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Synthesis of Optically Active Spiro-ß-lactams by Cycloadditions to α-Alkylidene-ß-lactams

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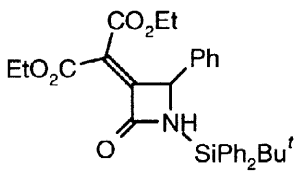
Abstract. New optically active α-methylene-ß-lactam **18** and the α-ethylidene-ß-lactams **11-E** and **11-Z** were synthesized and submitted to 1,3-dipolar cycloadditions with diazomethane, 4-methoxybenzonitrile oxide, and diphenylnitrone as well as to epoxidation by dimethyldioxirane. All cycloadditions proceed with complete regioselectivity giving products **20 - 25** in an *anti*-fashion with respect to the substituent at the C-4-position of the starting ß-lactam in diastereomeric ratios of about 80:20. Pure optically active compounds could be obtained in almost all cases after chromatography. Unambiguous structure elucidation could be achieved by X-ray crystal analysis and NOE investigations.

INTRODUCTION

Monocyclic ß-lactams, e.g. monobactams or nocardicines, are interesting pharmacologically active compounds [1] and can also serve as versatile synthetic precursors for ß-amino acid derivatives. [2] Although a number of mono- [3] and bicyclic [4] α-alkylidene-ß-lactams are known, cycloadditions to their exocyclic C-C-double bond in particular in the non-racemic series have been investigated only in selected cases [5] and with incomplete investigation of stereochemical aspects. Thus, racemic bis-(ethoxycarbonyl)-methylidene-ß-lactam **1** gave epoxidation, cyclopropanation and Diels-Alder reactions. [6] The reactivity of this compound is dominated by the effect of two electron-withdrawing ester groups. Similar α-alkylidene-ß-lactams **2** with two (R^1, $R^2 = CO_2Et$), one ($R^1 = CO_2Me$, $R^2 = H$) or no ester group (R^1, R^2 = H, Me) were recently reported to undergo 1,3-dipolar cycloadditions with diphenylnitrile imine, acetonitrile oxide, diazomethane, and N-methyl-C-phenylnitrone affording low yields of corresponding cycloadducts with varying diastereomeric ratios (*anti*-addition with respect to the 4-phenyl group) after long reaction times (up to 30 days). [7] No satisfactory structural proof of the relative configuration of the cycloadducts could be given. [8] The 4-unsubstituted α-methylene-ß-lactam **3** gave a 1,3-dipolar cycloaddition with a nitrone derived from glyoxylic acid. [9]



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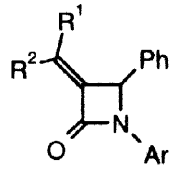

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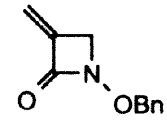

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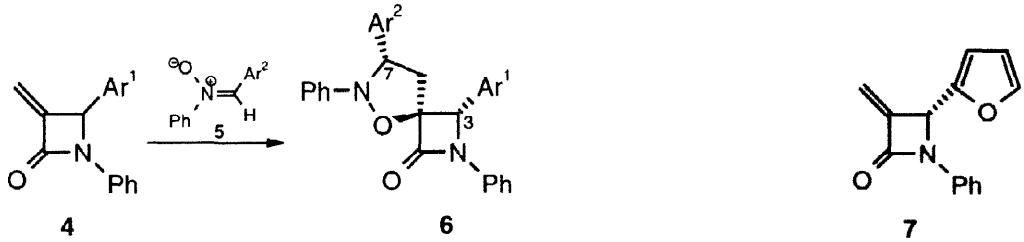
Analogous cycloaddition reactions of diarylnitrones **5** and 1,4-diaryl-ß-lactams **4** yielding spiroisoxazolidines **6** exhibited high *trans*-stereoselectivities (57-100% d.e.) governed by the aryl group in C-4 position (Scheme 1). [10] The same was found in the formation of an optically active spiroisoxazolidine **6** starting from the 4-(2-furyl)-3-methylene-1-phenyl-ß-lactam **7**. [11] No proof was given for the relative configuration of **6**.

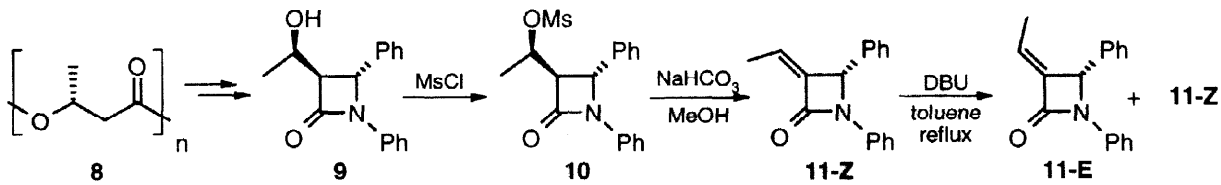


Scheme 1

We report here the synthesis of new optically active α-alkylidene-ß-lactams **11-Z**, **11-E** and **18** and their application to 1,3-dipolar cycloadditions and to epoxidation in order to get access to new optically active spirocyclic ß-lactams. Emphasis was given to the unambiguous elucidation of the configuration of the cycloadducts obtained.

RESULTS AND DISCUSSION

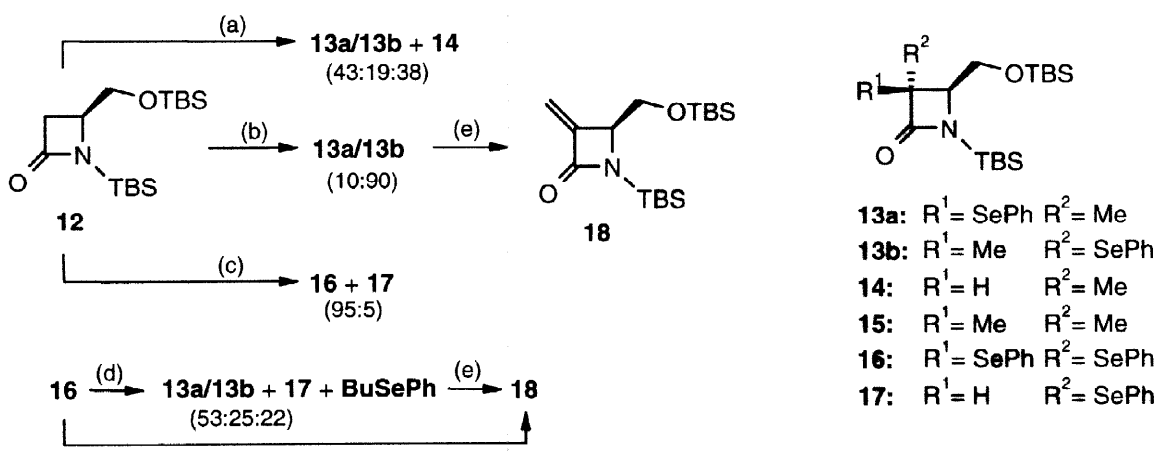
The synthesis of the (4*S*)-Z-3-ethylidene-1,4-diphenyl-azetidin-2-one **11-Z** was persued by elimination starting from the known 3-(1'-hydroxyethyl)-ß-lactam **9** [12] obtained from the naturally occurring (*R*)-3-polyhydroxybutyric acid (Scheme 2). While treatment with thionyl chloride in pyridine [13] gave mainly substitution of the hydroxy group by chlorine, the envisaged elimination to **11-Z** could be achieved by transforming **9** into the mesylate **10** followed by treatment with $NaHCO_3$ in MeOH [14] in a total yield of 55%. The corresponding (*E*)-3-ethylidene-1,4-diphenyl-ß-lactam **11-E** was obtained on refluxing the Z-isomer **11-Z** with DBU in toluene affording a 1:1 mixture of both diastereomers **11-E** and **11-Z**. This mixture could easily be separated by flash chromatography.



