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Bifunctional Chiral Auxiliaries 8: Utilisation of Tartaric Acid Derived Auxiliaries in Aldol and Alkylation Reactions

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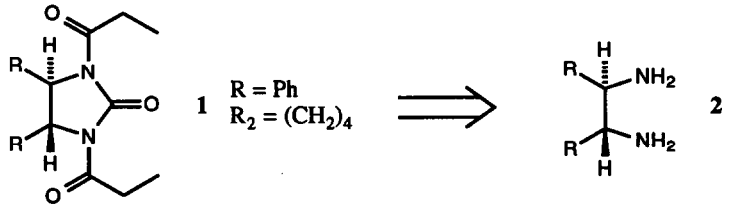
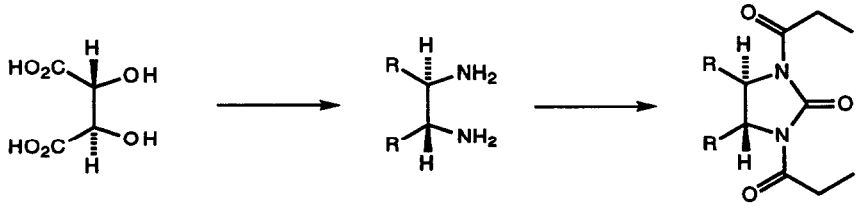
Abstract: The boron enolates of three new homochiral C_2 symmetric 1,3-diacylimidazolidin-2-ones prepared from natural tartaric acid undergo highly diastereoselective aldol and alkylation reactions. Cleavage of these diastereomerically pure, adducts gives homochiral *(1R,2S)*-1-phenyl-2-methylpropane-1,3-diol and *(2R,3R)*-3-hydroxy-3-phenyl-2-methylpropanoic acid and *(2S)*-3-phenyl-2-methylpropan-1-ol (>92% ee). One of these auxiliaries, 4,5-dimethylimidazolidin-2-one, has the lowest effective molecular weight of any previously reported chiral auxiliary.

Recently we described 1,3-diacylimidazolidin-2-ones **1** derived from diamines **2** as stoicheiometric chiral auxiliaries which combine a C_2 axis of symmetry and difunctionality and thus effectively reduce the molecular mass[1]. The rationale behind the design of 1,3-diacylimidazolidin-2-ones represents a natural extension of previous applications of a C_2 axis of symmetry in asymmetric synthesis[2] whereby those control elements necessary for high diastereoselection and mild cleavage of the elucidated acyclic component, embodied by Evans' oxazolidinone range of chiral auxiliaries[3], are duplicated within a single five membered ring. The obvious requirement that neither stereodirecting group impinges on the diastereofacial bias induced by the other has been previously demonstrated[4].



Depending on the nature of R we might expect to see some influence on the absolute or relative stereochemistry of the aldol or alkylation adduct and/or in the cleavage of the adduct[5] and to reduce further the effective molecular mass of this type of chiral auxiliary. Beginning from readily available natural tartaric acid, and thus precluding the need for a resolution step, three previously prepared diamines **3**[6], **4**[7], and **5**[8] were synthesised and converted to their respective 1,3-dipropionylimidazolidinones **6**, **7**, and **8**[4].

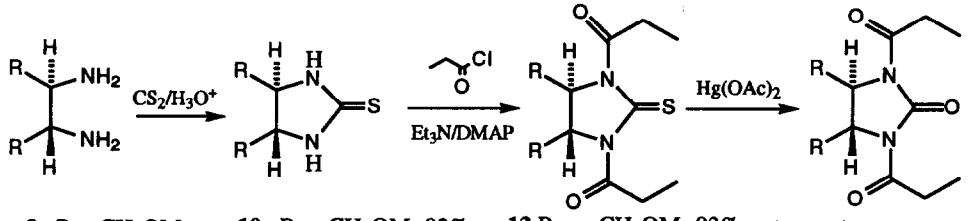


3 R = CH_2OMe
4 R = CH_2OBn
5 R = Me

6 R = CH_2OMe
7 R = CH_2OBn
8 R = Me

When the acylated stoicheiometric chiral auxiliaries **6**, **7**, and **8** were used in tandem with the highly stereoselective Evans aldol[9] and alkylation[10] methodology they provided a potent and effective method of achieving acyclic stereocontrol with high molecular efficiency.

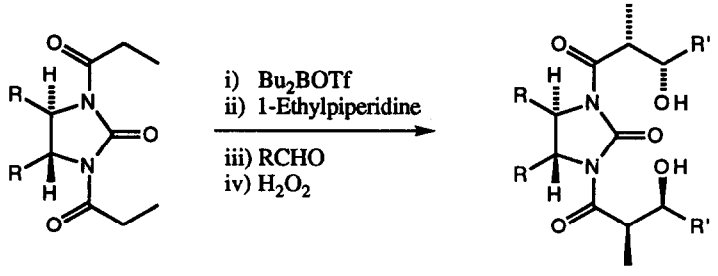
Reaction of diamines **3**, **4**, or **5** with carbon disulphide gave their respective imidazolidine-2-thiones **10**, **11**, and **12**. Diacylations of imidazolidine-2-thiones occur under mild conditions. Thus acylation with propionyl chloride gave the diacylated derivatives **13**, **14** , and **15** in good yields after refluxing for two hours followed by a standard work-up and chromatographic purification. Following the procedure previously reported,[11] dichloromethane solutions of diacylated imidazolidine-2-thiones **13**, **14**, and **15** were stirred with mercury (II) acetate (1.5 eq) for 15 h at ambient temperature. The mercury salts were removed by filtration through celite and purified by chromatography on silica to give 1,3-dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6**, 1,3-dipropionyl-4,5-di(benzyloxymethyl)imidazolidin-2-one **7** and 1,3-dipropionyl-4,5-dimethylimidazolidin-2-one **8** in good yields (scheme 1).



3	R = CH_2OMe	**10**	R = CH_2OMe 92%	**13**	R = CH_2OMe 93%	**6**	R = CH_2OMe 76%
4	CH_2OBn	**11**	CH_2OBn 86%	**14**	CH_2OBn 94%	**7**	CH_2OBn 76%
5	Me	**12**	Me 68%	**15**	Me 89%	**8**	Me 82%

Scheme 1

So as to illustrate the utility of these diacylated bifunctional chiral auxiliaries in the enantioselective formation of carbon-carbon bonds a series of representative asymmetric aldol and alkylation experiments were carried out. 1,3-Dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6** was treated with dibutylboron triflate (2.2 eq) and N-ethylpiperidine (2.4 eq) at 0°C before being cooled to -78 °C. Benzaldehyde (3.0 eq) was added and the reaction stirred at -78 °C for 1 h before being warmed to 0 °C and stirred for a further 2h and then quenched. Standard work-up followed by chromatography yielded the dialdol adduct **16** as a single



6 R = CH_2OMe
7 R = CH_2OBn
8 R = Me

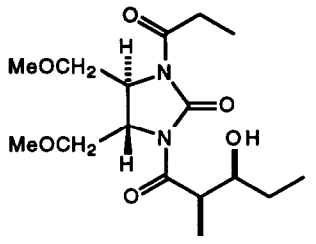
R	CH_2OMe	CH_2OBn	Me
R'			
Ph	**16** 90%	**20** 71%	**23** 51%
t-Bu	**17** 57%		
Et	**18** 53%	**21** 66%	**24** 24%
Me	**19** 35%	**22** 35%	**25** 54%

Scheme 2

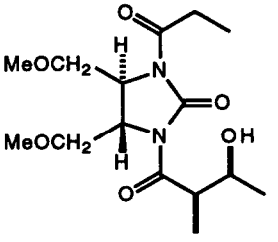
diastereoisomer. The aldol reaction for 1,3-dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6** was repeated under the same conditions with pivalaldehyde, propionaldehyde and acetaldehyde. 1,3-Dipropionyl-4,5-di(benzyloxymethyl)imidazolidin-2-one **7** and 1,3-dipropionyl-4,5-dimethylimidazolidin-2-one **8** were also treated with dibutylboron triflate, N-ethylpiperidine and a range of aldehydes to give the dialdol products **20** - **25**. Once again the reactions were completely diastereoselective and gave purely dialdol products (scheme 2).

