214. Dicarboxylates of 3-Methylidene-β-lactams: Addition Reactions to the Exocyclic Double Bond, Formation of Spiro-β-lactams, and Reductive Ring Opening by Hydrazines

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Dedicated to Prof. Dr. Dr. *h.c. mult. Horst Böhme*, Marburg, on the occasion of his 85th birthday

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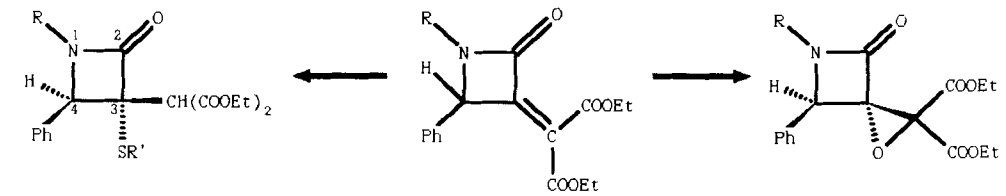
O-, S-, and N-Nucleophiles are added to the exocyclic double bond of the title compounds **1**. The addition of O- or S-nucleophiles yields stable products (*Scheme 1*), while addition of N-nucleophiles results in thermally labile compounds (*Scheme 2*). The reaction is studied by spectroscopic methods. From hydrazine adducts, a spiro[azetidine-3,3′-pyrazolidine] **7** is obtained, and the addition products of methyl- and benzylhydrazine rearrange to pyrazol-4-carboxylates **6**. Furthermore, the exocyclic double bond is used for the formation of spiro-β-lactams either by cyclopropane formation or by *Diels-Alder* reactions (*Scheme 4*). The steric course of all reactions is studied, and it is shown that all reactions with the double bond occur from the side opposite to the bulkier substituent at C(4) of the β-lactam ring.

Introduction. – Since the discovery of β-lactam antibiotics with an exocyclic double bond at C(7) like asparenomycins [1], the interest in other similar structures, *e.g.* monocyclic β-lactams with this structural component has grown [2]. Nucleophiles, *e.g.* amines [3] or thiols [4], are added to the double bond of unsubstituted 3-methylidene-β-lactams and do not open the lactam ring. Therefore, it seems to be of special interest to study the behaviour of substituted analogues. Principially, two types of substitution may be differentiated: 1) alkyl or aryl groups connected to the double bond directing a nucleophilic attack to the exocyclic C(α) atom or 2) electron-withdrawing groups at this position directing the attack towards C(3) of the β-lactam ring. In preceding papers [5], we described the synthesis of compounds **1** from 3-silylated β-lactams and mesoxalic esters as model compounds of the second type of substitution.

Now we wish to present some reactions at the double bond of **1** which show the synthetic possibilities and might allow a look into their mode of action when used in biological systems. These results should give some hints onto the hitherto unknown mechanism of the action of methylidene-β-lactams as β-lactamase inhibitors.

Results. – The introduction of an O-function at C(3) and C(α) of **1** may be effected by epoxidation [6] of the electron-poor double bond with nucleophilic reagents. Indeed, a large variety of reagents, *e.g.* H_2O_2 in alkali [7], *t*-BuOOH [8], KClO [9], 3-chloroperbenzoic acid [10], or urea/hydrogen peroxide complex [11] reacted with **1a–f** to produce the epoxides **2a–f** (only one isomer) in 65–90% yield as stable and crystalline compounds (*Scheme 1*). Their structures were established by spectroscopic methods.

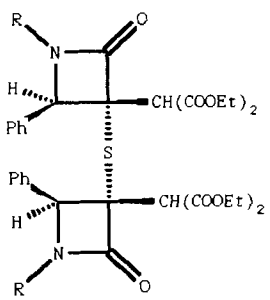
Scheme 1



3a R = 4-MeOC$_6$H$_4$, R' = Ph
b R = 4-MeOC$_6$H$_4$, R' = CH$_2$=CHCH$_2$
c R = 4-MeOC$_6$H$_4$, R' = i-Pr
d R = 4-MeOC$_6$H$_4$, R' = EtO$_2$CCH(NH$_2$)CH$_2$
e R = 4-MeOC$_6$H$_4$, R' = PhSO$_2$

1a R = 4-MeOC$_6$H$_4$
b R = (*t*-Bu)Ph$_2$Si
c R = Ph
d R = Ph (4-MeOC$_6$H$_4$ instead of Ph at C(4))
e R = 4-BrC$_6$H$_4$
f R = 3,4-(MeO)$_2$C$_6$H$_3$

2a R = 4-MeOC$_6$H$_4$
b R = (*t*-Bu)Ph$_2$Si
c R = Ph
d R = Ph (4-MeOC$_6$H$_4$ instead of Ph at C(4))
e R = 4-BrC$_6$H$_4$
f R = 3,4-(MeO)$_2$C$_6$H$_3$



4 R = 4-MeOC$_6$H$_4$

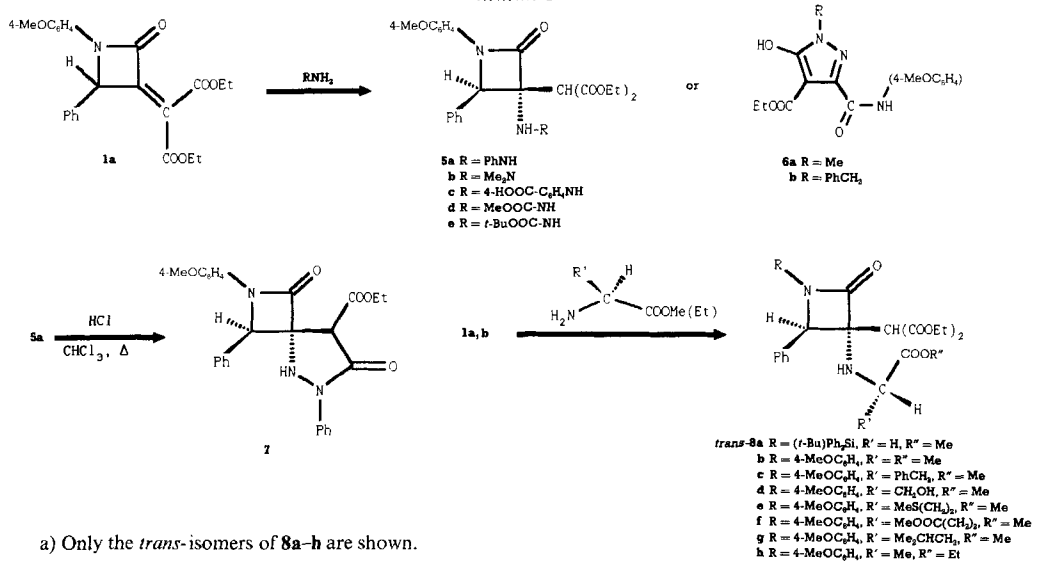
IR and ^{1}H-NMR spectra of **1** and **2** show only small differences. The lactam C=O bond of **2** is shifted to higher wave numbers by *ca.* 20–30 cm^{-1}, and δ(H) of H–C(4) is high-field shifted by 0.3–0.5 ppm. But the ^{13}C-NMR spectra of **2** clearly establish their structures: *e.g.*, the unsaturated compound **1c** shows signals for C(3) and C(α) at 154.23 and 122.57 ppm, while the ^{13}C-NMR of the corresponding epoxide **2c** clearly demonstrates the change from sp^2 C-atoms to epoxide C-atoms by the signals at 76.94 and 60.77 ppm. Spectroscopic data and TLC confirm that all epoxidations give only one single isomer. From NOE measurements, the *trans*-configuration (3*R**,4*S**) is deduced, assuming an O-attack from the side opposite to the Ph substituent at C(4) of the β-lactam ring.

