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The stereoselective synthesis of substituted 1-hydroxyazetidines

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Abstract. The four-membered cyclic nitrones (2,3-dihydroazete 1-oxides) **1a-d** and **2a-c** react with a variety of nucleophiles by stereoselective addition to the nitrone moiety. Reaction of the nitrones **1** and **2** with alkyl-, allyl-, benzyl-, and arylmagnesium halides yields the 1-hydroxyazetidines **3**, **4**, **5**, and **6**, with the nucleophile adding from the less hindered side of the molecule. The keto nitrone **1b** reacts with potassium cyanide to give the 1-hydroxyazetidine **4f**. Reduction of nitrone **1b** to give the 1-hydroxyazetidines **7** and **8** is achieved by reaction with lithium aluminum hydride at 0°C and at room temperature, respectively. In contrast, nitrone **1d** reacts with lithium aluminum hydride only at 45°C to give the 1-hydroxyazetidine **11**. The differences in the reactivity of the nitrones **1** and **2** towards nucleophilic reagents are explained in terms of steric hindrance in the addition step. Oxidation of the 1-hydroxyazetidine **3b** with lead(IV) oxide affords the 2,3-dihydroazete 1-oxide **15**. Reduction of nitrone **15** with sodium borohydride affords the 1-hydroxyazetidine **16**, the epimer of compound **3b**. Reaction of 1-hydroxyazetidine **3d** with PbO_2 yields the dimeric structure **17**. Nitrone **1a** reacts with the sodium salt of nitromethane to yield the 1-hydroxyazetidine **12**. Keto nitrone **1b** reacts with 4-nitrobenzaldehyde in the presence of a catalytic amount of potassium hydroxide to give the 4-benzylidene-2,3-dihydroazete 1-oxide **13**. Upon prolonged reaction, nitrone **13** isomerizes to oxime **14**, probably by an electrocyclic ring opening of an intermediate 1-hydroxy-1,2-dihydroazete.

Introduction

Previously we described the synthesis of a large number of four-membered cyclic nitrones (2,3-dihydroazete 1-oxides) by the reaction of nitro(cyclo)alkenes with ynamines[1,2] and by the oxidation of 1-hydroxyazetidines[3]. Since these four-membered cyclic nitrones belong to a class of virtually unknown heterocycles[4], we are currently investigating the chemical reactivity of the nitrone moiety of these compounds. In previous papers we have described the 1,3-dipolar cycloadditions[5a], some nucleophilic additions[5b], their conversion into β-lactams[6], and their reactions with non-nucleophilic bases[7].

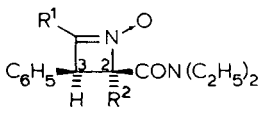
Since nitrones possess an "extended" carbonyl character[8], they typically undergo 1,3-addition with nucleophilic reagents to afford *N,N*-disubstituted hydroxylamine derivatives. Nitrones react readily with carbon-centered nucleophiles like cyanide[9], organometallic reagents[10], and active methylene carbanions[9,11], and with complex metal hydrides[4a,10c,12] to give the corresponding 1-hydroxylamines in high yields. Acyclic nitrones react with *Grignard* reagents to give instable adducts, which decompose to give imines[10a,b], whereas cyclic nitrones, like pyrroline 1-oxides, are converted into the corresponding 1-hydroxypyrrolidines on reaction with methyl- and ethylmagnesium halides[10c,d]. The activation of a methyl group by an adjacent nitrone system is demonstrated by the aldol-type condensations of 2-methyl-1-pyrroline 1-oxide with ethyl benzoate[11b], benzaldehydes[9], and with unsubstituted pyrroline 1-oxides[11a].

In this paper we describe the results of reactions of four-membered cyclic nitrones **1** and **2** with nucleophiles as a convenient way to prepare substituted four-membered cyclic nitrones and 1-hydroxyazetidines. The scope and limitations of these nucleophilic additions will be discussed and compared with those of other acyclic and cyclic nitrones.

Results and discussion

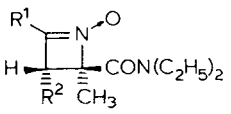
Reaction of nitrones 1 *and* 2 *with* Grignard *reagents*

Previously[5b] we described the synthesis of 1-hydroxyazetidine **3a**, by the reaction of aldonitrone **1a** with methylmagnesium iodide. When nitrone **1a** was allowed to react with ethylmagnesium iodide in a mixture of dry diethyl ether and dry benzene at room temperature an oil was obtained in 90% yield. By comparison of NMR spectroscopic data with those of **3a**[5b] and *N*-alkyl azetidines[13], we have assigned structure **3b** to this product with a stereochemistry as shown in Scheme 2. Reaction of nitrone **1a** with allylmagnesium bromide in a mixture of diethyl ether and benzene at room temperature gave the 4-allyl-1-hydroxyazetidine **3c** in 70% yield. Benzylmagnesium bromide, dissolved in diethyl ether, was allowed to react with a solution of nitrone **1a** in benzene to give the 4-benzyl-1-hydroxyazetidine **3d** in 43% yield. Reaction of nitrone **1a** with phenylmagnesium bromide gave a crystalline product with

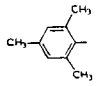
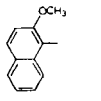


1

a. $R^1 = H$; $R^2 = CH_3$
b. $R^1 = CH_3$; $R^2 = CH_3$
c. $R^1 = C_6H_5$; $R^2 = C_6H_5$
d. $R^1 = C_6H_5$; $R^2 = CH_3$



2

a. $R^1 = H$; $R^2 =$ 
b. $R^1 = C_6H_5$; $R^2 =$ 
c. $R^1 = C_6H_5$; $R^2 =$ 

Scheme 1

melting point 148–150°C in 86% yield. On the basis of the coupling constant of the hydrogens at C(3) and C(4) (J 9.3 Hz) in the ^{1}H NMR spectrum, ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis we assigned structure **3e** to this product.

The recent availability of four-membered cyclic nitrones **2** in which the "bulky" aryl group at C-3 and the carbamoyl group at C(2) have a *trans* relation[2], enabled us to examine the influence of this substitution pattern in these addition reactions on the stereoselectivity. When nitrone **2a** was allowed to react with methylmagnesium iodide the hydroxyazetidine **6a** was isolated in 61% yield. A singlet at δ 1.24 in the ^{1}H NMR spectrum was assigned to the methyl group at C(4) of compound **6a**, and on this basis the stereochemistry shown in Scheme 2 was assigned.

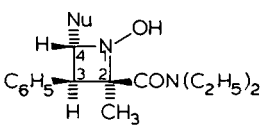
From these results it is obvious that the aldonitrones **1a** and **2a** react readily with alkyl-, aralkyl-, and arylmagnesium halides in a stereoselective manner with the nucleophile adding from the sterically less hindered side at C-3.

Reaction of ketonitrone **1b** with methylmagnesium iodide in a mixture of diethyl ether and benzene gave the 4,4-disubstituted hydroxyazetidine **4a** as a white solid in 44% yield with melting point 138–140°C. When nitrone **1b** was allowed to react with the alkylmagnesium halide prepared from deuterated methyl iodide, a white solid was isolated in 38% yield, which was shown to be hydroxyazetidine **4b**. Comparison of the ^{1}H NMR spectrum of **4b** with that of **4a** showed the absence of the methyl signal at δ 1.59. By comparison of the chemical shifts of the methyl groups with those of compound **3a** and derivatives of **3a**[5b], we could conclude that the methylmagnesium halide had added from the sterically less hindered side of the molecule.

Reactions of **1b** with the *Grignard* reagents prepared from ethyl iodide, allyl bromide and benzyl bromide, afforded the corresponding 4-substituted hydroxyazetidines **4c**, **4d** and **4e** in 54%, 86% and 24% yield, respectively (Scheme 2). The stereochemistry of hydroxyazetidine **4d** was established by Nuclear Overhauser Enhancement (NOE) ^{1}H NMR spectroscopy (Fig. 1).

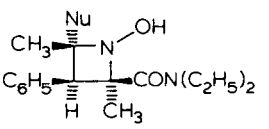
From the small but significant difference in the NOE effects for the interaction of the hydrogen atom at C(3) with the methyl group at C(2) (8%) and at C(4) (5%) it was concluded that the methyl group at C(4) is *trans*, relative to the hydrogen atom at C(3).

