Non-oxidative Conversion of Ketone Carbonyls into Carboxy Carbonyls. Comparison of 2-Acylthiazoles and 2-Acylimidazoles in the Aldol Condensation and the Stereospecific Cleavage of an Example of the Latter to a β-Hydroxy Ester *via* the Azolium Salt

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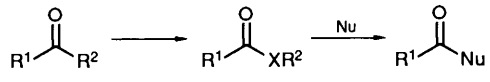
The synthesis of some 2-acyl-thiazoles and -imidazoles is described. In the subsequent aldol condensation of these ketones, the imidazole congeners were much better behaved. *N*-Methylation of the imidazole aldols was only partially successful and suffered from competing *O*-methylation of the hydroxy group. A diastereoisomeric imidazolium salt from one of the aldols did not close to a β-lactone on treatment with base but did undergo clean de-acylation in the presence of methanol and base to give the corresponding β-hydroxy ester stereospecifically.

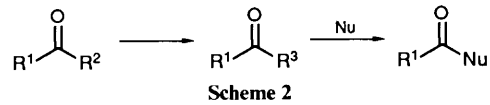
The most common way of transforming a ketonic carbonyl group into a carboxylic carbonyl group and, thereby, into an acylating agent is by inserting a heteroatom into the carbonyl alkyl single bond (effectively an oxidation) (Scheme 1) by means



Scheme 1

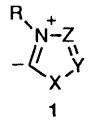
of the Baeyer–Villiger (X = O) or Schmidt (X = NH) reactions or, indirectly through the oxime, by way of the Beckmann rearrangement. The reagents used in the first two cases, peroxy acids and hydrazoic acid respectively, attack the ketone carbonyl directly.

The same sort of conversion could be achieved, in principle, by the use of a reaction which operates upon one of the groups attached to the ketone carbonyl in such a way as to transform it into a leaving group (Scheme 2). Since this alternative approach



Scheme 2

leaves the C–CO–C bonds intact, this transformation must create a *carbon* leaving group of which there are but few. One class of these is the azolium ring zwitterion **1**. Thus, 2-



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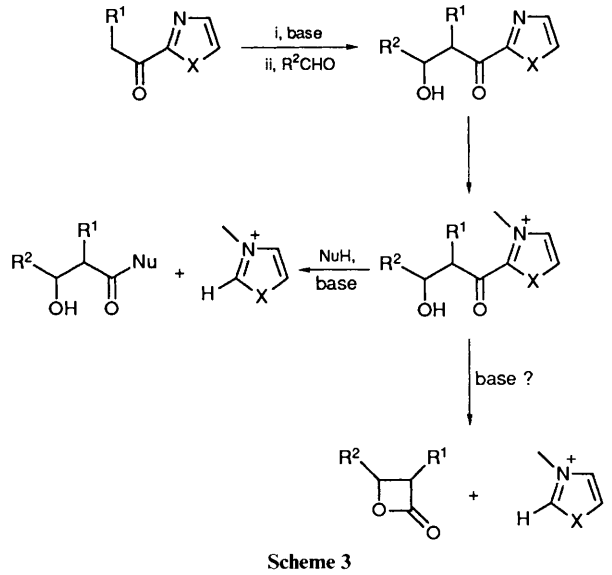
acylthiazolium salts are capable of acylating various oxygen, nitrogen and sulphur nucleophiles[1] as are 2-acylimidazolium salts.[2] Although largely represented to date by the thiazolium and imidazolium cases, the ready exchange of hydrogen for deuterium (*i.e.* formation of a leaving group) at C-2 of 4*H*-1,2,4,triazolium,[3] 1,5-tetrazolium,[3] 1,3,4-thiadiazolium[4] and oxazolium[5] salts and the nucleophilic de-acylation of 2-acyl-4,5-dihydroimidazolium salts[6] suggest that the process may be of wider applicability. In all these cases the operating reaction of Scheme 2 would be *N*-alkylation of the parent azole, a non-oxidative procedure.

In order to demonstrate the potential of the process of Scheme 2 we felt that we needed to show that the thiazole or imidazole ketones could undergo a typical ketone reaction and then be subsequently converted into a carboxylic acid derivative. We chose the aldol condensation as the archetypal reaction because its application to thiazole or imidazole ketones was new[7] and because the resultant aldols might close to give β-lactones after *N*-methylation (Scheme 3).

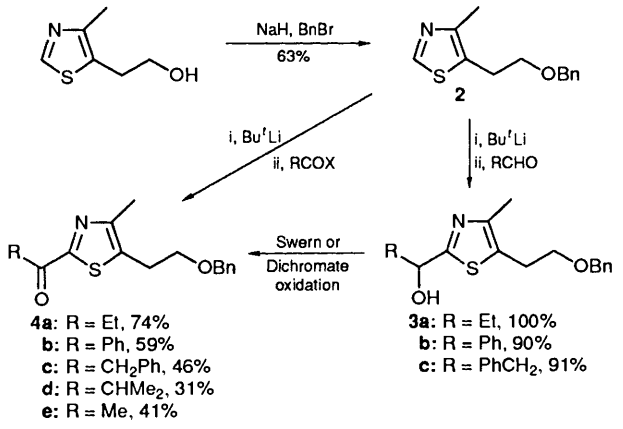


Scheme 3

Results and Discussion

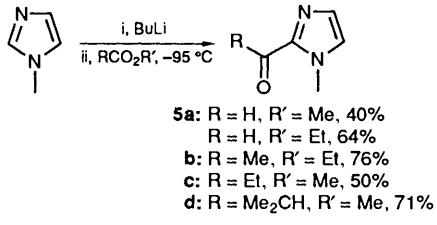
Preparation of 2-Acyl-thiazoles and -imidazoles.—As 5-(2′-hydroxyethyl)-4-methylthiazole is a cheap, readily available compound, it was chosen as the source of the 2-acylthiazoles. The hydroxy group in the side chain was first protected as the benzyl ether. This derivative **2** slowly decomposed on storage and in order to achieve reproducibly high yields in the subsequent deprotonation at C-2 it was necessary to purify it by silica-gel chromatography just prior to use. Cleaner solutions of the 2-lithiothiazole were obtained through the use of *tert*-butyllithium rather than butyllithium and consequently the stronger base was used throughout for the deprotonation of the

thiazole. Reaction of the lithio species of thiazole **2** with aldehydes (giving alcohols **3** subsequently oxidized to ketones **4a** and **4b**) or with an ester (**4c**), an acid chloride (**4d**), or an anhydride (**4e**) furnished the 2-acylthiazoles (Scheme 4).

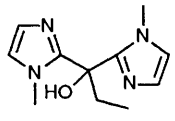


Scheme 4

2-Acylimidazoles have been synthesized previously by the reaction of 2-lithioimidazoles with acid chlorides or anhydrides[8] or with amides.[2,9] We found esters could act as suitable alternatives to these acylating agents provided that the temperature of the reaction was sufficiently low [−95 °C; at −78 °C the 2-acylimidazole **5c** (49%) was accompanied by the double addition product **6** (25%) from ethyl propionate] (Scheme 5).



