Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 4, pp. 585-606, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $6.00+0.00

0957-4166(94)E0081-K

Bifunctional Chiral Auxiliaries 6[1]: Alkylations of Enolates Derived from 1,3-Diacylimidazolidine-2-thiones and 1,3-Diacylimidazolidin-2-ones

Stephen G. Davies*†, Gary B. Evans and Andrew A. Mortlock

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, OX1 3QY, UK.

Abstract: Sodium and potassium enolates of 1,3-diacylimidazolidin-2-ones undergo clean alkylation reactions with reactive alkyl halides; the latter enolates reacting generally more stereoselectively due, it is proposed, to the lower temperature at which the reactions proceed. The reactions are all stereoregular, with the diastereoisomeric identity of products being established unambiguously by the synthesis of (2*S*)-3-phenyl-2-methylpropan-1-ol. The sense of asymmetric induction in these reactions is consistent with the intermediacy of chelated *syn* enolates which the electrophile approaches preferentially from the face *exo* to the proximate alkyl / aryl group on the five-membered ring. In contrast, 1,3-diacylimidazolidine-2-thiones are unable to act as bifunctional chiral auxiliaries in alkylation reactions due to enolate decomposition.

Introduction:

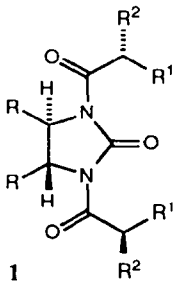
Enolate alkylation is a powerful synthetic method for asymmetric carbon-carbon bond formation[2]. The attainment of high levels of diastereoselection require the conformational restriction of an enolate of specified geometry followed by the differential shielding of one face of this restricted enolate. Initial restriction of the enolate conformation is usually achieved by chelation of the enolate counterion to a suitable lone-pair donor on the auxiliary. As the parameters that govern the accessibility of the two faces of the enolate are believed to be predominantly steric[3], incorporation of a suitable stereogenic centre can shield one face of the enolate, promoting reaction on the *exo* face. We have demonstrated that bifunctional chiral auxiliaries can be developed which allow the simultaneous stereoselective elaboration of two acyl side-chains[4]. In this paper we seek to investigate the alkylation of these reagents.

Alkylation of sodium and lithium enolates of N-acyl oxazolidinones has been demonstrated to occur with good stereocontrol and with the former enolates showing much greater reactivity[5]. The level of diastereoselection is found to be dependent on both the nature of the enolate counterion and the size of the electrophile. Thus, while sodium enolates show generally higher stereoselectivities than do their lithium counterparts, small electrophiles generally react less selectively due to their relative insensitivity towards the steric hinderance caused by the C-4 substituent. More recently, stereoselective alkylation of trichlorotitanium enolates has been reported to occur at 0°C, although only with the most reactive electrophiles[6].

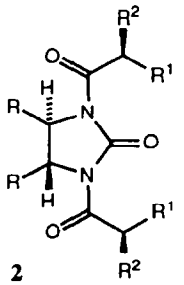
Alkylation of N-acyl oxazolidinone enolates creates a single stereogenic centre and therefore allows two possible diastereoisomers of the product to be formed. Alkylation of the two acyl side-chains on a bifunctional chiral auxiliary may generate two new stereogenic centres and consequently might be expected to allow the formation

† Member of the EC Human Capital and Mobility Network "Stereoselective Organic Synthesis"

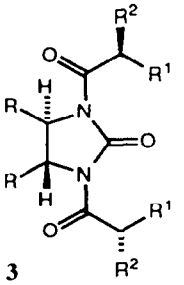
of four possible diastereoisomers of the product. However, only the three diastereoisomers **1**,**2** and **3** may be formed, due to considerations of symmetry[7]. Both **1** and **3** have a C_2 symmetry element whilst **2** is devoid of this feature, the situation being analogous in terms of the side-chains to the better-known case of the existence of *meso* compounds.



1

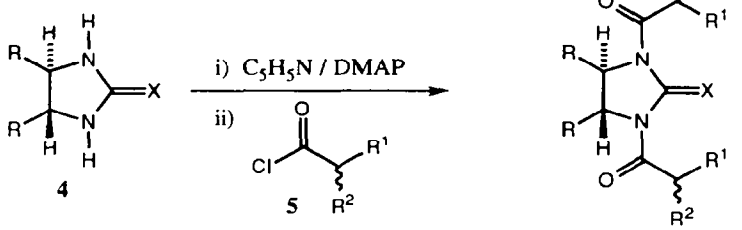


2



3

The point may be further discussed if we consider the specific case where the configurations of the two stereogenic centres on the five-membered ring are both *R* and where the substituents R^1 and R^2 are arbitrarily chosen so that the former has a higher priority when assigning a configuration. If the four asymmetric centres are listed in linear order, with those of the chiral auxiliary in the middle, **1** has the configuration (*R,R,R,R*), **3** is (*S,R,R,S*) and **2** corresponds to the (*R,R,R,S*) diastereoisomer. However, because there is no way to distinguish at which end of the molecule this listing has begun, there is no difference between the (R,R,R,S) and (S,R,R,R) diastereoisomers; they are the same compound, **2**. This method of rationalising the existence of only three diastereoisomers may be demonstrated if acylation of a generalised imidazolidine-2-thione or imidazolidin-2-one **4** is attempted with an α-substituted acyl halide **5**. In the absence of molecular recognition phenomena, a 25:50:25 mixture of **1**, **2** and **3** should result (Scheme 1).



Scheme 1

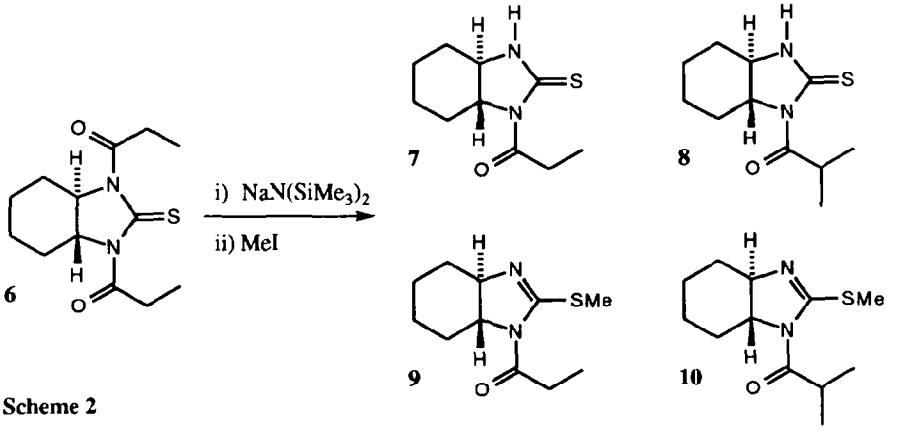
1 : **2** : **3** = 25 : 50 : 25

We herein report the stereoselective alkylation of these novel bifunctional chiral auxiliaries and the conversion of the dialkylated products to α-substituted chiral alcohols *via* reductive cleavage of both acyl side-chains. Part of this work has been the subject of a preliminary communication[8].

Results and Discussion

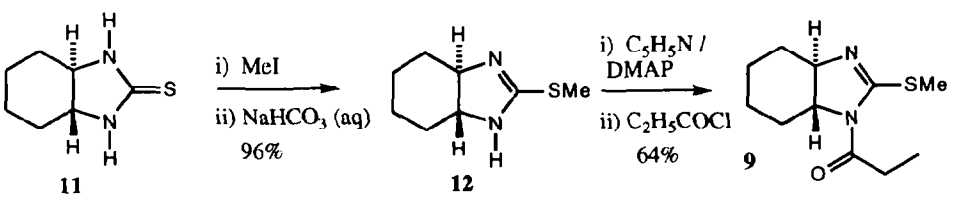
Although alkylation of N-acyl thioxazolidin-2-thiones has not been reported, alkylation of 1,3-diacylimidazolidine-2-thiones was attempted[1]. Thus, a solution of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **6** in THF at -78°C was treated sequentially with sodium bis(trimethylsilyl) amide and methyl iodide. After stirring for 2 h at -78°C the reaction was quenched and worked-up to give a

crude product which was separated into two fractions by chromatography on silica gel. The less polar fraction contained a 55:45 mixture of the 1-acyl-*trans*-4,5-tetramethyleneimidazolidine-2-thiones **7** and **8**. The more polar fraction contained an 85:15 mixture of the S-methylated products **9** and **10** (Scheme 2).



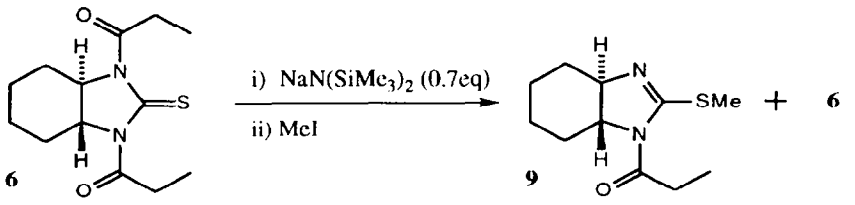
Scheme 2

As neither fraction could be further separated, **7**-**10** could not be characterised using elemental analysis. Whilst **7** and **8** were characterised using high resolution mass spectroscopy, it was decided to prepare the major product of the more polar fraction, **9**, by an alternative synthetic route. This would allow it to be purified more readily and make it amenable to full characterisation. We have previously described the synthesis of **12** *via* S-methylation of *trans*-4,5-tetramethyleneimidazolidine-2-thione **11**[1]. Acylation of **12** was achieved by treatment with propionyl chloride and pyridine in the presence of a catalytic quantity of 4-(dimethylamino)pyridine. This allowed the preparation of **9** in moderate yield but in a form that could be readily purified (Scheme 3).



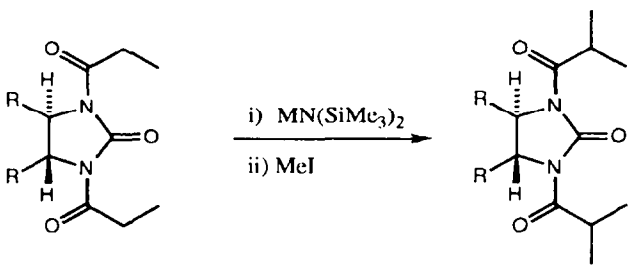
Scheme 3

It is clear that all four possible products are characterised by the loss of one of the two acyl side-chains. This indicates that 1,3-diacylimidazolidine-2-thiones are not capable of acting as bifunctional chiral auxiliaries in alkylation reactions. A mechanism that can account for the formation of all four products must be somewhat speculative and we have not sought to establish it conclusively. However, treatment of **6** with 0.7 equivalents of sodium bis(trimethylsilyl) amide, under conditions analogous to those described above, gave a mixture of **9** and recovered **6** after addition of excess methyl iodide, stirring at -78°C for 1 h and work-up. This strongly suggests that enolate decomposition occurs from the monoenolate and not *via* elimination of methylketene from the bisenolate. The failure of this reaction to give any of the mono C-alkylated material indicates that alkylation cannot even be achieved in two distinct steps, although such a strategy would negate the inherent advantage of using bifunctional chiral auxiliary methodology[4] (Scheme 4).



Scheme 4

To ensure that dialkylation of 1,3-diacylimidazolidin-2-ones would occur without enolate decomposition, methylation of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **13** and 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one **14** was attempted. Under conditions analogous to those described above, both **13** and **14** underwent clean dimethylation to furnish respectively **15** and **16** in moderate to good yield. The reaction was repeated on **13**, using potassium bis(trimethylsilyl)amide as base, which once again effected dimethylation to give **15** in good yield (Scheme 5).

