Olivanic Acid Analogues. Part 10.[1] X-Ray Crystallographic Study of the Stereochemistry of some 7-Heteroatom-substituted 7-Acetyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane-2-spirocyclohexanes: Functional Group Control of the Stereoselectivity of their Reduction Products Using Borohydride Reagents

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(6*RS*,7*SR*)-7-Acetyl-7-azido-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane-2-spirocyclohexane **3** was obtained by reaction of mesyl azide with the *trans*-ketone **2** in the presence of aqueous base, and the stereochemistry of its major sodium borohydride reduction product, (6*RS*,7*SR*,9*SR*)-7-azido-7-(1-hydroxyethyl)-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane-2-spirocyclohexane **4**, was determined by X-ray crystallography. X-Ray studies of the keto sulfide **17** and the chloro ketone **20** confirmed their (6*RS*,7*SR*) relative stereochemistry. Reduction of **17** gave the alcohol **18** also with (6*RS*,7*SR*,9*SR*) stereochemistry. In contrast, reduction of **20** with trialkylborohydride reagents gave the (6*RS*,7*SR*,9*RS*)-chloro alcohol **21**, and a mechanism is proposed to account for this reversal of C-9 stereoselectivity.

We have previously described[2] our preparation of synthetic precursors of the *cis*-substituted olivanic acids. A crucial aspect of the strategy comprised the stereoselective reduction of the methyl ketone group present in some substituted oxazetidinyl ketones. A choice either of a sulfide or of a halogen substituent (ultimately removed) α- to the β-lactam carbonyl group afforded opposite stereoselectivity in the resulting alcohols. This, therefore, permitted the synthesis from a common precursor of some *cis*-olivanic acid analogues possessing either of the possible hydroxyethyl group configurations. We now report the results of a study of the synthesis and stereoselective reduction of a corresponding α-azido derivative. For each substituent series, an X-ray crystallographic study has now defined fully the relative stereochemistries of ketone and alcohol, leading to an insight into the mechanisms of stereocontrol.

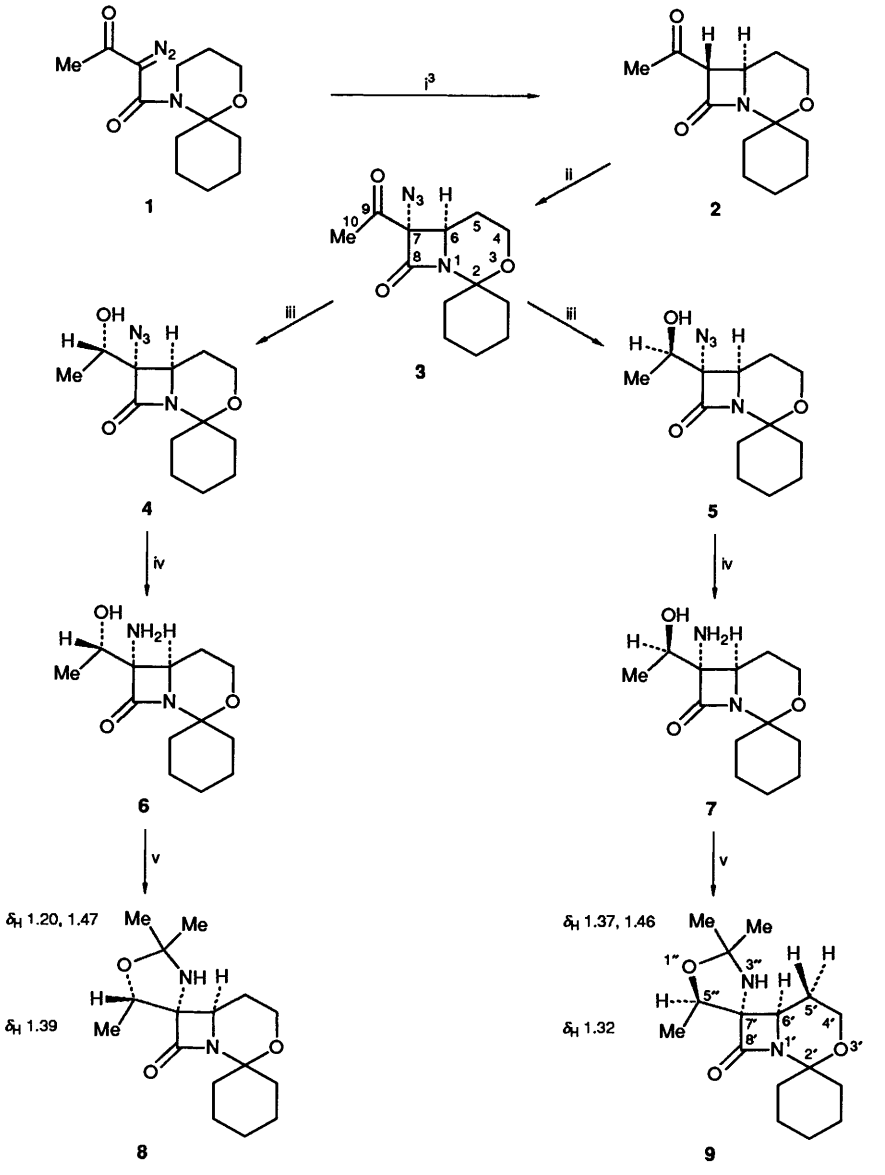
Results and Discussion

The rhodium(II) acetate-mediated carbenoid insertion reaction of diazo ketone **1**[3] gives the *trans*-ketone **2** (Scheme 1). During large-scale synthesis of this compound the presence of azido ketone **3** was detected as a minor impurity in some instances.[4] This arose from further reaction of **2** with a residual excess of the mesyl azide utilised to effect diazo transfer in the preparation of **1**. We therefore chose to examine the azide transfer reaction with ketone **2** using this reagent. Generation of the enolate of **2** using lithium diisopropylamide (LDA) or potassium hydride (anhydrous conditions), followed by reaction with mesyl azide, did not provide the expected azide **3** (Scheme 2, arrows a). Instead, a crystalline methanesulfonyltriazoline **11** was obtained (72%, 75%, respectively) arising from cyclisation of intermediate **10** (arrows b). A similar reaction of the lithium enolate of **2** with toluene-*p*-sulfonyl azide gave *p*-tolylsulfonyltriazoline **12** (48%). However, when aqueous potassium hydroxide was employed as the base, expulsion of methanesulfinic acid (arrows a) now produced the required azido ketone **3** (36%), m.p. 117–118 °C (ν_{max}/cm^{-1} 2110, 1765 and 1720). Prolonged exposure of mesyltriazoline **11** to the latter conditions also gave azido ketone **3**, but in reduced yield (22%) (arrows c). Thus, azido ketone **3** must arise directly from ketone **2** and not *via* the triazoline. This is consistent with Evans' observation[5] that for a different series of ketones, the use of the potassium enolate, followed by a protic anion quench, favoured the azide transfer reaction.

Reduction of the ketone group of **3** with sodium borohydride in ethanol gave (Scheme 1) a mixture of azido alcohols **4** and **5** [87%, 8:1 (NMR)]. Although chromatographically homogeneous, they were separable by crystallisation. On changing the solvent to ethanol–tetrahydrofuran (THF) (2:1) in the reduction, the stereoselectivity in favour of isomer **4** was enhanced (82%, 20:1). Provisional stereochemical assignments for the hydroxyethyl groups of **4** and **5** were made using the reaction sequence shown in Scheme 1. For each, the azido group was reduced catalytically (H_2, Pd–C) affording the respective amino alcohols **6** and **7**. These were then heated at reflux in acetone in the presence of molecular sieves, giving the corresponding crystalline isopropylidene derivatives **8** (80%) and **9** (69%). A chemical shift difference was apparent for just one of the isopropylidene methyl singlet resonances (isomer **8**, δ_H 1.20, 1.47; isomer **9**, δ_H 1.37, 1.46; $\Delta\delta \simeq +0.17$ and -0.01). Examination of molecular models shows the presence of a significant steric interaction between 5″-Me and the 5′-H_β for isomer **9**. The conformational changes required to relieve this interaction result in the movement of one isopropylidene methyl group closer to the deshielding plane of the β-lactam carbonyl group. This permits the assignment of structures **8** and **9** and, by inference,[2] that of azido ketones **4** and **5** to be as indicated.

