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Oxidation of 1-hydroxyazetidines to four-membered cyclic nitrones and β-lactams

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Abstract. The 1-(benzyloxy)azetidines **7a-c** and **16a,b** were synthesized by reductive cyclization of the corresponding oximes **5a-c** and **14a-d**. Oxidation of the 1-hydroxyazetidines **8a-c** and **17** with PbO_2 afforded the corresponding four-membered cyclic nitrones **18a-c** and the bicyclic four-membered nitrones **18d** and **18e**, which were characterized as the cycloadducts **19a-c** and **20** by reaction with dimethyl acetylenedicarboxylate. $Pb(OAc)_4$ oxidation of the monocyclic 1-hydroxyazetidine **8a** gave 1,4-bis(acetyloxy) β-lactam **22a** and 1,4,4-tris(acetyloxy) β-lactam **23a**, while oxidation of the 1-hydroxyazetidines **8b,c** gave exclusively the 1,4-bis(acetyloxy) β-lactams **22b** and **22c**. Oxidation of bicyclic 1-hydroxyazetidine **17** with $Pb(OAc)_4$ afforded the bicyclic bis(acetyloxy) β-lactam **21**.

Since the discovery of penicillins[1] and cephalosporins[2], in which a β-lactam moiety is present as an essential structural feature of the molecule, there has been considerable effort devoted to the development of new β-lactam antibiotics[3]. Hitherto this has resulted in the isolation and the synthesis of a wide variety of carbapenams, oxapenems and carbapenems.

4-(Acetyloxy)-2-azetidinone is a useful intermediate for the preparation of monocyclic and bicyclic β-lactams[4]. Its versatility in β-lactam synthesis is due to the facile substitution of the acetyloxy function by a number of different heteroatom and carbon-centred nucleophiles[5].

Until recently, it was generally accepted that the antibacterial activity of β-lactams was associated with molecules possessing a second fused ring. This changed however when the first members of a family of biologically active monocyclic β-lactams, the nocardicins[6] and the monobactams[7,8], were isolated.

1-(Acetyloxy)-2-azetidinones have been used as key intermediates in the synthesis of chiral monobactams[9,10] and of *N'*-unsubstituted β-lactams by reduction of the corresponding 1-hydroxy-2-azetidinones with titanium trichloride[11].

We have recently reported the synthesis of 1-(acetyloxy)-2-azetidinones via the lead tetraacetate oxidation of relatively stable four-membered cyclic nitrones[12,13]. In this paper we report the synthesis of monocyclic, and in particular bicyclic, β-lactams, having an acetyloxy function both at nitrogen and at the adjacent carbon atom, from four-membered cyclic nitrones which are obtained by the oxidation of the corresponding 1-hydroxyazetidines.

Results and discussion

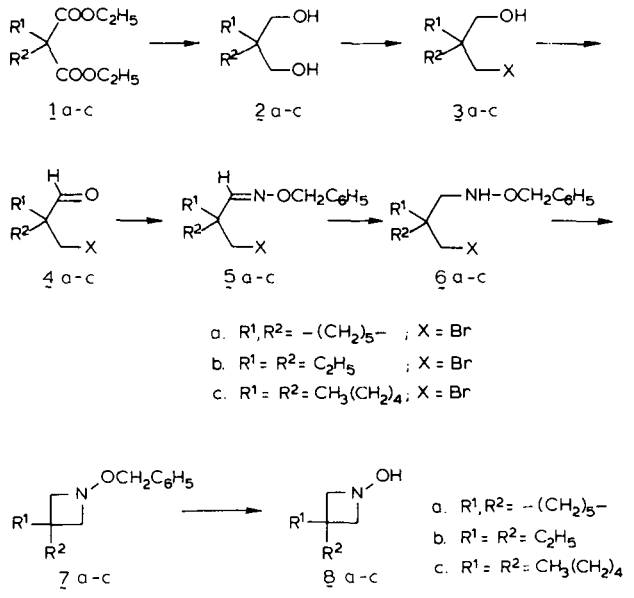
Synthesis of 1-hydroxy- and 1-(benzyloxy)azetidines

The 1-(benzyloxy)azetidines **7a-c** and **16a,b** were synthesized from the corresponding oximes, in which the hydroxyl function must be protected in order to avoid the formation of isoxazolidines.

The 3-bromo aldehydes **4a-c** were obtained from the diols **2a-c**[14,15], which were converted into the bromo alcohols **3a-c**[16] and subsequently oxidized with pyridinium chlorochromate in yields of 62–94%. Reaction of **4a-c** with *O*-benzylhydroxylamine hydrochloride, according to a standard procedure[13], gave the oximes **5a-c** in yields of 68–98%. Reduction of **5a-c** with $NaCNBH_3$ in acetic acid at room temperature gave the corresponding (benzyloxy)-amine derivatives **6a-c** in 85–92% yield. Compounds **6b** and **6c** were characterized as the corresponding hydrochlorides and compound **6a** was characterized by comparison of the spectral data with those of **6b** and **6c**. Heating of the (benzyloxy)amines **6a-c** in pyridine for 6 h gave the corresponding 1-(benzyloxy)azetidines **7a-c** in 63–92% yield.

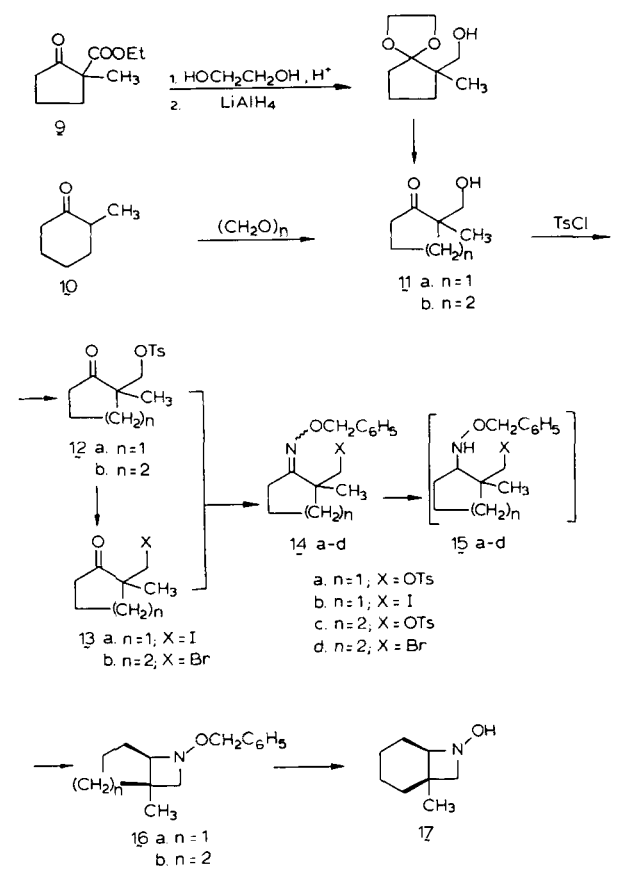
Debenzylation of the azetidines **7a-c** in acetic acid, in the presence of Pd/C (5%), afforded the 1-hydroxyazetidines **8a-c** in 62–74% yield, which were characterized by ^{13}C NMR spectroscopy, mass spectrometry and by comparison of the spectral data with those of 1-hydroxy-3,3-dimethylazetidine[13].