The expected *syn* selectivity of the aldol reactions was confirmed through consideration of the ^{1}H[12] and ^{13}C n.m.r.[13] spectroscopy data for these compounds. The mechanism is proposed to proceed via sequential monoenolates rather than through a bisenolate[1]. Clean dialdol reactions were achieved with good dibutyl boron triflate however where the dibutyl boron triflate was not freshly opened monoaldol products were isolated. In this way **26** and **27** were formed as single diastereomers and partially characterised.

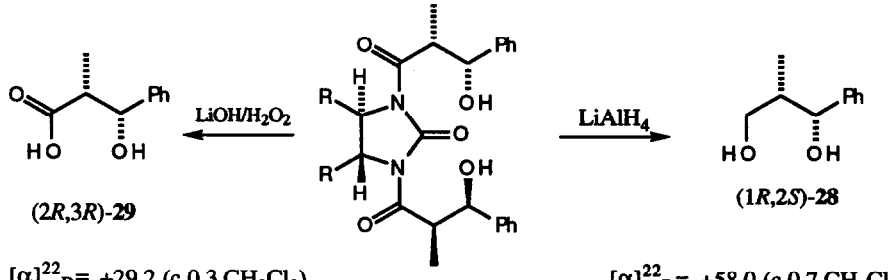
26



27



So as to determine the relative configuration of the side chain to the auxiliary, diastereomerically pure homochiral adducts **16** and **20** were cleaved using lithium aluminium hydride to give (1*R*,2*S*)-1-phenyl-2-methylpropane-1,3-diol **28** and with lithium hydroxide/hydrogen peroxide to give (2*R*,3*R*)-3-hydroxy-3-phenyl-2-methylpropanoic acid **29** (Scheme 3).

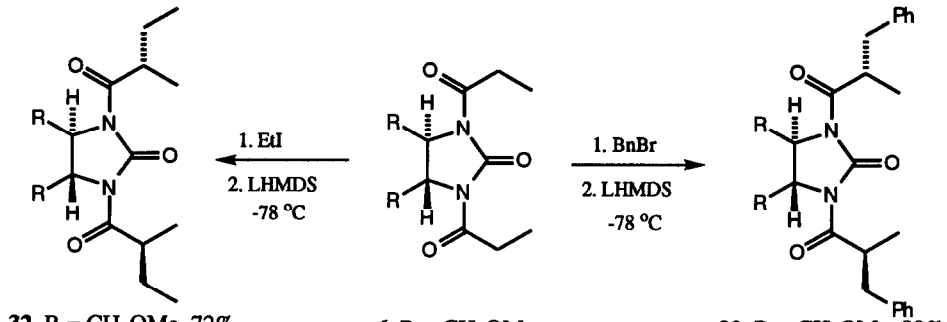


Scheme 3

Compounds **28** and **29** were assessed as homochiral by ^{1}H n.m.r. spectroscopy using the chiral shift reagent *(S)*-2,2,2-trifluoro-1-(9-anthryl)ethanol (e.e >97%). The specific rotations for **28** and **29** were consistent with the literature values[1,14,15,16] and allowed assignment of the absolute configurations. Given the absolute configurations of the starting amines the relative configurations within all the adducts are thus unambiguously assigned.

A more elementary but no less powerful method used in asymmetric carbon-carbon bond formation is the alkylation of enolates[10]. Such a reaction normally proceeds *via* an open transition state unlike the aldol reaction which requires the enolate counter ion to act as a Lewis acid to activate the electrophile.

Attempts to alkylate 1,3-dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6** and the 1,3-dipropionyl-4,5-di(benzyloxymethyl)imidazolidin-2-one **7** by consecutive treatment with either sodium bis(trimethylsilyl)amide or lithium bis(trimethylsilyl)amide and benzyl bromide appeared to lead to ketene elimination. Therefore diastereoselective alkylation reactions were performed on 1,3-dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6** and 1,3-dipropionyl-4,5-di(benzyloxymethyl)imidazolidin-2-one **7** at -78 °C in tetrahydrofuran where the electrophile (benzyl bromide or ethyl iodide) was added first followed by lithium bis(trimethylsilyl)amide. The resulting solution was left to warm to room temperature overnight followed by standard work-up and chromatography or recrystallisation to give diastereomerically pure products **30**, **31**, **32**, and **33** (scheme 4).



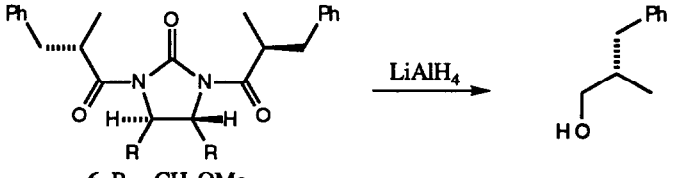
32 R = CH_2OMe, 72%
33 R = CH_2OBn, 57%

6 R = CH_2OMe
7 R = CH_2OBn

30 R = CH_2OMe, 80%
31 R = CH_2OBn, 75%

Scheme 4

The reductive cleavage of the acyl side-chain of the product from the alkylation with benzyl bromide was achieved by treatment of a tetrahydrofuran solution of diastereomerically pure **30** with excess lithium aluminium hydride at -20°C to give *(2S)*-2-methyl-3-phenylpropan-1-ol **34**. The specific rotation of the alcohol from the reaction was found to be $[\alpha]_D^{20}$ = - 10.1 (c =1.1, benzene) (scheme 5) [*(2R)*-**34** lit[16] $[\alpha]_D^{20}$= + 11.0 (c 1.13, benzene)]. The optical purity of **34** is thus >92% although it should be noted that given the method of analysis this would be consistent with the material being, as expected, homochiral. Thus as expected stereoselective alkylation had occurred by addition to the less hindered face of the Z enolate[17] with the enolate oxygen and the imidazolidinone oxygen chelating Li^+. The side chain ether oxygens on the imidazolidinone auxiliaries do not perturb the reaction or selectivity.



6 R = CH_2OMe
7 R = CH_2OBn

(2*S*)-**34**

Scheme 5

In summary we have demonstrated an efficient route to homochiral 1,3-diacylimidazolidin-2-ones from the chiral pool which in concert with existing aldol and alkylation methodology provides an effective route to homochiral alcohols.

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. Reagents were used as received or were purified by standard methods[18]. Flash chromatography was performed on silica gel (43-60 μm) under positive pressure.

(4S,5S)-4,5-Di(methoxymethyl)imidazoline-2-thione **10** - Crude 1,4-di(methoxymethyl)butane-2,3-diamine **3**[6] (2.3 g, 15.5 mmol) was dissolved in an ethanol: water mixture (20 cm^3, 1:1) and refluxed with carbon disulphide (1.1 cm^3, 18.6 mmol) for 1 h. Hydrochloric acid (1.2 cm^3, 36%) was added, hydrogen sulphide evolved and the resulting solution left at reflux overnight. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel, elution with diethyl ether gave **10** as a waxy solid, (2.1g, 92%), m.p. 74 °C, (Found; C, 44.4; H, 7.4; N, 14.5. $C_7H_{12}N_2O_2S$ requires C, 44.2; H, 7.4; N, 14.7%); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 3446 (NH), 1349 (NCSN); $[\alpha]_D^{22}$ + 111.7 (c = 0.73, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 3.38 (6H, s, OCH_3), H_A 3.43, H_B 3.41 (4H, J_{AB} 3.8 Hz, CH_2O), 3.83 (2H, br quintet, J 4.5 Hz, NCH), 6.29 (2H, brs, NH); δ_C, 59.3 (q), 59.5 (d), 73.8 (t), 181.4 (s); m/ z 191 (MH^+, 100%).

