

# Oxidative Cyclization by Lead(IV) Acetate of 1-(4-Methoxyphenyl)-4-(tetrazol-5-ylmethyl)azetidin-2-ones to 3-Methoxy-9,9a-dihydroazeto[1,2-*a*]tetrazolo[5,1-*d*][1,5]benzodiazepin-11(10*H*)-ones and Related Reactions<sup>1</sup>

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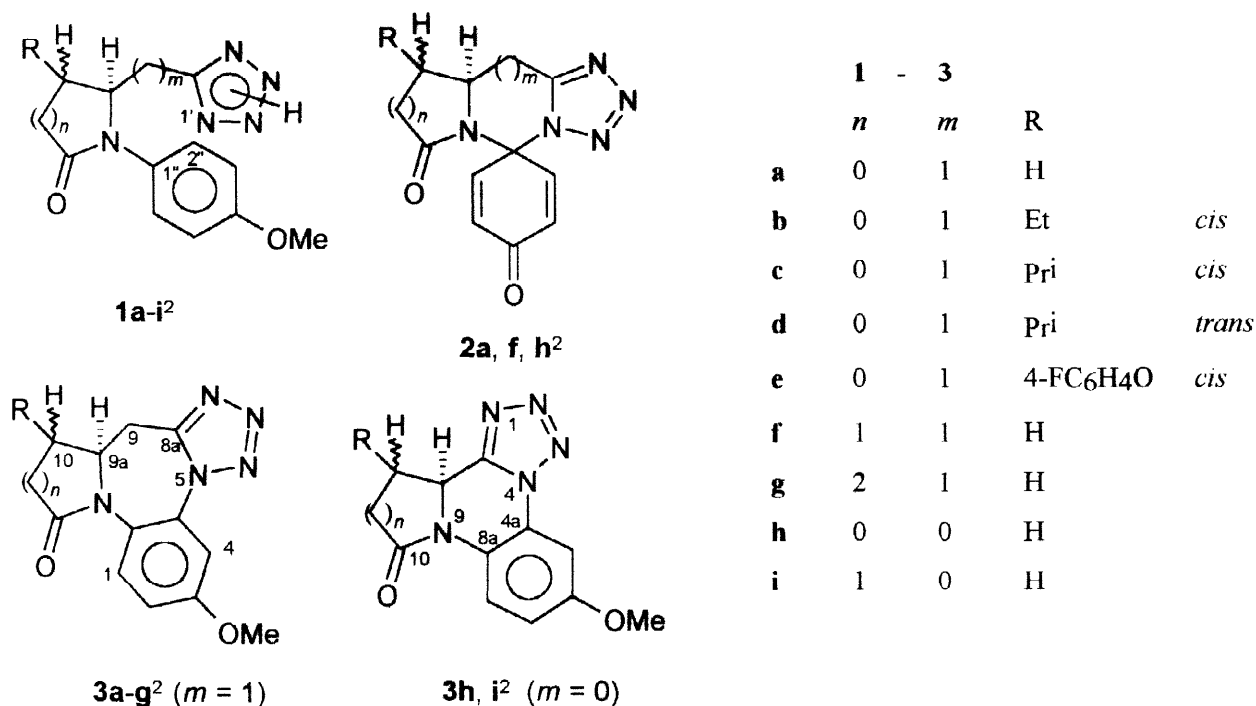
**Abstract:** The tetrazolyl groups of azetidin-2-ones **1a–e** and **1h** interfere with the normal reaction of related azetidin-2-ones with lead(IV) acetate, *viz.* acetoxylation at C-4, and cause formation of tetracyclic products **3a–e** and **3h**. Similar reactions take place with ring homologues **1f**, **1g** and **1i**, and with open-chain analogues **11a** and **11b**. © 1999 Elsevier Science Ltd. All rights reserved.

**Keywords:** Azetidinones; tetrazoles; oxidative aromatic nucleophilic substitution; condensed diazepines

*N*-(4-Demethoxyphenylation) of azetidin-2-one derivatives by oxidation with cerium(IV) ammonium nitrate (CAN) in aqueous acetonitrile [2] or by anodic oxidation [3] is one of the standard processes widely used in the synthesis of natural and non-natural  $\beta$ -lactam antibiotics. In an attempt to apply this reaction to compound **1a** it was noted that, rather than undergoing demethoxyphenylation, compound **1a** is converted into the spirocyclic product **2a** which was isolated in the form of its various transformation products [4]. Later [5]  $\gamma$ -lactam **1f** and  $\beta$ -lactam **1h** were found to behave analogously towards CAN, *i.e.* to afford spirocyclic compounds **2f** and **2h**, respectively, **2f** being the only one among the products **2** which could itself be isolated.

<sup>1</sup> Simple and Condensed  $\beta$ -Lactams. Part 34. For part 33, see ref. [1]

In continuation of these studies, the reaction of compounds **1a-1i** with another oxidant, viz. lead(IV) acetate (LTA) in boiling dioxane has now been studied. As shown by the elemental composition, the IR and the NMR spectra of the products, oxidative cyclization has again taken



place. The structure of the resulting products **3a-3i** (obtained in the **a-d**, **f** and **g** series in about 70-80% yield, the yields being lower in the **e**, **h** and **i** series), however, differed considerably from those of compounds **2a**, **2f** and **2h**: viz. the methoxy group and the aromaticity of the 4-methoxyphenyl groups of the starting compounds **1a-1i** have been retained and the 2"-H atoms of the methoxyphenyl groups have disappeared. Considering that, as in the course of formation of compounds **2a**, **2f** and **2h**, the hydrogen atom of the tetrazole-NH group has also disappeared, ring closure must have taken place between C-2" of the methoxyphenyl group and one of the nitrogen atoms, for steric reasons obviously N-1' of the tetrazole ring. This leads to structure **3**.<sup>3</sup>

The type of structure of the resulting oxidative cyclization products does not depend only on the type of oxidant used: LTA oxidation of the 4-(1-hydroxyphenyl) analogue **4** [5] of compound **1f** afforded compound **2f** (53%), while oxidation with CAN of compound **1f** in a mixture of dry dioxane and methanol afforded compound **3f** (37%) in addition to compound **2f**. Similarly, a mixture of compounds **2f** and **3f** was obtained on oxidation of compound **1f** with CAN in an acetonitrile methanol mixture.

The formation of compounds of type **2** in the oxidation of compounds of type **1** by CAN has

<sup>2</sup> Racemic compounds. For convenience only one enantiomer is shown

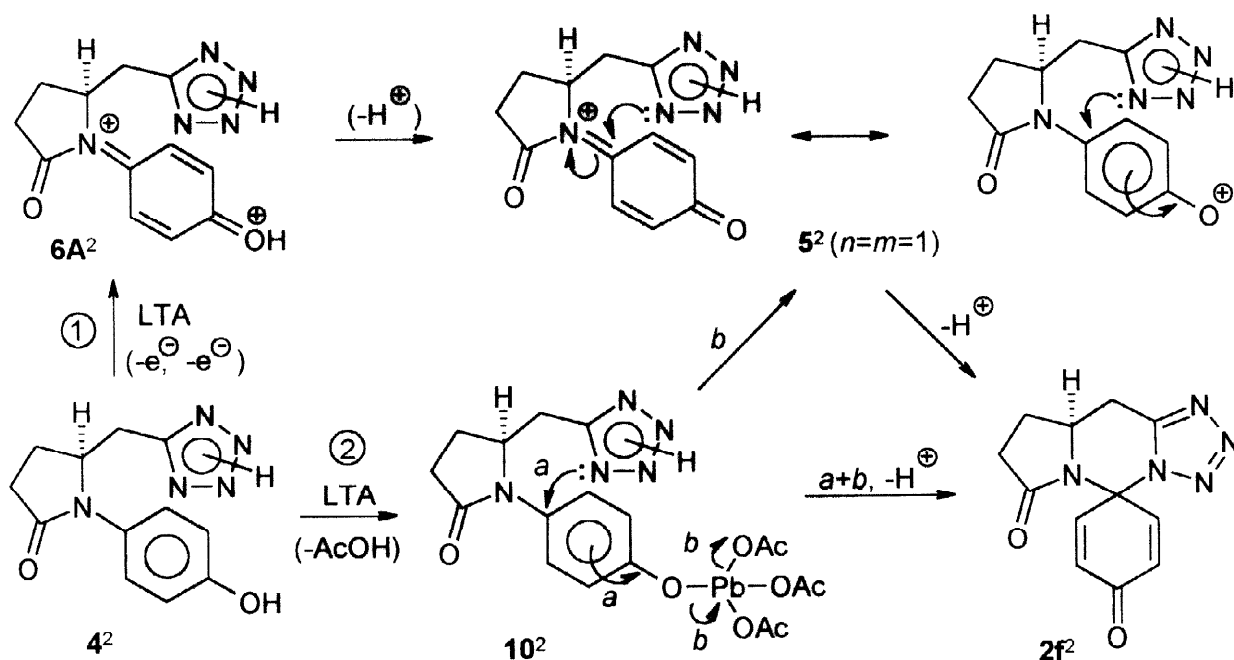
<sup>3</sup> The first example of oxidative LTA cyclization of compounds of type **1** (that of compound **1a** leading to compound **3a**) has been noticed by T. Czuppon [6]



affording cations **7** (rather than **8**) and again preventing the normal course of the reaction which, in the case 1-(4-methoxyphenyl)azetidin-2-ones, has been found to be acetoxylation at C-4 [7]. The cations **7** finally afford products **3** by deprotonation (see Scheme 1). Transformation **1**→**7** which, according to the mechanism discussed, would be the result of an EEC process, could equally well take place by an ECE process according to which formation of the new ring would start at the stage of radical  $1^{+\bullet}$  cation (path *b*, Scheme 1).