Reduction of iminium salts derived from 2-substituted cyclohexanones occurs with high diastereoselectivity, the *cis/trans* ratio of the resulting 2-substituted cyclohexanamines



Scheme 1

being about 9[17]. This diastereoselectivity, attributed to the hydride transfer preferably occurring at the least hindered side, prompted us to examine the possibility of reducing the *O*-protected oximes **14** in a diastereoselective manner to the hydroxylamines **15** and of then converting these into the corresponding 1-(benzyloxy)azetidines **16** (Scheme 2). Consequently, **12a** was synthesized from ethyl 1-methyl-2-oxocyclopentanecarboxylate (**9**)[18] in four steps in an overall yield of 54%. Ketalization of compound **9** with 1,2--ethanediol, followed by $LiAlH_4$ reduction in dry tetrahydrofuran and subsequent acid-catalyzed deketalization, gave



Scheme 2

2-(hydroxymethyl)-2-methylcyclopentanone (**11a**). This compound was identical with a sample prepared in low yield via the aldol condensation of 2-methylcyclopentanone and paraformaldehyde[19]. Tosylation of compound **11a** in pyridine gave 2-methyl-2-(tosyloxymethyl)cyclopentanone **12a**, which was characterized by ^{1}H NMR spectroscopy [δ: 3.85 (s, 2H, CH_2OTs), 0.96 (s, 3H, CH_3)]. The iodo derivative **13a** was synthesized from **12a** and lithium iodide in refluxing acetonitrile in quantitative yield and was characterized by ^{1}H NMR spectroscopy [δ: 3.30 and 3.10 (AB, J_{AB} 8.5 Hz, 2H, CH_2I), 2.2–1.7 (m, 6H, $-(CH_2)_3-$), 1.13 (s, 3H, CH_3)]. 2-(Hydroxymethyl)-2-methylcyclohexanone (**11b**) was synthesized according to literature procedures from 2-methylcyclohexanone (**10**)[20] and tosylation of **11b** in pyridine gave **12b** in 82% yield. The bromo derivative **13b** was obtained in a yield of 92% by reaction of **12b** with lithium bromide in refluxing acetonitrile.

Reaction of the ketones **12a,b** and **13a,b** with *O*-benzylhydroxylamine gave the corresponding oximes **14a-d**.

When oxime **14a** was reduced with $NaCNBH_3$ in acetic acid at 35°C for 24 h, a complex mixture of products was obtained, from which, after prolonged silica-gel column chromatography, a compound was isolated in approximately 5% yield, which was characterized as the annulated azetidine **16a** on the basis of ^{1}H NMR spectroscopy [δ: 4.57 (s, 2H, CH_2Ph), 3.8–3.7 (bd, 1H, NCH), 3.43 (s, 2H, NCH_2) and 1.26 (s, 3H, CH_3)] and mass spectrometry [*m/e* 217.146 (M^+, calcd. for $C_{14}H_{19}NO$: 217.147)]. The ^{13}C NMR spectrum could only be resolved when it was recorded at 50°C [δ: 80.6 (d, C-5), 68.1 (t, C-7), 40.0 (s, C-1), 25.3 (q, CH_3)]. Reduction of oxime **14b** with $NaCNBH_3$ in acetic acid for 24 h at 35°C gave two compounds which were separated by column chromatography (SiO_2). The slow eluting fraction gave a slightly coloured oil in a yield of 5% which was identified as hydroxylamine **15b** [δ: 5.2 (bs, 1H, NH), 3.48 and 3.29 (AB, J_{AB} 9.5 Hz, 2H, CH_2I)]; ^{13}C NMR spectroscopy [δ: 66.8 (d, NCH), 19.8 (t, CH_2I)] and mass spectrometry [*m/e* 345.056 (M^+, calcd. for $C_{14}H_{20}INO$: 345.059)]. The fast eluting fraction was isolated in 26% yield and identified as the bicyclic azetidine **16a** *(vide supra)*. Reduction of oxime **14c** with $NaCNBH_3$ in acetic acid for 24 h at 35°C afforded a mixture of compounds from which the bicyclic 1-(benzyloxy)azetidine **16b** was isolated in a yield of 32% [δ: 4.67 and 4.61 (AB, J_{AB} 1.2 Hz, 2H, CH_2Ph), 3.28 and 3.04 (ABC, *J* 6.6 and 1 Hz, 2H, NCH_2), 3.17 (m, 1H, NCH), 1.05 (s, 3H, CH_3)]; ^{13}C NMR spectroscopy [δ: 73.9 (d, C-6), 69.0 (t, C-8), 28.7 (s, C-1), 24.6 (q, CH_3)] and mass spectrometry [*m/e* 231.162 (M^+, calcd. for $C_{15}H_{21}NO$: 231.162)]. Reduction of oxime **14d** under the same reaction conditions gave a much higher yield of azetidine **16b** (50%). According to ^{1}H NMR and ^{13}C NMR spectroscopy, only one isomer of the products **16a** and **16b** was isolated. Since azetidines, *trans*-annulated to cyclopentanes, have never been isolated, we assigned the *cis*-annulated structure to compound **16a**. In the case of **16b**, the *cis* stereochemistry was proven by nuclear Overhauser enhancement ^{1}H NMR spectroscopy. On the basis of a NOE effect (8%) of the methyl group at C-1 with H_b at C-8 and a NOE effect (5%) of the methyl

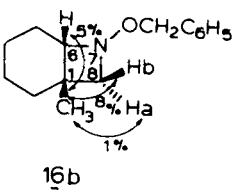


Fig. 1

group at C-1 with the hydrogen at C-6, compared to the effect of the methyl group at C-1 with H_a at C-8, it is obvious that the methyl group at C-1 and the hydrogen at C-6 have a *cis* relation (Fig. 1).

The synthesis of azetidines **16**, by cyclization of *in situ* generated hydroxylamines **15**, is a novel approach to these annulated systems. The increase in yields of the azetidines **16**, observed on replacing the tosyloxy group in oximes **14** by iodine or bromine, can be explained by the preference of hydride attack in the reduction step from the less hindered side of the oxime[21]. The isolation of a hydroxylamine (**15b**) in 5% yield, which does not cyclize to the azetidine **16a** even under drastic basic conditions, indicates that this compound has the *trans* stereochemistry. This implies that the hydride reduction of the oxime **14b** may not occur completely stereoselectively.

Debenzylation of compound **16a** was unsuccessful, however debenzylation of a solution of 1-(benzyloxy)azetidine **16b** in acetic acid in an atmosphere of hydrogen and in the presence of Pd/C (5%) afforded 1-hydroxyazetidine **17** in 78% yield.

Synthesis and characterization of four-membered cyclic nitrones

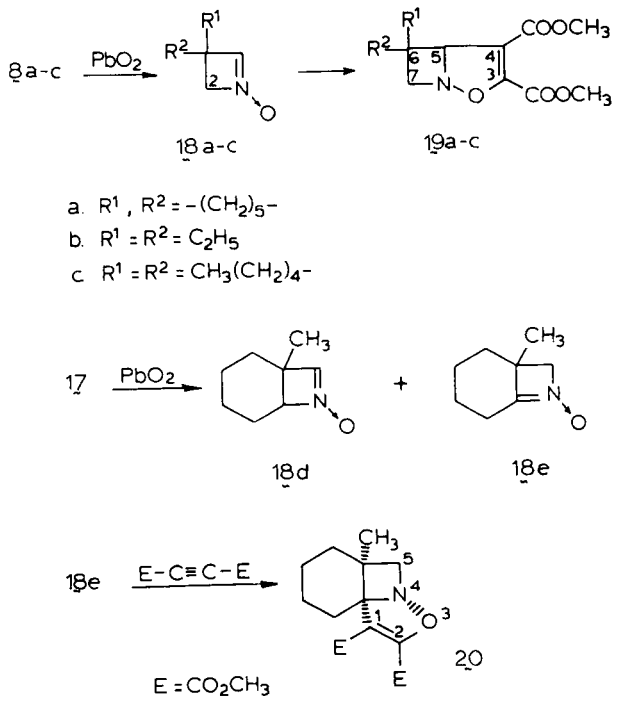
Oxidation of the 1-hydroxyazetidines **8a-c** with yellow mercury(II) oxide in dichloromethane gave the corresponding four-membered cyclic nitrones in only 30% yield. However, oxidation of the azetidines **8a-c** with freshly prepared "active" lead(IV) oxide[22] afforded the nitrones **18a-c** in approximately 80% yield, as is evident from the ^{1}H NMR spectra, which show a singlet at δ 6.8 $\pm$ 0.1 for the hydrogen atom at C-4 (Scheme 3). Oxidation of 1-hydroxyazetidine **17** with PbO_2 gave a mixture of two isomeric cyclic nitrones in 80% yield (Scheme 3). According to ^{1}H NMR spectroscopy, nitrone **18d** [δ 6.78 (s, 1H, HC-8)] was formed in 5% yield and **18e** in 75% yield. The latter compound showed characteristic absorptions in the ^{1}H NMR spectrum for the NCH_2 group at δ 4.08 (d, J 2 Hz, 2H) and for the allylic ring protons at δ 2.8–2.6 (m, 2H). Obviously, there is competition between hydrogen abstraction at C-6 and C-8. Thermodynamically, abstraction at C-6 will be favoured, whereas abstraction at C-8 is kinetically faster. Such a competition has also been reported for the dehydrogenation of 1-hydroxypyrrolidine and -piperidine derivatives to give the corresponding five- and six-membered cyclic nitrones[23].