(4S,5S)-4,5-Di(benzyloxymethyl)imidazoline-2-thione **11** - 1,4-Di(benzyloxymethyl)butane-2,3-diamine **4**[7](12.17 g, 38 mmol) was dissolved in an ethanol: water mixture (20 cm^3, 1:1) and refluxed with carbon disulphide (2.71 cm^3, 46 mmol) for 1 h. Hydrochloric acid (3.3 cm^3, 36%) was added, hydrogen sulphide evolved and the resulting solution left at reflux overnight. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel using ether as the eluent to give **11** as a yellow oil (12.0 g, 86%), (Found; C, 66.8; H, 6.8; N, 7.7; S, 9.13. $C_{19}H_{22}N_2O_2S$ requires C, 66.6; H, 6.5; N, 8.2; S, 9.4%); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 3445 (NH), 2970 (CH), 1345 (NCSN); $[\alpha]_D^{22}$ +92.1 (c = 0.39, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 3.49 (4H, d, J 5.6 Hz, CH_2O), 3.87 (2H, q, J 5.6 Hz, CHN), H_A 4.53, H_B 4.52 (4H, J_{AB} 21 Hz, CH_2O), 6.73 (2H, brs, NH), 7.40-7.26 (10H, m, Ph); δ_C 59.5 (d), 71.5 (t), 73.6 (t), 128.0 (d), 128.2 (d), 128.7 (d), 137.6 (s), 183.2 (s); m/ z 343 (MH^+, 100%).

(4R,5R)-4,5-Dimethylimidazolidine-2-thione **12** - A solution of butane-2,3-diamine bishydrochloride **5**[8] (4.0 g, 24.7 mmol) in ethanol (20 cm^3) and 3.1M sodium hydroxide (20 cm^3) was stirred at 60 °C for 20 min. Carbon disulphide (2.23 cm^3, 37.1 mmol) was added dropwise, the solution was stirred for 1 h at 60 °C and

then neutralised (pH 7) by dropwise addition of 12M hydrochloric acid. The reaction mixture was heated under reflux for a further 12 h. The solvent was removed, the residue dissolved in CH_2Cl_2 (100 cm^3) and washed with water (100 cm^3). Drying of the CH_2Cl_2 solution and removal of the solvent under reduced pressure afforded **12** as a cream solid (2.19 g, 68%), m.p. 119-120°C, (Found: C, 46.2; H, 7.8; N, 21.3. $C_5H_{10}N_2S$ requires C, 46.1; H, 7.7; N, 21.5%); $[\alpha]_D^{22}$ +72.2 (c 1.03, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3451 (NH), 2976 (CH), 1504 (NCSN), 1316 (NCSN); δ_H(200 MHz) 1.29 (6H, d, J 6 Hz, $CHC\underline{H}_3$), 3.61-3.68 (2H, m, $C\underline{H}CH_3$), 6.60 (2H, br, $N\underline{H}$); δ_C(50.3 MHz) 19.6 (q), 60.4 (t), 181.8 (s); m/z [Probe EI] 130 (M^+, 100%).

(4S,5S)-1,3-Dipropionyl-4,5-di(methoxymethyl)imidazolidine-2-thione **13** - Propionyl chloride (3.8 ml, 43.2 mmol) was added to a solution of 4,5-di(methoxymethyl)imidazoline-2-thione **10** (3.4 g, 18 mmol), pyridine (4.4 cm^3), and DMAP (10 mg, cat.) in dichloromethane (50 cm^3) and refluxed for 2 h. The organic layer was washed with water (2 x 20 cm^3), dried (magnesium sulphate) and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with 50% ether in hexane gave **13** as yellow crystals (5.0 g, 93%), m.p. 62 °C, (Found; C, 51.6; H, 7.4; N, 9.3. $C_{13}H_{22}N_2O_4S$ requires C, 51.6; H, 7.3; N, 9.3%); υ_{max}($CHCl_3$)/ cm^{-1} 2978 (CH), 1696 (CO), 1353 (NCSN); $[\alpha]_D^{22}$ -75.9 (c = 0.64, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.19 (6H, t, J 7.2 Hz, $C\underline{H}_3CH_2$), H_A 3.38, H_B 3.25 (4H, J_{AB} 17.9 Hz, J 7.2 Hz, $C\underline{H}_2CH_3$), 3.32 (6H, s, $OC\underline{H}_3$), H_A 3.52, H_B 3.51 (4H, J_{AB} 27.3 Hz, $C\underline{H}_2O$), 4.61 (2H, t, J 4.0 Hz, $C\underline{H}N$); δ_C 8.7 (q), 32.5 (t), 58.3 (d), 59.3 (q), 71.6 (t), 176.6 (s), 178.5 (s); m/z 303 (MH^+, 100%).

(4S,5S)-1,3-Dipropionyl-4,5-di(benzyloxymethyl)imidazolidine-2-thione **14** - Propionyl chloride (3.0 cm^3, 35 mmol) was added to a solution of 4,5-di(benzyloxymethyl)imidazoline-2-thione **11** (4.95 g, 14 mmol), pyridine (2.6 cm^3, 43 mmol), and DMAP (10 mg) in dichloromethane (50 cm^3) and refluxed for 2 h. The organic layer wash washed with water (2 x 10 cm^3), dried (magnesium sulphate) and evaporated under reduced pressure. The resultant residue was purified by flash chromatography on silica gel, with 50% ether in hexane as the eluent gave **14** as a yellow oil (7.4 g, 94 %), (Found; C, 66.3; H, 6.8; N, 6.2 $C_{25}H_{30}N_2O_4S$ requires C, 66.1; H, 6.7; N, 6.2%); υ_{max}($CHCl_3$)/ cm^{-1} 2986 (CH), 1693 (CO), 1353 (NCSN); $[\alpha]_D^{22}$ -94.7 (c = 0.93, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.10 (6H, t, J 9.3 Hz, $C\underline{H}_3CH_2$), H_A 3.20, H_B 3.08 (4H, J_{AB} 18.0 Hz, J 7.3 Hz, $C\underline{H}_2CH_3$), H_A 3.66, H_B 3.61 (4H, J_{AB} 9.9 Hz, J_{AX} 4.7 Hz, J_{BX} 2.8 Hz $C\underline{H}_2O$), 4.46 (4H, s, $PhC\underline{H}_2O$), 4.67 (2H, brt, J 3.5 Hz, $C\underline{H}N$), 7.36-7.20 (10H, m, Ph); δ_C 8.7 (q), 32.5 (t), 58.7 (d), 69.5 (t), 73.3 (t), 127.7 (d), 128.0 (d), 128.6 (d), 137.9 (s), 176.7 (s), 178.5 (s); m/ z 455 (MH^+, 100%).

(4R,5R)-1,3-Dipropionyl-4,5-dimethylimidazolidine-2-thione **15** - Propionyl chloride (2.36 cm^3, 27.2 mmol) was added to a solution of 4,5-dimethylimidazolidine-2-thione **12** (1.3 g, 10.1 mmol), pyridine (2.0 cm^3, 25.1 mmol), and DMAP (10 mg, cat.) in dichloromethane (30 cm^3). The solution was heated under reflux for 30 min and then stirred for a further 12 h.The reaction mixture was then diluted with CH_2Cl_2 (50 cm^3) washed with water (25 cm^3), saturated sodium bicarbonate (2 x 25 cm^3) and brine (20 cm^3). After drying (magnesium sulphate) the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel, with 50% ether in hexane as the eluent to give **15** as cream coloured crystals (2.16 g, 89%), m.p. 70-71°C, (Found: C, 54.6; H, 7.9 N, 11.4. $C_{11}H_{18}O_2N_2S$ requires C, 54.5; H, 7.5; N 11.6%); $[\alpha]_D^{23}$ -80.4 (c 3.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 2985 (CH), 1694 (CO), 1351 (NCSN); δ_H(200 MHz) 1.20 (6H, t, J 7 Hz, $CH_2C\underline{H}_3$), 1.28 (6H, d, J 6 Hz, $CHC\underline{H}_3$), 3.13-3.45 (4H, m, $C\underline{H}_2CH_3$), 4.26 (2H, q,

J 6 Hz, C<u>H</u>CH$_3$); δ_C(50.3 MHz) 8.7 (q), 18.4 (q), 32.7 (t), 58.7 (d), 176.3 (s), 176.5 (s); m/z 243 (MH^+, 100%).

