spirocyclopropyl γ-lactams by a novel tandem azetidine ring-opening/closing

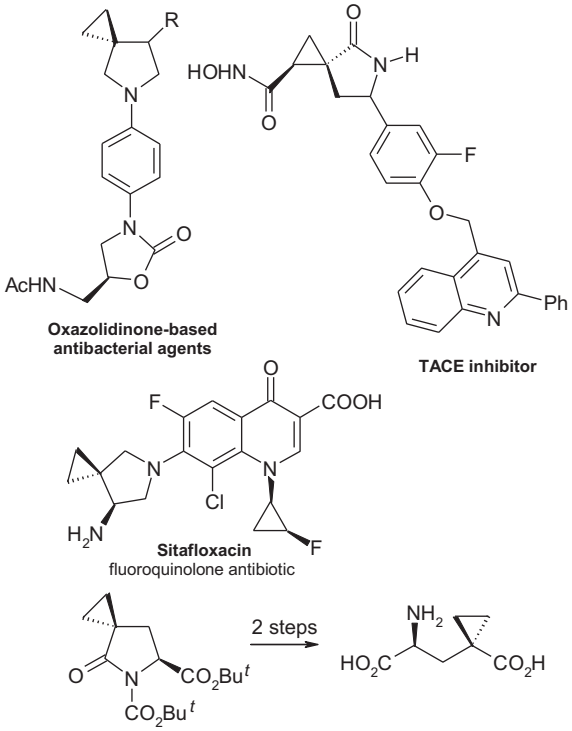

Fig. 1. Some examples of 5-azaspiro[2.4]heptane derivatives of biological interest.

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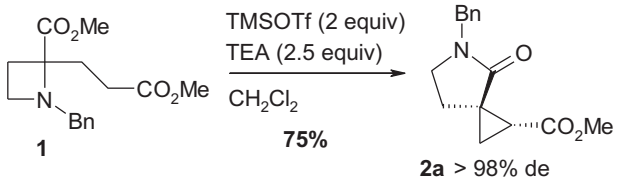
cascade reaction (Scheme 1).[6] In this intramolecular process, the cyclopropane and the pyrrolidine rings are created in a single synthetic operation in high stereoselectivity. Herein, we wish to describe the full details of this study including mechanistic aspects and reaction scope. We have especially investigated the effects of varying the key structural elements of the reaction substrate, such as chain length, ring size, and nitrogen atom basicity. The spiro-cyclization reaction depicted on Scheme 1 represents a very rare example of nucleophilic ring-opening of azetidines[7] without formation of quaternary azetidinium salts by N-alkylation or the use of *N*-electron-withdrawing group.[8–11] Ring-opening of azetidines indeed requires stronger activation than that of aziridines as a consequence of reduced ring strain and electrophilicity. In a recent relevant study, azetidinium derivatives were indeed shown to be 17,000 times less reactive than the corresponding aziridinium analogs toward nucleophilic ring-opening.[12]

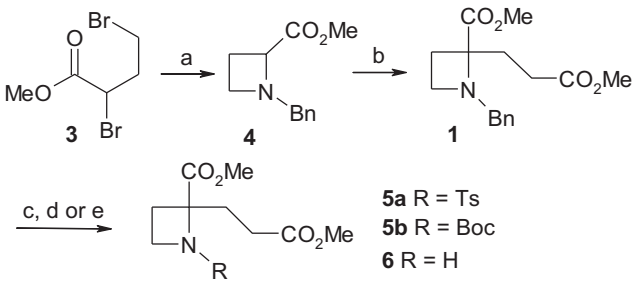


Scheme 1. Synthesis of spirocyclopropyl γ-lactam **2a** by tandem azetidine ring-opening/closing cascade reaction.

2. Results and discussion

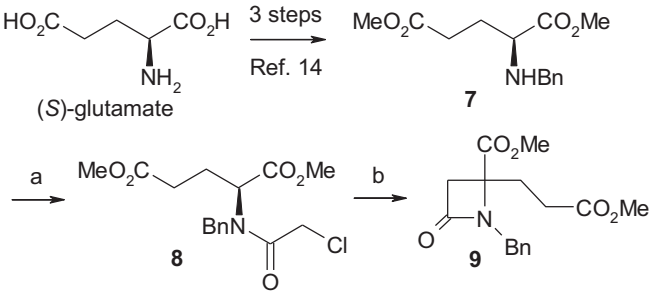
2.1. Optimization and exploration of reaction scope

A systematic study on the influence of the experimental conditions has shown that the best results were obtained when azetidine **1** was treated with 2 equiv of TMSOTf in the presence of 2.5 equiv of TEA in dichloromethane.[6] Decreasing the amount of TMSOTf or TEA to 1 equiv was found to be detrimental as no reaction took place, whereas the addition of more equivalents of Lewis acid or base did not improve significantly the yield of the reaction. The nature of the Lewis acid was also found to be crucial as conversion of the azetidine starting material was observed only with TMSOTf as indicated by a screening of various azaphilic or oxophilic Lewis acids.[6] To study the influence of diverse structural parameters in the outcome of the spiro-cyclization reaction, various test substrates were synthesized. We first explored azetidine derivatives bearing an electron-withdrawing group at the nitrogen center. The *N*-Boc or *N*-Tos azetidines **5** were obtained from the corresponding *N*-benzyl analogue **1** synthesized in two steps from commercially available α,γ-dibromo ester **3** (Scheme 2).[13]



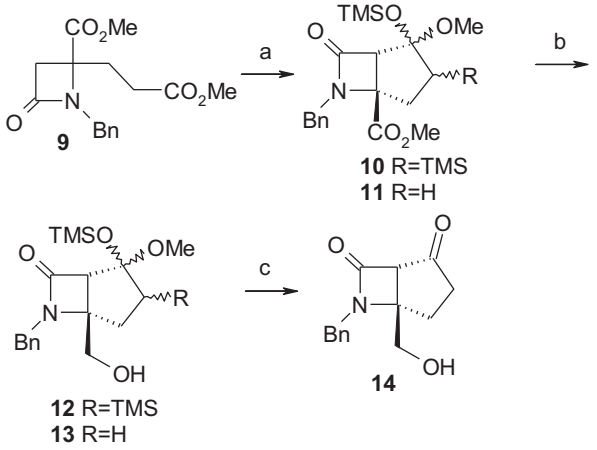
Scheme 2. Synthesis of test substrates **5** and **6**. Reaction conditions: (a) $BnNH_2$ (1 equiv), NEt_3 (3 equiv), CH_3CN, 4 h, rt, 67%; (b) (i) LDA (1.1 equiv), THF, 1 h, −78 °C→−65 °C; (ii) Methyl 3-bromopropionate (3 equiv), HMPA (6.3 equiv), THF, 16 h, −78 °C→rt, 41%; (c) (i) $Pd(OH)_2$/C 20%, HCO_2H, H_2, EtOH, 24 h, rt; (ii) TsCl (1 equiv), NEt_3 (3 equiv), CH_2Cl_2, 16 h, rt, **5a**, 29%; (d) $Pd(OH)_2$/C 20%, Boc_2O (1.5 equiv), H_2, EtOH, 16 h, **5b**, quant.; (e) Pd/C 10%, HCO_2H, H_2, MeOH, 24 h, rt, **6**, 55%.

To extend the synthetic scope of the spiro-cyclization reaction, we also synthesized β-lactam **9**, the 2-azetidinone analogue of **1** (Scheme 3). *N*-Benzyl glutamate diester **7** was readily obtained in three steps from (*S*)-glutamate[14] and converted to *N*-chloroacetyl amino acid **8** as a prelude to ring-closure reaction. Cs_2CO_3-assisted intramolecular alkylation[15] afforded the expected β-lactam **9** in acceptable yields.



Scheme 3. Synthesis of β-lactam **9**. Reaction conditions: (a) chloroacetyl chloride (1.5 equiv), propylene oxide (15 equiv), THF, 17 h, rt, 59%; (b) Cs_2CO_3 (3 equiv), CH_3CN, 72–96 h, rt, 62%.

Having test substrates **5** and **9** in hand, we investigated the tandem reaction. Deactivation of the azetidine endocyclic nitrogen atom was found to be detrimental to the process as no spiranic product could be obtained from *N*-Boc or *N*-Tos azetidines **5**, or β-lactam **9**. Azetidine **5a** remained almost unchanged after treatment with TMSOTf and TEA whereas the secondary amine **6** was the only product isolated in 20% yield from *N*-Boc azetidine **5b**. Addition of a carbonyl group to the azetidine ring to give a β-lactam led to a complete change in reactivity. Under typical spiro-cyclization conditions, 2-azetidinone **9** provided the 6-aza-bicyclo[3.2.0]heptane derivatives **10** and **11** as mixture of diastereoisomers (Scheme 4). This fused bicyclic system may reasonably be formed by a reaction sequence involving in situ formation of *O*-silyl imidate followed by intramolecular addition to the sterically less hindered ester group. While there are several examples of Mukaiyama aldol reaction of *N*,*O*-ketene acetals with aldehydes, the corresponding reaction of ketones has been found to be more challenging due to the lower reactivity of the ketone carbonyl group.[16] Remarkably, to our knowledge, the synthesis of **10** and **11** represents the first example of a reaction of this type where the carbonyl reactant is an ester. As shown by the results obtained with *N*-Boc and *N*-Tos



Scheme 4. Synthesis of bicyclic azetidinone **14**. Reaction conditions: (a) TMSOTf (3 equiv), NEt_3 (4 equiv), CH_2Cl_2, 24 h, rt; (b) $LiBH_4$, Et_2O, 8 h, rt; (c) HCl 1 N, THF, 5 h, rt, 36% (for the three steps).

azetidines **5**, deactivation of the endocyclic nitrogen atom blocks the key azetidine ring-opening step; when the reaction is performed with β-lactam **9**, the Mukaiyama aldol-like reaction pathway becomes thus preponderant. In this process, in the presence of an excess of TMSOTf and over time, a part of the silyl ketene acetal derived from **9** is converted to its isomeric α-silylated ester.[17a] It is noteworthy that 6-aza-bicyclo[3.2.0]heptane derivatives are known to display antimalarials activity and have been used as building blocks for the synthesis of bioactive β-amino acids.[18] To confirm unambiguously the rather complex structures of **10** and **11**, our aim was to obtain a structurally simpler compound that may crystallize and be characterized by X-ray crystallographic analysis (Scheme 4).

Chemoselective reduction of the ester group by treatment with 4 equiv of $LiBH_4$ provided the expected primary alcohol of **12** and **13** as a mixture. The one-pot acetal hydrolysis/desilylation reaction under acidic conditions greatly simplified the bicycle structure by removal of two asymmetric centers, providing ketone **14** as a single diastereoisomer in 36% yield for the three steps. The structure of **14**, which was nicely crystallized from the ternary solvent system CH_2Cl_2/hexane/diethyl ether, was unambiguously determined by NMR spectroscopy and X-ray crystallographic analysis (Fig. 2).

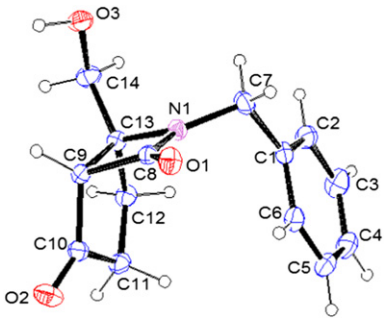
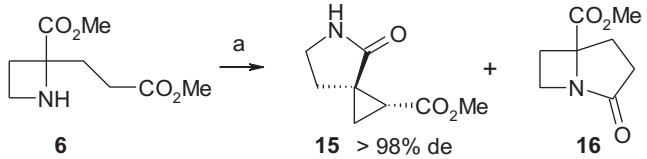


Fig. 2. Molecule structure (ORTEP)[19] of compound **14**. Thermal ellipsoid at 30% probability.

The spiro-cyclization process was found to proceed even in the absence of a nitrogen protecting group as shown by conversion of secondary amine **6** to β-lactam **15** (Scheme 5). However, not surprisingly, this reaction is in competition with the formation of γ-lactam **16**, arising from the nucleophilic addition of the free amine to the ester group in γ-position to the nitrogen atom. Lactams **15** and **16** were obtained in 21 and 20% yields, respectively, from azetidine **6**.