Scheme 2

Racemic 3-ethylidene-1,4-diphenyl-ß-lactams corresponding to **11-E** and **11-Z** were reported in the literature and showed similar ^1H NMR spectra. [3b] Although these racemic E/Z-isomers could be separated, mixtures were used in investigations of their cycloaddition reactions. [7]

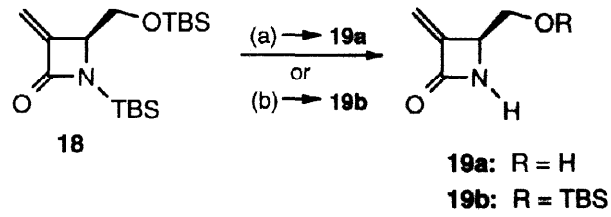
The synthesis of the disilylated 3-methylene-4-hydroxymethyl-ß-lactam **18** was envisaged by selenylation/ methylation of the 3-unsubstituted ß-lactam **12** and final oxidative elimination. This well elaborated protocol for the introduction of a methylene moiety into the α-position of a C=O group has not been applied to the ß-lactam series yet. But the oxidative elimination was successfully employed to transform a 3-methyl-3-phenylselenyl-ß-lactam obtained by ketene-imine cycloaddition into the corresponding racemic α-methylene-ß-lactam.[15] In order to synthesize the optically active α-methylene-ß-lactam **18** starting from the known disilylated 4-hydroxymethyl-ß-lactam **12**[16] several reaction sequences were used. Primary selenylation of **12** with LDA/PhSeBr followed by alkylation with methyl iodide gave a 43:19:38 mixture of **13a/13b** (69:31) and **14** (Method (a) in Scheme 3). The formation of the 3-methyl-ß-lactam **14** is presumably caused by incomplete selenylation. The reversed sequence, i.e. primary methylation of **12** and subsequent selenylation, seemed to be advantageous since only diastereomers **13a** and **13b** were formed via Method (b) in a 10:90 ratio. Unfortunately scaling up of Method (b) gave rise to the formation of larger amounts of 3,3-dimethyl-ß-lactam **15** which was hard to separate by chromatography. The diastereomeric mixtures of 3-methyl-3-phenylselenyl-ß-lactams **13a** and **13b** was transformed into the corresponding α-methylene-ß-lactam **18** with H_2O_2/pyridine in good yield (73 %). After all, the most reliable way for the synthesis of α-methylene-ß-lactam **18** was found by the transformation of **12** into the diselenylated product **16** via Method (c) with an excess of base (3 equivalents of LiHMDS) and phenylselenyl chloride (3 equivalents). Although some monoselenylated product **17** was also formed due to incomplete selenylation, pure **16** could be obtained by column chromatography. One of the phenylselenyl groups of **16** was removed by treatment with one equivalent of n-BuLi[17] generating an enolate that finally was alkylated with methyl iodide (Method (d)) affording a mixture of diastereomers **13a/13b** (68:32), **17** and the butylphenyl selenide. This crude product was subjected to oxidation and the α-methylene-ß-lactam **18** was isolated in a total yield of 43 % (starting from **16**) after chromatography.



Reagents: (a) 1.LDA, 2.PhSeBr, 3.MeI; (b) 1.LDA, 2.MeI, 3.PhSeBr; (c) 1.LiHMDS, 2.PhSeCl; (d) 1.n-BuLi, 2.MeI; (e) H_2O_2, pyridine

Scheme 3

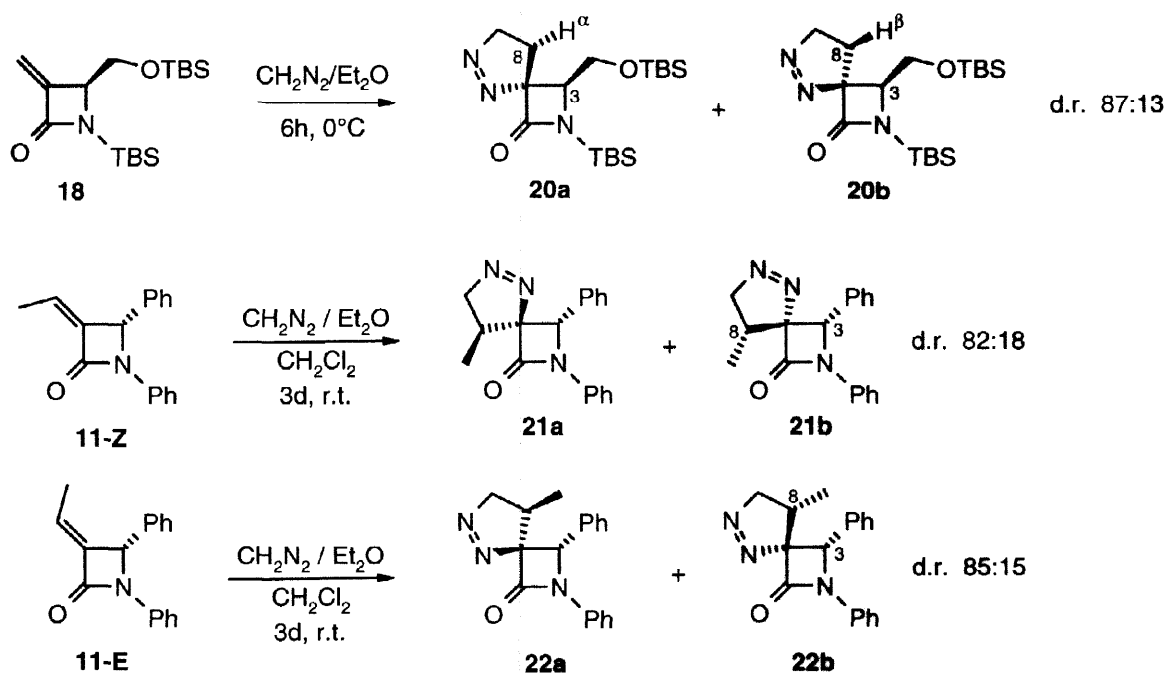
Both TBS groups of **18** could be removed by treatment with HCl/water/MeOH (formation of **19a**) without opening the lactam ring or giving a ring transformation to a butyrolactone.[18] Selective removal of the N-TBS group of **18** was achieved with potassium fluoride in methanol[19] affording **19b** (Scheme 4).



Reagents: (a) $HCl/H_2O/MeOH$; (b) KF/MeOH

Scheme 4

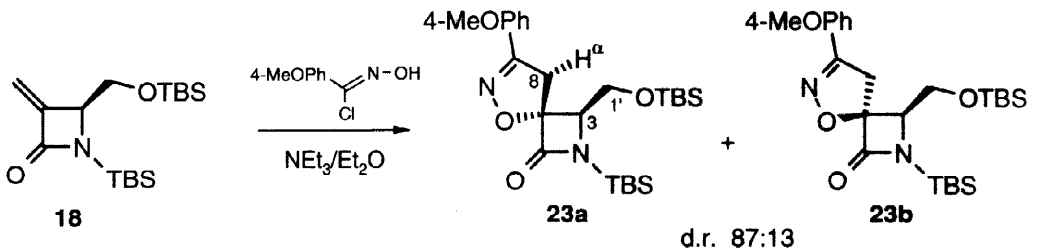
Diazomethane gave a clean reaction to the α-methylene-ß-lactam **18** affording spiropyrazolines **20a** and **20b** (d.r. 87:13, 93%) with preference of *anti*-addition with respect to the CH_2OTBS substituent (Scheme 5). These isomers could not be separated by column chromatography. The α-ethylidene-ß-lactams **11-Z** and **11-E** reacted much more slowly with diazomethane affording pyrazolines **21a/21b** (97%) and **22a/22b** (quantitative), respectively (Scheme 5). The stereoselectivity (82:18 and 85:15, respectively) was in the same magnitude as the cycloaddition of diazomethane to the methylene-ß-lactam **18**. The diastereomers were obtained in pure form by column chromatography. It is worth mentioning that we observed the formation of stereoisomeric products rather than tautomers as reported by Otto et al. for the analogous cycloaddition of diazomethane in the racemic case.[7] Furthermore we obtained much higher yields.



Scheme 5

The structure of **21a** was determined by X-ray crystal analysis (Fig. 1). The configurations of the other spiro-pyrazolines **20a/20b**, **21b**, and **22b** were assigned on the basis of qualitative NOE's. In **20a** and **b** the NOE's between the protons of the CH_2OTBS-group and 8-H^{α} (**20a**) and protons 3-H and 8-H^{β} (**21b**) were decisive for structure assignment. In analogy protons 3-H in **21b** and **22b** gave a positive NOE to 8-H and the 8-CH_3-group, respectively. Furthermore the anisotropy effects of the C-3-phenyl groups in the cycloadducts **21** and **22** to the 3-ethylidene-1,4-diphenyl-ß-lactams **11-Z** and **11-E** supported the given configurations. Attempts to include diphenyldiazomethane or ethyl diazoacetate in cycloadditions to lactams **11-Z**, **11-E** or **18** were unsuccessful. No reaction was observed even at high pressure conditions (9.5 kbar).

4-Methoxybenzonitrile oxide[20] turned out to give a cycloaddition just with the more reactive α-methylene-ß-lactam **18**. Similar diastereoselectivities (**23a**:**23b** = 87:13, 95%) were observed as in the previous cases, but this time the isomers were difficult to separate by chromatography.