Crystals of the major azido alcohol isomer **4** were suitable for X-ray crystallographic analysis and the structure (Fig. 1) confirmed the (6*RS*,7*SR*,9*SR*) relative stereochemistry. The crystal structure also proves that the azido ketone **3** has (6*RS*,7*SR*) stereochemistry and that the azido group is therefore transferred to the least hindered α-face of ketone **2**.

Our previously described synthesis (Scheme 3)[2] of precursors **15** of *cis*-olivanic acid derivatives utilised the halogen- and sulfur-substituted ketones **13**. Stereoselective reduction to give the alcohols **14**, followed by tributyltin hydride reductive removal of the heteroatom substituent, then afforded the



Scheme 1 *Reagents and conditions:* i, $Rh_2(OAc)_4$ (cat.), PhH or CH_2Cl_2, RT, 75%; ii, MsN_3, KOH, THF–H_2O, 36%; iii, $NaBH_4$, EtOH–THF, 0 °C, 82% (**4**:**5**, 20:1); iv, H_2, Pd–C, EtOAc–MeOH, 93–95%; v, acetone, 4Å mol. sieves, reflux, 16 h, 78–85%

Table 1 Reduction with $NaBH_4$ of the keto sulfide **17**[2,a]

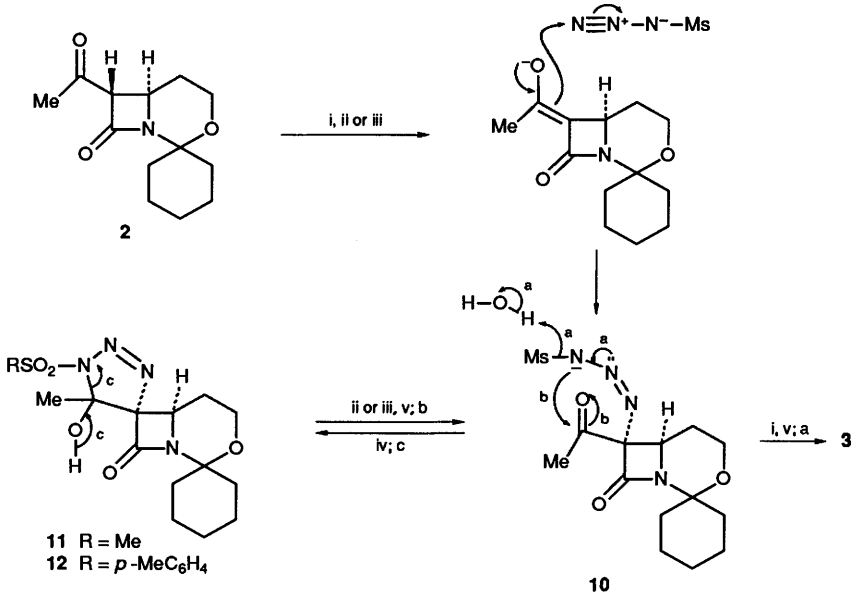
	Solvent	Yield (**18** + **19**%)	Ratio (**18**:**19**)[b]
a	EtOH–THF (1:1)	88	8:3
b	EtOH–THF (5:1)	95	10:1
c	EtOH–THF (10:1)	96	16:1
d	EtOH	89	9:1
e	MeOH	72	10:1
f	PrOH	86	12:1

[a] T = 0 °C, t = 30 min. [b] Ratio determined from integration of the respective 9-H signals, δ_H 4.41 (q, J 6.5) and 4.55 (q, J 6.3).

thermodynamically disfavoured *cis*-β-lactams **15**. The hydroxyethyl group stereochemistries were proven by E2 elimination of methanesulfinic acid from the corresponding methanesulfonates and determination of the geometry of the resulting ethylidene compounds **16**. The stereochemistry of the heterosubstituents is irrelevant to the ultimate disposition of β-lactam protons in **15**, since the carbon radical generated from **14** will, of necessity, be quenched by hydrogen atom transfer to the least hindered α-face during the tin hydride reduction. Although the stereochemistry of substituted ketones **13** and therefore also alcohols **14** is hitherto unproven, we had assumed that the substituents X would be α-disposed on steric grounds as a consequence of halogen and sulfenyl transfer to the least hindered face of the enolate of ketone **2** [chloramine-T and RS–$S(O)_2R$ reagents, respectively]. The structures from an X-ray crystallographic study of the keto sulfide **17** (Fig. 2) and of the chloro ketone **20** (Fig. 3) confirm such assumptions. It is of interest that, in the solid state, their spirocyclohexane rings have adopted different chair conformations.

As a consequence of the X-ray study, we are now also able to assign the structures of the alcohol reduction products with certainty. Although keto sulfide **17** reverts to the ketone **2** in the presence of Selectride® reagents,[2] Table 1 reports the results of an extended study of its reduction with sodium borohydride in protic solvents. The best conditions (entry c) achieve good stereoselectivity, providing alcohols **18** and **19** (96%, 16:1). The (6*RS*,7*SR*,9*SR*) relative stereochemistry of the major product **18** corresponds with that of the major azido alcohol **4** (*vide supra*).

In contrast, reductions of chloro ketone **20** using borohydride reagents proceed with opposite stereoselectivity, favouring the (6*RS*,7*SR*,9*RS*)-chloro alcohol **21**.



Scheme 2 *Reagents:* i, KOH, MsN_3, THF–H_2O; ii, LDA, MsN_3, THF; iii, KH, MsN_3, THF; iv, KOH, THF–H_2O; v, NH_4Cl, H_2O

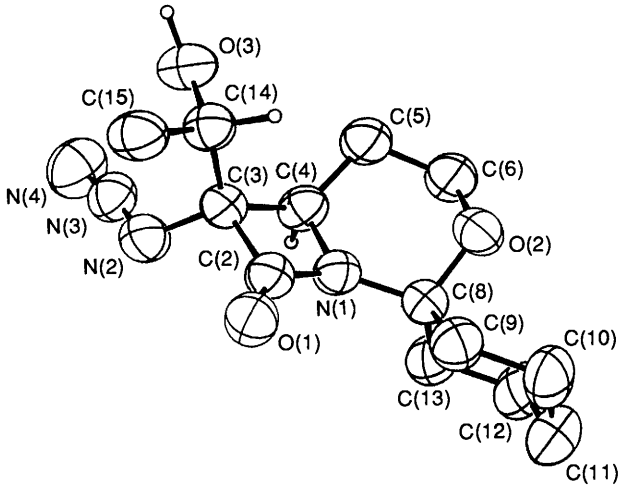
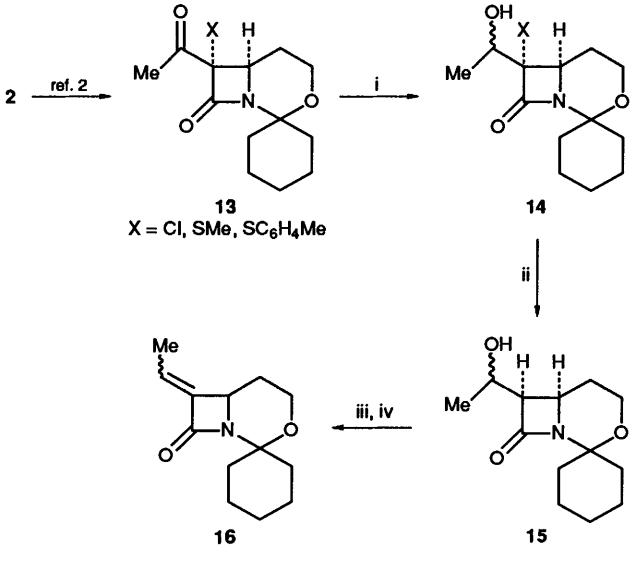


