On the Stereoselectivity of Epoxide Formation using Dimethyloxosulphonium Methylide. *X*-Ray Structure of (5*SR*)-5-[(1*RS*)-1-Methyl-2-oxacyclopropyl]pyrrolidin-2-one

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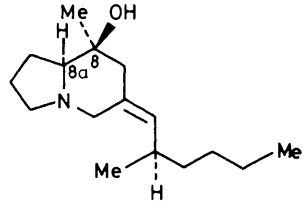
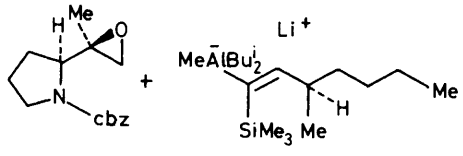
As background to a proposed dendrobatid toxin 251 D synthesis, the stereoselectivity of epoxide formation from 5-acetylpyrrolidin-2-one (4) and dimethyloxosulphonium methylide was investigated. In THF under ' salt-free ' conditions, the major epoxide product, selectivity 78 : 22, was (5*SR*)-5-[(1*SR*)-1-methyl-2-oxacyclopropyl]pyrrolidin-2-one (5), whereas addition of anhydrous $ZnCl_2$ to the reaction mixture reversed the stereoselectivity to give epoxides (5) and (6) in the ratio 23 : 77. Configurations were assigned to these epoxides by comparison of n.m.r. spectra of the derived carbamates (15) and (16), and by an *X*-ray structure determination for epoxide (6). Related reactions are discussed.

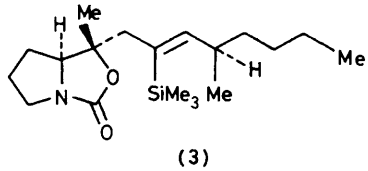
The determination of the structure of the dendrobatid toxin 251 D (1) reported in 1980 was of interest since it led to structural assignments to several pumiliotoxin A alkaloids.[1] Because of the biological activity and scarcity of some of these alkaloids there is considerable interest in their total synthesis. In 1981 Overman reported an elegant synthesis of toxin 251 D (1) in which the epoxide (2) was treated with a vinyl alanate to give the carbamate (3) which was subsequently hydrolysed and cyclized to toxin 251 D (1) on treatment with paraformaldehyde and acid.[2] We had intended to attempt a synthesis of toxin 251 D by a route which used epoxide (5) to establish the required configuration at C-8 and C-8a. In view of Overman's work this project has been discontinued; however we here wish to report on the stereoselectivity of the formation of the epoxides (5) and (6) from 5-acetylpyrrolidin-2-one (4) and dimethyloxosulphonium methylide together with related reactions.



(1)



(2)



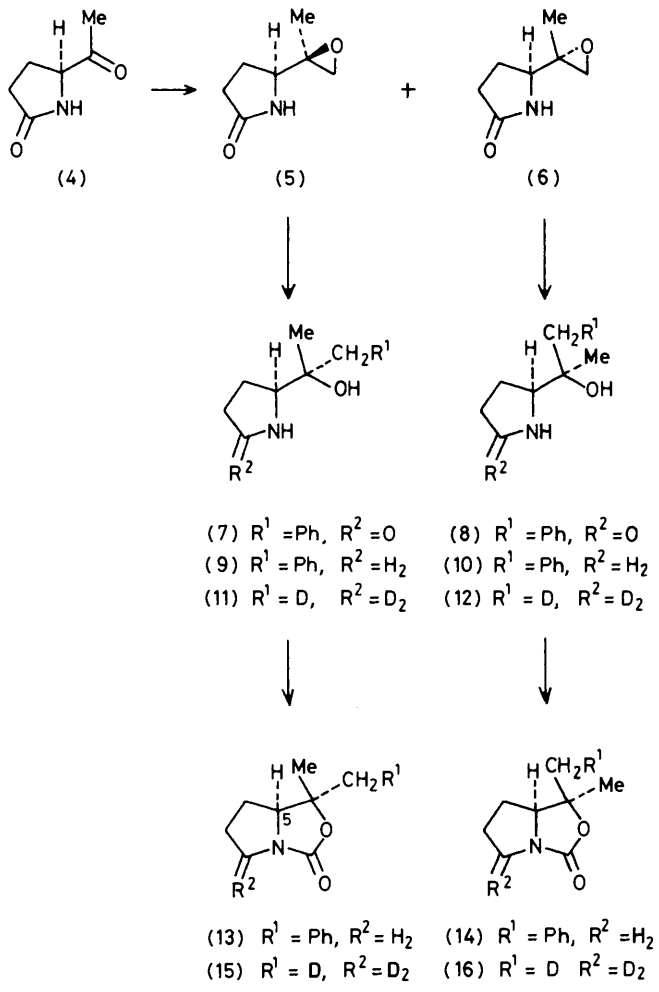
(3)

Results and Discussion

Racemic 5-acetylpyrrolidin-2-one (4) was prepared in two steps from L-glutamic acid by heating a mixture of the acid, pyridine, and acetic anhydride under reflux (a Dakin-West reaction), followed by hydrolysis of the *N*-acetyl product using aqueous Na_2CO_3.[3] Treatment of 5-acetylpyrrolidin-2-one (4) with 2.2 mol equiv. of a solution of dimethyloxosulphonium methylide in tetrahydrofuran (THF) † gave two epoxides, purified as a mixture by short-column chromatography, and identified as the epoxides (5) and (6), ratio 78 : 22, yield 48%. Recrystallization gave the major epoxide (5) free of the minor isomer (6). Because it was thought that the presence of a metal cation might influence the stereoselectivity by chelating with the amide and ketone groups, the dimethyloxosulphonium methylide reaction was repeated in the presence of anhydrous $ZnCl_2$. Under these conditions improved yields were obtained if the reaction mixture in THF was heated under reflux (66%), but the stereoselectivity was reversed. The epoxide (6) was now the major product, (5) : (6) = 23 : 77, and was obtained pure, free of its isomer (5), by recrystallization. When an attempt was made to use anhydrous $MgBr_2$ to influence the stereoselectivity the yield dropped markedly to 10%, although the stereoselectivity was better, 10 : 90, in favour of the epoxide (6).

