SIMPLE AND CONDENSED β-LACTAMS. PART 32+. BASE- AND ACID-CATALYZED RING EXPANSIONS OF 3-SUBSTITUTED 4-ACETYLAZETIDIN-2-ONES AND RELATED COMPOUNDS

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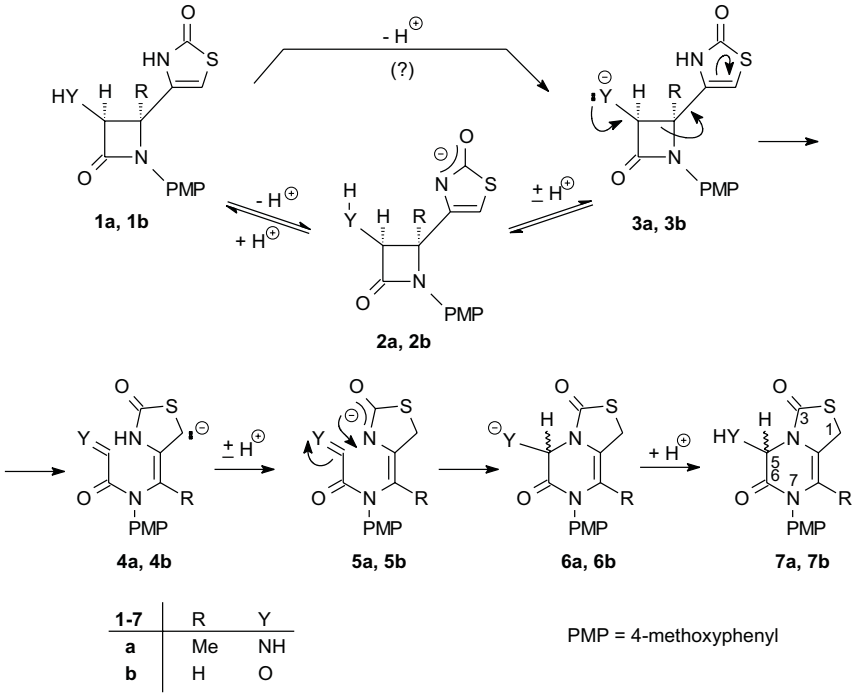
On treatment with bases, the C3–C4 bonds of the 3-substituted 4-(1-iminoethyl)- or 4-acetylazetidin-2-ones **8f**, **8g** and **8i** are cleaved heterolytically to afford, depending on the nature of the 3-substituent, ring expansion or other products (**14**, **19** and **27**, respectively). Related compound **8h** undergoes a base-induced ring transformation to afford compound **23** only after oxidation to the stereoisomeric disulfanes **20**. Compound **8d**, when treated with HCl, undergoes a ring transformation to pyrrolidin-2-one **32**.

Key words: Azetidin-2-ones; Pyrazines; Ring transformations; β-Lactams.

In previous parts[2,3] of the present series the base-catalyzed ring transformations with cleavage of the C3–C4 bond in the azetidin-2-one moiety of the 4-[(2*RS*,3*RS*)-(3-amino-4-oxoazetidin-2-yl)]thiazol-2(3*H*)-one (**1a**) and the 4-[(2*RS*,3*RS*)-4-(3-hydroxy-4-oxoazetidin-2-yl)]thiazol-2(3*H*)-one (**1b**) leading to the (5*RS*)-5-amino- (**7a**) and (5*RS*)-5-hydroxy-1,5-dihydro-3*H*-thiazolo[3,4-*a*]-pyrazine-3,6(7*H*)-diones (**7b**), respectively, were described (Scheme 1). Since cleavages of the C3–C4 bond in azetidin-2-ones have been observed rather rarely (for a brief review, see ref.[3]), an attempt has been undertaken to ex-

+ Part 31, see ref.[1].

tend the scope of this ring transformation. The mechanism depicted in Scheme 1 was suggested for the ring transformations of **1a** into **7a** and **1b** into **7b** (ref.[3]). Anions **3a** and **3b** are not necessarily discrete intermediates



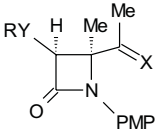
1-7	R	Y
a	Me	NH
b	H	O

SCHEME 1

of the reactions since deprotonation of the HY groups and cleavage of the azetidine ring might take place equally well simultaneously. The necessary structural requirements for the ring expansions appear to be the presence of a sufficiently acidic group HY in position 3 and of another group in position 4 (azetidin-2-one numbering) also containing an acidic hydrogen atom and being capable of accommodating a negative charge. As a consequence, the presence of the thiazolone moiety does not appear to be a necessary condition for the ring transformation; it should be possible to design further compounds capable of undergoing similar transformations in which the thiazolone moiety is replaced by suitable other groups, *e.g.* an acetyl group.

Here we report the synthesis of compounds **8a**–**8d**, deacylation of compounds **8a**–**8c** and **8e**, ring transformations and other reactions of compounds **8f**–**8i** induced by bases as well as a ring transformation of

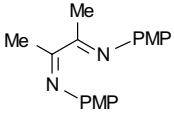
compound **8d** induced by hydrochloric acid. All compounds **8** were racemic. For convenience only one of their epimers, as well as of all other racemic compounds mentioned in the present paper, will be depicted.