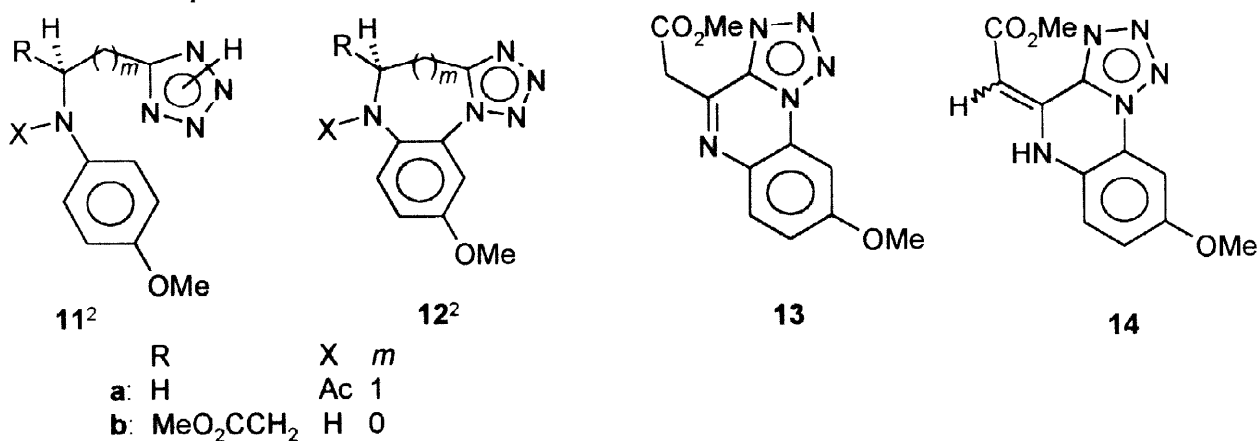
In both mechanisms shown in Scheme 1, the transformations **1**→**3** are aromatic nucleophilic substitutions. Oxidative nucleophilic substitutions of activated aromatic compounds, *e.g.* 4-chloronitrobenzene [8a], and electron deficient heteroaromatic compounds [8b], leading ultimately to replacement of a (*het*)aryl-hydrogen atom by the nucleophile, are well known. In the latter cases the nucleophile is thought to attack the non-oxidised substrates, and oxidation to take place at a later, *viz.* the  $\sigma$ -complex stage, converting the initially formed anionic  $\sigma$ -complexes into their cationic counterparts which finally rearomatize with loss of a proton. In contrast, the substrates **1** themselves are resistant to attack by nucleophiles and have to be previously oxidised in order to be able to be attacked intramolecularly by a nucleophilic tetrazole nitrogen atom. This leads directly or *via* their radicaloid analogues to the formation of cationic  $\sigma$ -complexes (**7**), which then rearomatize again with loss of a proton.

Two mechanisms (Scheme 2) offer themselves for the explanation of the different course of the LTA oxidation of compound **4** carrying a 4''-hydroxy rather than a 4''-methoxy group in the *N*-aryl substituent. According to the first, the reagent acts, as in the oxidation of compounds of type **1** (Scheme 1), by abstracting two electrons from the *N*-aryl group. [For the sake of simplicity, only the EEC pathway **4**→**6A**→**5**→**2f** is shown in Scheme 2 which, however, does not imply that the alternative ECE pathway (*cf.* Scheme 1) is thought to be ruled out for transformation **4**→**2f**.] The important difference between the resulting cation **6A** and its analogue **6** (Scheme 1) is the presence of a highly acidic  $^{\oplus}\text{OH}$  group in the former but not in the latter. As a result, ring closure of cation **6A** is preceded by deprotonation to monocation **5** ( $n=m=1$ ) which accounts for the difference in orientation of the cyclization step leading, in the present case, to spirocyclic product **2f**. According to the second mechanism, substrate **4** and the reagent react initially by ligand exchange to afford intermediate **10** containing an (aryl)O-Pb(IV) bond. Similar ligand exchange reactions between LTA and *alcohols* are known [9] and ligand exchange between LTA and phenols has been postulated to be the first step of LTA oxidation of mono- and dihydric phenols [10, 11] although products (similar to **10**) of the latter type of ligand exchange have, to our knowledge, so far never been detected. Heterolysis of the O-Pb(IV) bond of intermediate **10** (process *b*, Scheme 2) which may or may not be concerted with closure of the spirocycle (process *a*) then leads directly or again *via* cation **5** ( $n=m-1$ ) to compound **2f**.



**Scheme 2.** Suggested alternative mechanisms for reaction  $4 \rightarrow 2f$ .  
(For details, see text.)

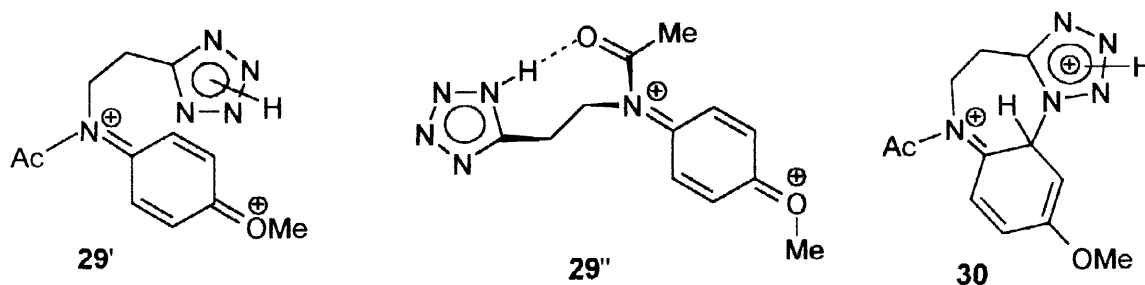
Whenever, at some stage of the oxidation of compounds of type **1**, the possibility of replacement of the 4''-methoxy group of the substrate (or of part of its molecules) by a 4''-hydroxy group exists (as in the case of CAN oxidations carried out in the presence of various amounts of water), the result should be similar, and spirocyclic products of type **2** or mixtures of compounds **2** and **3** have, indeed, been obtained.



Amide **11a** reacts with LTA in a similar fashion to the compounds **1** yielding compound **12a** (16%). Even nonacylated amine **11b** affords compound **12b** (4.6%), however, in this case further dehydrogenation affords an additional product (12.3%) which, according to its <sup>1</sup>H NMR spectrum, exists in CDCl<sub>3</sub> as a 80:20 to 90:10 mixture of the two tautomeric forms **13** and **14**.

In order to rationalize the considerable differences between the yields of compounds **3a** (75%), **3h** (2%) and **12a** (16%) isolated from the oxidation mixture of their precursors **1a**, **1h**

and **11a**, respectively, the minimum energy conformations of the neutral molecules **1a**, **3a**, **3h**, **11a** and **12a** and the dications **6a**, **6h**, **7a·H<sup>+</sup>**, **7h·H<sup>+</sup>**, **29** and **30** and their heats of formation in the minimum energy conformations were determined by combined molecular mechanics and semiempirical calculations. The following heats of formation were obtained by AM1 calculations for the minimum energy conformations: **3a** 570.69, **3h** 603.72, **6a** 1410.9, **6h** 1576.4, **7a·H<sup>+</sup>** 1515.1, **7h·H<sup>+</sup>** 1842.6, **11a'** 252.06, **11a''** 237.53, **29'** 1305.3, **29''** 1284.9 and **30** 1290.35 kJ/mol.



The higher yield of compound **3a** vs that of compound **3h** was rationalized by comparing the heats of reaction of steps **6a**→**7a·H<sup>+</sup>** (1515.1 - 1410.9 = 104.2) and **6h**→**7h·H<sup>+</sup>** (1842.6 - 1576.4 = 266.2 kJ/mol), the key steps of transformations **1a**→**3a** and **1h**→**3h**, respectively (see Scheme 1). The considerably higher value obtained in the **h** series is thought to be caused by the greater strain in the ring system of and the smaller distance of the cationic centers in dication **7h·H<sup>+</sup>**. Both effects should manifest themselves already in the transition state of the cyclization. As a result, cyclization **6h**→**7h·H<sup>+</sup>** should be more difficult than the analogous reaction in the **a** series and therefore to some extent suppressed by other, unidentified reactions of **6h**.

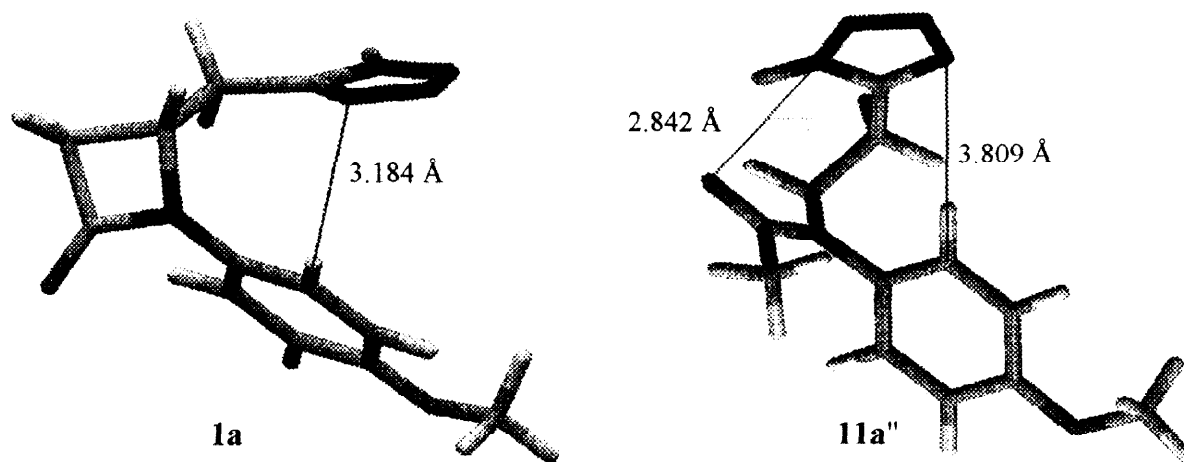
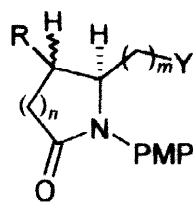


Fig. 1. Computer drawings of the minimum energy conformations of compounds **1a** and **11a''**

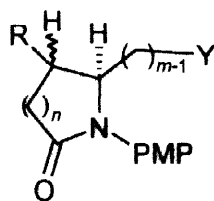
The mechanisms of the oxidative cyclization of compounds **11a** to **12a** and **1a** to **3a** (Scheme 1) should be analogous. The higher yield of compound **3a** vs that of compound **12a** should therefore reflect the difference in the ease of cyclization of dications **6a** to **7a·H<sup>+</sup>** and