Definite proof for the stereochemistry of the 1-hydroxyazetidines **4** was obtained by single crystal X-ray analysis of 1-hydroxyazetidine **4d** (Fig. 2). The dihedral or puckering



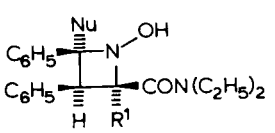
3

a. Nu = CH_3
b. Nu = C_2H_5
c. Nu = C_3H_5
d. Nu = $CH_2C_6H_5$
e. Nu = C_6H_5
f. Nu = CN



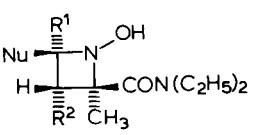
4

a. Nu = CH_3
b. Nu = CD_3
c. Nu = C_2H_5
d. Nu = C_3H_5
e. Nu = $CH_2C_6H_5$
f. Nu = CN

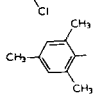
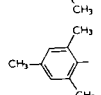
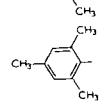


5

a. Nu = CH_3 ; $R^1 = C_6H_5$
b. Nu = CH_3 ; $R^1 = CH_3$
c. Nu = C_2H_5 ; $R^1 = C_6H_5$
d. Nu = C_3H_5 ; $R^1 = C_6H_5$
e. Nu = $CH_2C_6H_5$; $R^1 = C_6H_5$



6

a. Nu = CH_3 ; $R^1 = H$; $R^2 =$ 
b. Nu = CH_3 ; $R^1 = C_6H_5$; $R^2 =$ 
c. Nu = CD_3 ; $R^1 = C_6H_5$; $R^2 =$ 
d. Nu = C_2H_5 ; $R^1 = C_6H_5$; $R^2 =$ 
e. Nu = CH_3 ; $R^1 = C_6H_5$; $R^2 =$ 

Scheme 2

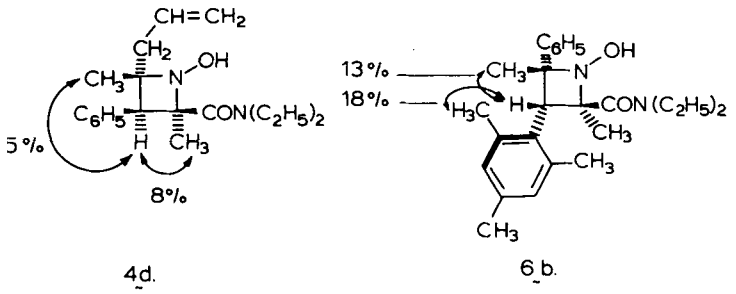


Fig. 1.

angle of azetidine **4d** is 21°, with C–C bond distances of 1.574 and 1.567 Å and C–N bond distances of 1.495 and 1.485 Å. The ring puckering of *N,N*-diethyl-1-hydroxy-4--methoxy-2-methyl-3-phenyl-2-azetidinecarboxamide[5b] with a methoxy substituent in the 4-position is 28.4°, whereas that of the parent azetidine[14] in the minimum energy conformation is 33.1°. Comparison of the crystallographic data of **4d** and the 4-methoxy-1-hydroxyazetidine[1] suggests that the 1,3-diaxial repulsion in **4d** is larger than in the latter 1-hydroxyazetidine, resulting in a four-membered ring, which is flatter and has a longer N–C bond (1.50 Å *vs.* 1.46 Å).

Compounds **4c-d** are the first examples of 1-hydroxyazetidines as stable adducts formed from reaction of a keto nitrone with allyl- and benzylmagnesium halides. The reaction of oxazoline *N*-oxides with allylmagnesium bromide has been reported to give adducts which are not stable[15]. In the literature the reaction of only one acyclic keto nitrone, *viz. N*-phenyl benzophenone nitrone with isopropylmagnesium bromide has been reported. In this reaction the corresponding imine is formed and not the corresponding hydroxylamine[10a].

Reactions of the 4-phenylnitrones **1c** and **1d** with various *Grignard* reagents showed large differences in reactivity of the nitrone function depending on the substituents at C(2). When nitrone **1c**, with a phenyl group at C(2), was allowed to react with methylmagnesium iodide in a mixture of diethyl ether and benzene the crowded 4-substituted 1-hydroxyazetidine **5a** was isolated in 42% yield, after a reaction time of 20 h. This reaction time remarkably *decreased* for the reaction of nitrone **1d**, with a methyl group at C(2) with methylmagnesium iodide. The reaction was complete after ½ h and the 1-hydroxyazetidine **5b** was isolated in 64% yield. Nitrone **1c** did not react with benzylmagnesium bromide after 20 h of reaction time. However, when nitrone **1c** was allowed to react with allylmagnesium bromide and benzylmagnesium chloride in a mixture of diethyl ether and benzene, the reaction was complete after ½ h and gave **5d** and **5e** in 82% and 37% yield, respectively. Finally, reaction of nitrone **1c** to yield 1-hydroxyazetidine **5c**, showed that ethylmagnesium iodide added remarkably slower to the nitrone moiety than ethylmagnesium bromide. Probably the combination of a bulky substituent at C(2) of the nitrone together with the "bulky" *Grignard* reagent accounts for the long reaction time of nitrone **1c**[16,17].

The availability of the four-membered cyclic keto nitrones **2b** and **2c**, in which the "bulky" aryl group at C(3) and the carbamoyl group at C(2) are *trans*[2], enabled us to examine the influence of this substitution pattern in these addition reactions and on the stereoselectivity. When nitrone **2b** was allowed to react with methylmagnesium iodide a slow addition reaction took place and a solid was isolated in 84% yield. On the basis of ^{1}H NMR spectroscopy we assigned the hydroxyazetidine structure to **6b**. Nitrone **2b** with deuteromethylmagnesium iodide led to a product, the ^{1}H NMR spectrum of which showed the absence of the signal at δ 1.77, thereby proving that this signal must be assigned to the methyl group of **6c** at C(4). NOE difference

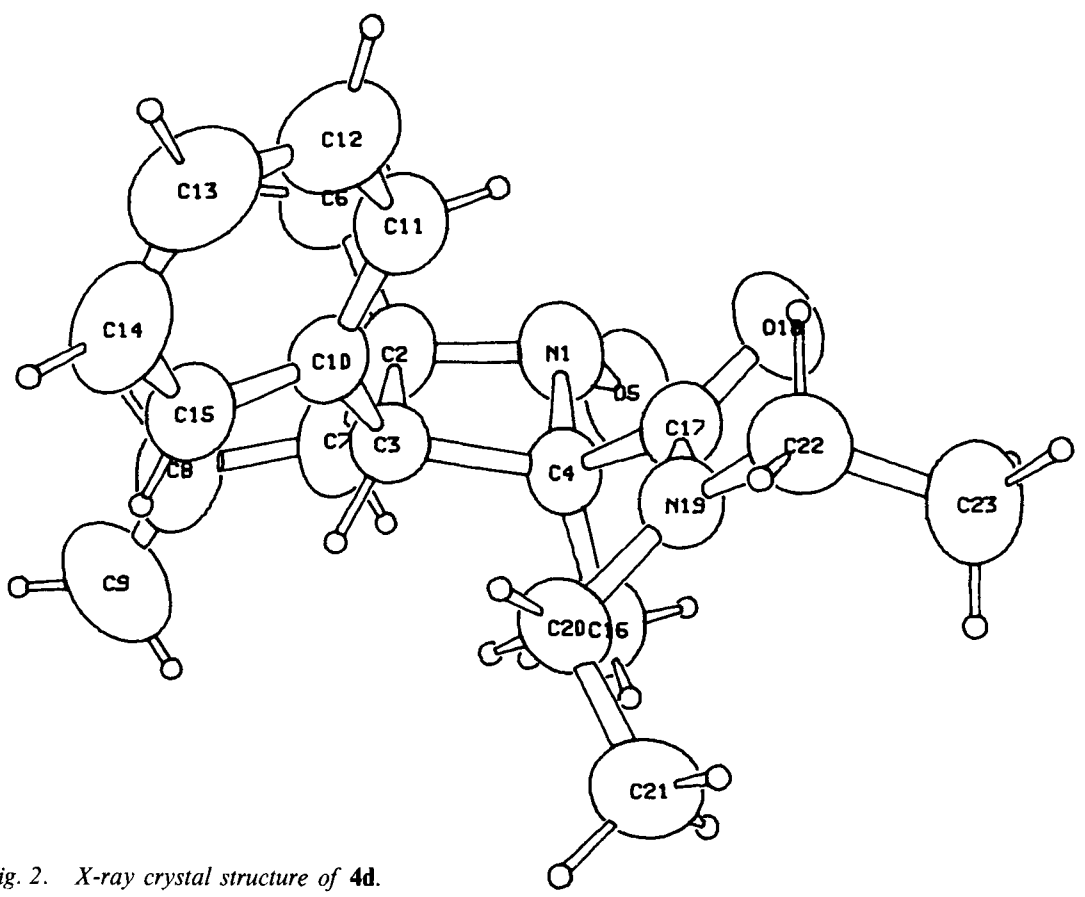
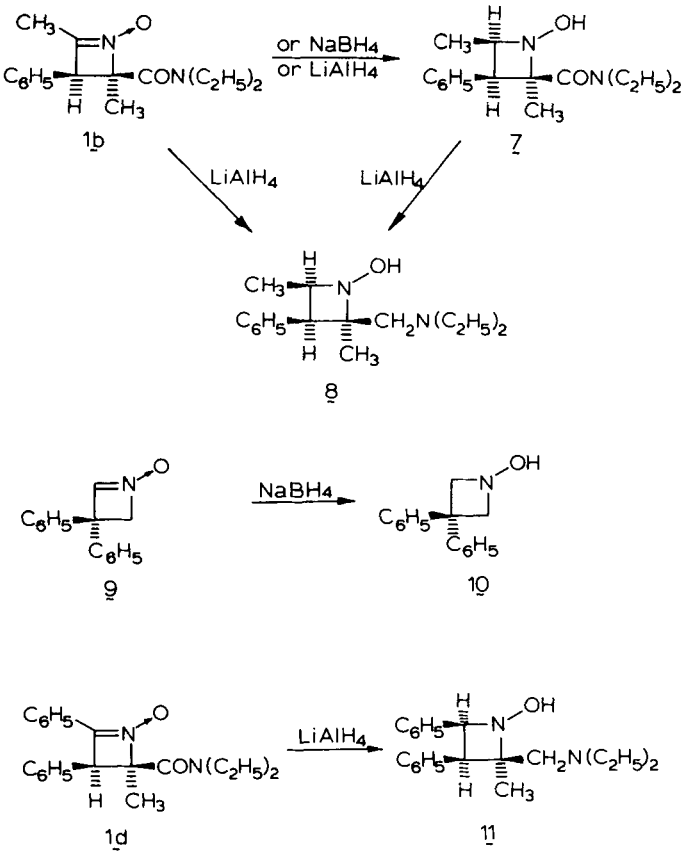


Fig. 2. X-ray crystal structure of **4d**.