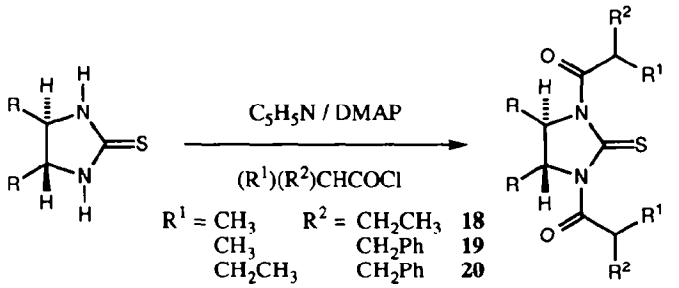


M = Na	R = $-(CH_2)_4-$	**13**		R = $-(CH_2)_4-$ **15**	69%
	Ph	**14**		Ph **16**	82%
M = K	R = $-(CH_2)_4-$	**13**		R = $-(CH_2)_4-$ **15**	87%

Scheme 5

Having established that dialkylation of 1,3-diacylimidazolidin-2-ones would occur in simple cases, attention was turned to alkylation reactions which would proceed with the formation of two new stereogenic centres. As it was intended to analyse the crude products of these reactions by ^1H n.m.r. spectroscopy, authentic samples, containing a statistical distribution of all three diastereoisomers of the dialkylated product, were prepared *via* acylation with the requisite α-substituted acyl halide. The three acyl halides **18-20** were prepared by standard methods[9] and coupled with imidazolidine-2-thiones **11** and **17** according to the protocol described previously[1]. No attempt was made to try and separate the three diastereoisomers of the products of these six reactions **21-26**, although the mixtures were partially characterised and all gave satisfactory elemental analyses. In all six cases, the diastereoisomeric distribution of products was found to be approximately 25 : 50 : 25, as expected if there were no molecular recognition between the components (Scheme 6).

Each crude mixture of diastereoisomers **21-26** was treated with mercury (II) acetate to effect conversion to the corresponding 1,3-diacylimidazolidin-2-ones according to the procedure previously described[1]. Although chromatographic separation of diastereoisomers was still not possible, the identity of all three diastereoisomers was achieved due to subsequent stereoselective synthesis of each of the two C_2 symmetric diastereoisomers. This allowed the major product of these dethionation reactions (the diastereoisomer without the C_2 symmetry element) to be identified as corresponding to those resonances not assigned to the other two diastereoisomers.



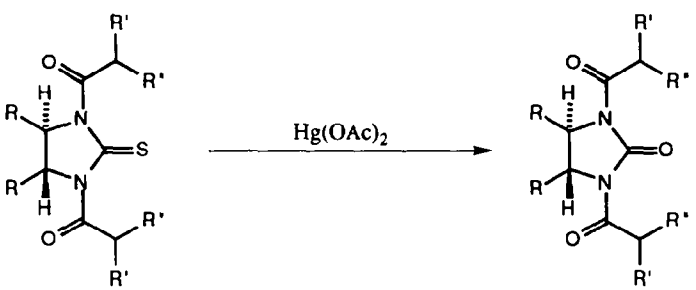
$R^1 = CH_3$ $R^2 = CH_2CH_3$ **18**
CH_3 CH_2Ph **19**
CH_2CH_3 CH_2Ph **20**

R = -$(CH_2)_4$- **11**
Ph **17**

R	R^1	R^2		
-$(CH_2)_4$-	CH_3	CH_2CH_3	**21**	78%
Ph	CH_3	CH_2CH_3	**22**	79%
-$(CH_2)_4$-	CH_3	CH_2Ph	**23**	94%
Ph	CH_3	CH_2Ph	**24**	87%
-$(CH_2)_4$-	CH_2CH_3	CH_2Ph	**25**	85%
Ph	CH_2CH_3	CH_2Ph	**26**	92%

Scheme 6

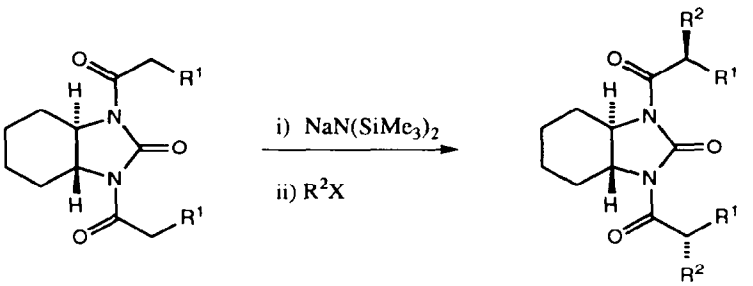
The assignment of configuration to those diastereoisomers with C_2 symmetry axes was achieved as a consequence of the stereoregularity of the alkylation reactions which allowed the structures of all these compounds to be correlated to that of **35**, which was assigned during the asymmetric synthesis of (2*S*)-3-phenyl-2-methylpropan-1-ol **52** (*vide infra*). Thus, all three diastereoisomers obtained in each of the six dethionation reactions were unambiguously identified (Scheme 7).



	R	R'	R"		
21	-$(CH_2)_4$-	CH_3	CH_2CH_3	**27-29**	99%
22	Ph	CH_3	CH_2CH_3	**30-32**	84%
23	-$(CH_2)_4$-	CH_3	CH_2Ph	**33-35**	84%
24	Ph	CH_3	CH_2Ph	**36-38**	83%
25	-$(CH_2)_4$-	CH_2CH_3	CH_2Ph	**39-41**	73%
26	Ph	CH_2CH_3	CH_2Ph	**42-44**	81%

Scheme 7

With these authentic samples now available, diastereoselective alkylation reactions could now be attempted. It was found that whilst methylation occurred readily at -78°C, alkylation with benzyl bromide and allyl bromide required that the reactions be warmed to -30°C while reaction with ethyl iodide did not occur to any appreciable degree, even under these latter conditions. However, clean dialkylation of those 1,3-diacylimidazolidin-2-ones derived from *trans*-1,2-diaminocyclohexane was achieved in good chemical yield within the limitations already described (Scheme 8).



R^1 = CH_3	**13**	R^1 = CH_3	R^2 = CH_2Ph	**35**
CH_2CH_3	**45**	CH_3	$CH_2CH{=}CH_2$	**47**
CH_2Ph	**46**	CH_2CH_3	CH_2Ph	**41**
		CH_2CH_3	CH_3	**27**
		CH_2Ph	CH_3	**33**

Scheme 8

If the diastereofacial selectivities of the two alkylation processes occurring in these reactions are x : 1 and y : 1, the observed distribution of the three diastereoisomers of the dialkylated product would be xy : (x+y) : 1. This expression would simplify, in the case that both reactions showed identical selectivities, to a product distribution of x^2 : 2x : 1. Thus, in this latter case, the diastereofacial selectivity, x, could be obtained from the observed product distribution as the ratio of the major diastereoisomer to the second diastereoisomer equals x/2. As, in those examples where all three diastereoisomers were observed, the product distribution was consistent with both alkylation processes proceeding with identical facial stereoselectivities, the selectivities quoted in the following tables are all calculated in this manner. Furthermore, in those cases where the third diastereoisomer was not readily observable, the figure quoted in parentheses is the value calculated from the ratio of the other two diastereoisomers, assuming that x and y are identical (Table 1).

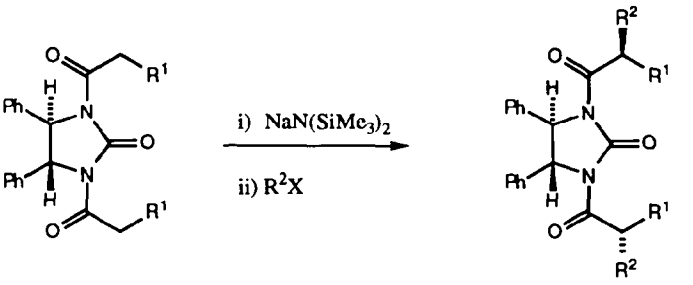
Table 1 Yields, product ratios and diastereofacial selectivities for the alkylation of sodium enolates of 1,3-diacyl-*trans*-4,5-tetramethyleneimidazolidin-2-ones as a function of enolate substituent (R^1) and electrophile (R^2X).

Starting Material	R^1	R^2X	Major Product	Ratio of Products*	Selectivity#	Yield
13	Me	BnBr	**35**	67 : 30 : 3	82 : 18	77%
13	Me	C_3H_5Br	**47**	73 : 25 :(2)	85 : 15	52%
45	Et	BnBr	**41**	84 : 15 :(1)	92 : 8	72%
45	Et	MeI	**27**	64 : 32 : 4	80 : 20	59%
46	CH_2Ph	MeI	**33**	81 : 18 :(1)	90 : 10	81%

* Values in parentheses are calculated # Calculated from the ratio of major to second diastereoisomer

It is clear that whilst these alkylation reactions are stereoselective, the magnitude of that diastereoselectivity is lower than might be expected on the basis of a direct comparison with the results obtained on the alkylation of N-acyl oxazolidinone enolates. This reduction in the level of diastereoselection could be due either to the cyclohexyl methylene groups being too small to effectively shield the *endo* face of the enolate, or due to the

intermediate enolate being too free to rotate due to inefficient chelation between the enolate counterions and the imidazolidin-2-one carbonyl group. To test out the former hypothesis, the reactions were repeated using 1,3-diacylimidazolidin-2-ones derived from 1,2-diphenyl-1,2-diaminoethane (Scheme 9).



R^1 = CH_3	**14**	R^1 = CH_3	R^2 = CH_2Ph	**38**
CH_2CH_3	**50**	CH_2CH_3	CH_2Ph	**44**
CH_2Ph	**51**	CH_2CH_3	CH_3	**30**
		CH_2Ph	CH_3	**36**

Scheme 9

However, as may be seen in the table below, the diastereoselectivities for these reactions were slightly lower than were observed above, indicating that the introduction of a larger blocking group does not lead to higher diastereoselectivities in alkylations (Table 2).

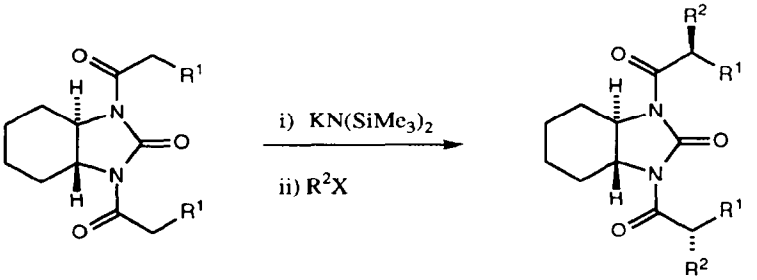
Table 2 Yields, product ratios and diastereofacial selectivities for the alkylation of sodium enolates of 1,3-diacyl-*trans*-4,5-diphenylimidazolidin-2-ones as a function of enolate substituent (R^1) and electrophile (R^2X).

Starting Material	R^1	R^2X	Major Product	Ratio of Products	Selectivity#	Yield
14	Me	BnBr	**38**	50 : 41 : 9	71 : 29	72%
50	Et	BnBr	**44**	47 : 43 : 10	69 : 31	53%
50	Et	MeI	**30**	63 : 33 : 4	80 : 20	71%
51	CH_2Ph	MeI	**36**	54 : 39 : 7	73 : 27	70%

Calculated from the ratio of major to second diastereoisomer

The reduced diastereoselectivity observed in the latter series of reactions suggested that the most likely cause of the rather poor diastereoselectivities was that the conformations of the two enolates were not being sufficiently restrained. This is probably a consequence of the imidazolidin-2-one carbonyl group being too electron poor to be able to chelate effectively to two metal cations. One approach that seemed to offer the possibility of circumventing this problem was to try and effect the reactions at lower temperature where the chelate might be less prone to collapse. This would require the enolate to be more reactive, a situation that could be brought about by introducing a more electropositive counterion. Thus, the initial series of reactions on the 1,3-diacyl-*trans*-4,5-tetramethyleneimidazolidin-2-ones were repeated using potassium bis(trimethylsilyl) amide to effect

deprotonation. The increase in enolate reactivity now even allowed alkylation with ethyl iodide to proceed, if the reactions were allowed to warm to -30°C before being quenched (Scheme 10).



