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Bifunctional Chiral Auxiliaries 7: Aldol Reactions of Enolates Derived from 1,3-Diacylimidazolidine-2-thiones and 1,3-Diacylimidazolidin-2-ones[1]

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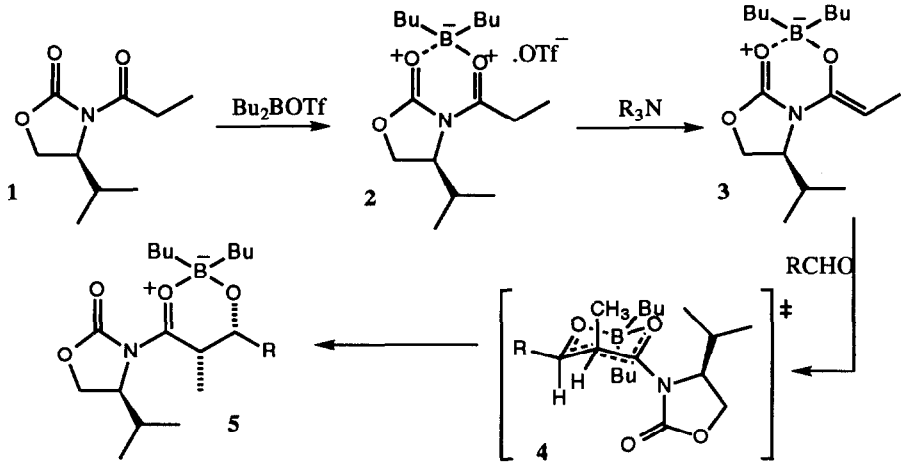
Abstract: Dibutylboron enolates of 1,3-diacylimidazolidine-2-thiones and 1,3-diacylimidazolidin-2-ones undergo highly *syn*-stereoselective aldol reactions with aldehydes to allow elaboration of both acyl sidechains. The reaction is proposed to occur *via* sequential enolisation rather than *via* a bisenolate and the stereochemistry of the product was elucidated by both X-ray crystallography and reductive cleavage of a homochiral aldol product to give (1*R*,2*S*)-1-phenyl-2-methylpropane-1,3-diol. In contrast, tin (II) triflate mediated aldol reactions result in only one of the two acyl sidechains reacting and exhibit reversed enantiofacial stereoselectivity.

The development of highly stereoselective aldol methodology has provided organic synthesis with a potent method for achieving acyclic stereocontrol.[2] To the initial understanding of those parameters which dominate *syn* / *anti* stereoselection[3] has been added a comprehension of how stoicheiometric chiral auxiliaries may be introduced so as to effect enantioselective carbon-carbon bond formation.[4] The result is the development of an asymmetric method whose power and flexibility have gained it a pre-eminent position in natural product synthesis.[5]

As part of our own goal of developing bifunctional chiral auxiliaries[1,6] (which can control a range of highly stereoselective carbon-carbon bond forming reactions on two attached sidechains on a C_2 symmetric chiral auxiliary) we have examined aldol reactions of enolates derived from 1,3-diacylimidazolidine-2-thiones and 1,3-diacylimidazolidin-2-ones. As has been described previously[7], these compounds seek to achieve high levels of stereocontrol by mimicking the transition states used by N-acyl oxazolidinones.[8] Dibutylboron enolates of N-acyl oxazolidinones have been shown to undergo highly *syn*-stereoselective aldol reactions with simple aldehydes.[9] Introduction of a Lewis acid, or merely the use of excess dibutylboron triflate, may catalyse *anti*-stereoselective aldol reactions which proceed *via* an open transition state.[10] Evans has reported that trichlorotitanium enolates react with high *syn*-stereoselectivity[11] without the disadvantages of inconsistent results which accompany the use of dibutylboron triflate.[12] Tin (II) triflate mediated aldol reactions have been reported by Evans, using N-acyl oxazolidinones,[13] and by Nagao, using N-acyl thioxazolidine-2-thiones[14]. Both reactions are *syn*-stereoselective and the latter has been used by Kocienski in a synthetic application where an attempted aldol reaction with a dibutylboron enolate of an N-acyl oxazolidinone was unsuccessful.[15]

The role played by the dibutylboron counterion is critical to an understanding of the mechanism of this reaction. Boron is typically tetracoordinate but, due to the two alkyl groups, there are only two free coordination sites on the dibutylboron fragment which boron may use for further chelation. Addition of dibutylboron triflate to N-acyl oxazolidinone **1** gives adduct **2** in which the boron is coordinated to both carbonyl groups. This chelation enhances the acidity of the acyl methylene group to such an extent that deprotonation may now occur

with a relatively weak base such as triethylamine or 1-ethylpiperidine (such bases could not deprotonate the propionyl group without this enhancement of acidity due to coordination of the Lewis acid). Enolate **3** has the boron associated with both carbonyl oxygens but, on addition of the electrophile, the association with the oxazolidinone carbonyl group must be broken to free a coordination site on boron so that it may chelate to the aldehydic carbonyl oxygen. Thus, in transition state **4**, boron is bound to the enolate oxygen and the carbonyl oxygen of the electrophile whilst in aldolate **5**, it is bonded to the latent hydroxy group as well as being coordinated to the acyl carbonyl group (Scheme 1).



Scheme 1

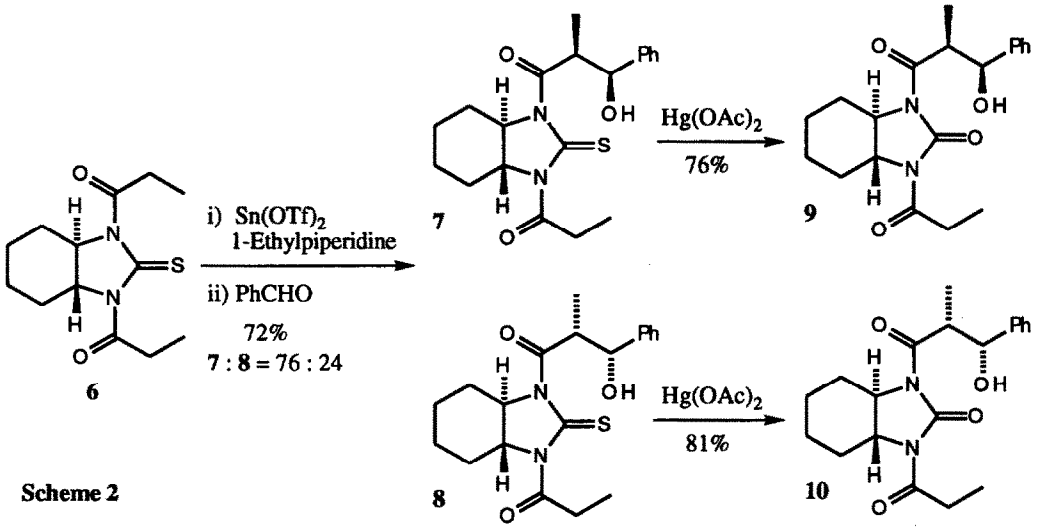
We herein report the aldol reactions of both tin and dialkylboron enolates of both 1,3-diacylimidazolidine-2-thiones and 1,3-diacylimidazolidin-2-ones. Preliminary communication of part of this work has already been reported.[6,7]

Results and Discussion

All of the initial work to establish the diastereoselectivities of the aldol reactions was performed with racemic imidazolidine-2-thiones and imidazolidin-2-ones before application in the homochiral series. Although tin (II) triflate has been employed in aldol reactions of N-acyl oxazolidinones,[13] it has seen more routine use with N-acyl thioxazolidine-2-thiones.[14] Using a method similar to that reported by Nagao,[14] 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **6** was enolised with a mixture of tin (II) triflate (2.3eq) and 1-ethylpiperidine (2.6eq) at -78°C. After addition of benzaldehyde (2.6eq) and further stirring at -78°C (2 h), a white solid was obtained on work-up. This was found to contain a mixture of the diastereoisomeric monoaldol products **7** and **8** in a ratio of 76 : 24. These were readily separable by chromatography on silica gel and were shown to have *syn*-stereochemistry within the elaborated sidechains as a result of the small H_2/H_3 coupling constants in the ^1H n.m.r. spectra[16] and the relatively upfield shifts of certain resonances in the ^{13}C n.m.r. spectra[17] (Scheme 2).

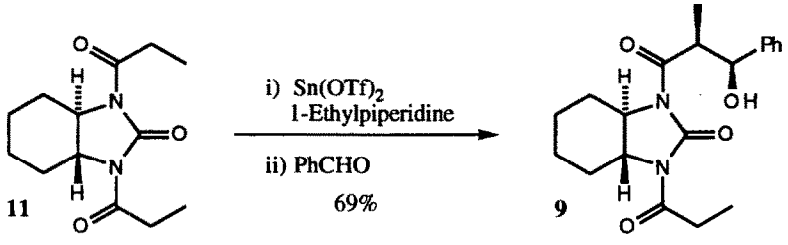
Although the relative stereochemistry within the acyl sidechains could be assigned, the stereochemical relationship between these newly-formed stereogenic centres and those of the chiral auxiliary could not be determined from spectroscopic data. Consequently both **7** and **8** were each treated with mercury (II) acetate to convert them to their oxocarbonyl analogues in a manner identical to that which we have already described for the synthesis of 1,3-diacylimidazolidin-2-ones.[18] Both **9** and **10** were formed as single diastereoisomers,

indicating that the dethionation reaction proceeds without detectable epimerisation (Scheme 2). Furthermore both had clearly retained the *syn*-stereochemistry in the β-hydroxy acyl sidechain. Assignment of the relative stereochemistry within **10** was possible because of this compound's intermediacy in the synthesis of **15** (*vide infra*) whose structure was elucidated by X-ray crystallographic analysis.



Scheme 2

The reaction was repeated with 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **11**, which gave monoaldol product **9** in 69% yield (Scheme 3).

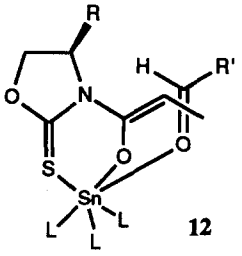


Diastereoselectivity 95 : 5

Scheme 3

It is clear that these tin (II) triflate mediated aldol reactions show reversed enantiofacial selectivity from the analogous reactions of dibutylboron enolates.[14] Furthermore, only one acyl sidechain reacts despite the use of more than two equivalents of all reagents. Both these observations may be rationalised by considering the two transition state models proposed for the aldol reactions of tin (II) **12** and dibutylboron enolates **13**.[14] It is proposed that the tin (II) enolate reacts *via* the *syn* enolate, due to it having a vacant coordination site with which it can be chelated to the carbonyl / thiocarbonyl group on the five-membered ring in transition state **12**. In contrast, the dibutylboron enolate cannot be chelated, as the boron has a maximum coordination number of four, and reacts *via* the *anti* enolate due, it is proposed, to dipolar organisation in transition state **13**. Clearly this difference will be manifested in opposite enantiofacial selectivity. That only one of the two acyl sidechains of the bifunctional chiral auxiliaries reacts must be due either to the second reaction being kinetically slow, or due to non-enolisation of the second sidechain. The latter explanation would seem to be the more reasonable as it could

be argued that if chelation of the tin (II) species is essential to increase the acidity of the α-methylene protons prior to their removal, the stability of the Lewis acid : substrate complex will be a critical factor. Although initial coordination of the first tin (II) species can occur, the second one cannot interact successfully with the substrate due both to the central carbonyl / thiocarbonyl group being too electron poor and the sterically crowded environment about this group.