(4S,5S)-1,3-Dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6** - Mercury (II) acetate (5.0g, 16 mmol) was added to a solution of 1,3-dipropionyl-4,5-di(methoxymethyl)imidazolidine-2-thione **13** (3.94 g, 13 mmol) in dichloromethane (50 cm^3) and allowed to stir overnight at ambient temperature. The reaction mixture was filtered through celite and the solvent removed to give a solid residue which was purified by flash chromatography on silica gel eluting with 50% ether in hexane gave **6** as white crystals (4.15 g, 76 %), m.p. 100 °C, (Found; C, 54.7; H,8.2; N, 9.3. $C_{13}H_{22}N_2O_5$ requires C, 54.5; H, 7.8; N, 9.7%); υ_{max}($CHCl_3$)/ cm^{-1} 2941 (CH), 1695 (CO, NCON); $[\alpha]_D^{22}$ -83.9 (c = 1.15, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.18 (6H, t, J 7.3 Hz, C<u>H</u>$_3$CH$_2$), H_A 2.97, H_B 2.90 (4H, J_{AB} 16.0 Hz, J 7.8 Hz, C<u>H</u>$_2$CH$_3$), 3.32 (6H, s, OC<u>H</u>$_3$), H_A 3.57, H_B 3.47 (4H, J_{AB} 9.6 Hz, J_{AX} 5.0 Hz, J_{BX} 2.6 Hz, C<u>H</u>$_2$O), 4.37 (2H, m, C<u>H</u>N); δ_C 8.2 (q), 29.6 (t), 53.8 (d), 59.2 (q), 71.4 (t), 152.4 (s), 174.8 (s); m/ z 287 (MH^+, 100%).

(4S,5S)-1,3-Dipropionyl-4,5-di(benzyloxymethyl)imidazolidin-2-one **7** - Mercury (II) acetate (10.2 g, 32 mmol) was added to a solution of 1,3-dipropionyl-4,5-di(benzyloxymethyl)imidazolidine-2-thione **14** (5.8 g, 13 mmol) in dichloromethane (50 cm^3) and allowed to stir overnight at ambient temperature. The reaction mixture was filtered through celite and the solvent removed to give a solid residue which was purified by recrystallisation from ethanol to give **7** as a white crystalline solid (4.15 g, 76 %), m.p. 103 °C, (Found; C, 68.3; H, 7.2; N, 6.5. $C_{25}H_{30}N_2O_5$ requires C, 68.5; H, 6.9; N, 6.4%); υ_{max}($CHCl_3$)/ cm^{-1} 3055 (CH), 1696 (NCON), 1604 (CO); $[\alpha]_D^{22}$ -68.6 (c = 0.64, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.12 (6H, t, J 7.4 Hz, C<u>H</u>$_3$CH$_2$), H_A 2.91, H_B 2.82 (4H, J_{AB} 17.6 Hz, J 7.4 Hz, C<u>H</u>$_2$CH$_3$), H_A 3.68, H_B 3.56 (4H, J_{AB} 9.7 Hz, J_{AX} 4.5 Hz, J_{BX} 2.3 Hz CHC<u>H</u>$_2$O), 4.44 (2H, brt, J 3.3 Hz, C<u>H</u>N), 4.47 (4H, s, PhC<u>H</u>$_2$O), 7.36-7.19 (10H, m, Ph); δ_C 8.2 (q), 29.6 (t), 54.1 (d), 69.2 (t), 73.3 (t), 127.6 (d), 128.0 (d), 128.6 (d), 137.9 (s), 152.6 (s), 174.8 (s); m/ z 439 (MH^+, 100%)

(4R,5R)-1,3-Dipropionyl-4,5-dimethylimidazolidin-2-one **8** - Mercury (II) acetate (6.8 g, 21.4 mmol) was added to a solution of 1,3-dipropionyl-4,5-dimethylimidazolidine-2-thione **15** (2.16 g, 8.9 mmol) in CH_2Cl_2 (25 cm^3) and allowed to stir overnight at ambient temperature. The reaction mixture was filtered through celite and the solvent removed to give a solid residue which was purified by flash chromatography on silica gel, with 50% ether in hexane as the eluent to give **8** as a white crystalline solid (1.66 g, 82%), m.p. 71-72°C, (Found: C, 57.9; H, 8.3; N, 12.3. $C_{11}H_{18}O_3N_2$ requires C, 58.4 H, 8.0; N, 12.4%); $[\alpha]_D^{21}$ -77.51 (c = 1.09, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3020 (CH), 1750 (NCON), 1699 (NCOC); δ_H(200 MHz) 1.09 (6H, t, J 7 Hz, CH_2C<u>H</u>$_3$), 1.21 (6H, d, J 6 Hz, CHC<u>H</u>$_3$), 2.80-2.95 (4H, m, C<u>H</u>$_2$CH$_3$), 3.94 (2H, q, J 6 Hz, C<u>H</u>CH$_3$); δ_C(50.3 MHz) 8.1 (q), 19.0 (q), 29.8 (t) 54.2 (d), 151.2 (s), 174.8 (s); m/z 227 (MH^+, 100%).

(4S,5S)-1,3-Di(3-phenyl-3-hydroxy-2-methylpropionyl)-4,5-di(methoxymethyl)imidazolidin-2-one **16** - Dibutylboron triflate (1.40 cm^3, 1.40 mmol of a 1M solution in CH_2Cl_2) was added dropwise to a solution of 1,3-dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6** (170 mg, 0.56 mmol) in CH_2Cl_2 (5 cm^3) at 0°C, under argon to form a brick red solution. N-ethylpiperidine (0.23 cm^3, 1.68 mmol) was added dropwise, causing a colour change to yellow followed by the reaction being cooled to -78°C. Freshly

distilled benzaldehyde (178 mg, 1.7 mmol) in CH_2Cl_2 (2 cm^3) was added the reaction stirred at -78°C for 1 h and then at 0°C for 2 h before being quenched by the addition of an aqueous phosphate buffer (4 cm^3). A solution of hydrogen peroxide (3 cm^3) in methanol (3 cm^3) was added cautiously and the reaction mixture allowed to warm to ambient temperature. Trituration of the resulting residue with CH_2Cl_2 (50 cm^3), washing of the resultant solution with water (2x 20 cm^3), drying (magnesium sulphate) of the CH_2Cl_2 layer and removal of the solvent under reduced pressure. The resultant residue was purified by flash chromatography on silica gel using 70% ether in hexane as the eluent gave **16** as a viscous oil (259 mg, 90%), (Found; C, 65.0; H, 7.1; N, 5.4. $C_{27}H_{34}N_2O_7$ requires C, 65.0; H, 6.9; N, 5.6%); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 3469 (OH), 1752 (NCON), 1692 (CO); $[\alpha]_D^{22}$ -46.0 (c = 1.0, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.17 (6H, d, J 7.2Hz, CH_3CH), 1.64 (2H, brs, OH), 3.31 (6H, s, OCH_3), 3.44 (4H, d, J 3.6 Hz, CH_2O), 4.10 (2H, dq, J 7.2 Hz, J 3.4 Hz, CH_3CH), 4.34 (2H, brt, J 3.4 Hz, CHN), 5.12 (2H, d, J 3.4 Hz, CHOH), 7.43-7.24 (10 H, m, Ph); δ_C (200 MHz, $CDCl_3$) 151.6 (s), 178.3 (s), 10.4 (q), 45.2 (d), 53.9 (d), 59.4 (q), 71.3 (t), 73.3 (d), 126.2 (d), 127.5 (d), 128.4 (d), 141.7 (s); m/ z 499 (MH^+, 100%).