R^1 =		
CH_3		**13**
CH_2CH_3		**45**
CH_2Ph		**46**

R^1 =	R^2 =	
CH_3	CH_2Ph	**35**
CH_3	$CH_2CH{=}CH_2$	**47**
CH_3	CH_2CH_3	**29**
CH_2CH_3	CH_3	**27**
CH_2Ph	CH_3	**33**
CH_2Ph	CH_2CH_3	**39**

Scheme 10

As may be seen in the table below, the diastereoselectivities of these alkylation reactions are much higher than were observed in the reactions of the analogous sodium enolates. Indeed, in the case of the reaction of the potassium enolate derived from **13** with allyl bromide, no second diastereoisomer could be detected in the 300 MHz ^{1}H n.m.r. spectrum of the crude reaction product (Table 3).

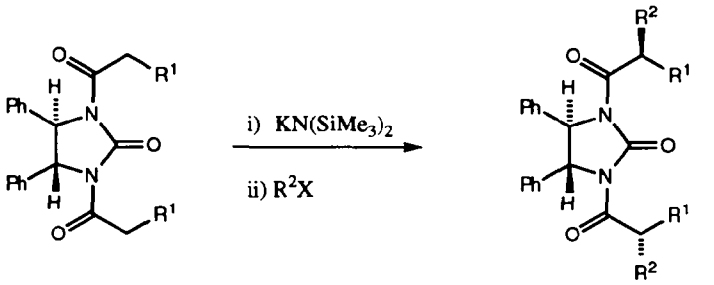
Table 3 Yields, product ratios and diastereofacial selectivities for the alkylation of potassium enolates of 1,3-diacyl-*trans*-4,5-tetramethyleneimidazolidin-2-ones as a function of enolate substituent (R^1) and electrophile (R^2X).

Starting Material	R^1	R^2X	Major Product	Ratio of Products*	Selectivity#	Yield
13	Me	BnBr	**35**	94 : 5 :(1)	97 : 3	72%
13	Me	C_3H_5Br	**47**	>96 : <3 :(0)	>98 : 2	81%
13	Me	EtI	**29**	85 : 14 :(1)	92 : 8	64%
45	Et	MeI	**27**	76 : 22 :(2)	88 : 12	66%
46	CH_2Ph	MeI	**33**	85 : 14 :(1)	92 : 8	72%
46	CH_2Ph	EtI	**39**	76 : 22 :(2)	88 : 12	71%

* Values in parentheses are calculated # Calculated from the ratio of major to second diastereoisomer

The greater levels of diastereoselection observed in these reactions can be rationalised as being a consequence of alkylation occurring at lower temperature than was possible when the sodium enolates were employed. That the potassium enolates are more reactive is clearly demonstrated by the successful reactions they undergo with ethyl iodide. Presumably the lower the temperature at which alkylation occurs, the greater the amount of the enolate which exists in the desired chelated form. Thus, in these reactions with potassium enolates, the levels of diastereoselection observed are approximately the same as were observed in the reactions of lithium and sodium enolates derived from N-acyl oxazolidinones[5]. This would tend to suggest that the stereoselectivity is at a level which cannot be enhanced by the structure of the chiral auxiliary but is limited by those variables associated with

the electrophile, such as its steric size. For this reason the reactions were repeated on the series of 1,3-diacylimidazolidin-2-ones derived from 1,2-diphenyl-1,2-diaminoethane in an attempt to see whether the increased steric bulk of the groups shielding the *endo* face of the enolate would lead to any enhancement in the stereoselectivity of alkylation (Scheme 11).



R^1 =		
CH_3	**14**	
CH_2CH_3	**50**	
CH_2Ph	**51**	

R^1 =	R^2 =	
CH_3	CH_2CH_3	**32**
CH_3	CH_2Ph	**38**
CH_2CH_3	CH_3	**27**
CH_2Ph	CH_3	**36**
CH_2Ph	CH_2CH_3	**42**

Scheme 11

Surprisingly, the diastereoselectivities were even lower than were recorded for the analogous reactions with sodium enolates although the chemical yields were generally higher (Table 4).

Table 4 Yields, product ratios and diastereofacial selectivities for the alkylation of potassium enolates of 1,3-diacyl-*trans*-4,5-diphenylimidazolidin-2-ones as a function of enolate substituent (R^1) and electrophile (R^2X).

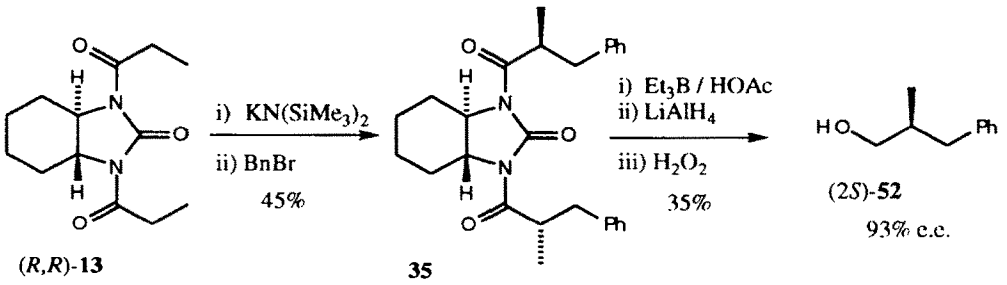
Starting Material	R^1	R^2X	Major Product	Ratio of Products	Selectivity#	Yield
14	Me	EtI	**32**	39 : 47 : 14	63 : 37	66%
14	Me	BnBr	**38**	30 : 49 : 21	55 : 45	79%
50	Et	MeI	**27**	36 : 48 : 16	60 : 40	80%
51	CH_2Ph	MeI	**36**	53 : 40 : 7	72 : 28	91%
51	CH_2Ph	EtI	**42**	66 : 31 : 3	81 : 19	56%

Calculated from the ratio of major to second diastereoisomer

Use of a phenyl group to block the *endo* face of each of the two enolates is clearly less effective, with both sodium and potassium enolates, than when the two blocking groups are the α-methylene groups of a cyclohexyl ring. It is difficult to see how a change in the nature of these substituents can greatly influence the ability of the imidazolidin-2-one carbonyl group to chelate the two enolate counterions and therefore it is more likely that the difference is due to steric effects.

The high diastereoselectivity of alkylation enjoyed by potassium enolates of 1,3-diacyl-*trans*-4,5-tetramethyleneimidazolidin-2-ones suggested that these reactions could be used with homochiral starting materials to prepare chiral alcohols in high enantiomeric excess. Benzylation of the potassium enolate derived

from (*R,R*)-1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one (*R,R*)-**13**[1] proceeded in 45% yield and with a diastereofacial selectivity of 97:3, identical to that observed in the reaction of the corresponding racemic enolate. We have previously described the reductive cleavage of both acyl side-chains of products resulting from the aldol reactions of dibutylboron enolates of 1,3-diacylimidazolidin-2-ones[8]. These compounds may be deacylated using lithium aluminium hydride provided that the β-hydroxy groups are protected so as to suppress the retro-aldol reaction[11]. Reductive cleavage of homochiral **35** was achieved by direct treatment of a THF solution of the substrate with excess lithium aluminium hydride at -20°C. The specific rotation of the alcohol obtained from the reaction was found to be $[\alpha]_D^{20}$ -10.2 (c = 1.1, benzene), corresponding to an enantiomeric excess of 93% of the (*S*)-enantiomer based on the literature value of $[\alpha]_D^{20}$ +11.0 (c = 1.1, benzene) for the (*R*)-enantiomer[11]. This allowed the configuration of **35** to be confirmed, and indicated that the sense of asymmetric induction in these reactions was as expected on the basis of the work reported on N-acyl oxazolidinones[5] (Scheme 12).



Scheme 12

As the diastereofacial selectivity in the alkylation reaction was 97:3, reductive cleavage should give a 97:3 mixture of the (*S*)- and (*R*)-enantiomers of **52**, corresponding to an enantiomeric excess of 94% for the S enantiomer. This was confirmed by the observed enantiomeric excess for **52** of 93%, based on the specific rotation which is within the limits of experimental error, and indicates that this method of acyl cleavage proceeds without significant racemisation. The low yield in the reductive cleavage was attributed to difficulties in isolating and purifying the product by chromatography. The reductive cleavage reaction was, therefore, repeated on racemic **35** and, by isolating the product by simply passing the crude product through a plug of silica gel, to remove the unwanted chiral auxiliary, the yield was optimised to 94%.

In order to make a comparison with Evans' results on lithium enolates on N-acyl oxazolidinones, benzylation of the lithium enolate of **13** was attempted. Formation of the enolate at -78°C, addition of benzyl bromide and warming to 0°C gave a clean dialkylation with diastereoisomers **33-35** being formed in a ratio of 5 : 35 : 60. This is consistent with both alkylation steps proceeding with the same diastereofacial selectivity, 78:22. This is only slightly lower than is observed in the corresponding reaction of the sodium enolate of **13**, a result that is in line with observations on the alkylation of N-acyl oxazolidinone enolates[5].

In summary, potassium enolates of 1,3-diacyl-*trans*-4,5-tetramethyleneimidazolidin-2-ones undergo highly diastereoselective alkylation reactions to afford products which are readily cleaved under reductive conditions to give 2-substituted chiral alcohols in high enantiomeric excess.

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 as 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[12]. Flash chromatography was performed on silica gel (43-60 μm) under positive pressure. Cy-C_α refers to the methylene group of the cyclohexyl ring α- to the bridgehead, Cy-C_β refers to that β- to the bridgehead.

*Methylation of 1,3-Dipropionyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione* **6** *to give* **7** - **10** - Sodium bis(trimethylsilyl)amide (3.0ml, 3.00mmol) was added to a solution of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **6** (268mg, 1.00mmol) in THF at -78°C with stirring for 1 h, during which time the solution became somewhat turbid. Methyl iodide (0.3ml, excess) was added and the reaction allowed to stir at -78°C for a further 2 h before being quenched by addition of saturated aqueous ammonium chloride solution (2ml). After warming to ambient temperature, 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 give a beige solid. Chromatography on silica gel gave an inseparable mixture of **7** and **8** with dichloromethane as eluent (92mg, 40%). Major diastereoisomer **7**, ν_{max} ($CHCl_3$)/cm^{-1} 1699 (N-CO), 1456 (N-CS-N) and 1328 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 7.01 (1H, bs, NH), 3.60, 3.22 (2H, dt, J 11.2, 3.1 Hz, CHN), 3.55, 3.04 (2H, ABX_3 system, J_{AB} 17.3 Hz, J_{AX} 7.3 Hz, J_{BX} 7.3 Hz, $COCH_2$), 2.65 (1H, m, Cy-C_α), 1.88 (2H, m, Cy-C_α), 1.55-1.22 (5H, m, Cy-C_α (1H), Cy-C_β) and 1.18 (3H, t, J 7.4 Hz, CH_2CH_3); δ_C (50 MHz, $CDCl_3$) 181.5, 179.2, 67.4, 60.8, 32.4, 28.7, 28.5, 24.0, 23.9, and 8.9; m/z 213 (MH^+, 100%); exact mass calcd 212.0983, found 212.0986. Minor diastereoisomer **8**, ν_{max} ($CHCl_3$)/cm^{-1} 1699 (N-CO), 1456 (N-CS-N) and 1328 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 7.01 (1H, bs, NH), 4.51 (1H, septet, J 6.9 Hz, COCH), 3.59, 3.23 (2H, dt, J 11.2, 3.1 Hz, CHN), 2.80 (1H, m, Cy-C_α), 2.10 (2H, m, Cy-C_α), 1.55-1.22 (5H, m, Cy-C_α (1H), Cy-C_β), 1.20 (3H, d, J 6.6 Hz, $CHCH_3$) and 1.19 (3H, d, J 6.6 Hz, $CHCH_3$); δ_C (50 MHz, CDCl3) 181.5, 179.2, 67.8, 60.8, 35.2, 29.1, 28.7, 24.0, 23.9, 20.8 and 17.4; m/z 227 (MH^+, 100%); exact mass calcd 226.1140, found 226.1139. Elution with ethyl acetate gave a second fraction containing **9** and **10** which could not be separated (72 mg, 33%). Major diastereoisomer **9**, ν_{max} ($CHCl_3$)/cm^{-1} 1675 (N-CO) and 1540 N-CS-N); δ_H (300 MHz, $CDCl_3$) 3.35, 3.23 (2H, dt, J 11.1, 3.0 Hz, CHN), 2.56 (1H, m, Cy-C_α), 2.45 (2H, m, $COCH_2$), 2.41 (3H, s, SCH_3), 2.36 (1H, m, Cy-C_α), 1.93-1.35 (6H, m, Cy-C_α (2H), Cy-C_β (4H)), 1.17 (3H, t, J 7.3 Hz, CH_2CH_3); ^{13}C n.m.r. δ_C 173.9, 162.4, 72.5,