Scheme 5



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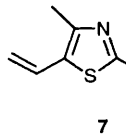
Aldol Reactions of 2-Acyl-thiazoles and -imidazoles.—2-Acylthiazoles **4a**, **c**, **d** were chosen to represent their class in the aldol condensation. Since Evans had shown that zinc enolates of *N*-protected pyrroles reacted well in the aldol condensation,[10] we chose the same derivative for the thiazoles. We quickly discovered that a number of problems beset the reaction. First, the zinc enolate of the ketone **4a** underwent elimination of benzyl alcohol to the vinyl derivative **7** to a small extent in the absence of a carbonyl trap. Although the condensation of the zinc enolate of 2-propionylthiazole **4a** with excess benzaldehyde proceeded with good diastereoselectivity (7:1) and reasonable yield (66%) (Scheme 6), the same success was not evident with



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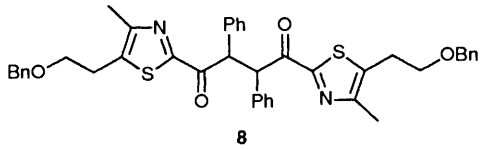

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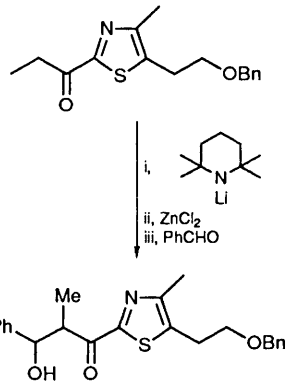
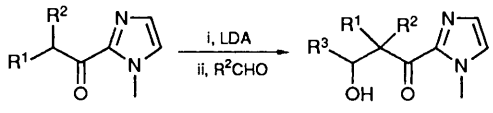


Scheme 6

other carbonyl traps. Thus, acetaldehyde showed essentially no diastereoselection and pivaldehyde failed to react. In the case of the 2-phenylacetylthiazole **4c** attempted reaction of its zinc enolate with acetone resulted in the recovery of starting ketone (49%) plus the dehydro dimer **8** (19%).

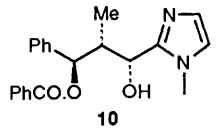
The aldol reaction of 2-acyl-*N*-methylimidazoles proved to be a more reproducible reaction than that of 2-acylthiazoles. Thus, LDA deprotonated the 2-acylimidazoles cleanly at −78 to −25 °C and reaction of the resultant lithium enolate with aldehydes at a similarly low temperature provided a range of β-hydroxy ketones **9** (Scheme 7) in moderate to good yields.



	R^1	R^2	R^3	Yield	Diast. Ratio
9a:	Me	H	Ph	52%	3 : 1
b:	Me	H	Pr^i	28%	3 : 1
c:	Me	H	Me	52%	3 : 2
d:	Me	Me	Me	78%	—
e:	Me	Me	Ph	57%	—
f:	H	H	Me	70%	—

Scheme 7

For aldol **9a** only the major diastereoisomer could be isolated after column chromatography on silica gel but the minor diastereoisomer could be clearly seen in the ^{1}H NMR spectrum of the crude product. Aldols **9b** and **9c** were isolated as mixtures of diastereoisomers after purification. We were concerned that the diastereoselectivity of the reaction in the imidazole series was not as good as the one clear case from the thiazole work. Since the aldol reaction is reversible a rise in temperature during the condensation should allow the product from the thermodynamically favoured enolate to accumulate. If this latter is different from the kinetic one a change in diastereoselection may thereby result. Indeed, such a change was observed on allowing the reaction mixture to warm to 0 °C before quenching but not for the better; the aldols were obtained as a 1:1 mixture and in lower yield (30%). A highly crystalline by-product was obtained in comparable yield (37%) which was identified as the monobenzoylated 1,3-diol **10**, the structure and relative configuration of which were confirmed by X-ray crystallography (Fig. 1).[11] This compound was presumed to arise from an intramolecular hydride transfer in the product of condensation



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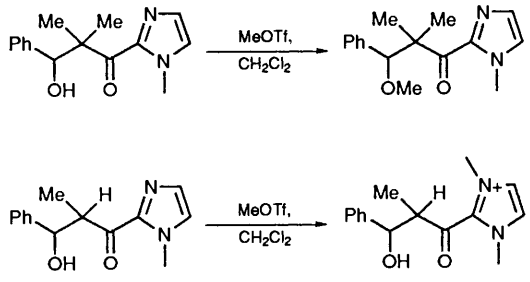
of the *threo*-aldolate with benzaldehyde. Only the *threo*-diastereoisomer can adopt the chair conformation in which both the phenyl and methyl groups are equatorially placed. Assuming coordination of both ketolate and ketone oxygen atoms with lithium, the hydride can then be delivered transannularly in the resultant eight-membered ring chelate to give the product with the observed stereochemistry (Fig. 2). Hydride transfer from both aromatic and aliphatic alkoxide anions in an intramolecular fashion has ample precedent [12] and the intermolecular version (Meerwein–Ponndorf–Verley reduction [13]) has been known for a long time.

Thus our best results in the imidazole series with regard to diastereoselection gave no higher than 3:1 ratios. However, since the aldols from 2-acylthiazoles were much more difficult to obtain, the ketone to carboxyl conversion was attempted only with the 2-acylimidazole congeners.

N-*Methylation and Methanolysis of the* 2-*Acylimidazoles.*—In common with the 2-thiazole ketones, N-3 of 2-acylimidazoles is a relatively poor nucleophile because of the electron-withdrawing capacity of the C-2 substituent. In spite of this we found that methyl triflate (trifluoromethanesulphonate) reacted exothermically with ketones **5c** and **5d** in dichloromethane to give the salts as white, crystalline solids after evaporation of the solvent. *N*-Methylation was less successful for the aldols **9** (Scheme 8). When reaction did occur,



competitive *O*-methylation became a serious problem particularly with the aldol **9e** and one of the diastereoisomers of **9c** neither of which underwent the desired attack at nitrogen. The alternative site of methylation was clearly signalled in the ^{1}H NMR spectrum of the crude reaction product by the presence of two methyl singlet peaks at 3.2–3.3 (OMe) and 3.9–4.0 (NMe) ppm. The only aldol which was cleanly methylated on nitrogen was the major diastereoisomer of **9a** albeit at a slower rate than for the simple ketones. Thus, this diastereoisomer required overnight reaction at room temperature. Salt formation was accompanied by a shift of the carbonyl stretching frequency from 1679 to 1702 cm^{-1} and both NMe groups appeared in the region of 4 ppm in the ^{1}H NMR spectrum. The salt was unstable in the solid state; it liquified over a period of 24 h with concomitant exhalation of a smell of benzaldehyde, presumably the product of a retro-aldol reaction.[10] In solution no decomposition could be detected even after many days.

Before we subjected this diastereoisomeric salt of aldol **9a** to methanolytic cleavage we decided to see if intramolecular alcoholysis could occur with the resultant formation of a β-lactone. Addition of triethylamine to a solution of the salt in dichloromethane led to its total decomposition without any

