Stereoelectronic Control of the Tertiary Ketol Rearrangement: Implications for the Mechanism of the Reaction Catalysed by the Enzymes of Branched-chain Amino Acid Metabolism, Reductoisomerase and Acetolactate Decarboxylase

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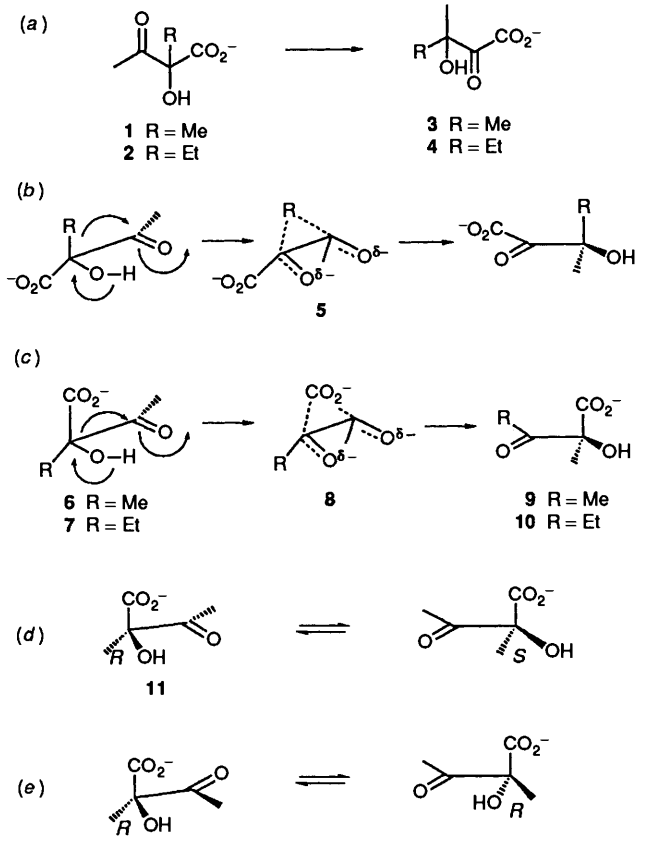
The alkali-catalysed rearrangement of (*R*)-[1-^{13}C]-3-hydroxy-3-methylpentan-2-one has been studied. Rearrangement *via* a transition state having an *anti* arrangement of C–O bonds was preferred over that with a *syn* arrangement by a factor of 1.8:1. The result is of interest in relation to the mechanism of action of the enzymes reductoisomerase and acetolactate decarboxylase, both of which are involved in the metabolism of the branched-chain amino acids. The structure and relative configuration of the product **23** of bromolactonisation of *N*-methacrylolyl L-proline **22** were determined by X-ray crystallographic analysis.

The enzyme reductoisomerase (ketol-acid reductoisomerase, EC 1.1.1.86) of the biosynthetic pathway of the branched-chain amino acids (valine, isoleucine, leucine) catalyses the rearrangement of the *S*-enantiomers of α-acetolactate (2-hydroxy-2-methyl-3-oxobutanoate) **1** and of α-acetohydroxybutyrate (2-ethyl-2-hydroxy-3-oxobutanoate) **2** into 3-hydroxy-3-methyl-2-oxobutanoate **3** and 3-hydroxy-3-methyl-2-oxopentanoate **4** respectively [Scheme 1(*a*)].[1] During this



Scheme 1

biological tertiary ketol rearrangement, the migrating alkyl group is transferred to the *re*-face of the trigonal carbonyl centre.[2] If it is assumed that the rearrangement is suprafacial, and takes place *via* a minimum energy pathway in which the bond to the migrating group is parallel to the adjacent π system, the transition state must be as shown in **5** [Scheme 1(*b*)], with a *syn* arrangement of the oxygen substituents.

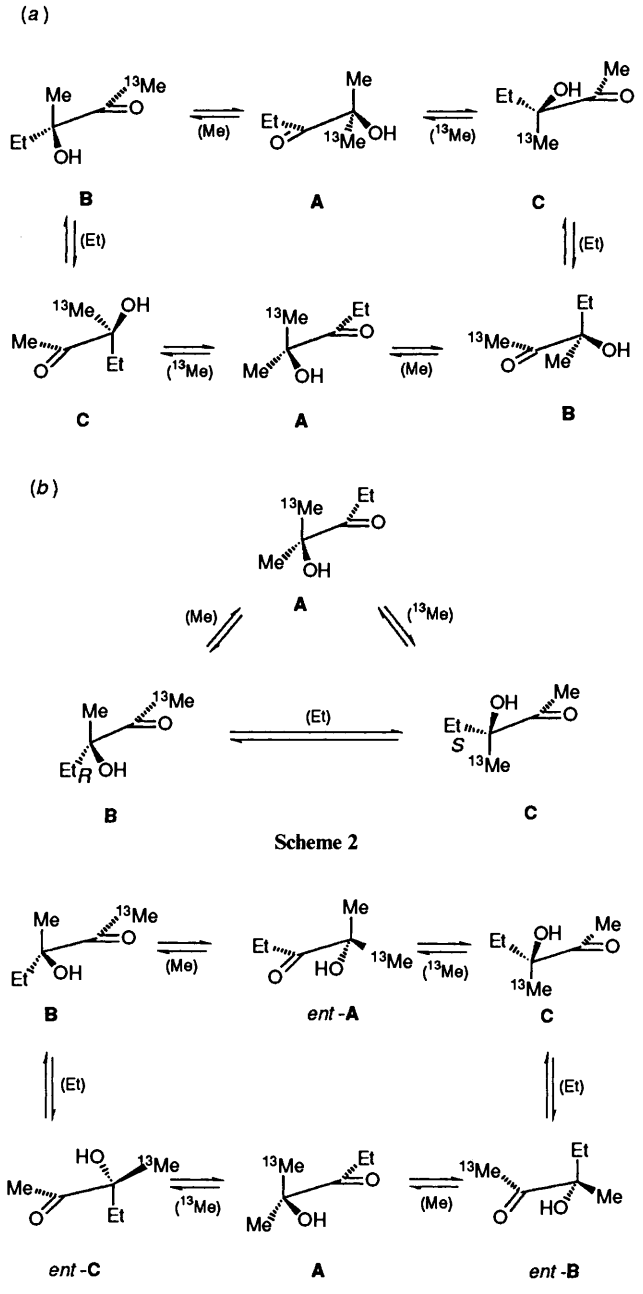
Recently, evidence has been obtained[3,4] which suggests that the enzyme acetolactate decarboxylase [(*S*)-2-hydroxy-2-methyl-3-oxobutanoate carboxy-lyase, EC 4.1.1.5] catalyses decarboxylation of the *R*-enantiomers of the carboxylates **6** and **7** *via* a tertiary ketol rearrangement to the isomeric species **9** and **10** with migration of the carboxylate group. The overall stereochemistry of this rearrangement again requires a *syn* arrangement of the oxygen substituents [**8**, Scheme 1(*c*)].[4]

When optically pure (*R*)-α-acetolactate **11** [Scheme 1(*d*)] was treated with alkali, it was racemised by a mechanism shown to involve degenerate tertiary ketol rearrangement with carboxylate migration.[5] For racemisation to occur, a *syn* arrangement of the oxygen substituents is again necessary [Scheme 1(*d*)]. An *anti* arrangement would lead overall to retention of configuration [Scheme 1(*e*)]. The actual mechanism might involve a mixture of *syn* and *anti* modes; it is only necessary for there to be a *syn* component for racemisation to occur.

It was thus pertinent to enquire whether this predilection for a '*syn*' transition state was attributable to a stereoelectronic imperative of the tertiary ketol rearrangement or whether, in the enzymatic reactions, the stereochemistry was imposed by the architecture of the active sites.

In order to investigate this question, it was necessary to use the simplest possible model system in order to avoid diastereoisomeric bias. It was also decided to eliminate the carboxylate group in order to avoid or reduce powerful electrostatic interactions. With these conditions in mind, the substrate **B** (Scheme 2) was chosen as a test vehicle for the investigation. This ketol was planned to be a pure enantiomer and to carry a ^{13}C label in the acetyl group so that analysis of the outcome of tertiary ketol rearrangement by NMR spectroscopy would be possible.

In Scheme 2(*a*) are shown the various species that would arise if ketol **B** were allowed to undergo tertiary ketol rearrangement, accepting the possibility that either group (methyl or ethyl) attached to the tertiary centre might migrate. The further restriction of a strictly '*syn*' transition state is imposed. For each equilibrium, the group migrating is indicated above the equilibrium arrows. Inspection of this scheme shows that only three discrete species are involved. Accordingly it can be described by the condensed version [Scheme 2(*b*)]. The salient features of this system are: (*i*) the *R*-enantiomer of ketol **B** has the ^{13}C label in the acetyl group; (*ii*) the *S*-enantiomer of the ketol **C** has the ^{13}C label in the methyl group attached to the



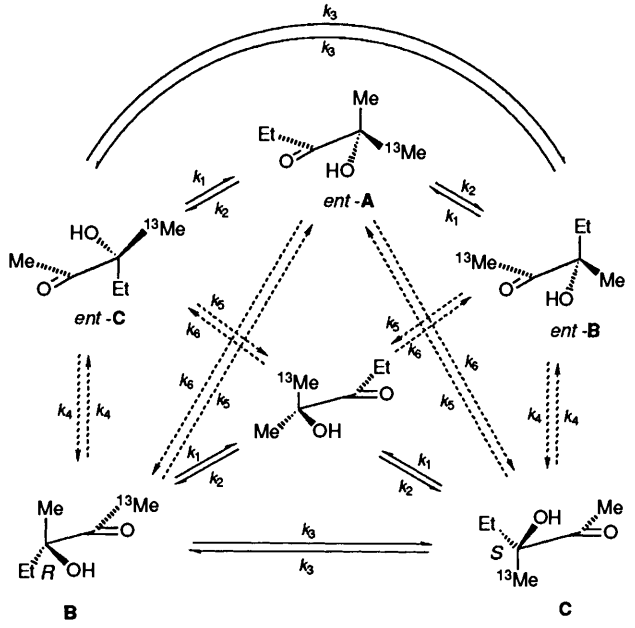
Scheme 2

Scheme 3

chiral centre; (*iii*) the prochiral ketol **A** has the ^{13}C label in the *pro-S* methyl group. If a similar scheme is drawn up that involves strictly '*anti*' transition states, six independent species are generated (Scheme 3). Three of these are identical with the three species of Scheme 2(*b*); the remaining three are their enantiomers.