68.0, 31.3, 30.8, 29.6, 24.9, 24.7, 15.1 and 8.3; m/z 227 (MH^+, 100%). Minor diastereoisomer **10**, δ_H (300 MHz, $CDCl_3$) 3.34, 3.23 (2H, m, C<u>H</u>N), 2.87 (1H, septet, J 7.0 Hz, C<u>H</u>$(CH_3)_2$), 2.42 (3H, s, SC<u>H</u>$_3$), 2.36 (2H, m, Cy-C_α), 1.91 (2H, m, Cy-C_α), 1.62-1.35 (4H, m, Cy-C_β), 1.18 (3H, d, J 7.0 Hz, CH(C<u>H</u>$_3)_2$) and 1.17 (3H, d, J 7.0 Hz, CH(C<u>H</u>$_3)_2$); δ_C (50 MHz, $CDCl_3$) 173.9, 162.4, 72.4, 68.3, 33.5, 31.2, 30.8, 24.9, 24.7, 19.0 and 15.1; m/z 241 (MH^+, 100%).

1-Propionyl-2-thiomethoxy-trans-*4,5-tetramethylene-4,5-dihydroimidazole* **9** *from* **12** - Treatment of 2-thiomethoxy-*trans*-4,5-tetramethylene-4,5-dihydroimidazole **12** (510mg, 3.00mmol) with pyridine (0.5ml, 6.27mmol) and propionyl chloride (0.6ml, 6.90mmol) in dichloromethane (15ml) gave a beige solid, after extended stirring (15 h) and work-up. Chromatography on silica gel (eluting with ethyl acetate) gave **9** as a white crystalline solid (433mg, 64%). The spectroscopic data recorded on this sample agreed with that obtained above. m.p. 83-85°C (Found; C, 58.7; H, 8.05;N, 12.5. $C_{11}H_{18}N_2OS$ requires C, 58.4; H, 8.0; N, 12.4%).

1,3-Di-i-propyl-trans-*4,5-tetramethyleneimidazolidin-2-one* **15** - Sodium bis(trimethylsilyl)amide (3.0ml of a 1.0M solution in THF, 3.00mmol) was added dropwise to a THF solution of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **13** (252mg, 1.00mmol) at -78°C with stirring (-78°C, 1 h). Methyl iodide (0.3ml, excess) was added and the reaction stirred at -78°C for 3 h before being allowed to warm to -30°C over 1 h. The reaction was quenched by addition of an aqueous pH 7 phosphate buffer solution (1ml), the volatiles were removed *in vacuo* and the residue triturated with dichloromethane (3x10ml). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo* to give a cream solid. Chromatography on silica gel with dichloromethane as eluent gave **15** as a white solid (193mg, 69%), m.p. 118-120°C (Found; C, 64.6; H, 8.6; N, 10.1. $C_{15}H_{24}N_2O_3$ requires C, 64.3; H, 8.6; N, 10.0%); ν_{max} 1742 (N-CO-N) and 1698 (N-CO); δ_H (300 MHz, $CDCl_3$) 3.68 (2H, septet, J 6.8 Hz, COC<u>H</u>), 3.41 (2H, m, C<u>H</u>N), 2.83 (2H, m, Cy-C_α), 1.88 (2H, m, Cy-C_α), 1.49-1.26 (4H, m, Cy-C_β), 1.19 (3H, d, J 6.9 Hz, CHC<u>H</u>$_3$) and 1.18 (3H, d, J 6.7 Hz, CHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 181.0 151.5, 60.4, 34.5, 28.6, 24.2, 20.1 and 17.7; m/z 281 (MH^+, 100%).
Enolisation of **13** (252mg, 1.00mmol) with potassium bis(trimethylsilyl)amide (5.2ml, 3.90mmol), followed by addition of methyl iodide (0.4ml, excess) with stirring (-78°C, 3 h) gave **15** after work-up and chromatography (245mg, 87%).

1,3-Di-i-propyl-trans-*4,5-diphenylimidazolidin-2-one* **16** - In a manner analogous to the synthesis of **15**, treatment of 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one **14** (350mg, 1.00mmol) with sodium bis(trimethylsilyl)amide (3.0ml of a 1.0M solution in THF, 3.00mmol) and methyl iodide (0.2ml, excess) at -78°C followed by warming to -30°C gave a clear oil. Chromatography on silica gel with dichloromethane as eluent gave **16** as a clear oil which slowly solidified (310mg, 82%), (Found; C, 72.9; H, 7.2; N, 7.2. $C_{23}H_{26}N_2O_3$ requires C, 73.0; H, 6.9; N, 7.4%); ν_{max} ($CHCl_3$)/cm^{-1} 1748 (N-CO-N) and 1698 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.43-7.34 (6H, m, Ph), 7.28-7.23 (4H, m, Ph), 5.15 (2H, br s, PhC<u>H</u>), 3.91 (2H, septet, J 6.9 Hz, COC<u>H</u>), 1.22 (3H, d, J 6.9 Hz, CHC<u>H</u>$_3$) and 1.21 (3H, d, J 6.9 Hz, CHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 177.7, 151.6, 140.1, 129.4, 128.7, 125.1, 62.4, 33.5, 18.9 and 18.5; m/z 379 (MH^+, 100%).

1,3-Di(2-methylbutanoyl)-trans-*4,5-tetramethyleneimidazolidine-2-thione* **21** - To a solution of *trans*-4,5-tetramethyleneimidazolidine-2-thione **11** (800mg, 5.12mmol) in dichloromethane (20ml) at ambient temperature was added 4-(dimethylamino)pyridine (~8mg, cat) and pyridine (1.01ml, 12.5mmol). The reaction was allowed

to stir for 5 min before cautious addition of 2-methylbutanoyl chloride **18** (1.80g, 14.9mmol) which caused an exothermic reaction bringing the reaction to reflux. The reaction was allowed to stir at ambient temperature for 12 h before the reaction was quenched by addition of water (20ml). The organic layer was separated and the combined organic layers dried over $MgSO_4$ before being evaporated *in vacuo* to give a beige solid. Chromatography on silica gel with dichloromethane as eluent gave a 25:50:25 mixture of the three diastereoisomers of **21** as a white crystalline solid (1.30g, 78%). Although chromatographic separation of diastereoisomers was not possible, the mixture was characterised, m.p. 76-78°C (Found; C, 62.8; H, 8.75; N, 8.6. $C_{17}H_{28}N_2O_2S$ requires C, 62.9; H, 8.7; N, 8.6%); ν_{max} ($CHCl_3$)/cm^{-1} 1703 (N-CO), 1456 (N-CS-N) and 1328 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 4.16-4.03 (2H, m, COC<u>H</u>), 3.51 (2H, m, C<u>H</u>N), 2.54 (2H, m, Cy-Cα), 1.89 (2H, m, Cy-Cα), 1.95-1.69 (2H, m, C<u>H</u>$_2$CH$_3$), 1.58-1.41 (6H, m, Cy-Cβ, C<u>H</u>$_2$CH$_3$), 1.23-1.15 (6H, d, J 7.0 Hz, CHC<u>H</u>$_3$) and 0.99-0.91 (6H, t, J 7.4 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 182.5, 180.9, 63.9-63.8, 43.2-42.9, 28.0-24.0, 28.6, 24.1, 18.1-15.0 and 11.2; m/z 325 (MH^+, 100%).

1,3-Di(2-methylbutanoyl)-trans-*4,5-diphenylimidazolidine-2-thione* **22** - In a manner analogous to that described for the synthesis of **21** from **11**, treatment of *trans*-4,5-diphenylimidazolidine-2-thione **17** (750mg, 2.95mmol) with pyridine (0.60ml, 7.45mmol) and 2-methylbutanoyl chloride **18** (1.0ml, 8.29mmol) in dichloromethane (10ml), with 4-(dimethylamino)pyridine as catalyst, gave a brown oil after work-up. Chromatography on silica gel with dichloromethane as eluent gave a 25:50:25 mixture of the three diastereoisomers of **22** as a yellow oil (972mg, 79%). Although chromatographic separation of diastereoisomers was not possible, the mixture was characterised, (Found; C, 71.0; H, 7.5; N, 6.4. $C_{25}H_{30}N_2O_2S$ requires C, 71.1; H, 7.2; N, 6.6%); ν_{max} ($CHCl_3$)/cm^{-1} 1692 (N-CO), 1351 (N-CS-N) and 700 (Ph:C-H); δ_H (300 MHz, $CDCl_3$) 7.43-7.32 (10H, m, Ph), 5.37-5.27 (2H, s, PhC<u>H</u>), 4.61-4.44 (2H, m, COC<u>H</u>), 1.88-1.71 (2H, m, C<u>H</u>$_2$CH$_3$), 1.52-1.34 (2H, m, C<u>H</u>$_2$CH$_3$), 1.20-1.13 (6H, d, J 6.8 Hz, CHC<u>H</u>$_3$) and 0.94-0.76 (6H, t, J 7.4 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 180.5, 179.3-177.5, 140.7-139.6, 129.4, 128.9-128.5 , 125.8-125.1, 67.4-66.9, 40.9-40.2, 27.1-26.5, 16.6-15.9 and 11.4-11.1; m/z 423 (MH^+, 100%).

1,3-Di(3-phenyl-2-methylpropionyl)-trans-*4,5-tetramethyleneimidazolidine-2-thione* **23** - In a manner analogous to that described for the synthesis of **21** from **11**, treatment of *trans*-4,5-tetramethyleneimidazolidine-2-thione **11** (800mg, 5.12mmol) with pyridine (1.0ml, 12.5mmol) and 3-phenyl-2-methylpropionyl chloride **19** (2.60g, 14.2mmol) in dichloromethane (20ml), with 4-(dimethylamino)pyridine as catalyst, gave, after work-up, a 25:50:25 mixture of the three diastereoisomers of **23** as a white crystalline solid (1.61g, 94%). Although chromatographic separation of diastereoisomers was not possible, the mixture was partially characterised, (Found; C, 72.25; H, 7.3; N, 6.3. $C_{27}H_{32}N_2O_2S$ requires C, 72.3; H, 7.2; N, 6.2%); ν_{max} ($CHCl_3$)/cm^{-1} 1701 (N-CO), 1451 (N-CS-N) and 1327 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 7.32-7.15 (10H, m, Ph), 4.57-4.43 (2H, m, COC<u>H</u>), 3.52-3.07 (2H, m, C<u>H</u>N), 2.99-2.59 (4H, m, PhC<u>H</u>$_2$), 2.56-2.12 (2H, m, Cy-Cα), 1.91-1.72 (2H, m, Cy-Cα), 1.52-1.22 (4H, m, Cy-Cβ) and 1.33-1.06 (6H, d, J 7.0 Hz, C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 182.1, 139.7-138, 129.5-129.2, 128.4, 126.3, 64.3-63.7, 43.3, 42.1-37.4, 27.9-27.3, 24.0-23.8 and 17.8-16.3; m/z 449 (MH^+, 100%).