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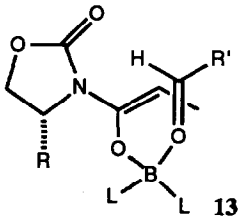
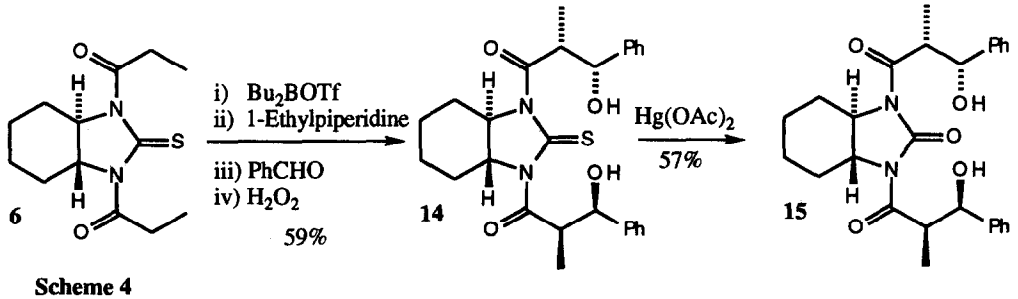


13

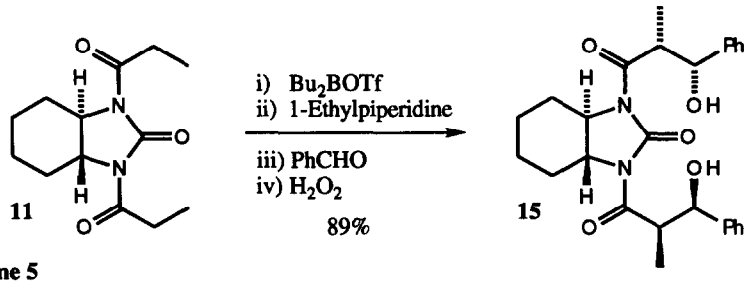
The greater stereoselectivity observed in the reaction of **11** over that of **6** is presumably a function of the shortness of the tin-oxygen bond compared to the tin-sulphur bond.[19] As it has been argued that the enolate counterion does not break its association with the central carbonyl / thiocarbonyl group, the reduced stereoselectivity observed in the reaction of **6** would indicate flexibility within the transition state rather than reaction occurring *via* a competing open transition state.

Although reactions of dibutylboron enolates of N-acyl thioxazolidine-2-thiones have not been reported it was reasoned that substitution of a thiocarbonyl group for the carbonyl group within the five-membered ring should not perturb the reaction unduly. Thus, 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **6** was treated with dibutylboron triflate (2.3 eq) and 1-ethylpiperidine (2.6eq) at 0°C before being cooled to -78°C. Benzaldehyde (2.6eq) was added and the reaction stirred at -78°C for 1 h then warmed to 0°C and stirred for a further 2 h before being quenched and worked-up to yield dialdol product **14** as a single diastereoisomer[20] (Scheme 4). Although it was clear from ^{1}H and ^{13}C n.m.r. data that both sidechains were *syn*, the stereochemical assignment of **14** was made by treating it with mercury (II) acetate to give **15**[18] (Scheme 4). This was identical to a sample of **15** prepared directly from **11** (*vide infra*) whose structure has been determined unambiguously by X-ray crystallographic analysis.



Scheme 4

Repetition of these conditions, with 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **11** as starting material gave **15** directly. Once again it was obtained as a single diastereoisomer although the chemical yield was much higher than previously (Scheme 5).



Scheme 5

The structure of **15** was elucidated by a single crystal X-ray diffraction study and is shown in the Figure. Fractional atomic coordinates for **15** are listed in Table 1 with selected torsional angles being given in Table 2.

Figure The molecular structure of racemic (4*RS*,5*RS*)-1,3-di[(3*SR*,2*RS*)-3-phenyl-3-hydroxy-2-methylpropionyl]-*trans*-4,5-tetramethyleneimidazolidin-2-one **15** as determined by X-ray crystallography.

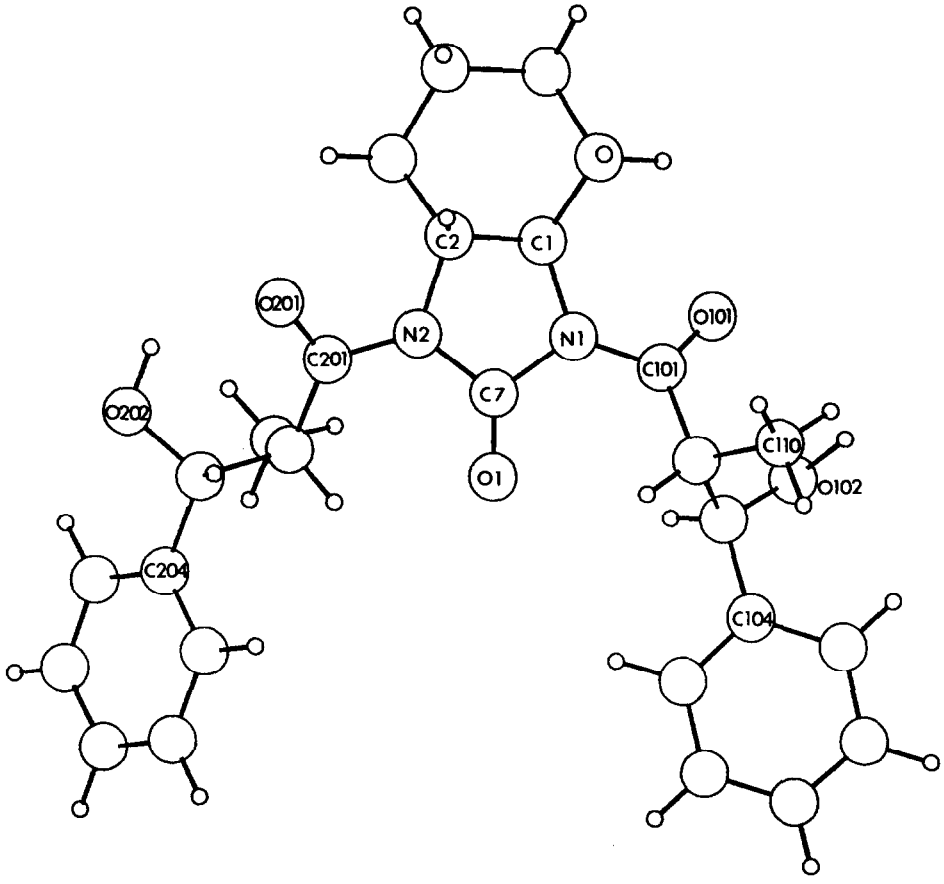


Table 1 Fractional atomic coordinates for racemic (4*RS*,5*RS*)-1,3-di[(3*SR*,2*RS*)-3-phenyl-3-hydroxy-2-methylpropionyl]-*trans*-4,5-tetramethyleneimidazolidin-2-one **15**.

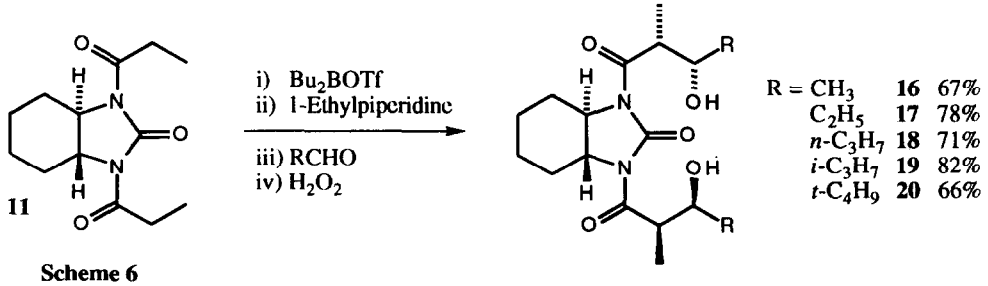
Atom	x/a	y/b	z/c	U(iso)
O(1)	0.0902(2)	-0.04447(9)	0.36588(8)	0.0620
O(101)	-0.1128(2)	0.0985(1)	0.45150(8)	0.0708
O(102)	-0.1850(3)	-0.0226(1)	0.51169(9)	0.0905
O(201)	0.3085(2)	0.0771(1)	0.27093(8)	0.0690
O(202)	0.4921(2)	-0.0150(1)	0.2625(1)	0.0801
N(1)	0.0124(2)	0.0714(1)	0.38378(7)	0.0478
N(2)	0.1831(2)	0.0641(1)	0.34146(8)	0.0476
C(1)	0.0643(2)	0.1456(1)	0.38667(9)	0.0472
C(2)	0.1476(2)	0.1422(1)	0.33844(9)	0.0464
C(3)	0.2354(2)	0.2015(1)	0.3464(1)	0.0581
C(4)	0.1717(3)	0.2750(1)	0.3440(1)	0.0679
C(5)	0.0722(3)	0.2791(1)	0.3850(1)	0.0680
C(6)	-0.0088(2)	0.2133(1)	0.3802(1)	0.0591
C(7)	0.0948(2)	0.0218(1)	0.36358(9)	0.0497
C(101)	-0.0788(2)	0.0531(1)	0.4175(1)	0.0553
C(102)	-0.1389(2)	-0.0195(1)	0.4109(1)	0.0568
C(103)	-0.1333(3)	-0.0605(2)	0.4673(1)	0.0653
C(104)	-0.1806(2)	-0.1376(2)	0.4640(1)	0.0628
C(105)	-0.2876(3)	-0.1551(2)	0.4838(1)	0.0813
C(106)	-0.3264(4)	-0.2281(3)	0.4801(2)	0.0939
C(107)	-0.2591(5)	-0.2809(2)	0.4566(2)	0.1002
C(108)	-0.1545(4)	-0.2634(2)	0.4372(2)	0.1031
C(109)	-0.1146(3)	-0.1920(2)	0.4410(1)	0.0826
C(110)	-0.2629(3)	-0.0045(2)	0.3926(2)	0.0924
C(201)	0.2715(2)	0.0375(1)	0.3081(1)	0.0543
C(202)	0.3261(2)	-0.0346(1)	0.3240(1)	0.0524
C(203)	0.4006(2)	-0.0632(1)	0.2754(1)	0.0575
C(204)	0.4493(2)	-0.1382(1)	0.28862(9)	0.0518
C(205)	0.3843(2)	-0.2005(1)	0.2801(1)	0.0640
C(206)	0.4286(3)	-0.2697(2)	0.2922(1)	0.0768
C(207)	0.5365(3)	-0.2763(2)	0.3130(1)	0.0776
C(208)	0.6013(3)	-0.2151(2)	0.3217(1)	0.0738
C(209)	0.5582(2)	-0.1458(2)	0.3091(1)	0.0636
C(210)	0.3929(3)	-0.0227(2)	0.3789(1)	0.0747
H(1)	-0.264(3)	0.010(2)	0.4940(7)	0.12(1)
H(2)	0.462(1)	0.036(2)	0.257(2)	0.17(2)

Table 2 Selected torsional angles (°) for racemic (4*RS*,5*RS*)-1,3-di[(3*SR*,2*RS*)-3-phenyl-3-hydroxy-2-methylpropionyl]-*trans*-4,5-tetramethyleneimidazolidin-2-one **15** (using crystallographic atom numbering).