Scheme 6

The configuration of the major diastereomer **23a** was established by X-ray crystal analysis (Fig. 2) and NOE investigations. Thus, one of the protons at C-1' in **23a** showed an NOE effect to 8-H^{α} in the 600 MHz-NOESY spectrum. No reaction could be achieved with the electron poor carbethoxyformonitrile oxide.

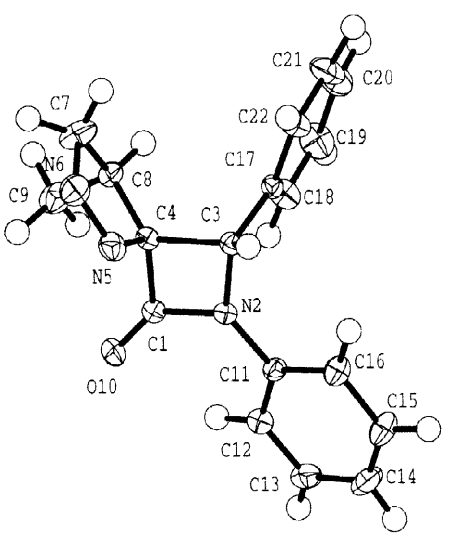


Figure 1: X-ray crystal analysis of **21a**

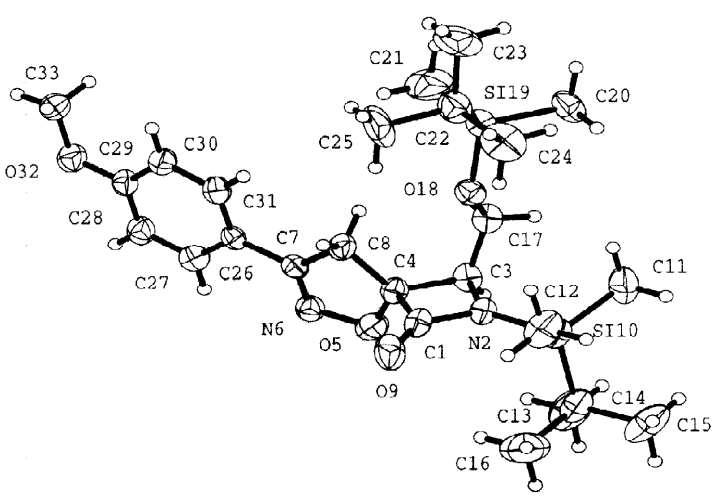
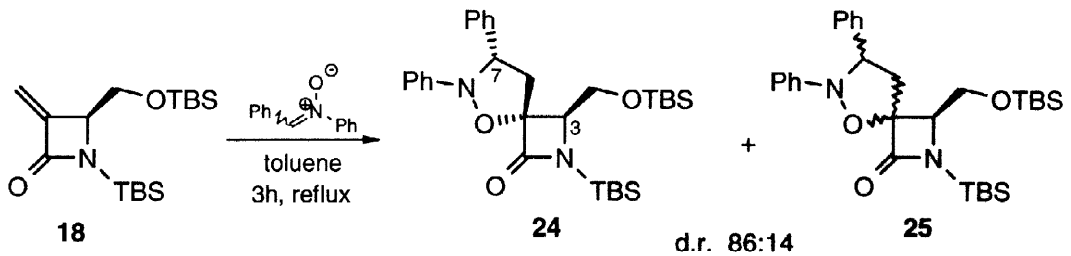


Figure 2: X-ray crystal analysis of **23a**

Diphenylnitrone gave a cycloaddition with the α-methylene-ß-lactam **18** in refluxing toluene forming the diastereomeric spiroisoxazolidines **24** and **25** (d.r. 86:14, 82%) again with strong preference of the *anti*-attack. The major diastereomer **24** could be obtained in pure state by crystallization.



Scheme 7

The configuration of **24** is based on NOE experiments, which are summerized in Figure 3. So, the protons at C-1' showed an NOE effect to H^{α} at C-8, while the geminal 8-H^{β} gave a positive effect to 7-H and therefore proved their *cis*-relationship. No proposal for the configuration of the minor isomer **25** could be given. Remarkably, the nitrone cycloadduct **24** showed a relative configuration at C-3 and C-7 which was opposite to that reported by Basak et al. [10] for the spiroisoxazolidine **6** obtained by cycloaddition of diarylnitrones **5** to the methylene-ß-lactams **4**. [21] Since the reported configuration was assumed just on the basis of secondary orbital interactions a verification by experimental structure determination seems to be necessary.

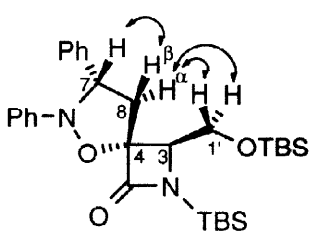
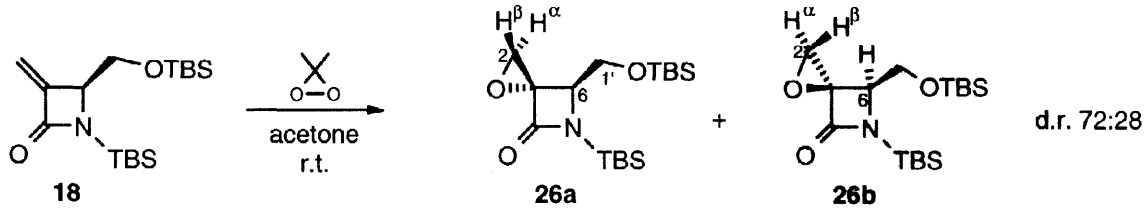


Figure 3: NOE investigations of the spiroisoxazolidine **24**

A cycloaddition of the diphenylnitrone to the ethylidene-ß-lactam **11-Z** was incomplete (50% conversion) even after 17 h of reflux. Performing the reaction in boiling xylene (18 h) gave a complete conversion but the resulting mixtures of regio and stereoisomers could not be separated by chromatography.

Epoxidation of **18** was achieved with dimethyldioxirane in acetone in high yield (93%) and with slightly lower stereoselectivity (d.r. 72:28) than in the 1,3-dipolar cycloadditions. The major isomer **26a** could be separated in pure state by chromatography. Analogous epoxidations were possible with the α-ethylidene-ß-lactams **11-E** and **11-Z**, but reaction times were much longer. Although the stereoselectivities were higher (85:15 and >95:5, respectively) problems arose in the isolation of the stereoisomers.



Scheme 8

The configurations of cycloadducts **26a** and **26b** were established by difference NOE spectroscopy, again. The positive NOE between the protons 1'-H of the CH_2OTBS group and 2-H^{α} in **26a** indicates their proximity, and therefore the given configuration at the spiro carbon-atom. In the minor diastereomer **26b** an NOE effect was found between 2-H^{β} and 6-H.

In conclusion, cycloadditions to α-alkylidene-ß-lactams **11-Z, 11-E** and **18** enabled the synthesis of new optically active derivatives of ß-lactams. Most of the cycloadditions run with complete regioselectivity but only with diastereoselectivities around 80:20. In most cases at least the major product could be obtained in pure state. As could be supposed, the α-methylene-ß-lactam **18** exhibited a higher reactivity than ethylidene-ß-lactams **11-E** and **11-Z**. The CH_2OTBS moiety found in the cycloadducts derived from **18** should offer the possibility of establishing tricyclic systems related to the carbapenam series.[4d, 22, 23] In addition, reductive ring opening of the pyrazoline, isoxazolidine, or isoxazoline ring of cycloadducts would be an approach to α-heteroatom substituted β-lactams.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker DPX-300. Chemical shifts were given in ppm downfield from TMS, while coupling constants were given in Hz. 2D-NOESY spectrum of compound **23a** was measured at 600 MHz on a Bruker AMX-600. Diastereomeric ratios were determined by ^{1}H NMR. Mass spectra (HP 5995 A) and high-resolution mass spectra (MAT 711, Varian) were measured at 70 eV. Optical rotation was determined with a Perkin Elmer polarimeter 241. IR spectra were measured on a FT-IR spectrometer (Perkin Elmer). Elemental analyses were obtained on Leco CNHS-932 analysator. T.l.c. plates were purchased from Merck (Silica gel 60 F_{254}). For preparative column chromatography silica gel (0.04-0.063 mm, Baker) was used. Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without purification. THF, Et_2O and toluene were distilled from sodium benzophenone ketyl and stored over molecular sieve A4 under argon. CH_2Cl_2 and MeOH were dried with P_4O_{10} and Mg-turnings, respectively. Starting materials **9**[12] and **12**[16, 22] were prepared according to known procedures. Diazomethane was prepared from Diazald® as about 0.8 M solution in Et_2O using the „Diazald-Kit" from Aldrich.[24] Dimethyldioxirane was produced as solution in acetone from $KHSO_5$ using Adams procedure.[25] All air and moisture sensitive reactions were performed in flame-dried glassware fitted with rubber septa under dry argon.