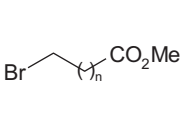
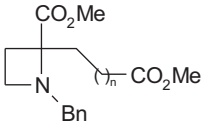
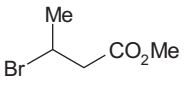
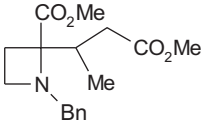
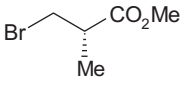
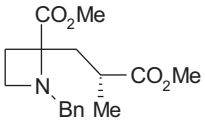


Scheme 5. Synthesis of spiro- and fused-γ-lactams. Reaction conditions: (a) TMSOTf (2 equiv), NEt_3 (2.5 equiv), CH_2Cl_2, 24 h, rt, **15** (21%), **16** (20%).

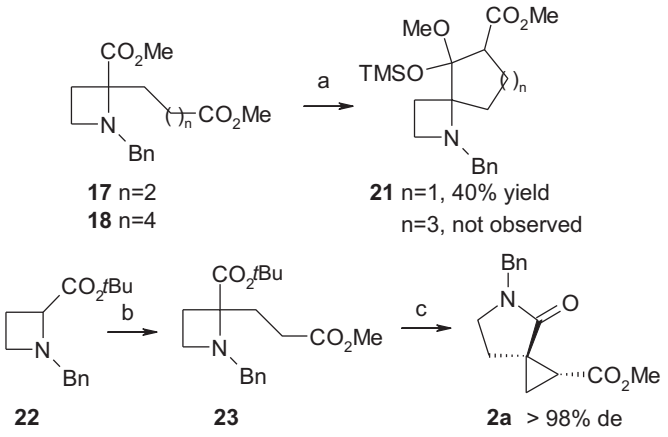
A set of alkylation reactions was performed from azetidine **4** to obtain test substrates with various alkyl chain length and substituents (Table 1). The reaction proved difficult to effect in good yields and the desired compounds were obtained in 11–45% yields.

Not surprisingly, treatment of **17** with TMSOTf and TEA provided the expected spirocyclopentane **21**, the increase of the alkyl chain length by one methylene unit favoring the Dieckmann reaction (Scheme 6).[17] Further increase of the alkyl chain length by two methylene units to favor azetidine ring-opening (formation of a six-membered ring) over the Dieckmann reaction (formation of a disfavored seven-membered ring)[17a] led to a substrate (**18**) that was not reactive under our typical cyclization conditions.

Table 1
Alkylation of azetidine **4**[a]

RBr	Product		Yield[b]
		**1** (n=1) **17** (n=2) **18** (n=4)	45% 11% 14%
		**19**[c]	12%
		**20**	14%

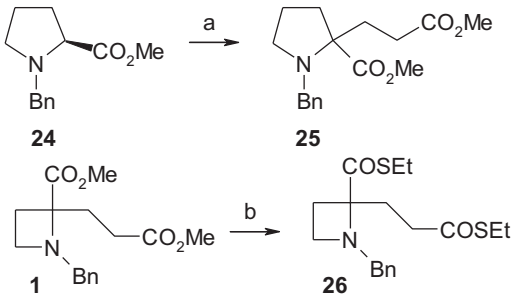
[a] Reaction conditions: (i) LDA (1.1 equiv), THF, 1 h, −78 °C→−65 °C; (ii) Bromoester (3 equiv), HMPA (6.3 equiv), THF, 20 h, −78 °C→rt.
[b] Isolated yield after purification by flash chromatography on silica gel.
[c] Addition of the bromoester at −5 °C in the absence of HMPA (see Experimental section).



Scheme 6. Reaction of test substrates **17**, **18**, and **23**. Reaction conditions: (a) TMSOTf (2 equiv), NEt_3 (2.5 equiv), CH_2Cl_2, 24 h, rt, 40%; (b) (i) LDA (1.1 equiv), THF, 1 h, −78 °C→−65 °C; (ii) Methyl 3-bromopropionate (3 equiv), HMPA (6.3 equiv), THF, 20 h, −78 °C→rt, 28%; (c) TMSOTf (2 equiv), NEt_3 (2.5 equiv), CH_2Cl_2, 3 h, reflux, 8%.

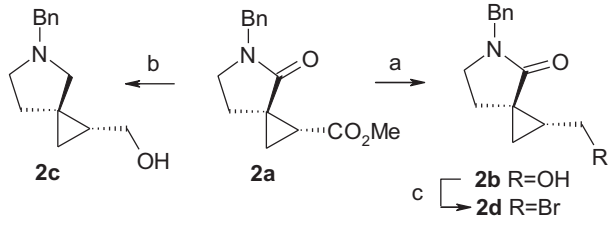
The reaction was found to be highly sensitive to the introduction of substituents in α- or β-position to the primary ester group; azetidines **19** and **20**, the methylated analogs of **1**, did not partake in the spiro-cyclization reaction. The influence of steric effects on the cyclization process was explored with *tert*-butyl ester **23**, which afforded the expected spiranic lactam in a much lower yield than the corresponding methyl ester analog **1** (Scheme 6). Reduction of ring strain was found to be detrimental to the spiro-cyclization process as demonstrated by the absence of reactivity of **25**, the pyrrolidine analog of **1**, toward treatment with TMSOTf and TEA (Scheme 7). Dithioester **26**, prepared from diester **1** following the procedure reported by Weinreb,[20] was also not a substrate of the spiro-cyclization reaction.

The limited substrate scope of the spiro-cyclization reaction may be overcome by exploiting the reactivity of the tandem reaction product **2a**. A range of various 5-azaspiro[2.4]heptane



Scheme 7. Synthesis of test substrates **25** and **26**. Reaction conditions: (a) (i) LDA (1.1 equiv), THF, 1 h, −78 °C→−65 °C; (ii) Methyl 3-bromopropionate (3 equiv), HMPA (6.3 equiv), THF, 20 h, −78 °C→rt, 45%; (b) $AlMe_3$ (4 equiv), EtSH (4 equiv), CH_2Cl_2, 25 h, rt, 37%.

derivatives have thus been obtained in one-step by way of chemoselective reduction of **2a**. Reduction of the ester group by treatment with Superhydride® afforded **2b** in high yield whereas access to the fully reduced pyrolidine analogue **2c** was also easily performed using LAH (Scheme 8). Primary alcohol **2b** was efficiently converted to bromide **2d** in 79% yield by using PPh_3/Br_2 and pyridine.



Scheme 8. Synthesis of 5-azaspiro[2.4]heptane derivatives **2** bearing different functional groups. Reaction conditions: (a) $LiBHEt_3$ (4 equiv), THF, 2.5 h, −78 °C→−65 °C, 89%; (b) LAH (3.5 equiv), THF, 3 h, reflux, quant.; (c) PPh_3 (1.05 equiv), Br_2 (1.05 equiv), Pyridine (1 equiv), CH_2Cl_2, 72 h, rt, 79%.

2.2. Mechanistic aspects

A tentative mechanism for the formation of the spirocyclopropyl γ-lactam **2a** is proposed in Fig. 3. We believe that the key step of the process is a S_N2-type ring-opening[8,21] of the TMSOTf-activated azetidine ring by the silyl ketene acetal generated by treatment with TMSOTf and TEA.[17a] The amino ester **A**, thus obtained, finally undergoes an intramolecular cyclization to afford the five-membered lactam **2a** by reaction of the amine function with the ester group in γ-position. This reaction proceeds in high regioselectivity as no formation of six-membered lactam was detected. Remarkably, in this process TMSOTf plays a triple role by generating the reactive nucleophilic intermediate (the silyl ketene acetal) and by activating the azetidine for the nucleophilic ring-opening and the carbonyl of the tertiary ester group for the final amide bond formation.

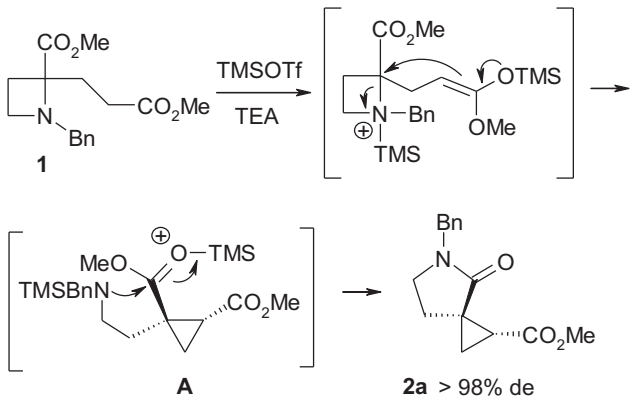
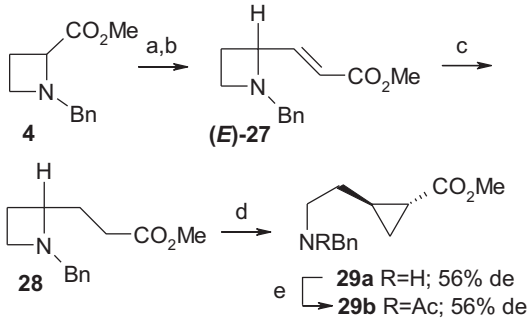


Fig. 3. Proposed mechanism for the spiro-cyclization reaction.

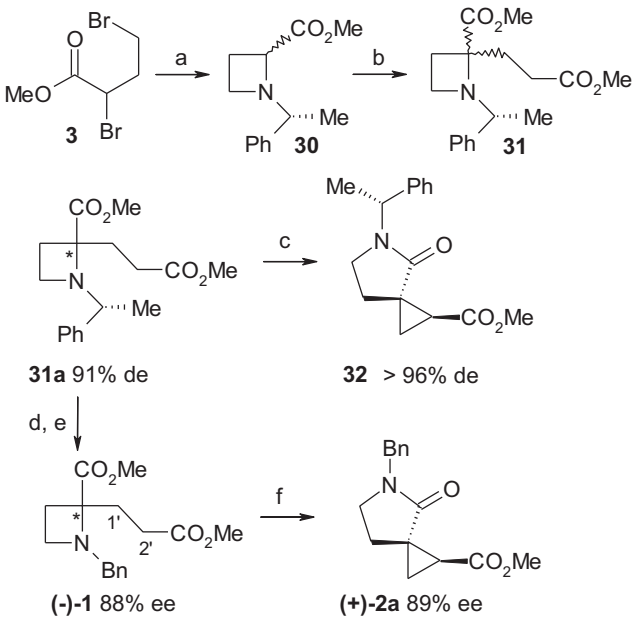
The proposed mechanism is supported by experimental evidences and explains why azetidines **5** and **9** are not substrates of the cyclization reaction; the best activation of the azetidine ring with TMSOTf is indeed expected for an endocyclic amine. To avoid the formation of the γ-lactam and isolate the amino cyclopropane intermediate of type **A**, the tertiary ester group was replaced by a hydrogen atom and the reaction was performed from azetidine **28**[22a] obtained from ester **4** in three steps (Scheme 9). Selective reduction to the corresponding aldehyde[22b] followed by Wittig olefination afforded α,β unsaturated esters **27** (*E*/*Z* mixture: 7/3) in 72% yield. Chemoselective reduction of the double bond in the presence of the ester group was performed by using a slight excess of $NaBH_4$ in the presence of CuCl at 0 °C to give the desired product **28**.[22c] Treatment of **28** with TMSOTf and TEA provided cyclopropane **29a** in 61% yield and 56% de (Scheme 9). It was established by 2D COSY and NOESY NMR experiments at the stage of the *N*-Ac derivative **29b** that the major epimer was in favor of the trans product (See Supplementary data).