Spectroscopic data were used to assign gross structures to epoxides (5) and (6). In order to determine epoxide stereochemistry, the major epoxide obtained under ' salt-free ' conditions, later identified as (5), was treated successively with phenylmagnesium bromide–copper(I) iodide,[6] lithium aluminium hydride, and *N*,*N*'-carbonyldi-imidazole, to give the bicyclic carbamate (13) *via* the hydroxypyrrolidinone (7) and hydroxypyrrolidine (9) (Scheme 1). However irradiation of the methyl singlet of the carbamate (13) gave only a small (1.5%) n.O.e. enhancement of 5-H which did not permit an unambiguous assignment of stereochemistry to be made; however, the configuration later assigned to the epoxide (5) is consistent with the small n.O.e. effect observed here. When this sequence of reactions was attempted starting with the major epoxide obtained in the presence of $ZnCl_2$, later identified as isomer (6), several problems were encountered, This epoxide reacted much more slowly than its isomer with phenylmagnesium bromide–copper(I) iodide, and only a low yield (29%) of hydroxypyrrolidinone (8) was obtained together with several unidentified side-products. Moreover the cyclization of the hydroxypyrrolidine (10) was not successful, perhaps because of excessive steric hindrance to ring closure

† Prepared by heating a suspension of trimethyloxosulphonium chloride and NaH in THF under reflux, and then filtering the cooled mixture under nitrogen using a Schlenk tube.[4,5]



Scheme 1

by the 4-phenylmethyl substituent which would be forced into an *endo*-position.

A preliminary assignment of stereochemistry was made to the epoxides (5) and (6) by reducing them using $LiAlD_4$ to give the deuteriated hydroxypyrrolidines (11) and (12) which were cyclized by *N,N'*-carbonyldi-imidazole to give the bicyclic carbamates (15) and (16). These two carbamates are identical apart from the positions of the deuterium labels. The deuteriated carbamate derived from the major epoxide obtained under ' salt-free ' conditions showed a singlet at 22.97 p.p.m., and a triplet at 28.8 p.p.m., downfield from $SiMe_4$, in its proton decoupled ^{13}C n.m.r. spectrum. For the deuteriated carbamate derived from the major epoxide obtained in the presence of $ZnCl_2$, the peak at 22.76 p.p.m. was present as a triplet, and the peak at 28.85 p.p.m. was present as a singlet. Since the carbon of the *endo* 4-methyl substituent would be expected to be shielded relative to the carbon of the *exo* 4-methyl substituent,[2] these data show that the major epoxide from the ' salt-free ' conditions had given the carbamate (15), and that the major epoxide from the $ZnCl_2$ conditions had given the carbamate (16). Thus the configurations of the epoxides were established.

To confirm these stereochemical assignments the major epoxide from the $ZnCl_2$ reaction was studied by *X*-ray diffraction. The Figure shows a computer-drawn projection of the molecule which clearly establishes the relative configuration of the two chiral centres as shown in formula (6).

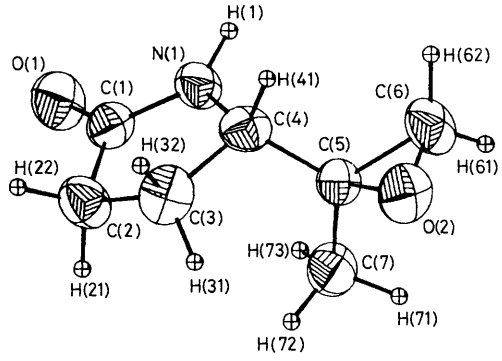


Figure. Molecular structure of epoxide (6) showing the crystallographic numbering scheme used (SNOOPI)

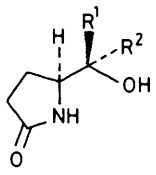
This structure determination confirms the stereochemistry of all the intermediates shown in Scheme 1.

For comparison the stereochemistry of the reaction between 5-acetylpyrrolidin-2-one (4) and phenylmagnesium bromide was examined. Treatment of the keto-lactam (4) with phenylmagnesium bromide gave a mixture of two adducts identified on the basis of their spectroscopic data as the hydroxylactams (17) and (18), ratio 71 : 29. These isomers could not be separated, but were reduced as a mixture by $LiAlH_4$, and the amino-alcohols so obtained treated with *N,N'*-carbonyldiimidazole to give the carbamates (19) and (20) which could be separated by chromatography. The major carbamate showed only a small (<1%) n.O.e. enhancement of the methine proton, 5-H, on irradiation of the exocyclic methyl singlet, whereas for the minor carbamate a significant (12%) n.O.e. enhancement was observed. The major carbamate was therefore identified as (19), and consequently the major hydroxylactam as isomer (17). The stereoselectivity of this reaction would appear to parallel that of the dimethyloxosulphonium methylide reaction in the absence of $ZnCl_2$.

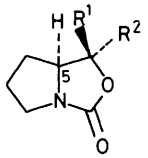
Finally, epoxide formation from the open-chain keto-amide (21) [8] and dimethyloxosulphonium methylide was examined. Use of 1.1 equivalents of ylide gave a good yield of epoxide product shown by ^1H n.m.r. spectroscopy to consist predominantly of one isomer. A small amount (*ca.* 5%) of the second isomer was detected in the crude product mixture, but could not be obtained pure. Reduction of the major epoxide with $LiAlD_4$, and cyclization of the hydroxyamine so obtained using *N,N'*-carbonyldi-imidazole gave a carbamate identified as (24) on the basis of its spectroscopic data. In particular, the D-labelled methyl group gave a 2 H broadened singlet at δ 1.44 in its ^1H n.m.r. spectrum considerably less shielded than the 3 H singlet at δ 0.96 due to the unlabelled methyl group. A phenyl ring is known to shield a vicinal *cis* methyl substituent in 5-membered ring by *ca.* 0.5 p.p.m. over a vicinal *trans* methyl substituent.[9] Thus the major epoxide was identified as isomer (22), and the stereoselectivity of this dimethyloxosulphonium ylide reaction would appear to follow that of the 5-acetylpyrrolidin-2-one case in the absence of $ZnCl_2$.

