186. Monocarboxylates of 3-Methylidene-β-lactams: Synthesis and Unusual Oxidative Rearrangement into a Spiro[azetidine-3,3′-pyrrolidine] Derivative

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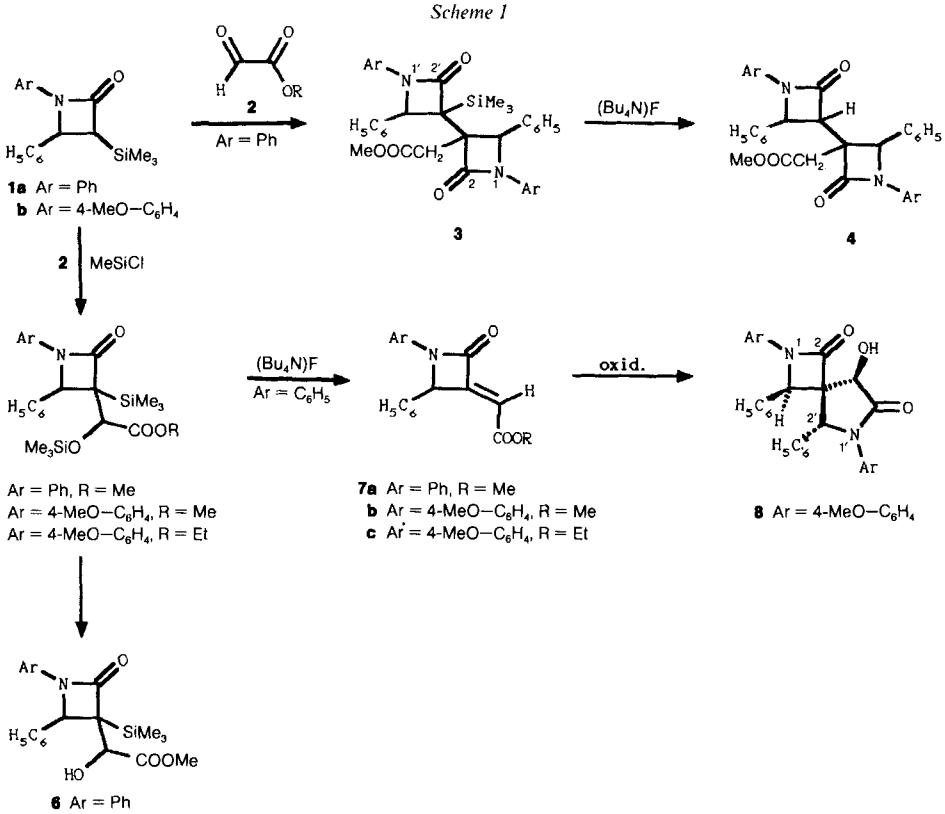
Reaction of the 3-silylated β-lactams **1** with glycoxalates gives bis-lactam **3**, but the same reaction in the presence of 1 equiv. of Me_3SiCl leads to the formation of the disilylated adducts **5**. The latter is desilylated by $(Bu_4N)F$ yielding the monocarboxylates **7** of 3-methylidene-β-lactams, which, with oxidizing agents, give the spiro compound **8**. The structure of **8** is established by spectroscopic data and a crystal-structure analysis.

Introduction. – As described in a previous paper [1], the epoxidation of the electron-poor double bond of dicarboxylates of 3-methylidene-β-lactams can be effected by a large variety of oxidizing agents yielding spiro[azetidine-3,2′-oxirane] derivatives. But until now, all experiments to open the oxirane ring by nucleophiles failed. Probably, a nucleophilic attack is not possible at the C-atoms of the tetrasubstituted oxirane. A nucleophilic ring opening of the epoxide would afford an easy route to introduce a heteroatom either into position 3 of the β-lactam ring or into the α-position of the side chain, and thereby open the possibility to develop an alternative route to potent antibiotics, hopefully being more stable against β-lactamases [2]. Therefore, we tried to synthesize the monocarboxylates **7** of 3-methylidene-β-lactams and the corresponding trisubstituted epoxides.