Scheme 3

^{1}H NMR spectroscopy of compound **6b** showed a large effect for the interaction between the hydrogen atom at C(3) and one of the methyl groups of the mesityl function (18%) and for the interaction of the hydrogen atom at C(3) and the methyl group at C(4) (13%) [Fig. 1]. Comparison of these NOE effects with the NOE effect of the interaction of the hydrogen atom at C(3) and the methyl group at C(2) (5%), which are *trans*, clearly shows that the methyl group at C(4) and the hydrogen atom at C(3) have a *cis* relation. From this we concluded that the nucleophile had added from the sterically less hindered side of the molecule.

Nitrone **2b** reacted also with ethylmagnesium iodide in a mixture of diethyl ether and benzene to give the substituted hydroxyazetidine **6d** in a yield of 78%. Nitrone **2b** did not react with allylmagnesium bromide and benzylmagnesium chloride and the starting material was recovered completely. Nitrone **2c**, with a "bulky" 2-methoxynaphthalenyl substituent at C(3), only reacted with methylmagnesium iodide to give the substituted hydroxyazetidine **6e** in 48% yield.

From these results we might conclude that the *trans*-substituted nitrones **2b** and **2c** react less readily with *Grignard* reagents than the *cis* substituted nitrones. This difference in reactivity may be due to the presence of a carbamoyl group in nitrones **2** on the same side where the nucleophilic attack takes place, which causes more steric hindrance in the addition than in the addition to nitrone **1d**.

Reaction of nitrones **1** *and* **2** *with complex metal hydrides*

When nitrone **1b** was allowed to react with $LiAlH_4$ in tetrahydrofuran at room temperature for 5 h, the reduced compound **8** was isolated in 61% yield (Scheme 3)[5b]. Reaction of nitrone **1b** with $LiAlH_4$ at 0°C for $1\frac{1}{2}$ h, gave selective reduction to yield hydroxyazetidine **7** in 80% yield.

Compound **7** was characterized by comparison of the spectral data with those of an independently prepared sample[5b]. When hydroxyazetidine **7** was allowed to react further with $LiAlH_4$ in tetrahydrofuran at room temperature for 5 h, the amide carbonyl group was reduced and hydroxyazetidine **8**[5b] was isolated in 85% yield. When nitrone **9**, with two phenyl groups at C(3), was treated with $NaBH_4$ in methanol the hydroxyazetidine **10**[3] was isolated in 86% yield.

Nitrone **1d** with a methyl group at C(2) and a phenyl group at C(4) reacted with $LiAlH_4$ at 45°C with reduction of both the nitrone moiety and the amide carbonyl group yielding hydroxyazetidine **11** in 67% yield. However, nitrone **1c**, with phenyl groups at C(2) and C(4), or the nitrones **2b** and **2c**, with the *trans* stereochemistry and a phenyl group at C(4), were not reduced with $NaBH_4$ or $LiAlH_4$ at various temperatures.

Nitrones **1c,d** and **2b,c** with a phenyl group at C(4) show a low reactivity towards complex metal hydrides. The reactivity of these 4-phenylnitrones towards complex metal hydrides is strongly influenced by the substituent at C(2). According to the literature, six-membered cyclic nitrones react readily with magnesium halides, like phenylmagnesium bromide, whereas complex metal hydrides cannot reduce these nitrones[10c].

The difference in reactivity of aldonitrone **1a** and the ketonitrones **1b-d** clearly demonstrates the influence of the substituent at C(4). Nitrone **1a**, which has a hydrogen atom at C(4), reacts readily with complex metal hydrides, and *Grignard* reagents. Nitrone **1b**, with a methyl group at C(4), reacts with *Grignard* reagents, complex metal hydrides, but not with phenylmagnesium bromide. Nitrone **1c**, with a phenyl group at C(4), reacts with alkylmagnesium halides, but not with complex metal hydrides and phenylmagnesium bromide.

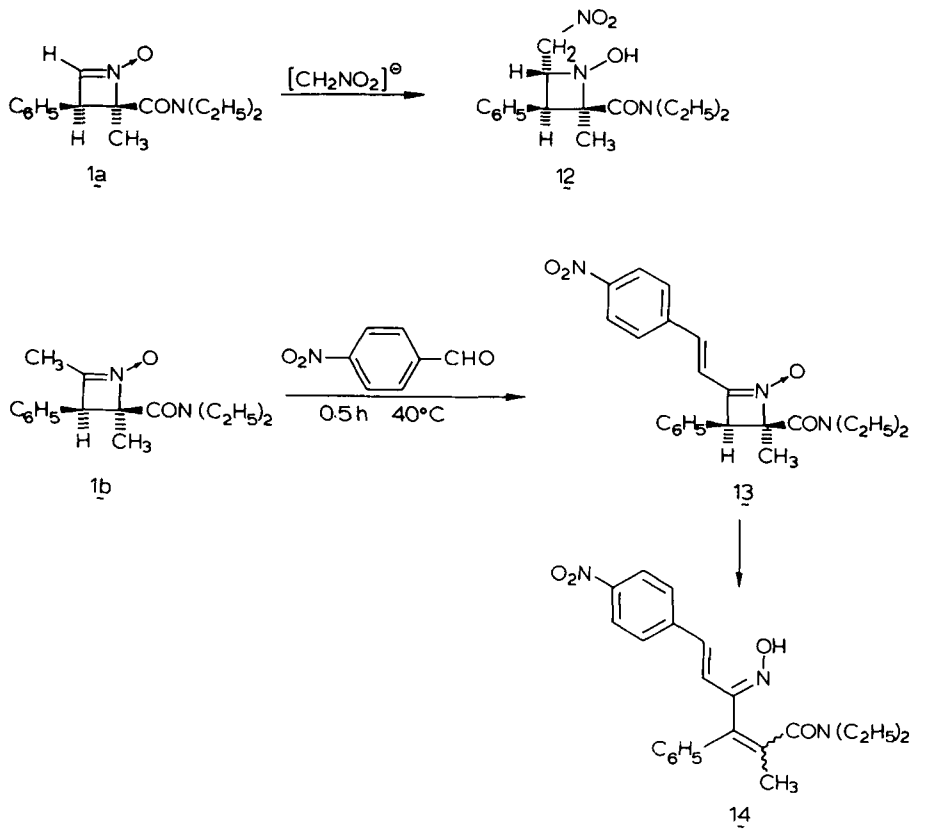
The influence of the substituent at C(2) is clearly demonstrated by the difference in reactivity of the nitrones **1c** and **1d**. The presence of a phenyl group at C(2) in nitrone **1c** results in a decrease in reactivity of this nitrone towards complex metal hydrides and methylmagnesium iodide. The presence of a "bulky" carbamoyl group at C(2) on the same side of the nucleophilic attack, as in the nitrones **2a-c**, results in a decrease in reactivity towards alkylmagnesium halides and complex metal hydrides.

Reactions of nitrones **1** *and* **2** *with KCN*

In previous work we reported the reaction of the aldonitrone **1a** with potassium cyanide, yielding the 4-cyano--1-hydroxyazetidine **3f** in 75% yield (Scheme 2)[5b]. When ketonitrone **1b** was allowed to react with KCN in methanol for 3 h, the 4-cyano-1-hydroxyazetidine **4f** was isolated in 33% yield. Compound **4f**, with the stereochemistry as shown, was characterized by ^{1}H NMR and ^{13}C NMR spectroscopy, and by elemental analysis. The ^{1}H NMR spectrum showed a singlet for the methyl group at C(4) at relatively high field (δ 1.24) due to the shielding caused by the *cis*-substituted phenyl group at C(3), thus establishing that the cyano group had added from the sterically less hindered side of the molecule. When the 4-phenylnitrones **1c**, **2b**, and **2c** were allowed to react with potassium cyanide in methanol for 72 h, only starting material was isolated. The reaction of nitrone **1b** with potassium cyanide represents the first example of the cyanide addition to keto nitrones.