Scheme 9. Synthesis of cyclopropanes **29**. Reaction conditions: (a) DIBAL-H (1.6 equiv), THF, 4 h, −78 °C; (b) $Ph_3P{=}CHCO_2Me$ (2.2 equiv), CH_2Cl_2, 16 h, 0 °C→rt, 72% for the two steps (*E*/*Z*:7/3); (c) $NaBH_4$ (2 equiv), CuCl (1.7 equiv), MeOH, 4 h, 0 °C, 41%; (d) TMSOTf (2 equiv), NEt_3 (2.5 equiv), CH_2Cl_2, 24 h, rt, 61%; (e) Ac_2O (1.1 equiv), CH_2Cl_2, 24 h, rt, 67%.

Disappointing results obtained with **19**, **20** and azetidine **23** bearing a bulky *t*-Bu ester group are compatible with the fact that S_N2 process is a mechanism known to be sensitive to steric hindrance. To confirm the ring-opening of the azetidine via a concerted S_N2 mechanism, the reaction was first performed from diastereoenriched azetidine **31a**. Compound **31a** was obtained from commercially available (*R*)-α-methylbenzylamine and dibromide **3** following the same strategy used for the synthesis of *N*-benzylazetidine **1** (Schemes 2 and 10). Diastereoenriched azetidine **31a** (91% de) was isolated after separation by flash chromatography on silica gel of the two diastereomers obtained after the alkylation step. We were pleased to find that the spiro-cyclization reaction performed from **31a** proceeded without loss of the diastereomeric excess (Scheme 10).

The tandem reaction was then performed with enantioenriched azetidine (−)-**1**, which was obtained from **31a** after a two step deprotection/reprotection sequence. ^1H NMR analysis of (−)-**1** using the Pirkle chiral shift reagent TFAE[23] showed that the enantiomeric excess was 88% (See Supplementary data). Azetidine (−)-**1** reacted under typical spiro-cyclization reaction conditions to give the expected γ-lactam (+)-**2a** with complete retention of the enantiomeric excess (Scheme 10).[24,25] These results are in good agreement with a mechanism involving a S_N2-type ring-opening reaction (Fig. 3). The high diastereoselectivity observed in favor of the trans product may be rationalized as follows (Fig. 4).



Scheme 10. Stereochemical aspects of the spiro-cyclization reaction. Reaction conditions: (a) K_2CO_3 (1 equiv), **3** (1 equiv), (*R*)-(+)-α-methylbenzylamine (1 equiv), CH_3CN/H_2O (1:5), 6.5 h, reflux, 64%; (b) (i) LDA (1.1 equiv), THF, 1 h, −78 °C→−65 °C, (ii) Methyl 3-bromopropionate (3 equiv), HMPA (6.3 equiv), THF, 20 h, −78 °C→rt, **31a** (18%), **31b** (4%); (c) TMSOTf (2 equiv), NEt_3 (2.5 equiv), CH_2Cl_2, 24 h, rt, 56%; (d) Pd/C 10%, HCO_2H, H_2, ^iPrOH, 24 h, rt; (e) BnBr (1.2 equiv), K_2CO_3 (1.2 equiv), CH_3CN, 24 h, rt, 54% (two steps); (f) TMSOTf (2 equiv), NEt_3 (2.5 equiv), CH_2Cl_2, 24 h, rt, 74%.

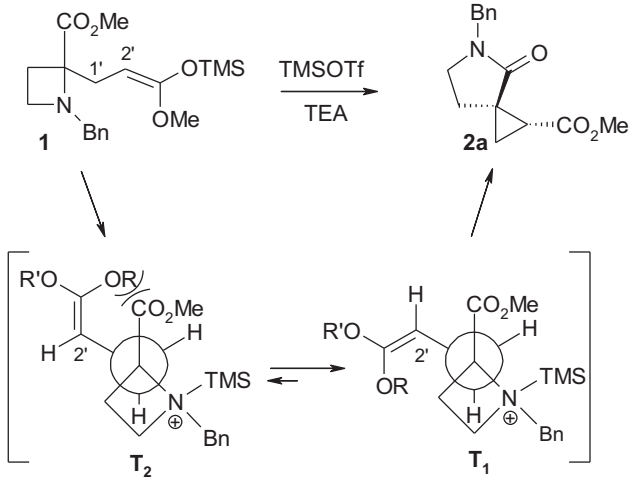


Fig. 4. Stereochemical pathway explaining the formation of **2a**.

In the TMSOTf-induced azetidine S_N2-type ring-opening, there are two limiting reactive geometry generated by the rotation about the $C_{1'}$–$C_{2'}$ bond: antiperiplanar structures $\mathbf{T_1}$ and $\mathbf{T_2}$ leading to the trans and the cis spiro-cyclization product, respectively. In these structures, $A_{1,3}$ steric strains are minimized and the C–N bond is approximately perpendicular to the plan of the silyl ketene acetal. $\mathbf{T_2}$ is expected to experience severe repulsion between the oxygen lone-pairs of the ester and the silyl ketene acetal, whereas $\mathbf{T_1}$ minimizes such unfavorable dipole–dipole/electrostatic interactions. Replacement of the ester group by a hydrogen atom to suppress this effect indeed reduced the stereoselectivity of the process and led to an inversion of the diastereoselectivity as shown by the conversion of **28** to **29a** (56% de, Scheme 9). This result may be explained by partial destabilization of structure $\mathbf{T_{1'}}$ due to steric interactions between the bulky silyl ketene acetal and the azetidine methylene group at C-3 (Fig. 5).

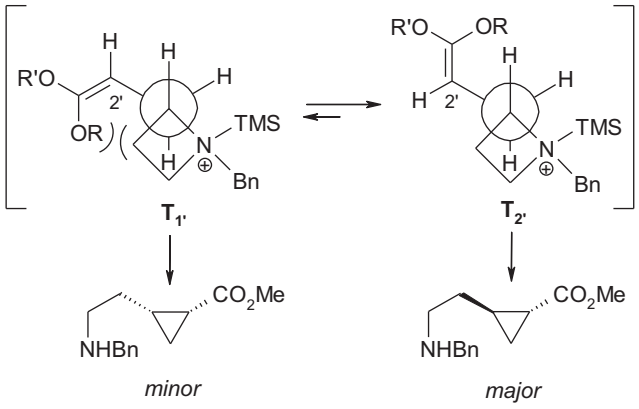


Fig. 5. Stereochemical pathway explaining the stereoselective formation of **29a**.

3. Conclusion

In conclusion, a novel, highly stereoselective tandem intramolecular azetidine ring-opening/closing cascade reaction is reported. In this one-step process, two cycles – a cyclopropane and a γ-butyrolactam, and two asymmetric centers are created. The spiro-cyclization process was found to be particularly sensitive to structural variations in the substrate because of the high density of potential reactive centers present in its structure. Nevertheless, chemoselective reduction of the tandem reaction product allows access to various 5-azaspiro[2.4]heptane derivatives bearing different functionalities. In addition, the tandem reaction performed with the 2-azetidinone analog of **1** led to the one-step formation of a completely different fused bicyclic skeleton to give 6-aza-bicyclo [3.2.0]heptane derivatives via an unprecedented Mukaiyama aldol-like reaction of an ester acceptor with a silyl imidate.

4. Experimental section

4.1. General methods

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by passage through an activated alumina column under Ar. Dichloromethane (CH_2Cl_2) was distilled over CaH_2 under Ar. Triethylamine (Et_3N) was distilled over KOH under Ar and stored over KOH. All reactions were performed in standard glassware under Ar. Flash chromatographies were performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm) purchased from E. Merck. Thin layer chromatography (TLC) was performed on aluminum sheets coated with silica gel 60 F_{254} purchased from E. Merck. IR spectra (cm^{-1}) were recorded on a Perkin–Elmer Spectrum One Spectrophotometer. NMR spectra were recorded on a Bruker AC 300 or AC 400 with solvent peaks as reference. Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. The ^1H signals were assigned by 2D experiments (COSY). ESI-HRMS mass spectra were carried out on a Bruker MicroTOF spectrometer. ESI-LRMS mass spectra were carried out on a MSQ Thermo Fisher spectrometer. Specific rotations were determined at room temperature (20 °C) in a Perkin–Elmer 241 polarimeter for sodium (λ=589 nm).

*4.1.1. Methyl N-benzyl-2-(3-methoxycarbonylethyl)azetidine-2-carboxylate (**1**).* A solution of LDA (2.68 mmol, 1.1 equiv) [prepared from diisopropylamine (0.38 mL, 2.68 mmol) in THF (6.5 mL) and *n*-BuLi (1.52 M in hexane, 1.8 mL, 2.68 mmol) stirred at −78 °C for 30 min] was added to a solution of methyl *N*-benzylazetidine-2-carboxylate **4** (500 mg, 2.44 mmol, 1 equiv) in THF (3.2 mL), cooled

to −78 °C. The reaction mixture was allowed to warm to −65 °C (l h), cooled again to −78 °C and a mixture of methyl 3-bromopropionate (0.8 mL, 7.31 mmol, 3 equiv) and HMPA (2.7 mL, 15.35 mmol, 6.3 equiv) in THF (2.5 mL) was added. The solution was allowed to warm to rt and then stirred for 16 h. Then the reaction was quenched with saturated aqueous NH_4Cl and was extracted with Et_2O (3×5 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:7 to 1:1) to afford the diester **1** (291 mg, 41%) as a yellow oil. TLC R_f 0.63 (silica gel, AcOEt/petroleum ether, 1:2); IR (film) 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.16 (m, 5H, Ph), 3.77 (s, 3H, CO_2Me), 3.69 (d, 1H, J=13.2 Hz, CH_2Ph), 3.65 (s, 3H, CO_2Me), 3.58 (d, 1H, J=13.0 Hz, CH_2Ph), 3.17 (m, 2H, H-4), 2.52–1.96 (m, 6H, H-3, H-1′, H-2′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (CO), 173.5 (CO), 138.3 (Cq–Ar), 128.6 (2CH–Ar), 128.3 (2CH–Ar), 127.0 (1CH–Ar), 71.5 (C-2), 56.0 (CH_2Ph), 51.7 (OCH_3), 51.6 (OCH_3), 49.7 (C-4), 29.6 (C-1′ or C-2′), 29.0 (C-1′ or C-2′), 25.6 (C-3); HRMS (ESI) $[M+Na]^+$ calcd for $C_{16}H_{21}NO_4Na$: 314.136, found 314.135.

*4.1.2. Methyl N-benzyl-2-(3-methoxycarbonylethyl)azetidine-2-carboxylate ((−)-**1**).* Pd/C 10% (50 mg) and two drops of HCO_2H were added to a solution of **31a** (126 mg, 0.41 mmol, 1 equiv) in ^{i}PrOH (3 mL). The solution was placed under H_2 atmosphere and stirred until disappearance of the starting material (24 h). Saturated aqueous $NaHCO_3$ (1 mL) was added and the solution was filtered through Celite and concentrated under reduced pressure. The solution was dissolved in CH_3CN (2 mL). K_2CO_3 (68 mg, 0.49 mmol, 1.2 equiv) and BnBr (59 μL, 0.49 mmol, 1.2 equiv) were added and the solution was stirred at rt until disappearance of the starting material (24 h). Then the reaction was quenched with water and was extracted with AcOEt (3×2 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:7 to 1:1) to afford the diester (−)-**1** (65 mg, 54%, ee 88%) as a yellow oil. $[\alpha]_D^{20}$ −14 (*c* 0.7, $CHCl_3$).