Similar results were obtained on addition of thiols. When **1a** was given to a solution of a thiol deprotonated with BuLi at −78°, addition to C(3) of the β-lactam ring occurred in the same way from the side opposite to the bulkier substituent at C(4), and only the *trans*-adducts **3a–c** were obtained (*Scheme 1*). Sulfide **4**, the product of a twofold addition, was isolated from the reaction of **1a** with H_2S at room temperature without using any base. The thiophenol adduct **3a** was oxidized by 3-chloroperbenzoic acid in CH_2Cl_2 to sulfone **3e**. The structures were clearly established by their NMR spectra. All thiol adducts were stable compounds and supported other reported observations [12] showing that *Michael* adducts of thiols to α,β-unsaturated compounds are much more stable than those of amines and do not show any *retro-Michael* reaction or isomerisation. In agreement with these reports, L-cysteine ethyl ester added to **1a** with the SH and not with the NH_2 group yielding **3d**. The product was unstable. Thus, an analytically pure sample

could not be obtained, but the structure of **3d** was well supported by spectroscopic data. Furthermore, 2-mercaptoethanol was added under very mild conditions only to C(3) [13].

In contrast to the addition of O- and S-nucleophiles to the double bond of substituted methylidene-β-lactams, the addition of N-nucleophiles usually is a thermally reversible reaction. As reported earlier [5b], the addition of amines occurred at room temperature under very mild conditions. At higher temperature and in solution, the reverse reaction was easily detected by the increasing yellow colour of the olefinic **1**. The hydrazine adducts **5a–e** which we obtained from **1a** in $CHCl_3$ by titration with a solution of the hydrazine derivative (*Scheme 2*) showed a similar behaviour. All adducts were single

Scheme 2



a) Only the *trans*-isomers of **8a–h** are shown.

products, no isomers could be detected by TLC or NMR. This has to be highlighted as *Michael* additions of amines normally do not show great diastereoselectivity [14]. NOE Experiments established the *trans*-configuration (3*R**,4*R**). Thus, the addition of hydrazine derivatives followed the same stereochemical course as the reduction [15], the epoxidation, and the addition of thiols. The thermal lability of the hydrazine adducts was comparable to that of some simple primary- or secondary-amine adducts [5b], as demonstrated by an ^{1}H-NMR study of **5b**.

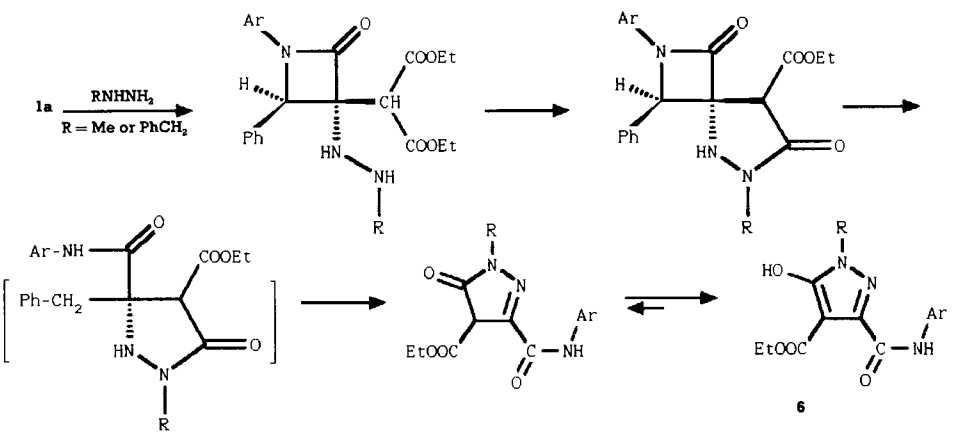
At 27°, the signal of H–C(4) of **5b** is at 5.34 ppm. On heating to 57°, an additional signal at 5.80 ppm appears arising from the starting material **1a**, and at 97° finally, a third signal at 5.60 ppm is detected caused by H–C(4) of this *cis*-isomers of **5b**. At 115°, the ratio *cis*-**5b**/*trans*-**5b**/**1a** is *ca.* 60:20:20. Similar results were obtained with the other hydrazine adducts.

When the phenylhydrazine adduct **5a** was heated in $CHCl_3$ solution with conc. HCl solution, the N-atom and one COOEt group underwent a reaction to the hitherto unknown spiro[azetidine-3,3′-pyrazolidine] derivative **7** (*Scheme 2*). The structure of **7** was clearly established by its ^{1}H-NMR spectrum (H–C(4) of **7** at 5.24 ppm, as compared to that of **5a** at 5.28 ppm; H–C(4′) at 3.13 ppm) which confirmed that the NH moiety is

located opposite to the Ph substituent of the β-lactam ring, thus, no configurational change had occurred on cyclisation.

We could not detect any addition product from the reaction of **1a** with methyl- or benzylhydrazine. TLC Studies showed mixtures of products from which we finally isolated **6a** and **6b**, respectively (*Scheme 2*). Their structures were established by spectroscopic means (IR: no β-lactam CO; ^{1}H-NMR: no H–C(4) signal at *ca.* 5.3 ppm, but *s*'s at 3.67 (MeN, **6a**) and 10.62 ppm (amide NH); ^{13}C-NMR: pyrazol structure, see *Exper. Part*). The formation of the hirtherto unknown pyrazoles **6** can be explained by the following sequence (*Scheme 3*). After addition of the hydrazine to the double bond and cyclisation to a spiro-structure analog to **7**, the β-lactam ring is reductively opened by the hydrazine; similar reactions were reported for other aryl-substituted β-lactams [16] and with other reagents [17] and may be due to their benzylamine structure. Finally, the benzyl group is eliminated. Pyrazole **6a** is an isomer of the one prepared by *Mitsuhashi et al.* [18] from ethyl 4,5-dihydro-1-methyl-5-oxo-1*H*-pyrazole-3-carboxylate and aryl isocyanate.

Scheme 3



To answer the question if oligopeptides can react with the β-lactams **1** by addition of their N-terminus, we submitted a number of amino-acid methyl and ethyl esters as model compounds[1]) to the addition to **1**. These reactions occurred very rapidly, and most were reversible at room temperature. Thus product isolation was more difficult. It was best done after titration of **1** with a solution of the ester in $CHCl_3$ at 0°, whereupon the addition products **8a–h** were obtained as colourless, slowly crystallising compounds (*Scheme 2*). (IR: strong N–H signal at *ca.* 3300 cm^{-1}; ^{1}H-NMR: H–C(4) signal high-field-shifted, additional signal of H–C(α)). From methyl L-alaninate and L-phenylalaninate only one isomer, *trans*-**8b** and -**8c**, respectively, could be isolated although small amounts of the *cis*-isomer were present (TLC). From methyl glycinate, we isolated the *trans*- and *cis*-isomer of **8a**, and from methyl L-methioninate, dimethyl L-glutamate, and methyl L-leucinate, the *cis*/*trans*-isomers **8e**, **8f**, and **8g**, respectively, were formed in a 1:1 ratio and could not be separated (see below). Finally, methyl L-serinate was added by the NH_2 and not by the OH group forming the very unstable product **8d**, which decomposed not

[1]) About our experiments with oligopeptides, we will report elsewhere.

only in solution but even in the crystalline state. This is noteworth, as methyl L-cysteinate was added by the SH and not by the NH_2 group yielding **3d** (*see above*). In additions where the *trans*-product could be isolated, the latter was formed by kinetic control, while the *cis*-isomer was the thermodynamically more stable product. This was demonstrated by the isomerisation of *trans*-**8a** monitored by ^{1}H-NMR spectroscopy.