Results. – The silylated β-lactams **1** were prepared as reported earlier [3a]. In contrast to the *Peterson* olefination of **1** with aldehydes or ketones [3b], we obtained from the reaction with alkyl glyoxalates **2** in the presence of lithium diisopropylamide (LDA) a variety of different products depending on the reaction conditions. Under the usual conditions [3b], no olefination product from **1a** and methyl glyoxalate was formed, but we isolated the 'dimeric' compound **3** in 70% yield (*Scheme 1*). Desilylation with $(Bu_4N)F$ in THF yielded **4** (77%). Both structures were formed in analogy to the reaction between dicarboxylates of 3-methylidene-β-lactams and dialkyl mesoxalates [3a]. On the other hand, the olefination of **1** in the presence of equimolar amounts of Me_3SiCl gave the disilylated intermediates **5**, which were partially hydrolyzed to **6**. Finally, when the disilyl derivatives **5** were treated with $(Bu_4N)F$, the monocarboxylates **7** of 3-methylidene-β-lactam were obtained.

It is known, that the *Peterson* olefination does not show any stereoselectivity [4]. Therefore, we expected to obtain **7** as (*E*/*Z*)-mixtures. But the isolated products always were uniformly (*E*)-isomers as shown by TLC and spectroscopic data. Although MMX calculations [5] only result in a small energy difference of *ca.* 2 kcal/mol between the (*E*)- and (*Z*)-isomers, they may explain the preferred formation of the (*E*)-isomers.

Scheme 1



From the reaction of **7b** or **7c** with H_2O_2 in alkali [6], *t*-BuOOH [7], or KOCl [8], we always isolated one single crystalline product, which obviously was not an oxirane. Its structure **8**, a spiro[azetidine-3,3′-pyrrolidine]-2,5′-dione, is established by MS and spectroscopic data. The IR spectrum is consistent with the β-lactam ring (C=O at 1750 cm^{-1}), the pyrrolidine carbonyl group (1712 cm^{-1}), and the OH group (strong band at 3420 cm^{-1}), and the ^{1}H- and ^{13}C-NMR spectra (see *Exper. Part*) are in agreement with this proposal. Finally, a crystal-structure analysis (*Fig.*) [9] confirms the structure of this very unusual reaction product.

Compound **8** crystallizes with two slightly different molecules in the asymmetric unit (one is shown in *Fig. a*). They differ mainly in the conformation of the MeO group of the $MeOC_6H_4$ substituent at N(1′). The β-lactam ring is nearly planar, the five-membered ring prefers the envelope conformation, wherein the 4 ring atoms lay in plane, while the spiro atom is found 0.56 (0.49) Å above that plane. The C(O)–N bonds are shortened compared to chains, being 1.351 Å long in the β-lactam ring, and 1.371(0) Å in the pyrrolidinone ring. The angle between the plane of the β-lactam ring and that of the ring at N(1) is 15°, the ring at N(1′) is *ca.* 6° (28°, molecule B) twisted out of the plane. More data are given in the *Exper. Part*. The package (*Fig. b*) is characterized by intermolecular H-bonds and *van der Waals* contacts. The O–O distances in the H-bonds between OH and O(2) are 2.749 (2.680) Å.