**29** to **30**, the key-steps of the transformations. The minimum energy conformation of compound **11a** was found to be **11a''** which is stabilized by a comparatively strong N-H...O=C hydrogen bond and whose stereochemistry strongly differs from that of the minimum energy conformation of compound **1a** (Fig. 1); for structural reasons formation of a hydrogen bond is impossible in the latter. It was furthermore found that the stereochemistry of the minimum energy conformations of the two-electron oxidation products **29''** and **6a** is very similar to that of their parents **11a''** and **1a**, respectively. In addition to the global minima **11a''** and **29''**, local minima **11a'** and **29'**, resembling **1a** and **6a**, respectively, very much, were also found. The hydrogen-bonded conformer **29''** is stabilized relative to **29'** by  $1305.3 - 1284.9 = 20.4$  kJ/mol, *i.e.* **29''** is the predominant conformer. The distance of the two centers involved in the cyclizations (N-4 of the tetrazole ring and C-2 of the PMP group) was found to be 3.81 Å in **11a''** and 3.18 Å in **1a**. Roughly the same distances between these centers may be assumed for the two-electron oxidation products **29''** and **6a**, respectively. Furthermore, an inspection of Fig. 1 shows that the two reacting centers in **1a** and, presumably, in **6a** as well are in a relative position which is favourable for cyclization  $6a \rightarrow 7a \cdot H^{\oplus}$  to take place while this is not the case in **11a''** and, therefore, in **29''** either. On the other hand, rupture of the hydrogen bond prior to or simultaneously with attack of N-4 of the tetrazole ring at C-2 of the PMP group as well as rotation about a C-N bond are necessary for cyclization **29''**  $\rightarrow$  **30** to take place. As a result, cyclization **29''**  $\rightarrow$  **30** should be more difficult than cyclization  $6a \rightarrow 7a \cdot H^{\oplus}$  and, therefore, other (yet not identified) reactions should be able to compete with the cyclization of **29''**.

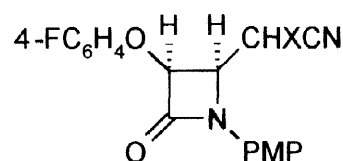
Compounds **1b-1e**, **1g** and **1i** were synthesised by treating nitriles **18b-18e**, **18g** and **18i**, respectively, with *in situ* prepared  $Al(N_3)_3$  as had been described [4, 5] for the synthesis of compounds **1a**, **1f** and **1h**. Nitriles **18b-18d** and **18g** were obtained by applying the method (described earlier [4] for the conversion of hydroxymethyl derivative **15a** into **18a**) to compounds **15b** [12], **15c** [13], **15d** [13] and **15g**, respectively. Compound **15g** was obtained in three steps from dimethyl (2*RS*)-2-bromohexanedioate (**25**) [14] as described in Experimental. Hydroxymethyl derivatives **15b-15d** and **15g** were, as had been described [4] for compound **15a**, treated with methanesulfonyl chloride, and the resulting methanesulfonates **16** were converted either through iodomethyl derivatives **17** or directly into nitriles **18b-18d** and **18g**, respectively. Since difficulties were often experienced in step **17**  $\rightarrow$  **18** of this synthesis sequence, an alternative method for the preparation of nitriles **18** was studied, *viz.* reaction of aldehyde **19e** [15] with *in situ* prepared HCN, followed by treatment of the resulting hydroxynitrile **21** with triphenylphosphine and tetrachloromethane, and finally reduction ( $H_2/Pd-C$ ). To our surprise, in addition to the expected nitrile **18e**, considerable amounts of ring-opened products **23** and **24** were also formed. Studies into this novel ring-opening reaction are in progress.



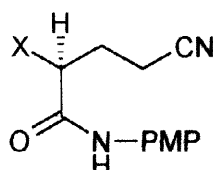
**15a-d, f, g:**<sup>2,5</sup> Y=OH  
**16a-d, g:**<sup>2,5</sup> Y=O<sub>3</sub>SMe  
**17a-d:**<sup>2,5</sup> Y=I  
**18a-e, g, h, i:**<sup>2,5</sup> Y=CN



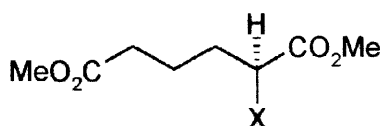
**19a, e, f:**<sup>2,5</sup> Y=CHO  
**20g:**<sup>2,5</sup> Y=CO<sub>2</sub>Me



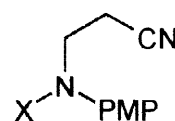
**21:**<sup>2</sup> X=OH  
**22:**<sup>2</sup> X=Cl



**23:**<sup>2</sup> X=4-FC<sub>6</sub>H<sub>4</sub>O  
**24:** X=H



**25:**<sup>2</sup> X=Br  
**26:**<sup>2</sup> X=NH-PMP



**27:** X=H  
**28:** X=Ac

Carbonitrile **18i** was obtained from compound **15f** [5] by the method used earlier [5] for the preparation of the lower ring-homologue **18h** from compound **15a**, *i.e.* oxidation of **15f** to carbaldehyde **19f** and conversion of the latter *via* its oxime into carbonitrile **18i**.

Open-chain analogue **11a** was obtained by *N*-acetylation of compound **27** [16], followed by reaction of the resulting product **28** with *in situ* prepared Al(N<sub>3</sub>)<sub>3</sub>. The other open-chain analogue **11b** was obtained by NaOMe induced methanolysis of compound **1h** [5].

## Experimental

All reactions were monitored by t.l.c. (DC-Alufolien 60F<sub>254</sub>, Merck) and allowed to go to completion. Separations of product mixtures by flash chromatography (c.c.) were carried out using Kieselgel G (Merck) as the adsorbent, unless otherwise stated (pressure differences between the two ends of the columns 10–25 kPa). For preparative t.l.c. separations 20×20 cm glass plates coated with Kieselgel PF<sub>254+366</sub> (Merck; thickness of adsorbent layer 1.5 mm) were used. The solvents are given in parentheses. Dichloromethane will be abbreviated as DCM. The purity of the products was checked, in combination with IR spectroscopy, by t.l.c. on DC-Alufolien 60F<sub>254</sub> (Merck); the individual compounds were detected in UV light or by using iodine, 5% ethanolic molybdo- or tungstophosphoric acids as the reagents. MgSO<sub>4</sub> was used as the drying agent. Evaporations to dryness as well as the removal of volatile components of reaction mixtures by distillation were carried out at reduced pressures (*ca* 2.5 kPa, unless otherwise stated).

<sup>5</sup> *n*, *m* and R in **a-i**, where applicable, as for compounds **1-3**. PMP = 4-methoxyphenyl



All new crystalline compounds described in this paper, except those noted, were colourless. Melting points were determined on a Kofler hot-stage m.p. apparatus. IR spectra were recorded on a Specord-75 (Zeiss, Jena) spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectra were obtained with Varian VRX-400 and Unity INOVA-400 spectrometers in  $\text{CDCl}_3$ - $\text{DMSO}-d_6$  solutions, unless otherwise stated, and using tetramethylsilane as the internal reference compound.  $J$  values in Hz are given in parentheses. The  $\delta$  values of the 4-methoxyphenyl groups were found in most cases at *ca* 3.8 ppm (MeO) and 6.9 + 7.3 ppm (AA'BB',  $J$  *ca* 9;  $4\times\text{ArH}$ ); therefore, except when differing by more than 0.1 ppm from these standard values, their chemical shifts will be omitted from the individual spectra. Exact molecular mass determinations were made at 70 eV with a Finnigan-MAT 95 SQ instrument of reversed geometry equipped with a direct inlet system using PFK (perfluorokerosene) as the reference.

The minimum energy conformations of the neutral molecules were determined with the particularly efficient LMOD search [17] implemented to the MacroModel package [18]. All calculations were performed on an SGI Indy workstation using Merck's MMFF94 force field in the MacroModel package. For the electrostatic treatments the value of  $\epsilon = 1$  was assumed for the dielectric constant and the atomic charges obtained from the force field were used. 1000 LMOD steps were applied for each conformational search. Low energy conformers were obtained using the TNCG algorithm and an energy window of 35 kJ/mol was used for the selection of chemically significant conformer populations. The minimum energy conformations of the mono- and dications were established by starting from the minimum energy conformations of the corresponding neutral molecules (e.g. for dications  $7\mathbf{a}\cdot\text{H}^{\oplus}$  and  $7\mathbf{h}\cdot\text{H}^{\oplus}$  from the molecules  $3\mathbf{a}$  and  $3\mathbf{h}$ , respectively) and optimization of the geometry of the ions, considering thereby the changes resulting from the removal of two electrons or the addition of the appropriate number of protons. The heats of formation of the various species in their minimum energy conformations were subsequently calculated by AM1 semiempirical calculations using the SPARTAN 3.1 package [19].

#### *Preparation of starting compounds 1b-1e, 1g, 1i, 11a and 11b*

##### *(3RS,4RS)-3-Ethyl-1-(4-methoxyphenyl)-4-(methylsulfonyloxymethyl)azetidin-2-one (16b)*

The title compound [74%; m.p. 107°C (MeOH); found: N, 4.7; S, 10.2;  $\text{C}_{14}\text{H}_{19}\text{NO}_5\text{S}$  (313.4) requires: N, 4.45; S, 10.2%;  $\nu_{\text{max}}$  (KBr) 1740, 1350, 1160  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.17t ( $J$  7.5) + 1.76m + 1.91m (3 H + 2 H, Et), 2.93s (3 H,  $\text{O}_3\text{SMe}$ ), 3.39 ddd (1 H,  $J$  9.2, 7.0, 5.5; 3-H), 4.43 ddd (1 H,  $J$  5.6, 5.2, 5.5; 4-H), 4.50 + 4.52 ABM (1 H + 1 H,  $J$  11.0, 5.2 and 5.6, respectively; 4- $\text{CH}_2\text{H}_b$ ) was obtained by methylsulfonylation of the known 4-(hydroxymethyl) compound  $15\mathbf{b}$  [12] as described for methylsulfonylation of compound  $15\mathbf{a}$  [4].

##### *4-(Iodomethyl)-1-(4-methoxyphenyl)azetidin-2-ones (17b-17d)*

The title compounds were obtained by allowing to react compounds  $16\mathbf{b}$ ,  $16\mathbf{c}$  [13] and  $16\mathbf{d}$  [13], respectively, with sodium iodide as described [4] for the analogous transformation  $16\mathbf{a} \rightarrow 17\mathbf{a}$ .