If Schemes 2(*b*) and 3 are combined, Scheme 4 results. This describes two stereochemical dimensions. The species joined by solid equilibrium arrows [the species of Scheme 2(*b*)] are locked into one stereochemical dimension by the imposition of a strictly '*syn*' transition state for their interconversion. They can only escape into the other stereochemical dimension (rearranging *via* the sequence joined by dotted equilibrium arrows) if some degree of '*anti*' rearrangement is permitted. However, once formed, members of the enantiomeric series may also undergo interconversion *via syn* rearrangements (Scheme 4).

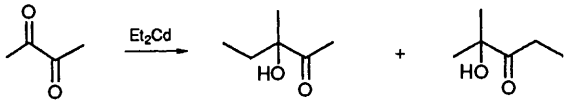
The degree to which a strictly '*syn*' transition state is avoided can thus, in principle, be determined by measuring the rate of leakage from the '*syn*' dimension (containing the species joined



Scheme 4

by the solid arrows of Scheme 4) into the total system which also contains the enantiomeric species.

It was proposed to use ^1H NMR spectroscopy for chiral analysis, since the position of the ^{13}C label would be readily determined from the ^{13}C satellite pattern. However, it was also planned to carry out this analysis on the total product mixture, since this would avoid tedious separation of isomeric species. Accordingly, a mixture of the required ketols was prepared as shown in Scheme 5.[6] The ketols were separated by spinning



Scheme 5

band distillation and from the pure ketols a 50:50 mixture was prepared. After numerous trials with this mixture it was found that baseline resolution of the signals attributable to the enantiotopic methyl groups of the prochiral ketol **12** and the quaternary methyl groups of the enantiomers of the chiral ketol **11** could be obtained for solutions in carbon tetrachloride in the presence of the chiral solvating agent (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol (Fig. 1).

Synthesis of the required optically pure ^{13}C-labelled ketol **20** was carried out as shown in Scheme 6. It was based on the published synthesis of (3*R*)-3-hydroxy-3-methylbutanoic acid **16** *via* bromolactonisation of *N*-tigloyl L-proline **13**.[7] A variety of methods was investigated for the methylation of this acid to the corresponding ketone. These included (using the free acid, salt or acid chloride as appropriate): (*i*) $Na_2[Fe(CO)_4]$/MeI[8]; (*ii*) MeLi/tetrahydrofuran(THF); (*iii*) MeMgI, CuCl; (*iv*) Me_2Cd; (*v*) MeMgI/**21**.[9] Although the CuCl-catalysed reaction (*iii*) worked well with EtMgI and the acid chloride of 2-benzyloxy-2-methylpropanoic acid **26** (Scheme 7), it failed with MeMgI. The same result was obtained with the acid chloride of the chiral homologue **18** (Scheme 6). Also, on a several gramme scale and using racemic starting material, the benzyl ether **19** of the required ketol could be obtained in good yield (74%) from the acid **18** and methyllithium. However, this method was difficult to carry out on the scale envisaged for the synthesis

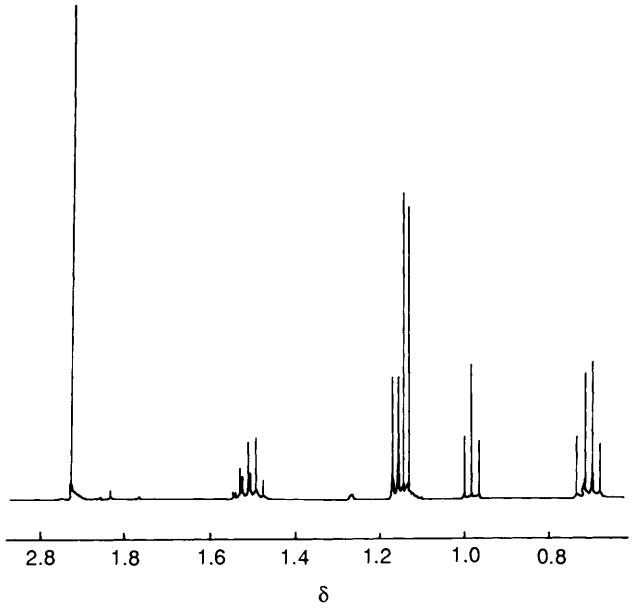
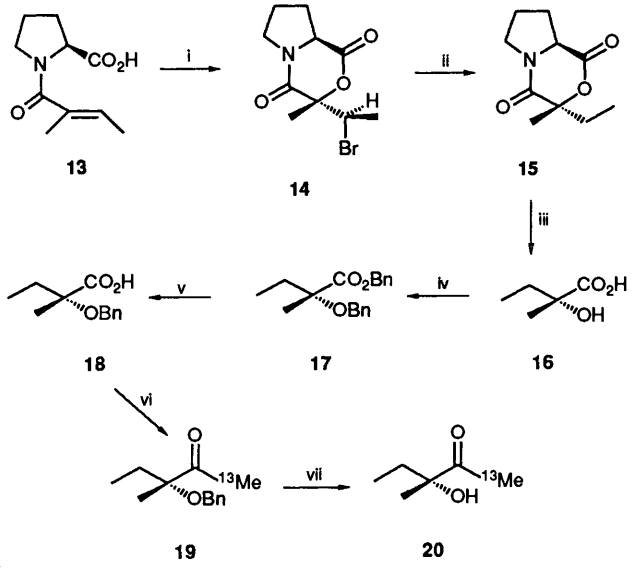


Fig. 1 The 400 MHz NMR spectrum of a mixture of 3-hydroxy-3-methylpentan-2-one and 2-hydroxy-2-methylpentan-3-one in CCl_4 in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. The upfield pair of signals in the group of four singlets near δ 1.1 are attributable to the carbinol methyl groups of the chiral ketol and the downfield pair to the enantiotopic methyl groups of the prochiral ketol.

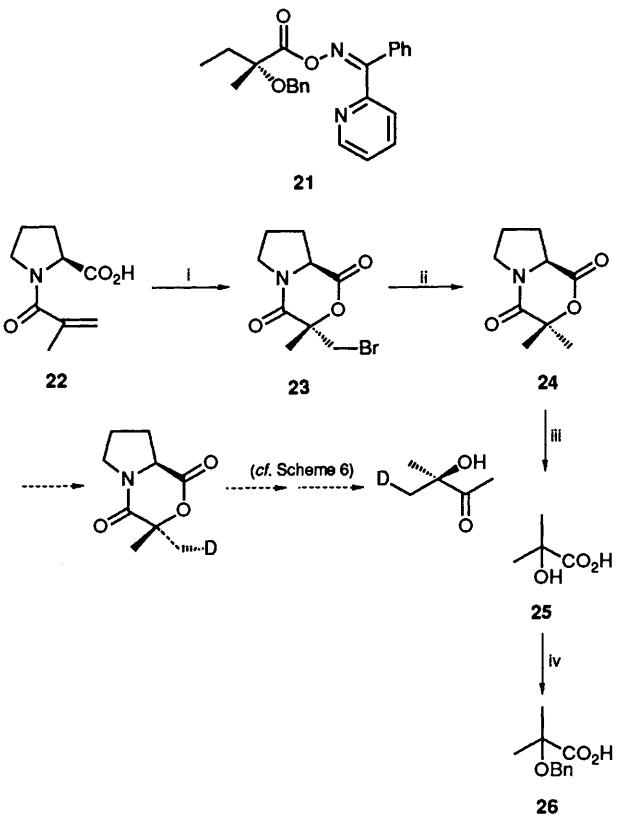


Scheme 6 *Reagents:* i, *N*-bromosuccinimide; ii, Bu_3SnH; iii, KOH/H_2O; iv, $PhCH_2Cl/NaH$; v, KOH/H_2O; vi, $SOCl_2$, $^{13}MeCu$; vii, H_2–Pd

using ^{13}C labelled iodomethane. Eventually, an acceptable yield of the benzyl ether **19** of the required methyl ketone was obtained on a small scale by reaction of methylcopper with 2-benzyloxy-2-methylbutanoyl chloride.

Preparation of the required benzyl-protected acid **18** required rather forcing conditions both for benzylation to the benzyl ether of the benzyl ester **17** and for hydrolysis of this. However, the optical purity of the product **18** was confirmed by ^1H NMR spectroscopic examination of the ion pair of the acid with (−)-α-methylbenzylamine. No trace of the *S*-enantiomer could be detected. The validity of the analysis was confirmed by addition of a small amount of racemate to the analytical solution.

Debenzylation of the ketone **19** by hydrogenolysis over palladium on charcoal proved capricious, but palladium black proved to be effective and reliable. The labelled ketol was isolated by preparative GLC.