Thus the reaction between dimethyloxosulphonium methylide and 5-acetylpyrrolidin-2-one (4) does proceed with modest stereoselectivity, 78 : 22, to give the epoxide (5) as major product. This epoxide has the required stereochemistry for a dendrobatid toxin 251 D precursor and should enable the relative configuration at C-8 and C-8a of the toxin to be controlled.

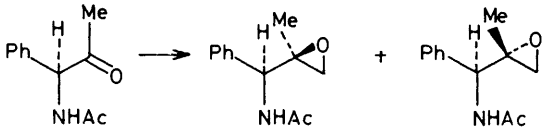
It is difficult to provide an explanation for this stereoselectivity without further data. The stereoselectivity of *irreversible* nucleophilic additions to aldehydes and ketones



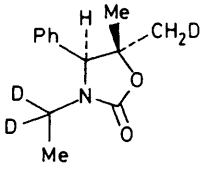
(17) R^1 = Me, R^2 = Ph
(18) R^1 = Ph, R^2 = Me



(19) R^1 = Me, R^2 = Ph
(20) R^1 = Ph, R^2 = Me

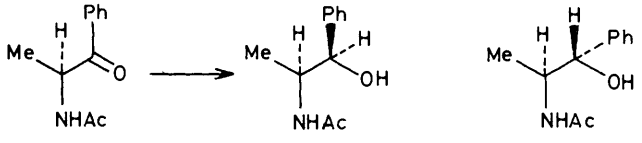


(21) (22) (23)



(24)

Scheme 2

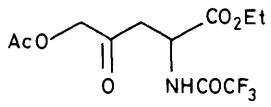


(25) (26) (27)

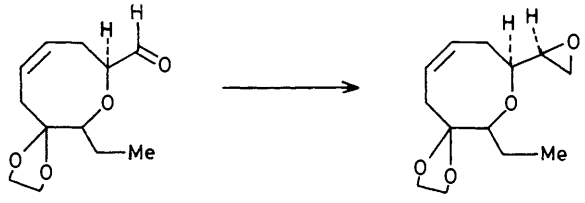
with chiral α-carbons bearing heteroatom substituents is usually discussed in terms of Cram's cyclic model, or in terms of Felkin's model or the ' dipolar repulsion model '.[10] The $NaBH_4$ reduction of amido-ketone (25) gives a mixture of amido-alcohols (26) and (27) in which isomer (26) predominates, (26) : (27) = 77 : 23, in agreement with Cram's cyclic model.[11] The stereoselectivity of the reaction between 5-acetylpyrrolidin-2-one (4) and phenylmagnesium bromide is similar and may be due to Mg^{2+} chelation between the deprotonated lactam and the ketone carbonyl oxygen.

However dimethyloxosulphonium ylide-ketone reactions are believed to involve a fast *reversible* carbonyl attack to give a betaine which then slowly cyclizes to an epoxide with loss of dimethyl sulphoxide.[12] The overall stereochemistry of these reactions depends upon the relative rates of fragmentation of the two possible intermediate betaines, as well as upon their rates of formation.

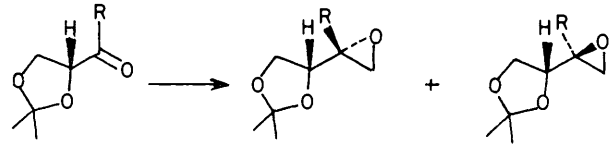
There are few results in the literature on the stereochemistry of reactions between dimethyloxosulphonium methylide and ketones with chiral α-carbons bearing heteroatom substituents. Reactions of benzoin [13] and the amidoketone (28) [14] with dimethyloxosulphonium methylide have been reported but the stereochemistry of the epoxide products was not



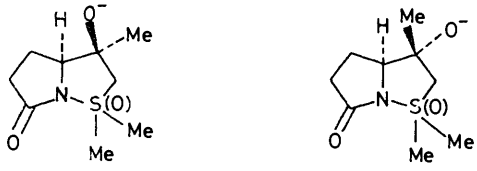
(28)



(29) (30)



(31) R = H 30 : 70
(32) R = Me 35 : 65
(33) R = Et 45 : 55



(34) (35)

determined. During a synthesis of (±)-laurencin, the aldehyde (29) was converted into the epoxide (30) using dimethyloxosulphonium methylide.[15] Only one isomer was isolated from this reaction which was carried out in Me_2SO in contrast to the reactions discussed here. Nevertheless the selective formation of the epoxide (30) does parallel the reactions between dimethyloxosulphonium methylide and the amido-ketones (4) and (21), although model studies for the laurencin synthesis were less stereoselective.[15] In contrast to these results, the reverse stereoselectivity was reported for the reactions between the triose derivatives (31)—(33) and dimethyloxo-sulphonium methylide in Me_2SO, although the selectivity was rather low being in the range 70 : 30 to 55 : 45.[16]

In the case of 5-acetylpyrrolidin-2-one (4), the intermediate betaines may best be represented by formulae (34) and (35) showing appreciable N–S bonding.[17] Loss of dimethyl sulphoxide from the betaine (34) to give the epoxide (5) would appear to involve less strain than loss of dimethyl sulphoxide from the betaine (35); here the methyl substituent would be compressed against the pyrrolidine ring in the transition state for elimination. Similar arguments would explain the stereoselectivity of epoxide formation from the amido-ketone (21).

The influence of $ZnCl_2$ in reversing the stereoselectivity of epoxide formation from 5-acetylpyrrolidin-2-one (4) is, as far as we are aware, unprecedented. The precise role of the $ZnCl_2$ in changing this stereoselectivity is not yet clear.

Further work is in progress to elucidate the factors which control the stereochemistry of these and related reactions.