(3RS,4RS)-3-Ethyl-4-(iodomethyl)-1-(4-methoxyphenyl)azetidin-2-one ( $17\mathbf{b}$ ) [95%; m.p. 95°C (EtOH); found: C, 45.1; H, 4.85; N, 4.15;  $\text{C}_{13}\text{H}_{16}\text{INO}_2$  (345.2) requires: C, 45.25; H, 4.65; N, 4.05%;  $\nu_{\text{max}}$  (KBr) 1750

$\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.24t ( $J$  7.5) + 1.84m + 1.99m (3 H + 2 x 1 H, Et), 3.15 + 3.58 ABM (1 H + 1 H,  $J$  10.4, 10.5 and 2.8, respectively, 4- $\text{CH}_2\text{H}_b$ ); 3.32 ddd (1 H,  $J$  10.5, 5.5, 5.5; 3-H), 4.46 ddd (1 H,  $J$  10.5, 5.5, 2.8; 4-H)];

(3*RS*,4*RS*)-4-(Iodomethyl)-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (17c) [99%; m.p. 113–115°C (MeOH); found: C, 46.75; H, 5.15; N, 4.05;  $\text{C}_{14}\text{H}_{18}\text{INO}_2$  (359.2) requires: C, 46.8; H, 5.05; N, 3.9%;  $\nu_{\text{max}}$  (KBr) 1730  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.14d (3 H) + 1.25d (3 H) + 2.33m (1 H,  $\text{Pr}^i$ ), 3.16 dd (1 H,  $J$  9.1, 5.6; 3-H), 3.43 + 3.54 (2 x 1 H, 2 x dd;  $J$  11.2, 7.8 and 3.1, respectively, 4- $\text{CH}_2\text{H}_b$ ), 4.40 ddd (1 H,  $J$  7.8, 3.1, 5.6; 4-H)];

(3*RS*,4*SR*)-4-(Iodomethyl)-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (17d) [84%; m.p. 81°C (MeOH); found: C, 46.95; H, 5.05; N, 3.7;  $\text{C}_{14}\text{H}_{18}\text{INO}_2$  (359.2) requires: C, 46.8; H, 5.05; N, 3.9%;  $\nu_{\text{max}}$  (KBr) 1730  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.11d (3 H) + 1.14d (3 H) + 2.14m (1 H,  $\text{Pr}^i$ ), 2.85 dd (1 H,  $J$  7.4, 2.1; 3-H); 3.30 + 3.65 (2 x 1 H, 2 x dd;  $J$  10.5, 8.4 and 2.7, respectively; 4- $\text{CH}_2\text{H}_b$ ), 3.83 ddd (1 H,  $J$  8.4, 2.7, 2.1; 4-H)].

#### 4-(Cyanomethyl)-1-(4-methoxyphenyl)azetidin-2-ones (18b–18d)

The title compounds were obtained by allowing to react compounds 17b–17d, respectively, with sodium cyanide as described [4] for the analogous transformation 17a  $\rightarrow$  18a.

(3*RS*,4*SR*)-4-(Cyanomethyl)-3-ethyl-1-(4-methoxyphenyl)azetidin-2-one (18b) [79%; m.p. 119–120°C (EtOH), found: C, 68.85; H, 6.5; N, 11.35;  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$  (244.3) requires: C, 68.85; H, 6.6; N, 11.45%;  $\nu_{\text{max}}$  (KBr) 2310w, 1740  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.22t (3 H,  $J$  7.5) + 1.84 dqd + 1.91 dqd (2 x 1 H,  $J$  13.5; 7.5 + 6.5 and 7.5 + 9.5, respectively; Et), 2.67 + 2.93 (2 x 1 H, 2 x dd;  $J$  17.2, 8.4 and 4.2, respectively; 4- $\text{CH}_2\text{H}_b$ ), 3.41 ddd (1 H,  $J$  9.5, 6.5, 5.5; 3-H), 4.40 ddd (1 H,  $J$  8.4, 4.2, 5.5; 4-H)];

(3*RS*,4*SR*)-4-(Cyanomethyl)-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (18c) [66%; m.p. 130°C; found: C, 69.85; H, 7.1; N, 11.0;  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2$  (258.3) requires: C, 69.75; H, 7.0; N, 10.85%;  $\nu_{\text{max}}$  (KBr) 2260w, 1740  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.08d (3 H) + 1.27d (3 H,  $J$  6.5) + 2.22m (1 H,  $\text{Pr}^i$ ), 2.84 + 2.88 (2 x 1 H, 2 x dd;  $J$  17.5, 6.5 and 4.5, respectively; 4- $\text{CH}_2\text{H}_b$ ), 3.19 dd (1 H,  $J$  10.6, 5.5; 3-H), 4.41 ddd (1 H,  $J$  6.5, 4.5, 5.5; 4-H)];

(3*RS*,4*RS*)-4-(Cyanomethyl)-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (18d) [80%; faint yellow oil; found: C, 69.65; H, 7.1; N, 10.95;  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2$  (258.3) requires: C, 69.75; H, 7.0; N, 10.85%;  $\nu_{\text{max}}$  (film) 2260w, 1750  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.09d (3 H) + 1.16d (3 H,  $J$  6.5) + 2.13m (1 H,  $\text{Pr}^i$ ), 2.74 + 2.98 (2 x 1 H, 2 x dd;  $J$  17.1, 7.3 and 3.8, respectively; 4- $\text{CH}_2\text{H}_b$ ), 2.96 dd (1 H,  $J$  8.2, 2.2; 3-H), 4.02 ddd (1 H,  $J$  7.3, 3.8, 2.2; 4-H)].

(3*RS*,4*SR*)-4-(1-Cyano-1-hydroxymethyl)-3-(4-fluorophenoxy)-1-(4-methoxyphenyl)azetidin-2-one (21), mixture of side-chain epimers

KCN (5.45 g, 83 mmol) in water (60 mL) was dropwise added to a mixture of (2*RS*,3*RS*)-3-(4-fluorophenoxy)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carbaldehyde (19e) [15] (17.5 g, 55.5 mmol), MeCN (280 mL) and acetic acid (4.9 mL, 83 mmol) with continuous stirring at room temperature. Stirring was continued for 24 h. The MeCN component of the mixture was distilled off and the resulting aqueous suspension was extracted with EtOAc. The combined organic phases were washed with water and saturated aqueous  $\text{Na}_2\text{CO}_3$  solution, dried and evaporated to dryness. The residue was triturated with diethyl ether and the crystalline product was filtered off to afford a mixture of the epimers of the title compound [17.5 g, 92%; m.p.

130–135°C; ratio of the epimers (NMR) 1:1<sup>6</sup>]. The filtrate of this product was found (t.l.c.; toluene - EtOAc, 8:2) to contain the less polar epimer *A* in almost pure form, contaminated by traces of the more polar epimer *B*. The filtrate was evaporated to dryness and the residue was worked up by preparative t.l.c. (toluene - EtOAc, 8:2) to afford pure epimer *A* [m.p. 158°C; found: C, 63.0; H, 4.5; F, 5.25; N, 8.15; C<sub>18</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>4</sub> (342.35) requires: C, 63.15; H, 4.4; F, 5.55; N, 8.2%;  $\nu_{\max}$  (KBr) 3400, 1750 cm<sup>-1</sup>;  $\delta_{\text{H}}$  4.74 dd (1 H, *J* 7.8, 5.4; 4-H), 4.91 dd (1 H, *J* 7.8, 6.4; 4-CH), 5.36d (1 H, *J* 5.4; 3-H), 6.77d (1 H, *J* 6.4; OH); 6.88 + 7.59 (2 x 2 Ar-H, PMP), 7.01 + 7.19 (2 x 2 Ar-H, 4-FC<sub>6</sub>H<sub>4</sub>O)] and a mixture of epimers *A* and *B* {the latter could not be obtained in pure form but the chemical shifts of its protons [ $\delta_{\text{H}}$  4.66 dd (1 H, *J* 5.4, 2.8; 4-H), 5.02d (1 H, *J* 2.8; CHOH), 5.39d (1 H, *J* 5.4; 3-H), 6.76 br (1 H, OH), 6.90 + 7.06 (2 x 2 Ar-H, PMP), 7.01 + 7.15 (2 x 2 Ar-H, 4-FC<sub>6</sub>H<sub>4</sub>O)] were extracted from the spectrum of the mixture of the two epimers}.

(3*RS*,4*RS*)-4-(1-Chloro-1-cyanomethyl)-3-(4-fluorophenoxy)-1-(4-methoxyphenyl)azetidin-2-one (**22**), mixture of side-chain epimers

Compound **21** (mixture of side-chain epimers) (29.5 g, 86 mmol), MeCN (340 mL), CCl<sub>4</sub> (17 mL), 175 mmol) and Ph<sub>3</sub>P (27 g, 103 mmol) was stirred for 18 h at room temperature. Kieselgel (0.063–0.2; 150 g) was added and the mixture was evaporated to dryness. The residue was transferred onto a column and worked up by c.c. (DCM). The eluate was evaporated to dryness to afford the colourless crystals of the title compound [20 g, 64%, 9:1 mixture of two epimers (NMR); m.p. 133°C; found: C, 59.9; H, 4.0; Cl, 9.85; N, 7.8; C<sub>18</sub>H<sub>14</sub>ClFN<sub>2</sub>O<sub>3</sub> (360.8) requires: C, 59.95; H, 3.9; Cl, 9.85; N, 7.75%;  $\nu_{\max}$  (KBr) 1760 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) main component 4.86 dd (1 H, *J* 5.1, 5.1; 4-H), 5.03d (1 H, *J* 5.1; CHCl), 5.40d (1 H, *J* 5.1; 3-H), 6.93 + 7.45 (2 x 2 Ar-H, PMP), 7.03 + 7.14 (2 x 2 Ar-H, 4-FC<sub>6</sub>H<sub>4</sub>O); minor component 4.88 dd (1 H, *J* 6.1, 5.1; 4-H), 5.01d (1 H, *J* 6.1; CHCl), 5.42d (1 H, *J* 5.1; 3-H), 6.93 + 7.41 (2 x 2 Ar-H, PMP), 7.03 + 7.17 (2 x 2 Ar-H, 4-FC<sub>6</sub>H<sub>4</sub>O)].