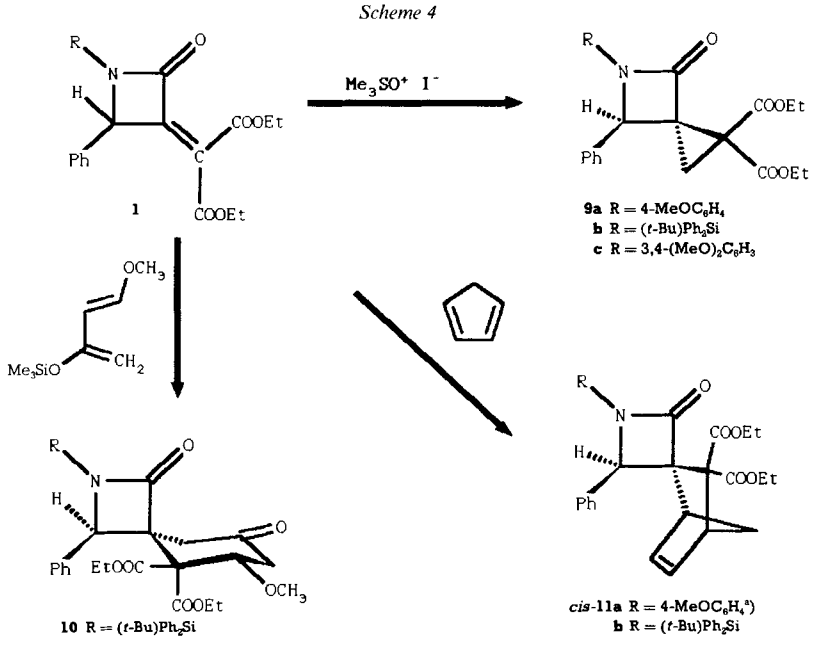
A (D_6)DMSO solution of *trans*-**8a** shows, after some min at 37°, a new signal at 5.63 ppm (H–C(4) of *cis*-**8a**), besides the signal at 5.02 ppm (H–C(4) of *trans*-**8a**). At 77° , the signal at 5.02 ppm has completely disappeared, while the integral of the signal of *cis*-**8a** corresponds exactly to 1 H. Above 77°, the addition becomes reversible showing growing amounts of the H–C(4) signal of **1b** at 5.80 ppm. The other adducts **8** show similar stabilities.

The separation of the *cis*/*trans*-isomers of **8e–g** by chromatographic methods was not possible, as the reverse reaction to **1a** occurred very rapidly in solution. Probably, even in these cases, the first addition product was the *trans*-isomer, but because of the reversibility of the reaction during workup, partial isomerisation occurred to the *cis*-product. Although during the addition of methyl L-lysinate the solution of **1a** became colouress, we could not isolate a stable adduct.

Finally, the α,β-unsaturated β-lactams **1** can be used for the construction of spirocyclic compounds, as examplified by the addition of a methylene group forming cyclopropane derivatives and the use of the electron-poor double bond as a dienophile in *Diels-Alder* reactions.

From the many possibilities for the construction of a spirocyclopropane, we used the reaction with the ylide from trimethylsulfoxonium iodide [19], as this reaction gave the best results. When the ylide in DMF reacted with a solution of **1a**, **1b**, or **1f** in THF, a fast reaction occurred, and after hydrolytic workup, we obtained the spiro compounds **9a–c**

Scheme 4



a) Only the *cis*-isomer, arising from *trans*-addition, is shown.

as crystalline products (*Scheme 4*). Their structure was supported by their NMR spectra. We could not detect any isomers and, therefore, we believe the *trans*-addition to be favoured. Although this is in agreement with the above described other results, it seems difficult to deduce it only from the spectroscopic data of the products.

Characteristic ^{1}H-NMR signals (*d*'s) are found at 2.0 and 2.2 (**9a**), 2.14 and 2.18 (**9b**), and 2.10 and 2.25 ppm (**9c**) for the CH_2 group. The corresponding small coupling constant ($J = 5$ Hz) indicates a relatively high s-character of the C-atom, whereby the three-membered ring is identified. The signals of H–C(4) are slightly shifted as compared to **1** and found at 4.66 (**9a**), 4.53 (**9b**), and 5.13 ppm (**9c**). Furthermore, the ^{13}C-NMR signal of C(3) of **1b** is shifted from 156.73 to 38.11 ppm (**9b**) and that of C(α) of **1b** from 121.98 to 49.89 ppm (**9b**). The J(H,C) of the CH_2 group is 168 Hz, indicating again the cyclopropane ring.

To demonstrate the use of **1** in *Diels-Alder* reactions, **1b** was reacted in toluene with *Danishefsky*'s diene [20]. A single product was obtained quantitatively from which by hydrolytic workup spirane **10** was obtained in 95% yield. NOE and 2D-NOESY spectra established the structure which is in agreement with the predictions concerning the regio- and stereoselectivity [21]. Moreover, **1a** and **1b** were reacted with cyclopentadiene in toluene to give only the *endo*-products[2]). While from **1b** only **11b** was obtained with 90% yield, **1a** yielded a mixture **11a** of two isomers which were separated by column chromatography. ^{1}H-NMR Spectra and NOE studies established that these isomers are not *endo*/*exo*-isomers but *cis*/*trans*-isomers, the main product being *cis*-**11a** formed by a *trans*-addition meaning that the *Diels-Alder* reaction at the side opposite to the bulkier substituent at C(4) is favoured.

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Experimental Part

General. BuLi Solution is 15% in hexane. THF (= tetrahydrofuran) is dried with $CaCl_2$ and distilled over $LiAlH_4$ prior to use. TLC: silica gel. Column Chromatography (CC): silica gel *60* (*Merck*, Darmstadt, No. 7734). M.p.: not corrected; *Kofler* hot stage, *Reichert AG*, Wien. IR Spectra (cm^{-1}): *Perkin-Elmer IR 1310*, *Beckman IR 4240*; in KBr, if not noted otherwise. NMR Spectra: *Varian T60*, *Bruker WP80*, and *Bruker WM250* for ^{1}H; *Bruker WM400* (100.614 MHz) for ^{13}C; δ in ppm rel. to Me_4Si as internal standard, J in Hz; values from 80-MHz spectra in $CDCl_3$, if not noted otherwise. MS (70 eV): *Finnigan 4000*, at 210°, or *MAT 312*, at 220°. Elemental analyses were performed at Pharmazeutisches Institut or Chemisches Laboratorium der Universität Freiburg.

Diethyl 2-[1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-ylidene]propanedioate (**1a**), *Diethyl 2-{1-[(*tert*-Butyl)diphenylsilyl]-2-oxo-4-phenylazetidin-3-ylidene}propanedioate* (**1b**), *Diethyl 2-(2-Oxo-1,4-diphenylazetidin-3-ylidene)propanedioate* (**1c**), *Diethyl 2-[4-(4-Methoxyphenyl)-2-oxo-1-phenylazetidin-3-ylidene]propanedioate* (**1d**), *and Diethyl 2-[1-(4-Bromophenyl)-2-oxo-4-phenylazetidin-3-ylidene]propanedioate* (**1e**). See [5a].

Diethyl 2-[1-(3,4-Dimethoxyphenyl)-2-oxo-4-phenylazetidin-3-ylidene]propanedioate (**1f**). From 1-(3,4-dimethoxyphenyl)-4-phenyl-3-(trimethylsilyl)azetidin-2-one (3.55 g, 10 mmol) in analogy to [5a]: 2.9 g (66%) of **1f**. Dark-yellow crystals. M.p. 115 (MeOH). IR: 1750, 1715 (CO), 1690 (C=C), 1660, 1590, 1510 (arom.). ^{1}H-NMR: 1.05, 1.36 (2*t*, each $J = 7$, 2 *Me*CH_2O); 3.75 (*s*, MeO); 4.05, 4.40 (2*q*, each $J = 7$, 2 MeCH_2O); 5.70 (*s*, H–C(4)); 6.45–6.75 (*m*, 2 arom. H); 7.1–7.6 (*m*, 6 arom. H). Anal. calc. for $C_{24}H_{25}NO_7$ (439.44): C 65.59, H 5.73, N 3.18; found: C 65.40, H 5.74, N 3.26.

Diethyl 1-(4-Methoxyphenyl)-2-oxo-4-phenylspiro[azetidine-3,2'-oxirane]-3',3'-dicarboxylate (**2a**). *Method A*: H_2O_2 (30% soln., 50 ml) is slowly added with stirring to a soln. of **1a** (1 g, 2.4 mmol) and Bu_4NBr (0.5 g) in

[2]) *endo* is related to the C=O function of the β-lactam ring and the C-atom bearing the 2 COOEt groups.

CH_2Cl_2 (50 ml). After addition of 0.5N KOH/EtOH (10 ml) stirring is continued for 12–14 h. The org. layer is separated, the aq. layer washed with CH_2Cl_2 (2 × 30–50 ml), and the combined org. layer washed with H_2O (50 ml), dried (Na_2SO_4), and evaporated: 760 mg (76%) of **2a**.