Hitherto, only one other four-membered cyclic nitrone, annulated to a six-membered ring, has been described as obtained from reaction of an ynamine with 1-nitrocyclohexene[24].

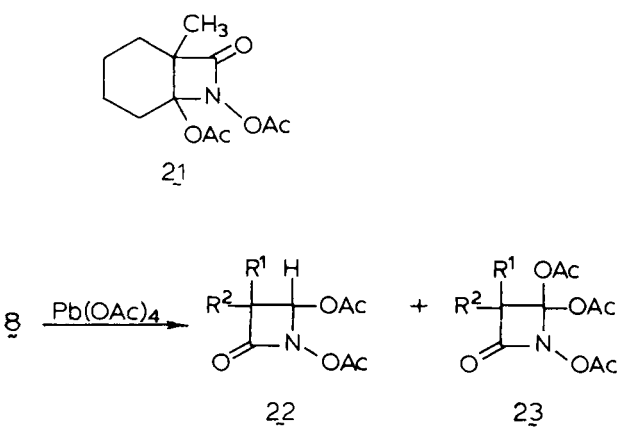
The four-membered cyclic nitrones **18a-c** were obtained as oils and were characterized as the stable adducts **19a-c** by reaction with dimethyl acetylenedicarboxylate (Scheme 3). On the basis of ^{1}H NMR spectroscopy, [*e.g.* compound **19a**: δ: 4.78 (t, J 1.6 Hz, HC-5), 3.91 and 3.55 (AB, J 10.5, 1.6 Hz, 2H, NCH_2), ^{13}C NMR δ: 163.2 and 159.4 (s, C=O), 154.0 (s, C-3), 108.0 (s, C-4), 80.8 (d, C-5), 69.8 (t, NCH_2) and mass spectrometry, *m/e* 281.126 (M^+, calcd. for $C_{14}H_{19}NO_5$: 281.126)] and comparison of these data with those of similar cycloadducts, which have been described previously[25], the structures of **19a-c** were proven.

Reaction of nitrone **18e** with dimethyl acetylenedicarboxylate yielded the tricyclic adduct **20** with characteristic absorptions in the ^{1}H NMR spectrum [δ: 3.60 and 3.41 (AB, J 9.3 Hz, 2H, NCH_2)] and in the ^{13}C NMR spectrum [δ: 163.5 (s, C=O), 160.4 (s, C=O), 154.0 (s, C-2), 111.7 (s, C-1), 70.1 (t, NCH_2)]. The conformation is most likely to be that shown in Scheme 3, since otherwise the cyclohexane ring would be *trans*-fused to the azetidine ring, resulting in a highly strained molecule. This result of the 1,3-dipolar cycloaddition is different from that of a similar bicyclic nitrone with a carbamoyl group at C-8, which, upon reaction with dimethyl acetylenedicarboxylate, yielded a bicyclic aziridine[25].

It is possible that in this 1,3-dipolar adduct the N–O bond is weakened by the repulsion of the oxygen atom of the carbamoyl group and the isoxazoline oxygen, which have the *cis* stereochemistry. As a consequence, the rearrangement of the initially formed 1,3-dipolar cycloadduct to the bicyclic aziridine is accelerated.



Scheme 3



8	22/23
a. $R^1, R^2 = -(CH_2)_5-$	65/35
b. $R^1 = R^2 = C_2H_5$	100/0
c. $R^1 = R^2 = CH_3(CH_2)_4$	100/0

Scheme 4

Synthesis of β-lactams **21**, **22a-c** *and* **23a** *from the 1-hydroxyazetidines* **17** *and* **8a-c**, *respectively*

Reaction of 1-hydroxyazetidine **17** with lead tetraacetate revealed that in this reaction three equiv. of the oxidizing agent are consumed to give an oil in a yield of 70%. On the basis of absorptions in the IR spectrum at 1810, 1785 and 1745 cm^{-1} and absorptions in the ^{13}C NMR spectrum at δ: 169.4, 168.6, 167.4 and 95.9, we have assigned the bis-(acetyloxy)-2-azetidinone structure **21** to this product. The previously discussed mechanism of the formation of 1,4-bis-(acetyloxy)-3,3,4-trimethyl-2-azetidinone[13] also explains the formation of the bicyclic β-lactam **21**.

Oxidation of 1-hydroxyazetidine **8a** with three equiv. of $Pb(OAc)_4$ gave a mixture of two β-lactams in 66% yield (Scheme 4). The major product, 1,4-bis(acetyloxy)-2-azetidinone **22a** (65%), exhibited a low-field signal in the ^1H NMR spectrum at δ 5.95 (1H, HC-4) and characteristic signals in the ^{13}C NMR spectrum at δ: 170.4, 168.6 and 168.0 for the C=O groups.

The minor product (35%) exhibited absorptions in the ^1H NMR spectrum corresponding to three acetyloxy groups and an extremely low-field absorption in the ^{13}C NMR spectrum at δ 109.1 (s, C-4), which pointed to the 1,4,4-tris(acetyloxy)-2-azetidinone **23a** (Scheme 4). Previously, *Pennings* and *Reinhoudt*[13] have reported the oxidation of 1-hydroxy-3,3-dimethylazetidine with three equiv. of $Pb(OAc)_4$, yielding a mixture of the corresponding 1,4-bis(acetyloxy) β-lactam and the corresponding 1,4,4--tris(acetyloxy) β-lactam in 60% and 40% yield, respectively.

Reaction of the 1-hydroxyazetidines **8b** and **8c** with three equiv. of lead tetraacetate resulted in the isolation of a single product. On the basis of three absorptions observed in the IR spectra (C=O, OAc, NOAc), the presence of a singlet at low field (1H, HC-4), two singlets at δ 2.0 ± 0.2 (3H, $COCH_3$) in the ^1H NMR spectra and three absorptions in the ^{13}C NMR spectra (C=O, OAc, NOAc), we assigned the 1,4-bis(acetyloxy) β-lactam structures **22b** and **22c** to the isolated products. Probably, the introduction of a second acetyloxy function into the four-membered ring is influenced by the nature of the substituents at C-3 of the β-lactam.

In conclusion, we have shown that the lead tetraacetate oxidation of 1-hydroxyazetidines constitutes a general approach to the synthesis of β-lactams. In this way, monocyclic and bicyclic 1-hydroxyazetidines have been converted regioselectively into the corresponding bis(acetyloxy) and tris(acetyloxy) β-lactams.

Experimental

Melting points were determined using a Reichert melting point apparatus and are uncorrected. ^1H NMR spectra ($CDCl_3$) and ^{13}C NMR spectra ($CDCl_3$) were recorded using a Bruker WP-80 spectrometer and a Nicolet NT-200-WB spectrometer, respectively (Me_4Si as internal standard). Mass spectra were obtained uing a Varian Mat 311A spectrometer and all mass values were calculated for ^{79}Br. IR spectra were recorded using a Perkin-Elmer 257 spectrophotometer. Elemental analyses were carried out by *E. Hoogendam* and *A. Christenhusz* of the Laboratory of Chemical Analysis of the University of Twente.

Preparative TLC was performed by using silica-gel precoated plates (Merck DC-Fertigplatten Kieselgel 60 F_{254}) and by using aluminum oxide (Merck PSC-Fertigplatten Aluminiumoxid 60 F_{254}). Petroleum ether refers to the fraction boiling at 40–60°C. Diethyl ether, methanol, acetonitrile, benzene and dichloromethane refer to molecular sieve dried solvents. Glacial acetic acid refers to $CuSO_4$-dried acetic acid.