Experimental

M.p.s were measured on a Kofler hot-stage apparatus, and are uncorrected. I.r. spectra were recorded on Perkin Elmer 257 and 297 spectrophotometers, n.m.r. spectra on a Bruker WH 300 spectrometer, and mass spectra on a VG Micromass ZAB 16F mass spectrometer.

Microanalyses were carried out by Dr. F. B. Strauss of the Dyson Perrins Laboratory.

Short column chromatography was used for preparative purposes using Merck silica gel for t.l.c. (M.F.C. without binder), and glass plates coated with silica gel blend 41 were used for analytical t.l.c.

All solvents were dried and distilled before use.

Dimethyloxosulphonium methylide was prepared by heating a mixture of sodium hydride (1.05 mol equiv.; 50% dispersion in oil, washed with light petroleum) and trimethyloxosulphonium chloride (best prepared from trimethyloxosulphonium iodide and benzyltributylammonium chloride [4]) in THF under reflux for 2—2.5 h, and filtering the cooled mixture under anhydrous nitrogen using a Schlenk tube.[5] The strength of the ylide solutions was estimated by quenching an aliquot with water and titrating it against standard HCl using phenolphthalein as indicator. Ether refers to diethyl ether.

5-Acetylpyrrolidin-2-one (4).—1,5-Diacetylpyrrolidin-2-one (22.2 g) [3] and Na_2CO_3 (55.8 g) were dissolved in water (300 ml), and the solution stirred at 20 °C for 5 h. The pH was adjusted to 7 using dilute HCl, and the product extracted into CH_2Cl_2 (350 ml) using a continuous extraction apparatus (25 h). After drying ($MgSO_4$), and concentration under reduced pressure, the organic phase gave an off-white solid (9.46 g) which recrystallized from ethyl acetate to give *5-acetylpyrrolidin-2-one* (4), m.p. 74—76 °C; $\nu_{max.}$ ($CHCl_3$) 3 300, 1 720, 1 690, 1 422, 1 360, and 1 187 cm^{-1}; δ($CDCl_3$) 2.02 (1 H, m, HC*H*), 2.22 (3 H, s, $COCH_3$), 2.40 (3 H, m, HC*H*CH_2), 4.25 (1 H, dd, *J* 8.5, 9.5 Hz, 5-H), and 7.33br (1 H, s, NH); *m/z* 128 ($M^+ + 1$) and 84 ($M^+ - COCH_3$) (Found: C, 56.7; H, 6.9; N, 10.8. $C_6H_9NO_2$ requires C, 56.7; H, 7.1; N, 11.0%).

Epoxide Formation from 5-Acetylpyrrolidin-2-one (4).—(a) *Under 'salt-free' conditions.* 5-Acetylpyrrolidin-2-one (4) (1.6 g) in anhydrous THF (60 ml) was added to dimethyloxosulphonium methylide [from NaH (50% dispersion in oil; 1·48 g) and trimethyloxosulphonium chloride (3.76 g)] in THF (30 ml) and the mixture stirred under nitrogen for 2 h at 20 °C and then for 1 h at 55 °C. After cooling, concentrated aqueous NH_4Cl was added, and the product extracted into CH_2Cl_2. The organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure to give a residue (1.56 g) which was chromatographed on silica (41 g) with ether–methanol (5 : 1) as eluant, to give a mixture of the epoxides (5) and (6) (893 mg), ratio (5) : (6) = 78 : 22 (^1H n.m.r.), which could not be separated by short-column chromatography. Recrystallization of a portion from ethyl acetate–light petroleum gave (5SR)-5-[(1SR)-1-*methyl*-2-*oxacyclopropyl*]*pyrrolidin*-2-*one* (5), m.p. 86—87 °C; $\nu_{max.}$ ($CHCl_3$) 3 425, 3 200, 1 690, 1 070, 990, 910, and 865 cm^{-1}; δ($CDCl_3$) 1.34 (3 H, s, CH_3), 2.05 and 2.38 (1 H and 3 H respectively, both m, CH_2CH_2), 2.66 and 2.73 (each 1 H, d, *J* 5 Hz, epoxide H), 3.49 (1 H, dd, *J* 5, 7 Hz, 5-H), and 6.24br (1 H, s, NH); *m/z* (Cl) 142 ($M^+ + H$) (Found: C, 59.4; H, 7.7; N, 9.85. $C_7H_{11}NO_2$ requires C, 59.55; H, 7.8; N, 9.95%).

(b) *In the presence of* $ZnCl_2$. Trimethyloxosulphonium chloride (3.84 g) and NaH (1.58 g; 50% dispersion in oil) were suspended in THF (30 ml). The mixture was heated under reflux under nitrogen for 2 h, and then added, without filtering, to 5-acetylpyrrolidin-2-one (4) (1.27 g) and anhydrous $ZnCl_2$ (1.36 g) in THF (60 ml). The reaction mixture was heated under reflux for 2 h, concentrated under reduced pressure, diluted with concentrated aqueous NH_4Cl (50 ml), and extracted into CH_2Cl_2 (7 × 50 ml). After drying ($MgSO_4$), the organic extracts were concentrated under reduced pressure to leave the impure epoxides (5) and (6) (1.5 g). Short-column chromatography on silica (45 g) with ether–methanol (5 : 1) as eluant, gave the epoxides (5) and (6) (887 mg), ratio (5) : (6) = 23 : 77 (^1H n.m.r.). A sample was recrystallized several times from ethyl acetate–light petroleum to give (5SR)-5-[(1RS)-1-*methyl*-2-*oxacyclopropyl*]*pyrrolidin*-2-*one* (6), m.p. 101—102 °C; $\nu_{max.}$ ($CHCl_3$) 3 425, 1 690, and 1 073 cm^{-1}; δ($CDCl_3$) 1.35 (3 H, s, CH_3), 1.88 and 2.30 (1 H and 3 H respectively, each m, CH_2CH_2), 2.57 and 2.76 (each 1 H, d, *J* 4 Hz, epoxide H), 3.75 (1 H, dd, *J ca.* 5, 5.5 Hz, 5-H), and 6.45br (1 H, s, NH); *m/z* (Cl) 142 ($M^+ + H$) (Found: C, 59.25; H, 7.6; N, 9.75%).