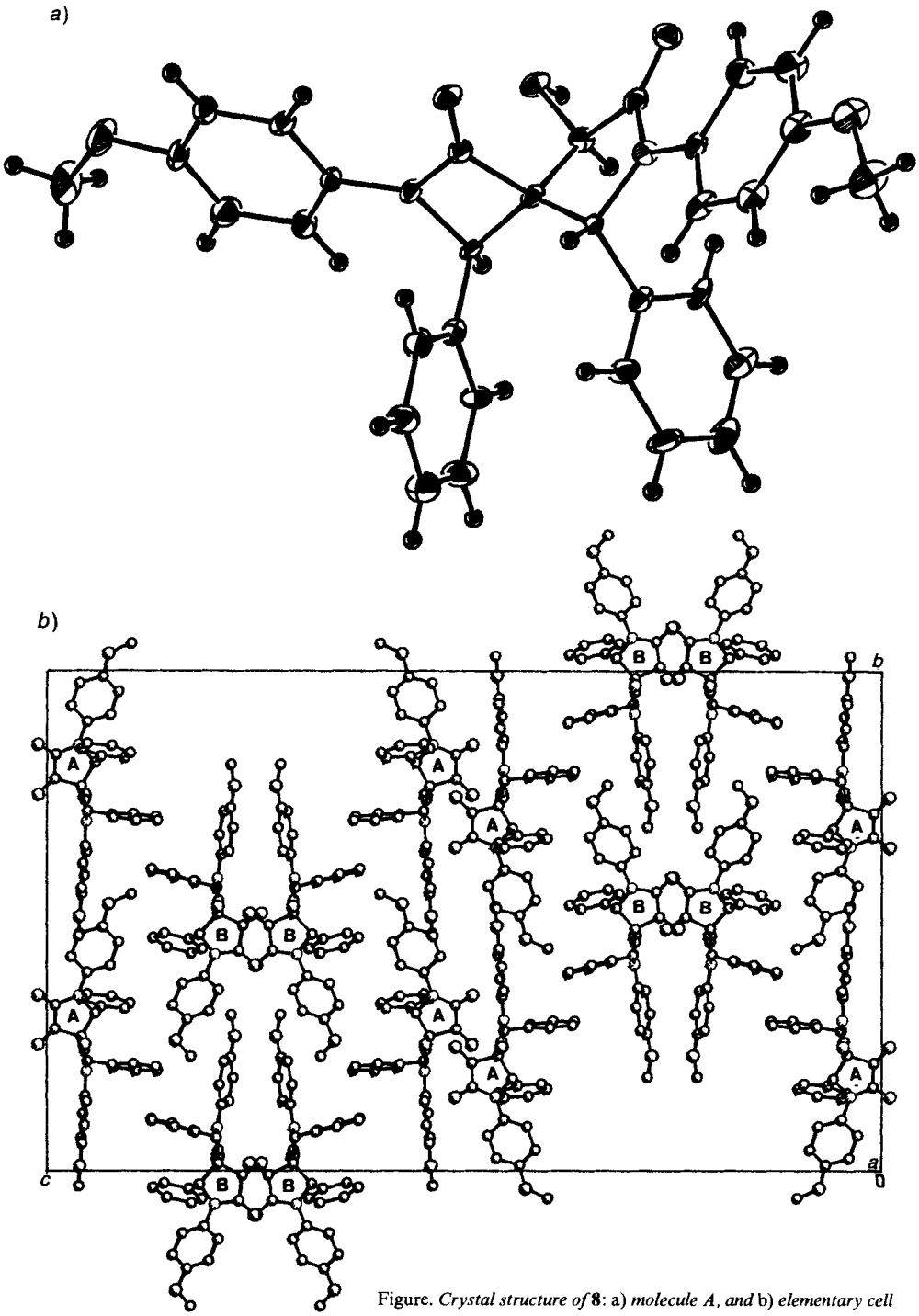
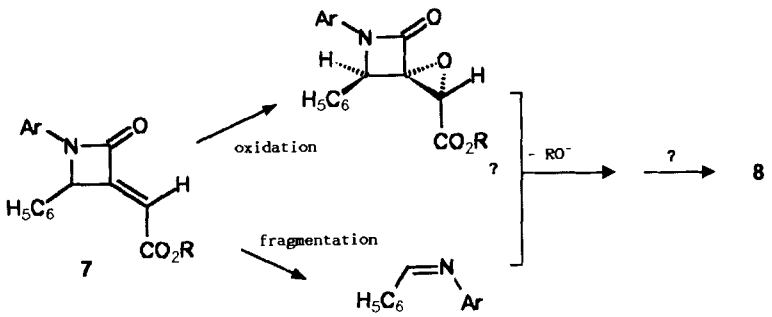