Reduction of compound **22**, mixture of side-chain epimers

Compound **22** (12 g, 33 mmol) in EtOAc (170 mL), NaHCO<sub>3</sub> (3.1 g, 36.3 mmol) in water (60 mL) and a 10% Pd-C catalyst (4 g) was vigorously stirred at room temperature. Hydrogen uptake did not stop abruptly when the calculated amount was consumed. Stirring under hydrogen was continued until *ca* 140% of the amount of H<sub>2</sub> necessary for reaction **22** → **18e** was consumed. The catalyst was filtered off and the organic phase of the filtrate was washed with water, dried and worked up by c.c. (DCM) to afford, in increasing order of their polarities, the colourless crystals of (3*RS*,4*SR*)-4-(cyanomethyl)-3-(4-fluorophenoxy)-1-(4-methoxyphenyl)azetidin-2-one (**18e**) [5.5 g, 51%; m.p. 113°C; found: C, 66.25; H, 4.6; N, 8.55; C<sub>18</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>3</sub> (326.3) requires: C, 66.25; H, 4.65; N, 8.6%;  $\nu_{\max}$  (KBr) 2250w, 1750 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 3.00d (2 H, *J* 6.0; 4-CH<sub>2</sub>), 4.70 td (1 H, *J* 6.0, 5.0; 4-H), 5.37d (1 H, *J* 5.0; 3-H), 7.03 + 7.15 (2 x 2 Ar-H, 4-FC<sub>6</sub>H<sub>4</sub>O)], (2*RS*)-4-cyano-2-(4-fluorophenoxy)-4'-methoxybutananilide (**23**) [3.5 g, 33%; m.p. 105°C; found: C, 65.75; H, 5.2; N, 8.5; C<sub>18</sub>H<sub>17</sub>FN<sub>2</sub>O<sub>3</sub> (328.35) requires: C, 65.85; H, 5.2; N, 8.55%;  $\nu_{\max}$  (KBr) 3250, 2240w, 1660 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 2.37m (2 H, CH<sub>2</sub>CH<sub>2</sub>CN), 2.60t (2 H, *J* 7.2; CH<sub>2</sub>CH<sub>2</sub>CN), 4.69 dd (1 H, *J* 7.0, 4.7; 4-FC<sub>6</sub>H<sub>4</sub>OCH), 6.87 + 7.41 (2 x 2 Ar-H, PMP), 6.97 + 7.04 (2 x 2 Ar-H, 4-FC<sub>6</sub>H<sub>4</sub>O), 8.08 br s (1 H, NH)] and

<sup>6</sup> The ratio of the epimers was found to change in the course of the reaction. E.g., in a sample taken after 2 h stirring at room temperature, the intensity ratio of the spots corresponding to the two epimers (t.l.c.; toluene - EtOAc, 8:2) was found to be *A*:*B* 4:1. The occurrence of this epimerization suggests that, under the reaction conditions applied, addition of HCN to the aldehyde group of compound **19e** is reversible.

*4-cyano-4'-methoxybutananilide (24)* [0.3 g, 4%; m.p. 102°C; found: C, 66.0; H, 6.5; N, 12.75;  $C_{12}H_{14}N_2O_2$  (218.25) requires: C, 66.05; H, 6.45; N, 12.85%;  $\nu_{\max}$  (KBr) 3330, 2260w, 1670  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 2.08m (2 H,  $CH_2CH_2CN$ ), 2.52t (2 H,  $J$  7.7) + 2.53t (2 H,  $J$  7.7;  $CH_2CH_2CN$  and  $CH_2CO$ ), 7.38 br s (1 H, NH);  $\delta_C$  ( $CDCl_3$ ) 16.56 ( $CH_2CH_2CN$ ), 20.94 ( $CH_2CH_2CN$ ), 34.69 ( $CH_2CO$ ), 55.43 (OMe), 114.05 (C-3 + C-5, PMP), 119.42 (CN), 121.92 (C-2 + C-6, PMP), 130.72 (C-1, PMP), 156.44 (C-4, PMP), 169.27 (CONH)].

*Dimethyl (2RS)-2-(4-Methoxyanilino)hexanedioate (26)*

A mixture of *p*-anisidine (13.5 g, 110 mmol), dimethyl (2RS)-2-bromohexanedioate (**25**) [14] (12.7 g, 50 mmol) and dry acetonitrile (100 mL) was refluxed until the starting ester was consumed (t.l.c., DCM-acetone, 10:0.3; *ca* 2 h) and allowed to cool. The crystalline anisidine-HBr was filtered off, the filtrate was evaporated to dryness and the residue was taken up in EtOAc. The solution was washed successively with water and 1N HCl until the anisidine was completely removed, dried and evaporated to dryness. The residue was distilled at 130 Pa (b.p. 170–180°C) to afford the title compound as a yellow oil [9.5 g, 64%; found: C, 61.25; H, 7.15; N, 5.05;  $C_{15}H_{21}NO_5$  (295.3) requires: C, 61.0; H, 7.15; N, 4.75%;  $\nu_{\max}$  (film) 3370, 1730, 1260, 1020  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.7–1.95m (4 H,  $MeO_2CCH_2CH_2CH_2$ ), 2.36t (2 H,  $MeO_2CCH_2$ ), 3.66s + 3.70s + 3.73s (3 x 3 H, 3 x MeO), 3.7 br (1 H, NH), 3.99t (1 H,  $CH_2CHXCO_2Me$ ), 6.59 + 6.77 (2 x 2 *Ar*-H, PMP)]. According to its NMR spectrum the product was slightly contaminated by its ring closure product **20g**.]

*Methyl (2RS)-1-(4-Methoxyphenyl)-6-oxopiperidine-2-carboxylate (20g)*

Compound **26** (20.7 g, 70 mmol) in acetic acid (130 mL) was refluxed under argon until compound **26** was consumed (*ca* 6 h; t.l.c., DCM-acetone, 10:0.5) and the mixture was evaporated to dryness. The residue was taken up in DCM, washed successively with saturated aqueous  $Na_2CO_3$  solution and water, and dried. Kieselgel G was added and the mixture was evaporated to dryness. The residue was transferred onto a Kieselgel G column and worked up by c.c. (toluene - acetone, 10:0.5  $\rightarrow$  8:2) to afford the title compound [14.7 g, colourless crystals, 80%; m.p. 82–83°C; found: C, 63.85; H, 6.55; N, 5.45;  $C_{14}H_{17}NO_4$  (263.3) requires: C, 63.85; H, 6.5; N, 5.3%;  $\nu_{\max}$  (KBr) 1750, 1660  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.90m (2 H, 4- $H_2$ ), 2.21m (2 H, 3- $H_2$ ), 2.52 + 2.67 (1 H + 1 H, 2 x ddd;  $J$  18.0; 8.8, 8.6 and 5.2, 4.8, respectively, 5- $H_aH_b$ ), 3.69s (3 H,  $CO_2Me$ ), 4.46t (1 H,  $J$  4.7; 2-H), 6.89 + 7.16 (2 x 2 *Ar*-H, PMP)].

*(6RS)-6-(Hydroxymethyl)-1-(4-methoxyphenyl)piperidin-2-one (15g)*

Compound **20g** (13.2 g, 50 mmol) in anhydrous THF (130 mL) was stirred for 30 min with  $NaBH_4$  (5.7 g, 150 mmol). The mixture was heated up to 40°C and methanol (*ca* 30 mL) was added dropwise within *ca* 10 min, whereby heat was evolved and the mixture started to boil moderately. The mixture was stirred for 1.5 h and acidified (pH 3) with conc. HCl with ice-cooling. The organic components of the solvent were distilled off and the residue was taken up in water. The resulting solution was extracted with DCM, the combined organic phases were dried and evaporated to dryness. The oily residue was crystallized from *i*-PrOH to afford the title compound [10.2 g, 87%; m.p. 163°C; found: C, 66.1; H, 7.2; N, 5.85;  $C_{13}H_{17}NO_3$  (335.3) requires: C, 66.35; H, 7.3; N, 5.95%;  $\nu_{\max}$  (KBr) 3250 br, 1620/1600d  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.75–2.15m (2 x 2 H, 4- $H_2$  + 5- $H_2$ ), 1.93t (1 H,  $J$  5.8; OH), 2.50m (2 H, 3- $H_2$ ), 3.48m (2 H,  $CH_2OH$ ), 3.77m (1 H, 6-H), 6.91 + 7.08 (2 x 2 *Ar*-H, PMP)].

*(6RS)-1-(4-Methoxyphenyl)-6-(methylsulfonyloxymethyl)piperidin-2-one (16g)*

Methanesulfonyl chloride (2.8 mL, 36 mmol) was added dropwise to a mixture of compound **15g** (7.1 g; 30 mmol), pyridine (12 mL) and DCM (15 mL) with continuous stirring and ice-water cooling. Stirring was continued for 1 h, and the mixture was poured into a mixture of DCM (120 mL) and 1N HCl (130 mL). The aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried and evaporated to dryness. The residue was crystallized from *i*-PrOH to afford the title compound [8.2 g, 87%; m.p. 125°C; found: C, 53.55; H, 6.0; N, 4.2; S, 9.8; C<sub>14</sub>H<sub>19</sub>NO<sub>5</sub>S (313.4) requires: C, 53.65; H, 6.1; N, 4.45; S, 10.25%;  $\nu_{\max}$  (KBr) 1650, 1370, 1180 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.83–2.19m (2 x 2 H, 4-H<sub>2</sub> + 5-H<sub>2</sub>), 2.56m (2 H, 3-H<sub>2</sub>), 2.93s (3 H, O<sub>3</sub>SMe), 4.02–4.12m (3 H, 6-H + CH<sub>2</sub>OSO<sub>2</sub>), 6.94 + 7.11 (2 x 2 *Ar*-H, PMP)].