(5SR)-5-[(2SR)-2-*Hydroxy*-1-*phenylpropan*-2-*yl*]*pyrrolidin*-2-*one* (7).—A mixture of epoxides (5) and (6) (350 mg), ratio (5) : (6) = 78 : 22, in THF (8 ml) was added to copper(I) iodide (105 mg) and phenylmagnesium bromide (11.9 ml; 0.46M in THF) at −30 °C during 15 min. The mixture was allowed to warm to 0 °C, stirred for 2.5 h, quenched by addition of NH_4Cl (50 ml), and extracted into CH_2Cl_2 (6 × 25 ml); the dried ($MgSO_4$) extract was, concentrated under reduced pressure to give the impure hydroxypyrrolidinone (7) (676 mg). Flash chromatography with ether–methanol as eluant gave (5SR)-5-[(2SR)-2-*hydroxy*-1-*phenylpropan*-2-*yl*]-*pyrrolidin*-2-*one* (7) which, recrystallized from ethyl acetate, had m.p. 130—132 °C; $\nu_{max.}$ ($CHCl_3$) 3 560, 3 430, 3 300br, 1 690, 1 095, 945, and 703 cm^{-1}; δ($CDCl_3$) 1.10 (3 H, s, CH_3), 1.91 (1 H, s, OH), 1.98 and 2.20 (each 1 H, m, HC*H*), 2.37 (2 H, m, CH_2), 2.74 and 2.77 (each 1 H, d, *J* 13.5 Hz, CH_2Ph), 3.66 (1 H, dd, *J* 7, 8 Hz, 5-H), 6.26br (1 H, s, NH), and 7.28 (5 H, m, aromatic H); *m/z* (Cl) 220 ($M^+ + H$) (Found: C, 71.15; H, 7.8; N, 6.45. $C_{13}H_{17}NO_2$ requires C, 71.25; H, 7.75; N, 6.4%).

(5SR)-5-[(2RS)-2-*Hydroxy*-1-*phenylpropan*-2-*yl*]*pyrrolidin*-2-*one* (8).—Using the procedure described above, the epoxide (6) (110 mg) was treated with phenylmagnesium bromide (10 ml; 0.45M in THF) and copper(I) iodide (16 mg). Repeated short-column chromatography of the product, using gradient elution ($CHCl_3$–MeOH), gave (5SR)-5-[(2RS)-2-*hydroxy*-1-*phenylpropan*-2-*yl*]*pyrrolidin*-2-*one* (8) (46 mg) which, recrystallized from ethyl acetate, had m.p. 165 °C; $\nu_{max.}$ ($CHCl_3$) 3 575, 3 430, 3 300br, 1 685, 1 450, 1 380, 1 262, 1 080, 1 010, 942, and 700 cm^{-1}; δ($CDCl_3$) 1.12 (3 H, s, CH_3), 1.66 (1 H, s, OH), 2.15 and 2.40 (each 2 H, m, CH_2), 2.64 and 2.86 (each 1 H, d, *J* 13 Hz, CH_2Ph), 3.70 (1 H, dd, *J* 6, 8 Hz, 5-H), 6.18br (1 H, s, NH), and 7.10—7.37 (5 H, m, aromatic H); *m/z* (Cl) 220 ($M^+ + 1$) (Found: C, 70.95; H, 7.6; N, 6.5%).

(4SR,5SR)-4-*Benzyl*-4-*methyl*-1-*aza*-3-*oxabicyclo*[3.3.0]-*octan*-2-*one* (13).—A mixture of the hydroxy-lactam (7) (92 mg) and $LiAlH_4$ (64 mg) in THF (5 ml) was heated under reflux for 7.5 h, and then quenched with concentrated aqueous potassium sodium tartrate (20 ml), and extracted into CH_2Cl_2 (6 × 10 ml). After drying ($MgSO_4$), concentration under reduced pressure gave (2SR)-2-[(2SR)-2-*hydroxy*-1-*phenylpropan*-2-*yl*]*pyrrolidine* (9) (73 mg), an oil, $\nu_{max.}$ (film) 3 350, 1 375, 1 095, 750, and 705 cm^{-1}; δ($CDCl_3$) 1.05 (3 H, s, CH_3),

1.75 (4 H, m, CH_2CH_2), 2.5br (2 H, s, NH and OH), 2.72 (2 H, m, CH_2Ph), 2.65—3.2 (3 H, m, CH_2NHCH), and 7.2 (5 H, m, aromatic H).

This amino-alcohol in THF (1.5 ml) and *N,N'*-carbonyldi-imidazole (64 mg) in THF (1.5 ml) were heated under reflux for 4 h. Dilution with CH_2Cl_2 (20 ml) gave, after washing with dilute HCl, drying ($MgSO_4$), and concentration under reduced pressure, the impure carbamate (13) (63 mg) recrystallized from benzene–hexane to give (4SR,5SR)-4-*benzyl*-4-*methyl*-1-*aza*-3-*oxabicyclo*[3.3.0]*octan*-2-*one* (13), m.p. 120.5—121.5 °C; $\nu_{max.}$ ($CHCl_3$) 1 737, 1 395, 1 353, 1 050, and 700 cm^{-1}; δ($CDCl_3$) 1.33 (3 H, s, CH_3), 1.53 and 1.74 (each 1 H, m, HC*H*), 1.89 and 2.07 (each 1 H, m, HC*H*), 2.97 and 3.11 (each 1 H, d, *J* 14 Hz, CH_2Ph), 3.13 and 3.59 (each 1 H, m, HC*H*N), 3.69 (1 H, dd, *J* 6, 11 Hz, 5-H), and 7.28 (5 H, m, aromatic H); *m/z* 231 (M^+) (Found: C, 72.8; H, 7.35, N, 5.9. $C_{14}H_{17}NO_2$ requires C, 72.75; H, 7.35; N, 6.05%).