Figure. *Crystal structure of* **8**: a) *molecule A, and* b) *elementary cell*

Discussion. – The formation of structure **8** is difficult to explain. Perhaps the reaction starts with a partial transformation of the methylidene-β-lactam **7** into an oxirane and a partial fragmentation to an imine (*Scheme 2*). Similar to the formation of β-lactams *via* the imine-ketene reaction [10], the imine could be acylated by the ester group and finally form **8** by rearrangement. The C(2′) of the pyrrolidine ring and the Ph group at C(4) of the β-lactam are in *cis*-positions. The Ph group at C(2′) is directed downward, as in this position the steric interaction with the Ph group at C(4) is unimportant. This is supported by the calculated structure of **8**.

Scheme 2



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Experimental Part

General. Lithium diisopropylamide (LDA) was obtained by mixing before use equimolar amounts of $(i\text{-Pr})_2NH$ and BuLi (15% in hexane). Tetrahydrofuran (THF) was dried with $CaCl_2$ and distilled over $LiAlH_4$ prior to use. Other solvents were dried according to standard procedures. M.p.: not corrected; *Linström* apparatus. IR Spectra (cm^{-1}): *Perkin-Elmer IR 1310, Beckman IR 4240, IR 33*; in KBr. NMR Spectra: *Varian T60, Bruker WP80, WM400* for ^1H; *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): *MAT 312*, at 220°. Elementary analyses were performed at the Pharmazeutisches Institut or Chemisches Laboratorium der Universität Freiburg i. Br.

1,4-Diphenyl-3-(trimethylsilyl)azetidin-2-one (**1a**) *and 1-(4-Methoxyphenyl)-4-phenyl-3-(trimethylsilyl)azetidin-2-one* (**1b**). See [5a].

Methyl 2,2′-Dioxo-1,1′,4,4′-tetraphenyl-3′-(trimethylsilyl)-3,3′-biazetidine-3-acetate (**3**). At −78°, **1a** (3.0 g, 10 mmol) in THF (50 ml) is dropwise added to a soln. of LDA (2.15 g, 20 mmol) in THF (10 ml). After 15 min stirring, methyl glyoxalate (**2**, R = Me; 4 ml, 60 mmol) is added. The mixture is warmed to r.t. and after 1 h hydrolyzed with a sat. NH_4Cl soln., the org. layer separated, the aq. layer once washed with $CHCl_3$, and the combined org. layer dried (Na_2SO_4) and evaporated: 2.1 g (71%) of **3**. Colorless crystals. M.p. 236° (MeOH). IR: 3060, 3025, 2940 (CH), 1750–1730 (CO). ^1H-NMR: 0.0 (*s*, Me_3Si); 2.80 (*s*, CH_2); 3.6 (*s*, MeO); 5.63 (*s*, H–C(4′)); 6.10 (*s*, H–C(4)); 7.1–7.6 (*m*, 20 arom. H). Anal. calc. for $C_{36}H_{36}N_2O_4Si$ (588.76): C 73.44, H 6.16, N 4.76; found: C 73.36, H 6.22, N 4.62.

Methyl 2,2′-Dioxo-1,1′,4,4′-tetraphenyl-3,3′-biazetidine-3-acetate (**4**). To **3** (0.6 g, 1.02 mmol) in THF (20 ml), 1M $(Bu_4N)F$ in THF (1 ml) is added at r.t., the mixture stirred for 2 h, conc. HCl soln. (1 ml) added, and the mixture evaporated. The residue is extracted with a few ml of $CHCl_3$ and the extract dried (Na_2SO_4) and evaporated: 0.4 g (77%) of **4**. Colorless crystals. M.p. 219–220° (MeOH). IR: 3060, 3020, 2940 (CH), 1745 (CO). ^1H-NMR (60

MHz): 2.65 (*s*, CH_2); 3.15 (*s*, Me); 4.30, 5.32 (*d*, $J = 2.5$, H–C(3'), H–C(4')); 5.65 (*s*, H–C(4)); 6.9–7.5 (*m*, 20 arom. H). Anal. calc. for $C_{33}H_{28}N_2O_4$ (516.59): C 76.73, H 5.46, N 5.42; found: C 76.50, H 5.42, N 5.52.

