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Bifunctional Chiral Auxiliaries 5: The Synthesis of 1,3-Diacylimidazolidine-2-thiones and 1,3-Diacylimidazolidin-2-ones from 1,2-Diamines[1]

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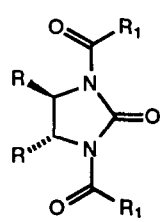
Abstract: Although 1,2-diamines fail to cyclise with urea, phosgene or 1,1'-carbonyl diimidazole, they react with carbon disulphide to give the corresponding imidazolidine-2-thiones. These undergo clean diacylation to give 1,3-diacylimidazolidine-2-thiones which are readily converted to 1,3-diacylimidazolidin-2-ones on treatment with mercury (II) acetate. An alternative two-step route to 1,3-diacylimidazolidin-2-ones uses carbonyl sulphide to effect cyclisation of the 1,2-diamine to the imidazolidin-2-one, which is subsequently diacylated. The ability to convert homochiral 1,2-diamines to homochiral 1,3-diacylimidazolidin-2-ones has also been demonstrated.

Introduction

The use of stoicheiometric chiral auxiliaries is a well-established and flexible method for asymmetric synthesis[2]. Whilst approaches to the design of such systems have allowed the development of a number of versatile and highly stereoselective examples, the additional criterion of minimising the mass of this stereodirecting group has not been tackled. Bifunctional chiral auxiliaries, in which a chiral auxiliary bearing two stereogenic centres is attached to two reactive sidechains, promise to address this latter point whilst embodying those control elements necessary to attain high diastereoselection[3]. The acyl sidechains of 1,3-diacylimidazolidin-2-ones **1** have been shown to be capable of undergoing highly stereoselective reactions before being cleaved from the auxiliary. Thus, dibutylboron enolates of these compounds react with aldehydes in *syn*-stereoselective aldol reactions[3,4] whilst the corresponding potassium enolates react stereoselectiviely with alkyl halides[1].



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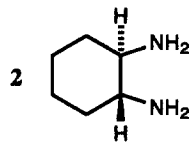
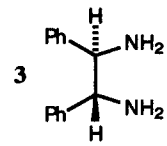
Drawing on the methods developed for the synthesis of N-acyl oxazolidones from 1,2-aminoalcohols[5], the most readily-conceived starting material for **1** was a symmetrically-substituted 1,2-diamine. Although such compounds are not available in homochiral form from natural sources, they may, in general, be resolved simply

via formation of the diastereoisomeric salts with tartaric acid. Most work in this area has concentrated on *trans*-1,2-diaminocyclohexane **2**[6] and 1,2-diphenyl-1,2-diaminoethane **3**[7]. The former is available in racemic form as a by-product from the synthesis of 1,6-diaminohexane (used for the manufacture of nylon) and comes from this source as a readily separable mixture of *cis* and *trans* isomers[8]. The latter is most easily prepared from benzoin, with resolution again being achieved using tartaric acid[9]. The use of both **2** and **3** as starting materials for the synthesis of chiral auxiliaries and chiral catalysts is a rapidly expanding area of contemporary research[10].