*(6RS)-6-(Cyanomethyl)-1-(4-methoxyphenyl)piperidin-2-one (18g)*

A mixture of compound **16g** (9.4 g, 30 mmol), KCN (2.4 g, 36 mmol), 18-crown-6 (0.8 g, 3 mmol) and dry DMF (95 mL) was stirred for 3 days at room temperature and poured into water (800 mL). The resulting mixture was extracted with DCM. The combined organic phases were dried and evaporated to dryness at *ca* 200 Pa. The residue was worked up by c.c. (Al<sub>2</sub>O<sub>3</sub>, Brockmann II, neutral; toluene - acetone, 10:0.5) to afford the title compound [4.4 g, 60%; m.p. 108°C; found: C, 68.6; H, 6.6; N, 11.15; C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub> (244.3) requires: C, 68.85; H, 6.6; N, 11.45%;  $\nu_{\max}$  (KBr) 2270, 1650 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.85–2.3m (2 x 2 H, 4-H<sub>2</sub> + 5-H<sub>2</sub>), 2.45 + 2.48 (1 H + 1 H, 2 x dd; *J* 16.8; 6.2 and 4.5, respectively; CH<sub>a</sub>H<sub>b</sub>CN), 2.58m (2 H, 3-H<sub>2</sub>), 4.05m (1 H, 6-H), 6.95 + 7.11 (2 x 2 *Ar*-H, PMP)].

*(2RS)-1-(4-Methoxyphenyl)-5-oxopyrrolidine-2-carbaldehyde (19f)*

The title compound [63%; faint yellow oil; found: M<sup>+</sup>, 219.08962; C<sub>12</sub>H<sub>13</sub>NO<sub>3</sub> requires: M<sup>+</sup>, 219.08954;  $\nu_{\max}$  (film) 1690, 1670/1660d cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 2.14+2.41 (2 x 1 H, 2 x dddd, *J* 13.3; 9.0 + 6.5 + 4.9 and 9.1 + 8.9 + 8.0, respectively; 3-H<sub>a</sub>H<sub>b</sub>), 2.56 + 2.59 (2 x 1 H, 2 x ddd, *J* 17.2; 8.9 + 6.5 and 9.0 + 8.0, respectively; 4-H<sub>a</sub>H<sub>b</sub>), 4.61 ddd (1 H, *J* 9.1, 4.9, 2.8; 2-H), 9.57d (1 H, *J* 2.8; CHO)] was obtained starting with compound **15f** [5] as described [5] for the analogous transformation **15a** → **19a**.

*(5RS)-5-Cyano-1-(4-methoxyphenyl)pyrrolidin-2-one (18i)*

The title compound [m.p. 132°C (MeOH); found: M<sup>+</sup>, 216.08917; C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> requires: M<sup>+</sup>, 216.08988;  $\nu_{\max}$  (KBr) 2260w, 1700 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 2.43–2.87m (4 H, 3-H<sub>2</sub> + 4-H<sub>2</sub>), 4.77m (1 H, 5-H)] was obtained from carbaldehyde **19f** in two steps (87 and 91%) *via* its oxime [m.p. 133°C;  $\nu_{\max}$  (KBr) 3250, 1660 cm<sup>-1</sup>] as described [5] for the analogous transformation **19a** → **18h**.

*N-(2-Cyanoethyl)-4'-methoxyacetanilide (28)*

A mixture of *N*-(2-cyanoethyl)-*p*-anisidine (**27**) [16] (2.0 g, 11.5 mmol), acetic acid (3.5 mL) and acetic anhydride (1.3 mL, 13.5 mmol) was refluxed for 30 min, poured into water (80 mL) and extracted with DCM. The combined organic phases were dried and evaporated to dryness. The residue was worked up by t.l.c. (DCM - acetone, 10:0.5) to afford the oily faint yellow title compound [2.2 g, 89%; found: M<sup>+</sup>, 218.10475; C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> requires: M<sup>+</sup>, 218.10553;  $\nu_{\max}$  (film) 2240, 1650, 820 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.86s (3 H, *N*-Ac), 2.68t

(2 H,  $J$  6.8;  $\text{CH}_2\text{CN}$ ), 3.91t (2 H,  $J$  6.8;  $\text{CH}_2\text{N}$ ), 6.95 + 7.16 (2 x 2  $\text{Ar-H}$ , PMP)] which was used in the following step [reaction with  $\text{Al}(\text{N}_3)_3$ ] without further purification.

*Reaction of 4-(cyanomethyl)azetidin-2-ones 18b–18e, the 6-(cyanomethyl)piperidin-2-one 18g, the 5-cyanopyrrolidin-2-one 18i and the open-chain analogue 28 with  $\text{Al}(\text{N}_3)_3$*

The reactions of the title compounds with *in situ* generated  $\text{Al}(\text{N}_3)_3$  were carried out out as described [4,5] for the analogous reactions of compounds **1a**, **1f** and **1h**, and afforded the corresponding (tetrazol-5-ylmethyl) derivatives **1b–1e**, **1g**, the tetrazol-5-yl derivative **1i** and the open-chain analogue **11a**, respectively.<sup>7</sup>

(3RS,4SR)-3-Ethyl-1-(4-methoxyphenyl)-4-(tetrazol-5-ylmethyl)azetidin-2-one (**1b**) [91%; m.p. 166–167°C; found:  $\text{M}^+$ , 287.1400;  $\text{C}_{14}\text{H}_{17}\text{N}_5\text{O}_2$  requires:  $\text{M}^+$ , 287.1382;  $\nu_{\text{max}}$  (KBr) 3300–2950 br (with several local maxima), 1750  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  1.53t (3 H,  $J$  7.3) + 1.62m (1 H) + 1.83m (1 H, Et), 3.22 + 3.48 (2 x 1 H, 2xdd;  $J$  15.5; 8.9 and 4.5, respectively; 4- $\text{CH}_a\text{H}_b$ ), 3.35 ddd (1 H,  $J$  9.8, 6.0, 5.6; 3-H), 4.73 ddd (1 H,  $J$  8.9, 4.5, 5.6; 4-H), 10.3 br (1 H, NH);

(3RS,4SR)-3-Isopropyl-1-(4-methoxyphenyl)-4-(tetrazol-5-ylmethyl)azetidin-2-one (**1c**) [92%; m.p. 114°C; found: C, 59.7; H, 6.25; N, 23.2;  $\text{C}_{15}\text{H}_{19}\text{N}_5\text{O}_2$  (301.35) requires: C, 59.8; H, 6.35; N, 23.25%;  $\nu_{\text{max}}$  (KBr) 1740/1730d  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.93d (3 H) + 1.25d (3 H,  $J$  6.6) + 2.15m (1 H,  $\text{Pr}^i$ ), 3.17 dd (1 H,  $J$  10.0, 5.5; 3-H), 3.39d (2 H,  $J$  6.4; acyclic  $\text{CH}_2$ ), 4.81 td (1 H,  $J$  6.4, 5.5; 4-H), 6.79 + 7.12 (2 x 2  $\text{Ar-H}$ , PMP)];

(3RS,4RS)-3-Isopropyl-1-(4-methoxyphenyl)-4-(tetrazol-5-ylmethyl)azetidin-2-one (**1d**) [60%; m.p. 118°C; found: C, 59.65; H, 6.25; N, 23.3;  $\text{C}_{15}\text{H}_{19}\text{N}_5\text{O}_2$  (301.35) requires: C, 59.8; H, 6.35; N, 23.25%;  $\nu_{\text{max}}$  (KBr) 1730  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.75d (3 H) + 0.94d (3 H,  $J$  6.7) + 1.97m (1 H,  $\text{Pr}^i$ ), 2.94 dd (1 H,  $J$  7.9, 2.1; 3-H), 3.17 dd + 3.66 dd (1 H + 1 H,  $J$  14.6; 8.9 and 4.2, respectively; acyclic  $\text{CH}_a\text{H}_b$ ), 4.18 ddd (1 H,  $J$  8.9, 4.2, 2.1; 4-H)];

(3RS,4SR)-3-(4-Fluorophenoxy)-1-(4-methoxyphenyl)-4-(tetrazol-5-ylmethyl)azetidin-2-one (**1e**) [94%; m.p. 216°C (MeCN); found: C, 58.5; H, 4.35; N, 18.65;  $\text{C}_{18}\text{H}_{16}\text{FN}_5\text{O}_3$  (369.4) requires: C, 58.55; H, 4.35; N, 18.95%;  $\nu_{\text{max}}$  (KBr) 3100–2600br, 1730  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  3.49 dd + 3.58 dd (1 H + 1 H,  $J$  15.6; 8.6 and 4.8, respectively; acyclic  $\text{CH}_a\text{H}_b$ ), 5.13 ddd (1 H,  $J$  8.6, 4.8, 5.0; 4-H), 5.38d (1 H,  $J$  5.0; 3-H), 6.93m (4 x  $\text{Ar-H}$ ; 4- $\text{FC}_6\text{H}_4\text{O}$ )];

(6RS)-1-(4-Methoxyphenyl)-6-(tetrazol-5-ylmethyl)piperidin-2-one (**1g**) [96%; m.p. 245°C; found: C, 58.35; H, 5.9; N, 24.1;  $\text{C}_{14}\text{H}_{17}\text{N}_5\text{O}_2$  (287.3) requires: C, 58.5; H, 5.95; N, 24.35%;  $\nu_{\text{max}}$  (KBr) 3200–2400br, 1620  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (DMSO- $d_6$ ) 1.6–2.05m (4 H, 4- $\text{H}_2$  + 5- $\text{H}_2$ ), 2.32–2.5m (2 H, 3- $\text{H}_2$ ), 3.03 dd + 3.14 dd (1 H + 1 H,  $J$  14.6, 4.2 and 9.6, respectively, 6- $\text{CH}_a\text{H}_b$ ), 4.24m (1 H, 6-H)];

(5RS)-1-(4-Methoxyphenyl)-5-(tetrazol-5-yl)pyrrolidin-2-one (**1i**) [74%; m.p. 112–113°C; found (FAB):  $(\text{M} + \text{H})^+$ , 260.11824;  $\text{C}_{12}\text{H}_{14}\text{N}_5\text{O}_2^+$  requires:  $(\text{M} + \text{H})^+$ , 260.11475;  $\nu_{\text{max}}$  (KBr) 3350br, 1680  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  2.22m + 2.55–2.90m (4 H, 4- $\text{H}_2$  + 3- $\text{H}_2$ ), 5.69 dd (1 H,  $J$  8.2, 4.2; 5-H), 7.3br (1 H, NH)];

4'-Methoxy-N-[2-(tetrazol-5-yl)ethyl]acetanilide (**11a**) [77%; m.p. 146°C (EtOAc); found:  $\text{M}^+$ , 261.12222;  $\text{C}_{12}\text{H}_{15}\text{N}_5\text{O}_2$  requires:  $\text{M}^+$ , 261.12257;  $\nu_{\text{max}}$  (KBr) 3200–2500br, 1640  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  1.74s (3 H,  $\text{N-Ac}$ ), 3.12t (2 H,  $\text{CH}_2$ -tetrazole), 4.00t (2 H,  $\text{NCH}_2$ ), 6.94 + 7.12 (2 x 2  $\text{Ar-H}$ ; PMP)].