8a-8i

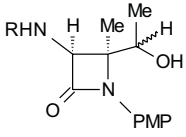
8	Y	R	X
a	O	Ac	N-PMP
b	O	Ac	O
c	S	Ac	O
d	NH	Ac	O
e	phthalimido		O

8	Y	R	X
f	O	H	N-PMP
g	O	H	O
h	S	H	O
i	NH	H	O

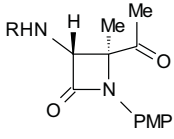


9

PMP = 4-methoxyphenyl



10	R
a	H
b	Ac

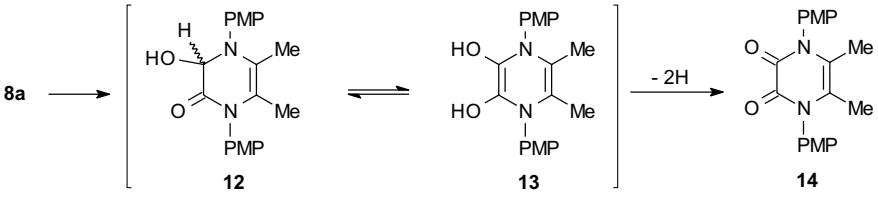


11	R
a	H
b	Ac

Treatment of *N*,*N*′-di(4-methoxyphenyl)butane-2,3-diimine **9** (ref.[2]) with acetoxyacetyl chloride in dichloromethane in the presence of triethylamine afforded compound **8a** which, on prolonged treatment with 1 M HCl, was hydrolyzed to acetyl derivative **8b**. The *cis* relation of 3-H and 4-Me in **8b** and, therefore, also in **8a** was proved by an NOE experiment. Compound **8c** was obtained similarly as compound **8a**, except that the (acetylsulfanyl)acetyl chloride was used in about threefold excess and the addition was very slow. Even so, the yield of compound **8c** was only 24% because of undesired side reactions of the acid chloride (polymerization of the corresponding ketene, formation of brown tarry products). The key intermediate for the preparation of compound **8d** was an epimeric mixture **10a** (ref.[4]) obtained from compound **8e** (ref.[2]). Acetylation of the epimeric mixture afforded compound **10b**, again as a mixture of epimers. Oxidation of compound **10b** with $KMnO_4$ finally afforded compound **8d**, contaminated by substantial amounts of its *trans* epimer **11b**.

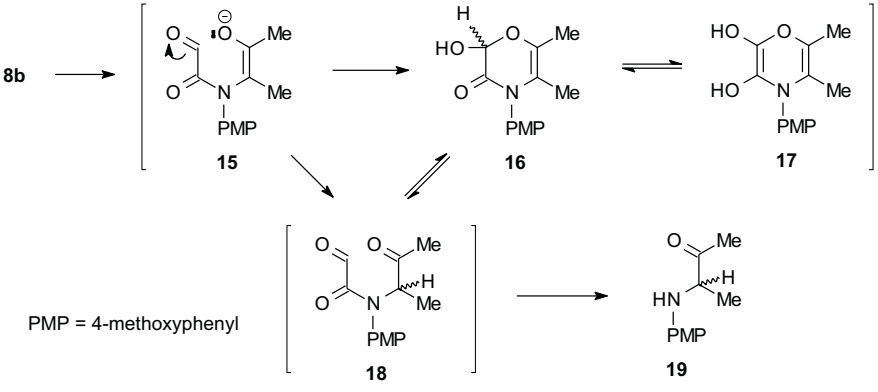
Treatment of compound **8a** with aqueous methanolic Na_2CO_3 afforded compound **14**, the oxidation product of the potential tautomers **12** and **13**, the hydroxyoxo tautomer **12** being an analogue of compounds **7a** and **7b**. Formation of compound **14** may be explained by assuming first *O*-deacetylation of compound **8a** to afford compound **8f** which *in situ* un-

dergoes ring expansion by a mechanism similar to those depicted in Scheme 1. The resulting product **12** (**13**) finally undergoes, probably through enediol tautomer **13**, oxidation with air (Scheme 2). Attempts of trapping the assumed intermediates **12** and **13**, remained unsuccessful.



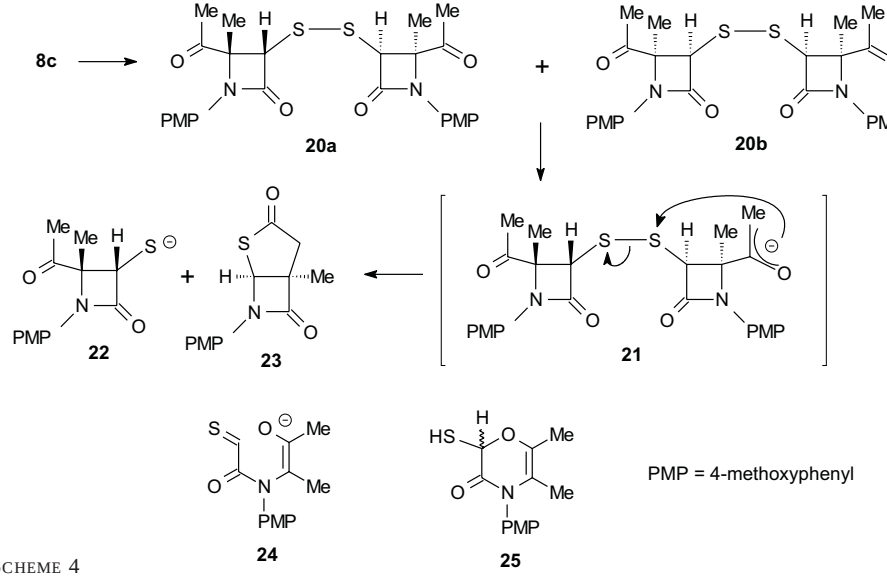
SCHEME 2

Similar treatment of compound **8b** with Na_2CO_3 or NaOH afforded compound **19**, rather than one or both tautomers **16** and **17** expected on the basis of the analogy. The formation of compound **19** may be explained by deacetylation of compound **8b**, transformation of the resulting **8g** into **16** (similarly as shown for conversion **1a**, **1b** to **7a**, **7b** in Scheme 1), ring opening of the hemiacetal-like intermediate **16** which, in contrast to compounds **7a**, **7b**, appears to be unstable to *in situ* hydrolysis and affords final product **19** *via* compound **18**. Alternatively, *C*-protonation of intermediate **15**, formed from compound **8g** similarly as the intermediates **5** from compounds **1** (Scheme 1), could lead directly to (glyoxyloylamino)ketone **18** (Scheme 3).