Fig. 1 X-Ray structure and crystallographic numbering system for the azido alcohol **4**



Scheme 3 *Reagents and conditions:* i, $NaBH_4$, EtOH or K-Selectride®, THF; ii, Bu_3SnH, acetone, AIBN, reflux 36 h; iii, MsCl, Et_3N, CH_2Cl_2; iv, $NaHCO_3$, MeOH, reflux, 30 min

With sodium borohydride in ethanol, the alcohols **21** and **22** were obtained with poor stereoselectivity (88%, 5:2).[2] Table 2 summarises the improvements achieved using trialkylborohydrides. Our optimum stereoselectivity was obtained using LS-Selectride® (entry e) (93%, 23:1).

Knowledge of the relative stereochemistry of the major reduction products **4**, **18** and **21** now suggests a rationale for the differing stereochemical outcome in the latter instance. Although there has been much controversy and conjecture concerning the precise mechanism of the reduction of carbonyl groups by borohydride reagents,[6] it is generally agreed that the nature of the counter cation is of little importance in the overall mechanism.[7] The stereochemistry of reduction of chiral open-chain ketones has been interpreted sterically by Felkin in terms of Cram's rule,[8] and the additional stereoselectivity often conferred by trialkylborohydride reagents is accepted also as resulting from steric factors. In the substituted ketones **3**, **17** and **20**, which contain a rigid azetidinone ring system as part of the β-dicarbonyl functionality, the heteroatom 7-substituent is of defined stereochemistry and in each case this is directed to the α-face of the molecule. As a result of the strong boron–nitrogen and boron–sulfur interactions, we propose that in the reductions of the azido ketone **3** and the keto sulfide **17** (which led to the same alcohol stereochemistry), the intermediate complexes contain the boron atom in chelation between the ketone carbonyl group and a heteroatom (Figs. 4 and 5). (This involves a similar principle to that invoked[9] by Guanti to explain the asymmetric reduction of a series of α-arylthio-β-oxo sulfides to α-hydroxy aldehydes). As a consequence of their structure, the complexes will favour the delivery of hydride ion to the *re*-face of the acyl carbonyl group of the enantiomer depicted. This results in the predominance of the alcohol isomers **4** and **18**.

For the chloro ketone **20**, preferred complexation of the reagent between the two carbonyl functions, rather than to the halogen atom, provides a model which explains the opposite stereochemistry for the reduction. Attack of hydride ion is now

Table 2 Reduction of the chloro ketone **20**[2]

	Reagent	Solvent	Yield (**21** + **22**%)	Ratio (**21**:**22**)[c]
a	$NaBH_4$[a]	EtOH	88	5:2
b	$NaBH_4$[a]	EtOH–THF (10:1)	91	5:2
c	K-Selectride®[b]	THF	89	10:1
d	L-Selectride®[b]	THF	91	12:1
e	LS-Selectride®[b]	THF	93	23:1

[a] $T = 0$ °C, $t = 30$ min. [b] $T = -70$–0 °C, $t = 1$ h. [c] Ratio determined from integration of the respective 9-H signals, δ_H 4.26 (q, J 6.3) and 4.36 (q, J 6.2).

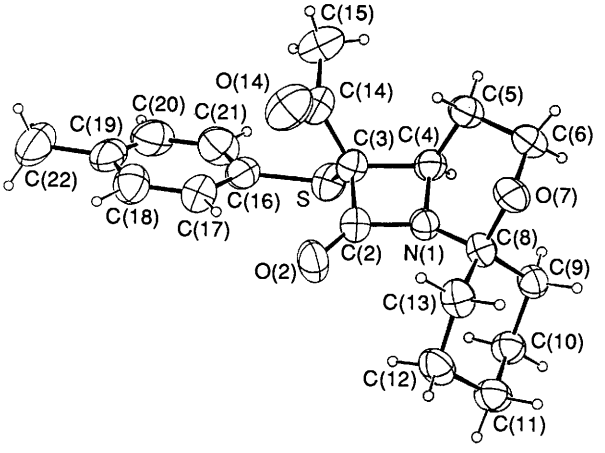


Fig. 2 X-Ray structure and crystallographic numbering system for the keto sulfide **17**

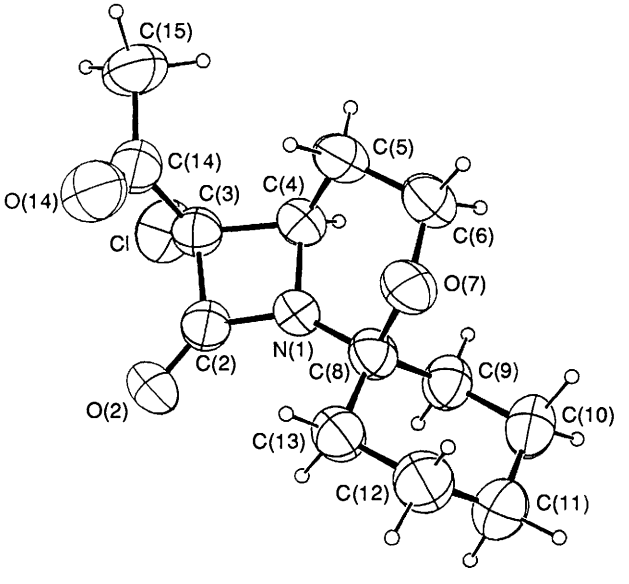
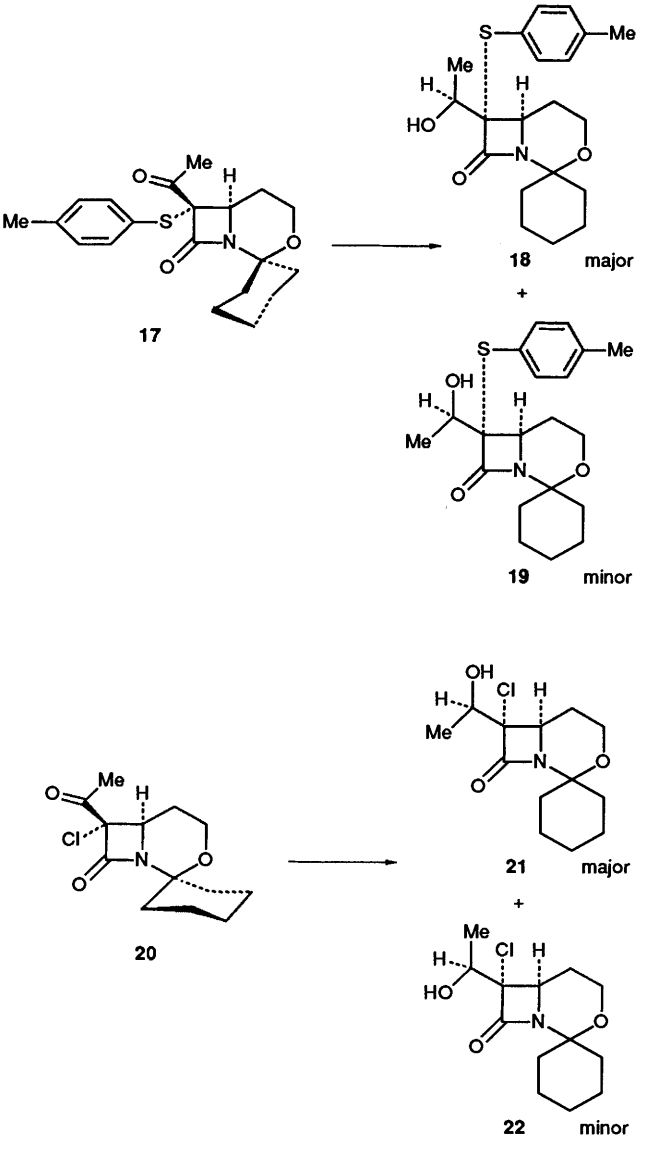