Method B: Under N_2, **1a** (500 mg, 1.2 mmol) is dissolved in $CHCl_3$ (a few ml). Pyridine (1.2 mg, 0.01 mmol) is added and the mixture poored onto $[MoO_2(acac)_2]$ (3.8 mg, 0.01 mmol) and stirred for 5 min. Then *t*-BuOOH (450.6 mg, 5 mmol) in benzene (20 ml) is added, the mixture refluxed for 1 h, and then cooled to r.t. $NaHCO_3$ soln. (50 ml) is added, the mixture extracted with AcOEt (3–4 × 20 ml), and the combined org. layer dried (Na_2SO_4), and evaporated: 360 mg (70%) of **2a**.

Method C: To a soln. of **1a** (500 mg, 1.2 mmol) in THF (50 ml), an 8-fold molar amount of a KClO soln. is added and the mixture stirred at r.t. for 10–12 h. Extraction with AcOEt and workup as described in *Method B*: 350 mg (68%) of **2a**.

Method D: To **1a** (500 mg, 1.2 mmol) in THF (30 ml) and 0.3N $NaHCO_3$ (60 ml), 3-chloroperbenzoic acid (2 g) is added with vigorous stirring. After 1–2 h, the mixture is worked up as described in *Method B*: 330 mg (65%) of **2a**.

Method E: Ac_2O (2.1 g, 20 mmol) is added dropwise at 0° to a mixture of urea/hydrogen peroxide complex [11] 3.8 g, 40 mmol), Na_2HPO_4 (9.9 g, 70 mmol) and **1a** (500 mg, 1.2 mmol) in CH_2Cl_2 (50 ml). Stirring is continued at r.t. for 10 h, $NaHCO_3$ soln. (30 ml) added to neutralize the mixture, the org. layer separated, the aq. layer extracted with CH_2Cl_2 (3 × 25–30 ml), and the combined org. layer dried (Na_2SO_4) and evaporated: 395 mg (78%) of **2a**. M.p. 133° (MeOH). IR: 1780, 1750, 1740 (CO), 1515 (arom.). ^{1}H-NMR: 0.95, 1.38 (2*t*, each J = 7, 2 *Me*CH_2O); 3.70 (*s*, MeO); 3.53, 4.4 (2*q*, each J = 7, 2 MeCH_2); 5.35 (*s*, H–C(4)); 6.67–7.55 (*m*, 9 arom. H). ^{13}C-NMR (100 MHz): 13.43, 13.87 (Me); 55.35 (MeO); 60.65 (C(3)); 62.71 (CH_2); 62.80 (CH_2); 64.05 (C(4)); 76.96 (C(α)); 114.36, 119.05, 127.74, 128.98, 129.36 (arom. C); 130.18, 133.14, 156.76 (quart. arom. C); 159.96 (C(2)); 162.02, 162.06 (CO, ester). Anal. calc. for $C_{23}H_{23}NO_7$ (425.44): C 64.93, H 5.45, N 3.29; found: C 64.99, H 5.40, N 3.21.

*Diethyl 1-[(*tert*-Butyl)diphenylsilyl)-2-oxo-4-phenylspiro[azetidine-3,2'-oxirane]-3',3'-dicarboxylate* (**2b**). From **1b** (0.5 g, 1 mmol) according to *Method A*: 0.35 g (63%) of **2b**. M.p. 137° (MeOH). IR: 1770, 1760, 1730 (CO), 1590, 1500 (arom.). ^{1}H-NMR: 0.83, 1.40 (2*t*, each J = 7, 2 *Me*CH_2O); 1.17 (*s*, *t*-Bu); 3.1–3.55, 4.2–4.6 (2*m*, 2 MeCH_2); 4.75 (*s*, H–C(4)); 6.6–7.5 (*m*, 15 arom. H). Anal. calc. for $C_{32}H_{35}NO_6Si$ (557.69): C 68.91, H 6.33, N 2.51; found: C 69.19, H 6.39, N 2.74.

Diethyl 2-Oxo-1,4-diphenylspiro[azetidine-3,2'-oxirane]-3',3'-dicarboxylate (**2c**). From **1c** (1.0 g, 2.64 mmol) according to *Method A*: 0.9 g (86%) of **2c**. M.p. 89–90° (MeOH). IR: 1770, 1750, 1730 (CO), 1595, 1500 (arom.). ^{1}H-NMR: 0.95, 1.40 (2*t*, each J = 7, 2 *Me*CH_2O); 3.5, 4.4 (2*q*, each J = 7, 2 MeCH_2O); 5.40 (*s*, H–C(4)); 7.0–7.5 (*m*, 10 arom. H). ^{13}C-NMR: 13.47, 13.92 (*qt*, ^1J(C,H) = 128, ^2J(C,H) = 2.5, Me); 60.77 (*s*, C(α)); 62.79 (*tq*, ^1J(C,H) = 149, ^2J(C,H) = 4, CH_2); 63.99 (*d*, ^1J(C,H) = 154, C(4)); 76.94 (*d*, ^2J(C,H) = 6, C(3)); 117.71, 125.05, 127.82, 129.06, 129.12, 129.45 (arom. C); 129.45, 133.19 (quart. arom. C); 160.75 (*d*, ^3J(C,H) = 2, C(2)); 162.04 (*t*, ^3J(C,H) = 3, CO). Anal. calc. for $C_{22}H_{21}NO_6$ (395.40): C 66.82, H 5.35, N 3.54; found: C 66.60, H 5.41, N 3.64.

Diethyl 4-(4-Methoxyphenyl)-2-oxo-1-phenylspiro[azetidine-3,2'-oxirane]-3',3'-dicarboxylate (**2d**). From **1d** (2.0 g, 4.9 mmol) according to *Method A*: 1.3 g (63%) of **2d**. M.p. 98° (MeOH). IR: 1770, 1760, 1740 (CO), 1615, 1600, 1515, 1500 (arom.). ^{1}H-NMR: 0.95, 1.32 (2*t*, each J = 7, 2 *Me*CH_2O); 3.80 (*s*, MeO); 3.6, 4.3 (2*q*, each J = 7, 2 MeCH_2O); 5.30 (*s*, H–C(4)); 6.75–7.4 (*m*, 9 arom. H). Anal. calc. for $C_{23}H_{23}NO_7$ (425.44): C 64.93, H 5.45, N 3.29; found: C 64.83, H 5.42, N 3.39.

Diethyl 1-(4-Bromophenyl)-2-oxo-4-phenylspiro[azetidine-3,2'-oxirane]-3',3'-dicarboxylate (**2e**). From **1e** (1.0 g, 2.18 mmol) according to *Method A*: 0.8 g (77%). M.p. 95° (MeOH). IR: 1775, 1755, 1740 (CO), 1590, 1490, (arom.). ^{1}H-NMR (60 MHz): 0.96, 1.36 (2*t*, each J = 7, 2 *Me*CH_2O); 3.33–3.76, 4.16–4.6 (2*m*, each MeCH_2); 5.38 (*s*, H–C(4)); 7.0–7.5 (*m*, 9 arom. H). Anal. calc. for $C_{22}H_{20}BrNO_6$ (474.30): C 55.71, H 4.25, Br 16.85, N 2.95; found: C 55.50, H 4.33, Br 16.98, N 2.85.

Diethyl 1-(3,4-Dimethoxyphenyl)-2-oxo-4-phenylspiro[azetidine-3,2'-oxirane]-3',3'-dicarboxylate (**2f**). From **1f** (2.0 g, 4.5 mmol) according to *Method A*: 1.55 g (76%) of **2f**. M.p. 116° (MeOH). IR: 1760 (CO), 1590, 1510 (arom.). ^{1}H-NMR: 0.95, 1.40 (2*t*, each J = 7, 2 *Me*CH_2O); 3.5, 4.4 (2*q*, each J = 7, 2 MeCH_2); 5.30 (*s*, H–C(4)); 6.4–6.7, 7.2–7.5 (*m*, 8 arom. H). Anal. calc. for $C_{24}H_{25}NO_8$ (455.48): C 63.29, H 5.53, N 3.08; found: C 63.36, H 5.52, N 3.12.