Scheme 7 *Reagents:* i–iv, as in Scheme 6

In order to assign the signals near δ 1.15 attributable to the methyl groups of the prochiral ketol (**12**, Scheme 5), its synthesis in stereospecifically deuteriated form was proposed as shown in Scheme 7. The outcome of this route was not certain as the bromolactonisation of αβ-unsaturated prolyl amides had been found to be highly structure-dependent. Thus the tigloyl derivative reacted as shown in Scheme 6. However, the 3-methylbut-2-enoyl (senecioyl) amide reacted to give a seven-membered ring lactone with bromine attack at C-2, and the *trans*-crotonyl amide failed to react.[10] Therefore, it was by no means certain that the methacryloyl amide **22** would react in the desired manner. However, the anticipated bromolactone **23** was indeed produced. The stereochemistry of the compound was the only remaining uncertainty. Although by analogy with the tigloyl case (**14**, Scheme 6), a product with the 3*S*-configuration was expected to be formed, the anticipated stereochemistry was confirmed by X-ray crystallographic analysis of the bromolactone. Although the refined molecular dimensions are not sufficiently accurate to convey detailed structural information, the overall stereochemistry of the molecule (Fig. 2) is clearly defined. Each of the three independent molecules in the asymmetric unit is identical and has the structure and stereochemistry expected by analogy with the higher homologue **14**. Reduction of the bromolactone proceeded smoothly to give the lactone **24**, which in turn was hydrolysed to give 2-hydroxy-2-methylpropanoic acid **25**, which could be converted into the corresponding benzyl ether **26** as with the higher homologue **18** (Scheme 6). Assignment of the NMR signals attributable to the enantiotopic methyl groups proved to be unnecessary for the purposes of this investigation (see below). It was necessary to establish suitable conditions for the tertiary ketol rearrangement. This was found to occur smoothly in 5 mol dm^{-3} NaOH at 80 °C.

For the key rearrangement experiment, it was clearly necessary to establish the optical purity of the starting ketol **20**. This was done by chiral analysis using the chiral solvating agent

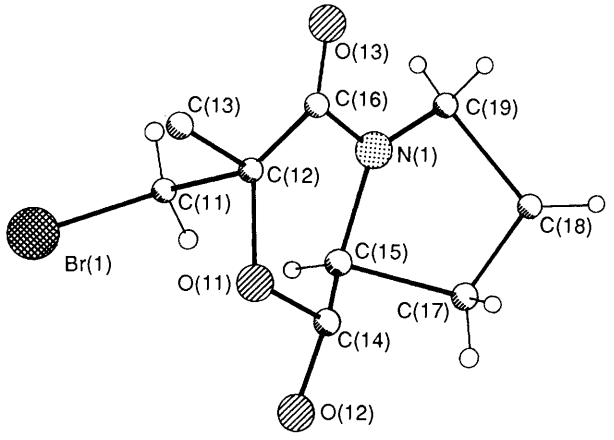


Fig. 2 The X-ray crystallographic structure of (3*S*, 8a *S*)-3-bromomethyl-3-methyl-1,4-dioxo-3,4,6,7,8,8a-hexahydro-1*H*-pyrrolo[2,1-*c*]-[1,4]-oxazine **23**

(*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol. The spectrum obtained is shown in Fig. 3(*a*). In Fig. 3(*b*) is shown the ^{1}H NMR spectrum of the same sample determined after addition of racemic unlabelled ketol. From these results the ketol **20** was judged to have an optical purity (e.e.) of >96%. These spectra also show that the upfield signal attributable to the methyl group attached to the carbinol carbon atom in the ketol (as **20**) can be assigned to the (*R*)-enantiomer.

The ketol **20** was heated at 80 °C in 5 mol dm^{-3} NaOH. After 16.3 h, almost full equilibrium had been achieved between all six species of Scheme 4. This is evident from the spectra of Fig. 4. Chemical shifts in these spectra vary slightly owing to small differences in the ratios of chiral solvating agent and substrate employed. However, because all peaks are readily assigned, it was possible, by using relative integrations, to plot the changes in four independent species (**B**, *ent*-**B**, **C**, *ent*-**C**) and the sum of **A** and *ent*-**A** (since the methyl signals attributable to **A**/*ent*-**A** had not been assigned). However, since in the t = 30 min spectrum, peaks attributable to **A**/*ent*-**A** were barely visible, and at t = 3, 6, 16.3 h, these peaks were of equal intensity, [**A**] was effectively equal to [*ent*-**A**] at all observation points. Taking these factors into account, the concentrations of all six species are shown to have varied as shown in Fig. 5.

With respect to '*syn*' and '*anti*' transition states, the 30 min spectrum was informative. At this time, only products attributable to ethyl group migration were apparent. The ^{13}C-coupled signals attributable to species **C** and *ent*-**C** were seen to have relative intensities 1:1.8, indicating preferred formation from **B** of *ent*-**C**, corresponding to an '*anti*' transition state. Also, since only 12% conversion of **B** had occurred at this time the ratio of **C** to *ent*-**C** could be taken as the ratio of the initial rates of conversion of **B** into **C** and *ent*-**C**, *i.e.* k_4/k_3 = 1.8:1.

Approximate values for the rate constants of Scheme 4 were obtained by an iterative fitting procedure using a numerical integration computer program (FACSIMILE). The rate constants extracted from the fitting procedure were: k_1, 0.19 × 10^{-3} ± 0.15 × 10^{-3}; k_3, 0.85 × 10^{-3} ± 0.14 × 10^{-3}; k_4, 1.21 × 10^{-3} ± 0.16 × 10^{-3}; k_5, 0.27 × 10^{-3} ± 0.16 × 10^{-3}; k_6, 0.55 × 10^{-3} ± 0.43 × 10^{-3}; k_2 ($=k_1k_6/k_5$), 0.38 × 10^{-3} ± 1.53 × 10^{-3} mol dm^{-3} min^{-1}. Owing to the cyclic nature of the equilibrating system (Scheme 4), there are only five independent rate constants. The dependent constant was chosen to be k_2. Second order kinetics were assumed, as for the closely related benzilic acid rearrangement.[11] The effectiveness of the simulation using these rate constants is shown in Fig. 5, in which are compared the observed changes in concentrations of the species of Scheme 4 and the changes simulated by the FACSIMILE program using the rate constants derived from the iterative fitting procedure.

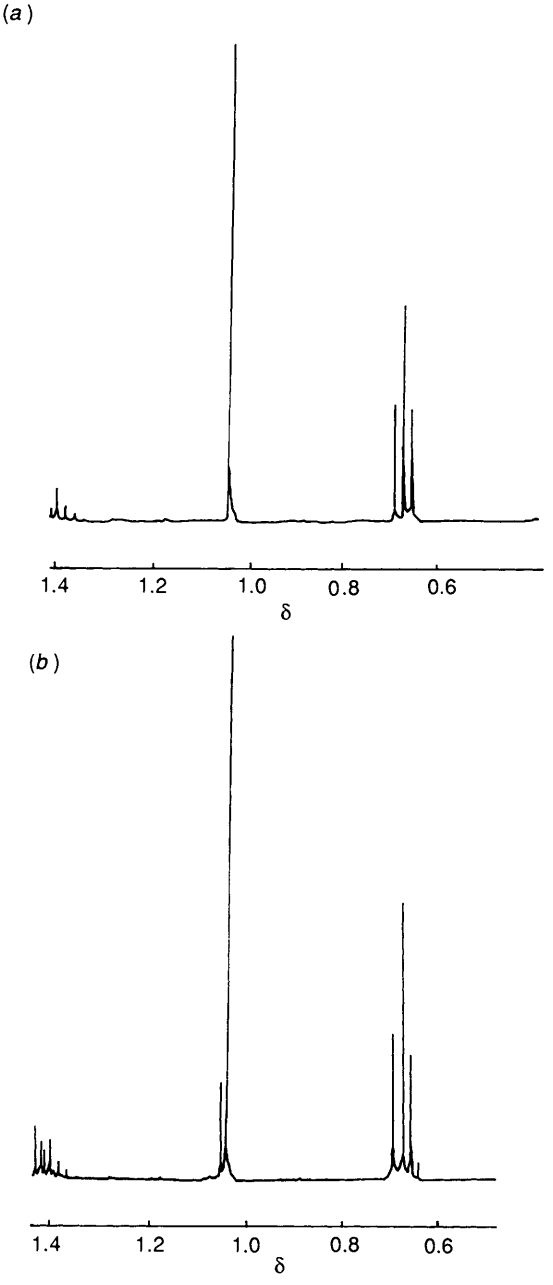


Fig. 3 The 400 MHz NMR spectra of (*a*) (*R*)-[1-^{13}C]-3-hydroxy-3-methylpentan-2-one **20** in CCl_4 in the presence of (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol; (*b*) the same sample after the addition of racemic, unlabelled ketol

The statistical significance of the computed rate constants is barely high enough to be used as kinetic evidence to support the proposition that an *anti* mode of migration for the alkyl group is preferred over a *syn* mode (k_4/k_3 = 1.4 ± 0.2). However, if the relative rates of ethyl *vs.* methyl migration in the *syn* (k_3/k_1) and *anti* (k_4/k_5) modes are calculated, the values obtained (4.6 ± 0.8 and 4.6 ± 0.6 respectively) give a reasonably accurate indication of the relative migratory aptitude of ethyl and methyl groups in this system.