Fig. 3 X-Ray structure and crystallographic numbering system for the chloro ketone **20**



directed to the *si*-face of the acyl carbonyl group, leading to the alcohol **21** (Fig. 6). The model also provides a rationale for the great improvement in stereoselectivity with this substrate when using trialkylborohydrides in place of sodium borohydride (R = H). In its complexes with the former type of reagent, the bulky alkyl groups [R = Bu^s, $Pr^i(Me)CH$] will be disposed towards the less-hindered α-face, and will therefore direct attack of hydride ion to the ketone *si*-face in the manner depicted.

A similar mechanism also explains the reduction behaviour of the *trans*-ketone **2** (Fig. 7). Sodium borohydride gave no stereoselectivity, affording a (1:1) mixture of the alcohol epimers **23** and **24**.[3] The use of K-Selectride®, however, leads to a predominance of the (6*RS*,7*SR*,9*RS*)-alcohol **23** over its (6*RS*,7*SR*,9*SR*)-epimer **24** (11:1). Examination of molecular models for this *trans*-substituted azetidinone confirms that the faces of the β-dicarbonyl functionality are less contrasted in their accessibility to reagents than in the previous cases where the acyl group is *cis*-disposed.

In conclusion, choice of a suitable heterosubstituent provides a means of control of the hydroxy group configuration in the reduction of this series of methyl ketones. The substituent may be retained, or alternatively, may be removed reductively[2] to give *cis*-substituted hydroxyethyl carbapenem derivatives of defined stereochemistry.

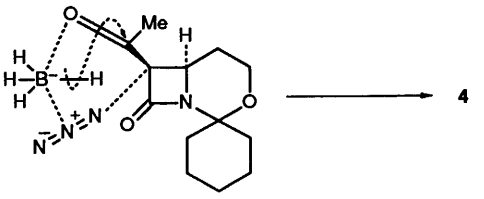


Fig. 4. Mechanism for stereoselective reduction of the azido ketone **3**; alpha (*re*-)-face attack

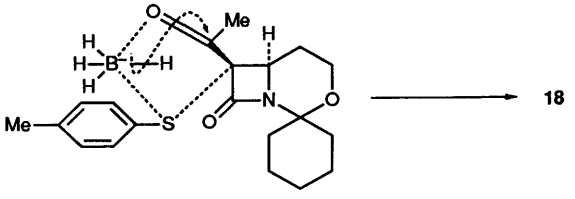


Fig. 5 Mechanism for stereoselective reduction of the keto sulfide **17**; alpha (*re*-)-face attack

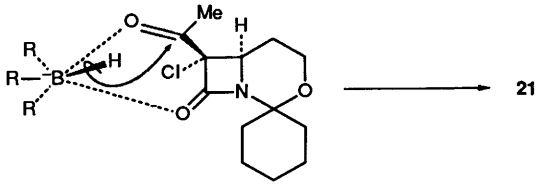


Fig. 6 Mechanism for stereoselective reduction of the chloro ketone **20**; beta (*si*)-face attack

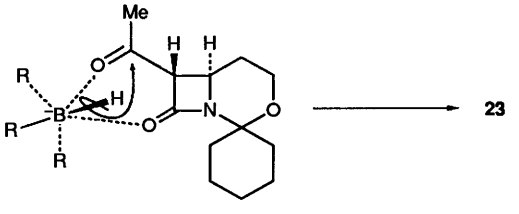
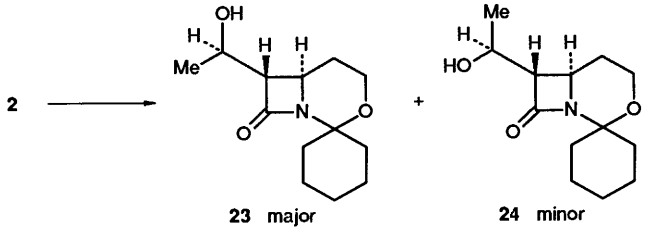


Fig. 7 Mechanism for stereoselective reduction of the *trans*-ketone **2**; beta (*si*)-face attack



Experimental

The experimental techniques, materials, solvents and spectroscopic instrumentation employed in this work were as described in Parts 2,[10] 4[11] and 8[2] of the series. Unless stated otherwise, IR spectra were recorded for $CHCl_3$ solutions and NMR spectra were obtained in $CDCl_3$. Coupling constant values J are given in Hz. Merck silica gel 60 Art. 7729 is finer than 230 mesh ASTM; Art. 9385 is 230–400 mesh ASTM. K- and L-Selectride® refers to potassium and lithium tri(*sec*-butyl)borohydrides, respectively. LS-Selectride® is lithium tris(1,2-dimethylpropyl)borohydride.

All compounds are racemic; stereochemical assignments, and references to relative stereochemistry in the Figures, are given with respect to that enantiomer which is depicted.

Synthesis and Reduction of the Azido Ketone **3**: (6RS,7SR)-7-*Acetyl-7-azido-8-oxo-3-oxa-1-azabicyclo*[4.2.0]*octane-2-spiro-cyclohexane* **3**.—(i) *From ketone* **2**. To a stirred solution of (6*RS*,7*SR*)-7-acetyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane-2-spirocyclohexane **2**[3] (4.32 g) in THF (30 cm^3) was added methanesulfonyl azide (2.21 g) in toluene (11 cm^3). A solution of potassium hydroxide (1.2 g) in water (3 cm^3) was added dropwise over 15 min, the temperature being maintained at 20 °C. The viscous emulsion was stirred at room temperature for 48 h. Saturated aqueous ammonium chloride (30 cm^3) was added, the THF removed on a rotary evaporator and the aqueous slurry extracted with ethyl acetate (3 × 25 cm^3). The combined extracts were dried and evaporated and the residue was chromatographed on silica gel (art. 9385, 8 × 4 cm). Elution with ethyl acetate–hexane (1:3), followed by crystallisation from isopropyl alcohol–hexane, gave the title *azido ketone* **3** (1.85 g, 36%), m.p. 117–118 °C (Found: C, 56.0; H, 6.6; N, 19.9. $C_{13}H_{18}N_4O_3$ requires C, 56.1; H, 6.5; N, 20.1%); ν_{max}/cm^{-1} 2110, 1765 and 1720; δ_H(250 MHz) 1.4–2.0 (11 H, m, 5-H and c-C_6H_{10}), *ca.* 2.3 (1 H, m, 5-H), 2.36 (3 H, s, Ac), 3.76 (1 H, dd, J 10, 6, 6-H) and 3.86 (2 H, m, $W_{\frac{1}{2}}$ 6.5, 4-H); m/z (CI, NH_3 gas) 296 (MNH_4^+) and 279 (MH^+).