Methyl [2-Oxo-1,4-diphenyl-3-(trimethylsilyl)azetidin-3-yl](trimethylsilyloxy)acetate (**5a**). At −78°, **1a** (3.0 g, 10 mmol) in THF (50 ml) is dropwise added to a soln. of LDA (2.15 g, 20 mmol) in THF (10 ml). After 15 min stirring, Me_3SiCl (3 g, 25 mmol) is added, and after another 15 min stirring methyl glyoxalate (**2**, R = Me; 4 ml, 60 mmol). With stirring the mixture is warmed to r.t. and after 1 h hydrolyzed with a sat. NH_4Cl soln., the org. layer separated, the aq. layer once extracted with 10–20 ml of $CHCl_3$, the combined org. layer dried (Na_2SO_4) and evaporated, the residue twice extracted with boiling pentane (each *ca.* 100 ml), the pentane evaporated, and the residue distilled: 1.9 g (42%) of **5a**. Light yellow, viscous liquid. B.p. 165°/0.03 Torr. IR (film): 3070, 3040, 2960, 2900, 2850 (CH), 1750–1730 (CO). ^{1}H-NMR (60 MHz): −0.13, 0.05 (2*s*, 2 Me_3Si); 3.8 (*s*, Me); 4.7 (*s*, H–C(4)); 5.7 (*s*, H–C(α)); 7.2–7.35 (*m*, 10 arom. H). ^{13}C-NMR: −1.49, −0.32 (*2q*, ^1J(C,H) = 119, Me_3Si); 51.89 (*q*, ^1J(C,H) = 148, Me); 56.67 (*d*, ^1J(C,H) = 154, C(4)); 62.19 (*s*, C(3)); 71.13 (*dd*, ^1J(C,H) = 149, ^3J(C,H) = 3, C(α)); 117.16, 123.26, 127.83, 128.22, 128.81, 136.20, 137.82 (arom. C); 167.83 (*dd*, ^3J(C,H) = 4, 2, C(2)); 172.01 (*m*, CO(ester)). Anal. calc. for $C_{24}H_{33}NO_4Si_2$ (455.68): C 63.25, H 7.30, N 3.07; found: C 63.42, H 7.26, N 3.17.

Methyl Hydroxy[2-oxo-1,4-diphenyl-3-(trimethylsilyl)azetidin-3-yl]acetate (**6**). A few ml of cyclohexane are added to the residue of the extraction (see **5a**), and after some h, the crystals are collected: 1.0 g (26%) of **6**. Colorless crystals. M.p. 109° (cyclohexane). IR: 3520, 3480 (OH), 3070, 3040, 2960, 2910 (CH), 1745, 1725 (CO). ^{1}H-NMR (60 MHz): −0.15 (*s*, Me_3Si); 3.8 (*s*, Me); 4.2 (br. *s*, OH); 4.85 (*s*, H–C(α)); 5.6 (*s*, H–C(4)); 6.9–7.5 (*m*, 10 arom. H). MS: 383 (11, M^+). Anal. calc. for $C_{21}H_{25}NO_4Si$ (383.50): C 65.77, H 6.57, N 3.65; found: C 65.73, H 6.69, N 3.76.