(1'*R*, 3*R*, 4*R*)-3-[1-(Methansulfonyloxy)-ethyl]-1,4-diphenyl-azetidin-2-one (10). Triethylamine (3.2 g, 31.6 mmol) and mesyl chloride (3.4 g, 29.7 mmol) were added to a solution of 3-(1'-hydroxyethyl)-1,4-diphenyl-azetidin-2-one **9** (6.76 g, 25.76 mmol) in CH_2Cl_2 (600 ml) at 0 °C. After stirring at 0 °C for 1 h and at r.t. for further 1 h the solution was concentrated to about one fourth of its volume. Triethylamine hydrochloride was precipitated by addition of Et_2O and was removed by filtration through Celite. The filtrate was concentrated and purified from remainings of hydrochloride by filtration using a short silica gel column (3.5x5cm) with Et_2O as eluent. After evaporation **10** was obtained and used without further purification. Crude yield: 8.79 g, 100%, colourless crystals, R_f = 0.30 (n-hexane/ethyl acetate: 1/1); ^{1}H NMR ($CDCl_3$) δ 1.65 (3H, d, *J* = 6.4, 2'-H_3), 3.02 (3H, s, $SO_2C\underline{H}_3$), 3.34 (1H, dd, *J* = 2.6 and 4.5, 3-H), 5.02 (1H, d, *J* = 2.6, 4-H), 5.23 (1H, dq, *J* = 4.5 and 6.4, 1'-H), 6.99-7.42 (10H, m, aromat); ^{13}C NMR ($CDCl_3$) δ 19.0 (q, C-2'), 38.7 (q, $\underline{C}H_3SO_3$), 56.8 (d, C-3), 63.6 (d, C-4), 74.3 (d, C-1'), 117.0, 124.1, 125.8, 128.7, 129.0, 129.2 (d, aromat), 136.6, 136.9 (s, aromat), 162.9 (s, C-2).

(4*S*)-*Z*-3-Ethylidene-1,4-diphenyl-azetidin-2-one (11-Z). A solution of crude mesyloxyethyl compound **10** (8.79 g, 25.67 mmol) and $NaHCO_3$ (3.5 g, 41.7 mmol) in dry MeOH (150 ml) was refluxed for 5 h. After cooling to r.t. water (200 ml) was added, the solution was neutralized with 2 M HCl and extracted with CH_2Cl_2 (3x150 ml). The organic phase was washed with brine (80 ml), dried (Na_2SO_4) and concentrated under vacuum. The remaining colourless crystalline product **11-Z** was recrystallized from ethyl acetate/MeOH twice. Yield: 3.48 g, 55%, colourless crystals, m.p. 189 °C, R_f = 0.47 (n-hexane/ethyl acetate: 7/3); $[\alpha]_D^{20}$ = +158.1 (c = 1.0 in $CHCl_3$); IR (KBr) 1726 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 2.10 (3H, d, *J* = 7.2, 2'-H_3), 5.29 (1H, d, *J* = 1.1, 4-H), 5.63 (1H, dq, *J* = 1.1 and 7.2, 1'-H), 6.9-7.45 (10H, m, aromat); ^{13}C NMR ($CDCl_3$) δ 14.7 (q, $CH\underline{C}H_3$), 62.6 (d, C-4), 116.8, 123.6, 126.4, 127.2, 128.5, 128.9, 129.0 (d, aromat, olefin), 137.2, 137.9, 141.9 (s, aromat, olefin), 161.8 (s, C-2); MS (EI) *m/z* 249 (M^+, 37), 180 (28), 129 (75), 115 (70), 91 (13), 77 (100), 51 (47).

(4*S*)-*E*-3-Ethylidene-1,4-diphenyl-azetidin-2-one (11-E). A solution of **11-Z** (1.5 g, 6.02 mmol) and DBU (0.90 ml, 6.02 mmol) in dry toluene (40 ml) was refluxed for 3 h. After evaporation of the solvent under vacuum the remaining solid was submitted to column chromatography (n-hexane/ethyl acetate: 15/1) resulting in 672 mg of pure **11-E**, 55 mg of a mixture of **11-E** and **11-Z**, and 578 mg **11-Z**. Total yield: 94%, m.p. 173 °C (ethyl acetate/MeOH), R_f = 0.37 (n-hexane/ethyl acetate: 7/3); $[\alpha]_D^{20}$ = +77.6 (c = 1.0 in $CHCl_3$); IR (KBr) 1732 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 1.58 (3H, d, *J* = 7.2, 2'-H_3), 5.43 (1H, d, *J* = 1.5, H-4), 6.32 (1H, dq, *J* = 1.5 and 7.2, 1'-H), 6.95-7.48 (10H, m, aromat); ^{13}C NMR ($CDCl_3$) δ 13.3 (q, C-2'), 62.7 (d, C-4), 116.8, 123.6, 123.7, 127.0, 128.7, 129.0, 129.0 (d, aromat, olefin), 136.6, 137.8, 142.6 (s, aromat, olefin), 161.5 (s, C-2).

(3*S*, 4*R*)-1-(tert-Butyldimethylsilyl)-4-(tert-butyldimethylsilyloxymethyl)-3-methyl-3-phenylselenyl-azetidin-2-one (13a) and (3*R*, 4*R*)-1-(tert-butyldimethylsilyl)-4-(tert-butyldimethylsilyloxymethyl)-3-methyl-3-phenylselenyl-azetidin-2-one (13b) *Method (a).* A solution of (4*S*)-1-(tert-butyldimethylsilyl)-4-

(tert-butyldimethylsilyloxymethyl)-azetidin-2-one **12** (96 mg, 0.291 mmol) in dry THF (1.5 ml) was added dropwise to a 0.5 M LDA-solution (1.8 ml, 0.90 mmol) in THF/n-hexane (2:1) at -78 °C. After stirring for 1 h phenylselenyl bromide (76 mg, 0.322 mmol) was added in one portion. The phenylselenyl bromide dissolves slowly. After 2 h of stirring at -78 °C methyl iodide (55µl, 0.88 mmol) was added. The mixture was allowed to warm up to r.t. overnight and was then poured into saturated aqueous NH_4Cl-solution (20 ml). The solution was extracted with $CHCl_3$ (3x30 ml). After drying over Na_2SO_4 the solvent was evaporated under vacuum. The residue contained traces of monomethyl product **14** that was removed by column chromatography (n-hexane/Et_2O: 95/5) affording the pure mixture of diastereomers **13a** and **13b** (d.r. 77:23) as yellowish oil. Yield: 67 mg, 46%.

Spectra were obtained from the diastereomeric mixture.

13a: ^{1}H NMR ($CDCl_3$) δ 0.09 and 0.11 (each 3H, s, $Si(C\underline{H}_3)_2$), 0.21 and 0.24 (each 3H, s, $Si(C\underline{H}_3)_2$), 0.91 and 0.93 (each 9H, s, 2 x $SiC(C\underline{H}_3)_3$), 1.60 (3H, s, 3-$C\underline{H}_3$), 3.47 (1H, t, *J* = 5.7, 4-H), 3.76 (1H, dd, *J* = 5.7 and 10.9, 1'-H), 3.99 (1H, dd, *J* = 5.7 and 10.9, 1'-H'), 7.2-7.8 (5H, 2 x m, aromat); ^{13}C NMR ($CDCl_3$) δ -5.6 to -5.3 (q, 2 x $Si(\underline{C}H_3)_2$), 18.3, 18.4 (s, 2 x $Si\underline{C}(CH_3)_3$), 23.6 (q, $\underline{C}H_3$), 26.0, 26.2 (q, 2 x $SiC(\underline{C}H_3)_3$), 57.3 (s, C-3), 64.7 (d, C-4), 64.9 (t, C-1'), 126.5 (s, aromat), 128.4, 128.7, 137.1 (d, aromat), 175.9 (s, C-2).

13b: ^{1}H NMR ($CDCl_3$) δ 0.02-0.09 (12H, 3 x s, 2 x $Si(C\underline{H}_3)_2$), 0.85 and 0.89 (each 9H, s, 2 x $SiC(C\underline{H}_3)_3$), 1.58 (3H, s, 3-CH_3), 3.56 (1H, dd, *J* = 5.3 and 6.8, 4-H), 3.69 (1H, dd, *J* = 6.8 and 10.6, 1'-H), 3.76 (1H, dd, *J* = 5.3 and 10.6, 1'-H'), 7.25-7.75 (5H, m, 2 x aromat) ; ^{13}C NMR ($CDCl_3$) δ -6.0, -5.7, -5.51, -5.46 (q, 2 x $Si(\underline{C}H_3)_2$), 16.1 (q, $\underline{C}H_3$), 18.17, 18.20 (s, 2 x $Si\underline{C}(CH_3)_3$), 26.0, 26.2 (q, 2 x $SiC(\underline{C}H_3)_3$), 56.4 (s, C-3), 61.5 (d, C-4), 63.1 (t, C-1'), 126.5 (s, aromat), 128.9, 129.0, 137.4 (d, aromat), 175.4 (s, C-2).