C(201) N(2) C(7) O(1)	13.6
O(201) C(201) N(2) C(2)	-9.8
N(2) C(2) C(1) N(1)	-34.9
C(210) C(202) C(201) O(201)	102.8
O(202) C(203) C(202) C(210)	-58.6
C(204) C(203) C(202) C(201)	-175.7
C(101) N(1) C(7) O(1)	10.9
O(101) C(101) N(1) C(2)	-3.1
C(110) C(102) C(101) O(101)	60.2
O(102) C(103) C(102) C(110)	-59.3
C(104) C(103) C(102) C(101)	-174.1

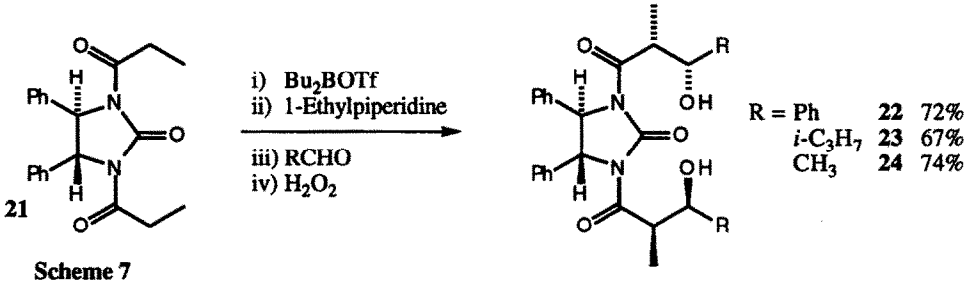
The Figure clearly shows the *syn*-stereochemistry of both acyl sidechains and further examination reveals the expected stereochemical relationship between these newly-formed stereogenic centres and those resident in the chiral auxiliary. The conformation that **15** has adopted in the crystal structure has the two acyl carbonyl groups orientated *anti* to the imidazolidin-2-one carbonyl group, presumably a dipolar effect. Consequently, we have chosen to draw 1,3-diacylimidazolidine-2-thiones and 1,3-diacylimidazolidin-2-ones in this conformation, with these three carbonyl groups roughly coplanar and the central one *anti* to the other two.

To try and establish the generality of this dialdol process, the reaction was repeated with a range of simple aliphatic aldehydes. With the exception of pivalaldehyde, all the examples listed below reacted on both sidechains to give dialdol products **16-19** in good chemical yield and without a second diastereoisomer being detectable in the 300 MHz n.m.r. spectrum[6]. With pivalaldehyde it did not prove possible to achieve a complete dialdol reaction, an 84 : 16 mixture of the dialdol **20** and monoaldol **26** products representing the highest conversion obtained (the yield of 66% is calculated from this non-separable mixture). The reaction of pivalaldehyde with a dibutylboron enolate of an N-acyl oxazolidinone has not been described and in a recent study, Yamada reported that the dibutylboron enolate of 1-propionyl-3-methyl-*trans*-4,5-diphenylimidazolidin-2-one failed to react with pivalaldehyde although simple aldehydes reacted stereoselectively and in good yield[21] (Scheme 6).



Scheme 6

Although the aldol reactions so far described have utilised chiral auxiliaries derived from *trans*-1,2-diaminocyclohexane, we have also prepared auxiliaries derived from 1,2-diphenyl-1,2-diaminoethane.[18] Thus, 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one **21** was treated with dibutylboron triflate, 1-ethylpiperidine and a range of aldehydes to give dialdol products **22-24**. Once again the reactions were completely stereoselective and all three could be made to give dialdol products without contamination with the monoaldol products[6,7] (Scheme 7).



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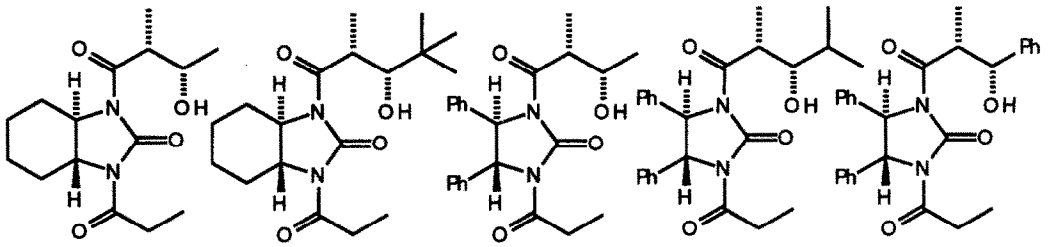
Scheme 7

Although clean dialdol reactions were possible (with the exception of the reaction of **11** with pivalaldehyde), monoaldol products were isolated in those cases where the dibutylboron triflate was not freshly opened. As **25-29** were all formed as single diastereoisomers, they were either partially (**25** and **26**) or fully (**27-29**) characterised.



25 **26** **27** **28** **29**

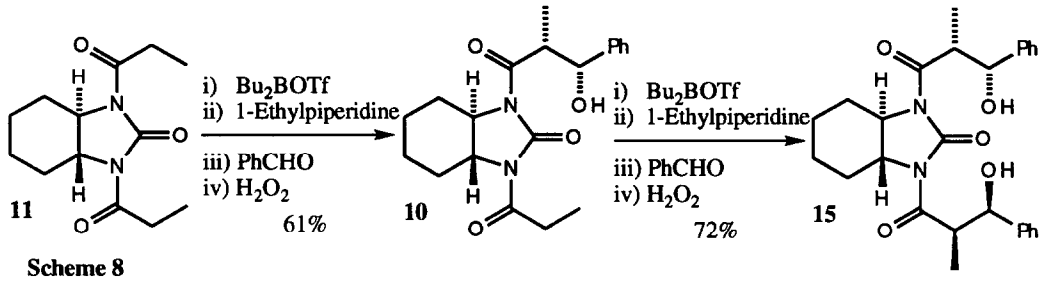
The relative configurations within aldol products **16-20** and **22-29** were assigned by analogy with that of **15** whose structure had been established unambiguously. That the aldol reactions were *syn*-stereoselective was readily shown by consideration of the ^1H and ^{13}C n.m.r. data for these compounds (Table 3). Furthermore, the monoaldol products showed ^{13}C n.m.r. resonances for the β-hydroxy acyl group that were characteristically displaced by less than 0.3 ppm from the corresponding resonances in the spectra of the dialdol analogues.

The mechanism of this reaction almost certainly proceeds *via* sequential formation of two monoenolates and not through a bisenolate. Some evidence in support of this argument comes from examination of the reaction mixture, before addition of the aldehyde, by ^1H n.m.r. spectroscopy. Although the excesses of the other reagents obscured certain regions of the spectrum, the loss of C_2 symmetry was apparent due to the non-equivalence of the bridgehead methine protons. Furthermore, there were signals due to both an enolised sidechain (δ 4.40 and δ 1.55) and a non-enolised acyl group (δ 2.90 and δ 1.15). In an attempt to elucidate the mechanism further, the reaction was repeated with only one equivalent of dibutylboron triflate to give cleanly monoaldol **10**. This was then resubjected to the same conditions used with **11** to give dialdol **15** (Scheme 8).

Table 3:

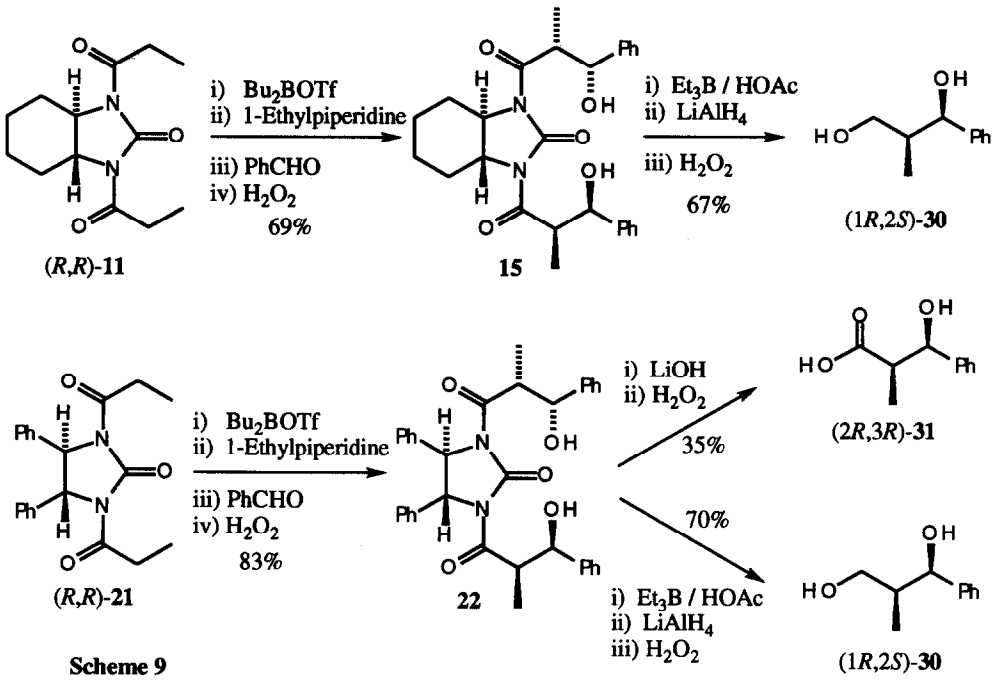
Selected ^{1}H and ^{13}C n.m.r. data for dialdol products **15-20** and **22-24** and monoaldol products **25-29**

Compound	H_2/H_3 / Hz	CH_3 / ppm	COCH / ppm	CH(OH) / ppm
15	2.8	10.9	46.1	72.1
16	2.4	11.2	45.0	66.8
17	2.4	10.3	43.6	72.0
18	2.3	11.0	44.0	70.2
19	2.3	10.7	41.3	75.6
20	2.7	13.6	40.5	76.6
22	4.6	11.3	45.5	73.7
23	3.3	10.4	40.7	76.6
24	2.7	10.5	44.2	67.6
25	2.6	11.2	44.8	66.8
26	2.6	13.5	40.5	76.7
27	2.6	11.3	45.5	73.7
28	3.1	10.2	40.4	76.5
29	2.8	10.4	44.0	67.6



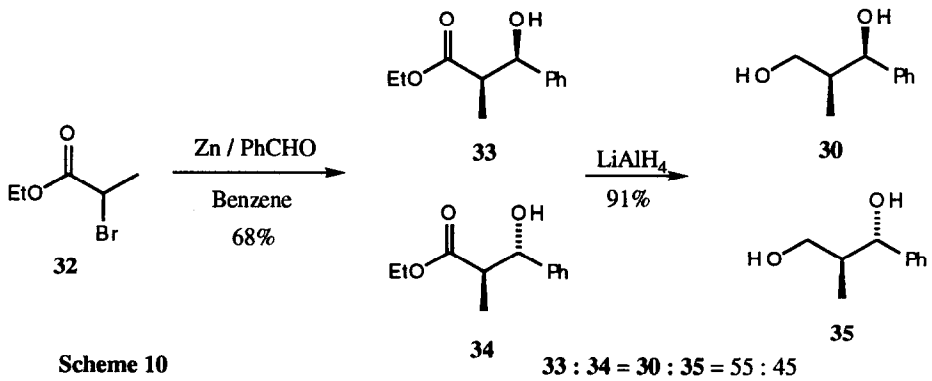
Scheme 8

To confirm the diastereoisomeric identity of the dialdol product, and to demonstrate that the elaborated acyl sidechains could be cleaved from the chiral auxiliary without loss of stereochemical integrity, the dialdol reaction was repeated with homochiral starting materials.[18] Thus (*R*,*R*)-**11** and (*R*,*R*)-**21** were converted into the corresponding homochiral aldol products **15** and **22** in yields similar to those recorded above for the synthesis of these compounds in racemic form. Reductive cleavage of the two β-hydroxy acyl groups was found to require protection of the hydroxyl groups to prevent the retro-aldol reaction. This was achieved by prior treatment of the aldol product with triethylborane and acetic acid;[22] the protecting group was easily removed after the reduction step by treatment with 30% hydrogen peroxide solution at 0°C. In this way both homochiral aldol products, **15** and **22**, were cleaved to give *syn*-diol **30**. Alternatively hydrolysis of **22** by treatment with lithium hydroxide and 30% hydrogen peroxide liberated the β-hydroxy acid (2*R*,3*R*)-**31** (Scheme 9).