4.1.3. (1R,3R*)-N-Benzyl-1-methoxycarbonyl-5-azaspiro[2.4]heptan-4-one (**2a**).* To a solution of azetidine **1** (80 mg, 0.28 mmol, 1 equiv) in CH_2Cl_2 (1 mL) cooled to 0 °C was added NEt_3 (96 μL, 0.69 mmol, 2.5 equiv) and TMSOTf (0.1 mL, 0.55 mmol, 2 equiv). The solution was stirred at rt for 24 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$ and was extracted with CH_2Cl_2 (3×2 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/pentane, 1:5 to 1:1) to afford **2a** (54 mg, 75%) as a yellow oil. TLC R_f 0.30 (silica gel, AcOEt/petroleum ether, 1:2); IR (film) 1728, 1688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5H, Ph), 4.51 (d, 1H, J=14.7 Hz, CH_2Ph), 4.45 (d, 1H, J=14.7 Hz, CH_2Ph), 3.71 (s, 3H, CO_2Me), 3.32 (m, 2H, H-6), 2.28 (dd, 1H, J=8.8, 6.1 Hz, H-1), 2.19 (dd, 2H, J=8.3, 6.3 Hz, H-7), 1.58 (dd, 1H, J=8.8, 4.0 Hz, H-2a), 1.35 (dd, 1H, J=5.9, 4.1 Hz, H-2b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6 (CO), 172.1 (NCO), 136.3 (Cq–Ar), 128.9 (2CH–Ar), 128.4 (2CH–Ar), 127.8 (1CH–Ar), 52.0 (OCH_3), 47.6 (CH_2Ph), 44.2 (C-6), 31.6 (C-3), 25.3 (C-1), 22.9 (C-7), 19.3 (C-2); HRMS (ESI) $[M+Na]^+$ calcd for $C_{15}H_{17}NO_3Na$: 282.110, found 282.110.

*4.1.4. (1S,3S)-N-Benzyl-1-methoxycarbonyl-5-azaspiro[2.4]heptan-4-one ((+)-**2a**).* To a solution of azetidine (−)-**1** (94 mg, 0.32 mmol, 1 equiv, ee 88%) in CH_2Cl_2 (1 mL) cooled to 0 °C was added NEt_3 (0.11 mL, 0.80 mmol, 2.5 equiv) and TMSOTf (0.12 mL, 0.64 mmol, 2 equiv). The solution was stirred at rt for 24 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$ and was extracted with CH_2Cl_2 (3×2 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/pentane, 1:5 to 1:1) to afford (+)-**2a** (62 mg, 74%, ee 89%) as a yellow oil. $[\alpha]_D^{20}$ +157 (*c* 0.8, $CHCl_3$).

4.1.5. (1R,3R*)-N-Benzyl-1-hydroxymethyl-5-azaspiro[2.4]heptan-4-one (**2b**).* To a solution of **2a** (84 mg, 0.32 mmol, 1 equiv) in THF (0.5 mL) cooled to −78 °C, was added $LiBHEt_3$ (1 M in THF, 1.3 mL, 1.30 mmol, 4 equiv). The solution was stirred 1 h at −78 °C and 1.5 h at −65 °C. Saturated aqueous $NaHCO_3$ (0.4 mL) was added and the solution was allowed to warm to 0 °C. H_2O_2 35% (90 μL) was added and the solution was stirred at 0 °C for 20 min. The solution was concentrated under reduced pressure. Water was added and the reaction was extracted with CH_2Cl_2 (3×2 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography ($MeOH/CH_2Cl_2$, 5:95) to afford **2b** (67 mg, 89%) as a white powder. TLC R_f 0.30 (silica gel, $MeOH/CH_2Cl_2$, 5:95); IR (film) 3389, 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.25 (m, 5H, Ph), 4.60 (d, 1H, J=14.6 Hz, CH_2Ph), 4.45 (d, 1H, J=14.6 Hz, CH_2Ph), 3.89 (dd, 1H, J=11.5, 5.7 Hz, CH_2OH), 3.46 (m, 1H, CH_2OH), 3.39 (m, 2H, H-6), 2.31 (m, 1H, H-1), 2.01 (m, 1H, H-7a), 1.77 (m, 1H, H-7b), 1.38 (dd, 1H, J=9.1, 4.2 Hz, H-2a), 0.64 (dd, 1H, J=6.3, 4.4 Hz, H-2b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1 (NCO), 136.7 (Cq–Ar), 128.8 (2CH–Ar), 128.3 (2CH–Ar), 127.7 (1CH–Ar), 63.1 (CH_2OH), 47.4 (CH_2Ph), 44.5 (C-6), 27.2 (C-3), 25.1 (C-1), 22.4 (C-7), 17.6 (C-2); HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{17}NO_2Na$: 254.115, found 254.117.

*4.1.6. (1S,3S)-N-Benzyl-1-hydroxymethyl-5-azaspiro[2.4]heptan-4-one ((+)-**2b**).* To a solution of (+)-**2a** (34 mg, 0.13 mmol, 1 equiv, ee 89%) in THF (1 mL) cooled to −78 °C, was added $LiBHEt_3$ (1 M in THF, 0.52 mL, 0.52 mmol, 4 equiv). The solution was stirred 1 h at −78 °C and 1.5 h at −65 °C. Saturated aqueous $NaHCO_3$ (0.2 mL) was added and the solution was allowed to warm to 0 °C. H_2O_2 35% (20 μL) was added and the solution was stirred at 0 °C for 20 min. The solution was concentrated under reduced pressure. Water was added and the reaction was extracted with CH_2Cl_2 (3×2 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography ($MeOH/CH_2Cl_2$, 5:95) to afford (+)-**2b** (26 mg, 85%) as a white powder. $[\alpha]_D^{20}$ +29 (*c* 1.0, $CHCl_3$).

4.1.7. (1R,3R*)-N-Benzyl-1-hydroxymethyl-5-azaspiro[2.4]heptane (**2c**).* LAH (34 mg, 0.89 mmol, 3.5 equiv) was added to a solution of **2a** (66.2 mg, 0.26 mmol) in THF (1.4 mL) cooled at 0 °C. The solution was stirred at reflux for 3 h. After cooling at 0 °C, H_2O (1 mL) was carefully added. Then 10% NaOH (2 mL) and H_2O (3 mL) were added. The solution was filtered through Celite and concentrated under reduced pressure to afford **2c** (55 mg, quant.) as a yellow oil. IR (film) 3342 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.16 (m, 5H, Ph), 4.12–3.88 (br s, 1H, OH), 3.64–3.51 (m, 3H, CH_2OH, CH_2Ph), 3.25 (dd, 1H, J=11.1, 8.6 Hz, CH_2OH), 2.80 (m, 1H, H-6), 2.61 (m, 1H, H-6), 2.49 (d, 1H, J=9.1 Hz, H-4a), 2.37 (d, 1H, J=9.1 Hz, H-4b), 1.97 (m, 1H, H-7a), 1.62 (m, 1H, H-7b), 1.04 (m, 1H, H-1), 0.68 (dd, 1H, J=8.8, 4.9 Hz, H-2a), 0.27 (t, 1H, J=5.2 Hz, 1H, H-2b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5 (Cq–Ar), 129.1 (2CH–Ar), 128.4 (2CH–Ar), 127.2 (1CH–Ar), 63.9 (C-4 or CH_2OH), 63.7 (C-4 or CH_2OH), 60.9 (CH_2Ph), 55.0 (C-6), 28.8 (C-7), 25.25 (C-1), 25.2 (C-3), 17.0 (C-2); HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{20}NO$: 218.154, found 218.153.

4.1.8. (1R,3R*)-N-Benzyl-1-bromomethyl-5-azaspiro[2.4]heptan-4-one (**2d**).* To a solution of PPh_3 (407 mg, 1.55 mmol, 1.05 equiv) in CH_2Cl_2 (7 mL) cooled at −30 °C, was added Br_2 (80 μL, 1.55 mmol, 1.05 equiv). The solution was stirred for 15 min between −30 °C and −15 °C. A mixture of **2b** (342 mg, 1.48 mmol, 1 equiv) and pyridine (120 μL, 1.48 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was added. The

solution was stirred at rt for 3 days. The solution was then concentrated under reduced pressure. The crude product was purified by flash chromatography ($MeOH/CH_2Cl_2$, 0:100 to 5:95) to afford **2d** (343 mg, 79%) as a pale yellow oil. TLC R_f 0.59 (silica gel, $MeOH/CH_2Cl_2$, 5:95); IR (film) 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.20 (m, 5H, Ph), 4.56 (d, 1H, J=14.7 Hz, CH_2Ph), 4.44 (d, 1H, J=14.9 Hz, CH_2Ph), 3.72 (dd, 1H, J=13.5, 5.9 Hz, CH_2Br), 3.38 (m, 2H, H-6), 3.07 (t, 1H, J=10.3 Hz, CH_2Br), 2.25 (m, 1H, H-7a), 2.08–1.87 (m, 2H, H-1, H-7b), 1.54 (dd, 1H, J=9.0, 4.7 Hz, H-2a), 0.66 (t, 1H, J=5.4 Hz, H-2b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (NCO), 136.5 (Cq–Ar), 128.8 (2CH–Ar), 128.1 (2CH–Ar), 127.6 (1CH–Ar), 47.3 (*C*H_2Ph), 44.4 (C-6), 33.8 (CH_2Br), 29.7 (C-3), 25.6 (C-1), 21.3 (C-7), 20.9 (C-2); HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{16}BrNONa$: 316.031, found 316.030.

*4.1.9. Methyl N-benzylazetidine-2-carboxylate (**4**).* To a solution of methyl 1,3-dibromopropionate (7.8 mL, 55.2 mmol, 1 equiv) in CH_3CN (120 mL), were added NEt_3 (23 mL, 166 mmol, 3 equiv) and benzylamine (6 mL, 55.2 mmol, 1 equiv). The solution was heated to reflux and stirred for 4 h. After cooling, water (70 mL) was added and the product was extracted with Et_2O (3×40 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:7 to 2:1) to afford azetidine **4** (7.58 g, 67%) as an orange oil. TLC R_f 0.21 (silica gel, AcOEt/petroleum ether, 1:3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.17 (m, 5H, Ph), 3.78 (d, 1H, J=12.6 Hz, CH_2Ph), 3.71 (t, 1H, J=8.4 Hz, H-1), 3.60 (s, 3H, CO_2Me), 3.56 (d, 1H, J=12.6 Hz, CH_2Ph), 3.29 (m, 1H, H-4a), 2.91 (m, 1H, H-4b), 2.34 (m, 1H, H-3a), 2.18 (m, 1H, H-3b). Spectroscopic data are in accordance with literature data.[26]

*4.1.10. Methyl N-tosyl-2-(3-methoxycarbonylethyl)azetidine-2-carboxylate (**5a**).* To a solution of azetidine **1** (200 mg, 0.69 mmol, 1 equiv) in EtOH (1 mL) was added $Pd(OH)_2/C$ 20% (20 mg) and few drops of HCO_2H. The solution was placed under H_2 atmosphere and stirred until disappearance of the starting material (24 h). The solution was filtered through Celite and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (7 mL) and cooled to 0 °C. NEt_3 (0.3 mL, 2.06 mmol, 3 equiv) and TsCl (131 mg, 0.69 mmol, 1 equiv) were added and the solution was stirred overnight at rt. The reaction was quenched with water and was extracted with CH_2Cl_2 (3×4 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:9 to 1:1) to afford **5a** (71 mg, 29%) as a white powder. TLC R_f 0.21 (silica gel, AcOEt/petroleum ether, 1:2); IR (film) 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 2H, J=6.4 Hz, CH–Ar), 7.29 (d, 2H, J=8.3 Hz, CH–Ar), 4.03 (m, 1H, H-4a), 3.82 (m, 1H, H-4b), 3.67 (s, 3H, CO_2Me), 3.60 (s, 3H, CO_2Me), 2.57–2.32 (m, 5H, H-3a, H-1′, H-2′), 2.41 (s, 3H, C(CH_3)-Ar), 2.20 (m, 1H, H-3b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3 (CO), 171.2 (CO), 143.5 (*C*(CH_3)-Ar), 137.2 (Cq–Ar), 129.6 (2CH–Ar), 127.3 (2CH–Ar), 74.4 (C-2), 52.6 (OCH_3), 51.9 (OCH_3), 47.5 (C-4), 31.0 (C-1′ or C-2′), 28.8 (C-1′ or C-2′), 24.9 (C-3), 21.6 (C(*C*H_3)-Ar); HRMS (ESI): *m*/*z* 378.096 ($[M+Na]^+$, calcd for $C_{16}H_{21}NO_6SNa$: 378.095).