The use of nitrones **1** *in aldol-type reactions*

The reaction of pyrroline 1-oxides with compounds containing active methylene groups, like nitroalkanes, has been reported to give the corresponding 2-substituted 1-hydroxy-



Scheme 4

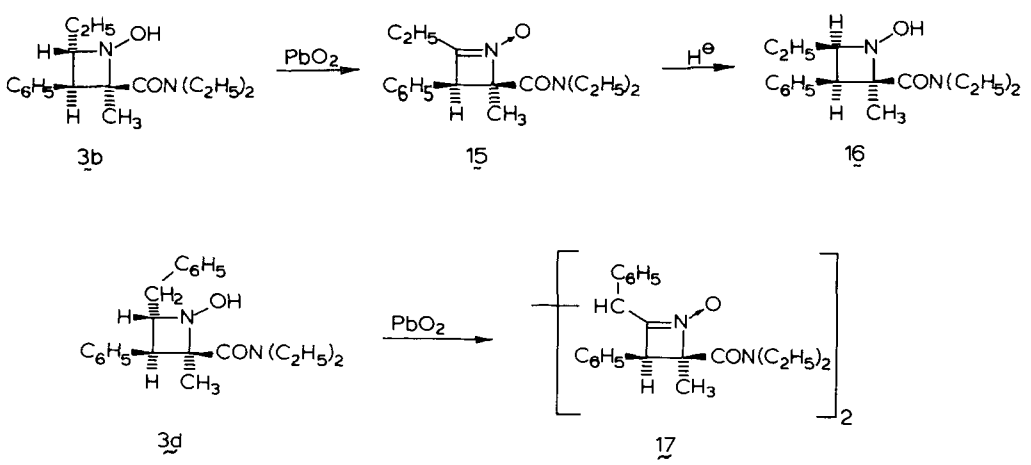
pyrrolidines[9,11]. 5-Membered cyclic nitrones and acyclic nitrones, possessing an active methylene group in 2-position, have been reported to give aldol-type reactions with benzaldehydes[9].

Reaction of nitrone **1a** with the sodium salt of nitromethane in ethanol at room temperature for 17 h gave **12** (Scheme 4). On the basis of the low-field absorption in the ^{1}H NMR spectrum of the CH_2NO_2 group (δ 4.8) it is likely that this group is *trans* to the phenyl group at C(3).

When nitrone **1b** was allowed to react with 4-nitrobenzaldehyde in the presence of a catalytic amount of potassium hydroxide in ethanol for $\frac{1}{2}$ h at 45 °C **13** was isolated in 41% yield. However, oxime **14** was isolated in 43% yield when the same reaction was carried out at 60 °C. From previous work we know that four-membered cyclic nitrones tend to give ring opening upon reaction with base[18]. This might indicate that the abstraction of the hydrogen from the activated methyl group at C(4) in nitrone **1b** and the subsequent reaction with 4-nitrobenzaldehyde occurs faster than the abstraction of the hydrogen at C(3) and the subsequent ring opening of nitrone **1b**.

Oxidation of hydroxyazetidines **3** *with* PbO_2

A general route for the synthesis of nitrones comprises the oxidation of the corresponding hydroxylamine derivatives. Several oxidizing reagents including lead(IV) oxide, yellow mercury(II) oxide and peroxides have been used[8]. Previously, we reported the oxidation of 1-hydroxyazetidines with HgO, yielding the corresponding four-membered cyclic nitrones[6a] and, more recently, we reported the oxidation of



Scheme 5

Table 1. Positional parameters and their estimated standard deviations

Atom	X	Y	Z
O5	0.8180(2)	0.0242(2)	0.02505(5)
O18	0.8053(2)	-0.1602(2)	-0.06456(6)
N1	0.8375(3)	0.0468(2)	-0.01990(6)
N19	0.6597(2)	-0.0934(2)	-0.10914(7)
C2	0.8547(3)	0.1787(3)	-0.02961(8)
C3	0.7622(3)	0.1621(3)	-0.06790(8)
C4	0.7264(3)	0.0372(2)	-0.04724(8)
C6	0.9863(3)	0.2075(4)	-0.03948(9)
C7	0.8073(3)	0.2648(3)	0.00487(9)
C8	0.7965(4)	0.3951(3)	-0.0102(1)
C9	0.7121(4)	0.4679(4)	-0.0031(1)
C10	0.8124(3)	0.1674(3)	-0.11310(8)
C11	0.8987(3)	0.0860(3)	-0.12818(9)
C12	0.9460(3)	0.0936(4)	-0.1689(1)
C13	0.9086(3)	0.1850(4)	-0.19608(9)
C14	0.8235(3)	0.2667(3)	-0.18242(9)
C15	0.7747(3)	0.2583(3)	-0.14064(9)
C16	0.6054(3)	0.0365(3)	-0.02258(9)
C17	0.7338(3)	-0.0792(3)	-0.07470(8)
C20	0.5749(3)	-0.0041(3)	-0.1265(1)
C21	0.4447(3)	-0.0526(3)	-0.1292(1)
C22	0.6783(3)	-0.2031(3)	-0.13534(8)
C23	0.6222(3)	-0.3170(3)	-0.1175(1)
H3	0.692(2)	0.217(2)	-0.0656(5)
H6A	1.020(3)	0.144(3)	-0.0606(8)
H6B	1.000(3)	0.282(3)	-0.0590(9)
H6C	1.026(2)	0.213(2)	-0.0141(7)
H7A	0.858(3)	0.263(3)	0.033(1)
H7B	0.732(3)	0.244(3)	0.0139(8)
H8	0.879(3)	0.425(3)	-0.030(1)
H9A	0.720(4)	0.556(4)	-0.005(1)
H9B	0.635(6)	0.435(5)	0.005(2)
H11	0.927(2)	0.019(2)	-0.1103(7)
H12	1.017(3)	0.047(3)	-0.179(1)
H13	0.948(3)	0.187(3)	-0.2257(8)
H14	0.791(3)	0.323(3)	-0.1968(9)
H15	0.720(2)	0.316(2)	-0.1324(7)
H16B	0.538(4)	0.019(4)	-0.043(1)
H16C	0.614(3)	-0.023(3)	0.0020(9)
H16A	0.595(2)	0.106(2)	-0.0051(8)
H20B	0.599(2)	0.017(2)	-0.1577(7)
H20A	0.570(2)	0.066(2)	-0.1071(7)
H21B	0.442(3)	-0.126(3)	-0.1513(9)
H21C	0.417(2)	-0.077(3)	-0.0993(8)
H21A	0.388(3)	0.020(3)	-0.140(1)
H22B	0.644(2)	-0.187(2)	-0.1647(7)
H22A	0.772(2)	-0.215(2)	-0.1397(7)
H23B	0.650(3)	-0.329(3)	-0.0905(9)
H23C	0.531(3)	-0.302(3)	-0.112(1)
H23A	0.642(3)	-0.393(3)	-0.1368(9)

3,3-disubstituted 1-hydroxyazetidines with PbO_2 to give the corresponding nitrones[3,6b]. Since we currently are interested in the use of aldonitrones like **1a** as the general precursor for 4-substituted nitrones and hydroxyazetidines, we examined the oxidation of the 4-substituted hydroxyazetidines **3**, which in turn were derived from the aldonitrone **1a**.

Reaction of **3b** with a suspension of activated PbO_2[19] in dry dichloromethane afforded the 4-ethyl-2,3-dihydroazete 1-oxide **15** in 82% yield (Scheme 5). Nitrone **15** was identical with a sample which was prepared independently, by the cycloaddition of the appropriate ynamine and nitroalkene[2]. When nitrone **15** was reduced with $NaBH_4$ in methanol, the hydroxyazetidine **16** was isolated in 98% yield. We assigned the azetidine structure with a stereochemistry as shown to hydroxyazetidine **16** on the basis of ^{1}H NMR, ^{13}C NMR spectroscopy, elemental analysis, and comparison of the spectral data with those of hydroxyazetidine **7**, which has a similar stereochemistry around C(4) and with those of its epimeric form, *viz.* hydroxyazetidine **3b**.

When nitrone **3d** was oxidized with PbO_2, a white solid was isolated in 16% yield. On the basis of ^{1}H NMR spectroscopy [δ: 4.88 (bs, 2H), 3.32 (s, 2H), 1.37 (s, 6H)], ^{13}C NMR spectroscopy [δ: 165.2 (s), 149.3 (s), 88.5 (d), 43.2 (d)] and mass spectrometry [*m/z* 698.378 (M^+, calcd. for $C_{44}H_{50}N_4O_4$: 698.383)] we assigned the dimeric structure **17** to the isolated compound (Scheme 5). The formation of the dimer **17** might be explained by a *radical* mechanism, via the abstraction of an activated hydrogen atom of the benzyl group in hydroxyazetidine **3d** and subsequent coupling of two benzylic radicals. Oxidation reactions with PbO_2 have been reported to occur through a radical mechanism[20] which might explain the observed radical dimerization. Similar dimerizations upon the oxidation of 1-hydroxypyrrolidines have been reported[11b].

From these results it might be concluded that four-membered cyclic ketonitrones react more readily with carbon-centered nucleophiles than acyclic ketonitrones and five-membered cyclic ketonitrones. Based on the conventional ring strain energy (CRSE) of cyclic hydrocarbons[21], a sequence in the reactivity of cycloalkenes towards hydrogenation has been given, which shows that four-membered rings and six-membered rings have a higher ring strain in the unsaturated form, in contrast with five-membered rings which have a lower ring strain in the unsaturated ring system.