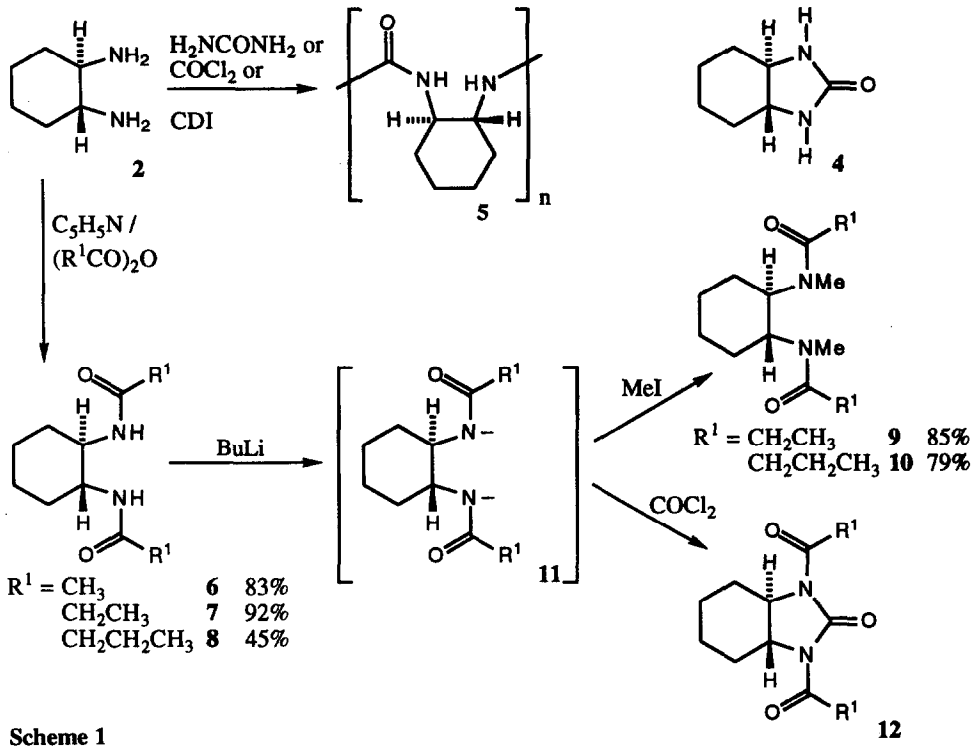
We report herein the synthetic elaboration of both **2** and **3** to give a range of 1,3-diacylimidazolidine-2-thiones and 1,3-diacylimidazolidin-2-ones. Part of this work has been described in a preliminary communication[11].

Results and Discussion

1,2-Aminoalcohols may be cyclised to oxazolidinones with urea[12], phosgene[13] or diethyl carbonate[14]. However, treatment of *trans*-1,2-diaminocyclohexane **2** with these reagents, under analogous conditions, failed to give the desired imidazolidin-2-one **4**, furnishing instead a polymeric material **5**. Butler and Hussain have reported that the reaction between 1,2-diaminoethane (ethylene diamine) and urea is highly solvent-dependent, proceeding *via* an intermediate β-amino isocyanate[15]. In organic solvents, polymerisation occurs, but if the reaction is performed in a small volume of water, the desired imidazolidin-2-one could be obtained. Repeating these conditions with *trans*-1,2-diaminocyclohexane **2** and urea did not result in formation of imidazolidin-2-one **4**. During the course of this work Yamada has reported the reaction of **3** with urea at much higher temperature and with 'a few drops of water'[16].

Acylation followed by introduction of the carbonyl group was an alternative, if less attractive, synthetic route. Diacylation of **2** was readily achieved by treatment with triethylamine and the requisite carboxylic anhydride to furnish the acetyl **6**, propionyl **7** and butanoyl **8** derivatives in moderate to good yield. It was reasoned that the relatively low nucleophilicity of anions derived from hindered amides would make introduction of the carbonyl group problematic. Before attempting this reaction, therefore, N-methylation of both sidechains was attempted to provide evidence for the formation of the desired dianionic intermediate **11**. Clean dimethylation of both **7** and **8** could be achieved by sequential treatment with butyllithium and methyl iodide, giving **9** and **10** respectively, although this was dependent on the reaction being performed under conditions of high dilution. Under similar conditions of high dilution, dianion **11** was treated with a range of phosgene equivalents which failed to give the desired product **12**. However, introduction of gaseous phosgene to a THF solution of **11** at -78°C, followed by warming to 0°C did give a small amount of **12** although the low chemical yield of this reaction (~20%), coupled with the potential difficulties associated with scale-up, required an alternative route to be found (Scheme 1).