*4.1.11. Methyl N-tert-butyloxycarbonyl-2-(3-methoxycarbonylethyl) azetidine-2-carboxylate (**5b**).* To a solution of azetidine **1** (150 mg, 0.51 mmol, 1 equiv) in EtOH (2 mL) was added $Pd(OH)_2/C$ 20% (22 mg) and Boc_2O (169 mg, 0.77 mmol, 1.5 equiv). The solution was placed under H_2 atmosphere and stirred overnight. The solution was filtered through Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:4 to 1:2) to afford **5b** (157 mg, quant.) as a pale yellow oil. TLC R_f 0.21 (silica gel, AcOEt/petroleum ether, 1:2); IR (film) 1737, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.97 (m, 1H, H-4a), 3.76 (s, 3H, CO_2Me), 3.74 (m, 1H, H-4b), 3.68 (s, 3H, CO_2Me), 2.70–2.10 (m, 6H, H-3, H-1′, H-2′), 1.41 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8 (CO), 172.7 (CO), 155.5 (NCO), 80.4 (*C*$(CH_3)_3$), 70.4 (C-2), 52.4 (OCH_3), 51.8 (OCH_3), 45.1 (C-4), 30.5 (C-1′ or C-2′), 29.1 (C-1′ or C-2′), 28.4 (C$(CH_3)_3$), 25.3 (C-3); HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{23}NO_6Na$: 324.142, found 324.142.

*4.1.12. Methyl 2-(3-methoxycarbonylethyl)azetidine-2-carboxylate (**6**).* To a solution of azetidine **1** (250 mg, 0.85 mmol, 1 equiv) in MeOH (4 mL) was added Pd/C 10% (250 mg) and few drops of HCO_2H. The solution was placed under H_2 atmosphere and stirred until disappearance of the starting material (24 h). Saturated aqueous $NaHCO_3$ (1 mL) was added and the solution was filtered through Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography ($MeOH/CH_2Cl_2$+1% NEt_3, 0:100 to 5:95) to afford **6** (96 mg, 55%) as a colorless oil. TLC R_f 0.26 (silica gel, $MeOH/CH_2Cl_2$, 5:95); IR (film) 1729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H, CO_2Me), 3.66 (s, 3H, CO_2Me), 3.53 (m, 1H, H-4a), 3.30 (m, 1H, H-4b), 2.50–2.31 (m, 4H, H-3, H-1′ or H-2′), 2.23 (m, 1H, H-1′a or H-2′a), 2.18–2.07 (m, 2H, NH, H-1′b or H-2′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9 (CO), 173.6 (CO), 67.0 (C-2), 52.6 (OCH_3), 51.8 (OCH_3), 41.6 (C-4), 34.5 (C-1′ or C-2′), 30.6 (C-1′ or C-2′), 28.7 (C-3); HRMS (ESI) $[M+Na]^+$ calcd for $C_9H_{15}NO_4Na$: 224.089, found 224.089.

*4.1.13. Dimethyl-(S)-2-[N-benzyl-N-(2-chloroacetyl)amino]pentanedioate (**8**).* To a solution of **7** (1.00 g, 3.77 mmol, 1 equiv) in THF (19 mL), was added chloroacetyl chloride (0.45 mL, 5.65 mmol, 1.5 equiv) and propylene oxide (4.0 mL, 56.5 mmol, 15 equiv). The solution was stirred for 17 h and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:3 to 1:1) to afford **8** (773 mg, 59%) as a colorless oil. TLC R_f 0.44 (silica gel, AcOEt/petroleum ether, 2:3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.20 (m, 5H, Ph), 4.77–4.56 (m, 2H, CH_2Cl), 4.41 (m, 1H, C*H*CO_2Me), 4.10 (d, 1H, J=12.9 Hz, CH_2Ph), 4.03 (d, 1H, J=12.6 Hz, CH_2Ph), 3.63 (s, 6H, CO_2Me), 2.48–2.00 (m, 4H, CH_2C$H_2$$CO_2Me$). Spectroscopic data are in accordance with literature data.[14]

*4.1.14. Methyl N-benzyl-2-(3-methoxycarbonylethyl)-4-oxoazetidine-2-carboxylate (**9**).* To a solution of **8** (372 mg, 1.07 mmol, 1 equiv) in CH_3CN (13 mL) was added Cs_2CO_3 (1.05 g, 3.21 mmol, 3 equiv). The solution was stirred at rt until disappearance of the starting material (72–96 h). The solution was concentrated under reduced pressure. Water and AcOEt were added. The reaction was extracted with AcOEt (3×5 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:3 to 1:1) to afford **9** (202 mg, 62%) as a yellow oil. TLC R_f 0.23 (silica gel, AcOEt/petroleum ether, 2:3); IR (film) 1754, 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.19 (m, 5H, Ph), 4.44 (d, 1H, J=15.4 Hz, CH_2Ph), 4.35 (d, 1H, J=15.4 Hz, CH_2Ph), 3.59 (s, 3H, CO_2Me), 3.51 (s, 3H, CO_2Me), 3.24 (d, 1H, J=14.7 Hz, H-3a), 2.84 (d, 1H, J=14.7 Hz, H-3b), 2.31–1.86 (m, 4H, H-1′, H-2′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6 (CO), 171.4 (CO), 166.0 (C-2), 135.9 (Cq–Ar), 128.83 (2CH–Ar), 128.75 (2CH–Ar), 127.9 (1CH–Ar), 61.8 (C-4), 52.6 (OCH_3), 52.0 (OCH_3), 45.9 (*C*H_2Ph), 45.1 (C-3), 28.8 (C-1′ or C-2′), 28.5 (C-1′ or C-2′); HRMS (ESI) $[M+Na]^+$ calcd for $C_{16}H_{19}NO_5Na$: 328.116, found 328.113.

4.1.15. (1S,5S*)-N-Benzyl-5-(hydroxymethyl)-6-azabicyclo[3.2.0] heptan-2,7-dione (**14**).* To a solution of **9** (150 mg, 0.49 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) cooled to 0 °C, was added NEt_3 (274 μL, 1.97 mmol, 4 equiv) and TMSOTf (267 μL, 1.47 mmol, 3 equiv). The solution was stirred at rt for 24 h. Saturated aqueous $NaHCO_3$ (1 mL)

was added and the product was extracted with CH_2Cl_2 (3×3 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether+1% NEt_3, 1:7) to afford **10** and **11** (131 mg, mixture of diastereomers) as a colorless oil. HRMS (ESI) $[M+Na]^+$ calcd for $C_{22}H_{35}NO_5Si_2Na$: 472.195, found 472.193; HRMS (ESI) $[M+Na]^+$ calcd for $C_{19}H_{27}NO_5SiNa$: 400.155, found 400.154.

Analytical samples of two diastereomers of **10** were obtained after a careful purification.

Compound **10a**: colorless oil. TLC R_f 0.70 (silica gel, AcOEt/petroleum ether, 1:3); IR (film) 1761, 1742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5H, Ph), 4.63 (d, 1H, J=14.9 Hz, CH_2Ph), 4.27 (d, 1H, J=14.9 Hz, CH_2Ph), 3.79 (s, 1H, H-1), 3.65 (s, 3H, CO_2Me), 3.17 (s, 3H, OCH_3), 1.79 (t, 1H, J=13.5 Hz, H-3), 1.48–1.30 (m, 2H, H-4), 0.25 (s, 9H, OTMS), −0.10 (s, 9H, C-TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (CO), 165.1 (C-7), 136.3 (Cq–Ar), 129.0 (2CH–Ar), 128.0 (2CH–Ar), 127.8 (1CH–Ar), 107.6 (C-2), 68.9 (C-5), 63.8 (C-1), 52.4 (OCH_3), 49.4 (OCH_3), 44.8 (CH_2Ph), 37.4 (C-3), 29.5 (C-4), 2.0 ($Si(CH_3)_3$), −1.1 ($Si(CH_3)_3$); HRMS (ESI) $[M+Na]^+$ calcd for $C_{22}H_{35}NO_5Si_2Na$: 472.195, found 472.193.

Compound **10b**: white powder. TLC R_f 0.59 (silica gel, AcOEt/petroleum ether, 1:3); IR (film) 1762, 1743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5H, Ph), 4.71 (d, 1H, J=14.9 Hz, CH_2Ph), 4.20 (d, 1H, J=14.9 Hz, CH_2Ph), 3.76 (s, 1H, H-1), 3.69 (s, 3H, CO_2Me), 3.45 (s, 3H, OCH_3), 1.80 (t, 1H, J=15.2 Hz, H-3), 1.48–1.36 (m, 2H, H-4), 0.15 (s, 9H, OTMS), −0.12 (s, 9H, C-TMS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4 (CO), 164.5 (C-7), 135.9 (Cq–Ar), 129.0 (2CH–Ar), 128.9 (2CH–Ar), 128.1 (1CH–Ar), 109.3 (C-2), 68.6 (C-5), 68.0 (C-1), 52.9 (OCH_3), 52.4 (OCH_3), 44.9 (CH_2Ph), 35.8 (C-3), 29.9 (C-4), 2.2 ($Si(CH_3)_3$), −1.3 ($Si(CH_3)_3$); HRMS (ESI) $[M+Na]^+$ calcd for $C_{22}H_{35}NO_5Si_2Na$: 472.195, found 472.193.

To a solution of $LiBH_4$ (25 mg) in Et_2O (5.5 mL), was added a solution of **10** and **11** (131 mg) in Et_2O (2.3 mL). The solution was stirred at rt for 8 h. The solution was filtered and washed with Et_2O then with MeOH. The solution was concentrated under reduced pressure and dissolved with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether gradient+1% NEt_3, 1:5 to 1:0) to afford **12** and **13** (91 mg, mixture of diastereomers) as a colorless oil. IR (film) 3410, 1728 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{21}H_{35}NO_4Si_2Na$: 444.200, found 444.198; HRMS (ESI) $[M+Na]^+$ calcd for $C_{18}H_{27}NO_4SiNa$: 372.160, found 372.159.

To a solution of **12** and **13** (91 mg) in THF (4 mL), was added HCl 1 N (0.5 mL). The mixture was stirred at rt for 5 h. Saturated aqueous $NaHCO_3$ (2 mL) was added and the product was extracted with CH_2Cl_2 (3×3 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (MeOH/CH_2Cl_2, 5:95) to afford **14** (43 mg, 36% in three steps) as a white solid. TLC R_f 0.18 (silica gel, MeOH/CH_2Cl_2, 5:95); IR (film) 1743, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.19 (m, 5H, Ph), 4.43 (d, 1H, J=15.2 Hz, CH_2Ph), 4.31 (d, 1H, J=15.2 Hz, CH_2Ph), 3.71–3.55 (m, 2H, CH_2OH), 3.50 (s, 1H, H-1), 2.53 (m, 1H, H-3a), 2.27 (m, 1H, H-3b), 1.90 (ddd, 1H, J=14.2, 9.1, 1.1 Hz, H-4a), 1.69 (m, 1H, H-4b), 1.36 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3 (CO), 160.5 (C-7), 136.1 (Cq–Ar), 129.3 (2CH–Ar), 128.52 (2CH–Ar), 128.49 (1CH–Ar), 68.4 (C-5), 66.2 (C-1), 63.5 (CH_2OH), 44.7 (CH_2Ph), 36.2 (C-3), 24.5 (C-4); HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{15}NO_3Na$: 268.094, found 268.091.

4.1.16. (1R,3R*)-1-Methoxycarbonyl-5-azaspiro[2.4]heptan-4-one (**15**) and methyl 2-oxo-1-azabicyclo[3.2.0]heptane-5-carboxylate (**16**).* To a solution of azetidine **6** (90 mg, 0.45 mmol, 1 equiv) in CH_2Cl_2 (1 mL) cooled to 0 °C was added NEt_3 (156 μL, 1.12 mmol, 2.5 equiv) and TMSOTf (162 μL, 0.89 mmol, 2 equiv). The solution was stirred at rt for 24 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$ and was extracted with CH_2Cl_2 (3×2 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (MeOH/CH_2Cl_2+1% NEt_3, 0:100 to 5:95) to afford **15** (16 mg, 21%) as a colorless oil and **16** (15 mg, 20%) as a yellow oil.