(ii) *From the mesyltriazoline* **11**. A solution of the mesyltriazoline **11** (0.180 g, 0.5 mmol) in THF (2 cm^3) was cooled to 0 °C. Potassium hydroxide (0.10 g) in water (1 cm^3) was added dropwise, and the mixture was stirred at room temperature for 48 h. Work-up with aqueous ammonium chloride, recovery in ethyl acetate and chromatography as before gave the azido ketone **3** (0.031 g, 0.11 mmol, 22%), which was identical (IR, NMR) with the previous sample.

5″-Hydroxy-5″-methyl-1″-methylsulfonyl-8′-oxo-(cyclo-hexane)spiro-2′-(3′-oxa-1′-azabicyclo[4.2.0]*octane)-7′-spiro-4″-*([1″H]-[4″,5″]*dihydro*[1″,2″,3″]*triazole*) **11**.—(i) *Using potassium hydride*. A solution of methyl ketone **2** (0.237 g) in THF (5 cm^3) was added to potassium hydride (20% suspension in paraffin oil; 0.200 g) at −30 °C in an argon atmosphere, and the stirred suspension was allowed to warm to room temperature over 1 h. The homogeneous solution was cooled to −50 °C and a toluene solution of mesyl azide (0.160 g cm^{-3}; 0.76 cm^3, 0.121 g) added. The stirred mixture was warmed to 0 °C (1 h) and partitioned between ethyl acetate (20 cm^3) and saturated aqueous ammonium chloride (10 cm^3). The organic layer was washed with brine, dried and evaporated to give an oil (0.420 g). This crystallised from chloroform–diethyl ether to give the *mesyltriazoline* **11** (0.268 g, 75%), m.p. 110–111 °C. Recrystallisation (acetonitrile–ethyl acetate–hexane) gave fine off-white needles, m.p. 112 °C (gas evolution) (Found: C, 47.3; H, 6.2; N, 15.4. $C_{14}H_{22}N_4O_5S$ requires C, 46.9; H, 6.2; N, 15.6%); ν_{max}/cm^{-1} 3250br, 1765, 1360 and 1170; ν_{max}/cm^{-1} (Nujol) 3330, 1745, 1360 and 1175; δ_H[90 MHz; $(CD_3)_2SO$] 1.3–2.2 (12 H, m), 1.87 [3 H, s, $CH_3C(OH)$], 3.25 (3 H, s, CH_3SO_2), 3.85 (2 H, m, $W_{\frac{1}{2}}$ 7, 4′-H), 4.44 (1 H, dd, J 9, 7, 6′-H) and 7.78 (1 H, br s, D_2O exch., OH); m/Z (EI) 358 (M^+).

(ii) *Using LDA*. A similar experiment using LDA (1 mol dm^{-3} in THF; 1.1 cm^3; 1.1 mol equiv.) at −70 °C gave the mesyltriazoline **11** (0.256 g, 72%), identical (IR) with the sample described above.

5″-Hydroxy-5″-methyl-8′-oxo-1″-p-tolylsulfonyl(cyclo-hexane)spiro-2′-(3′-oxa-1′-azabicyclo[4.2.0]*octane)-7′-spiro-4″-*([1″H][4″,5″]*dihydro*[1″,2″,3″]*triazole*) **12**.—Ketone **2** (0.474 g, 2 mmol) in THF (3 cm^3) was added to a rapidly stirred solution of LDA (2.2 mmol) in THF (5 cm^3) and hexane (1.5 cm^3) at −70 °C in an argon atmosphere, and the cream suspension was stirred for 20 min. A solution of toluene-*p*-sulfonyl azide (0.324 g, 2.2 mmol) in THF (2 cm^3) was added, and the mixture allowed to warm to −10 °C over 1.5 h. Saturated aqueous ammonium chloride (2 cm^3) was added and

the organic phase separated, diluted with ethyl acetate, washed with brine and dried. Evaporation and trituration of the residue with ethyl acetate–diethyl ether (1:1) gave the *tosyltriazoline* **12** as a white solid (0.417 g, 48%). Recrystallisation of an aliquot (acetonitrile–hexane) had m.p. 117–118 °C (gas evolution) (Found: C, 55.4; H, 6.0; N, 12.7. $C_{20}H_{26}N_4O_5S$ requires C, 55.3; H, 6.0; N, 12.9%); ν_{max}/cm^{-1} 3250br, 1765, 1730sh, 1590, 1365 and 1165; ν_{max}/cm^{-1} (Nujol) 3330, 1775, 1600, 1375 and 1180; δ_H[90 MHz; $(CD_3)_2SO$] 1.2–2.2 (*ca.* 12 H, m), 1.93 [3 H, s, CH_3(OH)], 2.37 (3 H, s, ArCH_3), 3.77 (2 H, m, $W_{\frac{1}{2}}$ 7 Hz, 4′-H), 4.27 (1 H, dd, *J* 9.5, 7, 6′-H), 7.30 (1 H, br s, D_2O exch., OH) and 7.40 (2 H, *J* 9) and 7.85 (2 H, *J* 9, AA′BB′); *m/z* (EI) (M − N_2^+, 406.1570. *M* − N_2 requires 406.1562).

7-Azido-7-(1-hydroxyethyl)-8-oxo-3-oxa-1-azabicyclo-[4.2.0]octane-2-spirocyclohexane; *Isomers* **4** *and* **5**.—The azido ketone **3** (0.250 g) in THF (5 cm^3) was added to ethanol (10 cm^3) and the solution cooled to 0 °C. Sodium borohydride (0.065 g) was added portionwise and the mixture stirred at 0 °C for 30 min. The solvents were evaporated and the residue was partitioned between ethyl acetate and brine. The aqueous layer was extracted once more with ethyl acetate and the organic layers were combined, dried and evaporated. The residue was chromatographed on silica gel 60 (Art. 7729), eluting with ethyl acetate, to give the title alcohol as a mixture of isomers (0.206 g, 82%) (20:1 ratio, NMR).* Crystallisation from ethyl acetate–hexane afforded the major (6*RS*,7*SR*,9*SR*)-*isomer* **4** as rosettes of rods, m.p. 124–125 °C (Found: C, 55.5; H, 7.1; N, 19.8. $C_{13}H_{20}N_4O_3$ requires C, 55.7; H, 7.2; N, 20.0%); ν_{max}/cm^{-1} 3580–3450, 2120 and 1755; δ_H(250 MHz) 1.42 (7 H, *J* 6.5, 10-H, c-$C_6H_4H_6$), 1.76–1.93 (6 H, m, c-$C_6H_6H_4$), 2.02–2.18 (1 H, m) and 2.24–2.34 (1 H, m, 5-H), *ca.* 2.56 (1 H, br s, OH), 3.80 (1 H, dd, *J* 11, 5, 6-H), 3.88 (2 H, dd, *J* 9, *ca.* 1, 4-H) and 4.27 (1 H, dq, *J* 8, 6.5, 9-H); *m/z* (CI, NH_3 gas) 298 (MNH_4^+) and 281 (MH^+).

A similar experiment in ethanol without THF as cosolvent gave the mixture of isomers **4** and **5** (87%) (Ratio 8:1). Although chromatographically inseparable, removal of the major component **4** as above, followed by crystallisation of the mother-liquors from chloroform–hexane, gave a sample of the pure (6*RS*,7*SR*,9*RS*)-*isomer* **5** as prisms, m.p. 97–100 °C (Found: C, 55.4; H, 7.2; N, 19.9%), ν_{max}/cm^{-1} 3350br, 2110 and 1750; δ_H(250 MHz) 1.21 (3 H, d, *J* 6.5, 10-H), 1.25–1.65 (4 H, m, c-$C_6H_4H_6$) 1.76–2.08 (6 H, m, c-$C_6H_6H_4$), 2.08–2.32 (2 H, m, 5-H), 2.82 (1 H, br s, OH), 3.56 (1 H, dd, *J* 11.5, 5, 6-H), 3.83 (2 H, m, $W_{\frac{1}{2}}$ 7 Hz, 4-H) and 4.47 (1 H, dq, *J* 6.6, 3.3, 9-H).