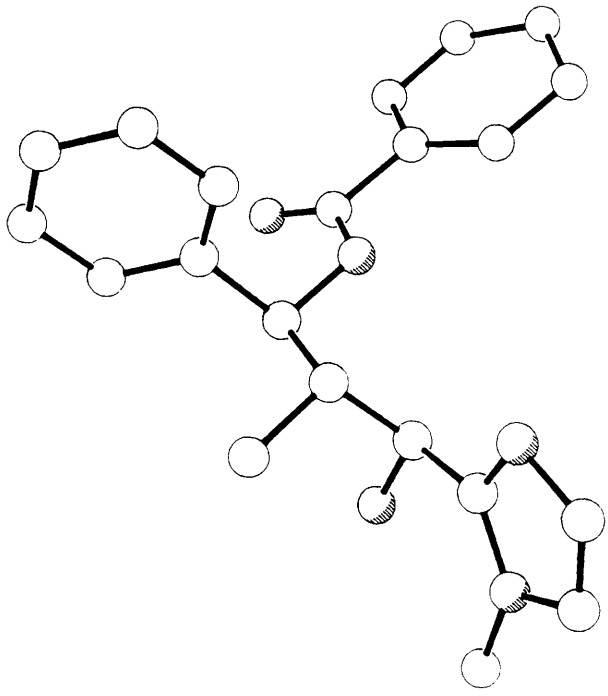


Fig. 1 Crystal structure of **10**

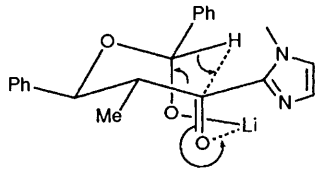
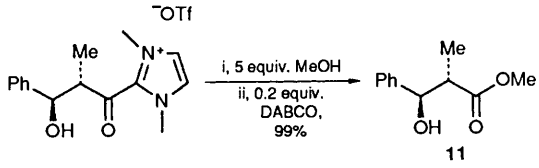


Fig. 2

evidence for the formation of the strained ring lactone by solution cell IR spectroscopy. Although internal acylation was obviously not possible, the acylation of methanol by the major diastereoisomeric salt of aldol **9a** proved to be very facile. In view of the possible formation of an enol (treatment of the simple ketone **5d** with 0.3 equiv. of 4-dimethylaminopyridine results in tautomerisation to a stable enol: two methyl singlets at 1.4 and 1.9 ppm and an OH stretch at 3300–2900 cm^{-1}) we were concerned that epimerisation may attend the esterification process. On the contrary, however, addition of 5 equiv. of methanol to a solution of the major diastereoisomer of aldol **9a** in dichloromethane followed by 0.2 equiv. of DABCO resulted, within 5 min, in an almost quantitative yield of only one isomer of methyl 3-hydroxy-2-methyl-3-phenylpropionate **11**. Inspec-



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Scheme 9

tion of the ^{1}H NMR spectra of each of the diastereoisomers of aldol **9a** and the sole diastereoisomer of ester **11** allowed a clear distinction between the major and minor series to be made. For the major isomers the benzylic proton resonated as a doublet (J 7 Hz for aldol; 8 Hz for ester) at 4.9 (aldol) and 4.7 (ester) ppm whereas for the minor isomer of aldol **9a** both a downfield shift (to 5.1 ppm) and a narrowing of the doublet (to 3 Hz) occurred. The coupling constants for the major and minor diastereoisomers of the aldol **9a** were close to the values recorded in the literature for the corresponding pyrrole aldols

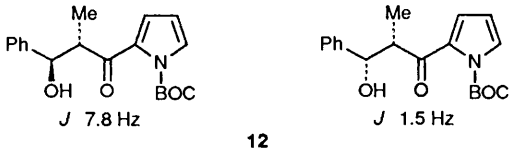

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Fig. 3

12 (Fig. 3) and suggested that they had the *anti*- and *syn*-stereochemistries respectively.[10] Moreover, the monobenzoylated diol **10** which has the *anti*-configuration established by X-ray crystallography shows a coupling constant for the benzylic proton of 7 Hz which conforms to the major series. With regard to the stereochemistry of the esters, Jacques and his co-workers had firmly established that a larger coupling constant (8.6 Hz) and a higher field chemical shift (4.73 ppm) for the benzylic proton characterised the *anti*-isomer.[14] It follows that either complete retention or complete inversion of configuration had occurred during esterification thus ruling out the possible involvement of an enol or ketene on the pathway from acylimidazolium to ester, both of which intermediates would be expected to lead to some scrambling of stereochemistry. The close correlation of coupling constants and chemical shifts for the major aldol diastereoisomer with the *anti*-ester and for the minor aldol diastereoisomer with the *syn*-ester strongly suggests that the configuration remained unaltered during esterification *i.e.* retention (Scheme 9). One candidate mechanism consistent with these stereochemical facts is the tetrahedral mechanism.

Conclusions

We have clearly established that for one compound (*anti*-**9a**), at least, the philosophy embodied in Schemes 2 and 3 works. The 2-acylimidazoles chosen for investigation were more reliable than the 2-acylthiazoles in terms of the aldol condensation although this may not be true if simpler 2-acylthiazoles were to be employed.[7] The success of *N*-methylation of 2-acylimidazoles was obviously critically dependent on the nature of the side chain, a feature seemingly peculiar to aldols since we have had no trouble in this regard with acyl groups bearing hydroxy functionality further removed from the ketone.[15] The latter study also showed that lactonisation from 2-acylimidazolium ions was inherently possible which means that the failure to form the β-lactones in the present work is probably a consequence of the extra strain in the smaller ring. This, in turn, might be the result of reversible attack on the carbonyl group of the azolium salt by the nucleophile since the formation of strained rings by reversible reactions is generally poor yielding. Such reversibility would, of course, fit with a tetrahedral mechanism, an aspect of the reaction which we are currently studying.

Experimental

Melting-points were determined on a Kofler hot-stage or Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer as thin films (oils) or as Nujol mulls (solids) unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded on JEOL FX 90Q, Bruker WM 250, JEOL GSX 270, Bruker WM 400 or Bruker WM 500 instruments, using tetramethylsilane or chloroform as internal standards in $CDCl_3$ unless otherwise stated. Coupling constants are in Hz. Signals are quoted as singlet (s), doublet (d), triplet (t), quartet (q), heptuplet (hep), multiplet (m) and broad (br). Mass spectra were recorded on a VG Micromass 7070B machine by EI or FAB (thiodiethanol matrix) methods.

Preparative gravity column chromatography was performed on Crosfield Sorbsil C60 silica gel. Petroleum refers to light petroleum of b.p. 40–60 °C unless otherwise indicated. Ether refers to diethyl ether. Ether and tetrahydrofuran (THF) were distilled from sodium and potassium metal respectively under argon immediately prior to use. Triethylamine, diisopropylamine, and 2,2,6,6-tetramethylpiperidine were distilled from calcium hydride and stored under an argon atmosphere. Dichloromethane was distilled from phosphorus pentoxide under argon just prior to use. *tert*-Butyllithium and butyllithium were purchased from Aldrich Chemicals as solutions in hexanes. 5-Hydroxyethyl-4-methylthiazole was purchased from Aldrich Chemicals and used without purification. All other solvents and reagents were purified by standard methods.

5-(2′-*Benzyloxyethyl*)-4-*methylthiazole* **2**.—To a suspension of sodium hydride (60% suspension in oil, 0.54 g, 13.5 mmol, 1.25 equiv.) in dry THF (30 cm^3) was added a solution of 5-hydroxyethyl-4-methylthiazole (1.54 g, 10.8 mmol) in THF (15 cm^3) dropwise over 5 min. Hydrogen evolution was initially rapid and then subsided. After 40 min the reaction mixture was heated under reflux for 30 min. The mixture was then allowed to cool to room temperature and a solution of benzyl bromide (1.28 cm^3, 11.72 mmol) in THF (15 cm^3) was added slowly dropwise. After addition the mixture was stirred for 30 min and then heated under reflux for 45 min. The reaction was cooled to room temperature and the suspension of white solid in a yellow solution was poured into aqueous hydrochloric acid (2 mol dm^{-3}, 50 cm^3). Any unchanged benzyl bromide was extracted with petroleum (2 × 20 cm^3) and then the aqueous phase was brought to pH 9 with solid sodium hydrogen carbonate. The product was extracted with chloroform (3 × 30 cm^3), the extracts were washed once with water and dried (Na_2SO_4). After removal of the solvent the resultant oil was distilled to give **2** as a colourless oil (1.58 g, 63%), b.p. 150–155 °C (Found: C, 67.2; H, 6.7; N, 6.1. $C_{13}H_{15}NOS$ requires C, 66.92; H, 6.48; N, 6.08%); δ_H(90 MHz) 2.5 (3 H, s, Me), 3.1 (2 H, t, *J* 7, CH_2), 3.7 (2 H, t, *J* 7, CH_2O), 4.6 (2 H, s, CH_2Ph), 7.4 (5 H, m, Ph) and 8.6 (1 H, s, 2-H); δ_C(22.5 MHz) 15 (Me), 27 (CH_2), 70 (CH_2O), 73 (CH_2O), 127, 128 (2 peaks), 138 and 149 (2 peaks).