Method (b). A solution of **12** (256 mg, 0.777 mmol) in dry THF (2 ml) was slowly added drop by drop to a 0.49 M LDA-solution (4.9 ml, 2.303 mmol) in THF/n-hexane (2:1) under stirring at -78 °C. After 15 min a solution of methyl iodide (53.2 µl, 0.85 mmol) in THF (1.5 ml) was added drowise at -78 °C causing formation of a precipitate. Stirring was continued at -78 °C for 15 min. The precipitate dissolved on exchanging the cooling bath by an ice bath for about 3 min. After cooling to -78 °C again a solution of phenylselenyl bromide (201 mg, 0.852 mmol) in dry THF (4 ml) was added dropwise under vigorous stirring. The solution was stirred at -78 °C for 2 h and without a cooling bath for 20 min. The mixture was quenched by pouring into saturated aqueous NH_4Cl (20 ml). Extraction with CH_2Cl_2 (3x25 ml), wasching with brine (20 ml), drying (Na_2SO_4) and evaporation under vacuum yielded an oil. It was purified by column chromatography (n-hexane/Et_2O: 9/1) affording a diastereomeric mixture of **13a** and **13b** (10:90). Yield: 216 mg, 55%.

An attempt to increase the scale of this procedure to 3.84 g of **12** (11.65 mmol) and using MeI and PheSeBr without a solvent gave a comparable yield of **13a** and **13b**, but the material contained some 3,3-dimethyl-ß-lactam **15** that could hardly be separated by chromatography. After oxidation the mixture of **18** and **15** (87:13) was also used in the cycloaddition reactions since **15** was inert towards 1,3-dipoles.

(4*S*)-1-(tert-Butyldimethylsilyl)-4-(tert-butyldimethylsilyloxymethyl)-3-methylene-azetidin-2-one (18). A solution of 30% aqueous H_2O_2 (140 µl, 1.36 mmol) was added dropwise to a solution of pyridine (69 µl, 0.851 mmol) and a mixture of **13a** and **13b** (10:90) (216 mg, 0.433 mmol) in CH_2Cl_2 (10 ml) at r.t.. After stirring for 2 h the temperature was increased to 40 °C for 40 min. The solution was diluted with CH_2Cl_2 (20 ml), dried over $MgSO_4$, filtered and concentrated. Column chromatography (n-hexane/Et_2O: 5/1) afforded **18** as a colourless oil. Yield: 108 mg, 73%. R_f = 0.37 (n-hexane/Et_2O: 2/1); IR (neat) 1747 cm $^{-1}$ (CO); ^{1}H NMR ($CDCl_3$) δ 0.03 (6H, s, Si(C<u>H</u>$_3$)$_2$), 0.2-0.27 (6H, 2 x s, Si(C<u>H</u>$_3$)$_2$), 0.83-0.98 (18H, 2 x s, 2 x SiC(C<u>H</u>$_3$)$_3$), 3.61 (1H, dd, *J* = 6.4 and 10.6, 1'-H), 3.80 (1H, dd, *J* = 4.9 and 10.6, 1'-H'), 4.04 (1H, m, 4-H), 5.12 (1H, t, *J* = 1.1, olefin. *E*-<u>H</u>), 5.60 (1H, t, *J* = 1.3, olefin. Z-<u>H</u>); ^{13}C NMR ($CDCl_3$) δ -5.6, -5.51, -5.46, -5.3 (q, 2 x Si(<u>C</u>H$_3$)$_2$), 18.3, 18.5 (s, 2 x Si<u>C</u>(CH$_3$)$_3$), 25.8, 26.2 (q, 2 x SiC(<u>C</u>H$_3$)$_3$), 59.8 (d, C-4), 65.2 (t, C-1'), 109.3 (t, C-1''), 149.7 (s, C-3), 168.1 (s, C-2); MS (EI) *m/z* 242 (M^++1, 23), 326 (6.4), 284 (100), 230 (81), 147 (34); Anal. Calcd. for $C_{17}H_{35}NO_2$: C, 59.77; H, 10.33; N, 4.10; found: C, 59.78; H, 10.41; N, 4.14.

(4*R*)-1-(tert-Butyldimethylsilyl)-4-(tert-butyldimethylsilyloxymethyl)-3,3-bis(phenylselenyl)-azetidin-2-one (16) (*Method (c)*). A 1.6 M solution of n-BuLi in hexane (0.625 ml, 1.00 mmol) was added dropwise to a solution of hexamethyldisilazane (220 µl, 1.043 mmol) in THF (1.5 ml) at -15 °C, stirred for 15 min and then cooled to -78 °C. After dropwise addition of the α-unsubstituted β-lactam **12** (130 mg, 0.38 mmol) in THF (1.8 ml) to the resulting LiHMDS-solution and further stirring for 45 min phenylselenyl chloride (192 mg, 1.00 mmol) in THF (2.5 ml) was added to the enolate-solution. Stirring was continued at -78 °C for 2 h and after removal of the cooling bath for further 1.5 h. The reaction was quenched with NH_4Cl-solution (10 ml) and extracted with Et_2O (3x15 ml). Drying of the combined organic phases (Na_2SO_4) and evaporation afforded a yellow oil (365 mg), which was chromatographed on silica gel (n-hexane/Et_2O: 97/3) yielding 101 mg of the diselenylated β-lactam **16** as a yellow oil and further 45 mg of a fraction containing **16** and the monoselenylated compound **17** (90:10) (total yield: 58%). R_f = 0.37 (Hexan/Et_2O: 95/5); ^{1}H NMR ($CDCl_3$) δ - 0.08, -0.03, 0.04 and 0.06 (each 3H, s, 2 x Si(C<u>H</u>$_3$)$_2$), 0.76 and 0.90 (each 9H, s, 2 x SiC(C<u>H</u>$_3$)$_3$), 3.63 (1H, dd, *J* = 4.9 and 6.6, 4-H), 3.69 (1H, dd, *J* = 6.6 and 10.5, 1'-H), 3.97 (1H, dd, *J* = 4.9 and 10.5, 1'-H'), 7.21-7.40 (6H, m, aromat), 7.66, 7.79 (4H, 2 x d, aromat); ^{13}C NMR ($CDCl_3$) δ -6.14, -6.09, -5.8, -5.4 (q, 2 x Si(<u>C</u>H$_3$)$_2$), 18.0, 18.3 (s, 2 x Si<u>C</u>(CH$_3$)$_3$), 25.8, 25.9 (q, 2 x SiC(<u>C</u>H$_3$)$_3$), 54.2 (s, C-3), 63.8 (d, C-4), 65.2 (t, C-1'), 127.3, 127.9 (s, aromat), 128.7, 128.9, 129.1, 129.2, 136.8, 137.2 (d, aromat), 171.0 (s, C-2); HRMS Calcd. for $C_{28}H_{43}NO_2Si_2Se_2$ + 1H: 642.1241, found 642.1243; MS (EI) *m/z* 642 (M^++1, 18), 626 (5), 484 (100), 456 (55), 427 (24), 353 (45), 288 (54), 213 (26), 157 (10), 73 (67), 57 (43).

One-pot procedure for the preparation of 18 starting from the bis-selenoacetal 16 (*Method (d)*). n-BuLi in hexane (0.95 ml of a 1.6 M-solution, 0.15 mmol) was added dropwise to a solution of **16** (92 mg, 0.144 mmol) in dry THF (3 ml) at -60 °C. After stirring for 40 min methyl iodide (45 µl, 0.723 mmol) was added in one portion and the solution was stirred at the same temperature for further 30 min. Afterwards, the solution was allowed to warm up to r.t. within 4 h and then poured into aqueous NH_4Cl (15 ml). Extraction

with CH_2Cl_2 (3x20 ml), drying (Na_2SO_4) and evaporation afforded an oily residue, which was dissolved in CH_2Cl_2 (4 ml) without further purification. Pyridine (23 µl, 0.284 mmol) and aqueous H_2O_2 (45 µl of a 30%-solution, 0.427 mmol) were added at r.t., the solution was stirred at this temperature for 2 h and at 40 °C for further 1 h. After evaporation and chromatography on silica gel (n-hexane/ethyl acetate: 9/1) 21 mg of pure **18** were obtained (43% starting from **16**).