From this sequence one may conclude that four-membered and six-membered cycloalkenes are converted more readily into the corresponding cycloalkanes than cyclopentenes into the corresponding cyclopentanes. *Cerichelli* et al.[22] and *Cox*[21] showed that the values of the ring strains of cyclic hydrocarbons can be used for the corresponding cyclic amines. The difference in rates of dimerization of five- and six-membered cyclic nitrones has been explained by *Thesing* and *Sirrenberg*[10c] using the difference in ring strain of these compounds and they concluded that six-membered cyclic nitrones dimerize more readily to give substituted piperidines, than five-membered cyclic nitrones, due to a larger relieve in *Pitzer* strain[23] in the six-membered species. In analogy with these results the high reactivity of 2,3-dihydroazete 1-oxides towards nucleophiles might be explained. The conversion of four-membered cyclic nitrones into 1-hydroxyazetidines might account for a large steric relieve of strain, whereas this is not the case in the conversion of five-membered cyclic nitrones into pyrrolidines. This might also account for the stability of 1-hydroxyazetidines, which, in contrast with other acyclic and cyclic hydroxylamines[10a], are not readily converted into imines.

It can be concluded that four-membered cyclic nitrones react in a stereoselective manner with nucleophiles, the nucleophile adding from the sterically less hindered side. In this way four-membered cyclic nitrones can be converted stereoselectively into 4-substituted nitrones and into highly substituted 1-hydroxyazetidines.

Experimental

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were recorded using a Bruker WP-80 spectrometer and ^{13}C NMR spectra ($CDCl_3$) were recorded with a Nicolet NT-200-WB spectrometer (Me_4Si as an internal standard). Mass spectra were obtained using a Varian Mat 311A spectrometer and IR spectra using a Perkin-Elmer 257 spectrophotometer. X-Ray data were obtained using a Philips PW1100 diffractometer. Elemental analyses were carried out by *E. Hoogendam* of the Laboratory of Chemical Analysis at the University of Twente. All reactions were carried out under an atmosphere of nitrogen.

Materials

Physical and spectroscopic properties of the nitrones **1a-d** have been described in ref. 1, the nitrones **2a-c** in ref. 2, and the nitrone **9** in ref. 3.

General procedure for the Grignard *additions to the nitrones* **1** *and* **2**

A solution of the *Grignard* reagent (4 mmol), which was prepared from magnesium (3 equiv.) and the appropriate halide (1.3 equiv.) in diethyl ether (4 ml), was added dropwise to a stirred solution of nitrone **1** or **2** (2 mmol) in dry benzene (6 ml). When the reaction was complete, the reaction mixture was hydrolyzed by the addition of a saturated NH_4Cl solution in water (25 ml). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 20 ml). The combined extracts were dried and filtered and the solution was concentrated under reduced pressure to give the hydroxyazetidines **3–6**.

(2α,3α,4β)-N,N,*4-Triethyl-1-hydroxy-2-methyl-3-phenyl-2-azetidinecarboxamide* (**3b**) *from* **1a** *and iodoethane*

After ½ h the reaction mixture was worked up as described above. Yield 90% (after purification by silica gel column chromatography; eluent: diethyl ether) (oil). ^{1}H NMR δ: 4.01 (ddd, *J* 8.3, 6.0 Hz, 1H, H–C-4), 2.92 (d, *J* 8.3 Hz, 1H, H–C-3), 1.78 (s, 3H, CH_3–C-2), 2.0–1.4 (m, 2H, $C\underline{H}_2CH_3$). ^{13}C NMR δ: 175.0 (s, C=O), 74.1 (d, C-4), 52.0 (d, C-3), 27.3 (t, $\underline{C}H_2CH_3$), 25.2 (q, CH_3), 10.0 (q, $CH_2\underline{C}H_3$). MS: accurate mass exp. 290.201 (M^+, calcd. for $C_{17}H_{26}N_2O_2$: 290.199).

(2α,3α,4β)-N,N-*Diethyl-1-hydroxy-2-methyl-3-phenyl-4-(2-propenyl)-2-azetidinecarboxamide* (**3c**) *from* **1a** *and 3-bromo-1-propene*

After ½ h the reaction mixture was worked up as described above. Yield 70% (after silica gel column chromatography; eluent: diethyl ether) (oil). ^{1}H NMR δ: 9.58 (bs, 1H, OH), 6.0–5.5 (m, 1H, $CH{=}CH_2$), 5.2–4.7 (m, 2H, $=CH_2$), 4.13 (ddd, *J* 8.0, 6.3 Hz, 1H, H–C-4), 2.92 (d, *J* 8.0 Hz, 1H, H–C-3), 1.75 (s, 3H, CH_3–C-2). ^{13}C NMR δ: 174.9 (s, C=O), 134.2 (d, $\underline{C}H{=}CH_2$), 116.6 (t, $=CH_2$), 75.0 (s, C-2), 72.0 (d, C-4), 51.6 (d, C-3), 38.5 (t, CH_2), 25.0 (q, $\underline{C}H_3$–C-2). MS: accurate mass exp. 302.196 (M^+, calcd. for $C_{18}H_{26}N_2O_2$: 302.199).

(2α,3α,4β)-N,N-*Diethyl-1-hydroxy-2-methyl-3-phenyl-4-(phenylmethyl)-2-azetidinecarboxamide* (**3d**) *from* **1a** *and (bromomethyl)benzene*

After ½ h the reaction mixture was worked up as described above. Yield 43% (after silica gel column chromatography; eluent: diethyl ether) (oil). ^{1}H NMR δ: 8.7 (bs, 1H, OH), 4.31 (ddd, *J* 3.9, 4.2, 2.6 Hz, 1H, H–C-4), 3.55–2.4 (m, 6H, $C\underline{H}_2$Ph and NCH_2), 1.75 (s, 3H, CH_3–C-2). ^{13}C NMR δ: 174.9 (s, C=O), 75.0 (s, C-2), 73.2 (d, C-4), 51.6 (d, C-3), 41.0, 40.0, and 39.6 (t, NCH_2 and $\underline{C}H_2$Ph), 25.0 (q, $\underline{C}H_3$–C-2). MS: accurate mass exp. 352.222 (M^+, calcd. for $C_{22}H_{28}N_2O_2$: 352.215).

(2α,3α,4β)-N,N-*Diethyl-1-hydroxy-2-methyl-3,4-diphenyl-2-azetidinecarboxamide* (**3e**) *from* **1a** *and bromobenzene*

After ½ h the reaction mixture was worked up as described above. Yield 86%; m.p. 148–150°C (diisopropyl ether). ^{1}H NMR δ: 10.1 (bs, 1H, OH), 5.20 (d, *J* 9.3 Hz, H–C-4), 3.15 (d, *J* 9.1 Hz, 1H, H–C-3), 1.87 (s, 3H, CH_3–C-2). ^{13}C NMR δ: 175.2 (s, C=O), 74.5 (s, C-2), 74.4 (d, C-4), 54.2 (d, C-3), 25.8 (q, $\underline{C}H_3$–C-2). MS: accurate mass exp. 338.196 (M^+, theor. 338.199). Anal. calcd. for $C_{21}H_{26}N_2O_2$ (338.199): C 74.53, H 7.74, N 8.28; found: C 74.55, H 8.07, N 8.35%.

(2α,3α)-N,N-*Diethyl-1-hydroxy-2,4,4-trimethyl-3-phenyl-2-azetidinecarboxamide* (**4a**) *from* **1b** *and iodomethane*

After ½ h the reaction mixture was worked up as described above. Yield 44%; m.p. 138–140°C (diisopropyl ether). ^{1}H NMR δ: 5.00 (bs, 1H, OH), 3.33 (s, 1H, H–C-3), 1.80 (s, 3H, CH_3–C-2), 1.59 (s, 3H, CH_3–C-4), 0.87 (s, 3H, CH_3–C-4). ^{13}C NMR δ: 173.9 (s, C=O), 73.3 (s, C-2), 67.4 (s, C-4), 59.4 (d, C-3), 26.1 (q, $\underline{C}H_3$–C-4), 24.3 (q, $\underline{C}H_3$–C-2), 20.1 (q, $\underline{C}H_3$–C-4). MS: accurate mass exp. 290.197 (M^+, theor. 290.199). Anal. calcd. for $C_{17}H_{26}N_2O_2$ (290.199): C 70.31, H 9.02, N 9.65; found: C 70.26, H 9.25, N 9.47%.

(2α,3α,4β)-N,N-*Diethyl-1-hydroxy-2,4-dimethyl-4-(methyl-d_3)-3-phenyl-2-azetidinecarboxamide* (**4b**) *from* **1b** *and iodomethane-d_3*

After ½ h the reaction mixture was worked up as described above. Yield 38%; m.p. 139–140°C (diisopropyl ether). ^{1}H NMR δ: 5.04 (bs, 1H, OH), 3.33 (s, 1H, H–C-3), 1.80 (s, 3H, CH_3–C-2), 0.89 (s, 3H, CH_3–C-4). MS: accurate mass exp. 293.217 (M^+, theor. 293.218). Anal. calcd. for $C_{17}H_{23}D_3N_2O_2$ (293.218): C 69.59, H 8.93, N 9.55; found: C 69.54, H 8.98, N 9.41%.