*Diethyl 2-[*trans*-1-(4-Methoxyphenyl)-2-oxo-4-phenyl-3-(phenylthio)azetidin-3-yl]propanedioate* (**3a**). At –78° and under N_2, thiophenol (1.2 ml, 10 mmol) and BuLi (6.3 ml, 10 mmol) are stirred in THF. After 15 min, **1a** (1.0 g, 2.44 mmol) in THF (40 ml) is slowly added, and after 10 min, the mixture is hydrolyzed with sat. NH_4Cl soln. (50 ml) and extracted with $CHCl_3$. The combined org. layers are dried (Na_2SO_4) and evaporated: 910 mg (72%) of **3a**. M.p. 141–142° (MeOH). IR: 1750, 1730 (CO), 1585 (arom.). ^{1}H-NMR: 1.08, 1.31 (2*t*, each J = 7, 2 *Me*CH_2O);

3.73 (*s*, MeO); 3.98 (*s*, H–C(α)); 4.09, 4.30 (2*q*, each $J = 7$, MeCH_2); 5.85 (*s*, H–C(4)); 6.7–7.75 (*m*, 14 arom. H). Anal. calc. for $C_{29}H_{29}NO_6S$ (519.62): C 67.03, H 5.63, N 2.70, S 6.17; found: C 66.75, H 5.51, N 2.80, S 6.29.

*Diethyl 2-[*trans-*1-(4-Methoxyphenyl)-2-oxo-4-phenyl-3-(prop-2-enylthio)azetidin-3-yl]propanedioate* (**3b**). From **1a** (1.0 g, 2.44 mmol) and prop-2-ene-1-thiol (0.8 ml, 10 mmol) as described for **3a**: 790 mg (67%) of **3b**. M.p. 71° (MeOH). IR: 1750, 1730 (CO), 1690 (C=C), 1590, 1515 (arom.). ^{1}H-NMR: 0.96, 1.20 (2*t*, each $J = 7$, 2 *Me*CH_2); 3.38–3.93 (*m*, CH_2S, MeCH_2O); 3.69 (*s*, MeO); 3.75 (*s*, H–C(α)); 4.15 (*q*, $J = 7$, MeCH_2O); 4.80–5.2 (*m*, CH_2=CH); 5.20 (*s*, H–C(4)); 5.55–6.10 (*m*, CH_2=C*H*); 6.64–7.33 (*m*, 9 arom. H). Anal. calc. for $C_{26}H_{29}NO_6S$ (483.59): C 64.58, H 6.04, N 2.90; found: C 64.76, H 6.02, N 2.96.

*Diethyl 2-[*trans-*1-(4-Methoxyphenyl)-3-(1-methylethylthio)-2-oxo-4-phenylazetidin-3-yl]propanedioate* (**3c**). From **1a** (1.0 g, 2.44 mmol) and 1-methylethanethiol (0.8 ml, 10 mmol) as described for **3a**: 720 mg (61%) of **3c**. M.p. 78° (MeOH). IR: 1755, 1735 (CO), 1510 (arom.). ^{1}H-NMR: 0.95, 1.21 (2*t*, each $J = 7$, 2 *Me*CH_2O); 0.95–1.55 (*m*, Me_2CH); 3.68 (*s*, MeO); 3.35–3.79 (*m*, MeCH_2O, H–C(α)); 4.14 (*q*, $J = 7$, MeCH_2); 5.19 (*s*, H–C(4)); 6.65–7.25 (*m*, 9 arom. H). Anal. calc. for $C_{26}H_{31}NO_6S$ (485.60): C 64.31, H 6.43, N 2.88, S 6.60; found: C 64.42, H 6.41, N 2.96, S 6.51.

Diethyl 2-{trans-*2-[(*R*)-2-Amino-2-(ethoxycarbonyl)ethylthio]-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl*}*propanedioate* (**3d**). From **1a** (1.0 g, 2.44 mmol) and ethyl L-cysteinate: 130 mg (10%) of **3d**. M.p. 120–124° (dec.; MeOH). IR: 3320 (NH), 1750–1715 (CO), 1585, 1510 (arom.). ^{1}H-NMR ($CDCl_3/D_2O$): 0.98, 1.20, 1.33 (3*t*, each $J = 7$, 3 *Me*CH_2O); 3.05 (*m*, CH_2S); 3.75 (*s*, MeO); 4.15 (*q*, $J = 7$, MeCH_2O); 3.48–4.55 (*m*, 2 MeCH_2O, 2 CH); 5.10 (*s*, H–C(4)); 6.58–7.38 (*m*, 9 arom. H).

*Diethyl 2-[*trans-*1-(4-Methoxyphenyl)-2-oxo-4-phenyl-3-(phenylsulfonyl)azetidin-3-yl]propanedioate* (**3e**). To a soln. of **3a** (500 mg, 1 mmol) in CH_2Cl_2 (20 ml), 3-chloroperbenzoic acid (492 mg, 3 mmol) is added and stirred for 1 h at r.t. The mixture is washed with NaOH soln. until it is free of peroxide and the org. layer dried (Na_2SO_4) and evaporated: 375 mg (68%) of **3e**. Light yellow crystals. M.p. 120° (MeOH). IR: 1755 (CO), 1510 (arom.). ^{1}H-NMR: 1.10, 1.40 (2*t*, each $J = 7$, 2 *Me*CH_2O), 3.74 (*s*, MeO); 3.95–4.5 (*m*, 2 MeCH_2O); 4.10 (*s*, H–C(α)); 6.23 (*s*, H–C(4)); 6.75–8.05 (*m*, 14 arom. H). Anal. calc. for $C_{29}H_{29}NO_8S$ (551.62): C 63.15, H 5.30, N 2.54, S 5.81; found: C 62.90, H 5.28, N 2.45, S 5.70.

Tetraethyl 2,2'-{*3,3'-Thiobis[1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]*}*bis(propanedioate)* (**4**). H_2S is passed through a soln. of **1a** (500 mg, 1.22 mmol) in $CHCl_3$/EtOH 1:1 (20 ml) until the soln. becomes colorless. Stirring is continued for 3–4 h and then the solvent evaporated: 410 mg (72%) of **4**. M.p. 185–188° (dec.; MeOH). IR: 1755, 1750, 1740 (CO), 1585, 1510 (arom.). ^{1}H-NMR (250 MHz): 0.89, 1.02, 1.12, 1.13 (4*t*, each $J = 7$, 4 *Me*CH_2O); 3.72 (*s*, 2 MeO); 3.63–4.18 (*m*, 4 MeCH_2O); 5.00, 5.26 (2*s*, 2 H–C(α)); 5.42, 5.68 (2*s*, 2 H–C(4)); 6.72–7.44 (*m*, 18 arom. H). ^{13}C-NMR: 13.58, 13.82, 13.98, 14.13 (Me); 53.82, 55.23 (CH(α)); 55.55, 55.58 (MeO); 61.28, 61.74, 61.78, 62.38 (CH_2); 63.08, 68.33 (C(4)); 63.90, 65.79 (C(3)); 114.47, 118.79, 119.22, 127.55, 128.01, 128.75, 128.89, 129.60 (arom. C); 130.50, 131.14, 131.20, 132.44 (quart. arom. C); 156.28, 156.50, 161.79, 162.22, 165.65, 166.08, 166.92, 167.83 (CO). Anal. calc. for $C_{46}H_{48}N_2O_{12}S$ (852.97): C 64.78, H 5.67, N 3.28, S 3.76; found: C 64.66, H 5.73, N 3.35, S 3.66.

*Diethyl 2-[*trans-*1-(4-Methoxyphenyl)-2-oxo-4-phenyl-3-(2-phenylhydrazino)azetidin-3-yl]propanedioate* (**5a**) *and Diethyl 2-[*trans-*3-(2,2-Dimethylhydrazino)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]propanedioate* (**5b**). See [5b].