1,3-Di(3-phenyl-2-methylpropionyl)-trans-*4,5-diphenylimidazolidine-2-thione* **24** - In a manner analogous to that described for the synthesis of **21** from **11**, treatment of *trans*-4,5-diphenylimidazolidine-2-thione **17**

(1.00g, 6.40mmol) with pyridine (1.0ml, 12.5mmol) and 3-phenyl-2-methylpropionyl chloride **19** (2.36g, 12.9mmol) in dichloromethane (25ml), with 4-(dimethylamino)pyridine as catalyst, gave a brown oil after work-up. Chromatography on silica gel with dichloromethane as eluent gave a 25:50:25 mixture of the three diastereoisomers of **24** as a colourless oil (1.77g, 87%). Although chromatographic separation of diastereoisomers was not possible, the mixture was partially characterised, (Found; C, 77.1; H, 6.6. $C_{35}H_{34}N_2O_2S$ requires C, 76.9; H, 6.3%); ν_{max} ($CHCl_3$)/cm^{-1} 1693 (N-CO), 1496 (N-CS-N) and 1351 (N-CS-N); ^1H n.m.r. δ_H (300 MHz, $CDCl_3$) 7.42-6.93 (20H, m, Ph), 5.28-5.19 (2H, s, PhC<u>H</u>), 5.05-4.88 (2H, m, COC<u>H</u>), 3.27-2.37 (4H, m, PhC<u>H</u>$_2$) and 1.23-1.07 (6H, d, J 6.8 Hz, C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 182.1, 178.7-178.5, 139.6-139.2, 129.4-129.1, 128.5, 126.1-125.5, 67.0-66.8, 41.4-40.8, 39.8-38.9 and 17.2-16.3; m/z 547 (MH^+, 100%).

1,3-Di(2-benzylbutanoyl)-trans-*4,5-tetramethyleneimidazolidine-2-thione* **25** - In a manner analogous to that described for the synthesis of **21** from **11**, treatment of *trans*-4,5-tetramethyleneimidazolidine-2-thione **11** (800mg, 5.12mmol) with pyridine (1.0ml, 12.5mmol) and 2-benzylbutanoyl chloride **20** (3.00g, 15.3mmol) in dichloromethane (25ml), with 4-(dimethylamino)pyridine as catalyst, gave a yellow oil after work-up. Chromatography on silica gel with dichloromethane as eluent gave a 25:50:25 mixture of the three diastereoisomers of **25** as a white crystalline solid (2.09g, 85%). Although chromatographic separation of diastereoisomers was not possible, the mixture was partially characterised, (Found; C, 73.0; H, 7.85; N, 6.1. $C_{29}H_{36}N_2O_2S$ requires C, 73.3; H, 7.6; N, 5.9); ν_{max} ($CHCl_3$)/cm^{-1} 1700 (N-CO) and 1327 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 7.36-7.13 (10H, m, Ph), 4.65-4.41 (2H, m, COC<u>H</u>), 3.71-2.91 (2H, m, C<u>H</u>N), 3.02-2.55 (4H, m, PhC<u>H</u>$_2$), 2.53-2.09 (2H, m, Cy-C$_\alpha$), 1.94-1.72 (2H, m, Cy-C$_\alpha$), 1.76-1.50 (4H, m, C<u>H</u>$_2$CH$_3$), 1.54-1.30 (4H, m, Cy-C$_\beta$) and 1.14-0.73 (6H, t, J 6.8 Hz, C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 181.4, 178.0, 139.8, 129.5, 128.4, 126.3, 64.2, 49.6, 35.8, 28.3, 25.5, 24.1 and 10.9; m/z 477 (MH^+, 100%).

1,3-Di(2-benzylbutanoyl)-trans-*4,5-diphenylimidazolidine-2-thione* **26** - In a manner analogous to that described for the synthesis of **21** from **11**, treatment of *trans*-4,5-diphenylimidazolidine-2-thione **17** (800mg, 3.15mmol) with pyridine (0.6ml, 7.45mmol) and 2-benzylbutanoyl chloride **20** (1.30g, 6.61mmol) in dichloromethane (25ml), with 4-(dimethylamino)pyridine as catalyst, gave a yellow oil after work-up. Chromatography on silica gel with dichloromethane as eluent gave a 25:50:25 mixture of the three diastereoisomers of **26** as a colourless oil (1.66g, 92%). Although chromatographic separation of diastereoisomers was not possible, the mixture was partially characterised, (Found; C, 77.5; H, 7.1. $C_{37}H_{38}N_2O_2S$ requires C, 77.3; H, 6.7%); ν_{max} ($CHCl_3$)/cm^{-1} 1691 (N-CO), 1496 (N-CS-N) and 1351 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 7.41-6.91 (20H, m, Ph), 5.29-5.20 (2H, s, PhC<u>H</u>), 5.07-4.94 (2H, m, COC<u>H</u>), 3.27-2.55 (4H, m, PhC<u>H</u>$_2$), 1.95-1.44 (4H, m, C<u>H</u>$_2$CH$_3$) and 0.93-0.70 (6H, d, J 7.3 Hz, C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 181.3, 178.2-177.7 , 139.9-139.1, 129.4-129.1, 128.5, 126.4-125.0, 67.4-66.4, 47.5-47.1, 37.6-37.1, 25.0-24.6 and 11.5-10.8; m/z 575 (MH^+, 100%).

1,3-Di(2-methylbutanoyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **28** - To a solution of the three diastereoisomers of 1,3-di(2-methylbutanoyl)-*trans*-4,5-tetramethylene-imidazolidine-2-thione **21** (301mg, 0.93mmol) in dichloromethane (15ml) at ambient temperature was added mercury (II) acetate (415mg, 1.30mmol). The reaction was allowed to stir for 12h before being filtered through celite (washed with dichloromethane) and then stirred with fresh mercury (II) acetate (135mg, 0.42mmol). At the end of this second

period, the reaction mixture was filtered through celite, dried over $MgSO_4$ and evaporated down to a cream solid. Chromatography on silica gel with dichloromethane as eluent gave a 25:50:25 mixture of the three diastereoisomers **27-29** as a white crystalline solid (284mg, 99%). m.p. 95-97°C (Found; C, 66.3; H, 9.5; N, 9.4. $C_{17}H_{28}N_2O_3$ requires C, 66.2; H, 9.15; N, 9.1%). Major diastereoisomer **28** (by difference spectroscopy), ν_{max} ($CHCl_3$)/cm^{-1} 1742 (N-CO-N) and 1696 (N-CO); δ_H (300 MHz, $CDCl_3$) 3.55 (2H, m, COC<u>H</u>), 3.40 (2H, m, C<u>H</u>N), 2.83 (2H, m, Cy-Cα), 1.88 (2H, m, Cy-Cα), 1.83-1.64 (2H, m, C<u>H</u>$_2$CH$_3$), 1.59-1.37 (2H, m, C<u>H</u>$_2$CH$_3$), 1.52-1.26 (4H, m, Cy-Cβ), 1.17 (3H, d, J 7.0 Hz, CHC<u>H</u>$_3$), 1.16 (3H, d, J 6.7 Hz, CHC<u>H</u>$_3$), 0.96 (3H, t, J 7.4 Hz, CH$_2$C<u>H</u>$_3$) and 0.89 (3H, t, J 7.4 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 180.4, 149.4, 60.4, 60.3, 41.1, 41.0, 28.5, 27.7, 25.3, 24.2, 17.8, 15.3, 11.5 and 11.1; m/z 309 (MH^+, 100%).

1,3-Di(2-methylbutanoyl)-trans-*4,5-diphenylimidazolidin-2-one* **31** - In an analogous manner to that described above for the synthesis of **27-29** from **21**, treatment of the 25:50:25 mixture of the three diastereoisomers of 1,3-di(2-methylbutanoyl)-*trans*-4,5-diphenylimidazolidine-2-thione **22** (940mg, 2.22mmol) with two batches of mercury (II) acetate (750mg, 2.35mmol and 300mg, 0.94mmol) in dichloromethane (2x25ml) gave an orange oil. Chromatography on silica gel with dichloromethane as eluent gave a 25:50:25 mixture of **30-32** as a yellow oil (756mg, 84%). (Found; C, 73.4; H, 7.3; N, 6.5. $C_{25}H_{30}N_2O_3$ requires C, 73.85; H, 7.4; N, 6.9%). Major diastereoisomer **31** (by difference spectroscopy), ν_{max} ($CHCl_3$)/cm^{-1} 1734 (N-CO-N) and 1687 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.43-7.31 (6H, m, Ph), 7.26-7.23 (4H, m, Ph), 5.15 (2H, br s, PhC<u>H</u>), 3.80 (2H, m, COC<u>H</u>), 1.83-1.73 (2H, m, C<u>H</u>$_2$CH$_3$), 1.54-1.41 (2H, m, C<u>H</u>$_2$CH$_3$), 1.19 (3H, d, J 6.8 Hz, CHC<u>H</u>$_3$), 1.18 (3H, d, J 6.8 Hz, CHC<u>H</u>$_3$), 0.94 (3H, t, J 7.4 Hz, CH$_2$C<u>H</u>$_3$) and 0.84 (3H, t, J 7.4 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 177.5, 177.3, 151.8, 140.2, 140.1, 129.4, 128.7, 125.3, 125.1, 62.4, 40.1, 39.8, 26.4, 26.3, 16.5, 16.0, 11.5 and 11.1; m/z 407 (MH^+, 100%).

1,3-Di(3-phenyl-2-methylpropionyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **34** - In an analogous manner to that described above for the synthesis of **27-29** from **21**, treatment of the 25:50:25 mixture of the three diastereoisomers of 1,3-di(3-phenyl-2-methylpropionyl)-*trans*-4,5-tetramethyleneimidazolidine-2-thione **23** (501mg, 1.12mmol) with two batches of mercury (II) acetate (500mg, 1.57mmol and 220mg, 0.69mmol) in dichloromethane (2x25ml) gave a white solid. Chromatography on silica gel with dichloromethane as eluent gave a 25:50:25 mixture of **33-35** as a white crystalline solid (408mg, 84%); m.p. 97-99°C (Found; C, 74.9; H, 7.8; N, 6.4. $C_{27}H_{32}N_2O_3$ requires C, 75.0; H, 7.5; N, 6.5%). Major diastereoisomer **34** (by difference spectroscopy), ν_{max} ($CHCl_3$)/cm^{-1} 1743 (N-CO-N) and 1697 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.31-7.14 (10H, m, Ph), 4.01-3.88 (2H, m, COC<u>H</u>), 3.28, 3.02 (2H, dt, J 12.0, 2.8 Hz, C<u>H</u>N), 3.16, 2.57 (2H, ABX system, J_{AB} 13.6 Hz, J_{AX} 6.1 Hz, J_{BX} 8.5 Hz, PhC<u>H</u>$_2$), 2.91, 2.76 (2H, ABX system, J_{AB} 13.4 Hz, J_{AX} 5.9 Hz, J_{BX} 8.4 Hz, PhC<u>H</u>$_2$), 2.75 (1H, m, Cy-Cα), 2.68 (1H, m, Cy-Cα), 1.81 (2H, m, Cy-Cα), 1.56-1.24 (3H, m, Cy-Cβ), 1.22 (3H, d, J 6.7 Hz, CHC<u>H</u>$_3$), 1.14 (3H, d, J 7.0 Hz, CHC<u>H</u>$_3$) and 1.01-0.89 (1H, m, Cy-Cβ); δ_C (50 MHz, $CDCl_3$) 179.7, 179.4, 153.9, 139.9, 139.3, 129.5, 129.3, 128.4, 128.3, 126.5, 126.3, 60.3, 41.5, 41.4, 41.2, 38.4, 28.5, 28.0, 24.1, 17.6 and 16.0; m/z 433 (MH^+, 100%).