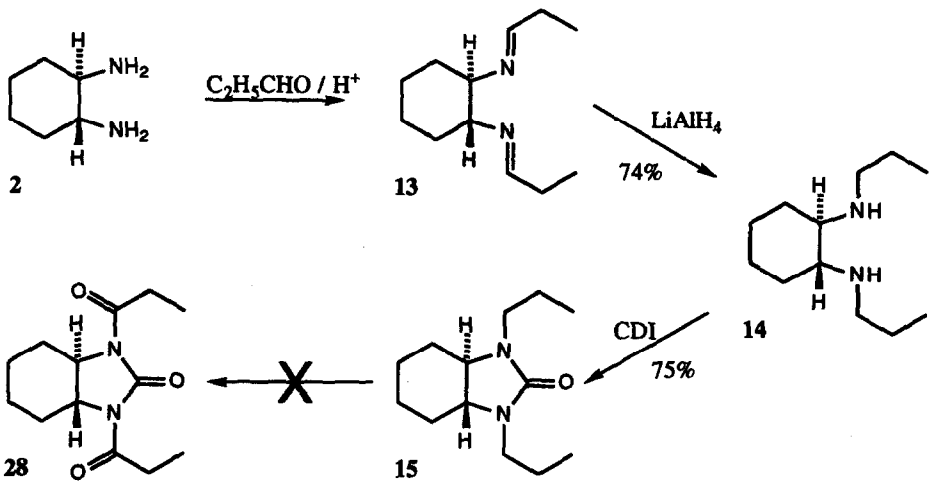
The problem of the low nucleophilicity of anions derived from hindered amides could be avoided if the molecular skeleton were to be constructed in a lower overall oxidation state. As oxidation of amides to imides



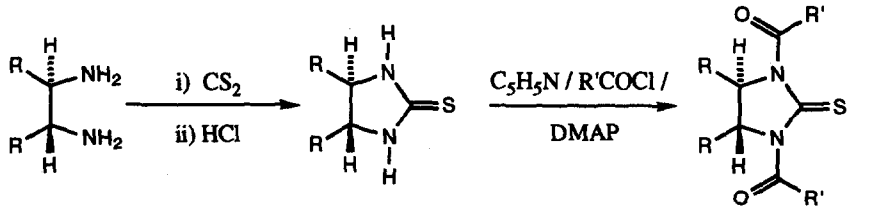
Scheme 1

has been reported[17], it was decided to introduce the acyl sidechains as alkyl groups which could be oxidised as a final step. Monoalkylation of both amino groups of **2** was achieved in 74% yield by *in situ* reduction of di-imine **13**, itself formed by condensation of **2** with propanal. Treatment of **14** with 1,1'-carbonyl di-imidazole then gave N,N'-di-*n*-propyl-*trans*-1,2-diaminocyclohexane **15** in 75% yield. However, attempts to oxidise **15** with either ruthenium tetroxide[18] or peroxy acids (in the presence of manganese (III) acetylacetonate[19]) failed to give **12**, only starting material being recovered (Scheme 2).

The reaction of 1,2-diaminoethane with carbon disulphide, to give imidazolidine-2-thione, is well known[20]. Provided that a simple method for the subsequent conversion of the thiocarbonyl group to an oxocarbonyl group could be found, it offered an attractive first step in a synthetic route to 1,3-diacylimidazolidin-2-ones. Under the experimental conditions previously described for the reaction of 1,2-diaminoethane[20], *trans*-1,2-diaminocyclohexane **2** gave *trans*-4,5-tetramethylene-imidazolidine-2-thione **16** in 94% yield, after work-up. The reaction was repeated using 1,2-diphenyl-1,2-diaminoethane **3**, which furnished *trans*-4,5-diphenylimidazolidine-2-thione **17** in 90% yield under identical conditions. Furthermore, the reaction was found to be amenable to large scale use, having been performed on a 0.5mol scale with comparable yield. Diacylation of **16** and **17** was found to occur under very mild conditions[21]. Thus, addition of the requisite acyl halide (2.6eq) to a dichloromethane solution of either **16** or **17** with pyridine (2.4eq) and a catalytic amount of 4-(dimethylamino)pyridine at ambient temperature gave the desired diacylated derivatives **18-25** in yields of 68-94% after stirring for 18 h at ambient temperature, work-up and chromatographic purification (Scheme 3).