(4S,5S)-1,3-Di(4,4-dimethyl-3-hydroxy-2-methylpentanoyl)-4,5-di(methoxymethyl)imidazolidin-2-one **17** - In a manner analogous to that described for the synthesis of **16** 1,3-dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6** (120 mg, 0.41 mmol) was enolised with dibutylboron triflate (1.05 cm^3, 1.05 mmol of a 1M solution in dichloromethane) and N-ethylpiperidine (0.13 cm^3, 1.3 mmol). Freshly distilled pivalaldehyde (0.14 mg, 1.6 mmol) was added after a standard reaction period followed by a standard workup. The resulting residue was purified by flash chromatography on silica gel using 50% ether in hexane as eluent gave **17** as a white crystalline solid (109 mg, 57%), m.p. 111 °C, (Found; C, 60.3; H, 9.4; N, 6.0. $C_{23}H_{42}N_2O_7$ requires C, 60.2; H, 9.2; N, 6.1%); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 3400 (OH), 2960 (CH), 1755 (NCON), 1688 (CO); $[\alpha]_D^{22}$ -44.9 (c = 0.29, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 0.97 (18H, s, $(CH_3)_3C$), 1.25 (6H, d, J 6.9 Hz, CH_3CH), 2.32 (2H, brd, J 4.1 Hz, CHOH), 3.31 (6H, s, OCH_3), H_A 3.57, H_B 3.47 (4H, J_{AB} 9.7 Hz, J_{AX} 4.2 Hz, J_{BX} 2.3 Hz, OCH_2CH), 3.67 (2H, brt, J 3.8 Hz, $CHCH_3$), 4.08 (2H, m, CHOH), H_X 4.34 (2H, brt, J 2.9 Hz, CHN); δ_C (200 MHz, $CDCl_3$) 12.9 (q), 26.6 (q), 39.5 (d), 54.2 (d), 59.3 (q), 71.7 (t), 77.8 (d), 151.6 (s), 178.9 (s); m/ z 459 (MH^+, 100%).

(4S,5S)-1,3-Di(3-hydroxy-2-methylpentanoyl)-4,5-di(methoxymethyl)imidazolidin-2-one **18** - In a manner analogous to that described for the synthesis of **16** 1,3-dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6** (104 mg, 0.36 mmol) was enolised with dibutylboron triflate (0.95 cm^3, 0.95 mmol of a 1M solution in dichloromethane) and N-ethylpiperidine (0.15 cm^3, 1.1 mmol). Freshly distilled propanal (87 mg, 1.5 mmol) was added after a standard reaction period followed by a standard workup. The resulting residue was purified by flash chromatography on silica gel using 60% ether in hexane as eluent gave **18** as a colourless oil (94 mg, 65 %), (Found; C, 55.5; H, 8.6; N, 7.8. $C_{19}H_{34}N_2O_7$ requires C, 55.8; H, 8.2; N, 7.8%); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 3493 (OH), 2934 (CH), 1752 (CO), 1692 (NCON); $[\alpha]_D^{22}$ -24.5 (c = 0.44, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 0.99 (6H, t, J 7.4 Hz, CH_2CH_3), 1.22 (6H, d, J 6.9 Hz, CH_3CH), 1.50 (4H, m, CH_2CH_3), 3.53 (6H, s, OCH_3), H_A 3.60, H_B 3.48 (4H, J_{AB}9.9 Hz, J_{AX}3.4 Hz, J_{BX}2.3 Hz, OCH_2CH), 3.82 (4H, m, $CHCH_3$, CHOH), H_X 3.48 (2H, brt, J 3.0 Hz, CHN); δ_C 10.2 (q), 10.4 (q), 26.7 (t), 42.6 (d), 54.0 (d), 59.4 (q), 71.7(t), 73.1 (t), 151.8 (s), 178.3 (s); m/ z 403 (MH^+, 100%).

(4S,5S)-1,3-Di(3-hydroxy-2-methylbutanoyl)-4,5-di(methoxymethyl)imidazolidin-2-one **19** - In a manner analogous to that described for the synthesis of **16** 1,3-dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6** (104 mg, 0.36 mmol) was enolised with dibutylboron triflate (0.95 cm^3, 0.95 mmol of a 1M solution in dichloromethane) and N-ethylpiperidine (0.15 cm^3, 1.1 mmol). Freshly distilled acetaldehyde (0.1 cm^3, excess) was added after a standard reaction period followed by a standard workup. The resulting residue was purified by flash chromatography on silica gel using 70% ether in hexane as eluent gave **19** as a colourless oil (48 mg, 35.0 %); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 3490 (OH), 1753 (NCON), 1693 (CO); δ_H (300 MHz, $CDCl_3$) 1.20 (6H, d, J 6.3 Hz, $CHC\underline{H}_3$), 1.24 (6H, d, J 7.0 Hz, $C\underline{H}_3CH$), 3.33 (6H, s, $OC\underline{H}_3$), H_A3.60, H_B3.48 (4H, J_{AB}9.9 Hz, J_{AX} 4.3 Hz, J_{BX} 2.6 Hz, $OC\underline{H}_2CH$), 3.75 (2H, dq, J 7.0 Hz, J 3.2 Hz, $C\underline{H}CH_3$), 4.39 (2H, brt, J 2.9 Hz, $C\underline{H}N$); δ_C 19.6 (q), 43.8 (d), 53.9 (d), 59.4 (q), 67.6 (d), 71.6 (t), 151.6 (s), 178.0 (s); m/ z 375 (MH^+, 100%).

(4S,5S)-1,3-Di(3-phenyl-3-hydroxy-2-methylpropionyl)-4,5-di(benzyloxymethyl)imidazolidin-2-one **20** - In a manner analogous to that described for the synthesis of **16** 1,3-dipropionyl-4,5-di(benzyloxymethyl)imidazolidin-2-one **7** (432 mg, 0.99 mmol) was enolised with dibutylboron triflate (2.5 cm^3, 2.5 mmol of a 1M solution in dichloromethane) and N-ethylpiperidine (0.41 cm^3, 3.0 mmol). Freshly distilled benzaldehyde (314 mg, 3.0 mmol) was added after a standard reaction period and workup. The resulting residue was purified by flash chromatography on silica gel using 60% ether in hexane as the eluent gave **20** as a viscous oil (444 mg, 70.6 %), (Found; C, 71.3; H, 6.9; N, 4.1. $C_{38}H_{42}N_2O_7$ requires C, 71.4; H, 6.6; N, 4.4%); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 3583 (OH), 3055 (CH), 1752 (NCON), 1695 (CO), 1605, 1551 (Ph); $[\alpha]_D^{22}$ -42.5 (c = 1.10, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.10 (6H, d, J 7.0 Hz, $C\underline{H}_3$-CH), 2.69 (2H, d, J 2.8 Hz, CHO$\underline{H}$), H_A3.68, H_B3.56 (4H, J_{AB} 9.8 Hz, J_{AX} 4.1 Hz, J_{BX} 2.2 Hz, $OC\underline{H}_2CH$), 3.99 (2H, dq, J 7.0 Hz, J 2.8 Hz, $C\underline{H}CH_3$), 4.93 (2H, brt, J 2.4 Hz, $C\underline{H}N$), 4.44 (4H, s, $C\underline{H}_2Ph$), 7.30–7.16 (20H, m, Ph); δ_C (200 MHz, $CDCl_3$) 9.6 (q), 45.0 (d), 54.4 (d), 69.3 (t), 72.9 (d), 73.6 (t), 127.6 (d), 126.1 (d), 128.5 (d), 127.9 (d), 128.7 (d), 137.5 (s), 141.6 (s), 152.6 (s), 177.3 (s); m/ z 639 (MH^+, 100%).