Similar reduction and cyclization of the hydroxy-lactam (8) gave rise to complex mixtures of products that did not include appreciable quantities of the bicyclic carbamate (14).

(4SR,5SR)- *and* (4RS,5SR)-4-*Deuteriomethyl*-8,8-*dideuterio*-4-*methyl*-1-*aza*-3-*oxabicyclo*[3.3.0]*octan*-2-*one* (15) *and* (16).—The epoxide (6) (233 mg) in THF (5 ml) was added to $LiAlD_4$ (223 mg) in THF (5 ml) at 0 °C, and the mixture heated under reflux for 7.5 h. The reaction mixture was cooled, quenched with concentrated aqueous sodium potassium tartrate (50 ml), and extracted into CH_2Cl_2 (5 × 30 ml). After drying ($MgSO_4$), concentration under reduced pressure gave (2*SR*)-2-[(2*RS*)-1-deuterio-2-hydroxypropan-2-yl]-5,5-dideuteriopyrrolidine (12) (194 mg), as an oil; δ($CDCl_3$) 1.12 (5 H, m, CH_3 + CH_2D), 1.7 (4 H, m, CH_2CH_2), 2.68 (2 H, s, NH and OH), and 2.94 (1 H, m, 2-H). This oily amino-alcohol and *N,N'*-carbonyldi-imidazole (529 mg) in THF (11 ml) were heated under reflux for 4 h. Work-up as above gave, after flash chromatography, (4RS,5SR)-4-*deuteriomethyl*-8,8-*dideuterio*-4-*methyl*-1-*aza*-3-*oxabicyclo*-[3.3.0]*octan*-2-*one* (16) (115 mg), m.p. 30—31 °C (from ether–hexane); $\nu_{max.}$ ($CHCl_3$) 1 735, 1 387, 1 347, 1 257, 1 102, and 1 045 cm^{-1}; δ($CDCl_3$) 1.34br (2 H, s, CH_2D), 1.50 (3 H, s, CH_3), 1.44 and 1.88 (each 1 H, m, HC*H*), 1.76 and 2.06 (each 1 H, m, HC*H*), and 3.49 (1 H, dd, *J* 5, 10 Hz, 5-H); δ_C($CDCl_3$) 22.76 (tt, CH_2D), 25.40 and 26.60 (both t, C-6 and C-7), 28.85 (q, CH_3), 45.05 (p, C-8), 69.25 (d, C-5), 79.62 (s, C-4), and 161.00 (s, C-2); *m/z* 158 (M^+) (Found: C, 60.75; H, D, 8.15; N, 8.75. $C_8H_{10}D_3NO_2$ requires C, 60.75; H, D, 8.25; N, 8.85%).

Similarly, a mixture of the epoxides (5) and (6) (319 mg), ratio (5) : (6) = 78 : 22, was reduced by $LiAlD_4$, and the impure amino-alcohol (11) treated with *N,N'*-carbonyldi-imidazole to give, after flash chromatography, (4SR,5SR)-4-*deuteriomethyl*-8,8-*dideuterio*-4-*methyl*-1-*aza*-3-*oxabicyclo*-[3.3.0]*octan*-2-*one* (15) (148 mg) containing *ca.* 20% of the (4*RS*,5*SR*)-isomer (16), m.p. 29—30 °C (from ether–hexane); $\nu_{max.}$ ($CHCl_3$) 2 110w, 1 735, 1 390, 1 347, 1 260, 1 100, and 1 045 cm^{-1}; δ($CDCl_3$) 1.39 (3 H, s, CH_3), and 1.53br (2 H, s, CH_2D); δ_C($CDCl_3$) 22.97 (q, CH_3) and 28.58 (tt, CH_2D); *m/z* 158 (M^+) (Found: C, 60.75; H, D, 8.35; N, 8.8%).

5-(1-*Hydroxy*-1-*phenylethyl*)*pyrrolidin*-2-*ones* (17) *and* (18).—Phenylmagnesium bromide (2.4 ml; 1.1M in THF) was added dropwise to 5-acetylpyrrolidin-2-one (4) (300 mg) in THF (10 ml) under nitrogen at 0 °C. After 10 min at 0 °C, the mixture was cooled to −60 °C, and more phenylmagnesium bromide (4.2 ml; 1.1M in THF) added. After being stirred at −60 °C for 0.5 h, the mixture was allowed to warm to 20 °C during *ca.* 1.5 h, and then quenched with dilute HCl and extracted with CH_2Cl_2 (5 × 25 ml). After drying ($MgSO_4$), the extracts were concentrated, and the impure adduct chromatographed, with ether–methanol (5 : 1) as eluant, to give a mixture of 5-(1-*hydroxy*-1-*phenylethyl*)*pyrrolidin*-2-*ones* (17) and (18) (218 mg) which could not be separated by chromatography, ratio (17) : (18) = 71 : 29 (^1H n.m.r.), recrystallized from benzene, m.p. 125—130 °C; $\nu_{max.}$ ($CHCl_3$) 3 420, 3 300br, 1 690, 1 415, 1 377, and 1 093 cm^{-1}; δ($CDCl_3$) 1.50 (2.1 H, s, CH_3 of major isomer), 1.58 (0.9 H, s, CH_3 of minor isomer), 1.8—2.3 (4 H, m, CH_2CH_2), 3.11 (0.7 H, s, OH of major isomer), 3.15 (0.3 H, s, OH of minor isomer), 3.87 (0.3 H, t, *J* 6 Hz, 5-H of minor isomer), 3.99 (0.7 H, dd, *J* 6, 6.5 Hz, 5-H of major isomer), 5.99br (0.7 H, s, NH of major isomer), 6.85br (0.3 H, s, NH of minor isomer), and 7.41 (5 H, m, aromatic H) (Found: C, 70.25; H, 7.35; N, 6.7. $C_{12}H_{15}NO_2$ requires C, 70.25; H, 7.3; N, 6.85%).