In studies of cationic rearrangements (pinacol, bis-t-alkylketone rearrangements) the concept of 'migratory tendency' was developed.[12] It was pointed out that 'migratory aptitudes' as measured by intramolecular competition experiments were not determined solely by inherent properties of the migrating groups. The relief of steric strain at the migration origin

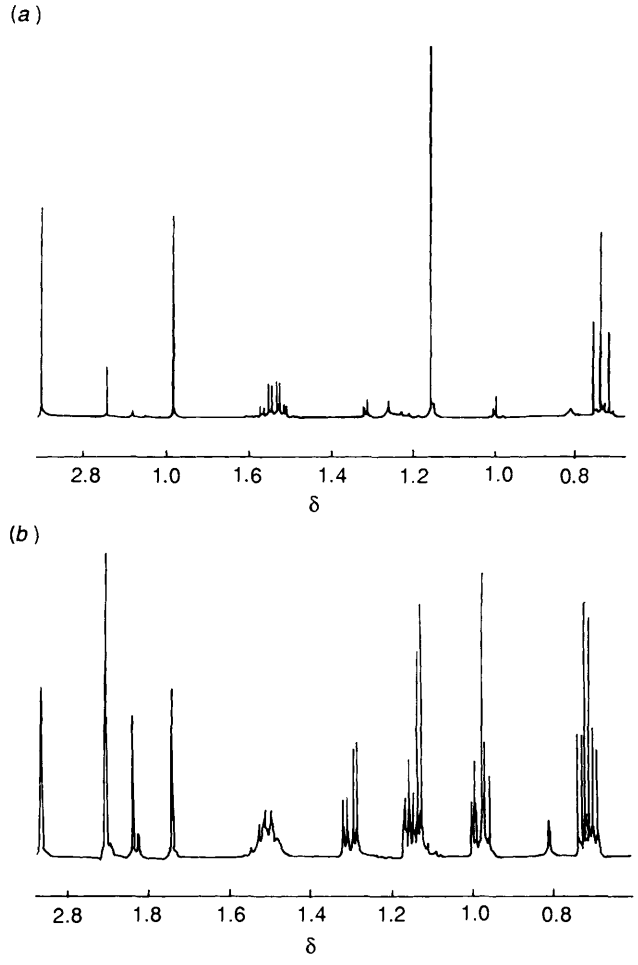


Fig. 4 The 400 MHz NMR spectra of the mixture in CCl_4 and in the presence of (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol extracted from a solution of (*R*)-[1-^{13}C]-3-hydroxy-3-methylpentan-2-one **20** in 5 mol dm^{-3} NaOH at 80 °C after (*a*) 30 min; (*b*) 16.3 h

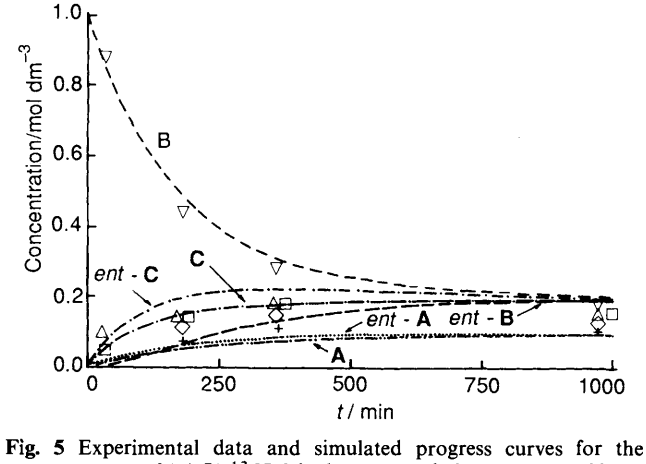


Fig. 5 Experimental data and simulated progress curves for the rearrangement of (*R*)-[1-^{13}C]-3-hydroxy-3-methylpentan-2-one **20**. +, **A**, *ent*-**A**; ▽, **B**; ◇, *ent*-**B**; □, **C**; △, *ent*-**C**

(accompanying changes in hybridisation from sp^3 to sp^2) would be different for the two groups. Correspondingly, increases in steric strain at the migration terminus would also be different. To quantify these effects the concept of partial rates was introduced, whereby the rates of migration of specified groups were related to that of a standard group (*e.g.* methyl). The partial rates so obtained could then be compared for a given migrating group in substrates with different non-migrating groups at the migration origin.[12–14] In this way it was shown

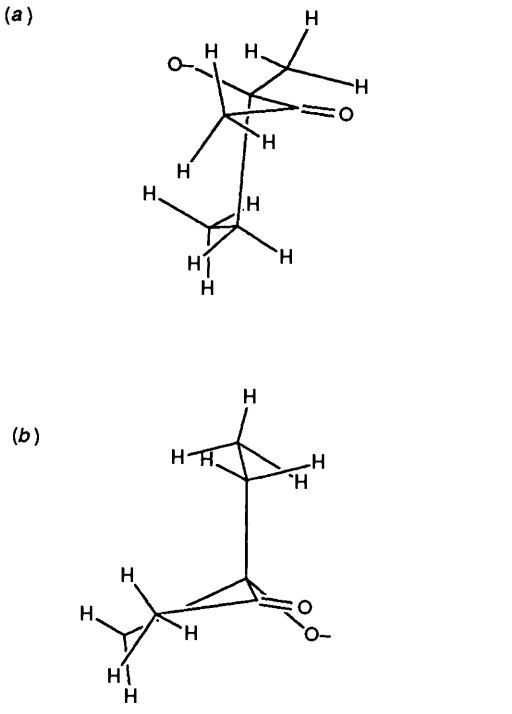
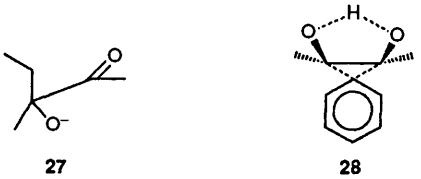


Fig. 6 (*a*) The energy minimised conformation of the alkoxide anion of 3-hydroxy-3-methylpentan-2-one; (*b*) conformation of the anion with an Et–C–C–C=O dihedral angle of 90° and a *syn* arrangement of C–O bonds

that in a pinacol rearrangement with methyl migration, changing the non-migrating group from methyl to ethyl increased the rate of methyl migration by a factor of five. (This value was derived on the assumption that the protonation behaviour of the different pinacols was similar.) In the present case, the relief of steric strain at the migration origin would be greater for methyl migration than for ethyl migration, and the increase of steric strain at the migration terminus would be lower. Thus the observed migratory aptitude of ethyl relative to methyl of 4.6:1 would translate into a migratory tendency of a higher value.

To explore further the reasons for the *anti* preference in the rearrangement studied in this work, starting conformations and their energies were explored using the molecular mechanics program PCMODEL. Global minimisation of the energy of anion **27** gave a conformation, Fig. 6(*a*), with an *anti*



27 **28**

arrangement of the C–O bonds and a dihedral angle for the Et–C–C=O system of 87°, very close to the presumed optimum angle for ethyl migration of 90°. However, when the carbinol methyl and ethyl groups were interchanged and minimisation was again performed with the Me–C–C=O dihedral angle fixed at 90°, the resulting conformation was found to have an energy (16.0 kJ mol^{-1}) only slightly higher than the energy (15.2 kJ mol^{-1}) of the conformation of Fig. 6(*a*). With a conformation with a fixed dihedral angle of 90° for Et–C–C=O, but with a *syn* relationship of the C–O bonds, Fig. 6(*b*), a much higher energy (50.1 kJ mol^{-1}) was found. The corresponding minimisation with the methyl and ethyl groups interchanged again gave an

energy only slightly higher (51.7 kJ mol^{-1}). The calculations take no account of solvation, which would reduce considerably the dipole–dipole repulsion terms for the *syn* conformations [*cf.* Fig. 6(*b*)] which make a major contribution to the total energy. However, it is clear that with respect to rearrangement, there is a considerable energy advantage in the *anti* rearrangement in the ground state. Thus, qualitatively, the molecular mechanics calculations are in agreement with the experimental results.

In the only previous study of stereochemical aspects of the tertiary ketol rearrangement[15] it was found that thermal rearrangement of optically active 3-hydroxy-3-phenylbutan-2-one occurred *via* a first-order, three-component cyclic equilibrium as proposed in the present study for the exclusively *syn* mode of rearrangement under pseudo unimolecular conditions. A three-component system was implied in the assumption that all rearrangement under the thermal conditions employed occurred *via* a *syn* transition state, **28**. This assumption is reasonable in view of the requirement for hydrogen transfer concomitant with alkyl or phenyl group migration. If the reaction were surface-catalysed, the assumption of purely *syn* rearrangement would not be justified. Since *anti* rearrangement would give a product enantiomeric with the product of *syn* rearrangement, measurements in the study referred to that were based on polarimetric observations, would be invalidated. Thermal rearrangement of tertiary ketols in contact with hot metal surfaces has been demonstrated.[16,17] Equally, however, it was shown that thermal rearrangement in the presence of glass-only surfaces does not occur at temperatures of 185[16] and 160 °C.[17] The temperatures used in the studies of thermal rearrangement ranged from 214 to 252 °C: a surface-catalytic effect cannot, therefore, be ruled out completely.

It can be concluded that the inherent stereoelectronic effect in the rearrangement of the tertiary ketol **B** (Scheme 4) is in favour of an *anti* mode. The effect of the charged carboxylate group, as in the species shown to undergo rearrangement *via* a *syn* conformation in the reactions catalysed by reductoisomerase and by acetolactate decarboxylase [Scheme 1(*b*, *c*)], will be the subject of a subsequent paper.

Experimental

^{1}H NMR spectroscopy was carried out at 220 MHz using a Perkin-Elmer R34 spectrometer, or at 400 MHz using a Bruker WH400 spectrometer. ^{13}C NMR spectra were determined at 100.62 MHz using a Bruker WH400 spectrometer. Mass spectra were determined using a Kratos MS80 mass spectrometer. [^{13}C]Iodomethane was purchased from the Aldrich Chemical Company Ltd. The software used was PCMODEL (Serena Software, Bloomington, IN, USA), TECHNICURVE (Aston Scientific Ltd, Ashton Clinton, Bucks, UK) and FACSIMILE (Computer Science and Systems Division, Harwell, UK).