Diethyl 2-{trans-*3-[2-(4-Carboxyphenyl)hydrazino]-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl*}*propanedioate* (**5c**). To a soln. of **1a** (1.0 g, 2.44 mmol) in $CHCl_3$ (10 ml), EtOH (10 ml) is added, followed by 4-hydrazinobenzoic acid with stirring until the mixture becomes colourless. The solvent is evaporated: 780 mg (57%) of **5c**. M.p. 212° (dec.; MeOH). IR: 3305 (NH), 2700–2540 (OH), 1760, 1740, 1675 (CO), 1610, 1515 (arom.). ^{1}H-NMR ($CDCl_3/(D_6)$DMSO 1:3): 0.91, 1.26 (2*t*, each $J = 7$, 2 *Me*CH_2O); 3.55–3.8 (*m*, MeCH_2O, H–C(α)); 3.65 (*s*, MeO); 4.19 (*q*, $J = 7$, MeCH_2O); 5.49 (*s*, H–C(4)); 5.70 (br. *s*, NH); 6.74–7.74 (*m*, 13 arom. H); 8.08 (br. *s*, PhN*H*); 12.0 (br. *s*, COOH). Anal. calc. for $C_{30}H_{31}N_3O_8$ (561.60): C 64.16, H 5.56, N 7.48; found: C 64.01, H 5.53, N 7.56.

Diethyl 2-{trans-*3-[2-(Methoxycarbonyl)hydrazino]-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl*}*propanedioate* (**5d**). From **1a** (1.0 g, 2.44 mmol) and methyl hydrazinecarboxylate (270 mg, 3 mmol): 500 mg (41%) of **5d**. M.p. 137° (MeOH). IR: 3390, 3300 (NH), 1765–1715 (CO), 1585, 1505 (arom.). ^{1}H-NMR: 0.93, 1.26 (2*t*, each $J = 7$, 2 *Me*CH_2O); 3.44–4.21 (*m*, H–C(α), MeCH_2); 3.54, 3.70 (2*s*, 2 MeO); 4.20 (*q*, $J = 7$, MeCH_2O); 5.35 (*s*, H–C(4)); 6.43 (*dd*, NH–NH); 6.59–7.35 (*m*, 9 arom. H). Anal. calc. for $C_{25}H_{29}N_3O_8$ (499.53): C 60.11, H 5.85, N 8.41; found: C 60.02, H 5.94, N 8.44.

Diethyl 2-{trans-*3-[2-(*tert*-Butoxycarbonyl)hydrazino]-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]-propanedioate* (**5e**). From **1a** (1.0 g, 2.45 mmol) and *tert*-butyl hydrazinecarboxylate: 870 mg (65%) of **5e**. M.p. 109° (dec.; MeOH). IR: 3340, 3295 (NH), 1760–1735 (CO), 1510, 1450 (arom.). ^{1}H-NMR: 0.94, 1.25 (2*t*, each

J = 7, 2 *Me*CH_2O); 1.43 (*s*, *t*-Bu); 3.45–3.93 (*m*, MeCH_2O, H–C(α)); 3.71 (*s*, MeO); 4.25 (*q*, J = 7, MeCH_2); 5.38 (*s*, H–C(4)); 6.21 (*dd*, NH–NH); 6.68–7.28 (*m*, 9 arom. H). Anal. calc. for $C_{28}H_{35}N_3O_8$ (541.61): C 62.10, H 6.51, N 7.76; found: C 61.82, H 6.54, N 7.96.

*Ethyl 5-Hydroxy-3-[*N*-(4-methoxyphenyl)carbamoyl]-1-methyl-1*H*-pyrazole-4-carboxylate* (**6a**). From **1a** (1.0 g, 2.44 mmol) and methylhydrazine: 370 mg (47%) of **6a**. M.p. 180° (MeOH). IR: 3290, 3210, 3160 (OH, NH), 2680, 2630 (OH), 1685, 1660, 1635 (CO), 1570, 1550, 1515 (arom.). ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.06 (*t*, J = 7, *Me*CH_2O); 3.67, 3.71 (2*s*, MeO, MeN); 4.07 (*q*, J = 7, MeCH_2O); 6.92, 7.59 (2*d*, each J = 7, 4 arom. H); 10.62 (br. *s*, NH). ^{13}C-NMR ((D_6)DMSO): 14.04 (*Me*CH_2O); 37.22 (MeN(1)); 55.19 (MeO); 59.31 (MeCH_2O); 96.39 (C(4)); 113.93, 121.12 (arom. C); 131.51 (quart. arom. C); 140.44 (C(3)); 155.83 (quart. arom. C); 157.34 (C(5)); 159.83, 161.88 (2 CO). MS: 319 (82, M^+), 273 (100), 321 (5, $[M + 2]^+$), 320 (15, $[M + 1]^+$). Anal. calc. for $C_{15}H_{17}N_3O_5$ (319.32): C 56.42, H 5.37, N 13.16; found: C 56.47, H 5.54, N 13.08.

*Ethyl 1-Benzyl-5-hydroxy-3-[*N*-(4-methoxyphenyl)carbamoyl]-1*H*-pyrazole-4-carboxylate* (**6b**). From **1a** (1.0 g, 2.44 mmol) and benzylhydrazine: 105 mg (11%) of **6b**. M.p. 184° (MeOH). IR: 3310, 3270, 3210, 3140 (NH, OH), 2670, 2610 (OH), 1685, 1660, 1635 (CO), 1575, 1550, 1510 (arom.). ^{1}H-NMR (90 MHz): 1.40 (*t*, J = 7, *Me*CH_2O); 3.73 (*s*, MeO); 4.50 (*q*, J = 7, MeCH_2O); 5.86 (*s*, PhCH_2); 6.87–7.92 (*m*, 9 arom. H); 11.34 (br. *s*, NH). ^{13}C-NMR: 14.35 (Me); 55.47 (MeO); 55.82 (CH_2N); 62.43 (CH_2O); 95.46 (C(4)); 114.19, 122.88, 127.88, 128.27, 128.49 (arom. C); 130.72, 136.40, 155.42 (quart. arom. C); 136.65 (C(3)); 156.78 (C(5)); 160.88, 164.87 (CO). MS: 395 (M^+, $C_{21}H_{21}N_3O_5^+$), 396 ($[M + 1]^+$), 91 (100).

Ethyl 1-(4-Methoxyphenyl)-2,5′-dioxo-1′,4-diphenylspiro[azetidine-3,3′-pyrazolidine]-4′-carboxylate (**7**). A mixture of **5a** (1.0 g, 1.9 mmol), $CHCl_3$ (20 ml), conc. HCl soln. (20 ml) is refluxed for 4–5 h. The mixture is then extracted with $CHCl_3$ (3×) and the combined org. layer dried (Na_2SO_4) and evaporated: 710 mg (79%) of **7**. M.p. 150° (dec.; MeOH). IR: 1745, 1725, 1700 (CO), 1590, 1610 (arom.). ^{1}H-NMR: 1.29 (*t*, J = 7, *Me*CH_2O); 3.13 (*s*, H–C(5)); 3.73 (*s*, MeO); 4.26 (*q*, J = 7, MeCH_2); 5.24 (*s*, H–C(4)); 5.86 (*s*, NH); 6.64–7.91 (*m*, 14 arom. H). Anal. calc. for $C_{27}H_{25}N_3O_5$ (471.52): C 68.78, H 5.34, N 8.91; found: C 68.60, H 5.35, N 8.99.

*Diethyl 2-{1-[(*tert*-Butyl)diphenylsilyl]3-{[(methoxycarbonyl)methyl]amino}-2-oxo-4-phenylazetidin-3-yl}-propanedioate* (**8a**). From **1b** (1.0 g, 2.44 mmol) and methyl glycinate in analogy to [5b].

trans-**8a**: 540 mg (45%). M.p. 92–93° (MeOH). IR: 3400 (NH), 1755 (CO), 1745, 1720 (CO), 1590, 1515 (arom.). ^{1}H-NMR (90 MHz): 0.93, 1.30 (2*t*, each J = 7, 2 *Me*CH_2O); 3.70, 3.74 (2*s*, 2 MeO); 3.26–3.99 (*m*, H–C(α), MeCH_2, CH_2N, NH); 4.26 (*q*, J = 7, MeCH_2O); 5.02 (*s*, H–C(4)); 6.67–7.37 (*m*, 9 arom. H). Anal. calc. for $C_{26}H_{30}N_2O_8$ (498.54): C 62.64, H 6.07, N 5.62; found: C 62.69, H 6.16, N 5.61.

cis-**8a**: From the filtrate of *trans*-**8a**: 380 mg (31%) of *cis*-**8a**. M.p. 94–97° (MeOH). IR: 3315 (NH), 1750, 1735, 1720 (CO), 1590, 1515 (arom.). ^{1}H-NMR (90 MHz): 1.13, 1.43 (2*t*, each J = 7, *Me*CH_2O); 2.08 (br. *t*, NH); 3.68, 3.75 (2*s*, 2 MeO); 3.45–4.40 (*m*, CH_2N, 2 MeCH_2O, H–C(α)); 5.63 (*s*, H–C(4)); 6.70–7.63 (*m*, 9 arom. H). Anal. calc. for $C_{26}H_{30}N_2O_8$ (498.54): C 62.64, H 6.07, N 5.62; found: C 62.36, H 5.98, N 5.46.