General Synthesis of 5-(2′-*Benzyloxyethyl*)-2-(1′-*hydroxyalkyl*)-4-*methylthiazoles* **3**.—To a solution of the thiazole **2** (619 mg, 2.66 mmol) in dry THF (25 cm^3) under argon at −78 °C was added a solution of *tert*-butyllithium (1.7 mol dm^{-3}; 1.56 cm^3, 2.66 mmol). The yellow solution was stirred at the same temperature for 30 min and then neat aldehyde was added by syringe. After being stirred at −78 °C for a further 35 min the reaction mixture was allowed to warm to −10 °C over a 20 min period. The reaction was quenched at this temperature by the addition of glacial acetic acid (1 cm^3) and then the mixture was poured into saturated aqueous sodium hydrogen carbonate (50 cm^3). The aqueous suspension was extracted with ether (2 × 20 cm^3), the combined extracts were washed once with water (20 cm^3) and dried ($MgSO_4$). Evaporation of the solvent left the crude product as a yellow oil. In this manner the following were prepared.

5-(2′-*Benzyloxyethyl*)-2-(1′-*hydroxypropyl*)-4-*methylthiazole* **3a**, from 2.2 equiv. of propionaldehyde, as an oil (774 mg, 100%), b.p. 250 °C (oven temperature, bulb-to-bulb) at 5 × 10^{-4} mmHg which could not be purified without some decomposition (Found: C, 64.65; H, 7.25; N, 5.8; S, 10.4. $C_{16}H_{21}NO_2S$ requires C, 65.95; H, 7.26; N, 4.81; S, 10.98%); ν_{max}/cm^{-1} 3600 (OH stretch); δ_H(90 MHz) 1.0 (3 H, t, *J* 7, CH_3CH_2), 1.8 (2 H, m, CH_2CH_3), 2.3 (3 H, s, 4-Me), 3.0 (2 H, t, *J* 7, CH_2), 3.6 (2 H, t, *J* 7, CH_2O), 4.5 (2 H, s, CH_2Ph), 4.8 (1 H, m, CHOH) and 7.3 (5 H, s, Ph); δ_C(22.5 MHz) 10 (Me), 15 (Me), 28 (CH_2), 32 (CH_2), 70 (CH_2O), 73 (CH_2O and CHOH), 127, 130–133, 138, 148 and 171.

5-(2′-*Benzyloxyethyl*)-2-(α-*hydroxybenzyl*)-4-*methylthiazole* **3b**, from benzaldehyde (2 equiv.), as a white solid (812 mg, 90%),

m.p. 71 °C (from ether) (Found: C, 70.6; H, 6.3; N, 4.15; S, 10.0. $C_{20}H_{21}NO_2S$ requires C, 70.78; H, 6.24; N, 4.13; S, 9.45%); δ_H(90 MHz) 2.2 (3 H, s, 4-Me), 2.9 (2 H, t, *J* 7, CH_2), 3.6 (2 H, t, *J* 7, CH_2O), 4.5 (2 H, s, CH_2Ph), 5.0 (1 H, br, OH), 5.9 (1 H, s, CHOH) and 7.3–7.4 (10 H, m, 2 × Ph).

5-(2″-*Benzyloxyethyl*)-2-(1′-*hydroxy*-2′-*phenylethyl*)-4-*methylthiazole* **3c**, from phenylacetaldehyde (1.5 equiv.), as a colourless oil (854 mg, 91%), ν_{max}/cm^{-1} 3400 (OH stretch); δ_H(90 MHz) 2.1 (3 H, s, Me), 2.9 (2 H, t, *J* 6, CH_2), 3.0–3.3 (2 H, ABq, *J* 4, *J*′ 14, $PhCH_2$), 3.6 (2 H, t, *J* 6, CH_2O), 4.5 (2 H, s, CH_2Ph), 5.1 (1 H, dd, *J* 4, *J*′ 4, C*H*OH) and 7.2–7.4 (10 H, s, 2 × Ph); δ_C(62.5 MHz) 15 (Me), 27 (CH_2), 44 (CH_2), 70 (CH_2O), 72 (CHOH), 73 (CH_2O), 126–129, 137, 138, 147 and 171.

5-(2′-*Benzyloxyethyl*)-4-*methyl*-2-*propionylthiazole* **4a**.—To a solution of oxalyl chloride (0.1 cm^3, 145.5 mg, 1.15 mmol) in dichloromethane (2 cm^3) at −60 °C under argon was added a solution of dimethyl sulphoxide (0.17 cm^3, 172 mg, 2.20 mmol) in dichloromethane (3 cm^3) at such a rate that the temperature did not rise above −50 °C (5 min). The mixture was stirred at this temperature for 5 min after which a solution of the alcohol **3a** (0.3 g, 1.03 mmol) in dichloromethane (3 cm^3) was added dropwise. The mixture was stirred for 15 min at the same temperature before triethylamine (0.70 cm^3, 508 mg, 5 mmol) was added dropwise. The cold bath was removed and when the solution had reached room temperature the reaction was quenched with water (10 cm^3). The organic layer was separated and the aqueous solution was extracted with dichloromethane (2 × 4 cm^3). The combined organic layers were washed with water (2 × 5 cm^3) and dried (Na_2SO_4). The solvent was removed to give a yellow oil which was subjected to Kugelrohr distillation to give the product as a colourless oil (223 mg, 74%), b.p. 250 °C (oven temperature) at 10^{-3} mmHg (Found: C, 66.7; H, 7.1; N, 4.45; S, 10.65. $C_{16}H_{19}NO_2S$ requires C, 66.40; H, 6.62; N, 4.84; S, 11.06%); ν_{max}/cm^{-1} 1680 (CO); δ_H(90 MHz) 1.2 (3 H, t, *J* 7, *Me*(CH_2), 2.4 (3 H, s, Me), 3.0 (2 H, q, *J* 7, C*H*$_2$Me), 3.0 (2 H, t, *J* 8, CH_2), 3.6 (2 H, t, *J* 8, CH_2O), 4.5 (2 H, s, CH_2Ph) and 7.3 (5 H, s, Ph); δ_C(22.5 MHz) 8 (Me), 15 (Me), 28 (CH_2), 32 (CH_2), 70 (CH_2O), 73 (CH_2Ph), 128, 129, 137, 151, 163 and 194 (CO).