Synthesis of 3-*Hydroxy*-3-*methylpentan*-2-*one* **11** *and* 2-*Hydroxy*-2-*methylpentan*-3-*one* **12**.—These were prepared according to the published procedure,[6] as a mixture of **11** (70%) and **12** (30%). The major component **11** (6.3 g) was isolated by distillation on a spinning band column of the mixture (14 g). δ_H(220 MHz, $CHCl_3$) 0.83 (3 H, t, *J*/Hz 7.3, *Me*CH_2), 1.38 [3 H, s, *Me*C(OH)], 1.75 (2 H, *J*/Hz 7.3, MeCH_2), and 2.22 (3 H, s, MeCO). A second fraction (4.8 g) consisting of **11** and **12** was obtained. Comparison of the ^{1}H NMR spectrum of the mixture with that of the pure ketol **11** showed that ketol **12** had the following NMR characteristics: δ_H(220 MHz, $CDCl_3$) 1.12 (3 H, t, *J*/Hz 7.3, *Me*CH_2), 1.39 [6 H, s, Me_2C(OH)], and 2.59 (2 H, q, *J*/Hz 7.3).

Synthesis of (±)-2-*Benzyloxy*-2-*methylbutanoic acid*.—To a vigorously stirred suspension of sodium hydride (80% dispersion in oil, 5.1 g) in redistilled benzyl chloride (10 cm^3), under nitrogen was added dropwise over 40 min a solution of racemic 2-hydroxy-2-methylbutanoic acid (5.0 g) in benzyl chloride (50 cm^3) at such a rate that the temperature remained below 50 °C. The mixture was heated to 120 °C over 80 min and kept at this temperature, with stirring, under nitrogen for 89 h. The source of heat was removed and to the stirred solution were added THF (20 cm^3) and, dropwise, with extreme caution, a solution of KOH (5 mol dm^{-3}, 100 cm^3). The mixture was boiled under reflux for 21 h, after which time all of the benzyl chloride had reacted. The reaction mixture was cooled and concentrated under reduced pressure, to remove THF. To the residual two-phase mixture were added water (150 cm^3) and chloroform (100 cm^3) and the whole was thoroughly shaken. The organic phase was removed and the aqueous residue was again extracted with chloroform (3 × 50 cm^3). The aqueous phase was brought to pH 1 (conc. HCl) and extracted with chloroform (4 × 50 cm^3). The extracts were washed with hydrochloric acid (2 mol dm^{-3}, 2 × 50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a clear oil (6.5 g) that crystallised as a mass of white needles, m.p. 50.5–54 °C. The product (6.3 g) was purified by sublimation (46 °C, 0.04 mmHg) to give the benzyl ether, as *compound* **18** (5.8 g, 68%), m.p. 52.5–54.5 °C; (Found: C, 69.2; H, 7.80; M^+ 208.111. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74%; M 208.1099); δ_H(220 MHz, $CHCl_3$) 0.99 (3 H, t, *J*/Hz 6.6, *Me*CH_2), 1.57 (3 H, s, *Me*CO), 1.96 (2 H, m, MeCH_2), 4.50 (2 H, s, PhCH_2), and 7.40 (5 H, m, Ph); *m*/*z* (EI) 208 (0.4%), 190 (1.3), 179 (1.3), 163 (9.1), 108 (17), 107 (38), 100 (46), and 91 (100).

Synthesis of (3S,8aS)-3-[(R)-*Bromoethyl*]-3-*methyl*-1,4-*dioxo*-3,4,6,7,8,8a-*hexahydro*-1H-*pyrrolo*[2,1-c][1,4]*oxazine* **14**.—This was prepared according to the published procedure,[7] m.p. 104.5–112.5 °C (lit.,[7] 99–108 °C), $[\alpha]_D^{20}$ −79.2° (lit.,[7] −77.2°), yield 70%. On recrystallisation $[\alpha]_D^{24}$ −85.1° (lit.,[7] −83.2°).

Reductive Debromination of the Bromo Lactone **14**. *Synthesis of* (3R,8aS)-3-*Ethyl*-3-*methyl*-1,4-*dioxo*-3,4,6,7,8,8a-*hexahydro*-1H-*pyrrolo*[2,1-c][1,4]*oxazine* **15**.—A solution of tri-n-butyltin hydride (2.77 g, 9.5 mmol) in dry benzene (5 cm^3) was added dropwise over 2 min to a stirred solution of the bromo lactone **14** (2.0 g, 7.26 mmol) in benzene (10 cm^3) at 75 °C under N_2. The mixture was boiled gently under reflux for 15 h. The benzene was removed under reduced pressure to leave a mixture of oil and crystalline material. The residue was washed with n-hexane. The crystalline material was filtered off and washed with n-hexane to give the lactone **15** (1.34 g, 94%), m.p. 106–106.5 °C (lit.,[7] m.p. 99–101 °C for comparable material), $[\alpha]_D^{24}$ −117° (lit.,[7] −112°). Recrystallisation (EtOAc) gave 1.12 g (78%) m.p. 105.5–106.5 °C (softening at 99.5–100.5 °C). When the optical rotation was measured on a methanolic solution it had fallen to $[\alpha]_D^{19}$ −5.3° (presumably owing to epimerisation at the α-propyl centre). The rotation was measured in a different solvent: $[\alpha]_D^{21}$ −121° (*c* 0.76, $CHCl_3$).

(2R)-2-*Hydroxy*-2-*methylbutanoic acid*.—A solution of the lactone **15** {2.58 g, $[\alpha]_D^{21}$ −121° (*c* 0.76, $CHCl_3$)} in KOH solution (5 mmol dm^{-3}, 40 cm^3) was boiled gently under reflux for 11 h, diluted with water (80 cm^3) and acidified (conc. HCl) to pH 1. The solution was extracted with diethyl ether (50 cm^3), saturated with NaCl and again extracted with diethyl ether (4 × 50 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to give the acid **16** (1.52 g, 98%), m.p. 70–74 °C (lit.,[7] m.p. 72–74 °C); $[\alpha]_D^{24}$ −8.9° (*c* 3.0, $CHCl_3$) {lit.,[7] $[\alpha]_D^{20}$ −8.9° (*c* 2.97, $CHCl_3$)}; δ_H(400 MHz, $CHCl_3$) 0.93 (3 H, t, *J*/Hz 7.45, *Me*CH_2), 1.46 (3 H, s, MeCO) and 1.715, 1.85 (each 1 H, dq, *J*/Hz 7.44, 14.00,

MeCH_2). A portion was sublimed (65 °C, 20 mmHg) to give fine needles m.p. 73.5–75 °C. For chiral analysis, a solution in $CDCl_3$ with an equimolar amount of (−)-α-methylbenzylamine was examined by ^{1}H NMR spectroscopy (400 MHz). No enantiomeric splitting of signals could be observed. The validity of the analysis was confirmed by the addition of racemic acid, whereupon signals attributable to the diastereoisomeric complex could be observed. This showed that <2% of the *S*-enantiomer would have been readily detectable.

Synthesis of (R)-2-*Benzyloxy*-2-*methylbutanoic acid* **18**.—To a suspension of NaH (80% dispersion in mineral oil, 1.28 g) in benzyl chloride (5 cm^3) was added under N_2 with stirring over 30 min a solution of (*R*)-2-hydroxy-2-methylbutanoic acid (1.24 g) in benzyl chloride (23 cm^3). The temperature was increased to 120 °C and stirring was continued for 69 h. The source of heating was removed and THF (10 cm^3) and KOH solution (5 mol dm^{-3}, 50 cm^3) were added cautiously. The mixture was boiled gently under reflux for 55 h, cooled and evaporated under reduced pressure to remove THF. Water (50 cm^3) and chloroform (50 cm^3) were added and the mixture was shaken. The organic layer was separated and the aqueous residue was extracted with chloroform (3 × 25 cm^3). The combined chloroform extracts were washed with sodium hydrogen carbonate solution (3 × 25 cm^3). These washings were added to the remaining aqueous phase which was acidified to pH 1 (conc. HCl) and extracted with chloroform (6 × 25 cm^3). The chloroform extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a clear oil (1.17 g, 54%). Examination by GLC (3% SE 30 on Chromosorb W, carrier gas N_2, temperature program 100 °C for 3 min, 8 °C min^{-1} temperature increase to 230 °C for 6 min), and ^{1}H NMR spectroscopy indicated that the product was of >98% purity. Unlike the corresponding racemate, it could not be induced to crystallise. However, chiral analysis using the ion pair with (−)-α-methylbenzylamine in $CDCl_3$ showed that the optical purity (e.e.) was >95%. Baseline separation of the signals attributable to the quaternary methyl groups was observed on addition of racemate. The methyl group of the *R*-acid **18** gave the signal at lower field.

Synthesis of (±)-3-*Benzyloxy*-3-*methylpentan*-2-*one* (*using Methyllithium*).—To a solution of (±)-2-benzyloxy-2-methylbutanoic acid (2.0 g, 9.62 mmol) in dry THF (20 cm^3) at 0 °C under N_2 was added by syringe low-halide MeLi (22 cm^3, 29.0 mmol) over 15 min. The mixture was kept at 0 °C for 12.6 h and added, with vigorous stirring, to water (25 cm^3). The mixture was brought to pH 7 (conc. HCl) and the THF was removed by evaporation under reduced pressure. The aqueous residue was brought to pH 12 (2 mol dm^{-3} NaOH) and extracted with $CHCl_3$ (5 × 20 cm^3). The combined $CHCl_3$ extracts were washed with NaOH solution (1 mol dm^{-3}, 2 × 20 cm^3). The $CHCl_3$ extracts were combined, dried ($MgSO_4$) and evaporated under reduced pressure to give the ketone (as **19**) as an oil (1.47 g, 7.14 mmol, 74%), substantially pure by ^{1}H NMR spectroscopy (220 MHz). A portion (1.09 g) was purified by flash chromatography, with elution by diethyl ether–light petroleum (b.p. 40–60 °C) (5:95). Fractions containing the ketone were combined and evaporated under reduced pressure. A portion (500 mg) of the product (829 mg) was further purified by bulb-tube distillation (120 °C, 1 mmHg) to give the pure *ketone* **19**, 460 mg (Found: C, 75.90; H, 9.00; M^+ 206.1271. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%; M, 206.1302); δ_H(220 MHz, $CHCl_3$) 0.88 (3 H, t, *J*/Hz 6.6, *Me*CH_2), 1.36 (3 H, s, MeCO), 1.80 (2 H, m, MeCH_2), 2.27 (3 H, s, MeCO), 4.37, 4.47 (2 H, AB system, *J*/Hz 11, OCH_2), and 7.4 (5 H, m, Ph); *m*/*z* (EI) 207 (M^+ + 1, 3%), 181 (38), 163 (71), 99 (11), 91 (100); *m*/*z* (CI, NH_3) 224 [$(M + NH_4)^+$, 88%], 207 [$(M + 1)^+$, 59], 181 (4), 163 (10), 108 (99), and 91 (64).