SCHEME 3

Prolonged treatment of compound **8c** with methanolic NaOMe in air afforded two products, disulfane **20** (as a mixture of the racemic **20a** and *meso* forms **20b**) and thienoazete derivative **23**, which were separated by TLC. The formation of disulfanes **20a** and **20b** indicates that compound **8h** or the corresponding thiolate anion is easily oxidized with air. Deprotonation of disulfane **20a**, followed by intramolecular attack of the proximal sulfur atom by the anionic center of the resulting **21** then affords compound **23** together with the thiolate anion **22**. *Meso* isomer **20b** should lead to the same products (Scheme 4).



SCHEME 4

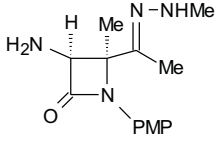
In order to prevent oxidation of compound **8h**, deacetylation of compound **8c** was carried out under argon. When a methanolic solution of compound **8c** was made slightly alkaline (pH 9) by adding 10% methanolic MeONa or aqueous Na_2CO_3 and the mixture was stirred at room temperature under argon, the starting compound was, according to TLC, consumed within 1 h to afford a more polar product thought to be anion **22** or compound **8h** itself. This compound did not undergo ring transformation to **25** *via* **24** even after stirring for 3 days but if the reaction mixture was treated with a slight excess of iodine, a crystalline mixture of the stereoisomeric disulfanes **20a** and **20b** (73%) was obtained. When a methanolic solution

of the crude product mixture was treated with MeONa under argon, bicyclic compound **23** (76%) was obtained.

A factor, which is probably responsible for the fact that transformation of **22** into **24** (which would be the key step of the expected transformation of **8h** into **25**) does not occur, is the comparative weakness of the C=S π-bond. While the average difference between the energies of the aldehyde C=O and the C–O single bonds is 176.7–85.5 = 91.2 kcal/mol (ref.[5]) and serves as a powerful driving force for transformation of **3b** into **4b** and the formation of anion **15**, the key steps of reactions of **1b** to **7b** and **8g** to **19**, respectively, the average difference between the energies of the thioketone (no values for thioaldehyde C=S bonds are available from the literature) C=S double and the C–S single bonds amounts to only 93–49.5 = 43.5 kcal/mol (ref.[6]).

The finding that compound **8h** is stable under alkaline conditions indicates that the structural requirements for the ring expansions discussed at the beginning of this paper are not sufficient. In addition the atom connecting HY to the azetidin-2-one ring should be capable of forming strong C=Y π-bonds.

In contrast to compounds **8a** and **8b** which were smoothly deacetylated by aqueous methanolic Na_2CO_3 solution at or below room temperature, the mixtures of compounds **8d** and **11b** proved to be stable to the same reagent even under reflux. As an alternative method for the preparation of desired compound **8i**, dephthaloylation of compound **8e** (ref.[2]) by methylhydrazine was tested. Dephthaloylation indeed took place and the resulting



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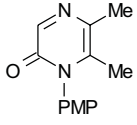

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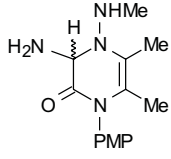

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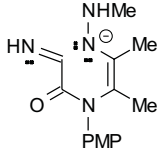

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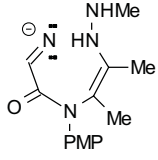

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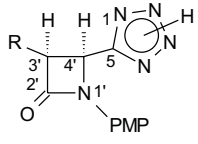


31	R
a	phthalimido
b	NH_2

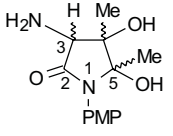
PMP = 4-methoxyphenyl

methylhydrazone **26**, derived from **8i**, subsequently underwent the expected ring expansion *in situ*. However, instead of the expected compound **28**, only 9% of compound **27** was isolated from the resulting complex multicomponent mixture. The formation of compound **27** may be explained by assuming that intermediate anion **29**, rather than undergoing the usual ring closure reaction to afford compound **28**, undergoes first an acid-base reaction to afford the tautomeric anion **30**, followed by cyclization with elimination of $MeNHNH^-$ to yield product **27**.

Finally, in a control experiment, 3-phthalimido-4-(tetrazol-5-yl)azetidin-2-one **31a** (ref.[7]) was treated with methylhydrazine in dichloromethane to afford 3-aminoazetidin-2-one **31b** without ring expansion. In contrast to compound **1a**, compound **31b** proved to be stable also to aqueous methanolic NaOH. This shows that the presence of an acidic hydrogen-containing group in position 4 of the azetidin-2-one ring is not sufficient for the base-catalyzed rearrangements.

Treatment of a mixture of epimers **8d** and **11b** with concentrated HCl in methanol afforded a product which, according to its IR spectrum (ν(C=O) 1 720 cm^{-1}), did not contain the azetidin-2-one moiety of the starting substances and whose structure was shown by ^1H, ^{13}C and 2D heterocorrelation NMR spectra to be **32** (mainly a single stereoisomer). Similar rearrangements leading to stereoisomeric mixtures of compounds **33** (ref.[1]) and **34** (ref.[8]) have been described.