(2α,3α,4β)-N,N,*4-Triethyl-1-hydroxy-2,4-dimethyl-3-phenyl-2-azetidinecarboxamide* (**4c**) *from* **1b** *and iodoethane*

After ½ h the reaction mixture was worked up as described above. Yield 54%; m.p. 147–149°C (diisopropyl ether). ^{1}H NMR δ: 5.26 (bs, 1H, OH), 3.36 (s, 1H, H–C-3), 2.09 (q, *J* 7.3 Hz, 2H, $C\underline{H}_2CH_3$), 1.79 (s, 3H, CH_3–C-2), 0.97 (t, *J* 7.3 Hz, 3H, CH_3), 0.90 (s, 3H, CH_3–C-4). ^{13}C NMR δ: 174.1 (s, C=O), 73.1 (s, C-2), 70.9 (s, C-4), 56.9 (d, C-3), 29.6 (t, $\underline{C}H_2CH_3$), 22.5 (q, $\underline{C}H_3$–C-4), 20.6 (q, $\underline{C}H_3$–C-2), 8.7 (q, CH_2CH_3). MS: accurate mass exp. 304.209 (M^+, theor. 304.215). Anal. calcd. for $C_{18}H_{28}N_2O_2$ (304.215): C 71.02, H 9.27, N 9.20; found: C 71.55, H 9.11, N 8.90%.

(2α,3α,4β)-N,N-*Diethyl-1-hydroxy-2,4-dimethyl-3-phenyl-4-(2-propenyl)-2-azetidinecarboxamide* (**4d**) *from* **1b** *and 3-bromo-1-propene*

After ½ h the reaction mixture was worked up as described above. Yield 86%; m.p. 148–150°C (diisopropyl ether). ^{1}H NMR δ: 6.1–5.6 (m, 1H, $C\underline{H}{=}CH_2$), 5.3–4.9 (m, 2H, $=CH_2$), 3.37 (s, 1H, H–C-3), 2.79 (d, *J* 6.8 Hz, 2H, CH_2–C=), 1.77 (s, 3H, CH_3–C-2), 0.84 (s, 3H, CH_3–C-4). ^{13}C NMR δ: 173.9 (s, C=O), 134.8 (d, $\underline{C}H{=}CH_2$), 117.6 (t, $=CH_2$), 73.1 (s, C-2), 69.6 (s, C-4), 56.5 (d, C-3), 38.2 (t, CH_2), 23.7 (q, CH_3–C-2), 20.4 (q, $\underline{C}H_3$–C-4). MS: accurate mass exp. 316.214 (M^+, theor. 316.215). Anal. calcd. for $C_{19}H_{28}N_2O_2$ (316.215): C 72.12, H 8.92, N 8.85; found: C 72.10, H 8.77, N 8.87%.

(2α,3α,4β)-N,N-*Diethyl-1-hydroxy-2,4-dimethyl-3-phenyl-4-(phenylmethyl)-2-azetidinecarboxamide* (**4e**) *from* **1b** *and (bromomethyl)benzene*

After ½ h the reaction mixture was worked up as described above. Yield 24%; m.p. 98–100°C (diisopropyl ether). ^{1}H NMR δ: 3.68 (s, 1H, H–C-3), 3.43 and 3.35 (AB, *J* 4.0 Hz, 2H, $C\underline{H}_2$Ph), 1.89 (s, 3H, CH_3–C-2), 0.92 (s, 3H, CH_3–C-4). ^{13}C NMR δ: 174.2 (s, C=O), 73.3 (s, C-2), 70.7 (s, C-4), 56.1 (d, C-3), 42.4, 41.0, and 38.5 (t, NCH_2 and $\underline{C}H_2$Ph), 24.0 (q, $\underline{C}H_3$–C-2), 20.5 (q, $\underline{C}H_3$–C-4). MS: accurate mass exp. 366.231 (M^+, theor. 366.231). Anal. calcd. for $C_{23}H_{30}N_2O_2$ (366.231): C 75.38, H 8.25, N 7.64; found: C 75.48, H 8.58, N 7.37%.

(2α,3α,4β)-N,N-*Diethyl-4-cyano-1-hydroxy-2,4-dimethyl-3-phenyl-2-azetidinecarboxamide* (**4f**)

Nitrone **1b** (0.6 g; 2.30 mmol) was added to a solution of KCN (0.76 g; 11.5 mmol) in methanol (30 ml). After being stirred for 3 h, the solution was quenched with a saturated NH_4Cl solution in water (50 ml) and extracted with chloroform (3 × 30 ml). The combined extracts were dried and filtered and the chloroform was removed under reduced pressure. The remaining solid was triturated with diisopropyl ether to give **4f** as a white solid in 33% yield; m.p. 138–140°C (diisopropyl ether). ^{1}H NMR δ: 3.82 (s, 1H, H–C-3), 1.96 (s, 3H, CH_3–C-2), 1.24 (s, 3H, CH_3–C-4). ^{13}C NMR δ: 171.8 (s, C=O), 121.8 (s, C≡N), 74.8 (s, C-2), 63.8 (s, C-4), 55.3 (d, C-3), 21.4 (q, $\underline{C}H_3$–C-4), 17.6 (q, $\underline{C}H_3$–C-2). MS: accurate mass exp. 301.179 (M^+, theor. 301.179). Anal. calcd. for $C_{17}H_{23}N_3O_2$ (301.179): C 67.75, H 7.69, N 13.94; found: C 67.63, H 7.79, N 13.84%.

(2α,3α,4α)-N,N-*Diethyl-1-hydroxy-4-methyl-2,3,4-triphenyl-2-azetidinecarboxamide* (**5a**) *from* **1c** *and iodomethane*

After 20 h the reaction mixture was worked up as described above. Yield 42%; m.p. 172–173°C (diisopropyl ether). ^{1}H NMR δ: 4.64 (s, 1H, H–C-3), 4.13 (bs, 1H, OH), 1.66 (s, 3H, CH_3–C-4), 0.50 and −0.10 (t, *J* 7.1 Hz, 3H, NCH_2CH_3). ^{13}C NMR δ: 171.0 (s, C=O), 79.9 (s, C-4), 74.3 (s, C-2), 53.3 (d, C-3), 24.6 (q, $\underline{C}H_3$–C-4). MS: accurate mass exp. 414.225 (M^+, theor. 414.231). Anal. calcd.

for $C_{27}H_{30}N_2O_2$ (414.231): C 78.23, H 7.29, N 6.76; found: C 77.96, H 7.39, N 6.43%.

(2α,3α,4α)-N,N-*Diethyl-1-hydroxy-2,4-dimethyl-3,4-diphenyl-2-azetidinecarboxamide* (**5b**) *from* **1d** *and iodomethane*

After ½ h the reaction mixture was worked up as described above. Yield 64%; m.p. 181–183°C (diisopropyl ether). ^{1}H NMR δ: 3.66 (s, 1H, H–C-3), 1.95 (s, 3H, CH_3–C-2), 1.91 (s, 3H, CH_3–C-4). ^{13}C NMR δ: 173.7 (s, C=O), 73.4 (s, C-2 and C-4), 60.8 (d, C-3), 25.8 (q, $\underline{C}H_3$–C-2), 20.1 (q, $\underline{C}H_3$–C-4). MS: accurate mass exp. 352.215 (M^+, theor. 352.215). Anal. calcd. for $C_{22}H_{28}N_2O_2$ (352.215): C 74.97, H 8.01, N 7.95; found: C 75.16, H 8.30, N 7.76%.

(2α,3α,4α)-N,N,*4-Triethyl-1-hydroxy-2,3,4-triphenyl-2-azetidinecarboxamide* (**5c**) *from* **1c** *and bromoethane*

After ½ h the reaction mixture was worked up as described above. Yield 41%; m.p. (diisopropyl ether). ^{1}H NMR δ: 8.0–7.2 (m, 15 H, PhH), 6.25 (s, 1H, OH), 4.70 (s, 1H, HC-3), 3.6–2.0 (m, 6H, NCH_2 and CH_2), 0.87 and 0.62 (t, *J* 7.1 Hz, 3H, $NCH_2\underline{C}H_3$), 0.03 (t, *J* 6.9 Hz, 3H, $CH_2\underline{C}H_3$). MS: accurate mass exp. 428.245 (M^+, theor. 428.246). Anal. calcd. for $C_{28}H_{32}N_2O_2$ (428.246): C 78.47, H 7.53, N 6.54; found: C 78.33, H 7.35, N 6.35%.

(2α,3α,4α)-N,N-*Diethyl-1-hydroxy-2,3,4-triphenyl-4-(2-propenyl)-2-azetidinecarboxamide* (**5d**) *from* **1c** *and 3-bromo-1-propene*

After ½ h the reaction mixture was worked up as described above. Yield 82%; m.p. 148–150°C (diisopropyl ether). ^{1}H NMR δ: 6.1–5.5 (m, 1H, $CH{=}CH_2$), 5.1–4.6 (m, 2H, $=CH_2$), 4.72 (s, 1H, H–C-3), 2.84 (d, *J* 7.1 Hz, 2H, $CH_2C{=}$), 0.50 and −0.10 (t, *J* 7.1 Hz, 3H, $NCH_2\underline{C}H_3$). ^{13}C NMR δ: 171.0 (s, C=O), 135.1 (d, $\underline{C}H{=}CH_2$), 117.2 (t, $=CH_2$), 80.0 (s, C-4), 76.4 (s, C-2), 50.6 (d, C-3), 41.1 (t, $\underline{C}H_2$–C=). MS: accurate mass exp. 440.245 (M^+, theor. 440.245). Anal. calcd. for $C_{29}H_{32}N_2O_2$ (440.245): C 79.06, H 7.32, N 6.36; found: C 79.35, H 7.20, N 6.24%.