(6RS,7SR)-7-*Amino*-7-(1-*hydroxyethyl*)-8-*oxo*-3-*oxa*-1-*aza-bicyclo*[4.2.0]*octane*-2-*spirocyclohexane*; *Isomers* **6** *and* **7**.—The azido alcohol **4** (0.110 g) in ethyl acetate–methanol (1:1; 5 cm^3) was shaken in an atmosphere of hydrogen in the presence of a 10% palladium–carbon catalyst (0.035 g) for 1.5 h. The suspension was filtered (Kieselguhr) and the filtrand washed well with ethyl acetate. Evaporation of the filtrate and washings gave the crude (6*RS*,7*SR*,9*SR*)-isomer **6** of the title amino alcohol as a foam (0.095 g, 95%); ν_{max}/cm^{-1} 3400br and 1735; δ_H(90 MHz) *inter alia* 1.31 (3 H, d, *J* 6.5, 10-H); *m/z* (CI, NH_3 gas) 255 (MH^+).

A similar experiment using the azido alcohol **5** (0.100 g) gave the crude (6*RS*,7*SR*,9*RS*)-isomer **7** of the amino alcohol as an insoluble white solid (0.084 g, 93%), m.p. 168 °C; ν_{max}/cm^{-1} 3300br and 1735; δ_H(90 MHz) *inter alia* 1.19 (3 H, d, *J* 6.5, 10-H); *m/z* (CI, NH_3 gas) 255 (MH^+) and 272 (MNH_4^+).

(6′RS,7′SR)-2″,2″,5″-*Trimethyl*-8′-*oxo*(*cyclohexane*)*spiro*-2′-(3′-*oxa*-1′-*azabicyclo*[4.2.0]*octane*)-7′-*spiro*-4″-(1″,3″-*oxazolidine*; *Isomers* **8** *and* **9**.—Amino alcohol **6** (0.095 g) in acetone (5 cm^3) was heated at reflux in an argon atmosphere in the presence of 4Å molecular sieves for 16 h. Filtration and evaporation gave a solid (0.102 g) which was recrystallised (EtOAc–hexane) to give the (6′*RS*,7′*SR*,5″*SR*)-*isomer* **8** of the title isopropylidene derivative as microcrystals (0.093 g, 85%), m.p. 116–117 °C (Found: C, 65.1; H, 8.8; N, 9.5. $C_{16}H_{26}N_2O_3$ requires C, 65.3; H, 8.9; N, 9.5%); ν_{max}/cm^{-1} 3470 and 1740; δ_H(90 MHz) 1.20 (3 H, s) and 1.47 (3 H, s) [$(CH_3)_2C$], 1.39 (3 H, d, *J* 6.5, 5″-Me), 1.4–2.0 (11 H, m, 5′-H, c-C_6H_{10}), 2.13–2.38 (1 H, m, 5′-H), 2.56 (1 H, br s, NH), 3.66 (1 H, dd, *J* 9, 7, 6′-H), 3.81–3.93 (2 H, m, 4′-H) and 4.39 (1 H, q, *J* 6.5, 5″-H).

A similar experiment using the amino alcohol **7** (0.080 g) gave the (6′RS,7′SR,5″RS)-*isomer* **9**. This crystallised from chloroform–hexane as the *hemihydrate* as fine needles (0.072 g, 78%), m.p. 152–154 °C (Found: C, 63.4; H, 8.8; N, 9.3. $C_{16}H_{16}N_2O_3$·0.5H_2O requires C, 63.3; H, 9.0; N, 9.2%); ν_{max}/cm^{-1} 3480, 3300br and 1745; δ_H(90 MHz) 1.32 (3 H, d, *J* 6.5, 5″-Me), 1.37 (3 H, s) and 1.46 (3 H, s) [$(CH_3)_2C$], 1.45–2.04 (11 H, 5′-H, c-C_6H_{10}), 2.07–2.31 (1 H, m, 5′-H), 2.65 (2 H, br s, NH, 0.5H_2O), 3.58–3.71 (1 H, m, 6′-H), 3.73-3.87 (2 H, m, 4′-H) and 4.35 (1 H, q, *J* 6.5, 5″-H).

Stereoselective Reduction of the Keto Sulfide **17** *and the Chloro Ketone* **20**.—This was carried out according to the methods described in ref. 2 and detailed in Tables 1 and 2.

Stereoselective Reduction of the trans-Ketone **2**: (1-*Hydroxy-ethyl*)-8-*oxo*-3-*oxa*-1-*azabicyclo*[4.2.0]*octane*-2-*spirocyclo-hexane* **23**.—A solution of the *trans*-ketone **2** (0.850 g) in THF (10 cm^3) was stirred at 0 °C in an argon atmosphere. K-Selectride® in THF (1 mol dm^{-3}; 4.3 cm^3; 1.2 mol equiv.) was added over 5 min, and the solution was stirred for 1.5 h. Saturated aqueous ammonium chloride (2 cm^3) was added, and the mixture stirred at room temperature for 15 min. The THF layer was separated and extracted once more with aqueous ammonium chloride. The aqueous phases were extracted with ethyl acetate, and the organic layers combined and dried. Evaporation gave a gum (0.79 g) which was shown (NMR) to comprise isomers **23** and **24** of the title alcohol (11:1 ratio).† Crystallisation from ethyl acetate–hexane gave the pure (6RS,7SR,9RS)-*isomer* **23** (0.670 g, 79%), m.p. 143–144 °C (Found: C, 69.9; H, 9.4; N, 6.1. $C_{13}H_{21}NO_2$ requires C, 69.9; H, 9.5; N, 6.3%); ν_{max}/cm^{-1} 3440br and 1740; δ_H(250 MHz) 1.30 (3 H, d, *J* 6, 10-H), 1.35–1.60 (4 H, m, c-$C_6H_4H_6$), 1.60–1.97 (7 H, m, 5-H, c-$C_6H_6H_4$), 2.05 (1 H, br d, D_2O exch., OH), 2.33 (1 H, m, 5-H), 2.79 (1 H, dd, *J* 6 and 1.5, 7-Hβ), 3.57 (1 H, ddd, *J* 10.5, 4.5, 1.5, 6-Hα), 3.86 (2 H, m, 4-H) and 4.14 (1 H, quin., *J* 6, C*H*OH). The (6*RS*,7*SR*,9*SR*)-isomer **24** remained in the mother liquors. It showed *inter alia* δ_H 2.82 (1 H, dd, *J* 6, 1.5, 7-Hβ) and 3.43 (1 H, ddd, *J* 10.5, 3.5, 1.5, 6-Hα).

Crystal Structure Determination of the Azido Alcohol **4**.—*Crystal data.* $C_{13}H_{20}N_4O_3$, *M* = 280.33. Monoclinic, *a* = 11.519(6), *b* = 9.304(4), *c* = 13.807(7) Å, β = 104.12(4)°, *V* = 1434.9(8) Å^3, space group $P2_1/c$ (#14), *Z* = 4, *D*(calc.) = 1.298 g cm^{-3}. Colourless plates (from ethyl acetate). Crystal dimensions 0.50 × 0.40 × 0.15 mm, μ(Cu-Kα) = 7.388 cm^{-1}, *F*(000) = 600.

Data collection and processing. Lattice parameters were determined from the setting angles of 25 reflections well distributed in reciprocal space measured on an Enraf Nonius Turbo CAD-4 diffractometer. Intensity data also were collected on the diffractometer at 295K using graphite monochromated

* Ratio determined from integration of the respective 6-H signals, δ_H 3.80 and 3.56.