Synthesis of (±)-3-*Benzyloxy*-3-*methylpentan*-2-*one* (*using Methylcopper*).—(±)-2-Benzyloxy-2-methylbutanoic acid **18** (522 mg, 2.51 mmol) in dry benzene (3 cm^3) was treated with thionyl chloride (0.66 cm^3, 1.08 g, 9.05 mmol). The mixture was boiled gently under reflux for 35 min and evaporated under reduced pressure to give the acid chloride as an oil (580 mg). To magnesium turnings (86 mg, 3.56 mmol) in dry diethyl ether (2 cm^3) was added iodomethane (438 mg, 3.08 mmol). When the vigorous reaction had subsided (10 min) the mixture was allowed to stand for 25 min and was added by syringe to a solution of a copper(I) bromide–dimethyl sulphide complex (620 mg, 3.02 mmol) in a vigorously stirred mixture of dimethyl sulphide (3 cm^3) and diethyl ether (1 cm^3) under N_2. The flask that had contained the Grignard reagent was washed out with dry diethyl ether (2 × 1 cm^3) and the washings were added to the methylcopper suspension. With the aid of dry diethyl ether (2 × 1 cm^3) the acid chloride was added rapidly to the suspension of methylcopper under dry N_2 at 0 °C with stirring. The progress of the reaction was followed by GLC (10% SE 30 on Chromosorb W, N_2 carrier gas, 150–250 °C) and was found to be complete after 4 h at 0 °C. The mixture was allowed to stand for a further 19 h, and was poured into hydrochloric acid (0.5 mol dm^{-3}, 20 cm^3). The flask was washed out with EtOAc (15 cm^3) and the mixed organic and aqueous phases were shaken together. The organic layer was separated and washed with more hydrochloric acid (2 × 10 cm^3). The combined acidic fractions were re-extracted with diethyl ether (3 × 5 cm^3). The combined organic extracts were washed with $NaHCO_3$ solution (5%, 2 × 5 cm^3, 2 × 10 cm^3), water (2 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a solid residue (1.07 g). The ketone was purified by flash chromatography as described under the method using methyllithium, above, to give the ketone **19** as an oil (254 mg, 49%). The spectroscopic properties of the ketone were identical with those of the material prepared as above.

Synthesis of (R)-[1-^{13}C]-3-*Benzyloxy*-3-*methylpentan*-2-*one* **19**.—(*R*)-2-Benzyloxy-2-methylbutanoic acid (1.04 g, 5 mmol) and thionyl chloride (1.1 cm^3, 1.79 g, 15 mmol) were boiled together under reflux in benzene (10 cm^3) for 30 min. The mixture was evaporated under reduced pressure to give the acid chloride (1.125 g, 4.97 mmol, 99%). Examination of the ^{1}H NMR spectrum of this material revealed only signals attributable to the acid chloride. To magnesium turnings (201 mg, 8.27 mmol) in dry ether (4 cm^3) under N_2 was added [1-^{13}C]iodomethane (1.01 g, 7.06 mmol) in small portions by syringe. The mixture was gently warmed to initiate the reaction, which proceeded vigorously for 5 min. The mixture was allowed to remain in the dark for 40 min and was then added over 3 min to a stirred solution of a copper(I) bromide–dimethyl sulphide complex (1.67 g, 8.12 mmol) in a mixture of dry dimethyl sulphide (8 cm^3) and diethyl ether (2 cm^3). The flask was rinsed with diethyl ether (2 cm^3) and the diethyl ether was added to the reaction mixture. The mixture was stirred in the dark for 10 min and cooled in an acetone–CO_2 bath. The acid chloride of (*R*)-2-benzyloxy-2-methylbutanoic acid was added by syringe as a solution in diethyl ether (4 cm^3). The cooling bath was replaced by an ice bath and stirring was continued for 22 h, after which time analytical GLC (10% SE 30 on Chromosorb W, N_2 carrier gas, temperature program 150 °C for 1 min, rising by 12 °C min^{-1} to 250 °C for 2 min) indicated that reaction was complete. The flask was alternately rinsed with EtOAc (total volume 60 cm^3) and hydrochloric acid (0.5 mol dm^{-3}, total volume 80 cm^3). The two phases were shaken together and separated. The organic phase was extracted with hydrochloric acid (0.5 mol dm^{-3},

2 × 10 cm^3). The combined acidic extracts were again extracted with diethyl ether (3 × 10 cm^3). The combined organic extracts were washed with sodium hydrogen carbonate solution (5%, 4 × 20 cm^3), water (3 × 20 cm^3) and saturated NaCl solution (2 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the ketone **19**, 2.40 g. This was purified by flash chromatography with diethyl ether–light petroleum (b.p. 40–60 °C) (5:95) as eluant. Fractions shown by TLC (same solvent system) to contain the ketone were combined and evaporated under reduced pressure to give the ketone **19**, 644 mg, 3.13 mmol, 63%, the ^1H NMR spectrum (220 MHz) of which revealed no impurities. The ketone was further purified by bulb-tube distillation to give 603 mg (59%) as a clear oil. δ_H(220 MHz, $CHCl_3$) 0.88 (3 H, t, *J*/Hz 7.5, *Me*CH_2), 1.35 (3 H, s, MeCO), 1.81 (2 H, m, MeCH_2), 2.26 (3 H, d, *J*/Hz 128, ^{13}Me), 4.37, 4.46 (2 H, AB system, *J*/Hz 13, PhCH_2), and 7.4 (5 H, m, Ph); *m/z* (EI) 208 [$(M + 1)^+$, 42%], 181 (36), 163 (67), 100 (9), 91 (100), $(M + 1)^+$ 208.1384. $^{12}C^{13}CH_{12}O_2$ requires 208.1414.

Synthesis of (R)-[1-^{13}C]-3-*Hydroxy*-3-*methylpentan*-2-*one*.—A solution of (*R*)-[1-^{13}C]-3-benzyloxy-3-methylpentan-2-one **19** (295 mg, 1.43 mmol) in ethanol (2 cm^3) was mixed with a suspension of palladium black (100 mg) in ethanol (1 cm^3). The mixture was hydrogenated at atmospheric pressure until reduction was complete as determined by GLC analysis (45 min). The reaction mixture was filtered and the product ketol was isolated by preparative GLC (N_2 carrier gas, 10% SE 30 on Chromosorb W). The column was held at 95 °C until all of the toluene had been eluted and raised to 110 °C to elute the ketol **20**. Finally, the temperature was raised to 160 °C for 4 min. By repeated injections, a total of 102 mg (0.87 mmol, 61%) of the ketol **20** was obtained. δ_H(220 MHz, $CDCl_3$) 0.82 (3 H, t, *J*/Hz 7.3, *Me*CH_2), 1.37 [3 H, s, *Me*C(OH)], 1.75 (2 H, q, *J*/Hz 7.3, CH_2), 2.21 (3 H, d, *J*/Hz 128, $^{13}CH_3$), and 3.85 (1 H, br s, OH). The ketol (3 mg) and (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (12 mg) in CCl_4 (0.5 cm^3) gave an NMR spectrum (400 MHz) in which the carbinol methyl group appeared as a single peak, Fig. 3(*a*). On the addition of unlabelled, racemic ketol, two peaks appeared, Fig. 3(*b*).

2-*Benzyloxy*-2-*methylpropanoic acid* **26**.—A mixture of 2-hydroxy-2-methylpropanoic acid (1.76 g, 16.9 mmol) and sodium hydride (2.03 g of an 80% dispersion in mineral oil, 1.62 g NaH, 68 mmol) was treated under N_2 with benzyl chloride (15 cm^3). The mixture was stirred and heated to 120–130 °C for six days. A solution of NaOH (2 mol dm^{-3}, 50 cm^3) was added cautiously, followed by THF (10 cm^3). The mixture was boiled under reflux for 42 h, then cooled, concentrated under reduced pressure to remove THF, diluted with NaOH solution (0.5 mol dm^{-3}, 50 cm^3), washed with $CHCl_3$, acidified (conc. HCl) to pH 2, and extracted with $CHCl_3$ (4 × 25 cm^3). The $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the benzyl ether **26** (2.9 g, 14.9 mmol, 88%) as a white crystalline mass, melting just above room temperature: δ_H(220 MHz, $CDCl_3$) 1.58 (6 H, s, Me), 4.56 (2 H, s, CH_2Ph), and 7.35 (5 H, m, Ph); ν_{max} 3700–2200br (CO_2H) and 1715 cm^{-1} (CO). The dicyclohexylamine salt crystallised (acetone) with m.p. 139–142 °C (with sublimation). (Found: C: 73.20; H, 9.95; N, 3.75. $C_{23}H_{37}NO_3$ requires C, 73.56; H, 9.93; N, 3.73%.)