Acetylation of compound **32** afforded its *N*-acetyl derivative in essentially quantitative yield. The ^1H and ^{13}C NMR spectra of the product, taken in $CDCl_3$ solution, proved it to be practically a single stereoisomer. In DMSO-d_6 solution, however, partial epimerization took place and the com-



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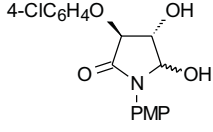

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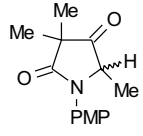

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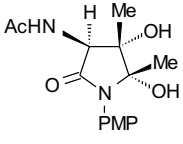

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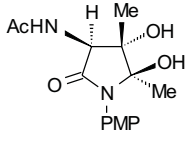

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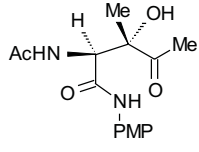

37

PMP = 4-methoxyphenyl

pound was shown by its ^{1}H NMR spectrum to exist as a 1 : 1 mixture of two stereoisomers, **35** and **36**. By a NOE study, carried out in DMSO-d_6 solution, the steric structure of isomer **36** was established unambiguously, while for isomer **35** only the *cis* relation of the 3-H and 5-OH groups could be deduced, and the relative configuration at C-4 remained uncertain. However, taking into account that epimerization at C-5 should take place easily in both directions *via* the unstable open-chain isomer **37**, while epimerization at C-4 as a result of dissolution in DMSO-d_6 should hardly be possible, it appears to be reasonable to assume that the only difference between both isomers are the opposite configurations at C-5.

The study of the stereochemistry in $CDCl_3$ solution was somewhat hampered due to the facts that the OH (and NH) signals were broad and, therefore, inapplicable for the NOE study, and that selective irradiation of the 4-Me and 5-Me signals was not feasible. The steric structure of the isomer seen in $CDCl_3$ solution was only partially established by a NOE study which showed the *cis* relation of 3-H and 5-Me but left the relative configuration of C-4 uncertain. Making, however, the reasonable assumption that the relative configurations of C-4 of the isomer in $CDCl_3$ and of both isomers seen in DMSO-d_6 solution should be identical, one arrives at the conclusion that the isomer seen in $CDCl_3$ solution is isomer **36**. On the basis of a similar argumentation the steric structure of **32** should correspond to that of isomer **36**.

EXPERIMENTAL

Magnesium sulfate was invariably used as the drying agent. Evaporations to dryness were carried out at reduced pressure (*ca* 2.5 kPa). Separations of product mixtures by column chromatography were mostly carried out at reduced pressures (10–25 kPa) using Silica gel G 60 (Merck) as an adsorbent. For preparative TLC separations, 20 × 20 cm precoated silica gel $PF_{254–366}$ glass plates (Merck; thickness of adsorbent layer 1.5 mm) were used. The purity of the products was checked by IR spectroscopy and TLC on TLC-aluminium sheets 60 F_{254} (Merck); individual compounds were detected by exposure to UV light or by iodine, 5% ethanolic molybdo- or tungstophosphoric acids.

Melting points were determined on a Kofler hot-stage apparatus. IR spectra (wavenumbers are given in cm^{-1}) were recorded on a Specord-75 (Zeiss, Jena) spectrometer using KBr pellets, unless otherwise stated. ^{1}H and ^{13}C NMR spectra were obtained, unless otherwise stated, with a Varian UNITY-INOVA-400 spectrometer using tetramethylsilane as the internal standard; *J* values are given in Hz, the chemical shifts (δ) in ppm. The results of the NOE studies are presented by listing the protons involved in decreasing order of the effects observed. Exact molecular mass determinations were made at 70 eV with a Finnigan MAT 95SQ instrument of reversed geometry equipped with a direct inlet system.

(3*RS*,4*SR*)-3-Acetoxy-1-(4-methoxyphenyl)-4-[1-(4-methoxyphenylimino)ethyl]-4-methylazetidin-2-one (**8a**)

A solution of acetoxyacetyl chloride (2.3 g, 17 mmol) in CH_2Cl_2 (25 ml) was added dropwise within 15 min to a stirred mixture of *N*,*N*′-di(4-methoxyphenyl)butane-2,3-diimine[2] (**9**; 5.0 g, 17 mmol), CH_2Cl_2 (150 ml) and Et_3N (2.7 ml, 19 mmol) at –10 °C. After 15 min, the cooling bath was removed, 1 M HCl (100 ml) was added and the mixture was stirred for 10 min at room temperature. Under these conditions the unchanged diimine **9** was completely hydrolyzed and the major part of compound **8a** remained unaffected. The two phases were separated, the organic phase was washed with water, dried and evaporated to dryness to afford an oily product which crystallized when triturated with diethyl ether to give the title compound (3.4 g, 53%); m.p. 122 °C (MeCN). Found: HRMS, 396.16915; $C_{22}H_{24}N_2O_5$ requires: HRMS, 396.16852. IR: 1 760, 1 740, 1 660, 1 250, 1 030. ^{1}H NMR ($CDCl_3$): 1.90 s, 3 H + 1.95 s, 3 H (4-Me + 4-C(=N–)Me); 2.15 s, 3 H (OAc); 3.79 s, 3 H + 3.80 s, 3 H (2 × OMe); 5.76 s, 1 H (3-H); 6.60 + 6.90, AA′BB′, 2 × 2 H, side-chain PMP; 6.88 + 7.39, AA′BB′, 2 × 2 H, 1-PMP.