† Ratio determined from integration of the respective 6-H signals δ_H 3.57 and 3.43.

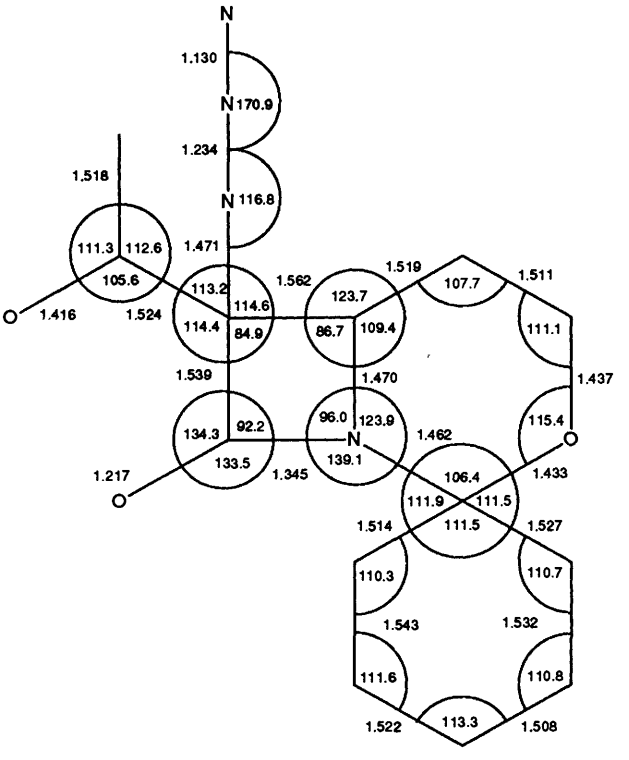


Fig. 8 Bond lengths (Å) (standard deviations 0.003–0.004 Å) and bond angles (°) (standard deviations 0.2–0.3°) of the azido alcohol **4**

Table 3 Fractional atomic coordinates for the azido alcohol **4**

Atom	*x*	*y*	*z*
O(1)	0.2250(2)	0.9250(2)	0.7825(2)
O(2)	0.3778(2)	0.5946(2)	0.6332(2)
O(3)	−0.0785(2)	0.6138(2)	0.6409(2)
N(1)	0.2513(2)	0.7826(3)	0.6485(2)
N(2)	−0.0076(2)	0.9060(3)	0.6066(2)
N(3)	−0.0977(2)	0.8736(3)	0.5413(2)
N(4)	−0.1820(3)	0.8628(4)	0.4795(2)
C(2)	0.1930(2)	0.8481(3)	0.7096(2)
C(3)	0.0716(2)	0.7873(3)	0.6518(2)
C(4)	0.1445(3)	0.7188(3)	0.5819(2)
C(5)	0.1631(3)	0.5580(4)	0.5738(2)
C(6)	0.2851(3)	0.5356(4)	0.5540(2)
C(8)	0.3740(2)	0.7474(3)	0.6451(2)
C(9)	0.4627(3)	0.7811(4)	0.7429(3)
C(10)	0.5913(3)	0.7468(4)	0.7353(3)
C(11)	0.6218(3)	0.8240(5)	0.6475(3)
C(12)	0.5324(3)	0.7894(4)	0.5509(3)
C(13)	0.4051(3)	0.8265(4)	0.5579(3)
C(14)	0.0136(3)	0.6842(3)	0.7118(2)
C(15)	−0.0356(3)	0.7603(4)	0.7905(3)

copper radiation and an $\bar{\omega}$–2θ variable speed scan technique. No decrease in the intensities of three monitor reflections measured at the beginning, end and every 3 h of exposure time was observed (maximum change 0.4%). Data were corrected for Lorentz and polarization effects. Symmetry equivalent zonal reflections were averaged (R_{int} = 0.019). Data were corrected for the effects of absorption using the DIFABS alogorithm: 2216 reflections were measured ($2° \leq 2\theta \leq 120°$, $h,k, \pm l$) of which 2106 were unique, giving 1659 with $I \geq 2\sigma(I)$.

Structure analysis and refinement. The structure was solved by direct methods using the MULTAN80 program series. Atomic positions were initially refined with isotropic temperature factors and subsequently with anisotropic displacement parameters. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$. Weights, w, were eventually assigned to the data as $w = 1/\sigma^2(F_o) = [\sigma^2(I_c) + (0.03F_o^2)^2]$. Positions for all hydrogen atoms were located from difference Fourier maps but were held fixed in the final refinement stages at positions calculated from geometrical considerations. Isotropic temperature factors for hydrogen atoms also were held fixed at 1.3 Beq of the attached atom. The full matrix least-squares refinement converged (max Δ/σ = 0.16) to values of the conventional crystallographic residuals R = 0.058, wR = 0.074 and S = 2.025. A final difference Fourier map was featureless with maximum density of ±0.298 e Å^{-3}. Values of the neutral atom scattering factors were taken from the International Tables for X-ray Crystallography. Atomic coordinates are given in Table 3 and bond lengths and bond angles in supplementary Fig. 8.* All programmes used were incorporated in a locally modified SDP package.[12]

Table 4 Fractional atomic coordinates for keto sulfide **17**

Atom	*x*	*y*	*z*
S	−0.021 04(9)	0.864 00(2)	0.639 30(7)
O(2)	−0.327 0(2)	0.840 09(6)	0.926 1(2)
O(7)	0.181 7(2)	0.824 86(5)	1.246 3(2)
O(14)	−0.162 6(3)	0.935 19(6)	0.954 8(2)
N(1)	0.012 5(2)	0.824 72(5)	0.999 0(2)
C(2)	−0.151 2(3)	0.845 12(7)	0.926 1(3)
C(3)	−0.023 6(3)	0.875 40(7)	0.840 6(3)
C(4)	0.157 9(3)	0.852 69(7)	0.936 6(3)
C(5)	0.282 6(3)	0.876 73(7)	1.065 4(3)
C(6)	0.349 6(3)	0.844 81(8)	1.192 4(3)
C(8)	0.065 5(3)	0.798 22(7)	1.136 4(2)
C(9)	0.183 7(3)	0.758 84(7)	1.096 3(3)
C(10)	0.053 5(3)	0.724 96(7)	1.008 3(3)
C(11)	−0.113 3(3)	0.711 54(8)	1.095 1(3)
C(12)	−0.238 9(3)	0.750 45(8)	1.124 3(3)
C(13)	−0.114 7(3)	0.785 45(8)	1.210 9(3)
C(14)	−0.042 1(4)	0.923 22(7)	0.877 0(3)
C(15)	0.097 3(5)	0.953 85(8)	0.816 5(4)
C(16)	−0.214 5(4)	0.895 94(7)	0.543 2(3)
C(17)	−0.396 4(4)	0.901 73(8)	0.593 2(3)
C(18)	−0.538 0(4)	0.927 57(8)	0.511 1(3)
C(19)	−0.503 7(4)	0.947 11(8)	0.375 7(3)
C(20)	−0.326 7(5)	0.939 59(9)	0.323 7(3)
C(21)	−0.180 2(4)	0.914 2(1)	0.405 7(3)
C(22)	−0.660 3(6)	0.975 9(1)	0.289 0(4)

Crystal Structure Determination of the Keto Sulfide **17**.—*Crystal data.* $C_{20}H_{25}NO_3S$, M = 359.48. Monoclinic, a = 6.819(5), b = 31.068(16), c = 8.799(4) Å, β = 97.65(5)°, V = 1847.4(17) Å^3, space group $P2_1/n$ (#14), Z = 4, D(calc.) = 1.285 g cm^{-3}. Colourless irregular prism from ethanol. Crystal dimensions 0.15 × 0.20 × 0.35 mm, μ(Cu-Kα) = 16.607 cm^{-1}, F(000) = 760.