(E)-Methyl (2-Oxo-1,4-diphenylazetidin-3-ylidene)acetate (**7a**). To a soln. of **5a** (1.6 g, 3.5 mmol) in THF (30 ml), 1M $(Bu_4N)F$ in THF (3.5 ml) is added. After stirring for 2 h, the mixture is hydrolyzed with dil. HCl soln., the org. layer separated, the aq. layer once extracted with $CHCl_3$, and the combined org. layer dried (Na_2SO_4) and evaporated: 0.8 g (78%) of **7a**. Light yellow crystals. M.p. 165° (MeOH). IR: 3060, 3030, 3000, 2955 (CH), 1740, 1725, 1710 (CO), 1690 (C=C). ^{1}H-NMR (60 MHz): 3.6 (*s*, Me); 5.73, 6.4 (*d*, $J = 1.5$, H–C(4), H–C(α)); 6.95–7.65 (*m*, 10 arom. H). Anal. calc. for $C_{18}H_{15}NO_3$ (293.31): C 73.70, H 5.15, N 4.78; found: C 73.82, H 5.27, N 4.91.

(E)-Methyl [1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-ylidene]acetate (**7b**). From **1b** (3.25 g, 10 mmol) as described for **5a**. Without distillation, the residue (crude **5b**) is dissolved in THF (30 ml), 1M $(Bu_4N)F$ in THF (10 ml) added, and the mixture worked up as described for **7a**: 1.0 g (31%) of **7b**. Light yellow needles. M.p. 152° (MeOH). IR: 3070, 3040, 3005, 2960, 2850 (CH), 1745, 1725, 1710 (CO). ^{1}H-NMR: 3.63, 3.76 (*2s*, 2 Me); 5.78, 6.41 (*d*, $J = 1.5$, H–C(4), H–C(α)); 6.75–7.75 (*m*, 9 arom. H). Anal. calc. for $C_{19}H_{17}NO_4$ (323.35): C 70.57, H 5.30, N 4.33; found: C 70.31, H 5.39, N 4.38.

(E)-Ethyl [1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-ylidene]acetate (**7c**). From **1b** (3.25 g, 10 mmol) and ethyl glyoxalate (**2**, R = Et; 5 ml) *via* **5c**, in analogy to **7b**: 1.0 g (31%) of **7c**. Yellow crystals. M.p. 138° (EtOH). IR: 3060, 3040, 3010, 2990, 2840 (CH), 1745, 1720 (CO). ^{1}H-NMR: 1.13 (*t*, $J = 7$, Me); 3.72 (*s*, MeO); 4.03 (*q*, $J = 7$, CH_2); 5.68 (*d*, $J = 2$, H–C(4)); 6.30 (*d*, $J = 2$, H–C(α)); 6.6–7.6 (*m*, 9 arom. H). Anal. calc. for $C_{20}H_{19}NO_4$ (337.38): C 71.20, H 5.68, N 4.15; found: C 71.24, H 5.76, N 4.11.

Potassium Hypochlorite Soln. Calcium hypochlorite (100 g) is dissolved with stirring in H_2O (100 ml). After 15 min, a soln. of KOH (20 g) and K_2CO_3 (70 ml) in H_2O (125 ml) is added. After another 15 min of vigorous stirring, the precipitate is separated. The clear yellowish soln. is *ca.* 1.5–2M KOCl. It can be stored in a refrigeratore at 4° for some weeks.

4'-Hydroxy-1,1'-bis(4-methoxyphenyl)-2',4-diphenylspiro[azetidine-3,3'-pyrrolidine]-2-5'-dione (**8**). *a*) To a soln. of **7b** or **7c** (506 mg, 1.5 mmol) and $(Bu_4N)Cl$ (0.3 g) in CH_2Cl_2 (40 ml), a 25% H_2O_2 soln. (25 ml) and 0.5N KOH (6 ml) are added with vigorous stirring. After 12 h stirring, the org. layer is separated, the aq. layer twice extracted with CH_2Cl_2 (20 ml) each, and the combined org. extract washed with half-sat. NH_4Cl soln. (30 ml), dried ($MgSO_4$), and evaporated: 180 mg (46%) and 194 mg (50%) of **8**, resp.