N-*Methacryloyl*-L-*Proline* **22**.—To an ice-cold solution of L-proline (20.8 g, 0.18 mol) in NaOH solution (2 mol dm^{-3}, 106 cm^3, 0.212 mol) was added acetone (106 cm^3). To the cooled, stirred solution were added alternately, and at such a rate that the temperature of the reaction mixture remained below 25 °C and the pH remained between 10 and 11, solutions of methacryloyl chloride (28.5 g, 0.27 mol) in acetone (75 cm^3) and NaOH (2 mol dm^{-3}). Addition took place over 35 min, during which time 170 cm^3 of the sodium hydroxide solution was added. The mixture was stirred overnight. The acetone was removed under reduced pressure, the aqueous residue was brought to pH 12 (2 mol dm^{-3} NaOH), extracted with diethyl ether (3 × 100 cm^3), acidified to pH 2 (conc. HCl), saturated with sodium chloride and extracted with ethyl acetate (3 × 100 cm^3). The combined ethyl acetate extracts were washed with saturated NaCl solution (3 × 100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallised from hexane–benzene (2:2, v/v) and then from ethyl acetate to give *N*-methacryloyl-L-proline **22** (22.7 g, 69%), m.p. 102–104 °C (lit.,[18] m.p. 103–104.5 °C); $[\alpha]_D^{28}$ −132.50° (*c* 1, $CHCl_3$); δ_H(220 MHz, $CDCl_3$) 1.98 (3 H, s, MeC=), 1.95 (2 H, m, $NCCH_2$), 2.25 (2 H, m, CH_2CCO_2H), 3.62 (2 H, app t, NCH_2), 4.60 (1 H, m, C*H*CO_2H), 5.28, 5.36 (each 1 H, app s, C=CH_2), and 6.45 (1 H, s, CO_2H).

Bromolactonisation of N-*Methacryloyl*-L-*Proline* **22**. *Synthesis of* (3S,8aS)-3-*Bromomethyl*-3-*methyl*-1,4-*dioxo*-3,4,6,7,8,8a-*hexahydro*-1H-*pyrrolo*[2,1-c][1,4]*oxazine* **23**.—To a stirred solution of *N*-methacryloyl-L-proline **22** (5.5 g, 30 mmol) in dry dimethylformamide (DMF; 45 cm^3) under N_2 was added a solution of *N*-bromosuccinimide (5.34 g, 30 mmol) in dry DMF (45 cm^3) over 5 min. The mixture was stirred for 17 h and diluted with ethyl acetate (1 dm^3). The solution was washed with sodium hydrogen carbonate solution (5%, 3 × 150 cm^3), water (3 × 200 cm^3) and saturated sodium chloride solution, dried ($MgSO_4$) and evaporated under reduced pressure to give the *bromo lactone* **23** (5.2 g, 66%), m.p. 158–159.5 °C; $[\alpha]_D^{28}$ −126.80° (*c* 1, $CHCl_3$); (Found: C, 41.40; H, 4.60; N, 5.20; Br, 29.65; $C_9H_{12}BrNO_3$ requires: C, 41.24; H, 4.61; N, 5.34; Br, 30.49%); *m/z* 264.0067 [$C_9H_{13}NO_3{}^{81}Br$ ($M^+ + 1$) requires 264.0058], 262.0058 [$C_9H_{13}NO_3{}^{79}Br$ $(M + 1)^+$ requires 262.0079], 264 (0.60%), 262 (0.70), 184 (40), 183 (20), 139 (55), 111 (17), 987 (21), 83 (9), and 70 (100). δ_H (400 MHz), 1.715 (3 H, s, Me), 2.00 (4 H, m, NCCH_2CH_2), 2.47 (2 H, m, CBrCH_2), 3.60 (2 H, m, NCH_2), 3.619, 3.850 (each 1 H, d, *J*/Hz 11.25, CHBr), and 4.509 (1 H, dd, *J*/Hz 6.5, 10.4, NCH).

Reduction of the Bromo Lactone **23**. *Synthesis of* (8aS)-3,3-*Dimethyl*-1,4-*dioxo*-3,4,6,7,8,8a-*hexahydro*-1H-*pyrrolo*[2,1-c]-[1,4]*oxazine* **24**.—To a stirred solution of the bromo lactone **23** (2.0 g) in dry benzene (20 cm^3) at 85 °C under dry nitrogen was added over 2 min a solution of tributyltin hydride (3.06 g) in dry benzene (5 cm^3). The temperature of the reaction mixture was raised to 94–95 °C and it was kept at this temperature for 20 h. The benzene was removed under reduced pressure. The semicrystalline residue was recrystallised (EtOAc) to give the *lactone* **24** (1.02 g), m.p. 107 °C (raised to 107.5–108 °C by sublimation at 90–100 °C, 0.03 mmHg); $[\alpha]_D^{28}$ −172.0° (*c* 1, $CHCl_3$); (Found: C, 58.75; H, 7.40; N, 7.60. $C_9H_{13}NO_3$ requires: C, 59.0; H, 7.15; N, 7.65%); δ_H(220 MHz) 1.63, 1.65 (each 3 H, s, Me), 2.10 (3 H, m, $NCCH_2CH$), 2.46 (NCCCH), 3.60 (2 H, m, NCH_2), and 4.28 (1 H, dd, *J*/Hz 7, 10, CHCO); *m/z* 183 (19%), 139 (35), 125 (11), 111 (11), 97 (19), 83 (5), and 70 (100).

Hydrolysis of Lactone **24**. *Synthesis of* 2-*Hydroxy*-2-*methylpropanoic Acid* **25**.—A solution of the lactone **24** (101 mg) in KOH solution (5 mol dm^{-3}, 5 cm^3) was boiled under reflux for 2 h. The solution was cooled, diluted with water (20 cm^3), brought to pH 1 (conc. HCl), saturated with NaCl, and extracted with EtOAc (5 × 10 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give 2-hydroxy-2-methylpropanoic acid **25** (36 mg, 63%), which had an NMR spectrum identical with an authentic sample.

Alkali-catalysed Isomerisation of 3-*Hydroxy*-3-*methylpentan*-

Table 1 Atom coordinates ($\times 10^4$)

Atom	x	y	z
Br(1)	586(6)	5 000	6 339(2)
Br(2)	7 181(7)	5 408(23)	3 039(2)
Br(3)	6 177(8)	349(37)	406(2)
O(11)	−1 575(42)	7 798(75)	5 554(13)
O(12)	−730(61)	8 823(123)	4 969(25)
O(13)	−3 955(30)	2 251(61)	5 662(10)
O(21)	4 761(38)	7 274(78)	2 294(12)
O(22)	2 688(44)	2 265(91)	2 308(15)
O(23)	5 577(48)	9 007(95)	1 632(17)
O(31)	8 338(26)	2 169(59)	1 137(8)
O(32)	7 817(29)	3 957(58)	1 763(10)
O(33)	10 433(43)	−2 353(89)	856(15)
N(1)	−3 200(43)	3 344(82)	5 070(14)
N(2)	3 580(32)	3 606(65)	1 713(11)
N(3)	9 487(58)	−1 469(137)	1 708(25)
C(11)	−741(61)	3 269(123)	5 767(22)
C(12)	−2 250(52)	5 271(148)	5 737(19)
C(13)	−2 301(63)	6 272(118)	6 340(20)
C(14)	−1 668(57)	7 141(120)	5 012(21)
C(15)	−1 880(70)	4 631(142)	4 900(25)
C(16)	−3 184(58)	3 396(116)	5 511(20)
C(17)	−2 828(59)	5 198(143)	4 301(20)
C(18)	−3 871(68)	2 609(130)	4 094(23)
C(19)	−4 013(57)	1 602(117)	4 755(19)
C(21)	5 618(53)	3 184(107)	2 673(19)
C(22)	4 409(54)	4 702(109)	2 570(18)
C(23)	3 852(41)	6 564(80)	2 853(14)
C(24)	5 144(62)	7 400(109)	1 834(20)
C(25)	4 501(38)	4 876(92)	1 505(14)
C(26)	3 596(41)	3 289(81)	2 111(14)
C(27)	4 303(85)	4 967(208)	994(29)
C(28)	3 010(59)	2 917(120)	902(20)
C(29)	2 432(76)	2993(276)	1 341(26)
C(31)	7 494(55)	−1 384(105)	711(20)
C(32)	8 573(35)	217(102)	829(11)
C(33)	9 287(52)	193(166)	368(20)
C(34)	8 232(58)	1 877(104)	1 553(16)
C(35)	8 659(63)	−340(114)	1 850(21)
C(36)	9 808(59)	−868(108)	1 118(20)
C(37)	9 454(45)	354(93)	2 347(15)
C(38)	10 015(38)	−2 339(73)	2 435(13)
C(39)	10 677(33)	−2 598(77)	2 014(11)

Table 2 Bond lengths (Å)

Br(1)–C(11)	2.155(60)	Br(2)–C(21)	2.134(54)
Br(3)–C(31)	1.756(55)	O(11)–C(12)	1.622(83)
O(11)–C(14)	1.565(72)	O(12)–C(14)	1.342(90)
O(13)–C(16)	1.149(71)	O(21)–C(22)	1.625(70)
O(21)–C(24)	1.435(71)	O(22)–C(26)	1.302(66)
O(23)–C(24)	1.152(80)	O(31)–C(32)	1.390(54)
O(31)–C(34)	1.219(54)	O(32)–C(34)	1.343(63)
O(33)–C(36)	1.322(77)	N(1)–C(15)	1.687(90)
N(1)–C(16)	1.251(72)	N(1)–C(19)	1.449(69)
N(2)–C(25)	1.387(56)	N(2)–C(26)	1.141(52)
N(2)–C(29)	1.499(85)	N(3)–C(35)	1.178(96)
N(3)–C(36)	1.797(94)	N(3)–C(39)	1.518(69)
C(11)–C(12)	1.891(89)	C(12)–C(13)	1.802(81)
C(12)–C(16)	1.456(86)	C(14)–C(15)	1.353(97)
C(15)–C(17)	1.849(85)	C(17)–C(18)	1.774(95)
C(18)–C(19)	1.981(88)	C(21)–C(22)	1.485(78)
C(22)–C(23)	1.446(72)	C(22)–C(26)	1.613(63)
C(24)–C(25)	1.686(70)	C(25)–C(27)	1.433(89)
C(27)–C(28)	1.715(113)	C(28)–C(29)	1.481(102)
C(31)–C(32)	1.403(70)	C(32)–C(33)	1.618(71)
C(32)–C(36)	1.525(67)	C(34)–C(35)	1.453(77)
C(35)–C(37)	1.560(70)	C(37)–C(38)	1.524(61)
C(38)–C(39)	1.491(54)		

2-*one* **11**.—The ketol **11** (9.8 mg) was dissolved in NaOH 5 mol dm^{-3}, 0.5 cm^3) in a 5 mm NMR tube. The sample was examined by 220 MHz NMR spectroscopy at intervals. No change was detected after 6 h. The tube was heated to 75 °C. Rearrangement occurred, reaching equilibrium after 16 h. At equilibrium, the relative concentrations of 3-hydroxy-3-methylpentan-2-one **11** and 2-hydroxy-2-methylpentan-3-one **12** were 2:1. Even after 10 days at 70–75 °C, no significant decomposition or polymerisation of the ketols was observable.