Compound **15**: TLC R_f 0.27 (silica gel, MeOH/CH_2Cl_2, 5:95); IR (film) 1728, 1698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (br s, 1H, NH), 3.72 (s, 3H, CO_2Me), 3.47 (m, 2H, H-6), 2.33 (m, 2H, H-7), 2.21 (dd, 1H, J=8.9, 6.1 Hz, H-1), 1.52 (dd, 1H, J=8.9, 4.1 Hz, H-2a), 1.36 (dd, 1H, J=6.0, 4.0 Hz, H-2b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0 (CO), 172.0 (NCO), 52.1 (C-1), 39.7 (C-6), 30.4 (C-3), 25.2 (C-7), 19.0 (C-2); HRMS (ESI) $[M+Na]^+$ calcd for $C_8H_{11}NO_3Na$: 192.063, found 192.065.

Compound **16**: TLC R_f 0.43 (silica gel, MeOH/CH_2Cl_2, 5:95); IR (film) 1735, 1706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (m, 1H, H-7a), 3.90 (td, 1H, J=9.6, 4.5 Hz, H-7b), 3.83 (s, 3H, CO_2Me), 2.88 (m, 1H, H-6a), 2.81–2.56 (m, 3H, H-4+H-6b), 2.44–2.20 (m, 2H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.7 (CO), 173.4 (NCO), 71.1 (C-5), 52.9 (OCH_3), 48.6 (C-7), 34.8 (C-3 or C-4), 34.4 (C-3 or C-4), 31.8 (C-6); HRMS (ESI) $[M+Na]^+$ calcd for $C_8H_{11}NO_3Na$: 192.063, found 192.061.

*4.1.17. Methyl N-benzyl-2-(4-methoxycarbonylpropyl)azetidine-2-carboxylate (**17**).* A solution of LDA (1.07 mmol, 1.1 equiv) [prepared from diisopropylamine (0.15 mL, 1.07 mmol) in THF (2.5 mL) and *n*-BuLi (1.5 M in hexane, 0.7 mL, 1.07 mmol) stirred at −78 °C for 30 min] was added to a solution of **4** (200 mg, 0.97 mmol, 1 equiv) in THF (1.4 mL), cooled to −78 °C. The reaction mixture was allowed to warm up to −65 °C (l h), cooled again to −78 °C and a mixture of methyl 4-bromobutyrate (0.37 mL, 2.92 mmol, 3 equiv) and HMPA (1.1 mL, 6.14 mmol, 6.3 equiv) in THF (2.3 mL) was added. The solution was allowed to warm to rt and then stirred for 16 h. Then the reaction was quenched with saturated aqueous NH_4Cl and was extracted with Et_2O (3×3 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:9 to 1:1) to afford **17** (32 mg, 11%) as a yellow oil. TLC R_f 0.66 (silica gel, AcOEt/petroleum ether, 1:2); IR (film) 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.16 (m, 5H, Ph), 3.76 (s, 3H, CO_2Me), 3.68 (d, 1H, J=12.9 Hz, CH_2Ph), 3.67 (s, 3H, CO_2Me), 3.59 (d, 1H, J=12.9 Hz, CH_2Ph), 3.20–3.08 (m, 2H, H-4), 2.52 (m, 1H, H-3a), 2.34 (t, 2H, J=7.4 Hz, H-3′), 2.02 (m, 1H, H-3b), 1.92 (dd, 1H, J=11.6, 5.2 Hz, H-1′a), 1.82 (m, 1H, H-1′b), 1.67 (m, 1H, H-2′a), 1.53 (m, 1H, H-2′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (2 CO), 138.5 (Cq–Ar), 128.6 (2CH–Ar), 128.3 (2CH–Ar), 127.0 (1CH–Ar), 72.1 (C-2), 56.1 (CH_2Ph), 51.7 (OCH_3), 51.6 (OCH_3), 49.8 (C-4), 34.2 (C-1′ or C-3′), 34.0 (C-1′ or C-3′), 26.0 (C-3), 19.6 (C-2′); HRMS (ESI) $[M+Na]^+$ calcd for $C_{17}H_{23}NO_4Na$: 328.152, found 328.151.

*4.1.18. Methyl N-benzyl-2-(6-methoxycarbonylpentyl)azetidine-2-carboxylate (**18**).* A solution of LDA (1.07 mmol, 1.1 equiv) [prepared from diisopropylamine (0.15 mL, 1.07 mmol) in THF (2.5 mL) and *n*-BuLi (1.5 M in hexane, 0.7 mL, 1.07 mmol) stirred at −78 °C for 30 min] was added to a solution of **4** (200 mg, 0.97 mmol, 1 equiv) in THF (1.4 ml), cooled to −78 °C. The reaction mixture was allowed to warm up to −65 °C (l h), cooled again to −78 °C and a mixture of methyl 6-bromohexanoate (0.46 mL, 2.92 mmol, 3 equiv) and HMPA (1.1 mL, 6.14 mmol, 6.3 equiv) in THF (2.3 mL) was added. The solution was allowed to warm to rt and then stirred for 16 h. Then the reaction was quenched with saturated aqueous NH_4Cl and was extracted with Et_2O (3×3 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under

reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:9 to 1:1) to afford **18** (45 mg, 14%) as a pale yellow oil. TLC R_f 0.67 (silica gel, AcOEt/petroleum ether, 1:2); IR (film) 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5H, Ph), 3.75 (s, 3H, CO_2Me), 3.66 (s, 3H, CO_2Me), 3.67–3.62 (m, 2H, CH_2Ph), 3.19–3.05 (m, 2H, H-4), 2.52 (m, 1H, H-3a), 2.30 (t, 2H, J=7.43 Hz, H-5′), 2.04–1.86 (m, 2H, H-3b+H-1′a), 1.79 (m, 1H, H-1′b), 1.70–1.56 (m, 2H, H-4′), 1.43–1.02 (m, 4H, H-2′, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3 (CO), 174.2 (CO), 138.7 (Cq–Ar), 128.7 (2CH–Ar), 128.4 (2CH–Ar), 127.0 (1CH–Ar), 72.3 (C-2), 56.1 (CH_2Ph), 51.61 (OCH_3), 51.56 (OCH_3), 49.8 (C-4), 34.1 (C-5′), 29.6 (C-1′), 26.3 (C-2′, C-4′), 25.0 (C-3), 23.7 (C-3′); HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{28}NO_4$: 334.201, found 334.201.

*4.1.19. Methyl N-benzyl-2-(3-methoxycarbonyl-1-methylethyl)azetidine-2-carboxylate (**19**).* A solution of **4** (200 mg, 0.97 mmol, 1 equiv) in THF (2.4 mL) was added to a solution of LDA (1.07 mmol, 1.1 equiv) cooled to −40 °C [prepared from diisopropylamine (0.15 mL, 1.07 mmol) in THF (2.5 mL) and *n*-BuLi (1.5 M in hexane, 0.7 mL, 1.07 mmol) stirred at −78 °C for 30 min]. The reaction mixture was stirred for 50 min and then warmed up to −5 °C. A solution of methyl 3-bromo-3-methylpropionate (185 mg, 1.02 mmol, 1.05 equiv) in THF (1 mL) was added. The solution was allowed to warm to rt and then stirred for 16 h. Then the reaction was quenched with brine and was extracted with Et_2O (3×3 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:7 to 1:3) to afford **19** (37 mg, 12%) as a yellow oil. TLC R_f 0.73 (silica gel, AcOEt/petroleum ether, 1:2); IR (film) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5H, Ph), 3.85 (d, 1H, J=13.2 Hz, CH_2Ph), 3.81 (s, 3H, CO_2Me), 3.66 (s, 3H, CO_2Me), 3.28 (d, 1H, J=13.2 Hz, CH_2Ph), 3.18 (m, 1H, H-4a), 2.98 (m, 1H, H-4b), 2.57 (m, 1H, C$H(CH_3)$), 2.48–2.36 (m, 2H, H-3a, CH_2CO_2Me), 2.25–2.13 (m, 1H, CH_2CO_2Me), 2.06 (m, 1H, H-3b), 1.04 (d, 3H, J=6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (CO), 172.8 (CO), 138.5 (Cq–Ar), 128.45 (2CH–Ar), 128.40 (2CH–Ar), 127.0 (1CH–Ar), 75.8 (C-2), 57.6 (CH_2Ph), 51.7 (OCH_3), 51.5 (OCH_3), 49.8 (C-4), 36.7 (C$H(CH_3)$), 36.3 (CH_2CO_2Me), 23.9 (C-3), 14.4 (CH_3); HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{24}NO_4$: 306.170, found 306.170.

*4.1.20. Methyl N-benzyl-2-(3-methoxycarbonyl-(S)-2-methylethyl) azetidine-2-carboxylate (**20**).* A solution of LDA (1.07 mmol, 1.1 equiv) [prepared from diisopropylamine (0.15 mL, 1.07 mmol) in THF (2.5 mL) and *n*-BuLi (1.38 M in hexane, 0.77 mL, 1.07 mmol) stirred at −78 °C for 30 min] was added to a solution of **4** (200 mg, 0.97 mmol, 1 equiv) in THF (1.3 mL), cooled to −78 °C. The reaction mixture was allowed to warm up to −65 °C (l h), cooled again to −78 °C and a mixture of methyl (*R*)-(+)-3-bromo-2-methylpropionate (0.37 mL, 2.92 mmol, 3 equiv) and HMPA (1.1 mL, 6.14 mmol, 6.3 equiv) in THF (2.3 mL) was added. The solution was allowed to warm to rt and then stirred for 16 h. Then the reaction was quenched with saturated aqueous NH_4Cl and was extracted with Et_2O (3×3 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:9 to 1:3) to afford **20** (41 mg, 14%) as a yellow oil. TLC R_f 0.58 (silica gel, AcOEt/petroleum ether, 1:3); IR (film) 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H, Ph), 3.77 (s, 3H, CO_2Me), 3.72 (d, 1H, J=12.9 Hz, CH_2Ph), 3.65 (s, 3H, CO_2Me), 3.50 (d, 1H, J=12.9 Hz, CH_2Ph), 3.21–3.10 (m, 2H, H-4), 2.65 (m, 1H, C$H(CH_3)$), 2.52 (m, 1H, H-3a), 2.41 (dd, 1H, J=13.9, 7.6 Hz, CH_2CH), 2.07 (m, 1H, H-3b), 1.88 (dd, 1H, J=13.9, 5.7 Hz, CH_2CH), 1.19 (d, 3H, J=7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0 (CO), 173.4 (CO), 138.4 (Cq–Ar), 128.7 (2CH–Ar), 128.4 (2CH–Ar), 127.1 (1CH–Ar), 71.9 (C-2), 56.0 (CH_2Ph), 51.8 (OCH_3), 51.6 (OCH_3), 50.1 (C-4), 38.6 (CH_2CH), 35.7 (C$H(CH_3)$), 26.7 (C-3), 18.8 (CH_3); HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{24}NO_4$: 306.170, found 306.169.

*4.1.21. N-Benzyl-5-methoxy-5-(trimethylsilyl)oxy-6-methoxycarbonyl-1-aza-spiro[3.4]octane (**21**).* To a solution of azetidine **17** (32 mg, 0.10 mmol, 1 equiv) in CH_2Cl_2 (1 mL) cooled to 0 °C was added TEA (37 μL, 0.26 mmol, 2.5 equiv) and TMSOTf (38 μL, 0.21 mmol, 2 equiv). The solution was stirred at rt for 24 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$ and was extracted with CH_2Cl_2 (3×2 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/pentane, 1:7 to 1:5) to afford **21** (16 mg, 40%) as a yellow oil: TLC R_f 0.72 (silica gel, AcOEt/petroleum ether, 1:2); IR (film) 1741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.11 (m, 5H, Ph), 4.01 (d, 1H, J=13.2 Hz, CH_2Ph), 3.62 (s, 3H, CO_2Me), 3.37 (d, 1H, J=13.0 Hz, CH_2Ph), 3.24 (s, 3H, OCH_3), 3.10–2.95 (m, 2H, H-2a, H-6), 2.74 (m, 1H, H-2b), 2.27–1.88 (m, 4H, H-3a, H-7a, H-8), 1.75 (m, 1H, H-7b), 1.57 (m, 1H, H-3b), 0.23 (s, 9H, $SiMe_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 172.7 (CO), 139.4 (Cq–Ar), 128.9–126.9 (5CH–Ar), 109.8 (C-5), 76.6 (C-4), 57.7 (CH_2Ph), 51.1 (OCH_3), 49.6 (OCH_3), 49.3 (C-2), 46.5 (C-6), 27.2 (C-8), 25.2 (C-3), 20.9 (C-7), 2.3 (Si(CH_3)$_3$); HRMS (ESI) $[M+H]^+$ calcd for $C_{20}H_{32}NO_4Si$: 378.210, found 378.212.