<sup>7</sup> For the preparation of compound **1g** prolongation of the reaction time to six days (at reflux temperature) and acidification of the mixture with conc. HCl until all the Al-containing co-products were dissolved, proved advantageous.

*Methyl (3RS)-3-(4-methoxyanilino)-3-(tetrazol-5-yl)propionate (11b)*

Metallic sodium (0.26 g, 11.4 mmol) and compound **1h** [5] (1.4 g, 5.7 mmol) were successively dissolved in anhydrous methanol (60 mL). The mixture was refluxed for 9 h (t.l.c., DCM - methanol, 7:2), neutralized with conc. HCl (*ca* 1 mL) and evaporated to dryness. The residue was triturated with water, and the insoluble material was filtered off. The filtrate was extracted with DCM. The combined DCM solutions were dried and evaporated to dryness. The residue was worked up by c.c. (DCM - MeOH, 7:2) to afford the title compound [0.7 g, 44%; m.p. 113–114°C; found:  $M^+$ , 277.1145;  $C_{12}H_{15}N_5O_3$  requires:  $M^+$ , 277.1175;  $\nu_{\max}$  (KBr) 3100–2900br (with several local maxima), 1730, 1230, 1015  $cm^{-1}$ ;  $\delta_H$  (CDCl<sub>3</sub>; 55°C) 3.04 + 3.08 ABX (1 H + 1 H, *J* 16.5, 5.6 and 6.0, respectively; 2- $H_aH_b$ ), 3.61s (3 H, CO<sub>2</sub>Me), 4.7br (2 H, 2 x NH), 5.19 dd (1 H, *J* 5.6 and 6.0; 3-H)] slightly contaminated by an unidentified impurity ( $M^+$ , 301).

*LTA oxidation of compounds 1a–1i, 11a and 11b*

Equimolar mixtures (unless otherwise stated) of the title compounds and LTA were refluxed in dioxane (40–60 mL/g substrate) for 1 h. Since, in most cases, the substrates were not consumed at this point, another portion of LTA (1 mol/mol substrate, unless otherwise stated) was added, and the mixtures were refluxed until the substrate was consumed. Subsequently Kieselgel G was added (1 g/g substrate) and the mixtures were evaporated to dryness. The residues were worked up by flash c.c., using DCM - acetone mixtures of variable compositions (10:0.5 - 7:1) as the solvent. The following compounds were obtained:

(9aRS)-3-Methoxy-9,9a-dihydroazeto[1,2-a]tetrazolo[5,1-d][1,5]benzodiazepin-11(10H)-one (**3a**) (LTA: 2 mol-equivalents) [75%; m.p. 228°C (toluene); found: C, 55.9; H, 4.45; N, 27.35;  $C_{12}H_{11}N_5O_2$  (257.25) requires: C, 56.0; H, 4.3; N, 27.2%;  $\nu_{\max}$  (KBr) 1740  $cm^{-1}$ ;  $\delta_H$  3.15 + 3.49 (1 H + 1 H, 2xddd; *J* 15.2; 2.6 and 5.2, respectively; 10- $H_aH_b$ ), 3.43 + 3.98 (1 H + 1 H, 2xddd; *J* 15.5; 10.5 and 2.0, respectively, 9- $H_aH_b$ ), 3.86s (3 H, MeO), 4.19 dddd (1 H, *J* 10.5, 5.2, 2.6, 2.0; 9a-H); 7.10 dd (1 H, *J* 9.0, 2.7; 2-H), 7.75d (1 H, *J* 2.7; 4-H), 8.17d (1 H, *J* 9.0; 1-H);  $\delta_C$  29.24 (C-9), 43.98 (C-10), 48.92 (C-9a), 55.62 (MeO), 107.06 (C-4), 115.87 (C-2), 121.72 (C-12a or C-4a), 122.07 (C-1), 122.79 (C-4a or C-12a), 152.31 (C-8a), 155.55 (C-3), 163.79 (C-11)] from compound **1a** [4],

(9aRS,10SR)-10-Ethyl-3-methoxy-9,9a-dihydroazeto[1,2-a]tetrazolo[5,1-d][1,5]benzo-diazepin-11(10H)-one (**3b**) [75%; m.p. 175°C (toluene); found:  $M^+$ , 285.1226;  $C_{14}H_{15}N_5O_2$  requires:  $M^+$ , 285.1241;  $\nu_{\max}$  (KBr) 1750  $cm^{-1}$ ;  $\delta_H$  (CDCl<sub>3</sub>) 1.20t (3 H) + 1.78m (1 H) + 1.95m (1 H, Et), 3.16 + 3.93 (1 H + 1 H, 2xddd; *J* 15.3; 10.9 and 1.7, respectively; 9- $H_aH_b$ ), 3.59 ddd (1 H, *J* 7.9, 8.3, 5.5; 10-H), 3.87s (3 H, MeO), 4.12 ddd (1 H, *J* 5.5, 10.9, 1.7, 9a-H), 6.99 dd (1 H, 2-H), 7.78d (1 H, 4-H), 8.24d (1 H, 1-H)] from compound **1b**;

(9aRS,10SR)-10-Isopropyl-3-methoxy-9,9a-dihydroazeto[1,2-a]tetrazolo[5,1-d][1,5]benzodiazepin-11(10H)-one (**3c**) [82%; m.p. 188°C (toluene); found: C, 60.2; H, 5.55; N, 23.25;  $C_{15}H_{17}N_5O_2$  (299.3) requires: C, 60.2; H, 5.7; N, 23.4%;  $\nu_{\max}$  (KBr) 1730  $cm^{-1}$ ;  $\delta_H$  (CDCl<sub>3</sub>) 1.09d (3 H) + 1.28d (3 H, *J* 6.5) + 2.18m (1 H, Pr<sup>i</sup>), 3.21 dd + 4.08 dd (1 H + 1 H, *J* 15.0; 11 and 1.5, respectively; 9- $H_aH_b$ ), 3.37 dd (1 H, *J* 11.4, 5.3; 10-H), 3.87s (3 H, MeO), 4.10 ddd (1 H, *J* 11, 1.5, 5.3; 9a-H), 6.99 dd (1 H, *J* 9.0, 2.8; 2-H); 7.79d (1 H, *J* 2.8; 4-H), 8.26d (1 H, *J* 9.0; 1-H)] from compound **1c**;

(9aRS,10RS)-10-Isopropyl-3-methoxy-9,9a-dihydroazeto[1,2-a]tetrazolo[5,1-d][1,5]benzodiazepin-11(10H)-one (**3d**) [77%; m.p. 160°C (toluene); found: C, 60.3; H, 5.65; N, 23.2;  $C_{15}H_{17}N_5O_2$  (299.3) requires: C, 60.2; H, 5.7; N, 23.4%;  $\nu_{\max}$  (KBr) 1750  $cm^{-1}$ ;  $\delta_H$  (CDCl<sub>3</sub>) 1.08d (3 H) + 1.16d (3 H,  $J$  6.6) + 2.21m (1 H, Pr<sup>i</sup>), 3.07 dd (1 H,  $J$  8.0, 2.5; 10-H), 3.18 dd + 4.05 dd (1 H + 1 H,  $J$  15.3; 10.5 and 1.8, respectively; 9-H<sub>a</sub>H<sub>b</sub>), 3.81 ddd (1 H,  $J$  10.5, 1.8, 2.5; 9a-H), 3.87s (3 H, MeO), 7.00 dd (1 H,  $J$  9.0, 2.7; 2-H), 7.79d (1 H,  $J$  2.7; 4-H), 8.27d (1 H,  $J$  9.0; 1-H)] from compound **1d**;

(9aRS,10SR)-10-(4-Fluorophenoxy)-3-methoxy-9,9a-dihydroazeto[1,2-a]tetrazolo[5,1-d][1,5]benzodiazepin-11(10H)-one (**3e**) [LTA: 3 x 1 mol-equivalents; 21%; m.p. 220°C; found: C, 58.9; H, 3.9; F, 5.35; N, 19.15;  $C_{18}H_{14}FN_5O_3$  (367.35) requires: C, 58.85; H, 3.85; F, 5.15; N, 19.05%;  $\nu_{\max}$  (KBr) 1760  $cm^{-1}$ ;  $\delta_H$  3.46 dd + 3.87 dd (1 H + 1 H,  $J$  16.0; 10.5 and 2.2, respectively; 9-H<sub>a</sub>H<sub>b</sub>), 3.90s (3 H, MeO), 4.53 ddd (1 H,  $J$  10.5, 2.2, 4.7; 9a-H), 5.73d (1 H,  $J$  4.7; 10-H), 7.05 + 7.13 (2 x 2 Ar-H; 4-FC<sub>6</sub>H<sub>4</sub>O), 7.05 dd (1 H,  $J$  9.0, 2.7; 2-H), 7.88d (1 H,  $J$  2.7; 4-H), 8.09 (9.0, 1-H)] from compound **1e**;

(9aRS)-3-Methoxy-9a,10-dihydro-9H-pyrrolo[1,2-a]tetrazolo[5,1-d][1,5]benzodiazepin-12(11H)-one (**3f**) [70%; m.p. 172°C (toluene); found:  $M^+$ , 271.1063;  $C_{13}H_{13}N_5O_2$  requires:  $M^+$ , 271.1069;  $\nu_{\max}$  (KBr) 1700  $cm^{-1}$ ;  $\delta_H$  1.91m + 2.33-2.64m (4 H, 10-H<sub>2</sub> + 11-H<sub>2</sub>), 3.30 dd + 3.48 dd (1 H + 1 H,  $J$  15.4; 6.5 and 1.7, respectively; 9-H<sub>a</sub>H<sub>b</sub>), 3.92s (3 H, OMe), 4.61m (1 H, 9a-H), 7.14 dd (1 H,  $J$  9.0, 2.7; 2-H), 7.40d (1 H,  $J$  2.7; 4-H), 7.49d (1 H,  $J$  9.0; 1-H)] from compound **1f** [5];