4-*Methyl*-4-*phenyl*-1-*aza*-3-*oxabicyclo*[3.3.0]*octan*-2-*ones* (19) *and* (20).—Hydroxy-pyrrolidinones (17) and (18) (273 mg) in THF (4 ml) were added to $LiAlH_4$ (193 mg) in THF (5 ml) under N_2, and the mixture heated under reflux for 7.5 h. Work-up as above gave crude amino-alcohols (220 mg), $\nu_{max.}$ (film) 3 360, 3 060, 3 040, 1 375, 1 075, 770, and 710 cm^{-1}; δ($CDCl_3$) 1.40 (2.1 H, s, CH_3 of major isomer), 1.47 (0.9 H, s, CH_3 of minor isomer), 1.6 (4 H, m, CH_2CH_2), 2.75 (2 H, m, CH_2N), 3.05br (2 H, s, NH and OH), 3.42 (1 H, m, 2-H), and 7.3 (5 H, m, aromatic H). This mixture of amino-alcohols was treated with *N,N'*-carbonyldi-imidazole (203 mg) in THF (5 ml) at 20 °C for 1.5 h, and heated under reflux for 2.5 h. Work-up as above gave the carbamates (19) and (20) (170 mg) separated by short-column chromatography, with ether–light petroleum as eluant. The first eluted product was (4SR,5SR)-4-*methyl*-4-*phenyl*-1-*aza*-3-*oxabicyclo*[3.3.0]-*octan*-2-*one* (20) (43 mg), an oil, $\nu_{max.}$ (film) 3 060, 3 030, 1 750, 1 380, 1 235, 1 070, 1 050, 936, 766, and 700 cm^{-1}; δ(C_6D_6) 0.47, 0.86, 1.11 and 1.27 (each 1 H, m, HC*H*), 1.52 (3 H, s, CH_3), 2.82 (1 H, m, HC*H*N), 3.14 (1 H, dd, *J* 6, 11 Hz, 5-H), 3.59 (1 H, m, HC*H*N), and 7.11 (5 H, m, aromatic H); *m/z* 217 (M^+). The second eluted product was (4RS,5SR)-4-*methyl*-4-*phenyl*-1-*aza*-3-*oxabicyclo*[3.3.0]*octan*-2-*one* (19) (121 mg), m.p. 61—62 °C; $\nu_{max.}$ ($CHCl_3$) 1 742, 1 350, 1 260, 1 055, 937, and 700 cm^{-1}; δ($CDCl_3$) 1.69 (3 H, s, CH_3), 1.76 (1 H, m, HC*H*), 1.94 (2 H, m, CH_2), 2.17 (1 H, m, HC*H*), 3.16 and 3.68 (each 1 H, m, HC*H*N), 3.92 (1 H, dd, *J* 5, 10 Hz, 5-H), and 7.38 (5 H, m, aromatic H); *m/z* 217 (M^+) (Found: C, 71.8; H, 7.05; N, 6.6. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 6.9; N, 6.45%).

Epoxide Formation from 3-*Acetamido*-3-*phenylpropan*-2-*one* (21).—The amido-ketone (21) (500 mg) in THF was treated with dimethyloxosulphonium methylide (4.2 ml; 0.7M solution in THF) at 20 °C for 2 h and at 55 °C for 1 h. Work-up as above gave the epoxides (22) and (23) (560 mg), ratio 95 : 5 (^1H n.m.r.), containing some Me_2SO as impurity. Recrystallization from ether–light petroleum gave a mixture of the epoxides (22) and (23) (380 mg), from which a sample of the *epoxide* (22) was obtained by repeated recrystallization, m.p. 130—132 °C; $\nu_{max.}$ ($CHCl_3$) 3 440, 3 340, 1 670, 1 390, 1 372, 1 080, 910, 850, 825, and 700 cm^{-1}; δ($CDCl_3$) 1.19 (3 H, s, CH_3), 1.95 (3 H, s, $COCH_3$), 2.61 and 2.83 (each 1 H, d, *J* 4.4 Hz, epoxide H), 5.28 (1 H, d, *J* 9 Hz, C*H*NH), 5.91br (1 H, d, *J* 9 Hz, N*H*), and 7.4 (5 H, m, aromatic H); *m/z* (Cl) 206 (M^+ + 1) (Found: C, 70.05; H, 7.4; N, 6.85. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%).

(4SR,5SR)-5-*Deuteriomethyl*-3-(1,1-*dideuterioethyl*)-5-*methyl*-4-*phenyl*-1,3-*oxazolidin*-2-*one* (24).—A mixture of the epoxides (22) and (23) (380 mg), ratio 95 : 5 (^1H n.m.r.), and $LiAlD_4$ (310 mg) in THF was heated under reflux for 6 h.

Table 1. Bond lengths in Å for the epoxide (6) with e.s.d.s in parentheses

O(1)–C(1)	1.239(5)	C(2)–C(3)	1.534(8)
O(2)–C(5)	1.450(5)	C(3)–C(4)	1.528(7)
O(2)–C(6)	1.446(7)	C(4)–C(5)	1.526(7)
N(1)–C(1)	1.341(6)	C(5)–C(6)	1.469(7)
N(1)–C(4)	1.456(6)	C(5)–C(7)	1.497(6)
C(1)–C(2)	1.498(7)		

Table 2. Bond angles (°) for epoxide (6) with e.s.d.s in parentheses

C(5)–O(2)–C(6)	61.0(3)	C(3)–C(4)–C(5)	114.8(4)
C(1)–N(1)–C(4)	114.2(4)	O(2)–C(5)–C(4)	111.9(4)
O(1)–C(1)–N(1)	124.7(5)	O(2)–C(5)–C(6)	59.4(3)
O(1)–C(1)–C(2)	125.8(4)	C(4)–C(5)–C(6)	117.8(4)
N(1)–C(1)–C(2)	109.5(4)	O(2)–C(5)–C(7)	114.9(4)
C(1)–C(2)–C(3)	104.9(4)	C(4)–C(5)–C(7)	118.5(4)
C(2)–C(3)–C(4)	105.6(4)	C(6)–C(5)–C(7)	119.6(5)
N(1)–C(4)–C(3)	104.2(4)	O(2)–C(6)–C(5)	59.6(3)
N(1)–C(4)–C(5)	110.3(4)		