1,3-Di(3-phenyl-2-methylpropionyl)-4,5-trans-*diphenylimidazolidin-2-one* **37** - In an analogous manner to that described above for the synthesis of **27-29** from **21**, treatment of the 25:50:25 mixture of the three diastereoisomers of 1,3-di(3-phenyl-2-methylpropionyl)-*trans*-4,5-diphenylimidazolidine-2-thione **24** (1.75g,

3.20mmol) with two batches of mercury (II) acetate (1.00g, 3.14mmol and 250mg, 0.78mmol) in dichloromethane (2x30ml) gave a yellow oil. Chromatography through a short plug of silica gel (eluting with dichloromethane) gave a 25:50:25 mixture of **36-38** as a clear oil (1.40g, 83%). (Found; C, 79.0; H, 6.7; N, 5.0. $C_{35}H_{34}N_2O_3$ requires C, 79.2; H, 6.5; N, 5.3%). Major diastereoisomer **37** (by difference spectroscopy), ν_{max} ($CHCl_3$)/cm^{-1} 1734 (N-CO-N) and 1689 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.40-7.17 (16H, m, Ph), 7.09-6.86 (4H, m, Ph), 5.07, 5.05 (2H, AB system, J_{AB} 1.7 Hz, PhC<u>H</u>), 4.30-4.22 (2H, m, COC<u>H</u>), 3.12, 2.71 (2H, ABX system, J_{AB} 13.4 Hz, J_{AX} 5.3 Hz, J_{BX} 8.1 Hz, PhC<u>H</u>$_2$), 3.08, 2.53 (2H, ABX system, J_{AB} 13.3 Hz, J_{AX} 6.5 Hz, J_{BX} 8.0 Hz, PhC<u>H</u>$_2$), 1.22 (3H, d, J 6.8 Hz, CHC<u>H</u>$_3$) and 1.16 (3H, d, J 6.8 Hz, CHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 176.7-, 176.6, 151.6, 139.9, 139.7, 139.5, 139.3, 129.4, 128.6, 126.4, 125.3, 125.0, 62.4, 62.2, 40.4, 40.3, 39.6, 39.2, 17.0 and 16.2; m/z 531 (MH^+, 100%).

1,3-Di(2-benzylbutanoyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **40** - In an analogous manner to that described above for the synthesis of **27-29** from **21**, treatment of the 25:50:25 mixture of the three diastereoisomers of 1,3-di(2-benzylbutanoyl)-*trans*-4,5-tetramethyleneimidazolidine-2-thione **25** (2.00g, 4.20mmol) with two batches of mercury (II) acetate (2.20g, 6.90mmol and 750mg, 2.35mmol) in dichloromethane (2x30ml) gave a yellow oil. Chromatography on silica gel with dichloromethane as eluent gave a 25:50:25 mixture of **39-41** as a white crystalline solid (1.40g, 73%). An analytical sample was prepared by recrystallisation from ethanol. (Found; C, 76.0; H, 7.9; N 5.9. $C_{29}H_{36}N_2O_3$ requires C, 75.6; H, 7.9; N, 6.1%). Major diastereoisomer **40** (by difference spectroscopy), ν_{max} ($CHCl_3$)/cm^{-1} 1748 (N-CO-N) and 1693 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.32-7.09 (10H, m, Ph), 3.96 (2H, m, COC<u>H</u>), 3.23, 2.87 (2H, dt, J 11.1 Hz, 2.8 Hz, C<u>H</u>N), 3.11, 2.64 (2H, ABX system, J_{AB} 13.5 Hz, J_{AX} 6.7 Hz, J_{BX} 7.9 Hz, PhC<u>H</u>$_2$), 2.89, 2.76 (2H, ABX system, J_{AB} 13.5 Hz, J_{AX} 5.8 Hz, J_{BX} 9.7 Hz, PhC<u>H</u>$_2$), 2.76-2.56 (2H, m, Cy-Cα), 1.78 (2H, m, Cy-Cα), 1.91-1.52 (4H, m, C<u>H</u>$_2$CH$_3$), 1.48-1.23 (4H, m, Cy-Cβ), 1.02 (3H, d, J 7.4 Hz, CHC<u>H</u>$_3$) and 0.93 (3H, d, J 7.4 Hz, CHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 178.7, 153.9, 139.7, 139.3, 129.5, 129.2, 129.0, 128.3, 126.5, 126.2, 60.3, 60.1, 47.8, 39.8, 36.4, 28.4, 27.9, 25.2, 24.5, 24.4, 24.0, 11.5 and 11.4; m/z 461 (MH^+, 100%).

1,3-Di(2-benzylbutanoyl)-trans-*4,5-diphenylimidazolidin-2-one* **43** - In an analogous manner to that described above for the synthesis of **27-29** from **21**, treatment of the 25:50:25 mixture of the three diastereoisomers of 1,3-di(2-benzylbutanoyl)-*trans*-4,5-diphenyl-imidazolidine-2-thione **26** (1.66g, 2.89mmol) with two batches of mercury (II) acetate (1.00g, 3.14mmol and 350mg, 1.10mmol) in dichloromethane (2x30ml) gave a yellow oil. Chromatography on silica gel with dichloromethane as eluent gave a 25:50:25 mixture of **42-44** as a pale yellow oil (1.31g, 81%). (Found C, 79.5; H, 7.1; N, 5.0. $C_{35}H_{34}N_2O_3$ requires C, 79.5; H, 6.9; N, 5.0%). Major diastereoisomer **43** (by difference spectroscopy), ν_{max} ($CHCl_3$)/cm^{-1} 1747 (N-CO-N) and 1694 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.41-7.17 (16H, m, Ph), 6.89-6.65 (4H, m, Ph:H$_{ortho}$), 5.01, 4.98 (2H, AB system, J_{AB} 1.7 Hz, PhC<u>H</u>), 4.39 (2H, m, COC<u>H</u>), 2.95, 2.63 (2H, ABX system, J_{AB} 13.4 Hz, J_{AX} 6.8 Hz, J_{BX} 9.6 Hz, PhC<u>H</u>$_2$), 2.92, 2.78 (2H, ABX system, J_{AB} 13.4 Hz, J_{AX} 5.8 Hz, J_{BX} 7.7 Hz, PhC<u>H</u>$_2$), 1.76-1.53 (4H, m, C<u>H</u>$_2$CH$_3$), 0.92 (3H, d, J 7.4 Hz, CH$_2$C<u>H</u>$_3$) and 0.86 (3H, d, J 7.4 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 176.5, 176.3, 151.6, 140.3, 139.7, 139.5, 139.3, 129.3, 128.5, 126.3, 125.3, 125.1, 62.2, 62.1, 46.8, 46.7, 38.4, 38.2, 25.7, 25.6, 11.5 and 11.4; m/z 559 (MH^+, 100%).

1,3-Di(3-phenyl-2-methylpropionyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **35** - Treatment of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **13** (252mg, 1.00mmol) with sodium bis(trimethylsilyl)amide (3.0ml, 3.00mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of benzyl bromide (515mg, 3.00mmol) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 3:30:67 mixture of **33**-**35** as a white solid (334mg, 77%). Major diastereoisomer **35**, m.p. 76-77°C (Found C, 74.9; H, 7.5; N, 6.5. $C_{27}H_{32}N_2O_3$ requires C, 75.0; H, 7.5; N, 6.5%); ν_{max} ($CHCl_3$)/cm^{-1} 1743 (N-CO-N) and 1697 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.31-7.14 (10H, m, Ph), 3.92 (2H, sextet, J 6.8 Hz, COC<u>H</u>), 2.98 (2H, m, C<u>H</u>N), 2.93, 2.74 (4H, ABX system, J_{AB} 13.3 Hz, J_{AX} 8.4 Hz, J_{BX} 6.7 Hz, PhC<u>H</u>$_2$), 2.65 (2H, m, Cy-Cα), 1.76 (2H, m, Cy-Cα), 1.41-1.24 (4H, m, Cy-Cβ) and 1.21 (6H, d, J 6.7 Hz, CHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 179.3, 154.1, 139.3, 129.3, 128.3, 126.5, 60.5, 41.6, 41.2, 28.0, 24.1 and 16.1; m/z 433 (MH^+, 100%).

Enolisation of **13** (252mg, 1.00mmol) with potassium bis(trimethylsilyl)amide (5.2ml, 3.mmol), followed by addition of benzyl bromide (685mg, 4.0mmol) with stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave, after work-up, a 0:5:95 mixture of the diastereoisomers **33**-**35** (311mg, 72%).

1,3-Di(3-phenyl-2-methylpropionyl)-trans-*4,5-diphenylimidazolidin-2-one* **38** - Treatment of 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one **14** (350mg, 1.00mmol) with sodium bis(trimethylsilyl)amide (4.0ml, 4.00mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of benzyl bromide (685mg, 4.00mmol) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 9:41:50 mixture of **36**-**38** as a white solid (382mg, 72%). Major diastereoisomer **38**, ν_{max} ($CHCl_3$)/cm^{-1} 1734 (N-CO-N) and 1689 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.40-7.17 (16H, m, Ph), 7.09 (4H, m, Ph), 5.13 (2H, s, PhC<u>H</u>), 4.25 (2H, m, COC<u>H</u>), 3.15, 2.56 (4H, ABX system, J_{AB} 13.3 Hz, J_{AX} 6.5 Hz, J_{BX} 7.9 Hz, PhC<u>H</u>$_2$) and 1.17 (3H, d, J 6.8 Hz, CHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 176.8, 151.7, 139.9, 139.3, 129.5, 129.0, 128.5, 126.5, 125.3, 62.5, 40.4, 39.5 and 16.5; m/z 531 (MH^+, 100%).

Enolisation of **14** (175mg, 0.50mmol) with potassium bis(trimethylsilyl)amide (4.0ml, 2.00mmol), followed by addition of benzyl bromide (345mg, 2.00mmol) with stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave, after work-up, a 21:49:30 mixture of the diastereoisomers **36**-**38** (210mg, 79%).

1,3-Di(2-methylpent-4-enoyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **47** - Treatment of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **13** (252mg, 1.00mmol) with sodium bis(trimethylsilyl)amide (4.0ml, 4.00mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of allyl bromide (480mg, 4.00mmol) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave **47** (in a 75:25 mixture with a second diastereoisomer **48**) as a white solid (171mg, 52%). Major diastereoisomer **47**, ν_{max} ($CHCl_3$)/cm^{-1} 1734 (N-CO-N), 1690 (N-CO) and 1630 (C=C); δ_H (300 MHz, $CDCl_3$) 5.72 (1H, ddt, J 17.1, 10.0, 7.1 Hz, C<u>H</u>=CH$_2$), 5.03 (2H, m, CH=C<u>H</u>$_2$), 3.66 (2H, sextet, J 6.7 Hz, COC<u>H</u>), 3.39 (2H, m, C<u>H</u>N), 2.79 (2H, m, Cy-Cα), 2.41 (2H, quintet, J 6.8 Hz, C<u>H</u>$_2$CH=CH$_2$), 2.22 (2H, quintet, J 6.8 Hz, C<u>H</u>$_2$CH=CH$_2$), 1.87 (2H, m, Cy-Cα), 1.52-1.21 (4H, m, Cy-Cβ) and 1.17 (6H, d, J 6.8 Hz, CHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 179.4, 154.2, 135.2, 117.2, 60.5, 39.4, 38.9, 28.4, 24.1 and 15.5; m/z 333 (MH^+, 100%).