(4*S*)-4-(Hydroxymethyl)-3-methylene-azetidin-2-one (19a). 2 M aqueous HCl (0.3 ml) was added to a solution of α-methylene-ß-lactam **18** (54.5 mg, 0.16 mmol) in MeOH (3 ml). The mixture was stirred at r.t. until the reaction had gone to completion (t.l.c.) and was then neutralized by adding solid $NaHCO_3$. After dilution with $CHCl_3$ (30 ml), drying (Na_2SO_4), filtration and evaporation the remaining oil was purified by column chromatography ($CHCl_3$/MeOH: 9/1). Yield: 13.9 mg, 77%; colourless oil, R_f = 0.21 ($CHCl_3$/MeOH: 9/1); ^{1}H NMR ($CDCl_3$) δ 2.59 (1H, br, OH), 3.73 (1H, dd, *J* = 6.8 and 11.3, 1'-H), 3.89 (1H, dd, *J* = 4.1 and 11.3, 1'-H'), 4.27 (1H, m, 4-H), 5.27 (1H, t, *J* = 1.3, olefin. *E*-H), 5.76 (1H, t, *J* = 1.6, olefin. *Z*-H), 7.60 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 58.2 (d, C-4), 63.4 (t, C-1'), 111.4 (t, C-1''), 147.0 (s, C-3), 164.7 (s, C-2).

(4*S*)-4-(tert-Butyldimethylsilyloxymethyl)-3-methylene-azetidin-2-one (19b). Potassium fluoride in MeOH (0.486 ml of a 0.06 M solution, 29.3 µmol) was added to a solution of α-methylene-ß-lactam **18** (10 mg, 29.3 µmol) in dry MeOH (0.5 ml). After stirring at r.t. for 6 h a 0.293 M solution of acetic acid in MeOH (0.1 ml, 29.3 µmol) was added and stirring was continued for further 15 min. The solution was concentrated and the residue purified by chromatography using a short column ($CHCl_3$/MeOH: 90/10). Yield: 7 mg, quantitative, colourless oil, R_f = 0.11 (n-hexane/Et_2O: 1/1); IR (KBr) 1760 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 0.06 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 3.67 (1H, dd, *J* = 6.4 and 10.6, 1'-H), 3.81 (1H, dd, *J* = 4.9 and 10.6, 1'-H'), 4.19 (1H, m, 4-H), 5.25 (1H, s, olefin. *E*-H), 5.74 (1H, t, *J* = 1.5, olefin. *Z*-H), 6.38 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ -5.42, -5.39 (q, $Si(CH_3)_2$), 18.2 (s, $SiC(CH_3)_3$), 25.8 (q, $SiC(CH_3)_3$), 57.8 (d, C-4), 65.1 (t, C-1'), 111.0 (t, C-1''), 148.0 (s, C-3), 163.6 (s, C-2).

(3*S*, 4*R*)-2-(tert-Butyldimethylsilyl)-3-(tert-butyldimethylsilyloxymethyl)-2,5,6-triaza-spiro[3,4]-oct-5-en-1-one (20a) and (3*S*, 4*S*)-2-(tert-butyldimethylsilyl)-3-(tert-butyldimethylsilyloxymethyl)-2,5,6-triaza-spiro[3,4]-oct-5-en-1-one (20b). An about 0.6 M solution of diazomethane in Et_2O (4 ml, 2.4 mmol) was added to a solution of α-methylene-ß-lactam **18** (43 mg, 0.126 mmol) in Et_2O (3 ml) at 0 °C. After stirring at 0 °C for 6 h the solvent was evaporated and the remaining yellow oil was purified by chromatography (n-hexane/Et_2O: 5/1). Yield 45 mg, 93%; **20a**:**20b** = 87:13 (not separable), light yellowish oil, (R_f = 0.13-0.19, n-hexane/Et_2O: 2/1); HRMS Calcd. for $C_{18}H_{37}N_3O_2Si_2$: 383.2424, found 383.2426; MS (EI) *m/z* 383 (M^+, 0.37), 326 (3.9), 169 (36), 147 (47), 100 (18), 75 (57), 73 (100), 57 (22).

The following spectra were obtained from the diastereomeric mixture.

20a: ^{1}H NMR ($CDCl_3$) δ 0.02 and 0.05 (each 3H, s, Si(C<u>H</u>$_3$)$_2$), 0.28 and 0.33 (each 3H, s, Si(C<u>H</u>$_3$)$_2$), 0.84 and 1.01 (each 9H, s, SiC(C<u>H</u>$_3$)$_3$), 1.80 (1H, ddd, J = 7.2, 9.1 and 13.6, 8-H$^{\alpha}$), 1.97 (1H, ddd, J = 6.0, 8.3 and 13.6, 8-H$^{\beta}$), 3.68 (1H, dd, J = 7.5 and 10.9, 1'-H), 3.82 (1H, dd, J = 3.4 and 10.9, 1'-H'), 4.08 (1H, dd, J = 3.4 and 7.5, 3-H), 4.53 (2H, m, 7-<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$) δ -5.63, -5.58, -5.5, -5.4 (q, 2 x Si(<u>C</u>H$_3$)$_2$), 18.0, 18.5 (s, 2 x Si<u>C</u>(CH$_3$)$_3$), 18.9 (t, C-8), 25.7, 26.1 (q, 2 x SiC(<u>C</u>H$_3$)$_3$), 58.2 (d, C-3), 61.9 (t, C-1'), 77.3 (t, C-7), 105.7 (s, C-4), 169.9 (s, C-1).

20b: ^{1}H NMR ($CDCl_3$) δ 0.02 and 0.05 (each 3H, s, Si(C<u>H</u>$_3$)$_2$), 0.30 and 0.32 (each 3H, s, Si(C<u>H</u>$_3$)$_2$), 0.82 and 0.99 (each 9H, s, SiC(C<u>H</u>$_3$)$_3$), 2.11 (1H, ddd, J = 5.7, 9.1 and 10.3, 8-H), 3.76 (1H, dd, J = 5.7 and 7.9, 3-H), 4.00 (1H, dd, J = 5.7 and 10.2, 1'-H), 4.14 (1H, dd, J = 7.9 and 10.2, 1'-H').

(3*S*, 4*S*, 8*S*)-8-Methyl-2,3-diphenyl-2,5,6-triaza-spiro[3,4]oct-5-en-1-one (21a) and (3*S*, 4*R*, 8*R*)-8-methyl-2,3-diphenyl-2,5,6-triaza-spiro[3,4]oct-5-en-1-one (21b). Diazomethane (11 ml of a 0.8 M solution in Et_2O, 8.8 mmol) was added to a solution of **11-Z** (250 mg, 1.003 mmol) in CH_2Cl_2 (8 ml). This mixture was stirred at r.t. for 3 days in a closed flask by exclusion of light. Excess diazomethane was removed by passing a weak stream of argon through the solution. Concentration and purification of the residue by chromatography (n-hexane/ethyl acetate: 9/1) afforded 200 mg of pure **21a** and 83 mg of a diastereomeric mixture of **21a** and **21b**. Total yield: 97%. Further chromatography of the diastereomeric mixture yielded 30 mg of **21a** and 52 mg of **21b**.

21a: Colourless crystals, m.p. 153 °C (n-hexane/ethyl acetate), R_f = 0.34 (n-hexane/ethyl acetate: 7/3); $[\alpha]_D^{20}$ = -226 (c = 1.0 in $CHCl_3$); IR (KBr) 1751 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, d, J = 7.1, 8-C<u>H</u>$_3$), 1.63 (1H, m, 8-H), 4.09 (1H, dd, J = 7.1 and 18.0, 7-H$^{\beta}$), 4.65 (1H, dd, J = 8.7 and 18.0, 7-H$^{\alpha}$), 5.66 (1H, s, 3-H), 7.05-7.43 (10H, m, aromat); ^{13}C NMR ($CDCl_3$) δ 14.6 (q, 8-<u>C</u>H$_3$), 28.4 (d, C-8), 62.5 (d, C-3), 84.4 (t, C-7), 106.9 (s, C-4), 117.5, 124.5, 126.6, 129.0, 129.1, 129.2 (d, aromat), 133.1, 137.0 (s, aromat), 160.3 (s, C-1); MS (EI) *m/z* 291 (M^+, 0.9), 262 (5.5), 180 (33), 129 (100), 91 (15), 77 (90); Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42; found: C, 74.23; H, 5.92; N, 14.27.