(9aRS)-3-Methoxy-9,9a,10,11-tetrahydropyrrolo[1,2-a]tetrazolo[5,1-d][1,5]benzodiazepin-13(12H)-one (**3g**) [LTA: 2 x 2.4 mol-equivalent; c.c., adsorbent Al<sub>2</sub>O<sub>3</sub> (Brockmann, grade II, neutral), eluent toluene - acetone, 8:2], [71%; m.p. 152°C; found: C, 58.7; H, 5.6; N, 24.75;  $C_{14}H_{15}N_5O_2$  (285.3) requires: C, 58.95; H, 5.3; N, 24.55%;  $\nu_{\max}$  (KBr) 1660  $cm^{-1}$ ;  $\delta_H$  (CDCl<sub>3</sub>) 1.79-2.21m (4 H, 10-H<sub>2</sub> + 11-H<sub>2</sub>), 2.32 ddd + 2.57 ddd (1 H + 1 H,  $J$  17.8; 10.0 + 6.7 and 5.6 + 3.9, respectively; 12-H<sub>a</sub>H<sub>b</sub>), 3.13 dd + 3.44 dd (1 H + 1 H,  $J$  15.5; 6.9 and 2.8, respectively; 9-H<sub>a</sub>H<sub>b</sub>), 3.90s (3 H, OMe), 4.36m (1 H, 9a-H), 7.09 dd (1 H,  $J$  8.8, 2.8; 2-H), 7.36d (1 H,  $J$  2.8; 4-H), 7.40d (1 H,  $J$  8.8; 1-H)] from compound **1g**;

(11aRS)-6-Methoxy-11,11a-dihydro-10H-azeto[1,2-a]tetrazolo[5,1-c]quinoxalin-10-one (**3h**) [2%; found:  $M^+$ , 243.0707;  $C_{11}H_9N_5O_2$  requires:  $M^+$ , 243.0755;  $\nu_{\max}$  (KBr) 1800br  $cm^{-1}$ ;  $\delta_H$  (CDCl<sub>3</sub>) 3.78 + 4.02 (1 H + 1 H,  $J$  15.7; 2.5 and 5.1, respectively; 11-H<sub>a</sub>H<sub>b</sub>), 3.91s (3 H, MeO), 5.29 dd (1 H,  $J$  2.5, 5.1; 11a-H), 6.98 dd (1 H,  $J$  8.7, 2.7; 7-H), 7.43d (1 H,  $J$  8.7; 8-H), 7.62d (1 H,  $J$  2.7; 5-H)] from compound **1h** [5];

(12aRS)-6-Methoxy-12,12a-dihydropyrrolo[1,2-a]tetrazolo[5,1-c]quinoxalin-10(11H)-one (**3i**) [40%; m.p. 180°C (toluene); found:  $M^+$ , 257.09184;  $C_{12}H_{11}N_5O_2$  requires:  $M^+$ , 257.09127;  $\nu_{\max}$  (KBr) 1710  $cm^{-1}$ ;  $\delta_H$  2.60-3.05m (4 H, 12-H<sub>2</sub> + 11-H<sub>2</sub>), 3.91s (3 H, OMe), 5.37m (1 H, 12a-H), 7.00 dd (1 H,  $J$  9.0, 2.8; 7-H), 7.56d (1 H,  $J$  2.8; 5-H), 8.17d (1 H,  $J$  9.0; 8-H)] from compound **1i**;

6-Acetyl-9-methoxy-5,6-dihydro-4H-tetrazolo[1,5-a][1,5]benzodiazepine (**12a**) [16%; m.p.: 148°C; found:  $M^+$ , 259.10672;  $C_{12}H_{13}N_5O_2$  requires:  $M^+$ , 259.10692;  $\nu_{\max}$  (KBr): 1750  $cm^{-1}$ ;  $\delta_H$  1.87s (3 H, *N*-Ac), 3.2-3.4m + 3.72m + 4.92m (4 H, 4-H<sub>2</sub> + 5-H<sub>2</sub>), 3.94s (3 H, OMe), 7.11 dd (1 H,  $J$  8.8, 2.8; 8-H), 7.45d (1 H,  $J$  8.8; 7-H), 7.64d (1 H,  $J$  2.8; 10-H)] from compound **11a**;

Methyl {(4RS)-8-Methoxy-4,5-dihydro-4H-tetrazolo[1,5-a]quinoxalin-4-yl}acetate (**12b**): 4.6%, yellowish crystals, m.p. 137°C; found:  $M^+$ , 275.1018;  $C_{12}H_{13}N_5O_3$  requires:  $M^+$ , 275.1013;  $\nu_{\max}$  (KBr) 3400, 1740  $cm^{-1}$ ;



$\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 3.00 dd + 3.30 dd (1 H + 1 H,  $J$  17.4; 10.5 and 2.5, respectively; side-chain  $\text{CH}_2\text{H}_b$ ), 3.79s + 3.84s (2 x 3 H, 2 x MeO), 5.36 dd (1 H,  $J$  10.5, 2.5; 4-H), 6.81d (1 H,  $J$  8.6; 6-H), 6.83 dd (1 H,  $J$  8.6, 2.4; 7-H), 7.45d (1 H,  $J$  2.4; 9-H);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 37.79 (side-chain  $\text{CH}_2$ ), 47.22 (C-4), 52.40 + 171.47 ( $\text{CO}_2\text{Me}$ ), 56.02 (8-MeO), 102.19 (C-9), 116.63 + 116.85 (C-6 + C-7), 120.27 (C-9a), 128.21 (C-5a), 148.85 (C-3a), 153.77 (C-8)] and a *ca* 85:15 tautomeric mixture (NMR) of *methyl (8-methoxy-tetrazolo[1,5-a]-quinoxalin-4-yl)acetate* (**13**) and *methyl (4,5-dihydro-8-methoxytetrazolo[1,5-a]quinoxalin-4-ylidene)acetate* (**14**) [12.3%; lemon yellow crystals, m.p. 153–154°C; found:  $\text{M}^+$ , 273.0864;  $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}_3$  requires:  $\text{M}^+$ , 273.0862;  $\nu_{\text{max}}$  (KBr) 1760, 1630  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ), major component 3.78s (3 H,  $\text{CO}_2\text{Me}$ ), 4.07s (3 H, 8-MeO), 4.46s (2 H, side-chain  $\text{CH}_2$ ), 7.41 dd (1 H,  $J$  9.0, 2.7; 7-H), 7.96d (1 H,  $J$  2.7; 9-H), 8.15d (1 H,  $J$  9.0; 6-H); minor component 3.81s (3 H,  $\text{CO}_2\text{Me}$ ), 3.92 (3 H, 8-MeO), 6.01 (1 H, side-chain CH), 7.07 dd (1 H,  $J$  9.0, 2.7; 7-H), 7.18d (1 H,  $J$  9.0, 6-H), 7.69d (1 H,  $J$  2.7; 9-H), 11.32br (1 H, NH);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ), major component 40.44 (side-chain  $\text{CH}_2$ ), 52.72 + 168.89 ( $\text{CO}_2\text{Me}$ ), 56.44 (8-MeO), 97.73 (C-9), 119.80 (C-7), 125.89 (C-9a), 131.26 (C-5a), 131.59 (C-6), 142.70 (C-3a), 143.12 (C-4), 161.76 (C-8); minor component<sup>8</sup> 51.35 + 170.64 ( $\text{CO}_2\text{Me}$ ), 56.12 (8-MeO), 84.21 (side-chain CH), 100.61 (C-9), 117.36 (C-7), 118.37 (C-6), 120.04 (C-9a), 122.79 (C-5a), 137.11 (C-4), 155.95 (C-8)] from compound **11b** (LTA: 1 mol-equivalent; reaction time: 15 min).

#### LTA oxidation of compound **4**

A mixture of compound **4** [5] (0.20 g, 0.77 mmol), 95% LTA (0.36 g, 0.77 mmol) and dry dioxane (8 mL) was refluxed for 1 h. Since the substrate was not consumed at this point, another portion of 95% LTA (0.18 g, 0.39 mmol) was added and the mixture was refluxed for another 30 min during which time the substrate was consumed. Kieselgel (1 g) was added and the mixture was evaporated to dryness. The residue was transferred onto a Kieselgel G column and worked up by c.c. (DCM - acetone, 7:1) to afford compound **2f** (0.11 g, 53%; m.p. > 195°C), which proved identical (m.p., t.l.c., IR) with an authentic sample [5].

#### Oxidation of compound **1f** with CAN

(a) A methanolic solution (30 mL) of CAN (2.75 g, 5 mmol) was added with continuous stirring at -5°C to a suspension of compound **1f** [5] (0.54 g, 2 mmol) in methanol (30 mL). Anhydrous acetonitrile (20 mL) was added to afford a clear solution. The mixture was allowed to warm up to room temperature and stirred overnight during which period the substrate was consumed. Kieselgel G (2 g) was added and the mixture was evaporated to dryness. The residue was transferred onto a Kieselgel G column and worked up by c.c. (DCM - acetone, 7:0.5) to afford, in this order, compounds **3f** (0.05 g, 10%; m.p. 170°C) and **2f** [5] (0.06 g, 12%; m.p. > 195°C) which proved identical (m.p., t.l.c., IR) with authentic samples.

(b) Methanol (10 mL) was added at room temperature under argon to a suspension of compound **1f** [5] (0.54 g, 2 mmol) and CAN (2.75 g, 5 mmol) in dioxane (40 mL). The resulting clear solution was stirred for 3 h. Since the substrate was not consumed at this point, another portion of CAN (1.1 g, 2 mmol) was added and stirring at room temperature was continued. By monitoring the reaction by t.l.c. the initially formed spiro compound **2f** was shown to decompose gradually and only traces of the unchanged substrate to be present after 72 h. The mixture was evaporated to dryness and the residue was taken up in ethyl acetate and water. The two phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases

<sup>8</sup> The signal of one of the quaternary carbon atoms (probably of C-3a) of the minor component was not discernible

were dried and evaporated to dryness. The residue was worked up by preparative t.l.c. (DCM - methanol - acetic acid, 7:1:0.1) to afford compound **3f** [0.20 g, 37%; m.p. 171°C] which proved identical (m.p., t.l.c., IR) with an authentic sample (see above).

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