(2α,3α,4α)-N,N-*Diethyl-1-hydroxy-2,3,4-triphenyl-4-(phenylmethyl)-2-azetidinecarboxamide* (**5e**) *from* **1c** *and (chloromethyl)benzene*

After ½ h the reaction mixture was worked up as described above. Yield 37%; m.p. 174–175°C (diisopropyl ether). ^{1}H NMR δ: 4.97 (s, 1H, H–C-3), 3.34 (s, 2H, $C\underline{H}_2Ph$), 0.51 and −0.10 (t, *J* 7.1 Hz, 3H, $NCH_2\underline{C}H_3$). ^{13}C NMR δ: 171.0 (s, C=O), 80.1 (s, C-4), 78.1 (s, C-2), 51.3 (d, C-3), 42.5 (t, $\underline{C}H_2Ph$). MS: accurate mass exp. 490.251 (M^+, theor. 490.262). Anal. calcd. for $C_{33}H_{34}N_2O_2$ (490.262): C 80.78, H 6.98, N 5.71; found: C 80.70, H 6.82, N 5.52%.

(2α,3β,4α)-N,N-*Diethyl-1-hydroxy-2,4-dimethyl-3-(2,6-dichlorophenyl)-2-azetidinecarboxamide* (**6a**) *from* **2a** *and iodomethane*

After 17 h the reaction mixture was worked up as described above. Yield 61%; m.p. 153–155°C (diisopropyl ether). ^{1}H NMR δ: 5.8 (bs, 1H, OH), 5.00 (dq, *J* 6.1 and 10.5 Hz, 1H, H–C-4), 4.03 (d, *J* 10.5 Hz, 1H, H–C-3), 1.60 (s, 3H, CH_3–C-2), 1.33 (d, *J* 6.1 Hz, 3H, CH_3–C-4), 1.14 (t, *J* 6.9 Hz, 6H, NCH_2CH_3). ^{13}C NMR δ: 172.5 (s, C=O), 78.7 (s, C-2), 63.8 (d, C-4), 46.5 (d, C-3), 41.0 and 40.7 (t, NCH_2), 19.3 (q, $\underline{C}H_3$–C-2), 14.2 and 12.4 (q, $CH_2\underline{C}H_3$), 14.0 (q, $\underline{C}H_3$–C-4). MS: accurate mass exp. 344.099 (M^+, theor. 344.106). Anal. calcd. for $C_{16}H_{22}N_2O_2Cl_2$ (344.106): C 55.66, H 6.42, N 8.11; found: C 55.75, H 6.44, N 8.07%.

(2α,3β,4β)-N,N-*Diethyl-1-hydroxy-2,4-dimethyl-3-(2,4,6-trimethylphenyl)-4-phenyl-2-azetidinecarboxamide* (**6b**) *from* **2b** *and iodomethane*

After 17 h the reaction mixture was worked up as described above. Oil; yield 84%, after purification by silica gel column chromatography (eluent: diethyl ether). ^{1}H NMR δ: 10.6 (bs, 1H, OH), 4.34 (s, 1H, H–C-3), 2.43, 2.16, and 1.90 (s, 3H, $ArC\underline{H}_3$), 1.77 (s, 3H, CH_3–C-4), 1.61 (s, 3H, CH_3–C-2). ^{13}C NMR δ: 181.5 (s, C=O), 74.5 (s, C-2), 69.3 (s, C-4), 51.8 (d, C-3), 27.5 (q, $\underline{C}H_3$–C-4), 22.6, 21.5, 21.3, and 20.6 (q, $\underline{C}H_3$–C-2 and $ArCH_3$). MS: accurate mass exp. 394.260 (M^+, calcd. for $C_{25}H_{34}N_2O_2$: 394.262).

(2α,3β,3β)-N,N-*Diethyl-1-hydroxy-2-methyl-4-(methyl-d$_3$)-3-(2,4,6-trimethylphenyl)-4-phenyl-2-azetidinecarboxamide* (**6c**) *from* **2b** *and iodomethane-d$_3$*

After 17 h the reaction mixture was worked up as described above. ^{1}H NMR δ: 10.8 (bs, 1H, OH), 4.34 (s, 1H, H–C-3), 2.43, 2.16, and 1.90 (s, 3H, $ArC\underline{H}_3$), 1.61 (s, 3H, CH_3–C-2).

(2α,3β,4β)-N,N-*Diethyl-4-ethyl-1-hydroxy-2-methyl-3-(2,4,6-trimethylphenyl)-4-phenyl-2-azetidinecarboxamide* (**6d**) *from* **2b** *and iodoethane*

After 17 h the reaction mixture was worked up as described above. Yield 78%, after purification by silica gel column chromatography (eluent: diethyl ether) (oil). ^{1}H NMR δ: 4.10 (s, 1H, H–C-3), 2.43, 2.16, and 1.90 (s, 3H, $ArC\underline{H}_3$), 2.10 (m, 2H, $C\underline{H}_2CH_3$), 1.62 (s, 3H, CH_3–C-2), 0.75 (t, *J* 7.1 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR δ: 181.8 (s, C=O), 78.0 (s, C-2), 69.2 (s, C-4), 50.5 (d, C-3), 32.6 (t, $\underline{C}H_2CH_3$), 22.6, 21.6, 21.3, and 20.6 (q, $\underline{C}H_3$–C-2 and $ArCH_3$), 9.7 (q, CH_2CH_3). MS: accurate mass exp. 408.272 (M^+, calcd. for $C_{26}H_{36}N_2O_2$: 408. 278).

(2α,3β,4β)-N,N-*Diethyl-1-hydroxy-2,4-dimethyl-3-(2-methoxynaphthalenyl)-4-phenyl-2-azetidinecarboxamide* (**6e**) *from* **2c** *and iodomethane*

After 17 h the reaction mixture was worked up as described above. Yield 48%, after purification by silica gel column chromatography (eluent: diethyl ether) (oil). ^{1}H NMR δ: 5.12 (s, 1H, H–C-3), 1.82 (s, 3H, CH_3–C-4), 1.54 (s, 3H, CH_3–C-2). ^{13}C NMR δ: 181.6 (s, C=O), 74.4 (s, C-2), 69.2 (s, C-4), 56.8 (q, OCH_3), 46.9 (d, C-3), 27.2 (q, $\underline{C}H_3$–C-4), 21.4 (q, $\underline{C}H_3$–C-2). MS: accurate mass exp. 432.234 (M^+, calcd. for $C_{27}H_{32}N_2O_3$: 432.241).

(2α,3α,4α)-N,N-*Diethyl-1-hydroxy-2,4-dimethyl-3-phenyl-2-azetidinecarboxamide* (**7**)

Nitrone **1b** (0.55 g; 2 mmol) was added in small portions at 0°C to a suspension of $LiAlH_4$ (0.16 g; 4 mmol) in freshly distilled tetrahydrofuran (20 ml). After the mixture was stirred for 1½ h, the excess of $LiAlH_4$ was destroyed by the dropwise addition of a 2*N* NaOH solution and the mixture was filtered. The tetrahydrofuran was removed under reduced pressure and the remaining solid was triturated with petroleum ether to give azetidine **7** as a white solid in 80% yield. See for characteristic data ref. 7.

(2α,3α,4α)-N,N-*Diethyl-1-hydroxy-2,4-dimethyl-3-phenyl-2-azetidinemethanamine* (**8**)

Hydroxyazetidine **7** (0.56 g; 2 mmol) was added in small portions at 0°C to a suspension of $LiAlH_4$ (0.16 g; 4 mmol) in freshly distilled tetrahydrofuran (20 ml). After the addition the reaction mixture was stirred at room temperature for 5 h and was worked up as described for **7**. Yield 85%, after trituration with diisopropyl ether. See for characteristic data ref. 7.

1-Hydroxy-3,3-diphenylazetidine (**10**)

Nitrone **9**[3] (2 mmol) was added to a solution of $NaBH_4$ (0.3 g; 8 mmol) in methanol (10 ml). After the mixture was stirred for 2 h, water (50 ml) was added and the resulting mixture was extracted with chloroform (3 × 20 ml). The combined extracts were dried and filtered and the chloroform was removed under reduced pressure. The remaining solid was triturated with petroleum ether to give the azetidine **10** in 86% yield. See for characteristic data ref. 3.

(2α,3α,4α)-N,N-*Diethyl-1-hydroxy-2-methyl-3,4-diphenyl-2-azetidinemethanamine* (**11**)

Hydroxyazetidine **1d** (0.34 g; 1 mmol) was added in small portions at 0°C to a suspension of $LiAlH_4$ (0.08 g; 2 mmol) in freshly distilled tetrahydrofuran (10 ml). After the addition the reaction was stirred at 45°C for 2 h and was worked up as described for **7**. Yield 67%. ^{1}H NMR δ: 5.25 (d, *J* 10.0 Hz, 1H, H–C-4), 3.60 (d, *J* 10.0 Hz, 1H, H–C-3), 2.6–2.1 (m, 6H, NCH_2). MS: accurate mass exp. 324.218 (M^+, calcd. for $C_{21}H_{28}N_2O$: 324.220).