Enolisation of **13** (5.04mg, 2.00mmol) with potassium bis(trimethylsilyl)amide (12.0ml, 6.00mmol), followed by addition of allyl bromide (0.6ml, excess) with stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave, after work-up, a 50:50 mixture of the dialkylated and monoalkylated products **47** and **49**, with only a single diastereoisomer of each being observable. Chromatography on silica gel with dichloromethane:hexane (2:3) as eluent allowed separation and gave **47**, (212mg, 32%) and **49**, (199mg, 34%). Monoalkylated product **49**, m.p. 63-65°C (Found; C, 65.4; H, 8.1; N, 9.7. $C_{16}H_{24}N_2O_3$ requires C, 65.7; H, 8.3; N, 9.6%); ν_{max} ($CHCl_3$)/cm^{-1} 1738 (N-CO-N), 1691 (N-CO) and 1631 (C=C); δ_H (300 MHz, $CDCl_3$) 5.72 (1H, ddt, J 17.1, 10.0, 7.1 Hz, C<u>H</u>=CH_2), 5.03 (2H, m, CH=C<u>H</u>$_2$), 3.66 (2H, sextet, J 6.7 Hz, COC<u>H</u>), 3.39 (2H, m, C<u>H</u>N), 3.04, 2.77 (4H, ABX system, J_{AB} 17.6 Hz, J_{AX} 7.4 Hz, J_{BX} 7.4 Hz, COC<u>H</u>$_2$), 2.89 (1H, m, Cy-Cα), 2.79 (1H, m, Cy-Cα), 2.41 (1H, quintet, J 6.8 Hz, C<u>H</u>$_2$CH=CH_2), 2.22 (1H, quintet, J 6.8 Hz, C<u>H</u>$_2$CH=CH_2), 1.87 (2H, m, Cy-Cα), 1.52-1.21 (4H, m, Cy-Cβ), 1.17 (3H, d, J 6.8 Hz, CHC<u>H</u>$_3$) and 1.16 (3H, t, J 7.4 Hz, CHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 179.5, 177.0, 154.5, 135.2, 117.2, 60.5, 39.5, 38.9, 30.8, 28.8, 28.5, 24.2, 24.1, 15.5 and 8.3; m/z 293 (MH^+, 100%). The reaction was repeated using a larger excess of the base to give only the dialkylated material although with reduced stereocontrol (15:1) (268mg, 81%).

1,3-Di(2-methylbutanoyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **27** - Treatment of 1,3-dibutanoyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **45** (140mg, 0.50mmol) with sodium bis(trimethylsilyl)amide (2.0ml, 2.00mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of methyl iodide (0.3ml, excess) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 64:32:4 mixture of **27**-**29** as a white solid (91mg, 59%). Major diastereoisomer **27**, ν_{max} ($CHCl_3$)/cm^{-1} 1734 (N-CO-N) and 1688 (N-CO); δ_H (300 MHz, $CDCl_3$) 3.56 (2H, sextet, J 6.7 Hz, COC<u>H</u>), 3.40 (2H, m, C<u>H</u>N), 2.83 (2H, m, Cy-Cα), 1.88 (2H, m, Cy-Cα), 1.83-1.64 (2H, m, C<u>H</u>$_2$CH$_3$), 1.59-1.37 (2H, m, C<u>H</u>$_2$CH$_3$), 1.69-1.26 (4H, m, Cy-Cβ), 1.17 (3H, d, J 7.0 Hz, CHC<u>H</u>$_3$) and 0.96 (3H, t, J 7.4 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 180.4, 154.3, 60.3, 41.0, 28.6, 25.3, 24.2, 17.8 and 11.5; m/z 309 (MH^+, 100%).
Enolisation of **45** (140mg, 0.50mmol) with potassium bis(trimethylsilyl)amide (2.6ml, 1.95mmol), followed by addition of methyl iodide (0.2ml, excess) with stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave, after work-up, a 76:22:2 mixture of the diastereoisomers **27**-**29** (102mg, 66%).

1,3-Di(2-methylbutanoyl)-trans-*4,5-diphenylimidazolidin-2-one* **30** - Treatment of 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one **46** (189mg, 0.50mmol) with sodium bis(trimethylsilyl)amide (2.0ml, 2.00mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of methyl iodide (0.2ml, excess) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 63:33:4 mixture of **30**-**32** as a white solid (144mg, 71%). Major diastereoisomer **30**, ν_{max} ($CHCl_3$)/cm^{-1} 1734 (N-CO-N) and 1687 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.43-7.31 (6H, m, Ph), 7.26-7.23 (4H, m, Ph), 5.14 (2H, s, PhC<u>H</u>), 3.79 (2H, sextet, J 6.8 Hz, COC<u>H</u>), 1.75 (2H, m, C<u>H</u>$_2$CH$_3$), 1.49 (2H, m, C<u>H</u>$_2$CH$_3$), 1.18 (3H, d, J 6.8 Hz, CHC<u>H</u>$_3$) and 0.93 (3H, t, J 7.3 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 177.3, 151.8, 140.1, 129.4, 128.6, 125.1, 62.4, 40.0, 26.4, 16.5 and 11.4; m/z 407 (MH^+, 100%).
Enolisation of **46** (189mg, 0.50mmol) with potassium bis(trimethylsilyl)amide (2.6ml, 1.95mmol), followed by addition of methyl iodide (0.2ml, excess) with stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave, after work-up, a 36:48:16 mixture of the diastereoisomers **30**-**32** (162mg, 80%).

1,3-Di(3-phenyl-2-methylpropionyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **33** - Treatment of 1,3-di(3-phenylpropionyl)-*trans*-4,5-tetramethyleneimidazolidin-2-one **46** (202mg, 0.50mmol) with sodium bis(trimethylsilyl)amide (2.0ml, 2.00mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of methyl iodide (0.3ml, excess) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 81:18:1 mixture of **33-35** as a white solid (175mg, 81%). Major diastereoisomer **33**, m.p. 105-106°C (Found; C, 74.9; H, 7.6; N, 6.2. $C_{27}H_{32}N_2O_3$ requires C, 75.0; H, 7.5; N, 6.5%); ν_{max} ($CHCl_3$)/cm^{-1} 1739 (N-CO-N) and 1687 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.31-7.19 (10H, m, Ph), 3.96 (2H, qt, J 7.0, 8.6 Hz, COC<u>H</u>), 3.36 (2H, m, C<u>H</u>N), 3.19, 2.57 (4H, ABX system, J_{AB} 13.4 Hz, J_{AX} 5.9 Hz, J_{BX} 8.5 Hz, PhC<u>H</u>$_2$), 2.85 (2H, m, Cy-Cα), 1.87 (2H, m, Cy-Cα), 1.48-1.20 (4H, m, Cy-Cβ) and 1.14 (6H, d, J 7.0 Hz, CHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 179.6, 153.9, 139.9, 129.5, 128.4, 126.3, 60.4, 41.3, 38., 28.7, 24.2 and 17.5; m/z 433 (MH^+, 100%).
Enolisation of **46** (202mg, 0.50mmol) with potassium bis(trimethylsilyl)amide (3.0ml, 1.50mmol), followed by addition of methyl iodide (0.2ml, excess) with stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave, after work-up, a 85:14:1 mixture of the diastereoisomers **33-35** (156mg, 72%).

1,3-Di(3-phenyl-2-methylpropionyl)-trans-*4,5-diphenylimidazolidin-2-one* **36** - Treatment of 1,3-di(3-phenylpropionyl)-*trans*-4,5-diphenylimidazolidin-2-one **51** (251mg, 0.50mmol) with sodium bis(trimethylsilyl)amide (2.0ml, 2.00mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of methyl iodide (0.3ml, excess) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 54:39:1 mixture of **36-38** as a white solid (185mg, 70%). Major diastereoisomer **36**, ν_{max} ($CHCl_3$)/cm^{-1} 1734 (N-CO-N) and 1689 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.40-7.17 (16H, m, Ph), 7.02 (4H, m, Ph), 5.00 (2H, s, PhC<u>H</u>), 4.25 (2H, m, COC<u>H</u>), 2.69, 3.10 (4H, ABX system, J_{AB} 13.4 Hz, J_{AX} 7.1 Hz, J_{BX} 5.3 Hz, PhC<u>H</u>$_2$) and 1.19 (3H, d, J 6.8 Hz, CHC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 176.6, 151.6, 139.6, 139.5, 129.4, 129.3, 128.6, 126.5, 125.2, 62.2, 40.4, 39.4 and 17.1; m/z 531 (MH^+, 100%).
Enolisation of **51** (251mg, 0.50mmol) with potassium bis(trimethylsilyl)amide (2.6ml, 1.95mmol), followed by addition of methyl iodide (0.3ml, excess) with stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave, after work-up, a 53:40:7 mixture of the diastereoisomers **36-38** (243mg, 91%).

1,3-Di(2-benzylbutanoyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **41** - Treatment of 1,3-dibutanoyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **45** (140mg, 0.50mmol) with sodium bis(trimethylsilyl)amide (2.0ml, 2.00mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of benzyl bromide (345mg, 2.00mmol) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 1:15:84 mixture of **39-41** as a white solid (184mg, 72%). Major diastereoisomer **41**, ν_{max} 1748 (N-CO-N) and 1693 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.32-7.09 (10H, m, Ph), 3.98 (2H, m, COC<u>H</u>), 2.89, 2.76 (4H, ABX system, J_{AB} 13.2 Hz, J_{AX} 5.8 Hz, J_{BX} 9.7 Hz, PhC<u>H</u>$_2$), 2.74 (2H, m, C<u>H</u>N), 2.58 (2H, m, Cy-Cα), 1.78 (2H, m, Cy-Cα), 1.91-1.52 (4H, m, C<u>H</u>$_2$CH$_3$), 1.48-1.23 (4H, m, Cy-Cβ) and 1.01 (6H, t, J 7.4 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 178.7, 153.9, 139.4, 129.2, 128.3, 126.5, 60.1, 47.8, 39.8, 27.8, 24.5, 24.1 and 11.6; m/z 461 (MH^+, 100%).

1,3-Di(2-benzylbutanoyl)-trans-*4,5-diphenylimidazolidin-2-one* **44** - Treatment of 1,3-dibutanoyl-*trans*-4,5-diphenylimidazolidin-2-one **50** (189mg, 0.50mmol) with sodium bis(trimethylsilyl)amide (2.0ml, 2.00mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of benzyl bromide (345mg, 2.00mmol) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 10:43:47 mixture of **42-44** as a white solid (143mg, 53%). Major diastereoisomer **44**, ν_{max} ($CHCl_3$)/cm^{-1} 1747 (N-CO-N) and 1694 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.41-7.17 (16H, m, Ph), 6.81 (4H, m, Ph), 5.06 (2H, s, PhC<u>H</u>), 4.39 (2H, m, COC<u>H</u>), 3.02, 2.73 (4H, ABX system, J_{AB} 13.4 Hz, J_{AX} 8.2 Hz, J_{BX} 6.7 Hz, PhC<u>H</u>$_2$), 1.76-1.53 (4H, m, C<u>H</u>$_2$CH$_3$) and 0.87 (6H, t, J 7.4 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 176.3, 151.6, 139.5, 139.3, 129.3, 128.5, 126.3, 124.9, 62.4, 46.8, 38.2, 24.9 and 11.6; m/z 559 (MH^+, 100%).