(4S,5S)-1,3-Di(3-hydroxy-2-methylpentanoyl)-4,5-dibenzyloxyimidazolidin-2-one **21** - In a manner analogous to that described for the synthesis of **16** 1,3-dipropionyl-4,5-dibenzyloxymethylimidazolidin-2-one **7** (161 mg, 0.37 mmol) was enolised with dibutylboron triflate (0.81 cm^3, 0.81 mmol of a 1M solution in dichloromethane) and N-ethylpiperidine (0.12 cm^3, 0.88 mmol). Freshly distilled propanal (64 mg, 1.1 mmol) was added after a standard reaction period followed by a standard workup. The resulting residue was purified by flash chromatography on silica gel using 60% ether in hexane as the eluent gave **21** as a clear oil (135 mg, 66%), (Found; C, 66.9; H, 7.9; N, 4.6. $C_{31}H_{42}N_2O_7$ requires C, 67.1; H, 7.6; N, 5.0%); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 3511 (OH), 2966 (CH), 1758 (CO), 1680 (NCON); $[\alpha]_D^{22}$ -52.3 (c = 0.12, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 0.92 (18H, t, J 7.3 Hz, $CH_2C\underline{H}_3$), 1.19 (6H, d, J 6.9 Hz, $CHC\underline{H}_3$), 2.74 (2H, brs, $C\underline{H}$-CH_3), H_B 3.54 (2H, J_{AB} 9.8 Hz, J_{BX} 2.1 Hz, $OC\underline{H}_2CH$), 3.70 (4H, m, $C\underline{H}_2CH$, $C\underline{H}OH$), 4.44 (2H, brs, $C\underline{H}N$), 4.46 (4H, s, $PhCH_2$), 7.26-7.13 (10H, m, Ph); δ_C (200 MHz, $CDCl_3$) 10.0 (q), 10.3 (q), 26.7 (q), 42.3 (d), 54.1 (d), 69.3 (t), 72.7 (d), 73.5 (t), 127.8 (d), 128.2(d), 137.6 (s), 152.6 (s), 178.3 (s); 555 m/ z (MH^+, 100%)

(4S,5S)-1,3-Di(3-hydroxy-2-methylbutanoyl)-4,5-di(benzyloxymethyl)imidazolidin-2-one **22** - In a manner analogous to that described for the synthesis of **16** 1,3-dipropionyl-4,5-di(benzyloxymethyl)imidazolidin-2-one **7** (104 mg, 0.36 mmol) was enolised with dibutylboron triflate (0.95 cm^3, 0.95 mmol of a 1M solution in dichloromethane) and N-ethylpiperidine (0.15 cm^3, 1.1 mmol). Freshly distilled acetaldehyde (0.1 ml, excess) was added after a standard reaction period followed by a standard workup. The resulting residue was purified by flash chromatography on silica gel using 70% ether in hexane as eluent gave **22** as a colourless oil (48 mg, 35 %), (Found; C, 66.4; H, 7.8; N, 5.0. $C_{29}H_{38}N_2O_7$ requires C, 66.1; H, 7.3; N, 5.3%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 2970 (CH), 1758 (CO), 1700 (NCON); $[\alpha]_D^{22}$ -36.1 (c = 0.19, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.11 (6H, d, J 6.5 Hz, CH-CH_3), 1.21 (6H, d, J 7.0 Hz, CH_3-CH), 3.61 (2H, dq, J 7.0 Hz, J 2.8 Hz, CH-CH_3), H_A 3.71, H_B 3.54 (4H, J_{AB} 9.8 Hz, J_{AX} 3.9 Hz, J_{BX} 2.1 Hz, OCH_2-CH), 3.97 (2H, brd, J 6.4 Hz, CHOH), 4.45 (6H, m, CH-N, $PhCH_2O$); δ_C 10.1 (q), 19.7 (q), 43.7 (d), 54.2 (d), 67.4 (d), 69.3 (t), 73.6 (t), 127.9 (d), 128.2 (d), 128.7 (d), 137.6 (s), 151.6 (s), 178.3(s); m/ z 523 (MH^+, 100%).

(4R,5R)-1,3-Di(3-phenyl-3-hydroxy-2-methylpropionyl)-4,5-dimethylimidazolidin-2-one **23** - In a mannner analogous to that described for the synthesis of **16** 1,3-dipropionyl-4,5-dimethylimidazolidin-2-one **8** (366 mg, 1.48 mmol) was enolised with dibutylboron triflate (3.26 cm^3, 3.26 mmol of a 1M solution in dichloromethane) and N-ethylpiperidine (0.61 cm^3, 4.44 mmol). Freshly distilled benzaldehyde (0.45 cm^3, 4.4 mmol) was added after a standard reaction period and workup. The resulting residue was purified by flash chromatography on silica gel using 50% ether in hexane as eluent gave **23** (361 mg, 51%); $[\alpha]_D^{20}$ -38.6 (c = 1.86, $CHCl_3$); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3516 (OH), 2984 (CH), 1751 (NCON), 1698 (NCOC); δ_H(200 MHz) 1.07-1.28 (12H, m, CH_3), 2.87-2.94 (2H, m, CH_2CH_3), 3.31 (1H, d, J 2.5 Hz, OH), 3.87-3.95 (2H, m, $NCHCH_3$), 4.06-4.12 (1H, m, $COCHCH_3$), 5.01-5.04 (1H, dd, J 2.5 Hz and J 4.5 Hz CHOH), 7.24-7.39 (5H, m, Ph); δ_C(50.3 MHz) 8.2 (q), 11.3 (q), 18.7 (q), 18.8 (q), 30.0 (t), 45.1 (d), 54.0 (d), 54.4 (d), 74.2 (d), 126.4 (d), 128.4 (d), 127.7 (d), 141.8 (s) 150.8 (s), 174.9 (s), 177.6 (s); m/z 333 (MH^+, 100%).

(4R,5R)-1,3-Di(3-ethyl-3-hydroxy-2-methylpropionyl)-4,5-dimethylimidazolidin-2-one **24** - In a manner analogous to that described for the synthesis of **16** 1,3-dipropionyl-4,5-dimethylimidazolidin-2-one **8** (71 mg, 0.313 mmol) was enolised with dibutylboron triflate (0.70 cm^3, 0.70 mmol of a 1M solution in dichloromethane) and N-ethylpiperidine (0.130 cm^3, 0.94 mmol). Freshly distilled propanal (0.07 cm^3, 0.94 mmol) was added after a standard reaction period and workup. The resulting residue was purified by flash chromatography on silica gel using 50% ether in hexane as eluent gave **24** a cream coloured solid (26 mg, 24%); $[\alpha]_D^{23}$ -34.2 (*c* 1.09 in $CHCl_3$); υ_{max} $(CHCl_3)/cm^{-1}$ 3566 (OH), 3068 (CH), 1752 (NCON), 1678 (NCOC); δ_H(300 MHz) 0.98 (6H, t, J 7.4 Hz, CH_2CH_3), 1.21 (6H, d, J 7.0 Hz, $COCHCH_3$), 1.28 (6H, d, J 6.3 Hz, $NCHCH_3$), 1.41-1.58 (4H, m, CH_2CH_3), 2,85 (2H, br OH), 3.72 (2H, dq, J 7.0 Hz, J 2.6 Hz, $NCHCH_3$), 3.82-3.87 (2H, m, $CH(OH)CH_2$), 4.05 (2H, q, J 6.3 Hz, $NCHCH_3$); δ_C(50.3 MHz) 10.2 (q), 10.3 (q), 18.9 (q) 26.7 (t), 42.5 (d), 54.1 (d), 73.1 (d), 150.5 (s), 178.6 (s).