2-*Benzoyl*-5-(2′-*benzyloxyethyl*)-4-*methylthiazole* **4b**.—To a rapidly stirred solution of the alcohol **3b** (559 mg, 1.65 mmol) in ether (10 cm^3) at 0 °C was added a solution of sodium dichromate dihydrate (480 mg, 1.61 mmol) in aqueous sulphuric acid (7%, 5 cm^3) dropwise at such a rate that the temperature did not rise above 5 °C. The two-phase system was stirred for 2.5 h at ice temperature and then overnight at room temperature. The two layers were separated and the aqueous phase was extracted with ether (2 × 5 cm^3). The combined organic layers were washed once with water (5 cm^3) and dried ($MgSO_4$). Removal of the solvent gave a yellow oil which was chromatographed on silica gel using petroleum–ether (2:1) as eluent. The product ketone was isolated as a yellow solid (328 mg, 59%), m.p. 61 °C (Found: M$^+$, 337.1143. $C_{20}H_{19}NO_2S$ requires *M*, 337.113 65); ν_{max}/cm^{-1} 1641 (CO); δ_H(90 MHz) 2.4 (3 H, s, Me), 3.1 (2 H, t, *J* 7, CH_2), 3.7 (2 H, t, *J* 7, CH_2O), 4.5 (2 H, s, CH_2Ph), 7.3 (5 H, s, Ph), 7.5 (3 H, m, PhCO) and 7.9 (2 H, m, PhCO); δ_C(22.5 MHz) 15 (Me), 28 (CH_2), 70 (CH_2O), 73 (CH_2Ph), 127, 128, 131, 133, 135, 138, 152, 163 and 184; *m*/*z* 337 (M$^+$).

5-(2′-*Benzyloxyethyl*)-4-*methyl*-2-*phenylacetylthiazole* **4c**.—A solution of the lithiated derivative was prepared from thiazole **2** (647 mg, 2.78 mmol) and *tert*-butyllithium as described above and was transferred to a jacketted dropping funnel pre-cooled to −78 °C. This solution was then added dropwise to a solution of methyl phenylacetate (417 mg, 2.78 mmol) in THF (8 cm^3) also at −78 °C. The cold bath was removed and the mixture was stirred overnight. Glacial acetic acid (2 cm^3) was then added and the mixture was poured into saturated aqueous sodium hydrogen carbonate (25 cm^3). The aqueous phase was extracted with ether (3 × 8 cm^3) and the extracts were washed once with water (10 cm^3) and dried ($MgSO_4$). Removal of the solvent yielded an oil which was purified by silica gel chromatography using petroleum–ether (1:1) as eluent to give the product as an oil (440 mg, 46%) (Found: C, 71.5; H, 6.1; N, 4.0; S, 9.1. $C_{21}H_{21}NO_2S$ requires C, 71.77; H, 6.02; N, 3.99; S, 9.12%); ν_{max}/cm^{-1} 1680 (CO); δ_H(250 MHz) 2.5 (3 H, s, Me), 3.1 (2 H, t, *J* 6, CH_2), 3.7 (2 H, t, *J* 6, CH_2O), 4.4 (2 H, s, CH_2CO), 4.55 (2 H, s, CH_2Ph) and 7.2–7.4 (10 H, m, Ph).

5-(2′-*Benzyloxyethyl*)-4-*methyl*-2-(2″-*methylpropionyl*)-*thiazole* **4d**.—A solution of the lithiated derivative was prepaed from thiazole **2** (329 mg, 1.41 mmol) and *tert*-butyllithium as described above. To this solution at −78 °C was added neat 2-methylpropionyl chloride (0.15 cm^3, 153 mg, 1.43 mmol) (previously dried over CaH_2) dropwise. After addition was complete the cold bath was removed and the mixture was allowed to warm to room temperature to provide a yellow solution containing a white precipitate. This was filtered and concentrated to give a brown oil (372 mg). This was applied to a silica gel column and eluted with petroleum–ether (1:1) to give the starting material (197 mg) in addition to the desired ketone, the latter as a colourless oil (131 mg, 31%) (Found: C, 67.65; H, 7.2; N, 4.55. $C_{16}H_{21}NO_2S$ requires C, 67.29; H, 6.97; N, 4.62%); ν_{max}/cm^{-1} 1673 (CO); δ_H(90 MHz) 1.3 (6 H, d, *J* 8, Me_2), 2.4 (3 H, s, Me), 3.1 (2 H, t, *J* 6, CH_2), 3.7 (2 H, t, *J* 6, CH_2O), 3.8 (1 H, hep, *J* 8, CHCO), 4.6 (2 H, s, CH_2Ph) and 7.4 (5 H, s, Ph).

2-*Acetyl*-5-(2′-*benzyloxyethyl*)-4-*methylthiazole* **4e**.—A solution of the lithiated derivative was prepared from thiazole **2** (265 mg, 1.14 mmol) and *tert*-butyllithium as described above. To this solution at −78 °C was added neat acetic anhydride (0.11 cm^3, 119 mg, 1.17 mmol) dropwise and the reaction mixture was stirred at this temperature for a further 2 h after which time the cold bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate (10 cm^3) and the resultant suspension was extracted with ether (3 × 5 cm^3). The combined extracts were washed once with water (5 cm^3) and dried (Na_2SO_4). Removal of the solvent left a yellow oil which was chromatographed on a neutral alumina column using petroleum–ether (2:1) as eluent to give the product as a colourless oil (127 mg, 41%) (Found: C, 65.5; H, 6.5; N, 5.2; S, 11.4. $C_{15}H_{17}NO_2S$ requires C, 65.43; H, 6.22; N, 5.09; S, 11.64%); ν_{max}/cm^{-1} 1680 (CO); δ_H(90 MHz) 2.42 (3 H, s, Me), 2.65 (3 H, s, Me), 3.07 (2 H, t, *J* 8, CH_2), 3.67 (2 H, t, *J* 8, CH_2O), 4.52 (2 H, s, CH_2Ph) and 7.31 (5 H, s, Ph); δ_C(22.5 MHz) 15 (Me), 26 (Me), 28 (CH_2), 70 (CH_2O), 73 (CH_2O), 127, 128, 138, 152, 163 and 192.

General Synthesis of 2-*Acylimidazoles* **5**.—To a THF solution of 1-methylimidazole (0.5 mol dm^{-3}) at −78 °C under argon was added butyllithium (1.6 mol dm^{-3} solution in hexanes, 1.05 equiv.) dropwise. The reaction mixture was stirred for 30 min and then allowed to warm to −50 °C before the temperature was reduced to −95 °C and a pre-cooled (−78 °C) solution of the ester (1.5 equiv.) in THF (20 mol dm^{-3}) was added dropwise slowly. After the addition the flask contents were allowed to warm to room temperature overnight. Water was added to the reaction mixture and the THF was removed by rotary evaporation. The resultant slurry was taken up in the dichloromethane, washed once with water and dried. Removal of the solvent gave the crude product which was purified by Kugelrohr distillation. In this way the following compounds were prepared.

2-Formyl-1-methylimidazole **5a** as a colourless oil (40% from methyl formate; 64% from ethyl formate), b.p. 56 °C at 0.6 mmHg (lit.,[16] 88–91 °C at 12 mmHg); ν_{max}/cm^{-1} 1688 (CO); δ_H(90 MHz) 4.0 (3 H, s, NMe), 7.1 (1 H, s), 7.2 (1 H, s) and 9.8 (1 H, s, CHO).

2-Acetyl-1-methylimidazole **5b** as a colourless oil (76% from ethyl acetate), b.p. 61 °C at 1 mmHg (lit.,[16] 105–106 °C at 15 mmHg); ν_{max}/cm^{-1} 1680 (CO); δ_H(270 MHz) 2.6 (3 H, s, CH_3CO), 3.9 (3 H, s, NMe), 7.0 (1 H, s) and 7.1 (1 H, s).