*4.1.22. tert-Butyl N-benzylazetidine-2-carboxylate (**22**).* To a solution of *tert*-butyl 1,3-dibromopropionate (0.2 mL, 1.03 mmol, 1 equiv) in CH_3CN (1.1 mL), was added benzylamine (0.34 mL, 3.10 mmol, 3 equiv). The solution was stirred at rt for 1 h then heated at 55 °C and stirred for 24 h. After cooling, 5% aqueous $NaHCO_3$ (5 mL) was added and the product was extracted with Et_2O (3×3 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:7 to 1:5) to afford azetidine **22** (163 mg, 64%) as a yellow oil. TLC R_f 0.42 (silica gel, AcOEt/petroleum ether, 1:3); IR (film) 1738, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.16 (m, 5H, Ph), 3.80 (d, 1H, J=12.6 Hz, CH_2Ph), 3.58 (t, 1H, J=8.4 Hz, H-2), 3.51 (d, 1H, J=12.6 Hz, CH_2Ph), 3.24 (m, 1H, H-4a), 2.85 (m, 1H, H-4b), 2.29 (m, 1H, H-3a), 2.11 (m, 1H, H-3b), 1.37 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (CO), 137.6 (Cq–Ar), 129.3 (2CH–Ar), 128.4 (2CH–Ar), 127.3 (1CH–Ar), 80.8 (C(CH_3)$_3$), 65.3 (C-2), 62.6 (CH_2Ph), 50.8 (C-4), 28.1 (C(CH_3)$_3$), 21.6 (C-3); HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{22}NO_2$: 248.165, found 248.165.

*4.1.23. tert-Butyl N-benzyl-2-(3-methoxycarbonylethyl)azetidine-2-carboxylate (**23**).* A solution of LDA (1.11 mmol, 1.1 equiv) [prepared from diisopropylamine (0.16 mL, 1.11 mmol) in THF (3 mL) and *n*-BuLi (1.43 M in hexane, 0.77 mL, 1.11 mmol) stirred at −78 °C for 30 min] was added to a solution of **22** (250 mg, 1.01 mmol, 1 equiv) in THF (1.3 mL), cooled to −78 °C. The reaction mixture was allowed to warm up to −65 °C (l h), cooled again to −78 °C and a mixture of methyl 3-bromopropionate (0.3 mL, 3.03 mmol, 3 equiv) and HMPA (1.1 mL, 6.37 mmol, 6.3 equiv) in THF (2.5 mL) was added. The solution was allowed to warm to rt and then stirred for 16 h. Then the reaction was quenched with saturated aqueous NH_4Cl and was extracted with Et_2O (3×4 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:9 to 1:7) to afford **23** (96 mg, 28%) as a yellow oil. TLC R_f 0.57 (silica gel, AcOEt/petroleum ether, 1:3); IR (film) 1738, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.16 (m, 5H, Ph), 3.71 (d, 1H, J=12.9 Hz, CH_2Ph), 3.66 (s, 3H, CO_2Me), 3.65 (d, 1H, J=12.9 Hz, CH_2Ph), 3.13 (m, 2H, H-4), 2.50–2.05 (m, 5H, H-3a, H-1′, H-2′), 1.94 (m, 1H, H-3b), 1.51 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0 (CO), 172.3 (CO), 138.7 (Cq–Ar), 128.6 (2CH–Ar), 128.4 (2CH–Ar), 127.0 (1CH–Ar), 81.5 (C(CH_3)$_3$), 71.9 (C-

2), 55.9 (CH_2Ph), 51.8 (OCH_3), 49.8 (C-4), 29.6 (C-1′ or C-2′), 29.1 (C-1′ or C-2′), 28.4 ($C(CH_3)_3$), 25.7 (C-3); HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{28}NO_4$: 334.201, found 334.200.

*4.1.24. Methyl N-benzyl-2-(3-methoxycarbonylethyl)pyrrolidine-2-carboxylate (**25**).* A solution of LDA (1.00 mmol, 1.1 equiv) [prepared from diisopropylamine (0.14 mL, 1.00 mmol) in THF (2.8 mL) and *n*-BuLi (1.4 M in hexane, 0.7 mL, 1.00 mmol) stirred at −78 °C for 30 min] was added to a solution of **24** (200 mg, 0.91 mmol, 1 equiv) in THF (1.1 mL), cooled to −78 °C. The reaction mixture was allowed to warm up to −65 °C (l h), cooled again to −78 °C and a mixture of methyl 3-bromopropionate (0.3 mL, 2.74 mmol, 3 equiv) and HMPA (1.0 mL, 5.75 mmol, 6.3 equiv) in THF (2.3 mL) was added. The solution was allowed to warm to rt and then stirred for 16 h. Then the reaction was quenched with saturated aqueous NH_4Cl and was extracted with Et_2O (3×4 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 0:100 to 20:80) to afford **25** (125 mg, 45%) as a yellow oil. TLC R_f 0.57 (silica gel, AcOEt/petroleum ether, 1:3); IR (film) 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.18 (m, 5H, Ph), 3.94 (d, 1H, *J*=13.5 Hz, CH_2Ph), 3.74 (s, 3H, CO_2Me), 3.68 (s, 3H, CO_2Me), 3.30 (d, 1H, *J*=13.5 Hz, CH_2Ph), 2.92 (m, 1H, H-5a), 2.61–2.33 (m, 3H, H-5b, H-1′ or H-2′), 2.33–2.14 (m, 2H, H-3a, H-1′a or H-2′a), 2.07 (m, 1H, H-1′b or H-2′b), 1.89–1.63 (m, 3H, H-3b, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (CO), 174.4 (CO), 140.1 (Cq–Ar), 128.37 (2CH–Ar), 128.36 (2CH–Ar), 126.9 (1CH–Ar), 70.0 (C-2), 53.4 (CH_2Ph), 51.8 (CH_3), 51.5 (C-5), 51.4 (CH_3), 33.9 (C-3), 29.6 (C-1′ or C-2′), 29.4 (C-1′ or C-2′), 22.0 (C-4); HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{24}NO_4$: 306.170, found 306.170.

*4.1.25. Ethyl N-benzyl-2-(3-ethylthiocarbonylethyl)azetidine-2-carboxylthioate (**26**).* To a solution of $AlMe_3$ (2 M in toluene, 0.69 mL, 1.37 mmol, 4 equiv) in CH_2Cl_2 (1.4 mL) cooled to 0 °C, was added EtSH (0.1 mL, 1.37 mmol, 4 equiv). The solution was stirred at rt for 15 min. A solution of **1** (100 mg, 0.34 mmol, 1 equiv) in CH_2Cl_2 (0.2 mL) was added. The solution was stirred for 25 h. After cooling to 0 °C, Et_2O (3 mL) followed by saturated aqueous NH_4Cl (1 mL) were added. The solution was stirred and then filtered. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:0 to 1:9) to afford **26** (45 mg, 37%) as a yellow oil. TLC R_f 0.56 (silica gel, AcOEt/petroleum ether, 1:2); IR (film) 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.20 (m, 5H, Ph), 3.98 (d, 1H, *J*=12.6 Hz, CH_2Ph), 3.59 (d, 1H, *J*=12.6 Hz, CH_2Ph), 3.22 (m, 1H, H-4a), 3.06 (m, 1H, H-4b), 2.90 (q, 2H, *J*=7.4 Hz, CH_2CH_3), 2.88–2.78 (m, 3H, H-2′a, CH_2CH_3), 2.69 (m, 1H, H-2′b), 2.43–2.24 (m, 3H, H-3, H-1′a), 2.03 (m, 1H, H-1′b), 1.32–1.22 (m, 6H, $2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0 (CO), 199.1 (CO), 137.9 (Cq–Ar), 128.8 (2CH–Ar), 128.5 (2CH–Ar), 127.2 (1CH–Ar), 74.8 (C-2), 55.1 (CH_2Ph), 48.6 (C-4), 39.5 (C-2′), 27.7 (C-1′), 26.5 (C-3), 23.5 (CH_2CH_3), 23.1 (CH_2CH_3), 14.9 (CH_2CH_3), 14.7 (CH_2CH_3); HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{26}NO_2S_2$: 352.140, found 352.135.

*4.1.26. Methyl 3-(1-benzylazetidin-2-yl)acrylate (**27**).* To a solution of azetidine **4** (285 mg, 1.40 mmol, 1 equiv) in THF (3 mL) cooled to −78 °C was added DIBAL-H (1 M in hexane, 2.2 mL, 2.2 mmol, 1.6 equiv). The solution was stirred at this temperature for 4 h. Then the reaction was quenched with MeOH (0.3 mL) and the solution was allowed to warm to 0 °C. Saturated aqueous NH_4Cl (0.7 mL) was added and the solution was stirred 15 min then filtered and concentrated to afford the corresponding aldehyde, which was used without purification for the Wittig reaction. To a solution of the aldehyde in CH_2Cl_2 (13 mL) cooled to 0 °C was added portionwise $Ph_3P{=}CHCO_2Me$ (1 g, 2.99 mmol, 2.1 equiv). The solution was allowed to warm to rt and stirred for 16 h. Saturated aqueous NH_4Cl was added at 0 °C and the reaction mixture was extracted with CH_2Cl_2 (3×2 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:4 to 1:3) to afford (*E*)-**27** (160 mg, 50%) and (*Z*)-**27** (72 mg, 22%) as yellow oils.

(*E*)-**27**: TLC R_f 0.40 (silica gel, AcOEt/petroleum ether, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.19 (m, 5H, Ph), 6.93 (dd, 1H, *J*=15.7, 5.6 Hz, C*H*=CHCO$_2$Et), 5.97 (dd, 1H, *J*=15.7, 1.3 Hz, CH=C*H*CO$_2$Et), 3.81–3.67 (m, 2H, H-2, CH_2Ph), 3.72 (s, 3H, CO_2Me), 3.44 (d, 1H, *J*=12.8 Hz, CH_2Ph), 3.33–3.24 (m, 1H, H-4a), 2.94–2.83 (m, 1H, H-4b), 2.25–2.13 (m, 1H, H-3a), 2.11–1.96 (m, 1H, H-3b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2 (CO), 149.2 (CH=CHCO$_2$Et), 137.8 (*C*q–Ar), 128.9 (2*C*H–Ar), 128.4 (2*C*H–Ar), 127.3 (1*C*H–Ar), 120.4 (CH=*C*HCO$_2$Et), 65.5 (C-2), 62.1 (CH_2Ph), 51.5 (OCH_3), 51.3 (C-4), 24.9 (C-3); LRMS (ESI): *m*/*z* 232.0 $[M+H]^+$. Spectroscopic data are in accordance with literature data.[22]

(*Z*)-**27**: TLC R_f 0.30 (silica gel, AcOEt/petroleum ether, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.17 (m, 5H, Ph), 6.26 (dd, 1H, *J*=11.7, 7.2 Hz, C*H*=CHCO$_2$Et), 5.57 (dd, 1H, *J*=11.5, 1.5 Hz, CH=C*H*CO$_2$Et), 4.74–4.62 (m, 1H, H-2), 3.70 (s, 3H, CO_2Me), 3.64 (d, 1H, *J*=12.4 Hz, CH_2Ph), 3.57 (d, 1H, *J*=12.5 Hz, CH_2Ph) 3.39–3.29 (m, 1H, H-4a), 2.99–2.82 (m, 1H, H-4b), 2.41–2.29 (m, 1H, H-3a), 2.09–1.93 (m, 1H, H-3b).