(4R,5R)-1,3-Di(3-methyl-3-hydroxy-2-methylpropionyl)-4,5-dimethylimidazolidin-2-one **25** - In a mannner analogous to that described for the synthesis of **16** 1,3-dipropionyl-4,5-dimethylimidazolidin-2-one **8** (80 mg, 0.35 mmol) was enolised with dibutylboron triflate (0.78 cm^3, 0.78 mmol of a 1M solution in dichloromethane) and N-ethylpiperidine (0.145 cm^3, 1.06 mmol). Freshly distilled acetaldehyde (0.06 cm^3,

1.06 mmol) was added after a standard reaction period and workup. The resulting residue was purified by flash chromatography on silica gel using 50% ether in hexane as eluent gave **25** a cream coloured solid (60 mg, 54%); $[\alpha]_D^{23}$ -60.9 (c = 1.04, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3550 (OH,), 3033 (CH), 1751 (NCON), 1699 (NCOC); δ_H(300MHz) 1.07-1.31 (15H, m, CH_3), 2.81-2.99 (3H, m, CH_2, OH), 3.67 (1H, dq, J 7.0 Hz, J 2.8 Hz , CH_3CHCH), 3.98-4.06 (3H, m, $NCHCH_3$), 4.16 (1H, dq, J 7.0 Hz, J 2.8 Hz, CH_3CHOH); δ_C(50.3 MHz) 8.2 (q), 10.2 (q), 18.9 (q), 19.1 (q), 19.6 (q), 30.0 (d), 43.7 (d), 54.1 (d), 54.3 (d), 67.7 (d), 150.6 (s), 174.9 (s), 178.5 (s).

(4S,5S)-1-(3-Hydroxy-2-methylpentanoyl)-3-propionyl-4,5-di(methoxymethyl)imidazolidin-2-one **26** - Monoaldol product **26** obtained as a by product in the synthesis of **18**, was partially characterised; (Found C, 55.5; H, 8.7; N 7.7. $C_{16}H_{28}N_2O_6$ requires C, 55.8; H, 8.2; N, 8.1%); 0.98 (3H, t, J 7.4Hz, CH_3CH_2), 1.17 (3H, t, J 7.4 Hz, CH_3CH_2), 1.22 (3H, d, J 6.9 Hz, CH_3CH), 1.53 (2H, m, CH_2CH_3), 2.94 (2H, m, CH_2CH_3), 3.32 (6H, s, OCH_3), H_A 3.62, $H_{A'}$3.54, H_B 3.47 (4H, J_{AB} 9.7 Hz, $J_{A'B}$ 9.7 Hz, J_{AX} 4.4 Hz, $J_{A'X}$4.8 Hz, J_{BX} 4.3 Hz, CH_2OCH_3), 3.81 (2H, m, CHOH, CHCO), H_X 4.37 (2H, m, CHN); M/z 345 (MH^+, 100%).

(4S,5S)-1-(3-Hydroxy-2-methylbutanoyl)-3-propionyl-4,5-di(methoxymethyl)imidazolidin-2-one **27** - Monoaldol product **27**, obtained as a by product in the synthesis of **17**, was partially characterised, (Found C, 54.6; H, 8.2; N, 8.3. $C_{15}H_{26}N_2O_6$ requires C, 54.5; H, 7.9; N, 8.5); 1.18 (3H, t, J 7.4 Hz, CH_3CH_2), 1.19 (3H, d, J 6.5 Hz, CH_3CH), 1.24 (3H, d, J 7.0 Hz, CH_3CH), 2.92 (2H, m, CH_2CH_3), 3.32 (6H, s, OCH_3), H_A 3.62, $H_{A'}$ 3.54, H_B 3.47 (4H, J_{AB} 9.7 Hz, $J_{A'B}$ 9.7 Hz, J_{AX} 2.5 Hz, $J_{A'X}$ 4.8 Hz, J_{BX} 4.3 Hz, CH_2OCH_3), 3.75 (1H, dq, J 7.0 Hz, J 2.9 Hz, CHOH), 4.14 (1H, m, CHCO), H_X 4.37 (2H, m, CHN); MH^+ 331 (100%).

(1R,2S)-(+)-1-Phenyl-2-methylpropane-1,3-diol **28** - Aldol product **16** (200 mg, 0.4 mmol) in THF (10 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (32 mg, 0.84 mmol) in THF (10 cm^3) at 0°C. After stirring for 1h at 0°C the reaction was allowed to warm to ambient temperature before being quenched with 15% sodium hydroxide filtered and the volatiles removed in *vacuo*. The resulting residue was purified by flash chromatography using ether as the eluent gave **28** as a colourless oil (36 mg, 54%), $[\alpha]_{22}^D$ +57.4 (c 0.7, CH_2Cl_2).

(1R,2S)-(+)-1-Phenyl-2-methylpropane-1,3-diol **28** - Aldol product **20** (320mg, 0.5 mmol) in THF (10 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (38 mg, 1.0 mmol) in THF (10 cm^3) at 0°C. After stirring for 1h at 0 °C the reaction was allowed to warm to ambient temperature before being quenched with 15% sodium hydroxide filtered and the volatiles removed in *vacuo* . The resulting residue was purified by flash chromatography using ether as the eluent gave **28** as a colourless oil (56 mg, 67%), $[\alpha]_{22}^D$ +58.0 (c 0.7, CH_2Cl_2).

(2R,3R)-3-Phenyl-3-hydroxy-2-methylpropanoic acid **29**- Aldol product **16** (100 mg, 0.2 mmol) was dissolved in THF (4 cm^3) and water (0.5 cm^3) and the resulting solution cooled to 0 °C. Hydrogen peroxide (0.3 cm^3, 2.9 mmol, 30%) was added followed by a solution of lithium hydroxide (30 mg, 1.13 mmol) in water (0.5 cm^3). After 1.5 h at 0 °C the reaction was treated with aqueous sodium thiosulphate solution (10 cm^3), the volatiles were removed in *vacuo* and the resulting residue triturated with dichloromethane (3 x 10

cm^3). The combined organic layers were dried (magnesium sulphate) and evaporated to yield **29** as a solid (17 mg, 47%); $[\alpha]_D^{22}$ +29.2 (c 0.30, CH_2Cl_2).

(2R,3R)-3-Phenyl-3-hydroxy-2-methylpropanoic acid **29**- Aldol product **20** (181 mg, 0.28 mmol) was dissolved in THF (4 cm^3) and water (0.5 cm^3) and the resulting solution cooled to 0 °C. Hydrogen peroxide (0.3 cm^3, 2.9 mmol, 30%) was added followed by a solution of lithium hydroxide (30 mg, 1.13 mmol) in water (0.5 cm^3). After 1.5 h at 0 °C the reaction was treated with aqueous sodium thiosulphate solution (10 cm^3), the volatiles were removed in *vacuo* and the resulting residue triturated with dichloromethane (3 x 10 cm^3). The combined organic layers were dried (magnesium sulphate) and evaporated to yield **29** as a solid (22 mg, 47%); $[\alpha]_D^{22}$ +28.8 (c=0.32, CH_2Cl_2).

(4S,5S)-1,2-Di(3-phenyl-2-methylpropionyl)-4,5-di(methoxymethyl)imidazolidin-2-one **30** - A solution of 1,3-dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6** (49 mg, 0.17 mmol) in THF (2 cm^3) was cooled to -78 °C and stirred for 15 min. Benzyl bromide (0.053 cm^3, 0.44 mmol), was added dropwise and immediately after this LHMDS (0.41 cm^3, 0.41 mmol, 1M solution in THF) was added and the resulting solution allowed to warm to ambient temperature overnight. Dilution with water (x 10), subsequent extraction with CH_2Cl_2, drying of the organic layer (magnesium sulphate) and removal under reduced pressure gave a crude crystalline residue. The residue was purified by flash chromatography on silica gel using 5% ether in CH_2Cl_2 (3 x 25 cm^3) as the eluent and gave **30** as white crystals (47 mg, 80 %), m.p. 71 °C (Found; C, 69.5; H, 7.4; N, 6.0. $C_{39}H_{42}N_2O_5$ requires C, 69.5; H 7.4, N 6.0%); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 2978 (CH), 1752 (NCON), 1696 (CO); $[\alpha]_D^{22}$ -50.2 (c = 0.56, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.13 (6H, d, J 6.8 Hz, $CHCH_3$), H_A 3.16, H_B 2.64 (4H, J_{AM} 13.4 Hz, J_{AX} 6.3 Hz, J_{MX} 8.2 Hz, $CHCH_2CH_3$), 3.22 (6H, s, OCH_3), 3.37 (4H, d, J 3.4 Hz, CH_2O), 4.11 (2H, br sextet, J 5.5 Hz, $CHCH_3$), 4.33 (2H, brt, J 3.3 Hz, CHN), 7.30-7.18 (10H, m, Ph); δ_C 16.2 (q), 39.4 (d), 39.9 (t), 53.8 (q), 59.2 (d), 71.6 (t), 126.4 (d), 128.4 (d), 129.5 (d), 139.7 (s), 151.2 (s), 177.3 (s); m/ z 467 (MH^+, 100%).