1-*Methyl-2-propionylimidazole* **5c** as a colourless oil (50% from methyl propionate), b.p. 58 °C at 1.1 mmHg (Found: C, 60.4; H, 7.45; N, 20.95. $C_7H_{10}N_2O$ requires C, 60.85; H, 7.30; N, 20.27%); ν_{max}/cm^{-1} 1679 (CO); δ_H(90 MHz) 1.2 (3 H, t, *J* 8, Me), 3.1 (2 H, q, *J* 8, CH_2), 4.0 (3 H, s, NMe), 7.0 (1 H, very fine d) and 7.1 (1 H, very fine d); δ_C(22.5 MHz) 12 (Me) 35 (CH_2), 40 (NMe), 130 (NCH), 132 (NCH), 147 (NCN) and 197 (CO); if the temperature of addition is not kept < −80 °C the double addition product **6** is obtained as a white, crystalline solid, m.p. 169 °C; δ_H(90 MHz) 0.9 (3 H, t, *J* 8, Me), 2.5 (2 H, q, *J* 8, CH_2), 3.3 (6 H, s, 2 × NMe), 5.9 (1 H, br, s, OH), 6.8 (2 × 1 H, very fine d) and 6.9 (2 × 1 H, very fine d); δ_C(22.5 MHz) 7 (Me), 31 (CH_2), 33 (NMe), 72 (COH), 125 (NCH), 126 (NCH) and 148 (NCN); *m/z* 220 (M^+), 191 (M^+ − Et, 100%), 109.

1-*Methyl-2-(2′-methylpropionyl)imidazole* **5d** as a colourless oil (71% from methyl isobutyrate), b.p. 63 °C at 0.8 mmHg (Found: C, 61.95; H, 8.05; N, 18.05%; M^+ 152.0946. $C_8H_{12}N_2O$ requires C, 63.13; H, 7.95; N, 18.41%; *M*, 152.094 96); ν_{max}/cm^{-1} 1680; δ_H(90 MHz) 1.2 (6 H, d, *J* 8, Me_2), 3.8 (1 H, hep, *J* 8, CH), 4.0 (NMe), 7.0 (1 H, very fine d) and 7.1 (1 H, very fine d); δ_C(22.5 MHz) 18 (2 × Me), 36 (NMe), 75 (CH), 127 (NCH), 129 (NCH), 142 (NCN) and 197 (CO); *m/z* 152 (M^+), 139 (M^+ − Me) and 109 (M^+ − Pr^i).

4-*Methyl-2-propionyl-5-vinylthiazole* **7**.—To a solution of diisopropylamine (2.15 cm^3, 155.5 mg, 1.54 mmol) in dry THF (10 cm^3) was added butyllithium (1.6 mol dm^{-3}; 0.96 cm^3) at −78 °C. The solution was allowed to warm to room temperature and then cooled to −78 °C. To this cooled solution was added a solution of thiazole **4a** (204 mg, 0.70 mmol) in dry THF (1 cm^3) and the mixture was stirred for 1 h at the same temperature. A solution of anhydrous zinc chloride (200 mg, 1.47 mmol) in dry THF (2 cm^3) was then added dropwise. The cold bath was removed and the reaction mixture was allowed to warm to −22 °C. After 90 min at that temperature glacial acetic acid (0.1 cm^3) was added followed by water (20 cm^3). The organic products were extracted into ether (3 × 8 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated to a yellow oil. This was applied to a silica gel column and eluted with petroleum–ether (2:1) to give the product a a colourless oil (12 mg, 9%) (Found: M^+, 181.0565. $C_9H_{11}NOS$ requires *M*, 181.0561); ν_{max}/cm^{-1} 1675 (CO); δ_H(270 MHz) 1.2 (3 H, t, *J* 8, Me), 2.5 (3 H, s, Me), 3.3 (2 H, q, *J* 8, CH_2), 5.4 (1 H, d, *J* 10, *cis* =CH_2), 5.65 (1 H, d, *J* 18, *trans* =CH_2) and 6.8 (1 H, dd, *J* 10, *J′* 18, =CH); *m/z* 181 (M^+), 152 (100%, M^+ − Et).

1,4-*Bis*[5-(2-*benzyloxyethyl*)-4-*methylthiazol*-2-*yl*]-2,3-*diphenylbutane*-1,4-*dione* **8**.—Butyllithium (1.6 mol dm^{-3}; 0.51 cm^3, 0.81 mmol) was added dropwise to a solution of 2,2,6,6-tetramethylpiperidine (0.14 cm^3, 114 mg, 0.81 mmol) in dry THF (5 cm^3) at −5 °C under argon. The solution was warmed to 10 °C, maintained at this temperature for 40 min and then cooled to −78 °C. To this was added a solution of thiazole **4c** (258 mg, 0.73 mmol) in dry THF (2 cm^3). After 1 h at this temperature a solution of anhydrous zinc chloride (220 mg, 1.61 mmol). in dry THF (2 cm^3) was added dropwise followed 10 min later by neat acetone (0.13 cm^3, 103 mg, 1.77 mmol). The reaction mixture was allowed to come to room temperature slowly. stirred overnight and then quenched with glacial acetic acid (0.05 cm^3). Water (20 cm^3) was added and the organic products were extracted into ether (3 × 8 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to an oil. This was chromatographed on silica gel to give the starting material (49%) along with the product as a solid (50 mg, 19%), m.p. 132 °C (Found: C, 71.4; H, 5.7; N, 3.9; S, 8.8. $C_{42}H_{40}N_2O_4S_2$ requires C, 72.0; H, 5.8; N, 4.0; S, 9.1%); ν_{max}/cm^{-1} 1680 (CO); δ_H(200 MHz) 2.4 (6 H, s, 2 × Me), 3.0 (4 H, t, *J* 7, 2 × CH_2), 3.6 (4 H, t, *J* 7, 2 × CH_2O), 4.5 (4 H, s, 2 × CH_2Ph), 6.3 (2 H, s, CHPh), 7.1–7.3 (6 H, m, Ph) and 7.7 (4 H, m, Ph); δ_C(50.3 MHz) 15 (Me), 29 (CH_2), 54 (CHPh), 66 (CH_2O), 69 (CH_2O), 127–130, 136–138, 152, 162 and 191 (CO); *m/z* (FAB) 701 (M^+ + H), 468.