Data collection and processing.—As for compound **4** (W scan width 0.9 + 0.15tanθ) with 3549 reflections measured ($2° \leq 2\theta \leq 135°$, $h, k, \pm l$) of which 3264 were unique (merging R = 0.026 after absorption correction), giving 2552 observations with $I \geq 3\sigma(I)$. Corrections were made for Lorentz and polarization effects and secondary extinction [2.51(5) × 10^{-6}] of the type described by Zachariasen.[13]

Structure analysis and refinement. Atom positions were located as for compound **4**. Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogen atoms isotropic converged (max Δ/σ = 0.02) to values of the crystallographic residuals R = 0.044, wR = 0.059 and S =

* Supplementary data (see 'Instructions for Authors' *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1). H-Atom coordinates, a full list of bond distances and angles including estimated standard deviations, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

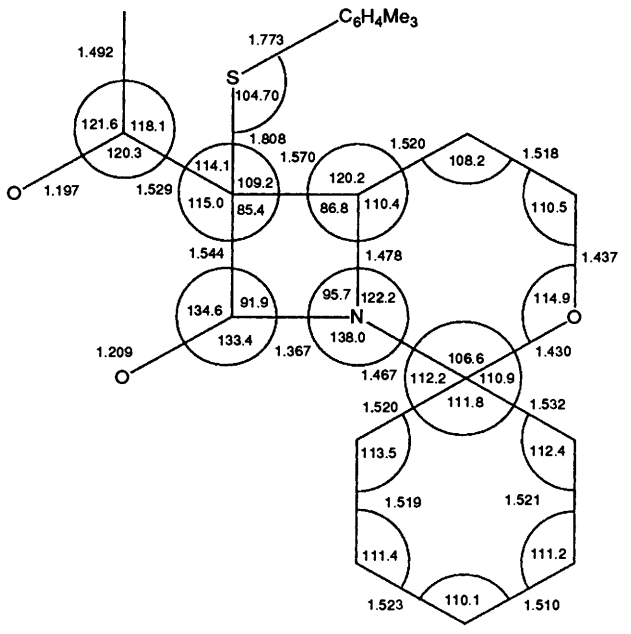


Fig. 9 Bond lengths (Å) (standard deviations 0.002–0.004 Å) and bond angles (°) (standard deviations 0.09–0.3°) of the keto sulfide **17**

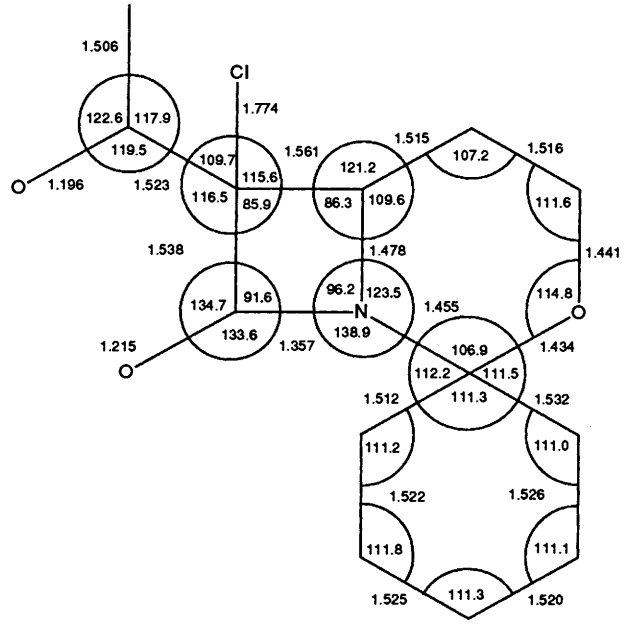


Fig. 10 Bond lengths (Å) (standard deviations 0.002–0.004 Å) and bond angles (°) (standard deviations 0.1–0.2°) of the chloro ketone **20**

1.621. A final difference Fourier map showed maximum density of ± 0.268 e Å^{-3}. Weights as for **4** with $\rho = 0.04$.

Atomic coordinates are given in Table 4 and bond lengths and bond angles in supplementary Fig. 9.

Crystal Structure Determination of the Chloro Ketone **20**.—*Crystal data*: $C_{13}H_{18}ClNO_3$, $M = 271.75$. Triclinic, $a = 6.334(5)$, $b = 6.439(3)$, $c = 18.262(8)$ Å, $\alpha = 96.86(4)°$, $\beta = 93.54(5)°$, $\gamma = 112.89(5)°$, $V = 676.4(10)$ Å^3, space group $P\bar{1}$ (#2), $Z = 2$, D(calc.) 1.334 g cm^{-3}. Colourless irregular prism (from ethanol). Crystal dimensions 0.50 × 0.20 × 0.20 mm, μ (Cu-Kα) = 25.368 cm^{-1}, $F(000) = 288$.

Data collection and processing. As for compound **4** (W scan width = 0.90 + 0.15tanθ); 2683 reflections were measured ($2° \leq 2\theta \leq 135°$, $h \pm k \pm l$), of which 2319 were unique [merging $R = 0.028$ after absorption correction], giving 1736 observations with $I \geq 3\sigma(I)$. Corrections for Lorentz and polarization factors and for secondary extinction [6.13(2) × 10^{-6}] of the type described by Zachariasen.[13]

Structure analysis and refinement. Direct methods, followed by Fourier maps were used to locate the atom positions. Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogen atoms isotropic, with the exception of two equal occupancy, disordered orientations for the methyl group hydrogens. Isotropic temperature factors were assigned to all hydrogens as 1.3 Beq of the attached atom. Convergence (max $\Delta/\sigma = 0.03$) to values of the crystallographic residuals $R = 0.055$, $wR = 0.069$ and $S = 2.68$. A final difference Fourier map showed maximum density of ± 0.300 e Å^{-3}. Weights as for compound **4** with $\rho = 0.02$.

Atomic coordinates are given in Table 5 and bond lengths and bond angles in supplementary Fig. 10.

Table 5 Fractional atomic coordinates for chloro ketone **20**

Atomic	x	y	z
Cl	0.152 4(2)	0.783 4(1)	0.047 06(5)
O(2)	−0.145 4(3)	0.781 4(4)	0.196 5(1)
O(7)	0.486 6(3)	1.072 9(3)	0.345 3(1)
O(14)	0.116 6(4)	1.282 6(4)	0.153 4(2)
N(1)	0.245 8(4)	0.869 7(4)	0.237 3(1)
C(2)	0.060 7(5)	0.854 9(5)	0.192 1(2)
C(3)	0.214 9(5)	0.965 0(5)	0.133 7(2)
C(4)	0.419 5(5)	0.968 9(5)	0.186 9(2)
C(5)	0.604 2(5)	1.191 8(5)	0.226 7(2)
C(6)	0.677 6(6)	1.148 9(6)	0.302 0(2)
C(8)	0.304 6(5)	0.857 5(5)	0.314 5(2)
C(9)	0.380 9(5)	0.660 3(5)	0.318 3(2)
C(10)	0.447 0(6)	0.644 4(6)	0.398 6(2)
C(11)	0.250 4(7)	0.622 6(7)	0.444 9(2)
C(12)	0.171 8(6)	0.817 0(6)	0.440 4(2)
C(13)	0.108 3(5)	0.835 3(5)	0.360 4(2)
C(14)	0.230 8(5)	1.200 0(5)	0.121 1(2)
C(15)	0.401 1(6)	1.324 4(6)	0.071 0(2)

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