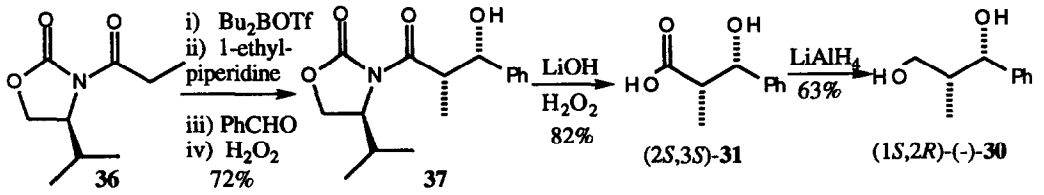
Scheme 9

The ^1H n.m.r. spectra recorded for both homochiral and racemic **30** were somewhat at variance with that reported in the literature.[23] To resolve this discrepancy, the literature synthesis of **30**, formed with diastereoisomeric diol **35** from the Reformatsky reaction of ethyl bromopropionate **32** with benzaldehyde, was repeated.[24] The major product of the reduction of the mixture of β-hydroxy esters **33** and **34** was identical in all respects to a sample of **30** prepared by reductive cleavage of racemic **15**. Furthermore, the major product of the preceding Reformatsky reaction was confirmed as the *syn* isomer on account of the upfield chemical shifts of certain resonances in the ^{13}C n.m.r. spectrum (relative to those recorded for **34**) (Scheme 10).



Scheme 10 **33** : **34** = **30** : **35** = 55 : 45

For comparison purposes the enantiomeric β-hydroxy acid (2*S*,3*S*)-**31** was prepared by Evans' established procedure[20] and reduced to the enantiomeric diol (1*S*,2*R*)-**30** (Scheme 11).



Scheme 11

Thus the reaction of the oxazolidinone (*S*)-**36** gave the *syn*-aldol product **37** as a single diastereoisomer and after hydrolysis β-hydroxy acid (2*S*,3*S*)-**31** $[\alpha]_D^{24}$ -26.7 (c = 1.10, CH_2Cl_2). The opposite sign of specific rotation for the β-hydroxy acid obtained by hydrolysis of **22** $[\alpha]_D^{24}$ +28.6 (c = 0.66, CH_2Cl_2) unambiguously establishes the configuration of the latter as (2*R*,3*R*)-**31**. Reduction of (2*S*,3*S*)-**31** gave the diol (1*S*,2*R*)-**30** $[\alpha]_D^{24}$ -54.7 (c = 0.30, $CHCl_3$) consistent with the literature value[25] for (1*R*,2*S*)-**30** of $[\alpha]_D^{20}$ +57.8 (c = 0.45, $CHCl_3$). The diol obtained from reduction of the homochiral bifunctional chiral auxiliary derivatives **15** $[\alpha]_D^{20}$ +52 (c = 0.57, $CHCl_3$) and **22** $[\alpha]_D^{20}$ +53 (c = 0.57, $CHCl_3$) can therefore be unambiguously assigned as (1*R*,2*S*).[26] The enantiomeric excess of the β-hydroxy acid **31** and diol **30** were assayed by ^1H n.m.r. studies in the presence of the chiral shift reagent (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[27] Both samples of β-hydroxy acid **37** and the three samples of diol **30** were estimated to be homochiral (>97% e.e.) on the basis of the clear splitting of the benzylic methine proton [the (1*S*,2*R*) enantiomer being at lower field] induced by ten equivalents of the shift reagent.

In summary, we have demonstrated that dibutylboron enolates derived from both 1,3-diacylimidazolidine-2-thiones and 1,3-diacylimidazolidin-2-ones undergo highly diastereoselective aldol reactions with a range of simple aldehydes to allow both sidechains to be elaborated. This reaction provides ready access to substituted 1,3-diols in homochiral form and may be understood mechanistically in terms of the transition state models already described for the reactions of N-acyl oxazolidinones.

Experimental

General - M.p.s were obtained on a Gallenkamp hot-stage melting point apparatus and are uncorrected. Elemental analyses were obtained by the Dyson Perrins analytical department. IR spectra were obtained as chloroform solutions in 1.0mm cells on a Perkin-Elmer 781 instrument calibrated against polystyrene (1601 cm^{-1}) and for clarity only salient, characteristic peaks are noted. ^1H n.m.r. spectra were recorded in deuteriochloroform on a Bruker WH 300 instrument at 300.13 MHz. ^{13}C n.m.r. spectra were recorded in deuteriochloroform on a Varian Gemini 200 instrument at 50.32 MHz. Mass spectra were obtained on a V.G. Micromass ZAB 1F instrument using chemical ionisation techniques. Specific rotations were obtained for chloroform solutions at the sodium D line using a Perkin-Elmer 241 polarimeter with values quoted in 10^{-1} deg cm^2 g^{-1}.

All reactions were performed under an inert artmosphere of dry argon. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen and dichloromethane distilled from calcium hydride under nitrogen. Dibutylboron triflate was used as a 1.0 mol dm^{-3} solution in dichloromethane (as purchased) or was redistilled and used as a 0.8 - 1.2 mol dm^{-3} solution in dichloromethane. Triethylborane was used as a 1.0 mol dm^{-3}

solution in hexane. Zinc was acid-washed prior to use and other reagents were used as received or were purified by standard methods.[28] Flash chromatography was performed on silica gel (43-60 μm) under positive pressure.

Tin (II) triflate - Trifluoromethanesulphonic acid (5.3ml, 57.9mmol) was added cautiously to tin (II) chloride (3.70g, 19.5mmol). On heating the reaction in a 100°C oil bath, a vigorous exothermic reaction occurred and the resulting mixture was heated at 100°C for a further 18 h. The reaction flask was fitted with a distillation head and the excess trifluoromethanesulphonic acid removed *in vacuo*. The last traces of acid were removed by repeated washing with sodium-dried diethyl ether to give tin (II) triflate as a white powdery solid after extended thermal drying *in vacuo*, (7.02g, 86%).

1-(3-Phenyl-3-hydroxy-2-methylpropionyl)-3-propionyl-trans-*4,5-tetramethylene-imidazolidine-2-thiones* **7** *and* **8** - 1-Ethylpiperidine (800mg, 7.10mmol) was added to a suspension of tin (II) triflate (2.30g, 5.52mmol) in dichloromethane (10ml) at 0°C causing the formation of a yellow solution. After 5 min the reaction was cooled to -78°C and 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **6** (1.12g, 4.21mmol) was added and allowed to stir for 1 h. Freshly distilled benzaldehyde (650mg, 6.13mmol) was added dropwise and the reaction stirred for a further 2 h at -78°C before addition of a pH 7 phosphate buffer solution (5ml) to quench the reaction. The reaction mixture was filtered through a sinter funnel to remove the insoluble tin salts, the organic layer was separated and the aqueous layer extracted with dichloromethane (3x10ml). The combined organic layers were dried over $MgSO_4$ and evaporated down to an oily solid contaminated with benzaldehyde. Chromatography on silica gel with dichloromethane as eluent gave **8** as a white amorphous solid (367mg, 23%), m.p. 92-94°C (Found; C, 64.1; H, 7.0; N, 7.5. $C_{20}H_{26}N_2O_3S$ requires C, 64.1; H, 7.0; N, 7.5%); ν_{max} ($CHCl_3$)/cm^{-1} 3400 (OH) and 1701 (N-CO-CH); δ_H (300 MHz, $CDCl_3$) 7.48-7.26 (5H, m, Ph), 5.45 (1H, m, C<u>H</u>(OH)), 4.61 (1H, dq, J 6.3, 1.9 Hz, COC<u>H</u>), 3.51 (3H, m, C<u>H</u>N, O<u>H</u>), 3.43, 3.01 (2H, ABX_3 system, J_{AB} 17.1 Hz, J_{AX} 7.4 Hz, J_{BX} 7.4 Hz, $COC\underline{H}_2$), 2.72, 2.55 (2H, m, Cy-Cα), 1.90 (2H, m, Cy-Cα), 1.49-1.21 (4H, m, Cy-Cβ), 1.22 (3H, t, J 7.1 Hz, $COCH_2C\underline{H}_3$) and 1.06 (3H, d, J 7.2 Hz, $COCHC\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 183.7, 180.9, 178.4, 141.5, 128.2, 127.2, 126.0, 71.2, 64.3, 63.9, 47.9, 33.5, 28.4, 27.7, 24.2, 24.0, 11.2 and 9.1; m/z 375 (MH^+, 100%). Further elution with dichloromethane as eluent afforded **7** as a white solid (771mg, 49%), m.p. 133-135°C (Found; C, 64.1; H, 7.0; N, 7.3. $C_{20}H_{26}N_2O_3S$ requires C, 64.1; H, 7.0; N, 7.5%); ν_{max} ($CHCl_3$)/cm^{-1} 3400 (OH) and 1701 (N-CO-CH); δ_H (300 MHz, $CDCl_3$) 7.36-7.28 (5H, m, Ph), 4.91 (1H, dd, J 6.1, 3.3 Hz, C<u>H</u>(OH)), 4.57 (1H, quintet, J 6.5 Hz, COC<u>H</u>), 3.43, 3.22 (2H, m, C<u>H</u>N), 3.37, 2.98 (2H, ABX_3 system, J_{AB} 17.0 Hz, J_{AX} 7.3 Hz, J_{BX} 7.3 Hz, $COC\underline{H}_2$), 2.62, 2.30 (2H, m, Cy-Cα), 2.27 (1H, d, J 3.5 Hz, O<u>H</u>),1.77 (2H, m, Cy-Cα), 1.35-1.17 (4H, m, Cy-Cβ), 1.33 (3H, d, J 6.6 Hz, $COCHC\underline{H}_3$) and 1.21 (3H, t, J 7.3 Hz, $COCH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 180.5, 180.0, 178.6, 141.6, 128.6, 128.1, 126.7, 76.2, 64.0, 63.9, 48.8, 33.5, 28.2, 27.3, 24.0, 23.9, 11.3 and 9.1; m/z 375 (MH^+, 100%).

1-(3-Phenyl-3-hydroxy-2-methylpropionyl)-3-propionyl-trans-*4,5-tetramethylene-imidazolidin-2-one* **9** - Mercury (II) acetate (340mg, 1.07mmol) was added to a solution of **7** (312mg, 0.83mmol) in dichloromethane (5ml) at ambient temperature and allowed to stir for 15 h. The reaction mixture was filtered through celite to give an oily solid which was purified by chromatography on silica gel (eluting with ethyl acetate:hexane, 1:2) to give **9** as a white crystalline solid (227mg, 76%), m.p. 101-103°C (Found; C, 66.8; H, 7.5; N, 7.5. $C_{20}H_{26}N_2O_4$

requires C, 67.0; H, 7.3; N, 7.8%); ν_{max} ($CHCl_3$)/cm^{-1} 3450 (OH), 1740 (N-CO-N) and 1692 (N-CO-CH); δ_H (300 MHz, $CDCl_3$) 7.37-7.24 (5H, m, Ph), 4.94 (1H, dd, J 5.3, 2.6 Hz, C<u>H</u>(OH)), 3.95 (1H, dq, J 6.0, 5.4 Hz, COC<u>H</u>), 3.30 (1H, dt, J 11.1, 2.8 Hz, C<u>H</u>N), 3.14 (1H, dt, J 11.1, 2.8 Hz, C<u>H</u>N), 3.01 (1H, d, J 2.9 Hz, O<u>H</u>), 3.03, 2.69 (2H, ABX_3 system, J_{AB} 17.0 Hz, J_{AX} 7.3 Hz, J_{BX} 7.3 Hz, $COC\underline{H}_2$), 2.92, 2.65 (2H, m, Cy-C_α), 1.81 (2H, m, Cy-C_α), 1.45-1.22 (4H, m, Cy-C_β), 1.21 (3H, d, J 6.7 Hz, $COCHC\underline{H}_3$) and 1.15 (3H, t, J 7.4 Hz, $COCH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 178.6, 176.8, 154.3, 142.0, 128.3, 127.8, 126.4, 75.4, 60.4, 47.2, 30.8, 28., 28.1, 24.1, 10.7 and 8.3; m/z 375 (MH^+, 100%).