*Diethyl 2-{*trans*-3-[(*S*)-1-(Methoxycarbonyl)ethylamino]-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl}-propanedioate* (*trans*-**8b**) *and Diethyl {*trans*-3-[(*S*)-1-(Methoxycarbonyl)-2-phenylethylamino)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl}propanedioate* (*trans*-**8c**). See [5b].

*Diethyl 2-{*trans*-3-[(*S*)-2-Hydroxy-1-(methoxycarbonyl)ethylamino]-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl}propanedioate* (*trans*-**8d**). From **1a** (1.0 g, 2.44 mmol) and methyl L-serinate: 450 mg (35%) of *trans*-**8d**. M.p. 84–85° (MeOH). $[\alpha]_D^{23} = -71.37$ (c = 2.70, l = 10 cm, $CHCl_3$). IR: 3600 (OH), 3340 (NH), 1760–1735 (CO), 1585, 1515 (arom.). ^{1}H-NMR: 0.96, 1.31 (2*t*, each J = 7, 2 *Me*CH_2O); 3.69 (*m*, MeCH_2O, H–C(α), $CHCH_2$, NH); 3.73 (*s*, MeO, COOMe); 4.20 (*q*, J = 7, MeCH_2O); 5.10, 5.18 (2*s*, 1 H, H–C(4)); 6.65–7.43 (*m*, 9 arom. H). Anal. calc. for $C_{27}H_{32}N_2O_9$ (528.56): C 61.36, H 6.10, N 5.30; found: C 61.08, H 6,01, N 5.26.

*Diethyl 2-{*cis/trans*-3-[(*S*)-1-(Methoxycarbonyl)-3-(methylthio)propylamino]-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl}propanedioate* (**8e**). From **1a** (1.0 g, 2.44 mmol) and methyl L-methioninate: 825 mg (59%) of **8e**. M.p. 100° (MeOH). $[\alpha]_D^{23} = -49.27$ (c = 3.13, l = 10 cm, $CHCl_3$). IR: 3390, 3310 (NH), 1760–1720 (CO), 1510 (arom.). ^{1}H-NMR: 0.93, 0.98 (2*t*, each J = 7, Me); 1.30 (*t*, J = 7, Me); 1.98, 2.63 (2*m*, CH_2, CH_2S); 2.05, 2.08 (2*s*, MeS); 3.65, 3.71 (2*s*, MeO); 3.55–4.08 (*m*, CH_2, 2 CH, NH); 4.23 (*q*, CH_2); 5.01, 5.20 (2*s*, 1 H, H–C(4)); 6.65–7.43 (*m*, 9 arom. H). Anal. calc. for $C_{29}H_{36}N_2O_8S$ (572.68): C 60.82, H 6.34, N 4.89, S 5.60; found: C 60.99, H 6.43, N 4.80, S 5.70.

*Diethyl 2-{*cis/trans*-3-[(*S*)-1,3-Bis(methoxycarbonyl)propylamino]-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl}propanedioate* (**8f**). From **1a** (1.0 g, 2.44 mmol) and dimethyl L-glutamate: 540 mg (38%) of **8f**. M.p. 101° (MeOH). IR: 3380, 3350 (NH), 1755–1725 (CO), 1505 (arom.). ^{1}H-NMR: 0.94, 0.98, 1.29, 1.45 (4*t*, each J = 7, Me); 1.89, 2.48 (2*m*, CH_2CH_2); 3.63, 3.68, 3.71 (3*s*, 3 MeO); 3.38–4.05 (*m*, CH_2, 2 CH, NH); 4.23 (*q*, J = 7, CH_2); 5.00, 5.08 (2*s*, 1 H, H–C(4)); 6.65–7.46 (*m*, 9 arom. H). Anal. calc. for $C_{30}H_{36}N_2O_{10}$ (584.63): C 61.63, H 6.21, N 4.79; found: C 61.62, H 6.11, N 4.72.

*Diethyl 2-{*cis/trans*-3-[(S)-1-(Methoxycarbonyl)-3-methylbutylamino]-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl}propanedioate* (**8g**). From **1a** (1.0 g, 2.44 mmol) and methyl L-leucinate: 450 mg (27%) of **8g**. M.p. 97° (MeOH). $[\alpha]_D^{23} = -42.81$ ($c = 1.28$, l = 10 cm, $CHCl_3$). IR: 3370, 3330 (NH), 1760–1740, 1730 (CO), 1510 (arom.). ^{1}H-NMR: 0.8–2.0 (*m*, 2 Me, $CH_2CH_2Me_2$); 3.55–3.7 (*m*, CH_2, H–C(α), NH, CH, MeO, COOMe); 4.22 (*q*, CH_2); 5.04, 5.06 (*s*, 1 H, H–C(4)); 6.67–7.25 (*m*, 9 arom. H). Anal. calc. for $C_{30}H_{38}N_2O_8$ (554.65): C 64.97, H 6.91, N 5.05; found: C 64.96, H 6.99, N 5.15.

*Diethyl 2-{*trans*-3-[(S)-1-(Ethoxycarbonyl)ethylamino]-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl}propanedioate* (*trans*-**8h**). From **1a** (1.0 g, 2.44 mmol) and ethyl L-alaninate: 497 mg (39%) of *trans*-**8h**. M.p. 92–95° (dec.; MeOH). IR: 3360 (NH), 1760–1735 (CO), 1590, 1515 (arom.). ^{1}H-NMR (60 MHz): 0.75–1.6 (*m*, 4 Me); 3.72 (*s*, MeO); 3.4–4.15 (*m*, 2 CH_2, MeCHN, H–C(α), NH); 4.22 (*q*, $J = 7$, CH_2), 5.10 (*s*, H–C(4)); 6.6–7.4 (*m*, 9 arom. H). Anal. calc. for $C_{28}H_{34}N_2O_8$ (526.59): C 63.87, H 6.51, N 5.32; found: C 63.65, H 6.41, N 5.27.

Diethyl 1-(4-Methoxyphenyl)-2-oxo-4-phenylspiro[azetidine-3,1′-cyclopropane]-2′,2′-dicarboxylate (**9a**). Under N_2, DMF (10 ml) is slowly added to trimethyloxosulfonium iodide (1.35 g, 6 mmol) and NaH (0.144 g, 6 mmol.). After 20 min at r.t., the mixture is cooled to 5–10° and the soln. of **1a** (1.0 g, 2.44 mmol) in THF (20 ml) added dropwise. Stirring is continued for 1–2 h at r.t., the mixture poored onto sat. NaCl soln. and crashed ice, the org. layer separated and washed with sat. NaCl soln. (3–4×), the aq. layer extracted with THF, and the combined org. layer dried (Na_2SO_4) and evaporated: 0.7 g (67%) of **9a**. M.p. 77–78° (MeOH). IR: 1765, 1720 (CO), 1510 (arom.). ^{1}H-NMR (60 MHz, (D_6)benzene): 0.6, 1.1 (2*t*, each $J = 7$, 2 *Me*CH_2O); 2.0, 2.2 (*d*, $J = 5$, CH_2); 3.2 (*s*, MeO); 3.3, 4.3 (2*q*, each $J = 7$, 2 MeCH_2O); 4.66 (*s*, H–C(4)); 6.5–7.6 (*m*, 9 arom. H). Anal. calc. for $C_{24}H_{25}NO_6$ (423.45): C 68.07, H 5.95, N 3.31; found: C 68.10, H 5.97, N 3.43.