1,3-Di(2-methylbutanoyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **29** - Treatment of 1,3-propionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **13** (252mg, 1.00mmol) with potassium bis(trimethylsilyl)amide (5.6ml, 3.9mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of ethyl iodide (0.5ml, excess) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h and -30°C, 15 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 1:14:85 mixture of **27-29** as a white solid (204mg, 64%). Major diastereoisomer **29**, ν_{max} ($CHCl_3$)/cm^{-1} 1733 (N-CO-N) and 1687 (N-CO); δ_H (300 MHz, $CDCl_3$) 3.54 (2H, sextet, J 6.7 Hz, COC<u>H</u>), 3.40 (2H, m, C<u>H</u>N), 2.83 (2H, m, Cy-C$_\alpha$), 1.88 (2H, m, Cy-C$_\alpha$), 1.83-1.64 (2H, m, C<u>H</u>$_2$CH$_3$), 1.59-1.37 (2H, m, C<u>H</u>$_2$CH$_3$), 1.69-1.26 (4H, m, Cy-C$_\beta$), 1.16 (3H, d, J 6.7 Hz, CHC<u>H</u>$_3$) and 0.89 (3H, t, J 7.0 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 180.2, 154.3, 60.4, 41.0, 28.5, 27.7, 24.2, 15.3 and 11.0; m/z 309 (MH^+, 100%).

1,3-Di(2-methylbutanoyl)-trans-*4,5-diphenylimidazolidin-2-one* **32** - Treatment of 1,3-propionyl-*trans*-4,5-diphenylimidazolidin-2-one **14** (350mg, 1.00mmol) with potassium bis(trimethylsilyl)amide (5.3ml, 4.00mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of ethyl iodide (0.4ml, excess) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h and -30°C, 15 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 14:47:39 mixture of **30-32** as a white solid (269mg, 66%). Major diastereoisomer **32**, ν_{max} ($CHCl_3$)/cm^{-1} 1734 (N-CO-N) and 1687 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.43-7.31 (6H, m, Ph), 7.26-7.23 (4H, m, Ph), 5.15 (2H, s, PhC<u>H</u>), 3.81 (2H, m, COC<u>H</u>), 1.75 (2H, m, C<u>H</u>$_2$CH$_3$), 1.49 (2H, m, C<u>H</u>$_2$CH$_3$), 1.19 (3H, d, J 6.8 Hz, CHC<u>H</u>$_3$) and 0.85 (3H, t, J 7.4 Hz, CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 177.3, 151.7, 140.2, 129.4, 128.7, 125.3, 62.4, 39.8, 26.5, 16.0 and 11.1; m/z 407 (MH^+, 100%).

1,3-Di(2-benzylbutanoyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **39** - Treatment of 1,3-(3-phenylpropionyl)-*trans*-4,5-tetramethyleneimidazolidin-2-one **46** (560mg, 1.38mmol) with potassium bis(trimethylsilyl)amide (7.5ml, 5.20mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of ethyl iodide (0.8ml, excess) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h and -30°C, 15 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 77:22:1 mixture of **39-41** as a white solid (400mg, 71%). Major diastereoisomer **39**, ν_{max} ($CHCl_3$)/cm^{-1} 1738 (N-CO-N) and 1683 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.32-7.09 (10H, m, Ph), 3.96 (2H, m, COC<u>H</u>), 3.11, 2.64 (4H, ABX system, J_{AB} 13.5 Hz, J_{AX} 6.7 Hz, J_{BX} 7.9 Hz, PhC<u>H</u>$_2$), 2.87 (2H, m, C<u>H</u>N), 2.68 (2H, m, Cy-C$_\alpha$), 1.78 (2H, m, Cy-C$_\alpha$), 1.91-1.52 (4H, m, C<u>H</u>$_2$CH$_3$), 1.48-1.32 (4H, m, Cy-C$_\beta$) and 0.84 (6H, t, J 7.4 Hz,

$CH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 179.0, 154.1, 140.0, 129.6, 128.7, 126.3, 60.5, 48.1, 36.8, 28.6, 25.2, 24.2 and 11.0; m/z 461 (MH^+, 100%).

1,3-Di(2-benzylbutanoyl)-trans-*4,5-diphenylimidazolidin-2-one* **42** - Treatment of 1,3-(3-phenylpropionyl)-*trans*-4,5-diphenylimidazolidin-2-one **51** (251mg, 0.50mmol) with potassium bis(trimethylsilyl)amide (2.6ml, 2.00mmol) at -78°C, followed by stirring (-78°C, 1 h), addition of ethyl iodide (0.4ml, excess) and further stirring (-78°C, 2 h; -78°C warming to -30°C, 3 h and -30°C, 15 h) gave a cream solid after quenching and work-up. Chromatography on silica gel with dichloromethane as eluent gave a 66:31:3 mixture of **42-44** as a white solid (156mg, 56%). Major diastereoisomer **42**, ν_{max} ($CHCl_3$)/cm^{-1} 1747 (N-CO-N) and 1694 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.41-7.17 (16H, m, Ph), 6.81 (4H, m, Ph), 4.86 (2H, s, PhC$\underline{H}$), 4.39 (2H, m, COC$\underline{H}$), 2.92, 2.80 (4H, ABX system, J_{AB} 13.4 Hz, J_{AX} 9.6 Hz, J_{BX} 5.8 Hz, PhC$\underline{H}_2$), 1.76-1.53 (4H, m, $C\underline{H}_2CH_3$) and 0.75 (6H, t, J 7.4 Hz, $CH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 176.5, 151.6, 140.3, 139.7, 129.3, 128.5, 126.4, 125.5, 61.9, 46.5, 38.3, 26.1 and 11.0; m/z 559 (MH^+, 100%).

Homochiral 1,3-Di(3-phenylpropionyl)-trans-*4,5-tetramethyleneimidazolidin-2-one* **35** - In a manner identical to that already described for the synthesis of racemic **35** from **13** *via* its potassium bisenolate, a THF solution of (4*R*, 5*R*)-1,3-dipropionyl-*trans*-4,5-*trans*-tetramethyleneimidazolidin-2-one (*R,R*)-**13** (252mg, 1.00mmol) at -78°C was treated with potassium bis(trimethylsilyl)amide (5.2ml, 3.90mmol). After 1 h at -78°C, benzyl bromide (685mg, 4.00mmol) was added and the reaction stirred (-78°C, 2 h; -78°C warming to -30°C, 3 h and -30°C, 15 h) before being quenched. Work-up gave, as before, a 0:5:95 mixture of diastereoisomers **33-35**, (195mg, 45%). The compounds were identical spectroscopically to the racemic samples prepared previously.

(2S)-3-Phenyl-2-methylpropane-1-ol (2*S*)-**52** - A solution of a 0:5:95 mixture of homochiral **33-35** (145mg, 0.34mmol) in THF (2ml) was added to a stirred suspension of lithium aluminium hydride (120mg, 3.16mmol) in THF (6ml) at 0°C. After stirring for 2 h at 0°C, the reaction was quenched by addition of water (0.15ml), 15% aqueous sodium hydroxide solution (0.15ml) and water (0.45ml). The resulting slurry was filtered through celite, the solvent was removed *in vacuo* and the crude product purified by chromatography on silica gel with dichloromethane as eluent to give (2*S*)-**52** as a colourless oil (35mg, 35%), δ_H (300 MHz, $CDCl_3$) 7.32-7.17 (5H, m, Ph), 3.52 (2H, m, C$\underline{H}_2$OH), 2.76, 2.44 (2H, ABX system, J_{AB} 13.4 Hz, J_{AX} 6.3 Hz, J_{BX} 8.0 Hz, PhC$\underline{H}_2$), 1.96 (1H, m, C$\underline{H}$CH$_3$), 1.33 (1H, bs, CH$_2$O$\underline{H}$) and 0.93 (3H, d, J 6.7 Hz, CHC$\underline{H}_3$); $[\alpha]_D^{20}$ -10.2 (c 1.1, benzene).

Racemic-3-Phenyl-2-methylpropane-1-ol **52** - In a manner analogous to that described above, treatment of a 95:5:0 mixture of racemic **33-35** (185mg, 0.43mmol) with lithium aluminium hydride (200mg, 5.30mmol) in THF (6ml) at 0°C gave a colourless oil after a standard reaction period and work-up. This was fritted through a plug of silica gel with dichloromethane as eluent to give **52** as a colourless oil (122mg, 94%), after prolonged drying *in vacuo*.

1,3-Di(3-phenyl-2-methylpropionyl)-trans-*4,5-tetramethylene-imidazolidin-2-one* **35** - Lithium diisopropylamide (2.0ml of a 2.0M solution in heptane, 4.00mmol) was added to a THF solution of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **13** (252mg, 1.00mmol) at -78°C and the reaction stirred at -78°C for 1 h before addition of benzyl bromide (515mg, 3.00mmol). After 1 h at -78°C, the reaction

was allowed to warm to 0°C and stirred thereat for 2 h before being quenched and worked-up in the conventional manner. Chromatography on silica gel with dichloromethane as eluent gave a 5:35:60 mixture of diastereoisomers **33**:**34**:**35** (350mg, 81%).

Acknowledgements

We thank the SERC for support (to GBE) and BP International for a Research Studentship (to AAM) and for a Venture Research Award (to SGD).

References

1. For part 5 see S.G. Davies and A.A. Mortlock, *Tetrahedron*, 1993, **49**, 4419.
2. D.A. Evans in *Asymmetric Synthesis*, ed. J.D. Morrison, Academic Press, New York, 1984, **3**, ch. 1.
3. H.O. House, B.A. Tefertiller and H.D. Olmstead, *J. Org. Chem.*, 1968, **33**, 935; T.M. Bare, N.D. Hershey, H.O. House and C.G. Swain, *J. Org. Chem.*, 1972, **37**, 997; H.O. House and M.J. Umen, *J. Org. Chem.*, 1973, **38**, 1000; B.J.L. Huff, F.N. Tuller and D. Caine, *J. Org. Chem.*, 1969, **34**, 3070.
4. S.G. Davies and A.A. Mortlock, *Tetrahedron Letters*, 1991, **32**, 4787.
5. D.A. Evans, *Aldrichimica Acta*, 1982, **15**, 23; D.A. Evans, M.D. Ennis and D.J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737; D.A. Evans, J.M. Takacs, L.R. McGee, M.D. Ennis, D.J. Mathre and J. Bartroli, *Pure Appl. Chem.* 1981, **53**, 1109.
6. D.A. Evans, F. Urpi, T.C. Somers, J.S. Clark and M.T. Bilodeau, *J. Am. Chem. Soc.*, 1990, **112**, 8215.
7. D. Seebach, H.F. Chow, R.F.W. Jackson, K.Lawson, M.A. Suttert, S. Thaisrivongs and J. Zimmermann, *J. Am. Chem. Soc.*, 1985, **107**, 5292.
8. S.G. Davies and A.A. Mortlock, *Tetrahedron Letters*, 1992, **33**, 1117.
9. L.M. Harwood and C.J. Moody, "Experimental Organic Chemistry", Blackwell Scientific Publications, Oxford, 1989.
10. D.A. Evans, S.W. Kaldor, T.K. Jones, J. Clardy and T.J. Stout, *J. Am. Chem. Soc.*, 1990, **112**, 7001.
11. D.A. Evans, M.D. Ennis and D.J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737; S. Terashima and S-I. Yamada, *Chem. Pharm. Bull.*, 1968, **16**, 1953.
12. D.D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd edn. Pergamon Press, Oxford, 1988.

(*Received in UK* 10 *February* 1994)