21b: Colourless crystals, sublimation, R_f = 0.24 (n-hexane/ethyl acetate: 7/3); IR (KBr) 1740 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d, J = 7.2, 8-C<u>H</u>$_3$), 2.45 (1H, m, 8-H), 4.10 (1H, dd, J = 7.9 and 17.3, 7-H$^{\alpha}$), 4.78 (1H, dd, J = 8.3 and 17.3, 7-H$^{\beta}$), 5.13 (1H, s, 3-H), 7.05-7.55 (10H, m, aromat); ^{13}C NMR ($CDCl_3$) δ 12.9 (q, 8-<u>C</u>H$_3$), 33.1 (d, C-8), 65.1 (d, C-3), 82.9 (t, C-7), 104.7 (s, C-4), 117.6, 124.6, 127.4, 128.8, 129.0, 129.2 (d, aromat), 132.6, 136.9 (s, aromat), 160.3 (s, C-1).

Crystal structure analysis of 21a [26] : <u>Crystal data</u>: $C_{18}H_{17}N_3O$, M_r = 291.35, orthorhombic, space group $P2_12_12_1$, a = 8.3401 (13), b = 12.259 (2), c = 15.088 (3) Å, V = 1542.6 (4) Å^3, Z = 4, T = 200 K. <u>Data collection and reduction:</u> prism 1.00 x 0.48 x 0.28 mm^3, $2\Theta_{max}$ 52° on a STOE IPDS diffractometer. 1647 reflections were measured of which 1494 were unique. <u>Structure solution and refinement:</u> The structure was solved by direct methods and refined anisotropically on F^2 (program SHELXL-93, G. M. Sheldrick, University Göttingen). The final $\omega R(F^2)$ was 0.0901 for 268 parameters, conventional $R(F)$ 0.0363.

(3*S*, 4*S*, 8*R*)-8-Methyl-2,3-diphenyl-2,5,6-triaza-spiro[3,4]oct-5-en-1-one (22a) and (3*S*, 4*R*, 8*S*)-8-Methyl-2,3-diphenyl-2,5,6-triaza-spiro[3,4]oct-5-en-1-one (22b). A diazomethane-solution (10 ml of a 0.8 M solution in Et_2O, 8.0 mmol) was added to a solution of α-ethylidene-ß-lactam **11-E** (149 mg, 0.598 mmol) in dry CH_2Cl_2 (5 ml). The mixture was stirred at r.t. for 3 days in a tightly closed flask in the dark. Exceeding diazomethane was removed by passing a weak argon stream through the solution. Evaporation and chromatography of the residue on silica gel (n-hexane/ethyl acetate: 15/1) afforded 148 mg of **21a** and 27 mg of **21b** (total yield almost 100%).

22a: Colourless crystals, m.p. 142 °C (n-hexane/ethyl acetate), R_f = 0.29 (n-hexane/ethyl acetate: 7/3); $[\alpha]_D^{20}$ = -788 (c = 1.1 in $CHCl_3$); IR (KBr) 1754 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 0.03 (3H, d, *J* = 7.2, 8-C$\underline{H}_3$), 2.59 (1H, m, 8-H), 4.43 (1H, dd, *J* = 6.0 and 16.6, 7-H^{α}), 4.56 (1H, dd, *J* = 0.8 and 16.6, 7-H^{β}), 6.13 (1H, s, 3-H), 7.04-7.55 (10H, m, aromat); ^{13}C NMR ($CDCl_3$) δ 14.6 (q, 8-$\underline{C}H_3$), 30.5 (d, C-8), 62.2 (d, C-3), 84.6 (t, C-7), 107.6 (s, C-4), 117.5, 124.4, 129.0, 129.2, 129.3 (d, aromat), 134.7, 136.5 (s, aromat), 160.8 (s, C-1); Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42; found: C, 74.06; H, 6.19; N, 14.32.

22b: Colourless crystals, sublimation, R_f = 0.19 (n-hexane/ethyl acetate: 7/3); $[\alpha]_D^{20}$ = +572 (c = 0.27 in $CHCl_3$); IR (KBr) 1743 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 1.11 (3H, d, *J* = 7.2, 8-C$\underline{H}_3$), 2.69 (1H, m, 8-H), 4.48 (1H, dd, *J* = 3.0 and 17.3, 7-H^{α}), 4.60 (1H, dd, *J* = 7.2 and 17.3, 7-H^{β}), 5.47 (1H, s, 3-H), 7.00-7.56 (10H, m, aromat); ^{13}C NMR ($CDCl_3$) δ 16.2 (q, 8-$\underline{C}H_3$), 29.6 (d, C-8), 61.4 (d, C-3), 84.6 (t, C-7), 105.6 (s, C-4), 117.5, 124.6, 127.5, 128.8, 129.2 (d, aromat), 133.0, 137.0 (s, aromat), 161.8 (s, C-1).

(3*R*, 4*R*)-2-(tert-Butyldimethylsilyl)-3-(tert-butyldimethylsilyloxymethyl)-7-(4-methoxyphenyl)-5-oxa-2,6-diaza-spiro[3.4]oct-6-en-1-one (23a) and (3*R*, 4*S*)-2-(tert-butyldimethylsilyl)-3-(tert-butyl-dimethylsilyloxymethyl)-7-(4-methoxyphenyl)-5-oxa-2,6-diaza-spiro[3.4]oct-6-en-1-one (23b). A solution of triethylamine (61.2µl, 0.439 mmol) in Et_2O (4 ml) was dropped very slowly into a stirred solution of **18** (43 mg, 0.126 mmol) and 4-methoxyphenylhydroximoyl chloride (41 mg, 0.221 mmol) in dry Et_2O (4 ml). After stirring overnight water (20 ml) was added and the mixture was extracted with Et_2O (2x20 ml). The organic phase was dried (Na_2SO_4), evaporated and the residue purified by column chromatography (n-hexane/ethyl acetate: 9/1) affording 59 mg of the mixture of diastereomers **23a** and **23b** (87:13) (R_f = 0.15-0.25, n-hexane/Et_2O: 2/1). Total yield: 95%. The major diasteomer **23a** could be obtained in pure state by recrystallization from n-hexane/ethyl acetate.

23a: Colourless crystals, m.p. 126-127 °C (n-hexane/ethyl acetate), R_f = 0.23 (n-hexane/Et_2O: 2/1); $[\alpha]_D^{20}$ = -20.7 (c = 1.0 in $CHCl_3$); IR (KBr) 1746 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 0.01 and 0.02 (each 3H, s, OSi(C$\underline{H}_3$)$_2$), 0.24 and 0.29 (each 3H, s, NSi(C$\underline{H}_3$)$_2$), 0.78 (9H, s, OSiC(C$\underline{H}_3$)$_3$), 0.98 (9H, s, NSiC(C$\underline{H}_3$)$_3$), 3.55 (1H, d, *J* = 17.3, 8-H^{β}), 3.63 (1H, d, *J* = 17.3, 8-H^{α}), 3.62 (1H, dd, *J* = 7.9 and 10.9, 1'-H), 3.78 (1H, dd, *J* = 3.4 and 7.5, 3-H), 3.83 (3H, s, OC$\underline{H}_3$), 3.89 (dd, *J* = 3.4 and 10.9, 1'-H'), 6.90 (2H, d, *J* = 9.0, 2''-H), 7.56 (2H, d, *J* = 9.0, 3''-H); ^{13}C NMR ($CDCl_3$) δ -5.7, -5.6, -5.5, -5.4 (q, 2 x Si($\underline{C}H_3$)$_2$), 17.9, 18.5 (s, 2 x Si$\underline{C}$(CH$_3$)$_3$), 25.6, 26.1 (q, 2 x SiC($\underline{C}H_3$)$_3$), 36.3 (t, C-8), 55.3 (q, O$\underline{C}H_3$), 61.5 (t, C-1'), 63.8 (d, C-3), 96.0 (s, C-4), 114.1 (d, C-3''), 121.3 (s, C-1''), 128.3 (d, C-2''), 156.0 (s, C-4''), 161.1 (s, C-7), 172.5 (s, C-1); MS

(EI) *m/z* 491 (M^++1), 333 (5.4), 276 (46), 201 (60), 147 (53), 73 (100); Anal. Calcd. for $C_{25}H_{42}N_2O_4Si_2$: C, 61.18; H, 8.63; N, 5.71; found: C, 60.83; H, 8.58; N, 5.64.