1-(3-Phenyl-3-hydroxy-2-methylpropionyl)-3-propionyl-trans-*4,5-tetramethylene-imidazolidin-2-one* **10** - Mercury (II) acetate (218mg, 0.69mmol) was added to a solution of **8** (180mg, 0.48mmol) in dichloromethane (3ml) at ambient temperature and allowed to stir for 15 h. The reaction mixture was filtered through celite to give an oily solid which was purified by chromatography on silica gel (eluting with chloroform) to give **8** as a white crystalline solid (140mg, 81%), m.p. 105-107°C (Found; C, 66.85; H, 7.6; N, 7.7. $C_{20}H_{26}N_2O_4$ requires C, 67.0; H, 7.3; N, 7.8%); ν_{max} ($CHCl_3$)/cm^{-1} 3500 (OH), 1740 (N-CO-N), and 1694 (N-CO-CH); ^1H n.m.r. δ_H (300 MHz, $CDCl_3$) 7.45-7.23 (5H, m, Ph), 5.25 (1H, m, C<u>H</u>(OH)), 4.05 (1H, dq, J 7.2, 2.6 Hz, COC<u>H</u>), 3.42 (2H, m, C<u>H</u>N), 3.05, 2.78 (2H, ABX_3 system, J_{AB} 17.7 Hz, J_{AX} 7.3 Hz, J_{BX} 7.4 Hz, $COC\underline{H}_2$), 2.89 (2H, m, Cy-C_α), 1.89 (2H, m, Cy-C_α), 1.53-1.31 (4H, m, Cy-C_β), 1.17 (3H, t, J 7.3 Hz, $COCH_2C\underline{H}_3$) and 1.09 (3H, d, J 7.2 Hz, $COCHC\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 180.6, 176.8, 154.2, 141.5, 128.3, 127.3, 126.2, 72.0, 60.6, 60.4, 46.0, 30.8, 28.8, 28.5, 24.2, 10.8 and 8.3 ($COCH_2\underline{C}H_3$); m/z 359 (MH^+, 100%).

1-(3-Phenyl-3-hydroxy-2-methylpropionyl)-3-propionyl-trans-*4,5-tetramethylene-imidazolidin-2-one* **9** - In a manner analogous to the synthesis of **7** and **8** from **6**, 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **11** (126mg, 0.50mmol) was enolised with tin (II) triflate (550mg, 1.32mmol) and 1-ethylpiperidine (170mg, 1.50mmol) at -78°C in dichloromethane. Benzaldehyde (160mg, 1.50mmol) was added and the reaction stirred at -78°C for 2 h before being quenched and worked-up, as before, to give **9** as a white crystalline solid (124mg, 69%). The spectroscopic properties were identical to those of the sample prepared earlier by treatment of **7** with mercury (II) acetate.

1,3-Di(3-phenyl-3-hydroxy-2-methylpropionyl)-trans-*4,5-tetramethylene-imidazolidine-2-thione* **14** - Dibutylboron triflate (5.0ml, 5.00mmol of a 1.0M solution in dichloromethane) was added dropwise to a solution of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **6** (536mg, 2.00mmol) in dichloromethane at 0°C causing a colour change to deep orange. 1-Ethylpiperidine (0.82ml, 5.92mmol) was added, causing a colour change to orange-red, the reaction cooled to -78°C and benzaldehyde (636mg, 6.00mmol) added. After stirring at -78°C for 1 h, the reaction was warmed to 0°C and stirred for 2 h before being quenched by addition of an aqueous pH 7 phosphate buffer solution (2ml). Hydrogen peroxide (3ml) in methanol (3ml) was added dropwise over 0.5 h before solvent evaporation *in vacuo*. Trituration of the resulting residue with dichloromethane (3x10ml) followed by solvent removal *in vacuo* gave a yellow oil which was filtered through silica gel to remove the boron residues. Recrystallisation from dichloromethane:hexane afforded **14** as a white crystalline solid (565mg, 59%), m.p. 172-174°C (Found; C, 67.8; H, 7.0; N, 5.9. $C_{27}H_{32}N_2O_4S$ requires C, 67.5; H, 6.7; N, 5.8%); ν_{max} ($CHCl_3$)/cm^{-1} 3500 (OH) and 1690 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.49-7.26 (10H, m, Ph), 5.44 (2H, m, C<u>H</u>(OH)), 4.66 (2H, dq, J 7.3, 2.3 Hz, COC<u>H</u>), 3.56

(2H, m, CHN), 3.41 (2H, d, J 1.8 Hz, CH(OH)), 2.58 (2H, m, Cy-C_α), 1.94 (2H, m, Cy-C_α), 1.56-1.22 (4H, m, Cy-C_β) and 1.10 (6H, d, J 7.3 Hz, $COCHCH_3$); δ_C (50 MHz, $CDCl_3$) 183.1, 180.8, 141.4, 128.3, 127.4, 126.0, 71.3, 64.1, 47.9, 27.7, 23.9 and 11.2; m/z 481 (MH^+, 100%).

1-(3-Phenyl-3-hydroxy-2-methylpropionyl)-3-propionyl-trans-*4,5-tetramethylene-imidazolidin-2-one* **15** - Mercury (II) acetate (60mg, 0.19mmol) was added to a solution of **14** (62mg, 0.13mmol) in dichloromethane (5ml) at ambient temperature and allowed to stir for 15 h. The reaction mixture was filtered through celite to give a yellow oil which was purified by chromatography on silica gel (eluting with chloroform) to give **15** as a white solid (34mg, 57%). The spectroscopic properties were identical to those of the sample prepared directly from **11**.

1,3-Di(3-phenyl-3-hydroxy-2-methylpropionyl)-trans-*4,5-tetramethylene-imidazolidin-2-one* **15** - In a manner analogous to that described for the synthesis of **14**, 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **11** (220mg, 0.87mmol) was enolised with dibutyl-boron triflate (2.0ml, 2.00mmol) and 1-ethylpiperidine (272mg, 2.40mmol). Benzaldehyde (215mg, 2.00mmol) was added and, after a standard reaction period and work-up, the reaction yielded a white solid, (362mg, 89%). Chromatography on a plug of silica gel (eluting with ethyl acetate-hexane, 1:1) gave **15** as a white crystalline solid (317mg, 78%), m.p. 162-164°C (Found; C, 69.95; H, 7.25; N, 6.0. $C_{27}H_{32}N_2O_5$ requires C, 69.8; H, 6.95; N, 6.0%); ν_{max} ($CHCl_3$)/cm^{-1} 1751 (N-CO-N), 1685 (N-CO) and 1199 (C-OH); δ_H (300 MHz, $CDCl_3$) 7.45-7.26 (10H, m, Ph), 5.24 (2H, m, CH(OH)), 4.04 (2H, dq, J 7.2, 2.8 Hz, COCH), 3.44 (2H, m, CHN), 3.27 (2H, d, J 2.2 Hz, CH(OH)), 2.88 (2H, m, Cy-C_α), 1.92 (2H, m, Cy-C_α), 1.57-1.33 (4H, m, Cy-C_β) and 1.12 (6H, d, J 7.2 Hz, $COCHCH_3$); δ_C (50 MHz, $CDCl_3$) 180.4, 153.7, 141.4, 128.3, 127.3, 126.2, 72.1, 60.4, 46.1, 28.5, 24.1 and 10.9; m/z 465 (MH^+, 100%).

Crystal Data for compound **15**. $C_{27}H_{32}N_2O_5$, M = 464.56, orthorhombic, *Pcab* (No. 61), a = 11.7861(7), b = 18.181(1), c = 23.692(1) Å (from least squares fitting of setting angles for 25 reflections $29.6 \leq \theta \leq 47.8°$), V = 5077 $Å^3$, Z = 8, D_x = 1.216 gcm^{-3}, CuK_α radiation, colourless prismatic crystal 1.0 x 0.8 x 0.7 mm, μ = 6.45 cm^{-1}, crystal mounted on glass fibre.

Data Collection and Processing: Data were collected on a CAD-4F diffractometer in ω:2 θ mode, $0 < 2\theta \leq 150°$, ($-1 \leq h \leq 14$, $-1 \leq k \leq 22$, $-1 \leq l \leq 29$). 7162 reflections measured, 5219 unique (R_{merge} = 0.030) of which 3303 were observed ($I \geq 3\sigma I$). An absorption correction[30] based on azimuthal scans was applied (min. 1.33, max. 1.40). No significant variation in intensity of 3 check reflections was observed.

Structure Solution and Refinement. The structure was solved by direct methods[31] which yielded coordinates for all non-hydrogen atoms. Full matrix least-squares refinement[32] of positional and anisotropic thermal parameters for all non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms (in calculated positions except for those of the hydroxyl groups which were refined) was continued to convergence. A 3-term Chebychev polynomial weighting scheme was employed. At convergence R = 0.056, R_w = 0.067 for 346 parameters [$R = \Sigma w|\Delta| (\Sigma wFo)^{-1}$, $R_w = \Sigma w\Delta_i^2(\Sigma wFo_i^2)^{-1}$].

1,3-Di(3-hydroxy-2-methylbutanoyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **16** - In a manner analogous to that described for the synthesis of **14**, 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **11** (250mg, 0.99mmol) was enolised with dibutylboron triflate (2.90ml, 2.32mmol) and 1-ethylpiperidine

(300mg, 2.62mmol). Acetaldehyde (~0.2ml, excess) was added and, after a standard reaction period and work-up, the reaction yielded a clear oil. Chromatography on silica gel (eluting with ethyl acetate-hexane, 1:1) gave a small amount of the monoaldol product **25**, (~55mg, 18%), and **16** as a white crystalline solid (225mg, 67%), m.p. 121-122°C (Found; C, 59.8; H, 8.3; N, 7.9. $C_{17}H_{28}N_2O_5$ requires C, 60.0; H, 8.3; N, 8.2%); ν_{max} ($CHCl_3$)/cm^{-1} 1748 (N-CO-N), 1687 (N-CO) and 1200 (C-OH); δ_H (300 MHz, $CDCl_3$) 4.22 (2H, m, C<u>H</u>(OH)), 3.67 (2H, dq, J 7.2, 2.4 Hz, COC<u>H</u>), 3.42 (2H, m, C<u>H</u>N), 2.83 (2H, bs, CH(O<u>H</u>)), 2.83 (2H, m, Cy-Cα), 1.89 (2H, m, Cy-Cα), 1.51-1.25 (4H, m, Cy-Cβ), and 1.20 (12H, d, J 7.0 Hz, COCHC<u>H</u>$_3$, CH(OH)C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 180.5, 154.2, 66.8, 60.4, 45.0, 28.5, 24.1, 19.3, 11.2; m/z 341 (MH^+, 100%).

1,3-Di(3-hydroxy-2-methylpentanoyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **17** - In a manner analogous to that described for the synthesis of **14**, 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **11** (222mg, 0.88mmol) was enolised with dibutylboron triflate (2.0ml, 2.00mmol) and 1-ethylpiperidine (272mg, 2.40mmol). Propanal (118mg, 2.03mmol) was added and, after a standard reaction period and work-up, the reaction yielded a clear oil. Chromatography on silica gel with ethyl acetate-hexane (2:3) as eluent gave **17** as a colourless oil (251mg, 78%), (Found; C, 61.65; H, 8.7; N, 7.6. $C_{19}H_{32}N_2O_5$ requires C, 61.9; H, 8.75; N, 7.6%); ν_{max} ($CHCl_3$)/cm^{-1} 1749 (N-CO-N), 1686 (N-CO) and 1201 (C-OH); δ_H (300 MHz, $CDCl_3$) 3.92 (2H, m, C<u>H</u>(OH)), 3.73 (2H, dq, J 7.2, 2.4 Hz, COC<u>H</u>), 3.41 (2H, m, C<u>H</u>N), 3.01 (2H, bs, CH(O<u>H</u>)), 2.82 (2H, m, Cy-Cα), 1.89 (2H, m, Cy-Cα), 1.65-1.25 (8H, m, Cy-Cβ, C<u>H</u>$_2$CH$_3$), 1.20 (6H, d, J 7.2 Hz, COCHC<u>H</u>$_3$) and 0.99 (6H, t, J 7.4 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 180.7, 153.9, 72.0, 60.3, 43.6, 28.4, 26.3, 24.1, 11.0 and 10.3; m/z 369 (MH^+, 100%).