Aldol Condensation of Thiazole **4a** *with Acetaldehyde*.—Lithium diisopropylamide (1.57 mmol) was prepared as a solution in THF (8 cm^3) as described above and to this base at −78 °C was added a solution of thiazole **4a** (411 mg, 1.42 mmol) in THF (2 cm^3). The solution was stirred at this temperature for 1 h and then a solution of anhydrous zinc chloride (400 mg, 2.94 mmol) was added. After a further 10 min neat acetaldehyde (0.5 cm^3, 394 mg, 8.95 mol) was added dropwise and the cold bath was then replaced by an ice–salt bath. Stirring was continued for 1.3 h in this bath and then the reaction was quenched with glacial acetic acid (0.1 cm^3). Water (25 cm^3) was added and the organic products were extracted with ether (3 × 10 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to leave a yellow oil. The diastereoisomeric aldol products 4-(2′-benzyloxyethyl)-2-(3″-hydroxy-2-methylbutyryl)-5-methylthiazole were obtained as a 1:1 mixture after chromatography on silica gel as a colourless oil (280 mg, 60%) (Found: M^+, 333.1405. $C_{18}H_{23}NO_3S$ requires *M*, 333.1399); ν_{max}/cm^{-1} 3437 (OH) and 1674 (CO); δ_H(400 MHz) one diastereoisomer: 1.2 (3 H, d, *J* 7, CH_3CHOH), 1.25 (3 H, d, *J* 7, CH_3CH), 2.45 (3 H, s, Me), 3.1 (2 H, t, *J* 7, CH_2), 3.7 (2 H, t, *J* 7, CH_2O), 3.7–3.8 (1 H, m, $CHCH_3$), 4.2 (1 H, m, CH_3CHOH), 4.55 (2 H, s, CH_2Ph) and 7.3–7.5 (5 H, m, Ph); other diastereoisomer: 1.3 (3 H, d, *J* 7, CH_3CHOH), 1.3 (3 H, d, *J* 7, CH_3CH), 2.45 (3 H, s, Me), 3.1 (2 H, t, *J* 7, CH_2), 3.7 (2 H, t, *J* 7, CH_2O), 3.7–3.8 (1 H, m, $CHCH_3$), 4.05 (1 H, m, CH_3CHOH), 4.55 (2 H, s, CH_2Ph) and 7.3–7.5 (5 H, m, Ph); δ_C(100 MHz) one diastereoisomer: 11.3 (Me), 14.4 (Me), 19.9 (Me), 27.7 (CH_2), 47.5 (CH), 67.8 (CHO), 69.6 (CH_2O), 73.1 (CH_2O), 127–128, 137.6, 151.4, 162.7 and 197; other diastereoisomer: 11.3 (Me), 15.0 (Me), 21.1 (Me), 27.7 (CH_2), 48.5 (CH), 69.2 (CHO), 69.3 (CH_2O), 73.1 (CH_2O), 127–128, 138.3, 151.6, 162.7 and 197.2; *m/z* 333 (M^+), 315 (M^+ − H_2O), 300, 289 and 168.

Aldol Condensation of the Thiazole **4a** *with Benzaldehyde*.—Lithium tetramethylpiperidide (0.77 mmol) was prepared as a solution in THF (5 cm^3) as described above. To this solution at −5 °C was added a solution of the thiazole **4a** (196 mg, 0.68 mmol) in THF (2 cm^3) dropwise. After 1 h at this temperature a solution of anhydrous zinc chloride (200 mg, 1.47 mmol) in THF (5 cm^3) was added followed 10 min later by neat benzaldehyde (0.30 cm^3, 313 mg, 2.95 mmol). The cold bath was removed and the reaction was quenched after a further 1 h at room temperature with glacial acetic acid (0.1 cm^3). Water (20 cm^3) was added and the organic products were extracted into ether (3 × 5 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to yield a yellow oil. This oil was applied to a column of silica gel and the products 4-(2′-benzyloxyethyl)-2-(3″-hydroxy-2″-methyl-3″-phenylpropanoyl)-5-methylthiazole were eluted with petroleum–ether (1:1). The first diastereoisomer off the column was an oil (20 mg, 7%); ν_{max}/cm^{-1} 3445 (OH). 1678 (CO); δ_H(200 MHz) 1.3 (3 H, d, *J* 7, CH_3CH), 2.4 (3 H, s, Me), 3.1 (2 H, t, *J* 7, CH_2), 3.7 (2 H, t, *J* 7, CH_2O), 3.9 (1 H, dq, *J* 3, *J′* 7, $CHCH_3$), 4.5 (2 H, s, CH_2Ph), 5.3 (1 H, d,

J 3, CHOH) and 7.2–7.5 (10 H, m, 2 × Ph). There followed fractions containing both diastereoisomers (45 mg, 17%) and then the second diastereoisomer came off as an oil (120 mg, 42%) (Found: $M^+ - 106$, 289.1140. $C_{16}H_{19}NO_2S$ requires 289.1137); δ_H(200 MHz) 1.1 (3 H, d, *J* 7, CH_3CH), 2.4 (3 H, s, Me), 3.1 (2 H, t, *J* 7, CH_2), 3.7 (2 H, t, *J* 7, CH_2O), 4.1 (1 H, dq, *J* 7, *J'* 7, $CHCH_3$), 4.5 (2 H, s, CH_2Ph), 4.9 (1 H, d, *J* 7, CHOH) and 7.3–7.5 (10 H, m, Ph); *m/z* 289 ($M^+ - 106$), 268.

Synthesis of the Aldols **9**. *General Procedure*.—To a solution (0.2 mol dm^{-3}) of lithium diisopropylamide (1.05 equiv.) in THF under argon at −78 °C was added a solution (0.5 mol dm^{-3}) of the 2-acylimidazole in THF dropwise. The cold bath was then removed and the reaction mixture was allowed to warm to −25 °C at which temperature the reaction was stirred for 2 h. The enolate solution so formed was then cooled to −78 °C and neat aldehyde (4 equiv.) was added dropwise. After the addition the temperature was allowed to rise to −40 °C over 1.5 h and then the reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with an equal volume of water and the organic products were extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated and the resultant crude product was purified. In this manner the following compounds were made.

2-(3′-*Hydroxy*-2′-*methyl*-3′-*phenylpropionyl*)-1-*methylimidazole* **9a**. This was obtained from benzaldehyde and the imidazole **5c**: only the *anti*-diastereoisomer of the product was isolated from a silica gel column using petroleum–ether (1:1) as eluent; it was obtained as a white solid (38%), m.p. 156 °C (Found: M^+, 244.1216. $C_{14}H_{16}N_2O_2$ requires *M*, 244.121 78); ν_{max}/cm^{-1} 3308 (OH), 1679 (CO); δ_H(90 MHz) 1.05 (3 H, d, *J* 7, CH_3CH), 3.95 (3 H, s, NMe), 4.2 (1 H, m, $CHCH_3$), 4.9 (1 H, d, *J* 7, CHOH), 7.0 (1 H, very fine d), 7.1 (1 H, very fine d) and 7.3 (5 H, m, Ph); δ_C(22.5 MHz) 15 (Me), 36 (NMe), 49 (CH), 77 (CHOH), 125–130, 143 (NCN + one phenyl C) and 196 (CO); *m/z* 244 (M^+), 215, 138 (100%, M^+ − PhCHO); the *syn*-isomer (14%, by integration) was inferred from the ^1H NMR spectrum of the crude product: δ_H(90 MHz) 1.15 (3 H, d, *J* 7, CH_3CH), 3.93 (3 H, s, NMe), 4.2 (1 H, m, $CHCH_3$), 5.15 (1 H, d, *J* 3, CHOH), 7.0 (1 H, very fine d), 7.1 (1 H, very fine d) and 7.3 (5 H, m, Ph); if the temperature of the aldol reaction was allowed to rise to 0 °C after the addition of benzaldehyde and was then maintained at this level for 2 h before quenching the benzoate **10** was obtained as a white solid (37%), m.p. 141 °C (Found: C, 71.6; H, 6.35; N, 7.9. $C_{21}H_{22}N_2O_3$ requires C, 71.98; H, 6.33; N, 7.99%); ν_{max}/cm^{-1} 3450 (OH), 1719 (CO); δ_H(270 MHz) 0.9 (3 H, d, *J* 7, CH_3CH), 2.7 (1 H, m, $CHCH_3$), 3.6 (3 H, s, NMe), 5.1 (1 H, d, *J* 6, CHOH), 6.0 (1 H, d, *J* 7, CHOCOPh), 6.6 (1 H, very fine d), 6.9 (1 H, very fine d), 7.2–7.6 (8 H, m, Ph) and 8.0 (2 H, m, *ortho*-Hs of COPh); *m/z* 350 (M^+), 292.