b) Under N_2, a soln. of **7b** or **7c** (506 mg, 1.5 mmol) and pyridine (1.2 mg, 0.01 mmol) in a few ml of CH_2Cl_2 is given to solid $MoO_2(acac)_2$ (3.8 mg, 0.01 mmol). The mixture is stirred for 5 min, *t*-BuOOH (450.6 mg, 5 mmol) in benzene (20 ml) added, and the mixture refluxed for 1 h and cooled to r.t. Then aq. $NaHCO_3$ soln. (50 ml) is added, the mixture 3–4 times extracted with AcOEt (20 ml each), and the combined org. layer dried ($MgSO_4$) and evaporated: 143 mg (37%) and 143 mg (37%) of **8**, resp.

c) To a soln. of **7b** (506 mg, 1.5 mmol) in THF (50 ml), an 8-fold molar amount of KOCl soln. is added and the mixture stirred at r.t. After 10–12 h, it is extracted with AcOEt, and worked up as described under *b*): 102 mg (26%) of **8**. **8**: Colorless crystals. M.p. 260° (MeOH). IR: 3420 (OH), 3060, 3005, 2910, 2835 (CH), 1750, 1712 (CO). ^{1}H-NMR (400 MHz): 3.70 (*s*, MeO); 3.73 (*s*, MeO); 3.78 (br. *s*, OH); 4.95 (*s*, H–C(4)); 5.25 (*s*, H–C(2')); 5.45 (*s*, H–C(4')); 6.5–7.3 (*m*, 18 arom. H). ^{13}C-NMR: 55.36 ($MeOC_6H_4N$(1)); 55.43 ($MeOC_6H_4N$(1')); 61.44

(C(2')); 65.09 (C(4)); 68.53 (C(3')); 71.23 (C(4')); 114.32, 118.99, 125.73, 127.35, 127.52, 128.21, 128.53, 128.87 (arom. C); 130.11, 130.16, 133.96, 134.15, 156.22, 158.26 (quart. arom. C); 164.24 (C(2) or C(5')); 171.44 (C(5') or C(2)). EI-MS: 520 (58, M^+), 521 (21, $[M+1]^+$), 522 (4, $[M+2]^+$), 149 (100). Anal. calc. for $C_{32}H_{28}N_2O_5$ (520.58): C 73.83, H 5.42, N 5.38; found: C 73.26, H 5.39, N 5.33.

Crystal-Structure Analysis of **8**. A colorless needle-shaped crystal of $C_{32}H_{28}N_2O_5$ having approximate dimensions of 0.50 × 0.16 × 0.12 mm was mounted on a glass fibre. Measurements were made on a *Enraf-Nonius-CAD4* diffractometer with graphite monochromated CuK_α (= 1.5418 Å) radiation. The crystal belongs to the orthorhombic space group *Pbca* with $a = 8.333(1)$ Å, $b = 27.757(2)$ Å, $c = 46.138(3)$ Å, $V = 10671$ Å^3, $Z = 16$, $D_{cal} = 1.296$ gcm^{-3}. The intensities were corrected for *Lorentz* and polarization effects. A total of 8875 independent intensities were measured of which 6020 were classified as observed with $I > 3\,(I)$. The structure was solved by direct methods using the program MULTAN80 [11]. The structure was refined using full-matrix least-squares calculations with anisotropic displacement parameters for non-H-atoms. The positions of the H-atoms were calculated assuming normal geometry. Their parameters were not refined. The final R factor for 703 variables was 0.066. The highest peak in the final difference *Fourier* map was 0.71 e/Å^3. The conformations of the two crystallographically independent molecules are very similar to each other. The only difference concerns the orientation of one of the MeO groups. Selected distances (Å): N(1')–C(5') 1.371(6), C(5')–C(4') 1.509(7), C(4')–C(3'), 1.537(6), C(3')–C(2') 1.529(6), C(2')–N(1') 1.489(6), N(1)–C(2) 1.351(6), C(2)–C(3) 1.508(7), C(3)–C(4) 1.575(6), C(4)–N(1) 1.479(6). Complete positional and thermal parameters and bond lengths were deposited with the *CCDC*.

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