All reactions described were carried out under an atmosphere of nitrogen.

Materials

Sodium cyanoborohydride (Janssen), pyridinium chlorochromate (Janssen), *O*-benzylhydroxylamine hydrochloride (Janssen), lithium aluminum hydride (Merck), diethyl malonate (Merck), dimethyl acetylenedicarboxylate (Merck) and lead tetraacetate (Merck) are commercially available. Lead tetraacetate was washed with diethyl ether immediately prior to use in order to remove the acetic acid.

Preparation of the aldehydes **4a-c**

A solution of alcohol **3a-c**[16] (20 mmol) in dry dichloromethane (25 ml) was added dropwise to a suspension of pyridinium chlorochromate (6.5 g; 30 mmol) in dry dichloromethane (25 ml). After being stirred for 7 h, the solution was diluted with dry diethyl ether (250 ml) and the supernatant liquid was filtered through Florisil. The remaining sticky solid was washed with dry diethyl ether (3 × 30 ml) and the combined liquids were again filtered through Florisil. The remaining solution was concentrated under reduced pressure to give compounds **4** which were used without further purification.

1-(Bromomethyl)cyclohexanecarboxaldehyde (**4a**). Yield 94%; oil. ^1H NMR δ: 9.40 (s, 1H, CHO), 3.40 (s, 2H, CH_2Br), 1.9–1.3 (m, 10H, $-(CH_2)_5-$).

2-(Bromomethyl)-2-ethylbutanal (**4b**). Yield 62%; oil. ^1H NMR δ: 9.30 (s, 1H, CHO), 3.43 (s, 2H, CH_2Br), 1.66 (q, *J* 7.5 Hz, 4H, CH_2), 0.80 (t, *J* 7.5 Hz, 6H, CH_3).

2-(Bromomethyl)-2-pentylheptanal (**4c**). Yield 87%; oil. ^1H NMR δ: 9.43 (s, 1H, CHO), 3.50 (s, 2H, CH_2Br). ^{13}C NMR δ: 203.7 (d, C=O), 53.0 (s, C-2), 34.9 (t, CH_2Br). Mass spectrum, *m/e* 247.108 [$(M-CHO)^+$; calcd. for $C_{12}H_{24}Br$: 247.106)].

Preparation of oximes **5a-c**

A suspension of *O*-benzylhydroxylamine hydrochloride (3.18 g; 20 mmol) in methanol (25 ml) was neutralized by the addition of NaOH (0.8 g; 20 mmol), after which compound **4** (20 mmol) was added to this solution. After being stirred for 4 h, the solution was diluted with water (150 ml). The aqueous solution was acidified with 2 N HCl and extracted with chloroform (3 × 30 ml). The combined extracts were dried and filtered and the chloroform was removed under reduced pressure. The resulting oils were purified by distillation in the case of the oximes **5a-c**.

1-(Bromomethyl)cyclohexanecarboxaldehyde O-(phenylmethyl)oxime (**5a**). Yield 68%; b.p. 100–103°C (0.05 mm); n_D^{20} 1.5455. ^1H NMR δ: 7.33 (s, 5H, PhH), 7.24 (s, 1H, =CH), 5.09 (s, 2H, CH_2Ph), 3.37 (s, 2H, CH_2Br). ^{13}C NMR δ: 154.3 (d, HC=N), 75.8 (t, CH_2Ph), 42.7 (t, CH_2Br), 40.7 (s, C-2). Mass spectrum, *m/e* 230.155 [$(M-Br)^+$, calcd. for $C_{15}H_{20}NO$: 230.155].

2-(Bromomethyl)-2-ethylbutanal O-(phenylmethyl)oxime (**5b**). Yield 89%; b.p. [kugelrohr] 120°C (0.05 mm); n_D^{20} 1.5272. ^1H NMR δ: 7.36–7.24 (m, 5H, PhH); 7.24 (s, 1H, =CH), 5.06 (s, 2H, CH_2Ph), 3.49 (s, 2H, CH_2Br), 1.48 and 1.62 (ABX, *J* 14.0 Hz, *J* 7.1 Hz, 4H, $C\underline{H}_2CH_3$), 0.78 (t, *J* 7.1 Hz, 6H, CH_3). ^{13}C NMR δ: 154.1 (d, HC=N), 75.8 (t, CH_2Ph), 44.0 (s, C-2), 37.5 (t, CH_2Br). Mass spectrum, *m/e* 218.155 $(M-Br)^+$, calcd. for $C_{14}H_{20}NO$: 218.155].

2-(Bromomethyl)-2-pentylheptanal O-(phenylmethyl)oxime (**5c**). Yield 98%; b.p. [kugelrohr] 110°C (0.05 mm); n_D^{20} 1.5068. ^1H NMR δ: 7.32 (s, 5H, PhH), 7.27 (s, 1H, =CH), 5.06 (s, 2H, CH_2Ph), 3.49 (s, 2H, CH_2Br). ^{13}C NMR δ: 154.6 (d, HC=N), 75.8 (t, CH_2Ph), 43.5 (s, C-2), 38.4 (t, CH_2Br). Mass spectrum, *m/e* 302.249 [$(M-Br)^+$, calcd. for $C_{20}H_{32}NO$: 302.248].

Reduction of oximes **5a-c**

$NaCNBH_3$ (1.1 g; 18 mmol) was added in portions to a solution of the oxime (15 mmol) in glacial acetic acid (40 ml). After the reaction had been completed, the acetic acid was removed under reduced pressure and the residue was neutralized using a saturated aqueous $NaHCO_3$ solution and extracted with chloroform (3 × 40 ml). The combined extracts were dried and filtered and the chloroform was removed under reduced pressure to give compounds **6** which were used without further purification.

1-(Bromomethyl)-N-(phenylmethoxy)cyclohexanemethanamine (**6a**). Yield 87%; **6a** · HCl, m.p. 113–115°C (diisopropyl ether). ^{1}H NMR δ: 7.32 (s, 5H, PhH), 5.42 (bs, 1H, NH), 4.66 (s, 2H, CH_2Ph), 3.48 (s, 2H, CH_2Br), 2.96 (s, 2H, NCH_2). ^{13}C NMR δ: 77.0 (t, CH_2Ph), 55.3 (t, NCH_2), 40.8 (t, CH_2Br), 36.9 (s, C-2). Mass spectrum, *m/e* 311.092 [$(M - HCl)^+$ calcd. for $C_{15}H_{22}BrNO$: 311.089]. Anal. calcd. for $C_{15}H_{22}BrNO \cdot HCl$: C 51.69, H 6.60, N 4.02; found: C 51.58, H 6.71, N 4.02%.

2-(Bromomethyl)-2-ethyl-N-(phenylmethoxy)-1-butanamine (**6b**). Yield 92%; **6b** · HCl, white solid, m.p. 103°C (subl.) [chloroform/diisopropyl ether]. ^{1}H NMR δ: 10.40 (bs, 1H, NH), 7.36 (s, 5H, PhH), 5.54 (s, 2H, CH_2Ph), 3.66 (s, 2H, CH_2Br), 3.37 (s, 2H, CH_2N), 1.58 (q, *J* 7.1 Hz, 4H, $C\underline{H}_2CH_3$), 0.85 (t, *J* 7.1 Hz, 6H, CH_3). ^{13}C NMR δ: 76.8 (t, CH_2Ph), 53.6 (t, NCH_2), 39.9 (s, C-2), 39.3 (t, CH_2Br). Mass spectrum, *m/e* 299.090 [$(M - HCl)^+$, calcd. for $C_{14}H_{22}BrNO$: 299.089]. Anal. calcd. for $C_{14}H_{22}BrNO \cdot HCl$: C 49.97, H 7.12, N 4.16; found: C 50.32, H 6.83, N 4.14%.