(2α,3α,4β)-N,N-*Diethyl-1-hydroxy-2-methyl-4-(nitromethyl)-3-phenyl-2-azetidinecarboxamide* (**12**)

Nitrone **1a** (0.30 g; 1.14 mmol) was added to a suspension of the sodium salt of nitromethane [prepared from 25 mg (1.10 mmol) sodium and 0.14 g (2.3 mmol) nitromethane in dry ethanol (10 ml)]. The solution was stirred at room temperature for 17 h and quenched by the addition of acetic acid (1 ml). The reaction mixture was extracted with chloroform (3 × 20 ml) and the organic layer was neutralized with a saturated $NaHCO_3$ solution, dried and filtered. The chloroform was removed under reduced pressure leaving a yellow coloured oil. The product was purified by silica gel column chromatography (eluent: chloroform/ethyl acetate 1 : 3 v/v), leaving a viscous oil which solidified after a longer period of storage. Trituration with diisopropyl ether afforded **12** as a white solid. Yield 49%; m.p. 111–112°C (diisopropyl ether). ^{1}H NMR δ: 4.75 (m, 3H, H–C-4 and CH_2NO_2), 3.6–2.0 (m, 4H, NCH_2), 3.25 (d, *J* 8.1 Hz, H–C-3), 1.70 (s, 3H, CH_3–C-2), 0.96 and 0.62 (t, *J* 7.0 Hz, 3H, CH_3). ^{13}C NMR δ: 169.6 (s, C=O), 89.0 (d, C-4), 75.7 (t, CH_2NO_2), 72.6 (s, C-2), 62.9 (d, C-3), 28.2 (q, $\underline{C}H_3$–C-2). MS: accurate mass exp. 321.168 (M^+, theor. 321.169). Anal. calcd. for $C_{16}H_{23}N_3O_4$ (321.169): C 59.80, H 7.21, N 13.08; found: C 59.62, H 7.29, N 12.99%.

(E)-Cis-N,N-*Diethyl-2,3-dihydro-2-methyl-4-[2-(4-nitrophenyl)-ethenyl]-3-phenyl-2-azetecarboxamide 1-oxide* (**13**)

To a solution of nitrone **1b** (300 mg; 1.10 mmol) and 4-nitrobenzaldehyde (181 mg; 1.20 mmol) in 5 ml of dry ethanol was added a catalytic amount of powdered potassium hydroxide (16 mg; 0.28 mmol). The reaction mixture was stirred at 45°C for ½ h and subsequently quenched by the addition of a saturated NH_4Cl solution in water (20 ml). The mixture was extracted with chloroform (3 × 20 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a yellow coloured solid. Purification by column chromatography, using aluminum oxide (act. IV; eluent: chloroform/diethyl ether 1 : 1 (v/v)), followed by trituration with diisopropyl ether gave compound **13**. Yield 41%; m.p. 133–135°C (chloroform/diisopropyl ether). ^{1}H NMR δ: 8.13 and 7.45 (AB, *J* 9.0 Hz, 2H, ArH), 7.35 (s, 5H, ArH), 6.92 and 7.04 (AB, *J* 16.6 Hz, 2H, $C\underline{H}$=$C\underline{H}$Ph), 4.16 (s, 1H, H–C-3), 3.5–2.13 (m, 4H, NCH_2), 2.02 (s, 3H, CH_3), 0.92 and 0.66 (t, *J* 7.1 Hz, 3H, CH_3). ^{13}C NMR δ: 165.2 (s, C=O), 146.8 (s, C-4), 142.2 (s, $ArNO_2$), 132.1 (d, CH=$\underline{C}$HPh), 115.5 (d, $\underline{C}$H=CHPh), 89.8 (s, C-2), 52.8 (d, C-3), 41.3 and 39.1 (t, NCH_2), 20.6 (q, $\underline{C}H_3$C-3), 13.3 and 11.6 (q, $CH_2\underline{C}H_3$). MS: accurate mass exp. 407.184 (M^+, calcd. for $C_{23}H_{25}N_3O_4$: 407.185).

(E,E)-N,N-*Diethyl-4-(hydroximino)-2-methyl-6-(4-nitrophenyl)-3-phenyl-2,5-hexadienamide* (**14**)

Yield 43%. ^{1}H NMR δ: 8.10 and 7.52 (AB, *J* 8.8 Hz, 2H, ArH), 7.53 and 6.96 (AB, *J* 16.6 Hz, 2H, $C\underline{H}$=$C\underline{H}$Ph), 7.6–7.1 (m, 5H, PhH), 3.8–2.7 (m, 4H, NCH_2), 2.07 (s, 3H, CH_3), 1.5–0.75 (m, 6H, $NCH_2C\underline{H}_3$).

General procedure for the oxidation of the hydroxyazetidines **3** *with lead(IV) oxide*

A solution of the hydroxyazetidine (0.72 mmol) in dry dichloromethane (3 ml) was added to a suspension of active PbO_2[19] (0.24 g; 1.10 mmol) in dry dichloromethane (10 ml). The suspension was stirred at room temperature for 2 h and $MgSO_4$ was added. The suspension was filtered over Hyflo and the dichloromethane was removed under reduced pressure to give a solid which was triturated with diisopropyl ether.

Cis-N,N-*Diethyl-2,3-dihydro-4-ethyl-2-methyl-3-phenyl-2-azetecarboxamide 1-oxide* (**15**) *from* **3b**

Yield 82%. See for characteristic data ref. 2.

(2α,3α,4α)-N,N-*Diethyl-4-ethyl-1-hydroxy-2-methyl-3-phenyl-2-azetidinecarboxamide* (**16**)

Nitrone **15** (0.57 g; 2 mmol) was added to a solution of $NaBH_4$ (0.3 g; 8 mmol) in methanol (10 ml). After the mixture was stirred for 2 h, the reaction mixture was worked up as described for compound **10**. Yield 98%; m.p. 123–124°C (diisopropyl ether). ^{1}H NMR δ: 6.25 (bs, 1H, OH), 3.75 (dt, *J* 8.9 and 6.0 Hz, H–C-4), 3.44 (d, *J* 8.9 Hz, 1H, H–C-3), 1.68 (s, 3H, CH_3–C-2), 1.65–1.49 (m, 1H, CH_2CH_3), 1.3–1.08 (m, 1H, $C\underline{H}_2CH_3$), 0.66 (t, *J* 6.6 Hz, $CH_2C\underline{H}_3$). ^{13}C NMR δ: 172.9 (s, C=O), 73.7 (s, C-2), 69.1 (d, C-4), 50.9 (d, C-3), 22.5 (t, $\underline{C}H_2CH_3$), 17.1 (q, $\underline{C}H_3$–C-2), 9.9 (q, $CH_2\underline{C}H_3$). MS: accurate mass exp. 290.195 (M^+, theor. 290.199). Anal. calcd. for $C_{17}H_{26}N_2O_2$ (290.199): C 70.31, H 9.02, N 9.65; found: C 70.34, H 8.98, N 9.72%.

*4,4'-(1,2-Diphenyl-1,2-ethanediyl)bis(*cis-N,N-*diethyl-2,3-dihydro-2-methyl-3-phenyl-2-azetecarboxamide)* (**17**) *from* **3d**

Yield 16%; m.p. 217–218°C (diisopropyl ether). ^{1}H NMR δ: 4.88 (bs, 2H, C$\underline{H}$Ph), 3.32 (s, 2H, H–C-3), 1.37 (s, 6H, CH_3–C-2). ^{13}C NMR δ: 165.2 (s, C=O), 149.1 (s, C-4), 88.5 (s, C-2), 53.1 (d, C-3), 43.2 (d, $\underline{C}$HPh), 19.5 (q, $\underline{C}H_3$–C-2). MS: accurate mass exp. 698.378 (M^+, calcd. for $C_{44}H_{50}N_4O_4$: 698.383)[24].

X-ray crystal structure determination of **4d**

Crystals of **4d** belong to the tetragonal space group $P4_12_12$ (or $P4_32_12$) with cell constants $a = b = 10.976$ (3), $c = 31.016(7)$ Å, $Z = 8$, $d_c = 1.12\ g \cdot cm^{-3}$. Data collection parameters: MoK_α radiation, $\lambda = 0.7107$ Å, graphite monochromator, ω-scan mode, $3 < \omega < 22.5°$, scan width (ω) 1.4°. Determination and refinement based on 1054 reflections with $I > 3\sigma(I)$. The structure was solved by direct methods (MULTAN)[25] and was refined by full-matrix least-squares, using the SDP package[26]. Hydrogen atoms were found from difference *Fourier* synthesis and included in the refinement with isotropic thermal parameters. The other atoms were refined anisotropically. The hydrogen at the ring oxygen atom could not be found and has not been incorporated in the refinement. Final *R* factor 2.9%. The absolute configuration has not been determined.

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