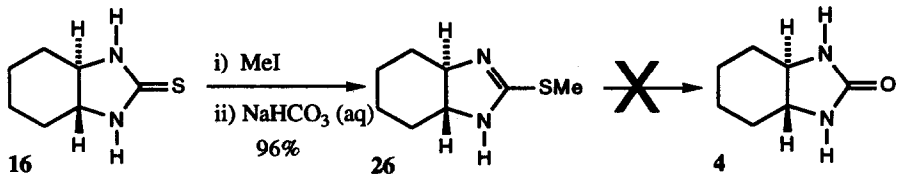
Scheme 2



R = -$(CH_2)_4$-	**2**	R = -$(CH_2)_4$-	**16**	R = -$(CH_2)_4$-	R' = CH_3	**18** 71%
Ph	**3**	Ph	**17**	-$(CH_2)_4$-	CH_2CH_3	**19** 85%
				-$(CH_2)_4$-	$CH_2CH_2CH_3$	**20** 83%
				-$(CH_2)_4$-	CH_2CH_2Ph	**21** 75%
				Ph	CH_3	**22** 94%
				Ph	CH_2CH_3	**23** 88%
				Ph	$CH_2CH_2CH_3$	**24** 88%
				Ph	CH_2CH_2Ph	**25** 68%

Scheme 3

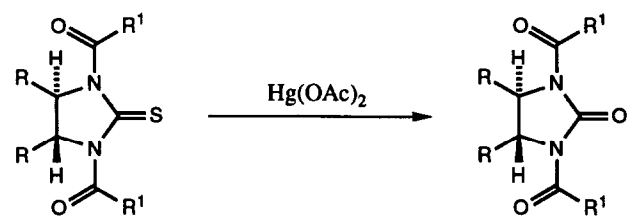
A diverse range of methods have been described for the conversion of thioketones and thioamides to the corresponding ketones and amides[22]. An attractive method for the latter reaction has been developed by Hojo, but treatment of **19** with trifluoroacetic anhydride followed by a basic work-up gave only recovered starting material[23]. Similarly, attempted alkaline hydrolysis of **16** failed to give any of the desired product **4**[24]. S-Methylation of **16** was, however, achieved by simply stirring with excess methyl iodide at ambient temperature followed by basic work-up to dissociate the hydrogen iodide salt[25]. Attempted hydrolysis of **26**, under both alkaline and acidic conditions, gave only recovered starting material (Scheme 4).



Scheme 4

The well known thiophilicity of mercury (II) salts has been widely employed to catalyse the hydrolysis of thioacetals[26]. In an extension of this work, Kende has used mercuric oxide and boron trifluoride in methanol to convert methyl thioesters to methyl esters[27], whilst mercury (II) acetate has been shown to convert 2-thio-1,3-dithia-4-cyclopentene to 2-oxo-1,3-dithia-4-cyclopentene in moderate yield[28].

A dichloromethane solution of **19** was stirred with a small excess of mercury (II) acetate for 15 h at ambient temperature. The reaction was worked-up by filtering the reaction mixture through celite and purifying the resultant white solid by chromatography on silica gel to give 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **28** as a white crystalline solid in 88% yield. It was found, however, that small amounts of starting material were sometimes obtained. An improved protocol, whereby the substrate was treated sequentially with two batches of mercury (II) acetate (1.1eq, 0.3eq) was adopted, which circumvented this problem. Using this modified procedure, all eight 1,3-diacylimidazolidine-2-thiones **18-25**, prepared above, were converted to their imidazolidin-2-one analogues **27-34** in uniformly high yield (Scheme 5).