2-(Bromomethyl)-2-pentyl-N-(phenylmethoxy)-1-heptanamine (**6c**). Yield 85%; **6c** · HCl, m.p. 72–73°C (petroleum ether). ^{1}H NMR δ: 7.33 (s, 5H, PhH), 5.12 (bs, 1H, NH), 4.66 (s, 2H, CH_2Ph), 3.37 (s, 2H, CH_2Br), 2.89 (s, 2H, NCH_2). ^{13}C NMR δ: 75.8 (t, CH_2Ph), 55.1 (t, NCH_2), 41.6 (t, CH_2Br), 39.9 (s, C-2). Mass spectrum, *m/e* 383.182 [$(M - HCl)^+$, calcd. for $C_{20}H_{34}BrNO$: 383.182][26].

Synthesis of 3,3-disubstituted 1-(phenylmethoxy)azetidines (**7a-c**) *from* **6a-c**

A solution of **6** (23.4 mmol) in dry pyridine (110 ml) was heated at 100°C for 6 h. The solution was cooled, diluted with water (70 ml) and acidified with a 6 N HCl solution. The aqueous mixture was extracted with chloroform (3 × 50 ml) and the combined extracts were dried and filtered. The chloroform was removed under reduced pressure and the residue was dissolved in chloroform and passed through a small silica-gel column. The resulting solution was concentrated under reduced pressure to give **7**.

2-(Phenylmethoxy)-2-azaspiro[3.5]nonane (**7a**). Yield 92%; b.p. 85–90°C (0.05 mm); n_D^{20} 1.5207; **7a** · HCl, m.p. 129–132°C (diisopropyl ether). ^{1}H NMR δ: 7.31 (s, 5H, PhH), 4.62 (s, 2H, CH_2Ph), 3.32 (bs, 4H, NCH_2). ^{13}C NMR δ: 74.6 (t, CH_2Ph), 68.6 (t, NCH_2), 38.2 (s, C-3). Mass spectrum, *m/e* 231.162 (M^+, calcd. for $C_{15}H_{21}NO$: 231.162). Anal. calcd. for $C_{15}H_{21}NO \cdot HCl$: C 67.32, H 8.22, N 5.23; found: C 66.86, H 8.44, N 5.18%.

3,3-Diethyl-1-(phenylmethoxy)azetidine (**7b**). Yield 63%; **7b** · HCl, m.p. 103–105°C (chloroform/petroleum ether), ^{1}H NMR δ: 7.31 (s, 5H, PhH), 4.62 (s, 2H, CH_2Ph), 3.32 (bs, 4H, NCH_2), 1.54 (q, *J* 7.3 Hz, 4H, $C\underline{H}_2CH_3$), 0.78 (t, *J* 7.1 Hz, 6H, CH_3). ^{13}C NMR δ: 74.7 (t, CH_2Ph), 67.3 (t, CH_2N), 35.8 (s, C-3), 29.8 and 27.8 (t, $\underline{C}H_2CH_3$), 8.5 (q, CH_3). Mass spectrum, *m/e* 219.162 (M^+, calcd. for $C_{14}H_{21}NO$: 219.162). Anal. calcd. for $C_{14}H_{21}NO \cdot HCl$: C 65.78, H 8.61, N 5.48; found: C 65.45, H 8.98, N 5.32%.

3,3-Dipentyl-1-(phenylmethoxy)azetidine (**7c**). Yield 77%; b.p. 128–132°C (0.3 mm); n_D^{20} 1.4810. ^{1}H NMR δ: 7.31 (s, 5H, PhH), 4.61 (s, 2H, CH_2Ph), 3.32 (bs, 4H, NCH_2), 1.5–1.2 (m, 16H, $-(CH_2)_4-$), 0.88 (t, *J* 7 Hz, 6H, CH_3). ^{13}C NMR δ: 74.7 (t, CH_2Ph), 68.2 (t, NCH_2), 34.9 (s, C-3). Mass spectrum, *m/e* 303.257 (M^+, calcd. for $C_{20}H_{33}NO$: 303.256).

Debenzylation of 1-(phenylmethoxy)azetidines **7**

A solution of the azetidine **7** (20 mmol) in glacial acetic acid (40 ml) was hydrogenated at atmospheric pressure in the presence of a palladium on charcoal catalyst (5%). After hydrogen take-up had ceased, the reaction mixture was filtered over Hyflo and the acetic acid removed under reduced pressure at 30°C. The residue was neutralized with a saturated aqueous $NaHCO_3$ solution and extracted with chloroform (5 × 30 ml). The combined extracts were dried and filtered and the chloroform was removed under reduced pressure. The remaining liquid was distilled under reduced pressure to give the hydroxyazetidines **8**.

2-Hydroxy-2-azaspiro[3.5]nonane (**8a**). Yield 74%; b.p. 63–65°C (0.05 mm); n_D^{20} 1.4881. ^{1}H NMR δ: 8.16 (bs, 1H, OH), 3.50 and 3.22 (bAB, 4H, NCH_2). ^{13}C NMR δ: 69.6 (t, NCH_2), 32.9 (s, C-3). Mass spectrum, *m/e* 141.116 (M^+, calcd. for $C_8H_{15}NO$: 141.116).

3,3-Diethyl-1-hydroxyazetidine (**8b**). Yield 62%; b.p. [kugelrohr] 70°C (3 mm); n_D^{20} 1.4560. ^{1}H NMR δ: 7.99 (bs, 1H, OH), 3.45 and 3.26 (bAB, 4H, NCH_2), 1.54 (q, *J* 7.3 Hz, 4H, $C\underline{H}_2CH_3$), 0.80 (t, *J* 7.3 Hz, 6H, CH_3). ^{13}C NMR δ: 68.3 (t, NCH_2), 35.4 (s, C-3), 30.0 and 27.6 (t, $\underline{C}H_2CH_3$), 8.7 and 8.3 (q, CH_3); mass spectrum, *m/e* 129.115 (M^+, calcd. for $C_7H_{15}NO$: 129.115).

1-Hydroxy-3,3-dipentylazetidine (**8c**). Yield 62%; b.p. [kugelrohr] 70°C (0.05 mm); n_D^{20} 1.4661. ^{1}H NMR δ: 7.77 (bs, 1H, OH), 3.45 and 3.25 (bAB, 4H, NCH_2), 1.5–1.2 [m, 16H, $-(CH_2)_4-$], 0.88 (t, *J* 5.9 Hz, 6H, CH_3). ^{13}C NMR δ: 69.3 (t, NCH_2), 34.6 (s, C-3). Mass spectrum, *m/e* 213.210 (M^+, calcd. for $C_{13}H_{27}NO$: 213.209).

2-Methyl-2-[[[(4-methylphenyl)sulfonyl]oxy]methyl]cyclopentanone (**12a**)

Ethyl 1-methyl-2-oxocyclopentanecarboxylate (**9**)[18] was converted into the ketal by reaction with ethylene glycol according to standard procedures. The resulting product was reduced with $LiAlH_4$ in tetrahydrofuran to give the ketal of 2-(hydroxymethyl)-2-methylcyclopentanone, which was deprotected according to standard procedures with dilute hydrochloric acid to give compound **11a**, which was reacted with tosyl chloride in pyridine to give compound **12a**. Yield 54%. ^{1}H NMR δ: 7.70 and 7.33 (AB, 4H, SO_2Ar), 3.85 (s, 2H, $C\underline{H}_2OTs$), 2.43 (s, 3H, $ArCH_3$), 1.7–1.4 [m, 6H, $-(CH_2)_3-$], 0.96 (s, 3H, CH_3).

2-Methyl--2-[[[(4-methylphenyl)sulfonyl]oxy]methyl]cyclohexanone (**12b**)

By tosylation in pyridine according to standard procedures[14]. Yield 82%. ^{1}H NMR δ: 7.70 and 7.33 (AB, 4H, SO_2ArH), 3.95 (s, 2H, $C\underline{H}_2OTs$), 2.43 (s, 3H, $ArCH_3$), 2.3–1.6 [m, 8H, $-(CH_2)_4-$], 1.10 (s, 3H, CH_3).