1,3-Di(3-hydroxy-2-methylhexanoyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **18** - In a manner analogous to that described for the synthesis of **14**, 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **11** (252mg, 1.00mmol) was enolised with dibutylboron triflate (3.3ml, 2.33mmol) and 1-ethylpiperidine (300mg, 2.61mmol). *n*-Butyraldehyde (187mg, 2.60mmol) was added and, after a standard reaction period and work-up, the reaction yielded a clear oil. Chromatography on silica gel with ethyl acetate-hexane (1:2) as eluent gave **18** as a colourless oil which slowly solidified (282mg, 71%), m.p. 66-68°C (Found; C, 63.45; H, 9.3; N, 7.2. $C_{21}H_{36}N_2O_5$ requires C, 63.6; H, 9.15; N, 7.1%); ν_{max} ($CHCl_3$)/cm^{-1} 1750 (N-CO-N), 1685 (N-CO) and 1200 (C-OH); δ_H (300 MHz, $CDCl_3$) 4.02 (2H, m, C<u>H</u>(OH)), 3.71 (2H, dq, J 7.2, 2.3 Hz, COC<u>H</u>), 3.41 (2H, m, C<u>H</u>N), 2.95 (2H, bs, CH(O<u>H</u>)), 2.83 (2H, m, Cy-Cα), 1.89 (2H, m, Cy-Cα), 1.64-1.23 (12H, m, Cy-Cβ, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 1.20 (6H, d, J 7.3 Hz, COCHC<u>H</u>$_3$) and 0.95 (6H, t, J 7.0 Hz, CH$_2$CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 180.8, 153.9, 70.2, 60.3, 44.0, 35.6, 28.5, 24.1, 19.1, 13.8, 11.0; m/z 397 (MH^+, 100%).

1,3-Di(4-methyl-3-hydroxy-2-methylpentanoyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **19** - In a manner analogous to that described for the synthesis of **14**, 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **11** (320mg, 1.27mmol) was enolised with dibutyl-boron triflate (2.7ml, 2.94mmol) and 1-ethylpiperidine (385mg, 3.40mmol). *i*-Butyraldehyde (230mg, 3.20mmol) was added and, after a standard reaction period and work-up, the reaction yielded a white solid. Chromatography on silica gel with dichloromethane as eluent gave **19** as a white crystalline solid (412mg, 82%), m.p. 161-163°C (Found; C, 63.4; H, 9.4; N, 7.2. $C_{21}H_{36}N_2O_5$ requires C, 63.6; H, 9.15; N, 7.1%); ν_{max} ($CHCl_3$)/cm^{-1} 3350 (OH), 1752

(N-CO-N) and 1685 (N-CO); δ_H (300 MHz, $CDCl_3$) 3.92 (2H, dq, J 7.3, 2.2 Hz, COC<u>H</u>), 3.61 (2H, dt, J 8.9, 2.3 Hz, C<u>H</u>(OH)), 3.42 (2H, m, C<u>H</u>N), 3.00 (2H, d, J 2.6 Hz, CH(O<u>H</u>)), 2.83 (2H, m, Cy-C_α), 1.90 (2H, m, Cy-C_α), 1.73 (2H, d,septet, J 6.4, 2.2 Hz, C<u>H</u>$(CH_3)_2$), 1.56-1.26 (4H, m, Cy-C_β), 1.19 (6H, d, J 7.2 Hz, COCHC<u>H</u>$_3$), 1.07 (6H, d, J 6.6 Hz, CH(C<u>H</u>$_3)_2$) and 0.91 (6H, d, J 6.8 Hz, CH(C<u>H</u>$_3)_2$); δ_C 181.3, 153.5, 75.6, 60.3, 41.3, 30.2, 28.4, 24.1, 19.4, 18.7 and 10.7; m/z 397 (MH^+, 100%).

1,3-Di(4,4-dimethyl-3-hydroxy-2-methylpentanoyl)-trans-*4,5-tetramethylene-imidazolidin-2-one* **20** - In a manner analogous to that described for the synthesis of **14**, 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **11** (504mg, 2.00mmol) was enolised with dibutylboron triflate (5.0ml, 5.00mmol) and 1-ethylpiperidine (678mg, 6.00mmol). Pivalaldehyde (trimethylacetaldehyde) (516mg, 6.00mmol) was added and, after a standard reaction period and work-up, the reaction yielded a thick oil. Radial chromatography on silica gel with ethyl acetate:hexane (2:5) gave a 1:5 mixture of monoaldol **26** and dialdol **29** as a highly viscous oil (540mg, 66%), ν_{max} ($CHCl_3$)/cm^{-1} 3500 (OH) 1744 (N-CO-N) and 1692 (N-CO); δ_H (300 MHz, $CDCl_3$) 4.08 (2H, dq, J 7.1, 2.7 Hz, COC<u>H</u>), 3.74 (2H, d, J 2.9 Hz, C<u>H</u>(OH)), 3.39 (2H, m, C<u>H</u>N), 2.82 (2H, m, Cy-C_α), 2.54 (2H, d, J 3.5 Hz, CH(O<u>H</u>)), 1.89 (2H, m, Cy-C_α), 1.52-1.25 (4H, m, Cy-C_β), 1.24 (6H, d, J 7.1 Hz, COCHC<u>H</u>$_3$) and 1.00 (18H, s, CH(C<u>H</u>$_3)_3$); δ_C (50 MHz, $CDCl_3$) 181.4, 153.6, 76.6, 60.2, 40.5, 35.2, 28.4, 26.7, 24.1 and 13.6; m/z 425 (MH^+, 100%).

1,3-Di(3-phenyl-3-hydroxy-2-methylpropionyl)-trans-*4,5-diphenylimidazolidin-2-one* **22** - In a manner analogous to that described for the synthesis of **14**, 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one **21** (350mg, 1.00mmol) was enolised with dibutylboron triflate (3.0ml, 3.00mmol) and 1-ethylpiperidine (452mg, 4.00mmol). Benzaldehyde (424mg, 4.00mmol) was added and, after a standard reaction period and work-up, the reaction yielded a clear oil. Chromatography on silica gel with ethyl acetate:hexane (1:1) as eluent gave **22** as a white crystalline solid (406mg, 72%), m.p. 75-77°C (Found; C, 74.5; H, 6.4; N, 4.8. $C_{35}H_{34}N_2O_5$ requires C, 74.7; H, 6.1; N, 5.0%); ν_{max} ($CHCl_3$)/cm^{-1} 1750 (N-CO-N), 1692 (N-CO) and 1183 (C-OH); δ_H (300 MHz, $CDCl_3$) 7.43-7.28 (16H, m, Ph), 7.09-7.04 (4H, m, Ph), 5.09 (2H, s, PhC<u>H</u>), 5.04 (2H, m, C<u>H</u>(OH)), 4.26 (2H, dq, J 7.0, 4.6 Hz, COC<u>H</u>), 2.94 (2H, d, J 2.7 Hz, O<u>H</u>) and 1.20 (6H, d, J 7.0 Hz, COCHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 176.8, 151.4, 141.6, 139.5, 129.6, 128.9, 128.5, 127.8, 125.1, 124.9, 73.7, 62.1, 45.5 and 11.3; m/z 563 (MH^+, 100%).

1,3-Di(4-methyl-3-hydroxy-2-methylpentanoyl)-trans-*4,5-diphenylimidazolidin-2-one* **23** - In a manner analogous to that described for the synthesis of **14**, 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one **21** (350mg, 1.00mmol) was enolised with dibutylboron triflate (3.0ml, 3.00mmol) and 1-ethylpiperidine (452mg, 4.00mmol). *i*-Butyraldehyde (300mg, excess) was added and, after a standard reaction period and work-up, the reaction yielded a clear oil. Chromatography on silica gel with ethyl acetate-hexane (1:1) as eluent gave **23** as a white crystalline solid (330mg, 67%) (as well as a small amount of the monoaldol product **28**), m.p. 48-50°C (Found; C, 70.3; H, 8.0; N, 5.3. $C_{29}H_{38}N_2O_5$ requires C, 70.4; H, 7.7; N, 5.7%); ν_{max} ($CHCl_3$)/cm^{-1} 1752 (N-CO-N), 1686 (N-CO) and 1186 (C-OH); δ_H (300 MHz, $CDCl_3$) 7.45-7.34 (6H, m, Ph), 7.27-7.22 (4H, m, Ph), 5.15, (2H, s, PhC<u>H</u>), 4.07 (2H, dq, J 7.0, 3.3 Hz, COC<u>H</u>), 3.57 (2H, m, C<u>H</u>(OH)), 2.79 (2H, d, J 3.5 Hz, O<u>H</u>), 1.72 (2H, septet, J 6.8 Hz, C<u>H</u>$(CH_3)_2$), 1.24 (6H, d, J 7.0 Hz, COCHC<u>H</u>$_3$), 1.04 (6H, d, J 6.6

Hz, $CH(C\underline{H}_3)_2$) and 0.96 (6H, d, J 6.8 Hz, $CH(C\underline{H}_3)_2$); δ_C (50 MHz, $CDCl_3$) 178.0, 151.4, 139.5, 129.6, 128.9, 124.9, 76.6, 62.3, 40.7, 30.5, 19.0, 18.8 and 10.4; m/z 495 (MH^+, 100%).

1,3-Di(3-hydroxy-2-methylbutanoyl)-trans-*4,5-diphenylimidazolidin-2-one* **24** - In a manner analogous to that described for the synthesis of **14**, 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one **21** (350mg, 1.00mmol) was enolised with dibutylboron triflate (3.0ml, 3.00mmol) and 1-ethylpiperidine (452mg, 4.00mmol). Acetaldehyde (~0.2ml, excess) was added and, after a standard reaction period and work-up, the reaction yielded a clear oil. Chromatography on silica gel with ethyl acetate-hexane (1:1) as eluent gave a small amount of the monoaldol product **29**, and **24** as a white crystalline solid (323mg, 74%), m.p. 137-139°C, (Found; C, 68.5; H, 7.0; N, 6.45. $C_{25}H_{30}N_2O_5$ requires C, 68.5; H, 6.9; N, 6.4%); ν_{max} ($CHCl_3$)/cm^{-1} 3450 (OH), 1735 (N-CO-N) and 1684 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.59-7.23 (10H, m, Ph), 5.15 (2H, s, PhC$\underline{H}$), 4.19 (2H, m, C$\underline{H}$(OH)), 3.85 (1H, dq, J 7.1, 2.7 Hz, COC$\underline{H}$), 1.25 (3H, d, J 7.1 Hz, $COCHC\underline{H}_3$) and 1.21 (3H, d, J 6.5 Hz, $CH(OH)C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 177.4, 151.9, 139.6, 129.6, 128.9, 125.0, 67.6, 62.4, 44.2, 19.5 and 10.5; m/z 439 (MH^+, 100%).