23b: R_f= 0.29 (n-hexane/Et_2O: 2/1); ^{13}C NMR ($CDCl_3$) δ -5.6, -5.5, -5.3 (q, 2 x Si($\underline{C}H_3)_2$), 18.26, 18.35 (s, 2 x Si$\underline{C}(CH_3)_3$), 25.9, 26.2 (q, 2 x SiC($\underline{C}H_3)_3$), 41.9 (t, C-8), 55.4 (q, O$\underline{C}H_3$), 62.8 (t, C-1'), 67.7 (d, C-3), 92.8 (s, C-4), 114.4 (d, C-3''), 121.1 (s, C-1''), 128.7 (d, C-2''), 155.3 (s, C-4''), 161.2 (s, C-7), 172.8 (s, C-1) (obtained from the diastereomeric mixture).

Crystal structure analysis of 23a [27] : Crystal data: $C_{25}H_{42}N_2O_4Si_2$, M_r = 490.77, orthorhombic, space group $P2_12_12_1$, a = 7.161 (3), b = 19.177 (5), c = 21.540 (11) Å, V = 2958.2 (22) Å^3, Z = 4, T = 295 K. Data collection and reduction: needle 1.14 x 0.53 x 0.11 mm^3, $2\Theta_{max}$ 29.6° (MoKα) on a STOE STADI-4 diffractometer. 3851 reflections were measured of which 2388 were unique. Structure solution and refinement: The structure was solved by direct methods and refined anisotropically on F^2 (program SHELXL-93, G. M. Sheldrick, University Göttingen). The final $\omega R(F^2)$ was 0.1714 for 299 parameters, conventional $R(F)$ 0.0753.

(3*R*, 4*R*, 7*S*)-2-(tert-Butyldimethylsilyl)-3-(tert-butyldimethylsilyloxymethyl)-6,7-diphenyl-5-oxa-2,6-diaza-spiro[3.4]octan-1-one (24) and (3*R*)-2-(tert-Butyldimethylsilyl)-3-(tert-butyldimethylsilyloxymethyl)-6,7-diphenyl-5-oxa-2,6-diaza-spiro[3.4]octan-1-one (25). A solution of α-methylene-ß-lactam **18** (43 mg, 0.126 mmol) and α,N-diphenylnitrone (43 mg, 0.218 mmol) in toluene (4 ml) was refluxed for 3 h. The reaction mixture was diluted with Et_2O (20 ml) and washed with water (20 ml). The aqueous phase was extracted with Et_2O (2x20 ml). The combined etheral phases were dried (Na_2SO_4) and concentrated. Column chromatography (n-hexane/ethyl acetate: 7/3) afforded 56 mg of the mixture of diastereomers **24** and **25** (86:14) in 82% yield. Pure **24** could be obtained by recrystallization and the major portion by chromatography of the resulting mother liquid (yield 27 mg, 40%).

24: Light yellow crystals, m.p. 105-109 °C, R_f = 0.46 (n-hexane/Et_2O: 2/1); IR (KBr) 1755 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ -0.05 and -0.03 (each 3H, s, Si($C\underline{H}_3)_2$), 0.23 and 0.31 (each 3H, s, Si($C\underline{H}_3)_2$), 0.84 and 1.00 (each 9H, s, SiC($C\underline{H}_3)_3$), 2.72 (1H, dd, J = 5.65 and 12.8, 8-H$^{\alpha}$), 2.90 (1H, dd, J = 6.8 and 12.8, 8-H$^{\beta}$), 3.37 (1H, dd, J = 4.2 and 11.3, 1'-H), 3.49 (1H, dd, J = 4.2 and 11.3, 1'-H'), 3.75 (1H, t, J = 4.1, 3-H), 4.79 (1H, t, J = 6.8, 7-H), 6.92-7.53 (10H, aromat); ^{13}C NMR ($CDCl_3$) δ -5.54, -5.47 (q, 2 x Si($\underline{C}H_3)_2$), 18.1, 18.7 (s, 2 x Si$\underline{C}(CH_3)_3$), 25.8, 26.2 (q, 2 x SiC($\underline{C}H_3)_3$), 39.6 (t, C-8), 61.9 (t, C-1'), 63.9 (d, C-3), 70.8 (d, C-7), 93.5 (s, C-4), 117.3, 123.3, 126.6, 127.6, 128.5, 128.5 (d, aromat), 140.3, 151.1 (s, aromat), 173.9 (s, C-1); HRMS Calcd. for $C_{30}H_{46}N_2O_3Si_2$: 538.3047, found 538.3044; MS (EI) *m/z* 538 (M^+, 0.4), 324 (0.4), 195 (28), 181 (16), 104 (24), 91 (6.0), 77 (24), 73 (100), 57 (34).

25: Not isolated in pure state. ^1H NMR obtained from diastereomeric mixture: ^1H NMR ($CDCl_3$) δ -0.02 and 0.03 (each 3H, 2 x s, Si($C\underline{H}_3)_2$), 0.25 and 0.30 (each 3H, 2 x s, Si($C\underline{H}_3)_2$), 3.09 (1H, dd, J = 7.5 and 13.2), 4.67 (1H, t, J = 7.9) (Missing signals overlapped by major diastereomer.).

(3*S*, 6*R*)-5-(tert-Butyldimethylsilyl)-6-(tert-butyldimethylsilyloxymethyl)-1-oxa-5-aza-spiro[2.3]-hexan-4-one (26a) and (3*R*, 6*R*)-5-(tert-Butyldimethylsilyl)-6-(tert-butyldimethylsilyloxymethyl)-1-oxa-5-aza-spiro[2.3]hexan-4-one (26b). α-Methylene-ß-lactam **18** (33.7 mg, 98.74 µmol) was stirred in an about 0.1 M solution of freshly prepared dimethyldioxirane in acetone (15 ml, 1.5 mmol) over $MgSO_4$ (6.0 g) at r.t. for 3 days. After filtration and evaporation the residue was purified by column chromatography (n-hexane/Et_2O: 5/1) affording 17 mg of pure **26a** and 16 mg of a mixture of **26a** and **26b** (48:52). Total yield: 93%.

26a: Colourless oil, R_f = 0.33 (n-hexane/Et_2O: 2/1); $[\alpha]_D^{20}$ = -2.46 (c = 1.3 in $CHCl_3$); $[\alpha]_{546}$ = -3.08 (c = 1.3 in $CHCl_3$); IR (KBr) 1750 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 0.047 and 0.052 (each 3H, s, $Si(C\underline{H}_3)_2$), 0.27 and 0.30 (each 3H, s, $Si(C\underline{H}_3)_2$), 0.87 and 0.98 (each 9H, s, $SiC(C\underline{H}_3)_3$), 3.10 (1H, d, *J* = 5.7, 2-H^{α}), 3.15 (1H, d, *J* = 5.7, 2-H^{β}), 3.73 (1H, dd, *J* = 5.7 and 10.9, 1'-H), 3.80 (1H, dd, *J* = 3.8 and 10.9, 1'-H'), 3.92 (1H, dd, *J* = 3.8 and 5.3, 6-H); ^{13}C NMR ($CDCl_3$) δ -5.7, -5.6, -5.5, -5.4 (q, 2 x $Si(\underline{C}H_3)_2$), 18.1, 18.5 (s, 2 x $Si\underline{C}(CH_3)_3$), 25.7, 26.1 (q, 2 x $SiC(\underline{C}H_3)_3$), 46.7 (t, C-2), 59.8 (d, C-6), 62.5 (t, C-1'), 67.9 (s, C-3), 173.3 (s, C-4); HRMS Calcd. for $C_{17}H_{35}O_3Si_2$ + 1H: 358.2234, found 358.2231; **MS** (EI) *m/z* 358 (M^++1, 10), 300 (48), 147 (100), 143 (34), 101 (28), 75 (30), 73 (64), 57 (15).

26b: Not isolated in pure state. R_f = 0.27 (n-hexane/Et_2O: 2/1), spectra were obtained from diastereomeric mixture of **26a** and **26b**, ^1H NMR ($CDCl_3$) δ 0.06 and 0.07 (each 3H, s, $Si(C\underline{H}_3)_2$), 0.28 and 0.31 (each 3H, s, $Si(C\underline{H}_3)_2$), 0.89 and 0.98 (each 9H, s, $SiC(C\underline{H}_3)_3$), 3.02 (1H, d, *J* = 5.7, 2-H^{β}), 3.19 (1H, d, *J* = 5.7, 2-H^{α}), 3.69-3.85 (2H, 1'-H_2), 3.91-3.98 (1H, 6-H); ^{13}C NMR ($CDCl_3$) δ -5.8 to -5.5 (q, 2 x $Si(\underline{C}H_3)_2$), 18.1, 18.4 (s, 2 x $Si\underline{C}(CH_3)_3$), 25.8, 26.2 (q, 2 x $SiC(\underline{C}H_3)_3$), 47.4 (t, C-2), 59.6 (d, C-6), 62.4 (t, C-1'), 66.0 (s, C-3), 173.7 (s, C-4).

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