Table 3. Fractional atomic co-ordinates for the epoxide (6)

Atom	*X/A*	*Y/B*	*Z/C*	U_{iso}
O(1)	0.172 4(5)	0.033 5(7)	0.012 2(2)	0.0546
O(2)	−0.572 1(6)	0.090 3(7)	0.196 1(2)	0.0496
N(1)	−0.177 2(6)	0.077 7(7)	0.054 2(2)	0.0434
C(1)	0.018 7(7)	−0.024 5(8)	0.049 3(2)	0.0414
C(2)	0.020 6(9)	−0.219 1(9)	0.094 7(3)	0.0526
C(3)	−0.216(1)	−0.233 2(8)	0.122 6(3)	0.0527
C(4)	−0.327 9(8)	−0.018 9(8)	0.102 9(2)	0.0426
C(5)	−0.368 0(7)	0.138 9(8)	0.160 8(2)	0.0376
C(6)	−0.559 4(8)	0.287(1)	0.156 0(3)	0.0512
C(7)	−0.176 3(8)	0.199(1)	0.204 7(3)	0.0534
H(1)	−0.2175	0.2099	0.0267	0.0700
H(21)	0.1316	−0.2015	0.1309	0.0700
H(22)	0.0567	−0.3554	0.0681	0.0700
H(31)	−0.2128	−0.2488	0.1728	0.0700
H(32)	−0.2990	−0.3600	0.1032	0.0700
H(41)	−0.4785	−0.0467	0.0842	0.0700
H(61)	−0.5534	0.4341	0.1789	0.0700
H(62)	−0.6460	0.3012	0.1138	0.0700
H(71)	−0.2267	0.3028	0.2399	0.0700
H(72)	−0.1158	0.0636	0.2265	0.0700
H(73)	−0.0566	0.2681	0.1772	0.0700

Work-up as above gave the impure amino-alcohol (390 mg), $\nu_{max.}$ (film) 3 400, 3 060, 3 030, 2 180, 2 060, 1 185, 920, 730, and 700 cm^{-1}; δ($CDCl_3$) 1.04 and 1.05 (each 3 H, s, CH_3), 1.14br (2 H, s, CH_2D), 1.8br (2 H, s, NH and OH), 3.49 (1 H, s, CHN), and 7.27 (5 H, m, aromatic H). This amino-alcohol was treated with *N,N'*-carbonyldi-imidazole (345 mg) as described above. Short-column chromatography of the product gave (4SR, 5SR)-5-*deuteriomethyl*-3-(1,1-*dideuterioethyl*)-5-*methyl*-4-*phenyl*-1,3-*oxazolidin*-2-*one* (24) (170 mg), m.p. 61—62 °C; $\nu_{max.}$ ($CHCl_3$) 1 735, 1 245, 1 060, and 700 cm^{-1}; δ($CDCl_3$) 0.82 (3 H, s, CD_2CH_3), 0.96 (3 H, s, CH_3), 1.44br (2 H, s, CH_2D), 4.36 (1 H, s, CHN), 7.1 (2 H, m, aromatic H), and 7.3 (3 H, m, aromatic H); *m/z* 222 (M^+) (Found: C, 70.15; H, D, 7.55; N, 6.4. $C_{13}H_{14}D_3NO_2$ requires C, 70.2; H, D, 7.7; N, 6.3%).

Crystal Structure Determination for (5SR)-5-[(1RS)-1-*Methyl*-2-*oxacyclopropyl*]*pyrrolidin*-2-*one* (6).—A racemic mixture of the epoxide (6) was recrystallized from benzene to give orthorhombic crystals (space group $P2_12_12_1$; cell dimensions $a = 6.030$ (5), $b = 6.126$ (2), $c = 19.968$ (6) Å, $V = 737.16$ Å^3; $Z = 4$) of a single enantiomer. *X*-Ray diffraction data (Mo-K_α radiation) was collected by an $\omega-2\theta$ scan technique (θ_{lim} 28°) on an Enraf Nonius CAD4F four-circle diffractometer at room temperature. Lorentz and polarization corrections were applied, equivalent reflections merged, and structure factor amplitudes derived for 1 060 unique reflections. The structure was solved by direct methods (MULTAN 80 [18]) and refined using the 615 reflections for which $I > 3\sigma(I)$ by full-matrix least squares to a final *R* value of 0.055. Hydrogen atoms were located in a difference Fourier map, but were subsequently placed in calculated positions with isotropic temperature factors set at 0.07. The final rounds of refinement included anisotropic temperature factors for the non-hydrogen atoms and used the weighting scheme [19] computed from the Chebyshev series.

$$\omega = [41.73\ t_3(X) + 50.81t_1(X) + 10.67t_2(X)]^{-1} \text{ where } X = F_o/F_{max.}$$

All calculations were performed with the CRYSTALS [20] programs package on a VAX 11/750 computer.

As a further proof of the stereochemistry of the epoxide ring, the assignment of the methylene carbon, C(6), and oxygen, O(2), atoms were exchanged, atoms H(61) and H(62) were deleted (see Figure), and the structure was refined using isotropic temperature factors for all atoms. The *R* value was 0.155, and the isotropic temperature factors for the reassigned carbon and oxygen atoms were 0.018 and 0.112 respectively, thus showing the original assignment of stereochemistry to be correct. The figure shows a SNOOPI [7] plot of the epoxide illustrating the Crystallographic Numbering Scheme used.

Bond lengths, bond angles, and fractional co-ordinates for the epoxide (6) are listed in Tables 1—3 respectively. Thermal parameters and structure factors for the crystallographic determination are listed in a Supplementary publication [Sup No. 23464 (12 pages)].*

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