2-(3′-*Hydroxy*-2′,4′-*dimethylpentanoyl*)-1-*methylimidazole* **9b**. This was obtained from isobutyraldehyde and the imidazole **5c** as a mixture (3:1) of two diastereoisomers as an oil after removal of the starting material by Kugelrohr distillation (28%) (Found: M^+, 210.1371. $C_{11}H_{18}N_2O_2$ requires *M*, 210.136 83); ν_{max}/cm^{-1} 3450 (OH) and 1670 (CO); δ_H(270 MHz) 1.0 (6 H, 2 × dd, Me_2C), 1.3 (3 H, 2 × d, each *J* 4, CH_3CHCO), 1.7 (1 H, hep, $CHMe_2$), 3.6 (1 H, dd, *J* 1, *J'* 5, CHOH), 3.8 (1 H, br s, OH), 3.9 (1 H, dq, *J* 1, *J'* 6, CHMe), 4.0 (3 H, s, NMe), 7.0 (1 H, very fine d) and 7.2 (1 H, very fine d); *m/z* 210 (M^+), 192, 177, 167, 139 (100%) and 109.

2-(3′-*Hydroxy*-2′-*methylbutyryl*)-1-*methylimidazole* **9c**. This was obtained from acetaldehyde and the imidazole **5c** obtained as a mixture (3:2) of two diastereoisomers from a silica gel column after elution with ether as a colourless oil (52%) (Found: M^+, 182.1050. $C_9H_{14}N_2O_2$ requires *M*, 182.105 52); ν_{max}/cm^{-1} 3380 (OH) and 1679 (CO); δ_H(90 MHz) 1.1–1.3 (6 H, m, 2 × Me), 3.7–4.2 (2 H, m, 2 × MeC*H*), 4.0 (3 H, s, NMe), 7.0 (1 H, br s) and 7.1 (1 H, br s); δ_C(22.5 MHz) 11 (Me), 14 (Me), 20 (Me), 21 (Me), 36 (2 × NMe), 48 (CHCO), 49 (CHCO), 68 (CHOH), 69 (CHOH), 127 (2 × NCH), 129 (2 × NCH), 142 (NCN), 195 (CO) and 196 (CO); *m/z* 182 (M^+), 167, 139 (100%) and 109.

2-(3′-*Hydroxy*-2′,2′-*dimethylbutyryl*)-1-*methylimidazole* **9d**. This was obtained from acetaldehyde and the imidazole **5d**: isolated from a silica gel column after elution with ether as an oil (78%), ν_{max}/cm^{-1} 3400 (OH) and 1676 (CO); δ_H(90 MHz) 1.1 (3 H, d, *J* 8, CH_3CH), 1.2 (3 H, s, Me), 1.4 (3 H, s, Me), 3.8 (1 H, br q, $CHCH_3$), 7.0 (1 H, very fine d) and 7.1 (1 H, very fine d); *m/z* 196 (M^+), 181, 163, 153, 152, 109 and 82.

2-(3′-*Hydroxy*-2′,2′-*dimethyl*-3′-*phenylpropionyl*)-1-*methylimidazole* **9e**. This was obtained from benzaldehyde and the imidazole **5d**: isolated from a silica gel column after elution with ether as a colourless oil (57%) (Found: M^+, 258.1370. $C_{15}H_{18}N_2O_2$ requires *M*, 258.1368); ν_{max}/cm^{-1} 3300 (OH) and 1664 (CO); δ_H(270 MHz) 1.3 (3 H, s, Me), 1.5 (3 H, s, Me), 3.8 (3 H, s, NMe), 5.0 (1 H, s, CHOH), 7.0 (1 H, s) and 7.1–7.3 (6 H, m, ArH); δ_C(67.5 MHz) 22 (Me), 24 (Me), 36 (NMe), 54 (Me_2C), 79 (CHOH), 126–127, 142, 143 and 196 (CO); *m/z* 258 (M^+), 229, 152, 109, 86 and 84.

2-(3′-*Hydroxybutyryl*)-1-*methylimidazole* **9f**. This was obtained from acetaldehyde and the imidazole **5b**: isolated as an oil (70%) (Found: M^+, 168.0899. $C_8H_{12}N_2O_2$ requires *M*, 168.0899); ν_{max}/cm^{-1} 3300 (OH) and 1680 (CO); δ_H(270 MHz) 1.3 (3 H, d, *J* 7, CH_3CH), 3.2 (2 H, d ABq, CH_2), 4.0 (3 H, s, NMe), 4.2 (1 H, m, CHOH), 7.0 (1 H, very fine d) and 7.3 (1 H, very fine d); *m/z* 168 (M^+), 153, 125 (100%), 109 and 82.

Methylation of 2-*Acylimidazoles: General Procedure*.—To a solution of the 2-acyl imidazole in dichloromethane (0.2 mol dm^{-3}) at room temperature under argon was added neat methyl triflate (1 equiv.). The reaction was monitored by withdrawing small samples (0.1 cm^3) for solution cell IR spectroscopy and was deemed complete when all of the carbonyl absorption of the starting material (typically *ca.* 1670–1680 cm^{-1}) had moved to higher frequency (1700–1705 cm^{-1}). The following salts were isolated.

1,3-*Dimethyl*-2-*propionylimidazolium triflate*, isolated as a white solid (87%), m.p. 112 °C; δ_H(90 MHz, [$^2H_6$]DMSO) 1.1 (3 H, t, *J* 9, CH_3CH_2), 3.0 (2 H, q, *J* 9, CH_3CH_2), 4.0 (6 H, s, 2 × NMe) and 7.3 (2 H, s, 2 × Ar-H).

1,3-*Dimethyl*-2-(2′-*methylpropionyl*)*imidazolium triflate*, isolated as a white solid (100%), m.p. 67–69 °C; δ_H(90 MHz, CD_2Cl_2) 1.3 (6 H, d, *J* 7, Me_2CH), 3.3 (1 H, hep, *J* 7, $CHMe_2$), 4.1 (6 H, s, 2 × NMe) and 7.6 (2 H, s, 2 × Ar-H).

anti-2-(3′-*Hydroxy*-2′-*methyl*-3′-*phenylpropionyl*)-1,3-*dimethylimidazolium triflate*, isolated as an unstable, white solid (100%); δ_H(270 MHz, $CDCl_3$) 1.0 (3 H, d, *J* 7, *Me*CH), 3.8 (1 H, m, *CH*Me), 4.0 (6 H, s, 2 × NMe), 4.7 (1 H, d, *J* 10, CHOH) and 7.3–7.4 (7 H, m, Ph + Ar-H).

Methyl anti-3-*Hydroxy*-2-*methyl*-3-*phenylpropionate*[14] **11**.—To a solution of the above aldol salt (322 mg, 0.79 mmol) in dichloromethane (4 cm^3) was added methanol (0.16 cm^3, 127 mg, 4 mmol) followed immediately by solid DABCO (18 mg, 0.161 mmol). After 5 min, water (10 cm^3) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 5 cm^3). The combined organic layers were washed with water once (5 cm^3), dried (Na_2SO_4) and evaporated to give the product (151 mg, 99%); ν_{max}/cm^{-1} 1731; δ_H(90 MHz) 1.0 (3 H, d, *J* 7, *Me*CH), 2.8 (1 H, m, *CH*Me), 3.7 (3 H, s, OMe), 4.7 (1 H, d, *J* 8, CHOH) and 7.3 (5 H, s, Ph); *m/z* 194 (M^+), 163.

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