(3*RS*,4*RS*)-3-Acetoxy-4-acetyl-1-(4-methoxyphenyl)-4-methylazetidin-2-one (**8b**)

A solution of acetoxyacetyl chloride (4.6 g, 34 mmol) in CH_2Cl_2 (50 ml) was added to a mixture of diimine **9** (10 g, 34 mmol) in CH_2Cl_2 (300 ml) and Et_3N (5.3 ml, 37.5 mmol) as in the preparation of compound **8a**. Stirring was continued for 30 min with the cooling bath removed, 1 M HCl (400 ml) was added and the mixture was stirred for 24 h at room temperature. The two phases were separated, the organic phase was washed with water and dried. Silica gel G 60 (10 g) was added and the mixture evaporated to dryness. The residue was transferred onto a column of silica gel G 60 and chromatographed (CH_2Cl_2) to afford the title compound (7.1 g, 71%) as an oil which crystallized; m.p. 62 °C. Found: HRMS, 291.11038; $C_{15}H_{17}NO_5$ requires: HRMS, 291.11067. IR: 1 770/1 760 d, 1 725, 1 260, 1 010. ^{1}H NMR ($CDCl_3$): 1.81 s, 3 H (4-Me); 2.13 s, 3 H (AcO); 2.28 s, 3 H (4-Ac); 5.70 s, 1 H (3-H). NOE: 5.70 (3-H) → 1.81 (4-Me); 1.81 (4-Me) → 5.70 (3-H), 7.28 (2-H + 6-H, PMP), 2.28 (4-Ac); 7.28 (2-H + 6-H, PMP) → 6.90 (3-H + 5-H, PMP), 1.81 (4-Me), 2.28 (4-Ac).

(3*RS*,4*SR*)-4-Acetyl-3-acetylsulfanyl-1-(4-methoxyphenyl)-4-methylazetidin-2-one (**8c**)

A solution of (acetylsulfanyl)acetyl chloride (4.6 g, 30 mmol) in dry CH_2Cl_2 (150 ml) was added dropwise within 2 h to a stirring mixture of diimine **9** (3.0 g, 10 mmol) in dry CH_2Cl_2 (150 ml) and Et_3N (4.7 ml, 33 mmol) at –5 °C. The resulting brown solution was allowed to warm up to room temperature, 1 M HCl (200 ml) was added and the mixture was stirred overnight at room temperature. The reaction mixture was worked up as in the preparation of **8b** to afford the title compound (0.7 g, 24%); m.p. 115 °C. Found: HRMS, 307.08800; $C_{15}H_{17}NO_4S$ requires: HRMS, 307.08783. IR: 1 750, 1 730 sh, 1 720. ^{1}H NMR ($CDCl_3$): 1.89 s, 3 H (4-Me); 2.19 s, 3 H (4-Ac); 2.41 s, 3 H (AcS); 4.97 s, 1 H (3-H). ^{13}C NMR ($CDCl_3$): 19.23 (4-Me); 27.22 (4-Ac); 30.39 (AcS); 55.49 (OMe); 57.06 (C-3); 71.22 (C-4); 114.62 (C-3 + C-5, PMP); 119.05 (C-2 + C-6, PMP); 129.59 (C-1, PMP); 156.81 (C-4, PMP); 160.83 (C-2); 192.16 ($SCOCH_3$); 205.61 (4-$COCH_3$).

(3*RS*,4*RS*)-3-Acetylamino-4-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-1-(4-methoxyphenyl)-4-methylazetidin-2-one (Mixture of Side-Chain Epimers) (**10b**)

Acetyl chloride (1.4 ml, 19.5 mmol) was added dropwise to compound **10a**·HCl (ref.[4], mixture of side-chain epimers; 5.6 g, 19.5 mmol) in a mixture of dry CH_2Cl_2 (100 ml) and pyridine (3.4 ml, 39 mmol) at room temperature. Stirring was continued for 30 min; the initial suspension turned into a clear solution which was washed with water, dried and evaporated to dryness. The residue was recrystallized from MeCN to give a mixture of the pure title compounds (4.5 g, 73%); m.p. 128 °C. Found: HRMS, 292.14209; $C_{15}H_{20}N_2O_4$ requires: HRMS, 292.14231. IR: 3 300 br, 1 730, 1 650. In some cases, the mass spectrum indicated that the product was contaminated by the corresppponding 4-[(1*RS*)- and (1*SR*)-1-acetoxyethyl] derivatives (found: HRMS, 334.15281; $C_{17}H_{22}N_2O_5$ requires: HRMS, 334.15284). In the following oxidation step the ester group of the contaminant was apparently hydrolyzed; therefore the contaminant reacted in the same way as compound **10b** itself.

Mixture of (3*RS*,4*RS*)-4-Acetyl-3-acetylamino-1-(4-methoxyphenyl)-4-methylazetidin–2-one (**8d**) and Its (3*RS*,4*SR*) Isomer (**11b**)

A solution of **10b** (1.0 g, 3.4 mmol) in acetonitrile (25 ml) was refluxed for 1 h with $KMnO_4$ (1.6 g, 10.2 mmol). The mixture was allowed to cool to room temperature and the MnO_2 was filtered off. The residual $KMnO_4$ was removed by boiling up with methanol (5 ml). The insoluble portion was filtered off and the colourless filtrate was evaporated to dryness. The residue was triturated with diethyl ether to afford a 45 : 55 mixture of the title compounds (0.74 g, 75%); m.p. 160–164 °C. Found: HRMS, 290.12621; $C_{15}H_{18}N_2O_4$ requires: HRMS, 290.12666. IR: 3 350, 1 760, 1 720, 1 700, 1 680. ^{1}H NMR ($CDCl_3$): **8d**, 1.93 s, 3 H (4-Me); 1.99 s, 3 H (AcNH); 2.24 s, 3 H (4-Ac); 5.11 d, 1 H, *J* = 7.5 (3-H); 6.78 br d, 1 H, *J* = 7.5 (NH); **11b**, 1.62 s, 3 H (4-Me); 2.08 s, 3 H (AcNH); 2.36 s, 3 H (4-Ac); 5.13 d, 1 H, *J* = 7.6 (3-H); 7.09 br d, 1 H, *J* = 7.6 (NH). ^{13}C NMR ($CDCl_3$): **8d**, 18.93 (4-Me); 22.60 + 171.03 (N-Ac); 27.40 + 205.85 (4-Ac); 55.49 (OMe); 66.03 (C-3); 72.56 (C-4); 114.51 (C-3 + C-5, PMP); 120.17 (C-2 + C-6, PMP); 129.03 (C-1, PMP); 156.96 (C-4, PMP); 162.06 (C-2); **11b**, 14.74 (4-Me); 22.65 + 170.91 (N-Ac); 25.40 + 205.49 (4-Ac); 55.45 (OMe); 62.38 (C-3); 70.95 (C-4); 114.46 (C-3 + C-5, PMP); 119.80 (C-2 + C-6, PMP); 129.47 (C-1, PMP), 157.02 (C-4, PMP); 162.79 (C-2).