*4.1.27. N-Benzyl-2-methoxycarbonylethylazetidine (**28**).* To a solution of (*E*)-**27** (74 mg, 0.32 mmol 1 equiv) in MeOH (2 mL) cooled to 0 °C, was added CuCl (54 mg, 0.54 mmol, 1.7 equiv). After 1 or 2 min, $NaBH_4$ (24 mg, 0.63 mmol, 2 equiv) was added. The solution was stirred 4 h at 0 °C. The reaction mixture was diluted with ether and saturated aqueous NH_4Cl was added. The mixture was extracted with AcOEt (3×2 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:5 to 1:0) to afford desired product **28** (30 mg, 41%). TLC R_f 0.15 (silica gel, AcOEt/petroleum ether, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.19 (m, 5H, Ph), 3.71 (d, 1H, *J*=12.7 Hz, CH_2Ph), 3.65 (s, 3H, CO_2Me), 3.44 (d, 1H, *J*=12.7 Hz, CH_2Ph), 3.33–3.12 (m, 2H, C*H*N), 2.84–2.73 (m, 1H, C*H*N), 2.38–2.17 (m, 2H), 2.07–1.95 (m, 1H), 1.90–1.71 (m, 3H). Spectroscopic data are in accordance with literature data.[22]

*4.1.28. 1-Methoxycarbonyl-2-(2-benzylamino)ethylcyclopropane (**29a**).* To a solution of **28** (85 mg, 0.36 mmol, 1 equiv) in CH_2Cl_2 (1 mL) cooled to 0 °C was added NEt_3 (0.13 mL, 0.91 mmol, 2.5 equiv) and TMSOTf (0.13 mL, 0.73 mmol, 2 equiv). The solution was stirred at rt for 24 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$ and was extracted with CH_2Cl_2 (3×2 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography ($MeOH/CH_2Cl_2$, 1:99 to 10:90) to afford **29a** (52 mg, 61%, 56% de) as a yellow oil. TLC R_f 0.33 (silica gel, $MeOH/CH_2Cl_2$, 1:9); IR (film) 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.18 (m, 5H, Ph), 3.85 (s, 2H, CH_2Ph), 3.66 (s, 3H, CO_2Me), 2.76 (t, 2H, *J*=7.4 Hz, H-5), 1.67–1.51 (m, 2H, H-4), 1.45–1.32 (m, 2H, H-1, H-2), 1.17 (m, 1H, H-3a), 0.73 (m, 1H, H-3b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (CO), 140.1 (Cq–Ar), 128.5 (2CH–Ar), 128.2 (2CH–Ar), 127.1 (1CH–Ar), 54.0 (CH_2Ph), 51.8 (OCH_3), 48.8 (C-5), 33.4 (C-4), 20.9 (C-1 or C-2), 19.9 (C-1 or C-2), 15.4 (C-3); HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{20}NO_2$: 234.159, found 234.151.

*4.1.29. Methyl 2-(2-(N-benzylacetamido)ethyl)cyclopropanecarboxylate (**29b**).* To a solution of **29a** (52 mg, 0.22 mmol, 1 equiv) in CH_2Cl_2 (1.4 mL), was added Ac_2O (23 μL, 0.24 mmol, 1.1 equiv). The solution

was stirred at rt for 24 h and then concentrated. Et_2O (3 mL) was added and the organic phase was washed with saturated aqueous $NaHCO_3$ (2×2 mL) and with water (2 mL). The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:5 to 1:0) to afford **29b** (41 mg, 67%, 56% de) as a yellow oil. TLC R_f 0.19 (silica gel, AcOEt/petroleum ether, 1:1); IR (film) 1723, 1641 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 373 K) δ 7.37–7.20 (m, 5H, Ph), 4.59–4.45 (m, 2H, CH_2Ph), 3.60 (s, 3H, CO_2Me), 3.42–3.21 (m, 2H, CH_2NBnAc), 2.05 (s, 3H, $COCH_3$), 1.59–1.48 (m, 2H, CHCH_2CH_2N), 1.42 (m, 1H, CHCO_2Me), 1.31–1.20 (m, 1H, CH), 1.03 (m, 1H, CHCH_2CH), 0.82–0.70 (m, 1H, CHCH_2CH); HRMS (ESI) $[M+Na]^+$ calcd for $C_{16}H_{21}NO_3Na$: 298.141, found 298.142.

*4.1.30. Methyl (2R,5R)-α-methylbenzylazetidine-2-carboxylate (**30a**) and methyl (2S,5R)-α-methylbenzylazetidine-2-carboxylate (**30b**).* To a solution of K_2CO_3 (1.5 g, 10.6 mmol, 1 equiv) in CH_3CN/H_2O (1:5, 30 mL), were added methyl 1,3-dibromopropionate (1.5 mL, 10.6 mmol, 1 equiv) and (*R*)-(+)-α-methylbenzylamine (1.4 mL, 10.6 mmol, 1 equiv). The solution was heated to reflux and stirred for 6.5 h. After cooling, water (10 mL) was added and the product was extracted with Et_2O (3×8 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/petroleum ether, 1:7 to 1:2) to afford azetidines **30a** (735 mg, 32%) and **30b** (734 mg, 32%) as yellow oils.

Compound **30a**: TLC R_f 0.54 (silica gel, AcOEt/petroleum ether, 1:2); $[\alpha]_D^{20}$ +122 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.16 (m, 5H, Ph), 3.73–3.65 (m, 1H, H-2), 3.69 (s, 3H, CO_2Me), 3.39 (q, 1H, *J*=6.6 Hz, H-5), 3.05 (m, 1H, H-4a), 2.74 (m, 1H, H-4b), 2.29–2.05 (m, 2H, H-3), 1.16 (d, 3H, *J*=6.6 Hz, CH_3). Spectroscopic data are in accordance with literature data.[27]

Compound **30b**: TLC R_f 0.30 (silica gel, AcOEt/petroleum ether, 1:2) $[\alpha]_D^{20}$ −31 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.16 (m, 5H, Ph), 3.63–3.52 (m, 2H, H-2, H-4a), 3.41–3.29 (m, 1H, H-5), 3.33 (s, 3H, CO_2Me), 3.01 (m, 1H, H-4b), 2.30 (m, 1H, H-3a), 2.13 (m, 1H, H-3b), 1.28 (d, 3H, *J*=6.4 Hz, CH_3). Spectroscopic data are in accordance with literature data.[27]

*4.1.31. Methyl N-(R)-α-methylbenzyl-2-(3-methoxycarbonylethyl) azetidine-2-carboxylate (**31**).* A solution of LDA (3.01 mmol, 1.1 equiv) [prepared from diisopropylamine (0.42 mL, 3.01 mmol) in THF (7 mL) and *n*-BuLi (1.56 M in hexane, 1.9 mL, 3.01 mmol) stirred at −78 °C for 30 min] was added to a solution of **30** (600 mg, 2.74 mmol, 1 equiv) in THF (3.6 mL), cooled to −78 °C. The reaction mixture was allowed to warm up to −65 °C (l h), cooled again to −78 °C and a mixture of methyl 3-bromopropionate (0.9 mL, 8.21 mmol, 3 equiv) and HMPA (3.0 mL, 17.2 mmol, 6.3 equiv) in THF (6.5 mL) was added. The solution was allowed to warm to rt and then stirred for 16 h. Then the reaction was quenched with saturated aqueous NH_4Cl and was extracted with Et_2O (3×6 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2) to afford **31a** (147 mg, 18%) and **31b** (36 mg, 4%) as yellow oils.

Compound **31a**: TLC R_f 0.67 (silica gel, Et_2O/CH_2Cl_2, 1:5); $[\alpha]_D^{20}$ +64 (*c* 1.0, $CHCl_3$); IR (film) 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.16 (m, 5H, Ph), 3.70 (s, 3H, CO_2Me), 3.64 (s, 3H, CO_2Me), 3.62 (m, 1H, CHCH_3), 3.37–3.27 (m, 2H, H-4), 2.37–2.15 (m, 3H, H-3a, H-2′), 2.00 (m, 1H, H-3b), 1.85–1.61 (m, 2H, H-1′), 1.18 (d, 1H, *J*=3.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (CO), 173.2 (CO), 144.0 (Cq–Ar), 128.0 (2CH–Ar), 127.6 (2CH–Ar), 127.3 (1CH–Ar), 71.6 (C-2), 61.0 (CHCH_3), 51.5 (OCH_3), 51.2 (OCH_3), 48.7 (C-4), 30.4 (C-1′ or C-2′), 28.9 (C-1′ or C-2′), 24.8 (C-3), 21.6 (CH_3); HRMS (ESI) $[M+Na]^+$ calcd for $C_{17}H_{23}NO_4Na$: 328.152, found 328.152.

Compound **31b**: TLC R_f 0.76 (silica gel, Et_2O/CH_2Cl_2, 1:5); $[\alpha]_D^{20}$ +76 (*c* 0.5, $CHCl_3$); IR (film) 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.16 (m, 5H, Ph), 3.74 (s, 3H, CO_2Me), 3.70 (s, 3H, CO_2Me), 3.63 (q, 1H, *J*=6.3 Hz, CHCH_3), 3.12 (m, 1H, H-4a), 2.96 (m, 1H, H-4b), 2.59–2.37 (m, 2H, H-2′), 2.34–2.17 (m, 3H, H-3a, H-1′), 1.97 (m, 1H, H-3b), 1.16 (d, 1H, *J*=6.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2 (CO), 173.5 (CO), 144.0 (Cq–Ar), 128.4 (2CH–Ar), 127.5 (2CH–Ar), 127.2 (1CH–Ar), 71.2 (C-2), 61.8 (CHCH_3), 51.8 (OCH_3), 51.6 (OCH_3), 48.6 (C-4), 31.5 (C-1′ or C-2′), 29.3 (C-1′ or C-2′), 24.6 (C-3), 22.3 (CH_3); HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{24}NO_4$: 306.170, found 306.169.

4.1.32. (1S,3S*)-N-(R)-(α)-Methylbenzyl-1-methoxycarbonyl-5-aza-spiro[2.4]heptan-4-one (**32**).* To a solution of azetidine **31a** (90 mg, 0.29 mmol, 1 equiv) in CH_2Cl_2 (1 mL) cooled to 0 °C was added NEt_3 (102 μL, 0.74 mmol, 2.5 equiv) and TMSOTf (106 μL, 0.59 mmol, 2 equiv). The solution was stirred at rt for 24 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$ and was extracted with CH_2Cl_2 (3×2 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/pentane, 1:9 to 1:7) to afford **32** (48 mg, 56%) as a yellow oil. TLC R_f 0.23 (silica gel, AcOEt/petroleum ether, 1:3); $[\alpha]_D^{20}$ +296 (*c* 1.0, $CHCl_3$); IR (film) 1728, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.17 (m, 5H, Ph), 5.45 (q, 1H, *J*=7.1 Hz, CHCH_3), 3.66 (s, 3H, CO_2Me), 3.32 (m, 1H, H-6a), 3.00 (td, 1H, *J*=8.9, 6.0 Hz, H-6b), 2.25–1.97 (m, 3H, H-1+H-7), 1.51 (m, 1H, H-2a), 1.50 (d, 3H, *J*=6.6 Hz, CH_3), 1.25 (m, 1H, H-2b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (CO), 172.1 (NCO), 140.0 (Cq–Ar), 128.7 (2CH–Ar), 127.6 (2CH–Ar), 127.2 (1CH–Ar), 52.0 (OCH_3), 50.0 (CHCH_3), 39.9 (C-6), 31.9 (C-3), 25.2 (C-1), 22.8 (C-7), 19.1 (C-2), 16.2 (CH_3); HRMS (ESI) $[M+Na]^+$ calcd for $C_{16}H_{19}NO_3Na$: 296.126, found 296.126.

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Supplementary data

The copies of the ^1H NMR spectra for all products (except for **27** and **28**) and copies of ^{13}C NMR spectra for all new products (except for **29b**). Crystal data for compounds (+)-**2b** and **14**. The copies of ^1H NMR spectra related to the ee. determination of (−)-**1** and (+)-**2** using Pirkle's reagent. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.03.111.

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