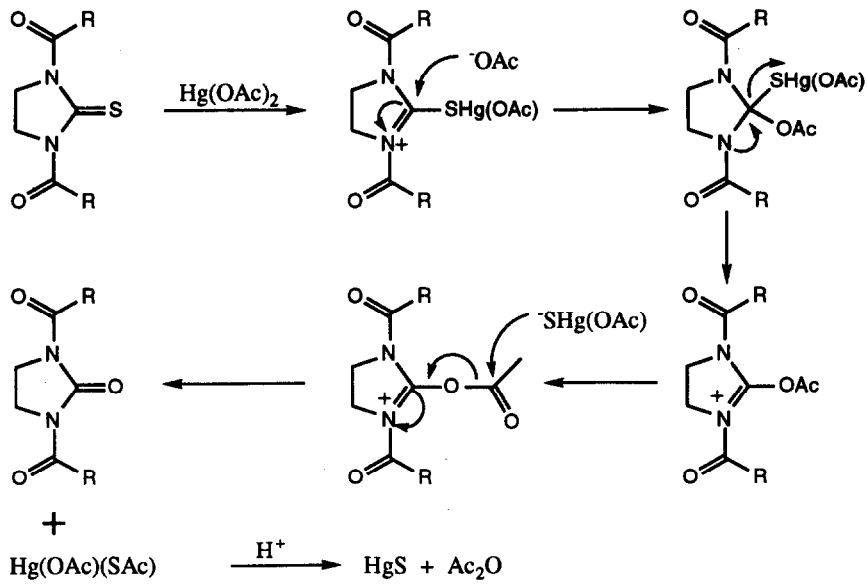


R =	-$(CH_2)_4$-	R^1 = CH_3	**18**	R =	-$(CH_2)_4$-	R^1 = CH_3	**27** 76%
	-$(CH_2)_4$-	CH_2CH_3	**19**		-$(CH_2)_4$-	CH_2CH_3	**28** 88%
	-$(CH_2)_4$-	$CH_2CH_2CH_3$	**20**		-$(CH_2)_4$-	$CH_2CH_2CH_3$	**29** 70%
	-$(CH_2)_4$-	CH_2CH_2Ph	**21**		-$(CH_2)_4$-	CH_2CH_2Ph	**30** 82%
	Ph	CH_3	**22**		Ph	CH_3	**31** 93%
	Ph	CH_2CH_3	**23**		Ph	CH_2CH_3	**32** 91%
	Ph	$CH_2CH_2CH_3$	**24**		Ph	$CH_2CH_2CH_3$	**33** 87%
	Ph	CH_2CH_2Ph	**25**		Ph	CH_2CH_2Ph	**34** 93%

Scheme 5

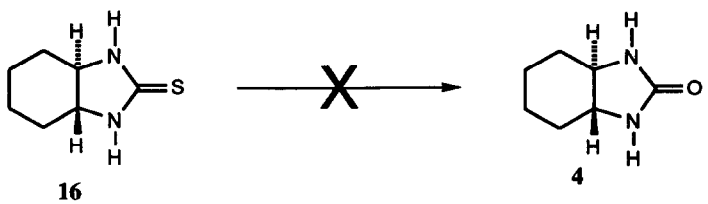
The success of this novel reaction raised the question as to its mechanism. Although the reaction bears a superficial resemblance to that described by Hojo, utilising trifluoroacetic anhydride[23], there is a crucial difference in that the present reaction does not require a hydrolytic work-up to liberate the product. This also suggests that neither the sulphur nor the mercury are associated with the product at the end of the reaction. The

initial logic behind the reaction assumed that the metal would be converted to mercury (II) sulphide, but the absence of a black precipitate suggested that this was not being formed. However, if the starting material were slightly acidic, due to contamination with carboxylic acids from the acylation step, mercury (II) sulphide was observed, suggesting that the first-formed reaction product may be degraded to this compound under acid catalysis. Consistent with these observations, and the fact that the reaction requires a stoicheiometric quantity of mercury (II) acetate, is the proposed mechanism shown below. That mercury (II) acetate thioacetate was the other product of the reaction was supported by the observation of resonances due to its two different acyl methyl groups in the ^1H n.m.r. spectra of crude reaction products, before chromatography. (Scheme 6).