*Diethyl 1-[(*tert*-Butyl)diphenylsilyl]-2-oxo-4-phenylspiro[azetidine-3,1′-cyclopropane]-2′,2′-dicarboxylate* (**9b**). From **1b** (2.7 g, 5 mmol) as described for **9a**: 0.6 g (18%) of **9b**. M.p. 108–109°. (MeOH). IR: 1750, 1740, 1730 (CO). ^{1}H-NMR (250 MHz): 0.83, 1.42 (2*t*, each $J = 7$, 2 *Me*CH_2O); 1.0–1.2 (*m*, *t*-Bu)); 2.14, 2.18 (*d*, $J = 5$, CH_2); 3.23, 4.37 (2*m*, 2 MeCH_2O); 4.53 (*s*, H–C(4)); 6.85–7.73 (*m*, 15 arom. H). ^{13}C-NMR: 13.51, 14.08 (*qt*, ^1J(C,H) = 127, ^2J(C,H) = 3, Me); 19.22 (*s*, Me_3C); 20.69 (*td*, ^1J(C,H) = 168, ^3J(C,H) = 3, CH_2); 27.37, 27.86 (Me_3C); 38.11 (*s*, C(3)); 49.89, (*s*, C(α)); 61.45, 61.61 (*tq*, ^1J(C,H) = 147, ^2J(C,H) = 5, CH_2); 61.99 (*d*, ^1J(C,H) = 154, C(4)); 127.31, 127.45, 127.65, 127.85, 128.07, 129.36, 129.82, 129.97, 135.77, 135.82, 135.89 (arom. C); 165.38, 165.64 (CO); 173.56 (C(2)). MS: 556 (0.87, M^+), 498 (100, $[M - C_4H_9]^+$). Anal. calc. for $C_{33}H_{37}NO_5Si$ (555.72): C 71.32, H 6.71, N 2.52; found: C 71.42, H 6.75, N 2.72.

Diethyl 1-(3,4-Dimethoxyphenyl)-2-oxo-4-phenylspiro[azetidine-3,1′-cyclopropane]-2′,2′-dicarboxylate (**9c**). From **1f** (1.0 g, 2.3 mmol) as described for **9a**: 0.5 g (48%) of **9c**. M.p. 110° (MeOH). IR: 1760, 1735, 1725 (CO), 1605, 1590, 1510 (arom.). ^{1}H-NMR: 0.88, 1.30 (2*t*, each $J = 7$, 2 *Me*CH_2O); 2.1, 2.25 (*d*, $J = 5$, CH_2); 3.35, 4.3 (2*q*, each $J = 7$, 2 MeCH_2O); 3.75 (*s*, 2 MeO); 5.13 (*s*, H–C(4)); 6.4–7.6 (*m*, 8 arom. H). Anal. calc. for $C_{25}H_{27}NO_7$ (453.48): C 66.21, H 6.00, N 3.09; found: C 66.24, H 6.02, N 3.18.

*Diethyl 1-[(*tert*-Butyl)diphenylsilyl]-3′-methoxy-2,5′-dioxo-4-phenylspiro[azetidine-2,1′-cyclohexane]-2′,2′-dicarboxylate* (**10**). A mixture of **1b** (1.08 g, 2 mmol) and 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene (0.4 ml, 0.34 g, 2 mmol) in toluene (10 ml) is stirred for 1 h at r.t., the solvent evaporated, and the residue dissolved in a few ml of MeOH. Conc. HCl soln. (5 ml) is added and the precipitate collected: 1.2 g (95%). M.p. 167–169° (MeOH). IR: 1750, 1735, 1725 (CO). ^{1}H-NMR (250 MHz): 0.98, 1.04 (2*t*, each $J = 7$, 2 *Me*CH_2O); 1.18 (*s*, (*t*-Bu)); 2.62 (*dd*, $J = 17$, 11.5, H_a–C(4′)); 2.82 (*d*, $J = 17$, 1 H–C(6′)); 2.97 (*ddd*, $J = 17$, 4.5, 1.5, H_e–C(4′)); 3.13 (*d*, $J = 17$, 1 H–C(6′)); 3.31 (*s*, MeO); 3.74, 3.92–4.11 (2*dq*, each $J = 11.3$, 7, 2 MeCH_2O); 4.15 (*s*, H–C(4)); 4.9 (*dd*, $J = 11.5$, 4.5, H–C(3′)); 6.83–7.84 (*m*, 15 arom. H). MS: 642 (8.39, M^+). Anal. calc. for $C_{37}H_{43}NO_7Si$ (641.84): C 69.24, H 6.75, N 2.18; found: C 69.45, H 6.86, N 2.27.

Diethyl 1-(4-Methoxyphenyl)-2-oxo-4-phenylspiro[azetidine-3,2′-bicyclo[2.2.1]hept-5′-ene]-3′,3′-dicarboxylate (**11a**). Freshly distilled cyclopentadiene (5 ml) is added to a soln. of **1a** (1.0 g, 2.44 mmol) in toluene (10 ml) and the mixture refluxed for 30 min. After evaporation, the residue was purified by CC ($CHCl_3$). Anal. calc. for $C_{28}H_{29}NO_6$ (459.52): C 70.72, H 6.14, N 2.95; found: C 70.96, H 6.19, N 3.20.

trans-**11a**: Yield 7 mg (0.6%). M.p. 111° (MeOH). IR: 1740 (CO), 1510 (arom.). ^{1}H-NMR (250 MHz): 1.04, 1.27 (2*t*, each $J = 7$, 2 *Me*CH_2O); 1.45 (*ddd*, $J = 1.5$, 1.5, 9, H_e–C(7′)); 2.31 (*dm*, $J = 9$, H_a–C(7′)); 3.01, 3.49 (*m*, H–C(1′), H–C(4′)); 3.76 (*s*, MeO); 4.08–4.31 (*m*, 2 MeCH_2O); 5.04, 5.86 (*dd*, $J = 3$, 5.5, H–C(6′), H–C(5′)); 6.03 (*s*, H–C(4)); 6.74–6.82, 7.21–7.59 (*m*, 9 arom. H).

cis-**11a**: Yield 0.9 g (80%). M.p. 129° (MeOH). IR: 1740, 1710 (CO), 1510 (arom.). ^{1}H-NMR (250 MHz): 0.93, 1.39 (2*t*, each $J = 7$, 2 *Me*CH_2O); 1.6 (*ddd*, $J = 1.5$, 1.5, 9, H_e–C(7′)); 2.25 (*dm*, $J = 9$, H_a–C(7′)); 3.02, 3.54 (*m*, H–C(1′), H–C(4′)); 3.75 (*s*, MeO); 4.21–4.45 (*m*, 2 MeCH_2O); 4.86 (*s*, H–C(4)); 6.2, 6.51 (*dd*, $J = 3$, 5.5, H–C(5′), H–C(6′)); 6.7–6.81, 7.31–7.72 (*m*, 9 arom. H).

*Diethyl 1-[(*tert*-Butyl)diphenylsilyl]-2-oxo-4-phenylspiro[azetidine-3,2'-bicyclo[2.2.1]hept-5'-ene]-3',3'-dicarboxylate* (**11b**). From **1b** (1.08 g, 2 mmol) as described for **11a**: 1.1 g (90%) of **11b**. M.p. 161° (MeOH). IR: 1735, 1720 (CO). ^{1}H-NMR (250 MHz): 0.85, 1.45 (*2t*, each $J = 7$, 2 $MeCH_2O$); 1.19 (*s*, (*t*-Bu)); 1.58 (*ddd*, $J = 1.5, 1.5, 9$, H_e–C(7')); 2.27 (*dm*, $J = 9$, H_a–C(7')); 3.07, 3.2, 4.31, 4.53 (*2dq*, each $J = 11, 7$, 2 $MeCH_2O$); 3.28 (*m*, H–C(1')); 3.51 (*m*, H–C(4')); 4.11 (*s*, H–C(4)); 6.06, 6.39 (*dd*, $J = 3, 5.5$, H–C(5'), H–C(6')); 6.04, 6.67–7.83 (*m*, 15 arom. H). MS: 608 (6.82, M^+). Anal. calc. for $C_{37}H_{41}NO_5Si$ (607.79): C 73.11, H 6.80, N 2.30; found: C 73.16, H 6.82, N 2.39.

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