1-(3-hydroxy-2-methylbutanoyl)-3-propionyl-trans-*4,5-tetramethylene-imidazolidin-2-one* **25** - Monoaldol product **25**, obtained as a by-product in the synthesis of **16**, was partially characterised, m.p. 74-76°C, ν_{max} ($CHCl_3$)/cm^{-1} 1748 (N-CO-N), 1704 (N-CO) and 1203 (C-OH); δ_H (300 MHz, $CDCl_3$) 4.22 (1H, dq, J 6.4, 2.6 Hz, C$\underline{H}$(OH)), 3.71 (1H, dq, J 7.2, 2.6 Hz, COC$\underline{H}$), 3.41 (2H, m, C$\underline{H}$N), 3.03, 2.76 (2H, ABX_3 system, J_{AB} 17.6 Hz, J_{AX} 7.4 Hz, J_{BX} 7.3 Hz, $COC\underline{H}_2CH_3$), 2.88 (2H, m, Cy-C_α), 1.89 (2H, m, Cy-C_α), 1.52-1.22 (4H, m, Cy-C_β), 1.21 (6H, d, J 7.0 Hz, $COCHC\underline{H}_3$, $CH(OH)C\underline{H}_3$) and 1.16 (3H, t, J 7.3 Hz, $COCH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 180.5, 178.9, 154.9, 66.8, 60.6, 60.4, 44.8, 30.8, 28.8, 28.5, 24.1, 19.2, 11.2 and 8.3; m/z 297 (MH^+, 100%).

1-(4,4-dimethyl-3-hydroxy-2-methylpentanoyl)-3-propionyl-trans-*4,5-tetramethylene-imidazolidin-2-one* **26** - Monoaldol product **26**, obtained as a by-product in the synthesis of **20**, was partially characterised, ν_{max} ($CHCl_3$)/cm^{-1} 1751 (N-CO-N) and 1692 (N-CO); δ_H (300 MHz, $CDCl_3$) 4.07 (1H, dq, J 7.2, 2.6 Hz, COC$\underline{H}$), 3.73 (1H, d, J 2.6 Hz, C$\underline{H}$(OH)), 3.37 (2H, m, C$\underline{H}$N), 3.03, 2.74 (2H, ABX_3 system, J_{AB} 17.8 Hz, J_{AX} 7.3 Hz, J_{BX} 7.3 Hz, $COC\underline{H}_2CH_3$), 2.91-2.76 (2H, m, Cy-C_α), 1.86 (2H, m, Cy-C_α), 1.51-1.26 (4H, m, Cy-C_β), 1.22 (3H, dd, J 7.2, 0.9 Hz, $COCHC\underline{H}_3$), 1.14 (3H, t, J 7.3 Hz, $COCH_2C\underline{H}_3$) and 0.97 (9H, s, $CH(C\underline{H}_3)_3$); δ_C (50 MHz, $CDCl_3$) 181.6, 176.9, 154.1, 76.7, 60.5, 60.2, 40.5, 35.2, 30.8, 28.8, 28.4, 26.8, 24.2, 24.1, 13.5 and 8.2; m/z 339 (MH^+, 100%).

1-(3-phenyl-3-hydroxy-2-methylbutanoyl)-3-propionyl-trans-*4,5-diphenylimidazolidin-2-one* **27** - Monoaldol product **27**, obtained as a by-product in the synthesis of **22**, was fully characterised, m.p. 53-55°C (Found; C, 73.9; H, 6.2; N, 6.0. $C_{28}H_{28}N_2O_4$ requires C, 73.7; H, 6.2; N, 6.1%); ν_{max} ($CHCl_3$)/cm^{-1} 3450 (OH), 1750 (N-CO-N) and 1692 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.44-7.31 (11H, m, Ph), 7.22-7.18 (2H, m, Ph), 7.14-7.10 (2H, m, Ph), 5.13 (2H, bs, PhC$\underline{H}$), 5.08 (1H, d, J 1.8 Hz, CH(O$\underline{H}$)), 4.26 (1H, dq, J 7.0, 2.6 Hz, COC$\underline{H}$), 3.04 (2H, q, J 7.3 Hz, $COC\underline{H}_2$), 2.98 (1H, m, O$\underline{H}$), 1.21 (3H, d, J 7.0 Hz, $COCHC\underline{H}_3$) and 1.15 (3H, t, J 7.3 Hz, $CH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 176.8, 174.1, 151.9, 141.7, 139.7, 129.5, 128.8, 128.5, 127.7, 126.5, 125.5, 124.9, 73.7, 62.3, 45.5, 30.1, 11.3 and 8.1; m/z 457 (MH^+, 100%).

1-(4-methyl-3-hydroxy-2-methylpentanoyl)-3-propionyl-trans-*4,5-diphenylimidazolidin-2-one* **28** - Monoaldol product **28**, obtained as a by-product in the synthesis of **23**, was fully characterised, m.p. 102-104°C (Found; C, 70.85; H, 7.1; N, 6.6. $C_{25}H_{30}N_2O_4$ requires C, 71.1; H, 7.2; N, 6.6%); ν_{max} ($CHCl_3$)/cm^{-1} 1751 (N-CO-N), 1701 (N-CO) and 1185 (C-OH); δ_H (300 MHz, $CDCl_3$) 7.45-7.34 (6H, m, Ph), 7.28-7.22 (4H, m, Ph), 5.19, 5.15 (2H, AB system, J_{AB} 1.8 Hz, PhC<u>H</u>), 4.09 (1H, dq, J 7.0, 3.1 Hz, COC<u>H</u>), 3.58 (1H, m, C<u>H</u>(OH)), 3.07 (2H, q, J 7.3 Hz, $COC\underline{H}_2CH_3$), 2.86 (1H, bs, O<u>H</u>), 1.73 (1H, septet, J 6.8 Hz, $C\underline{H}(CH_3)_2$), 1.25 (3H, d, J 7.0 Hz, $COCHC\underline{H}_3$), 1.17 (3H, t, J 7.3 Hz, $CH_2C\underline{H}_3$), 1.05 (3H, d, J 6.6 Hz, $CH(C\underline{H}_3)_2$) and 0.96 (3H, d, J 6.8 Hz, $CH(C\underline{H}_3)_2$); δ_C (50 MHz, $CDCl_3$) 178.2, 174.1, 151.9, 139.8, 139.6, 129.5, 128.8, 125.3, 124.9, 76.5, 62.4, 62.3, 40.4, 30.5, 30.1, 18.9, 10.2 and 8.0; m/z 423 (MH^+, 100%).

1-(3-hydroxy-2-methylbutanoyl)-3-propionyl-trans-*4,5-diphenylimidazolidin-2-one* **29** - Monoaldol product **29**, obtained as a by-product in the synthesis of **24**, was fully characterised, m.p. 123-125°C (Found; C, 70.2; H, 6.65; N, 7.1. $C_{23}H_{26}N_2O_4$ requires C, 70.0; H, 6.6; N, 7.1%); ν_{max} ($CHCl_3$)/cm^{-1} 3500 (OH), 1743 (N-CO-N) and 1692 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.44-7.33 (6H, m, Ph), 7.28-7.21 (4H, m, Ph), 5.19, 5.13 (2H, AB system, J_{AB} 1.7 Hz, PhC<u>H</u>), 4.19 (1H, dq, J 6.4, 2.8 Hz, C<u>H</u>(OH)), 3.86 (1H, dq, J 7.0, 3.7 Hz, COC<u>H</u>), 3.05 (2H, q, J 7.3 Hz, $COC\underline{H}_2CH_3$), 1.26 (3H, d, J 7.0 Hz, $COCHC\underline{H}_3$), 1.22 (3H, d, J 6.4 Hz, $CH(OH)C\underline{H}_3$) and 1.16 (3H, t, J 7.3 Hz, $COCH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 177.6, 174.1, 152.1, 139.8, 139.7, 129.5, 128.8, 125.4, 124.9, 67.6, 62.4, 44.0, 30.1, 19.5, 10.4 and 8.1; m/z 395 (MH^+, 100%).

1-(3-Phenyl-3-hydroxy-2-methylpropionyl)-3-propionyl-trans-*4,5-tetramethylene-imidazolidin-2-one* **10** - In a manner analogous to that described for the synthesis of **14**, 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **11** (504mg, 2.00mmol) was enolised with dibutylboron triflate (2.0ml, 2.00mmol) and 1-ethylpiperidine (272mg, 2.40mmol). Benzaldehyde (212mg, 2.00mmol) was added and, after a standard reaction period and work-up, the reaction yielded an oily solid. Chromatography on silica gel with ethyl acetate-hexane (1:2) as eluent gave a small amount of the starting material **141** (82mg, 16%) and **10** as a white crystalline solid, (568mg, 61%). This was found to be identical to samples prepared *via* dethionation of **8** and as a by-product in the synthesis of dialdol product **15**.

1,3-Di(3-phenyl-3-hydroxy-2-methylpropionyl)-trans-*4,5-tetramethylene-imidazolidin-2-one* **15** *from* **10** - In a manner analogous to that described for the synthesis of **14**, 1-(3-phenyl-3-hydroxy-2-methylpropionyl)-3-propionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **10** (179mg, 0.50mmol) was enolised with dibutylboron triflate (3.0ml, 3.00mmol) and 1-ethylpiperidine (452mg, 4.00mmol). Benzaldehyde (424mg, 4.00mmol) was added and, after a standard reaction period and work-up, the reaction yielded a white solid. Chromatography on silica gel with ethyl acetate-hexane (1:2) as eluent gave **15** as a white crystalline solid (168mg, 72%). This was found to be identical to samples prepared directly from **11** *via* the dialdol reaction.

Homochiral 1,3-Di(3-phenyl-3-hydroxy-2-methylpropionyl)-trans-*4,5-tetramethylene-imidazolidin-2-one* (*R,R*)-(+)-**15** - In a manner analogous to that described for the synthesis of **14**, (*R,R*)-(-)-1,3-dipropionyl-*trans*-4,5-tetramethylene-imidazolidin-2-one (*R,R*)-(-)-**11** (252mg, 1.00mmol) was enolised with dibutylboron

triflate (3.0ml, 3.00mmol) and 1-ethylpiperidine (452mg, 4.00mmol). Benzaldehyde (424mg, 4.00mmol) was added and, after a standard reaction period and work-up, the reaction yielded an oily solid. Chromatography on silica gel with ethyl acetate-hexane (1:2) as eluent gave (*R,R*)-(+)-**15** as a white crystalline solid (318mg, 69%). Spectroscopic data was in accord with that recorded previously on a racemic sample; $[\alpha]_D^{20}$ +61.0 (c 1.00, $CHCl_3$).

Homochiral 1,3-Di(3-phenyl-3-hydroxy-2-methylpropionyl)-trans-*4,5-diphenylimidazolidin-2-one* (*R,R*)-(+)-**22** - In a manner analogous to that described for the synthesis of **14**, (R,R)-(-)-1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one (*R,R*)-(-)-**21** (1.05g, 3.00mmol) was enolised with dibutylboron triflate (7.5ml, 7.50mmol) and 1-ethylpiperidine (1.24g, 9.00mmol). Benzaldehyde (0.92ml, 9.00mmol) was added and, after a standard reaction period and work-up, the reaction yielded a clear oil. Chromatography on silica gel with ethyl acetate-hexane (1:1) as eluent gave (*R,R*)-(+)-**22** as a white fluffy solid (1.402g, 83%). Spectroscopic data was in accord with that recorded previously on a racemic sample; $[\alpha]_D^{20}$ +49.8 (c 1.00, $CHCl_3$).