Table 3 Bond angles (°)

C(12)–O(11)–C(14)	100.5(37)	C(22)–O(21)–C(24)	126.9(40)
C(32)–O(31)–C(34)	125.3(39)	C(15)–N(1)–C(16)	114.0(45)
C(15)–N(1)–C(19)	120.0(44)	C(16)–N(1)–C(19)	122.7(49)
C(25)–N(2)–C(26)	126.7(36)	C(25)–N(2)–C(29)	109.9(43)
C(26)–N(2)–C(29)	122.9(48)	C(35)–N(3)–C(36)	120.1(58)
C(35)–N(3)–C(39)	125.8(61)	C(36)–N(3)–C(39)	109.5(44)
Br(1)–C(11)–C(12)	103.7(34)	O(11)–C(12)–C(11)	92.8(37)
O(11)–C(12)–C(13)	99.1(43)	C(11)–C(12)–C(13)	106.1(37)
O(11)–C(12)–C(16)	134.4(45)	C(11)–C(12)–C(16)	98.7(50)
C(13)–C(12)–C(16)	119.2(49)	O(11)–C(14)–O(12)	91.5(48)
O(11)–C(14)–C(15)	115.0(53)	O(12)–C(14)–C(15)	134.5(66)
N(1)–C(15)–C(14)	115.2(59)	N(1)–C(15)–C(17)	89.1(40)
C(14)–C(15)–C(17)	96.0(50)	O(13)–C(16)–N(1)	118.3(51)
O(13)–C(16)–C(12)	130.5(54)	N(1)–C(16)–C(12)	110.6(54)
C(15)–C(17)–C(18)	113.1(48)	C(17)–C(18)–C(19)	91.6(38)
N(1)–C(19)–C(18)	106.9(43)	Br(2)–C(21)–C(22)	111.9(37)
O(21)–C(22)–C(21)	105.9(43)	O(21)–C(22)–C(23)	82.3(35)
C(21)–C(22)–C(23)	131.4(44)	O(21)–C(22)–C(26)	96.8(34)
C(21)–C(22)–C(26)	103.8(42)	C(23)–C(22)–C(26)	123.1(43)
O(21)–C(24)–O(23)	133.3(55)	O(21)–C(24)–C(25)	108.8(43)
O(23)–C(24)–C(25)	116.3(50)	N(2)–C(25)–C(24)	112.2(37)
N(2)–C(25)–C(27)	117.1(48)	C(24)–C(25)–C(27)	120.8(55)
O(22)–C(26)–N(2)	126.8(41)	O(22)–C(26)–C(22)	99.5(38)
N(2)–C(26)–C(22)	130.8(43)	C(25)–C(27)–C(28)	96.3(58)
C(27)–C(28)–C(29)	106.5(61)	N(2)–C(29)–C(28)	101.7(57)
Br(3)–C(31)–C(32)	110.7(38)	O(31)–C(32)–C(31)	111.1(37)
O(31)–C(32)–C(33)	132.3(48)	C(31)–C(32)–C(33)	105.8(41)
O(31)–C(32)–C(36)	99.1(31)	C(31)–C(32)–C(36)	119.5(47)
C(33)–C(32)–C(36)	87.7(37)	O(31)–C(34)–O(32)	114.9(43)
O(31)–C(34)–C(35)	126.3(53)	O(32)–C(34)–C(35)	118.3(42)
N(3)–C(35)–C(34)	111.8(63)	N(3)–C(35)–C(37)	96.3(52)
C(34)–C(35)–C(37)	114.1(46)	O(33)–C(36)–N(3)	127.9(48)
O(33)–C(36)–C(32)	112.0(44)	N(3)–C(36)–C(32)	106.8(44)
C(35)–C(37)–C(38)	94.0(36)	C(37)–C(38)–C(39)	99.9(32)
N(3)–C(39)–C(38)	88.4(36)		

Alkali-catalysed Rearrangement of (R)-[1-^{13}C]-3-*Hydroxy*-3-*methylpentan*-2-*one* **20**.—The ketol **20** (44 mg) was heated in NaOH (5 mol dm^{-3}, 1.0 cm^3) at 80 °C. At intervals of 0, 30 min, and 3, 6 and 16.3 h, aliquots of 0.15–0.2 cm^3 were withdrawn. A special technique was devised for isolating the ketol as a solution in CCl_4 suitable for chiral analysis by NMR spectroscopy, as illustrated by the following method using unlabelled ketol. A sample of the ketol (40 mg) was dissolved in NaOH solution (5 mol dm^{-3}, 1 cm^3). Molecular sieves (4 Å, activated) were ground to a powder and placed in a Pasteur pipette, plugged with cotton wool, to a depth of 2 cm. An aliquot (0.2 cm^3) of the alkaline solution was applied to the pipette and forced into the molecular sieve by gentle pressure from a teat. Carbon tetrachloride (0.5 cm^3 total) was applied in portions and gently forced through the molecular sieve by gentle pressure from the rubber teat into a 5 mm bore NMR tube. Cyclohexane (3 mm^3) was added as an internal standard and the ^{1}H NMR spectrum was determined. The solution was found to contain 5.1 mg of the ketol, indicating a recovery of 64%. To the samples isolated from the optically pure, labelled ketol **20**, the chiral solvating agent (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol was added in four times excess, by weight (*i.e.* 4 mg chiral solvating agent, 1 mg ketol).

Crystal Structure of the Bromo Lactone **23**.—$C_9H_{12}BrNO_3$, monoclinic, space group $P2_1$, a = 10.541(3), b = 5.200(2), c = 28.450(9) Å, β = 99.79(2)°, U = 1536.6(8) Å^3, M = 262.0, Z = 6, D_c = 1.67 g cm^{-3}, Mo-Kα radiation, λ = 0.710 69 Å,

m(Mo-Kα) = 39.5 cm^{-1}, F(000) = 792. Crystal character: colourless laths with a weak diffraction pattern. Data were collected with a Syntex $P2_1$ four-circle diffractometer. Maximum 2θ was 45°, with scan range $\pm 1.1°$ (2θ) around Kα_1–Kα_2 angles, scan speed 1.5–29° min^{-1}, depending on the intensity of a 2 s pre-scan; backgrounds were measured at each end of the scan for 0.25 of the scan time. Three standard reflections were monitored every 200 reflections, and showed some decrease during data collection; the data were rescaled to correct for this. Unit cell dimensions and standard deviations were obtained by least-squares fit to 15 reflections. 2398 reflections [885 with $(I/\sigma I) > 2.0$ used in refinement] corrected for Lorentz, polarisation and absorption effects (Gaussian method); maximum and minimum transmission factors were 0.66 and 0.79. The crystal dimensions were 0.17 × 0.32 × 0.08 mm. Systematic absences: $0k0$, $k = 2n$ indicate space groups $P2_1$ or $P2_1/m$; in view of the chirality of the material, the first was selected. Careful search revealed no higher crystal symmetry than monoclinic for alternative unit cells. The bromine atoms were located by the Patterson interpretation section of SHELXTL, and light atoms were found on successive Fourier syntheses. Structure solution was relatively easy and Fourier maps showed the three independent but identical molecules clearly. However, in least-squares refinement, several of the atoms moved to give unsatisfactory molecular dimensions, and it was necessary to apply loose constraints to some bonds (by the DFIX procedure of SHELXTL), while some temperature factors were held fixed. These problems undoubtedly arose from the small number of observed reflections, and their limited angular resolution, which also led to the high final R-value. Hydrogen atoms were given fixed isotropic temperature factors, $U = 0.07$ Å. Those defined by the molecular geometry were inserted at calculated positions and not refined; H-atoms of methyl groups were omitted. Final refinement was by cascaded least squares methods with anisotropic temperature factors for Br only; the y-co-ordinate of Br(1) was fixed to define the origin. The largest peak on a final difference Fourier synthesis was of height 1.7 e A^{-3}. A weighting scheme of the form $w = 1/s^2(F + gF^2)$ with $g = 0.0048$ was used. This was shown to be satisfactory by weight analysis. The final R-value was 0.116 ($R_w = 0.127$). Computing was with the SHELTX system[19] on a Data General DG 30 computer. Scattering factors in the analytical form and anomalous dispersion factors were taken from ref. 20. Non-hydrogen atom co-ordinates, bond lengths and bond angles are given in Tables 1–3. Isotropic and anisotropic temperature factors have been deposited at the Cambridge Crystallographic Data Centre.*

* For details of the CCDC deposition scheme, see 'Instructions for Authors (1991),' *J. Chem. Soc., Perkin Trans. 2*, 1991, issue 1.

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