1,4-Di(4-methoxyphenyl)-5,6-dimethyl-2,3-dihydropyrazine-2,3-dione (**14**)

A solution of Na_2CO_3 (80 mg, 0.8 mmol) in water (2 ml) was added to a stirred solution of compound **8a** (0.6 g, 1.6 mmol) in methanol (30 ml) with ice-water cooling. Stirring was continued at room temperature until the starting substance was consumed. The faintly coloured solution was evaporated to dryness and the resulting reddish brown crystalline material was recrystallized from acetonitrile to afford colourless crystals of the title compound (0.5 g, 87%); m.p. 265 °C. Found: HRMS (FAB), 353.15187; $C_{20}H_{21}N_2O_2$ requires: HRMS, 353.15013. IR: 1 680, 1 650/1 640 d. ^{1}H NMR ($CDCl_3$ + DMSO-d_6):1.75 s, 6 H (5-Me + 6-Me); 3.85 s, 6 H (2 × MeO); 7.05 + 7.19, AA'BB', 2 × 4 H (Ar-Hs, 2 × PMP). ^{13}C NMR ($CDCl_3$ + DMSO-d_6): 16.38 (5-Me + 6-Me); 55.64 (2 × MeO); 114.87 (C-3 + C-5, PMPs); 116.16 (C-5 +C-6); 129.29 (C-2 + C-6, PMPs); 130.90 (C-1, PMPs); 156.13 (C-2 + C-3); 159.43 (C-4, PMPs).

3-(4-Methoxyanilino)butan-2-one (**19**)

A) A solution of Na_2CO_3 (0.73 g, 6.9 mmol) in water (10 ml) was added to a stirred solution of **8b** (2.0 g, 6.9 mmol) in methanol (50 ml) at room temperature. Stirring was continued for 15 min, methanol was distilled off and the resulting aqueous solution was extracted with CH_2Cl_2. The combined organic phases were dried and evaporated to dryness to give the title compound (1.0 g, 75%) as a faint yellow oil which gradually darkened when kept in air. IR (neat): 3 380, 1 700. ^{1}H NMR ($CDCl_3$): 1.39 d, 3 H, *J* = 6.8 (CH**Me**); 2.19 s, 3 H (Ac); 3.73 s, 3 H (MeO); 3.84 br (NH); 4.00 q, 1 H, *J* = 6.8 (C**H**Me); 6.53 + 6.77 AA′BB′, 2 × 2 H (PMP). ^{13}C NMR ($CDCl_3$): 18.06 (NHCH**Me**); 25.84 + 210.85 (Ac); 55.73 (MeO); 59.55 (N**C**HMe); 114.38 + 114.98 (C-2 + C-6 and C-3 + C-5, PMP); 140.71 (C-1, PMP); 152.40 (C-4, PMP).

B) A mixture of compound **8b** (0.8 g, 2.7 mmol), methanol (20 ml), NaOH (0.11 g, 2.7 mmol) and water (4 ml) was stirred until compound **8b** was consumed (about 30 min). The mixture was worked up as described in *A*), followed by column chromatography (CH_2Cl_2) to afford compound **19** (0.3 g, 59%), identical with the product obtained as described in *A*).

3,3′-Disulfanediylbis[4-acetyl-1-(4-methoxyphenyl)-4-methylazetidin-2-one], Mixture of the (3*RS*,4*SR*,3′*RS*,4′*SR*) or Racemic (**20a**) and the (3*RS*,4*SR*,3′*SR*,4′*RS*) or *meso* Forms (**20b**) and (2a*RS*,5a*RS*)-1-(4-Methoxyphenyl)-5a-methyl-2a,5a-dihydrothieno-[3,2-*b*]azete-2(1*H*),5(4*H*)-dione (**23**)

A) Two drops of a 10% methanolic NaOMe solution were added to a methanolic solution (10 ml) of compound **8c** (0.3 g, 1 mmol) and the mixture was stirred in air for 2 days at room temperature. The residue after evaporation was purified by preparative TLC (CH_2Cl_2–acetone, 10 : 0.5) to afford compound **23** (7 mg) and a mixture of compounds **20a** and **20b** (20 mg) in increasing order of their polarities. The products proved to be identical with the products obtained as described below in *C*) and *B*), respectively.