2-(Iodomethyl)-2-methylcyclopentanone (**13a**)

To a solution of compound **12a** (7.92 g; 28.1 mmol) in dry acetonitrile (200 ml) was added 8.5 g (63.7 mmol) of dry lithium iodide. The reaction mixture was refluxed for 4 h and the solvent removed under reduced pressure. The residue was dissolved in dry diethyl ether (100 ml) and the organic layer was washed with water (2 × 50 ml), dried and concentrated under reduced pressure to give crude **13a** in quantitative yield, which was used without further purification. ^{1}H NMR δ: 3.30 and 3.10 (AB, *J* 8.5 Hz, 2H, CH_2I), 2.2–1.7 [m, 6H, $-(CH_2)_3-$], 1.13 (s, 3H, CH_3).

2-(Bromomethyl)-2-methylcyclohexanone (**13b**)

To a solution of compound **12b** (30 g; 101.4 mmol) in dry acetonitrile (150 ml) was added dry lithium bromide (19.8 g; 228.2 mmol). The reaction mixture was refluxed for 24 h and the solvent removed under reduced pressure. The residue was dissolved in diethyl ether (100 ml) and the organic layer was washed with water (2 × 50 ml). The extracts were dried and concentrated under reduced pressure to give crude **13b**. The product was purified by silica-gel column chromatography (dichloromethane). Yield 92%. ^{1}H NMR δ: 3.56 (s, 2H, CH_2Br), 2.5–2.1 (m, 2H, CH_2CO), 1.9–1.6 [m, 6H, $-(CH_2)_3-$], 1.20 (s, 3H, CH_3).

Preparation of oximes **14**

A suspension of *O*-benzylhydroxylamine hydrochloride (3.18 g; 20 mmol) in MeOH (25 ml) was neutralized by the addition of NaOH (0.8 g; 20 mmol), after which the carbonyl compound (20 mmol) was added to the suspension. After being stirred for 16 h, the reaction mixture was worked up as described for compounds **5a-c** to give the oximes.

2-Methyl-2-[[[(4-methylphenyl)sulfonyl]oxy]methyl]cyclopentanone O-(phenylmethyl)oxime (**14a**) *from* **12a**. Yield 64%; m.p. 80–81°C (diisopropyl ether). ^{1}H NMR δ: 7.75 and 7.26 (AB, 4H, SO_2ArH), 7.30 (s, 5H, PhH), 4.99 (s, 2H, CH_2Ph), 3.92 (s, 2H, $C\underline{H}_2OTs$), 2.43 (s, 3H, $ArCH_3$), 2.0–1.5 (m, 6H, $-(CH_2)_3-$), 1.10 (s, 3H, CH_3). ^{13}C NMR δ: 166.8 (s, C=N), 75.8 (t, $\underline{C}H_2OTs$), 75.0 (t, CH_2Ph), 45.6 (s, C-2), 35.8, 27.8 and 20.9 [t, $-(CH_2)_3-$], 22.3 (q, CH_3), 21.6 (q, $ArCH_3$). Mass spectrum, *m/e* 387.148 (M^+, calcd. 387.150). Anal. calcd. for $C_{21}H_{25}NO_4S$: C 65.09, H 6.50, N 3.64; found: C 65.29, H 6.39, N 3.45%.

2-(Iodomethyl)-2-methylcyclopentanone O-*(phenylmethyl)oxime* (**14b**) *from* **13a**. Yield 84%; b.p. [kugelrohr] ± 125°C (0.08 mm). ^{1}H NMR δ: 7.31 (s, 5H, PhH), 5.07 (s, 2H, CH_2Ph), 3.31 (s, 2H, CH_2I), 2.7–2.3 (m, 2H, CH_2C=), 1.9–1.5 [m, 4H, $-(CH_2)_2-$], 1.25 (s, 3H, CH_3). ^{13}C NMR δ: 166.7 (s, C=N), 65.7 (t, CH_2Ph), 45.6 (s, C-2), 39.7, 28.1 and 20.4 [t, $-(CH_2)_3-$], 25.1 (q, CH_3), 18.8 (t, CH_2I). Mass spectrum, *m/e* 343.040 (M^+, calcd. for $C_{14}H_{18}INO$: 343.044).

2-Methyl-2-[[[(4-methylphenyl)sulfonyl]oxy]methyl]cyclohexanone O-*(phenylmethyl)oxime* (**14c**) *from* **12b**. The product was purified by silica-gel column chromatography (chloroform). Yield 63%; m.p. 66–67°C (diisopropyl ether/chloroform). ^{1}H NMR δ: 7.78 and 7.31 (AB, 4H, SO_2ArH), 7.30 (s, 5H, PhH), 4.96 (s, 2H, CH_2Ph), 4.07 (s, 2H, CH_2OTs), 2.43 (s, 3H, $ArCH_3$), 1.75–1.2 [m, 8H, $-(CH_2)_4-$], 1.11 (s, 3H, CH_3). ^{13}C NMR δ: 161.0 (s, C=N), 75.9 (t, CH_2OTs), 75.5 (t, CH_2), 40.6 (s, C-2), 35.3, 25.3, 21.6 and 20.8 [t, $-(CH_2)_4-$], 21.4 (q, $ArCH_3$ and CH_3). Mass spectrum, *m/e* 217.149 [$(M-CH_2OTs)^+$, calcd. for $C_{14}H_{19}NO$: 217.147]. Anal. calcd. for $C_{22}H_{27}NO_4S$: C 65.84, H 6.73, N 3.49; found: C 66.17, H 6.87, N 3.51%.

2-(Bromomethyl)-2-methylcyclohexanone O-*(phenylmethyl)oxime* (**14d**) *from* **13b**. Yield 84%; b.p. 100–102°C (0.15 mm); n_D^{20} 1.5479. ^{1}H NMR δ: 7.20 (s, 5H, PhH), 4.99 (s, 2H, CH_2Ph), 3.55 (s, 2H, CH_2Br), 2.7–2.6 (m, 2H, CH_2C=), 1.8–1.5 [m, 6H, $-(CH_2)_3-$], 1.20 (s, 3H, CH_3). ^{13}C NMR δ: 162.0 (s, C=N), 75.5 (t, CH_2Ph), 43.8 (t, CH_2Br), 41.0 (s, C-2), 37.2 (t, CH_2C=), 25.5, 21.8 and 21.3 [t, $-(CH_2)_3-$], 23.4 (q, CH_3). Mass spectrum, *m/e* 309.075 (M^+, calcd. for $C_{15}H_{20}BrNO$: 309.073).

Cis-1-Methyl-6-(phenylmethoxy)-6-azabicyclo[3.2.0]heptane (**16a**) *from* **14b**

To a solution of **14b** (6.16 g; 18.0 mmol) in glacial acetic acid (50 ml) was added, in portions, $NaCNBH_3$ (1.70 g; 27 mmol). The reaction mixture was stirred for 24 h at 35°C and the acetic acid was removed under reduced pressure. The residue was neutralized with a saturated $NaHCO_3$ solution in water and extracted with chloroform (3 × 40 ml). The organic layer was dried and the solvent was removed under reduced pressure. The residue was dissolved in dry pyridine (60 ml) and stirred for 16 h at 45°C. The reaction mixture was worked up by the addition of water (100 ml) and was acidified with 6N hydrochloric acid until the apparent pH was 3. Extraction with chloroform (3 × 50 ml), followed by drying and removal of the solvent under reduced pressure, afforded a mixture, consisting of several compounds. Purification by silica-gel column chromatography (dichloromethane), followed by bulb-to-bulb distillation, afforded azetidine **16a**. Yield 26%; b.p. [kugelrohr] ± 90°C (0.1 mm); n_D^{26} 1.5127. ^{1}H NMR δ: 7.30 (s, 5H, PhH), 4.57 (s, 2H, CH_2Ph), 3.8–3.7 (bd, 1H, NCH), 3.43 (bs, 2H, NCH_2), 1.9–1.4 [m, 6H, $-(CH_2)_3-$], 1.26 (s, 3H, CH_3). ^{13}C NMR (toluene-d_8; 50°C) δ: 80.6 (d, C-5), 75.6 (t, CH_2Ph), 68.1 (t, C-7), 40.0 (s, C-1), 38.3, 31.5 and 26.7 [t, $-(CH_2)_3-$], 25.3 (q, CH_3). Mass spectrum, *m/e* 217.146 (M^+, calcd. for $C_{14}H_{19}NO$: 217.147). Prolonged elution with ethyl acetate afforded compound **15b**.