*Racemic (1*RS,2SR*)-1-Phenyl-2-methylpropane-1,3-diol* **30** - Triethylborane (0.3ml, 0.30mmol) was added to a solution of acetic acid (25mg, 0.42mmol) and racemic aldol product **15** (55mg, 0.12mmol) in THF (1ml) at ambient temperature and allowed to stir for 2 h. The reaction was cooled to 0°C and added *via* cannula to a stirred suspension of lithium aluminium hydride (42mg, 1.11mmol) in THF (1ml) at -20°C and stirred for 2 h before being quenched and worked up in the conventional manner. The crude product was taken-up in dichloromethane (2ml) and treated with 30% hydrogen peroxide (0.3ml, 0.30mmol) at 0°C for 1 h before being treated with aqueous sodium thiosulphate solution (2ml). Solvent removal *in vacuo*, trituration of the product with dichloromethane (2x3ml), drying of the combined organic layers over $MgSO_4$ and chromatography on silica gel with dichloromethane-methanol (19:1) as eluent gave **30** as a colourless oil (26mg, 67%), δ_H (300 MHz, CCl_4) 7.49-7.35 (5H, m, Ph), 5.12 (1H, d, J 3.3 Hz, C<u>H</u>(OH)), 3.82 (2H, m, C<u>H</u>$_2$OH), 2.65 (1H, bs, CH$_2$O<u>H</u>), 2.17 (1H, m, C<u>H</u>CH$_3$) and 1.01 (3H, d, J 7.1 Hz, CHC<u>H</u>$_3$); lit[24] δ_H (60 MHz, CCl_4) 4.76 (1H, d, J 3.1 Hz, C<u>H</u>(OH)), 3.41 (2H, m, C<u>H</u>$_2$OH), 1.82 (1H, m, C<u>H</u>CH$_3$) and 0.67 (3H, d, J 7.1 Hz, CHC<u>H</u>$_3$).

Ethyl 3-phenyl-3-hydroxy-2-methylpropionates **33** *and* **34** - Ethyl-2-bromopropionate **32** (5.84ml, 45.0mmol), benzaldehyde (4.54ml, 44.7mmol) and benzene (10ml) were placed in a dropping funnel above a 100ml RB flask containing acid-washed zinc (3.7g, 56.6mmol). A small portion (2ml) of the benzene solution was added to the zinc, the reaction brought to reflux and the balance of the benzene solution added dropwise over 0.5 h. After a further 2 h under reflux, the reaction was cooled to 0°C and quenched by addition of 20% sulphuric acid solution (20ml). The organic layer was separated, the aqueous phase extracted with benzene (2x10ml) and the combined organic layers dried over $MgSO_4$ before being evaporated to give a 5:4 mixture of **33** and **34** as a clear oil (6.32g, 68%). Major diastereoisomer **33**, δ_H (300 MHz, $CDCl_3$) 7.40-7.27 (5H, m, Ph), 5.11 (1H, m, C<u>H</u>(OH)), 4.14 (2H, q, J 7.2 Hz, C<u>H</u>$_2$O), 3.03 (1H, d, J 5.7 Hz, CH(O<u>H</u>)), 2.79 (1H, q, J 7.1 Hz, COC<u>H</u>), 1.22 (3H, t, J 7.1 Hz, OCH$_2$C<u>H</u>$_3$) and 1.14 (3H, d, J 7.1 Hz, CHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 176.0, 141.9, 128.3, 128.1, 126.2, 73.8, 60.6, 46.6, 13.9 and 10.9; m/z 209 (MH^+, 100%). Minor diastereoisomer **34**, δ_H (300 MHz, $CDCl_3$) 7.40-7.27 (5H, m, Ph), 4.76 (1H, dd, J 8.4, 4.4 Hz, C<u>H</u>(OH)), 4.20 (2H, q, J 7.2 Hz, C<u>H</u>$_2$O), 3.01 (1H, d, J 3.2 Hz, CH(O<u>H</u>)), 2.82 (1H, quintet, J 7.2 Hz, COC<u>H</u>), 1.27

(3H, t, J 7.2 Hz, $OCH_2C\underline{H}_3$) and 1.03 (3H, d, J 7.2 Hz, $CHC\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 176.2, 141.9, 128.5, 127.6, 126.8, 76.3, 60.6, 47.1, 14.3 and 14.0 ($OCH_2\underline{C}H_3$); m/z 209 (MH^+, 100%).

*Racemic (1*RS,*2*SR*)-1-Phenyl-2-methylpropane-1,3-diols* **30** *and* **35** - A diethyl ether solution of the 5:4 mixture of **33** and **34** (4.96g, 23.8mmol), obtained above, was added to a suspension of lithium aluminium hydride (2.70g, 71.1mmol) in diethyl ether (10ml) at ambient temperature and allowed to stir for 18 h. The reaction was quenched by addition of water (2.7ml), 15% aqueous sodium hydroxide solution (2.7ml) and water (8.1ml) before being filtered through celite (to remove the aluminium salts) to give a 5:4 mixture of the diastereoisomeric alcohols **30** and **35** as a clear oil, after solvent removal *in vacuo* (3.61g, 91%). Major diastereoisomer **30**, δ_H (300 MHz, $CDCl_3$) 7.40-7.27 (5H, m, Ph), 4.96 (1H, d, J 3.8 Hz, C$\underline{H}$(OH)), 3.69 (2H, m, $C\underline{H}_2OH$), 2.08 (1H, m, $C\underline{H}CH_3$) and 0.86 (3H, d, J 7.1 Hz, $CHC\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 142.8, 128.2, 127.3, 126.3, 76.4, 66.1 , 41.2 and 10.5; m/z 167 (MH^+, 100%). Minor diastereoisomer **35**, δ_H (300 MHz, $CDCl_3$) 7.40-7.27 (5H, m, Ph), 4.55 (1H, d, J 8.4 Hz, C$\underline{H}$(OH)), 3.74 (2H, m, $C\underline{H}_2OH$), 2.08 (1H, m, $C\underline{H}CH_3$) and 0.71 (3H, d, J 7.0 Hz, $CHC\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 143.5, 128.5, 127.9, 126.9, 80.7, 67.8, 41.4 and 13.6; m/z 167 (MH^+, 100%).

3-(3-Phenyl-3-hydroxy-2-methyl)-4-i-propyloxazolidin-2-one **37** - In a manner analogous to that described for the synthesis of **14**, 3-propionyl-4-*i*-propyloxazolidin-2-one **36** (370mg, 2.00mmol) was enolised with dibutylboron triflate (3.0ml, 3.00mmol) and 1-ethylpiperidine (452mg, 4.00mmol). Benzaldehyde (424mg, 4.00mmol) was added and, after a standard reaction period and work-up, the reaction yielded a beige solid. Chromatography on silica gel with ethyl acetate-hexane (1:3) as eluent gave **37** as a colourless oil which crystallised on standing (420mg, 72%), δ_H (300 MHz, $CDCl_3$) 7.41-7.24 (5H, m, Ph), 5.11 (1H, d, J 3.8 Hz, C$\underline{H}$(OH)), 4.41 (1H, m, C$\underline{H}$N), 4.19 (2H, m, $C\underline{H}_2O$), 3.22 (1H, d, J 2.8 Hz, CH(O$\underline{H}$)), 2.36 (1H, m, $C\underline{H}(CH_3)_2$), 1.23 (3H, d, J 6.8 Hz, $CHC\underline{H}_3$), 0.93 (3H, d, J 7.0 Hz, $CH(C\underline{H}_3)_2$) and 0.89 (3H, d, J 7.0 Hz, $CH(C\underline{H}_3)_2$).

(2S,3S)-3-Phenyl-3-hydroxy-2-methylpropanoic acid **31** - Aldol product **37** (582mg, 2.00mmol) was dissolved in THF (4ml) and water (1ml) and the resulting solution cooled to 0°C. 30% Hydrogen peroxide (1.5ml, 15.0mmol) was added, followed by a solution of lithium hydroxide (320mg, 8.00mmol) in water (1ml). After 1.5 h at 0°C the reaction was treated with aqueous sodium thiosulphate solution (25ml), the volatiles were removed *in vacuo* and the resulting residue triturated with dichloromethane (3x10ml). The combined organic layers were dried over $MgSO_4$ and evaporated to yield **31** as a waxy solid (295mg, 82%), m.p. 89-91°C, δ_H (300 MHz, $CDCl_3$) 7.40-7.27 (5H, m, Ph), 5.20 (1H, d, J 3.8 Hz, C$\underline{H}$(OH)), 2.86 (1H, m, $C\underline{H}CH_3$) and 1.17 (3H, d, J 7.2 Hz, $C\underline{H}_3$), $[\alpha]_D^{22}$ -26.7 (c=1.10, CH_2Cl_2). (lit[21] m.p. 89-89.5°C, lit $[\alpha]_D^{22}$ -26.4 (c=1.04, CH_2Cl_2)).

(2R,3R)-3-Phenyl-3-hydroxy-2-methylpropanoic acid **31** - Aldol product **22** (562mg, 1.00mmol) was dissolved in THF (4ml) and water (1ml) and the resulting solution cooled to 0°C. 30% Hydrogen peroxide (0.82ml, 8.0mmol) was added, followed by a solution of lithium hydroxide (80mg, 3mmol) in water (1ml). After 1.5 h at 0°C the reaction was treated with aqueous sodium thiosulphate solution (25ml), the volatiles were removed *in vacuo* and the resulting residue triturated with dichloromethane (3x10ml). The combined organic

layers were dried over $MgSO_4$ and evaporated to yield **31** as a solid (120mg, 35%), $[\alpha]_D^{24}$ +28.6 (c=0.66, CH_2Cl_2).

(1S,2R)-(-)-1-Phenyl-2-methylpropane-1,3-diol **30** from homochiral **31** - A solution of homochiral (2*S*,3*S*)-3-phenyl-3-hydroxy-2-methylpropanoic acid **31** (270mg, 1.50mmol) in THF (3ml) was added dropwise to a stirred suspension of lithium aluminium hydride (120mg, 3.16mmol) in THF (5ml) at 0°C. After stirring for 1h at 0°C the reaction was allowed to warm to ambient temperature over 2 h before being quenched and worked-up in the standard manner to yield a beige oil. Chromatography on silica gel with dichloromethane-methanol (19:1) as eluent gave (-)-**30** as a colourless oil (171mg, 63%). This was identical by ^1H n.m.r. to the major diastereoisomer prepared previously; $[\alpha]_D^{20}$ -53.1 (c 0.75, $CHCl_3$).

(1R,2S)-(+)-3-Phenyl-2-methylpropane-1,3-diol **30** *from homochiral* **22** - Triethylborane (1.3ml, 1.30mmol) was added to a solution of homochiral 1,3-di(3-phenyl-3-hydroxy-2-methylpropionyl)-*trans*-4,5-diphenylimidazolidin-2-one **22** (281mg, 0.50mmol) in THF (3ml) containing acetic acid (100mg, 1.66mmol) at ambient temperature. After stirring for 2 h the reaction mixture was added by cannula to a stirred suspension of lithium aluminium hydride (120mg, 3.16mmol) in THF (4ml) at -20°C. After 2 h the reaction was quenched and worked-up in the normal manner to give an oily solid. This was dissolved in dichloromethane (4ml), cooled to 0°C and 30% hydrogen peroxide (0.5ml, 5.00mmol) in methanol (1ml) added dropwise. After stirring for 1 h the reaction was quenched by addition of aqueous sodium thiosulphate solution (5ml), the volatiles were removed *in vacuo* and the residue triturated with dichloromethane (3x5ml). The combined organic layers were dried over $MgSO_4$, evaporated *in vacuo* and the resulting oil chromatographed on silica gel with dichloromethane-methanol (19:1) to give (+)-**30** as a colourless oil (116mg, 70%). This was identical by ^1H n.m.r. to the sample prepared by reduction of **31**; $[\alpha]_D^{20}$ +52.6 (c 0.57, $CHCl_3$).

(1R,2S)-(+)-1-Phenyl-2-methylpropane-1,3-diol **30** *from homochiral* **15** - In a manner analogous to the synthesis of **30** from **22**, homochiral aldol product **15** (300mg, 0.65mmol) was protected with triethylborane (2.0ml, 2.00mmol) and acetic acid (165mg, 2.74mmol) in THF (5ml). This THF solution was reduced with lithium aluminium hydride (450mg, 11.8mmol) and the resulting protected diol cleaved with hydrogen peroxide (2.0ml, 2.00mmol) to give (+)-**30** as a colourless oil, after chromatography (144mg, 67%). This was identical by ^1H n.m.r. to the sample prepared previously from homochiral **22**; $[\alpha]_D^{20}$ +51.8 (c 0.67, $CHCl_3$).

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