B) A methanolic solution (15 ml) of compound **8c** (0.3 g, 1 mmol) was made slightly alkaline (pH 9) by adding 10% methanolic NaOMe and stirred at room temperature under Ar. When the starting **8c** was consumed (1 h), a dilute solution of iodine (0.25 g) in methanol (10 ml) was added dropwise until the solution became faint yellow and gave a positive test for I_2 with starch. The slight excess of I_2 was removed by adding a few drops of 10% $NaHSO_3$. The resulting colourless solution was evaporated to dryness and the yellow oily residue was purified by preparative TLC (CH_2Cl_2–acetone, 10 : 0.5) to afford *ca* 55 : 45 mixture of compounds **20a** and **20b** (0.18 g, 73%); m.p. 63–66 °C. Found: HRMS, 528.13835; $C_{26}H_{28}N_2O_6S_2$ requires: HRMS, 528.13888. IR: 1 750, 1 710. ^{1}H NMR ($CDCl_3$): 1.71 s, 3 H + 1.77 s, 3 H (4-Me + 4′-Me); 2.31 s, 3 H + 2.32 s , 3 H (4-Ac + 4′-Ac); 3.79 s, 6 H (2 × MeO); 4.81 s, 1 H + 4.78 s, 1 H (3-H + 3′-H); 6.87 + 7.24 AA′BB′ and 6.87 + 7.28 AA′BB′, 2 × 4 H (Ar-Hs, 2 × PMP). ^{13}C NMR ($CDCl_3$): 15.51 + 15.55 (4-Me + 4′-Me); 24.49 + 24.72 and 205.36 + 205.73 (4-Ac + 4′-Ac); 55.50 (2 × MeO); 65.28 + 64.44 (C-3 + C-3′); 68.84 + 69.36 (C-4 + C-4′); 114.68, 118.93, 119.17, 129.50, 129.55, 156.87, 156.92 (aromatic C atoms, 2 × PMP); 161.15 + 160.37 (C-2 + C-2′).

C) A mixture of crude disulfanes **20a** and **20b** was obtained from compound **8c** (0.3 g, 1 mmol) as described in *B*). The yellow oily product was taken up in CH_2Cl_2. The solution was washed with water, dried and evaporated to dryness. The anhydrous methanolic (10 ml) solution of the oily residue was made slightly alkaline by adding two drops of 10% methanolic NaOMe, stirred for 36 h at room temperature under Ar and evaporated to dryness. The residue was worked up by preparative TLC (CH_2Cl_2–acetone, 10 : 0.2) to afford

compound **23** (0.1 g, 76%); m.p. 118 °C. Found: HRMS, 263.06164; $C_{13}H_{13}NO_3S$ requires: HRMS, 263.06161. IR: 1 750, 1 730. ^{1}H NMR ($CDCl_3$): 1.72 s, 3 H (5a-Me); 3.33 d, 1 H + 3.86 d, 1 H, J = 15.6 (4-H_2); 4.24 s, 1 H (2a-H). ^{13}C NMR ($CDCl_3$): 13.56 (5a-Me); 35.13 (C-4); 55.47 (MeO); 56.14 (C-2a); 62.64 (C-5a); 114.57 (C-3 + C-5, PMP); 118.97 (C-2 + C-3, PMP); 129.27 (C-1, PMP); 156.82 (C-4, PMP); 162.86 (C-2); 203.73 (C-5).

1-(4-Methoxyphenyl)-5,6-dimethylpyrazine-2(1*H*)-one (**27**)

A mixture of compound **8e** (ref.[2]; 0.5 g, 1.3 mmol), dry CH_2Cl_2 (15 ml) and methylhydrazine (0.2 ml, 4 mmol) was stirred for 2 days at room temperature. The crystalline co-product was filtered off and the filtrate was evaporated to dryness to afford an ether soluble reddish yellow oil (0.3 g). Purification by column chromatography (EtOAc) afforded the main component of the mixture, contaminated by small amounts of a slightly less and a slightly more polar component (0.14 g). The crude product was purified by preparative TLC (CH_2Cl_2–MeOH, 10 : 0.5) to afford (**27**) (30 mg, 9%) as an oil. Found: HRMS, 230.1045; $C_{13}H_{14}N_2O_2$ requires: HRMS, 230.1055. IR: 1 660. ^{1}H NMR ($CDCl_3$): 1.95 s, 3 H (6-Me); 2.35 s, 3 H (5-Me); 3.86 s, 3 H (MeO); 7.04 + 7.07 AA′BB′, 2 × 2 H (Ar-Hs, PMP); 8.11 s, 1 H (3-H); NOE: 1.95 (6-Me) → 7.07 (2-H + 6-H, PMP), 2.35 (5-Me); 2.35 (5-Me) → 1.95 (6-Me). ^{13}C NMR ($CDCl_3$): 17.11 (6-Me); 20.13 (5-Me); 55.56 (MeO); 115.33 (C-3 + C-5, PMP); 128.32 (C-2 + C-6, PMP); 129.58 (C-5); 129.67 (C-1, PMP); 134.23 (C-6); 145.78 (C-3); 156.71 (C-2); 160.01 (C-4, PMP).

(3*RS*,4*RS*)-3-Amino-1-(4-methoxyphenyl)-4-(tetrazol-5-yl)azetidin–2-one (**31b**)

A mixture of **31a** (ref.[7], 2.1 g, 5.4 mmol), CH_2Cl_2 (30 ml) and methylhydrazine (0.9 ml, 16.5 mmol) was stirred for 1 day at room temperature. The initial suspension turned within 1 h first into a clear solution and later on into a thick paste. The product was filtered off and washed with MeOH to afford the title compound (0.89 g, 63%) as colourless crystals, m.p. 218 °C (dec.). Found: HRMS (FAB), 283.09114; $(C_{11}H_{12}N_6O_2 + Na)^+$ requires: HRMS, 283.09194. IR: 3 400 v br, 1 750, 1 650. ^{1}H NMR (Bruker, DRX-500 instrument; DMSO-d_6): 3.65 s, 3 H (MeO); 4.58 d, 1 H, J = 5.2 (3-H); 5.46 d, 1 H, J = 5.2 (4-H); 6.81 + 7.17 AA′BB′, 2 × 2 H (Ar-Hs, PMP).