*2-(Iodomethyl)-2-methyl-*N*-(phenylmethoxy)cyclopentanamine* (**15b**). Yield 5%. ^{1}H NMR δ: 7.33 (s, 5H, PhH), 5.2 (bs, 1H, NH), 4.67 (s, 2H, CH_2Ph), 3.48 and 3.29 (AB, *J* 9.5 Hz, 2H, CH_2I), 3.5–3.2 (m, 1H, NCH), 1.8–1.2 [m, 6H, $-(CH_2)_3-$], 1.05 (s, 3H, CH_3). ^{13}C NMR δ: 76.0 (t, CH_2Ph), 66.8 (d, NCH), 44.6 (s, C-2), 39.9, 29.8 and 23.7 [t, $-(CH_2)_3-$], 19.8 (t, CH_2I), 19.6 (q, CH_3). Mass spectrum, *m/e* 345.056 (M^+, calcd. for $C_{14}H_{20}INO$: 345.059).

Cis-1-Methyl-7-(phenylmethoxy)-7-azabicyclo[4.2.0]octane (**16b**) *from* **14c**. To a solution of **14c** (6.50 g; 16.2 mmol) in glacial acetic acid (65 ml) was added, in portions, $NaCNBH_3$ (1.53 g; 24.3 mmol). The reaction mixture was stirred for 24 h at 35°C. The product was purified by silica-gel column chromatography (dichloromethane) to give the azetidine **16b**. Yield 32%; b.p. 108–110°C (0.05 mm); n_D^{20} .5150. ^{1}H NMR δ: 7.35–7.25 (m, 5H, PhH), 4.67 and 4.61 (AB, *J* 1.2 Hz, 2H, CH_2Ph), 3.28 and 3.04 (ABC, *J* 6.6 and 1 Hz, 2H, NCH_2), 3.2 (m, 1H, NCH), 1.7–1.1 [m, 8H, $-(CH_2)_4-$], 1.05 (s, 3H, CH_3). ^{13}C NMR δ: 75.7 (t, CH_2Ph), 73.9 (d, NCH), 69.0 (t, NCH_2), 35.6, 25.8, 21.8 and 21.5 [t, $-(CH_2)_4-$], 28.7 (s, C-1), 24.6 (q, CH_3). Mass spectrum, *m/e* 231.162 (M^+, calcd. for $C_{15}H_{21}NO$: 231.162).

Cis-1-Methyl-7-(phenylmethoxy)-7-azabicyclo[4.2.0]octane (**16b**) *from* **15d**. The product was worked up as described above and distilled to give azetidine **16b**. Yield 48%.

Cis-7-Hydroxy-1-methyl-7-azabicyclo[4.2.0]octane (**17**).

A solution of compound **16b** (5.4 g; 23.4 mmol) in glacial acetic acid (45 ml) was hydrogenated in the presence of Pd/C (5%) at atmospheric pressure. After hydrogen take-up had ceased, the reaction was worked up as described for compounds **8** to give the hydroxyazetidine as a coloured oil. Distillation of the crude product afforded compound **17**. Yield 78%; b.p. [kugelrohr] 95°C (0.07 mm); n_D^{20} 1.4800; **17**·HCl, m.p. 128–130°C (chloroform/diisopropyl ether). ^{1}H NMR δ: 8.43 (bs, 1H, OH), 3.35 and 2.98 (ABC, *J* 6.8 and 1 Hz, 2H, NCH_2), 3.18 (m, 1H, NCH), 2.0–1.2 [m, 8H, $-(CH_2)_4-$], 1.11 (s, 3H, CH_3). ^{13}C NMR δ: 74.8 (d, NCH), 70.1 (t, NCH_2), 35.6, 24.9, 21.6 [t, $-(CH_2)_4-$], 29.1 (s, C-1), 24.5 (q, CH_3). Mass spectrum, *m/e* 141.115 (M^+, calcd. for $C_8H_{15}NO$: 141.115). Anal. calcd. for $C_8H_{15}NO \cdot HCl$: C 54.12, H 9.01, N 7.89; found: C 54.15, H 9.31, N 7.76%.

Oxidation of 1-hydroxyazetidines **8** *and* **17** *with lead(IV) oxide*

1-Hydroxyazetidine **8** (1.9 mmol) was added to a suspension of "active" PbO_2[23] (0.57 g; 2.38 mmol) in dry CH_2Cl_2 (10 ml). After being stirred for 45 min, $MgSO_4$ was added and the resulting mixture was filtered over Hyflo. The solvent was removed under reduced pressure to give the nitrones **18**. The nitrones **18a-e** could not be purified and were characterized as the 1,3-dipolar cycloadducts **19a-c** and **20**.

2-Azaspiro[3.5]non-2-ene N-*oxide* (**18a**) *from* **8a**. Yield according to ^{1}H NMR spectroscopy ~80%; unstable oil. ^{1}H NMR δ: 6.95 (s, 1H, HC=N), 3.97 (s, 2H, NCH_2), 1.67 (m, 4H, $-CH_2-$), 1.53 [m, 6H, $-(CH_2)_3-$].

3,3-Diethyl-2,3-dihydroazete 1-oxide (**18b**) *from* **8b**. Yield according to ^{1}H NMR spectroscopy ~80%; unstable oil. ^{1}H NMR δ: 6.92 (s, 1H, HC=N), 3.99 (s, 2H, NCH_2), 1.73 and 1.71 (q, *J* 7.3 Hz, 4H, $C\underline{H}_2CH_3$), 0.96 (t, *J* 7.3 Hz, 6H, $CH_2C\underline{H}_3$).

2,3-Dihydro-3,3-dipentylazete 1-oxide (**18c**) *from* **8c**. Yield according to ^{1}H NMR spectroscopy ~80%; unstable oil. ^{1}H NMR δ: 6.86 (s, 1H, HC=N), 3.96 (s, 2H, NCH_2), 1.56 (m, 4H, $-CH_2-$), 1.45–1.3 [m, 12H, $-(CH_2)_3-$], 0.90 (t, *J* 4.6 Hz, 6H, CH_3).

1-Methyl-7-azabicyclo[4.2.0]oct-7-ene N-*oxide* (**18d**) *from* **17**. Yield according to ^{1}H NMR spectroscopy ~5%; unstable oil. ^{1}H NMR δ: 6.78 (s, 1H, HC=N), 4.3 – 4.2 (m, 1H, HC-6), 2.1–1.0 [m, 8H, $-(CH_2)_4-$], 1.33 (s, 3H, CH_3).

1-Methyl-7-azabicyclo[4.2.0]-oct-6-ene N-*oxide* (**18e**) *from* **17**. Yield according to ^{1}H NMR spectroscopy ~75%; unstable oil. ^{1}H NMR δ: 4.08 (d, *J* 2 Hz, 2H, NCH_2), 2.80 (m, 2H, HC-5), 2.1-1.0 [m, 6H, $-(CH_2)_3-$], 1.30 (s, 3H, CH_3).

Characterization of nitrones **18**: *synthesis of dimethyl 6,6-disubstituted 2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4-dicarboxylates* **19**

The crude **18** (1.9 mmol) was dissolved in dry CH_2Cl_2 (5 ml) and reacted with dimethyl acetylenedicarboxylate (227 mg; 1.6 mmol) at 0°C for 30 min after which the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ and passed through a small Florisil column to give pure **19**, after removal of the solvent under reduced pressure.

Dimethyl spiro[cyclohexane-1,6'-[2]oxa[1]azabicylo[3.2.0]hept-3'-ene]-3',4'-dicarboxylate (**19a**) *from* **18a**. Yield 51%; oil. ^{1}H NMR δ: 4.78 (t, *J* 1.6 Hz, 2H, HC-5), 3.91 and 3.55 (dAB, *J* 10.5 and 1.6 Hz, 2H, HC-7'), 3.91 and 3.76 (s, 3H, OCH_3), 1.9–1.3 [m, 10H, $-(CH_2)_5-$]. ^{13}C NMR δ: 163.2 and 159.4 (s, C=O), 154.0 (s, C-3'), 108.0 (s, C-4'), 80.8 (d, C-5'), 69.8 (t, C-7'), 44.3 (s, C-6'). Mass spectrum, *m/e* 281.126 (M^+, calcd. for $C_{14}H_{19}NO_5$: 281.126).