(4S,5S)-1,2-Di(3-phenyl-2-methylpropionyl)-4,5-di(benzyloxymethyl)imidazolidin-2-one **31** - A solution of 1,3-Dipropionyl-4,5-di(benzyloxymethyl)imidazolidin-2-one **7** (329 mg, 0.75 mmol) in THF (4 cm^3) was cooled to -78 °C and stirred for 15 min. Benzyl bromide (0.22 cm^3, 1.9 mmol), was added dropwise and immediately after this LHMDS (1.65 ml, 1.65 mmol 1M solution in THF) was added and the resulting solution allowed to warm to ambient temperature overnight. Dilution with water (x 10), subsequent extraction with CH_2Cl_2 (3 x 25 cm^3), drying of the organic layer (magnesium sulphate) and removal under reduced pressure gave a crude crystalline residue. This was recrystallised from ethanol and gave **31** as white crystals (464 mg, 75 %) m.p. 110 °C, (Found; C, 75.2; H, 6.5; N, 4.3. $C_{39}H_{42}N_2O_5$ requires C, 75.7; H 6.5, N 4.3%); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 3055 (CH), 1753 (NCON), 1693 (CO); $[\alpha]_D^{24}$ -34.1 (c 1.2, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.02 (6H, d, J 6.9 Hz, $CHCH_3$), H_A 3.13, H_M 2.60 (4H, J_{AM} 13.4 Hz, J_{AX} 6.5 Hz, J_{MX} 8.2 Hz, $CHCH_2CH_3$), H_A 3.48, H_B 3.47 (4H, J_{AB} 9.8 Hz, J_{AX} 4.1 Hz, J_{BX} 2.5 Hz, CH_2OCH3), 4.07 (2H, sextet, J 6.6 Hz, $CHCH_3$), 4.34 (4H, s, OCH_2Ph), 4.41 (2H, brt, J 3.0 Hz, CHN), 7.31-7.18 (10H, m, Ph); δ_C 16.2 (q), 39.4 (d), 39.9 (t), 54.0 (d), 69.4 (t), 73.4 (t), 126.4 (d), 127.2 (d), 128.0 (d), 128.4 (d), 129.5 (d), 137.9 (s), 139.8 (s), 151.9 (s), 177.2 (s); m/ z 619 (MH^+, 100%).

(4S,5S)-1,2-Di(2-methylbutanoyl)-4,5-di(methoxymethyl)imidazolidin-2-one **32** - A solution of 1,3-dipropionyl-4,5-di(methoxymethyl)imidazolidin-2-one **6** (57 mg, 0.2 mmol) in THF (2 cm^3) was cooled to -78 °C and stirred for 15 min. Ethyl iodide (0.041 cm^3, 0.52 mmol), was added dropwise and immediately after this LHMDS (0.48 cm^3, 0.48 mmol, 1M solution in THF) was added and the resulting solution allowed to warm to ambient temperature overnight. Dilution with water (x 10), subsequent extraction with CH_2Cl_2 (3 x 25 cm^3), drying of the organic layer (magnesium sulphate) and removal under reduced pressure gave a crude crystalline residue. The residue was purified by flash chromatography on silica gel using 4% ether in CH_2Cl_2 as the eluent and gave **32** as white crystals (49 mg, 72 %) m.p. 75 °C (Found; C, 59.3; H, 9.0; N, 7.9%). $C_{39}H_{42}N_2O_5$ requires C, 59.6; H 8.8; N 8.2%); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 2989 (CH), 1751 (CO), 1691 (NCON); $[\alpha]_D^{22}$ -45.8 (c = 0.17, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 0.93 (6H, d, J 7.4 Hz, $CH_2C\underline{H}_3$), 1.13 (6H, d, J 6.8 Hz, $C\underline{H}_3CH$), H_A 1.76, H_B 1.48 (4H, J_{AB} 28.3 Hz, J_{AX} 7.4 Hz, J_{BX} 7.4 Hz, $C\underline{H}_2CH3$), H_A 3.53, H_B 3.46 (4H, J_{AB} 9.6 Hz, J_{AX} 4.7 Hz, J_{BX} 2.5 Hz, $C\underline{H}_2O$), 3.30 (6H, s, $OC\underline{H}_3$), 3.70 (2H, q, J 6.8 Hz, $CH_3C\underline{H}CH_2$), 4.36 (2H, brt, J 3.1 Hz, C<u>H</u>N), δ_C 11.3 (q), 16.1 (q), 26.5 (t), 39.4 (d), 53.9 (q), 71.8 (t), 150.4 (s), 178.2 (s); m/ z 343 (MH^+, 100%).

(4R,5R)-1,2-Di(2-methylbutanoyl)-4,5-di(benzyloxymethyl)imidazolidin-2-one **33** - A solution of 1,3-dipropionyl-4,5-di(benzyloxymethyl)imidazolidin-2-one **7** (220 mg, 0.5 mmol) in THF (2 cm^3) was cooled to -78 °C and stirred for 15 min. Ethyl iodide (0.12 cm^3, 2.0 mmol), was added dropwise and immediately after this LHMDS (1.2 cm^3, 1.2 mmol, 1M solution in THF) was added and the resulting solution allowed to warm to ambient temperature overnight. Dilution with water (x 10), subsequent extraction with CH_2Cl_2 (3 x 25 cm^3), drying of the organic layer (magnesium sulphate) and removal under reduced pressure gave a crude crystalline residue. The residue was purified by flash chromatography on silica gel using 4% ether in CH_2Cl_2 as the eluent and gave **33** as white crystals (140 mg, 57 %), m.p. 42 °C, (Found; C, 70.2; H, 8.0; N, 5.8%. $C_{39}H_{42}N_2O_5$ requires C, 70.1; H 8.1; N 5.6%); $\upsilon_{max}(CHCl_3)$/ cm^{-1} 2996 (CH), 1752 (CO), 1692 (NCON); $[\alpha]_D^{22}$ -41.7 (c = 0.18, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 0.92 (6H, d, J 7.4 Hz, $CH_2C\underline{H}_3$), 1.04 (6H, d, J 6.9 Hz, $C\underline{H}_3CH$), 1.61 (4H, m, $C\underline{H}_2CH3$), H_A 3.70, H_B 3.53 (4H, J_{AB} 9.5 Hz, J_{AX} 6.4 Hz, J_{BX} 2.5 Hz, $C\underline{H}_2O$), 4.45 (6H, s, OCH_2Ph, C<u>H</u>N); δ_C 11.3 (q), 16.1 (q), 26.5 (t), 39.4 (d), 54.1 (d), 69.5 (t), 73.4 (t), 127.7 (d), 128.0 (d), 128.6 (d), 137.9 (s), 152.0 (s), 178.0 (s); 495 m/ z (MH^+, 100%).

(2S)-2-methyl-3-phenylpropan-1-ol **34** - Alkylation product **30** (80 mg, 0.17 mmol) in THF (5 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (19 mg, 0.5 mmol) in THF (5 cm^3) at 0°C. After stirring for 1h at 0°C the reaction was allowed to warm to ambient temperature before being quenched with 15% sodium hydroxide filtered and the volatiles removed in *vacuo* . The resulting residue was purified by flash chromatography using ether as the eluent gave **34** as a colourless oil (20 mg, 95%), $[\alpha]^D{}_{22}$ - 10.1 (c=1.0, CH_2Cl_2).

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