An aliquot (50 mg, 0.19 mmol) of the product did not change according to TLC (CH_2Cl_2–MeOH, 4 : 1) when stirred with NaOH (8 mg, 0.2 mmol) in 1 : 10 (v/v) aqueous methanol (2.2 ml) for 1 day at room temperature.

3-Amino-4,5-dihydroxy-1-(4-methoxyphenyl)-4,5-dimethylpyrrolidin-2-one (**32**) Hydrochloride

A mixture of compounds **8d** and **11b** (0.2 g, 0.7 mmol) was stirred with concentrated HCl (0.3 ml) in methanol (10 ml) at room temperature until the starting compounds were consumed (2 days), and then evaporated to dryness. The residue was triturated with diethyl ether to afford the title compound (0.19 g, 85%); m.p. 162 °C. Found: HRMS, 266.12689; $C_{13}H_{18}N_2O_4$ requires: HRMS, 266.12666. IR: 3 300, 2 950 br, 1 730 sh, 1 720. ^{1}H NMR (DMSO-d_6): 1.12 s, 3 H + 1.24 s, 3 H (4-Me + 5-Me); 3.77 s, 3 H (MeO); 4.34 s, 1 H (3-H); 5.6 br, 2 H (2 × OH); 6.99 + 7.20 AA′BB′, 2 × 2 H (Ar-Hs, PMP). ^{13}C NMR (DMSO-d_6): 19.21 + 20.32 (4-Me + 5-Me); 55.80 (MeO); 58.21 (C-3); 76.64 (C-4); 91.28 (C-5); 114.62 (C-3 + C-5, PMP); 129.24 (C-2 + C-6, PMP); 127.85 (C-1, PMP); 159.07 (C-4, PMP); 168.07 (C-2).

3-Acetamido-4,5-dihydroxy-1-(4-methoxyphenyl)-4,5-dimethylpyrrolidin-2-ones (**35** and **36**)

Triethylamine (0.08 ml, 0.6 mmol) and acetic anhydride (0.06 ml, 0.5 mmol) were successively added to a suspension of **32**·HCl (0.1 g, 0.3 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred for 15 min at room temperature, diluted with additional CH_2Cl_2 (20 ml) and the mixture was washed with water, dried and evaporated to dryness to afford **36** (0.1 g, 96%); m.p. 181 °C. Found: HRMS, 308.1376; $C_{15}H_{20}N_2O_5$ requires: HRMS, 308.1372. IR: 3 400 br, 3 290, 1 705, 1 640. ^{1}H NMR ($CDCl_3$): 1.17 s, 3 H + 1.26 s, 3 H (4-Me + 5-Me); 2.13 s, 3 H (N-Ac); 3.82 s, 3 H (MeO); 4.4 br + 6.2 br (2 × OH); 4.63 d, 1 H, *J* = 2.5 (3-H); 6.55 br (AcN**H**); 6.94 + 7.24 AA′BB′, 2 × 2 H (Ar-Hs, PMP). NOE: 7.22 (2-H + 6-H, PMP) → 1.24 (5-Me); 4.60 (3-H) → 6.45 (AcN**H**), 1.15 (4-Me), 1.24 (5-Me). ^{1}H NMR (DMSO-d_6): *isomer* **35**, 1.09 s, 2 × 3 H (4-Me + 5-Me); 1.96 s, 3 H (N-Ac); 3.77 s, 3 H (OMe); 5.01 s, 1 H (4-OH); 5.01 d, 1H, *J* = 9.2 (3-H); 5.96 s, 1 H (5-OH); 6.97 + 7.16 AA′BB′, 2 × 2 H (Ar-Hs, PMP); 8.11d, 1H, *J* = 9.2 (AcN**H**). NOE: 7.16 (2-H + 6-H, PMP) → 6.97 (3-H + 5-H, PMP); 5.96 (5-OH), 1.09 (5-Me); 5.96 (5-OH) → 7.16 (2-H + 6-H, PMP), 5.01 (3-H), 1.09 (5-Me and/or 4-Me); 8.11 (AcN**H**) → 5.01 (3-H), 1.96 (N-Ac), 1.09 (4-Me and/or 5-Me); *isomer* **36**, 1.13 s, 3 H (4-Me); 1.20 s, 3 H (5-Me); 1.94 s, 3 H (N-Ac); 3.77 s, 3 H (OMe); 4.26 d, 3 H, *J* = 8.8 (3-H); 5.37 s, 1 H (4-OH); 6.03 s, 1 H (5-OH); 6.96 + 7.16 AA′BB′, 2 × 2 H (Ar-Hs, PMP); 8.27 d, 1 H, *J* = 8.8 (AcN**H**). NOE: 7.16 (2-H + 6-H, PMP) → 6.96 (3-H + 5-H, PMP), 6.03 (5-OH), 1.20 (5-Me); 4.26 (3-H) → 5.37 (4-OH), 8.27 (AcN**H**), 1.20 (5-Me), 1.13 (4-Me); 5.37 (4-OH) → 4.26 (3-H), 1.20 (5-Me), 1.13 (4-Me); 6.03 (5-OH) → 7.16 (2-H + 6-H, PMP), 1.20 (5-Me), 1.13 (4-Me), 8.27 (AcN**H**); 8.27 (AcN**H**) → 4.26 (3-H), 1.94 (N-Ac), 1.13 (4-Me), 6.03 (5-OH). ^{13}C NMR ($CDCl_3$): 18.10 + 21.10 (4-Me + 5-Me); 22.32 + 173.60 (N-Ac); 55.48 (MeO); 61.68 (C-3); 77.87 (C-4); 90.60 (C-5); 114.44 (C-3 + C-5, PMP); 127.37 (C-1, PMP); 128.51 (C-2 + C-6, PMP); 159.27 (C-4, PMP); 169.79 (C-2).

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