Dimethyl 6,6-diethyl-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4-dicarboxylate (**19b**) *from* **18b**. Yield 42%; oil. IR (KBr): 1758 (C=O) and 1720 (C=O) cm^{-1}. ^{1}H NMR δ: 4.87 (t, *J* 1 Hz, 1H, HC-5), 3.80 and 3.63 (dAB, *J* 10 and 1 Hz, 2H, HC-7), 3.91 and 3.74 (s, 3H, OCH_3), 1.8–1.4 (m, 4H, $C\underline{H}_2CH_3$), 0.94 and 0.72 (t, *J* 7.3 Hz, 3H, CH_3). ^{13}C NMR δ: 163.0 and 159.5 (s, C=O), 154.2 (s, C-3), 108.1

(s, C-4), 79.2 (d, C-5), 69.2 (t, C-7), 53.4 (s, C-6), 28.3 and 24.3 (t, $\underline{C}H_2CH_3$), 8.4 and 7.5 (q, CH_3). Mass spectrum, *m/e* 269.126 (M^+, calcd. for $C_{13}H_{19}NO_5$: 269.126).

Dimethyl 6,6-dipentyl-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4-dicarboxylate (**19c**) *from* **18c**. Yield 30%; oil. ^1H NMR δ: 4.87 (t, *J* 1 Hz, 1H, HC-5), 3.91 and 3.75 (s, 3H, OCH_3), 3.78 and 3.56 (dAB, *J* 10.5 and 1 Hz, 2H, HC-7), 1.6–1.2 [m, 16H, $-(CH_2)_4-$], 0.91 and 0.87 (t, *J* 4.6 Hz, 3H, CH_3). ^{13}C NMR δ: 163.0 and 159.6 (s, C=O), 154.0 (s, C-3), 108.1 (s, C-4), 79.9 (d, C-5), 70.7 (t, C-7), 46.5 (s, C-6). Mass spectrum, *m/e* 353.220 (M^+, calcd. for $C_{19}H_{31}NO_5$: 353.220).

Dimethyl 5a,6,7,8,9,9a-hexahydro-5a-methyl-5H-benz[2,3]azeto-[1,2-b]-isoxazole-1,2-dicarboxylate (**20**) *from* **18e**. Yield 56%; oil. IR (KBr): 1755 and 1715 (C=O), 1640 (C=C) cm^{-1}. ^1H NMR δ: 3.90 and 3.75 (s, 3H, OCH_3), 3.60 and 3.41 (AB, *J* 9.3 Hz, 2H, HC-5), 2.1–1.2 [m, 8H, $-(CH_2)_4-$], 1.13 (s, 3H, CH_3). ^{13}C NMR δ: 163.5 and 160.4 (s, C=O), 154.0 (s, C-2), 111.7 (s, C-1), 84.3 (s, C-9a), 70.1 (t, C-5), 53.2 and 51.7 (q, OCH_3), 21.9 (q, CH_3). Mass spectrum, *m/e* 281.124 (M^+, calcd. for $C_{14}H_{19}NO_5$: 281.126).

Oxidation of 1-hydroxyazetidines **8** *and* **17** *with lead tetraacetate*

A solution of the 1-hydroxyazetidine (3 mmol) in dry toluene (5 ml) was added to a stirred solution of lead tetraacetate (4.43 g; 10 mmol) in dry toluene (40 ml) at 0°C. After being stirred for 30 min, the mixture was filtered over hyflo and the filtrate was washed with brine (2 × 10 ml). The organic layer was dried and filtered and the solvent was removed under reduced pressure. From the compounds **8a-c**, the resulting oil could be purified by silica-gel column chromatography using dichloromethane as eluent.

6,7-Bis(acetyloxy)-1-methyl-7-azabicyclo[4.2.0]octan-8-one (**21**) *from* **17**. Yield 70%; oil. IR (NaCl): 1810 ($NOCOCH_3$), 1785 (C=O) and 1745 ($OCOCH_3$) cm^{-1}; ^1H NMR δ: 2.15 and 2.08 (s, 3H, $COCH_3$), 1.3–1.0 [m, 8H, $-(CH_2)_4-$], 1.35 (s, 3H, CH_3). ^{13}C NMR δ: 169.4, 168.6 and 167.4 (s, C=O), 95.9 (s, C-6), 54.8 (s, C-1), 21.2 and 18.0 (q, $OCOCH_3$), 17.6 (q, CH_3). Mass spectrum, *m/e* 255.111 (M^+, calcd. for $C_{12}H_{17}NO_5$: 255.111).

2,3-Bis(acetyloxy)-2-azaspiro[3.5]nonan-1-one (**22a**) *from* **8a**. Isolated as a mixture with compound **23a** in a ratio of 65:35. Yield 66%; oil. IR (KBr): 1815 (NOAc), 1785 (C=O), 1750 (OAc) cm^{-1}. ^1H NMR δ: 5.96 (s, 1H, HC-3), 2.17 and 2.14 (s, 3H, $COCH_3$), 2.0–1.3 [m, 10H, $-(CH_2)_5-$]. ^{13}C NMR δ: 170.4, 168.6 and 168.0 (s, C=O and OC=O), 87.1 (d, C-3), 55.8 (s, C-4), 20.8 and 18.0 (q, $CO\underline{C}H_3$). Mass spectrum, *m/e* 255.112 (M^+, calcd. for $C_{12}H_{17}NO_5$: 255.111).

2,3,3-Tris(acetyloxy)-2-azaspiro[3.5]nonan-1-one (**23a**) *from* **8a**. Oil. IR (KBr): 1825 (NOAc), 1785 (C=O), 1770 (OAc) cm^{-1}. ^1H NMR δ: 2.17 (s, 3H, $COCH_3$), 2.10 (s, 3H, $NOCOCH_3$), 2.0–1.3 [m, 10H, $-(CH_2)_5-$]. ^{13}C NMR δ: 167.0 (s, C=O), 109.1 (s, C-3), 60.4 (s, C-4). Mass spectrum, *m/e* 254.108 [$(M-OAc)^+$, calcd. for $C_{12}H_{16}NO_5$: 254.109].

1,4-Bis(acetyloxy)-3,3-diethyl-2-azetidinone (**22b**) *from* **8b**. Yield 46%; oil. IR (KBr): 1818 (NOAc), 1785 (C=O), 1765 (OAc) cm^{-1}. ^1H NMR δ: 6.04 (s, 1H, HC-4), 2.17 and 2.14 (s, 3H, $COCH_3$), 1.9–1.7 (m, 4H, $C\underline{H}_2CH_3$), 1.04 and 1.03 (t, *J* 7.5 Hz, 6H, CH_3). ^{13}C NMR δ: 170.3, 167.9 and 167.8 (s, C=O), 86.0 (d, C-4), 59.5 (s, C-3), 24.4 and 21.5 (t, $\underline{C}H_2CH_3$), 20.8 and 17.9 (q, $COCH_3$), 8.9 and 8.5 (q, CH_3). Mass spectrum, *m/e* 243.112 (M^+, calcd. for $C_{11}H_{17}NO_5$: 243.111).

1,4-Bis(acetyloxy)-3,3-dipentyl-2-azetidinone (**22c**) *from* **8c**. Yield 47%; oil. IR (KBr): 1815 ($NOCOCH_3$), 1785 (C=O), 1750 ($OCOCH_3$) cm^{-1}. ^1H NMR δ: 6.03 (s, 1H, HC-4), 2.16 and 2.13 (s, 3H, $COCH_3$), 1.9–1.1 [m, 16H, $-(CH_2)_4-$], 0.90 (bt, 6H, CH_3). ^{13}C NMR δ: 170.3, 168.1 and 167.8 (s, C=O), 86.2 (d, C-4), 58.6 (s, C-3), 20.8 and 17.9 (q, CH_3). Mass spectrum, *m/e* 327.209 (M^+, calcd. for $C_{17}H_{29}NO_5$: 327.205).

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