Scheme 6

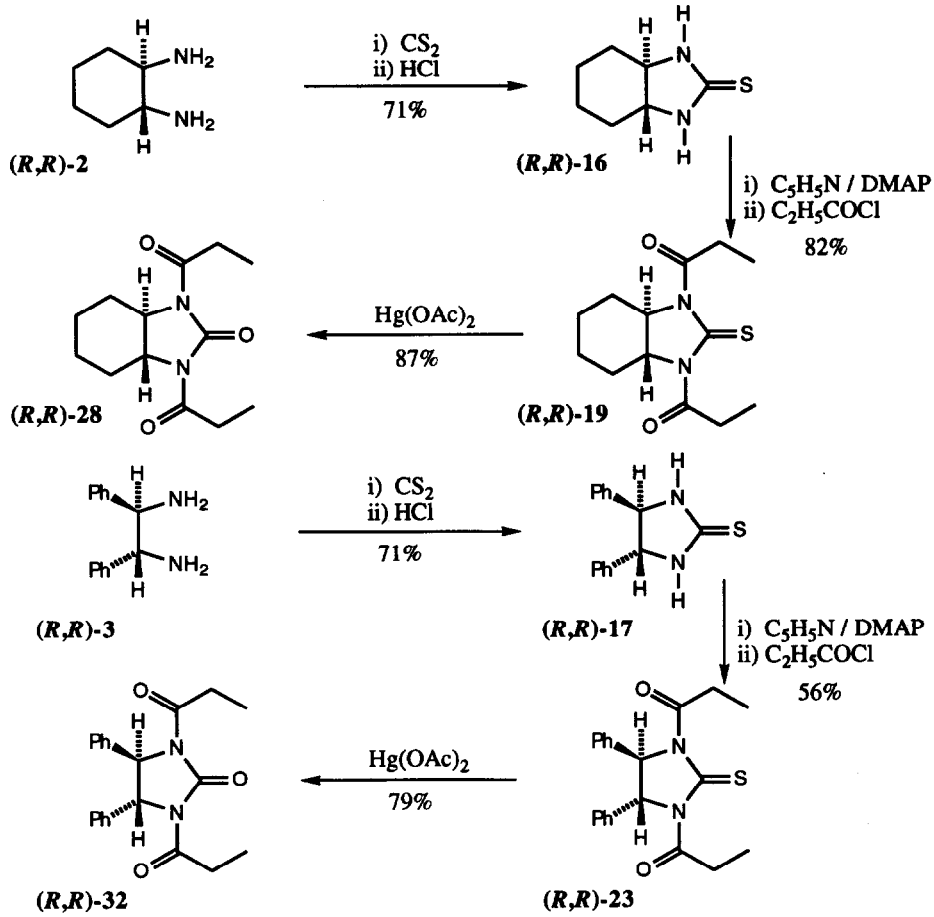
The reaction was also performed on the non-acylated imidazolidine-2-thione **16** in an attempt to synthesise **4**. The product of this reaction could not be fully identified although mass spectroscopy suggested that it contained oligomerised **4** (Scheme 7).



16 **4**

Scheme 7

Having developed a successful and general route to 1,3-diacylimidazolidin-2-ones, it was important to demonstrate that it could be used to prepare such compounds in homochiral form. As both **2** and **3** are commercially available[29], and as epimerisation during the proposed synthetic route seemed unlikely, it was

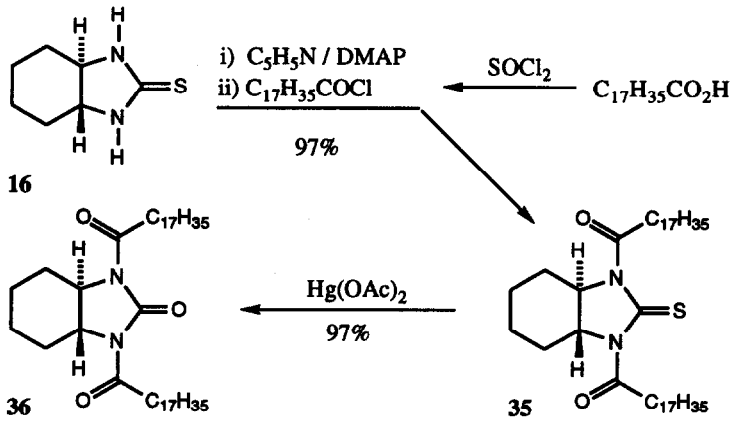


Scheme 8

decided to elaborate homochiral diamines rather than seek to effect resolution during the synthetic sequence. Thus, (*R*,*R*)-**2** and (*R*,*R*)-**3** were converted to (*R*,R)-**28** and (*R*,*R*)-**32** in a manner analogous to that employed for the syntheses of these compounds in racemic form (Scheme 8).

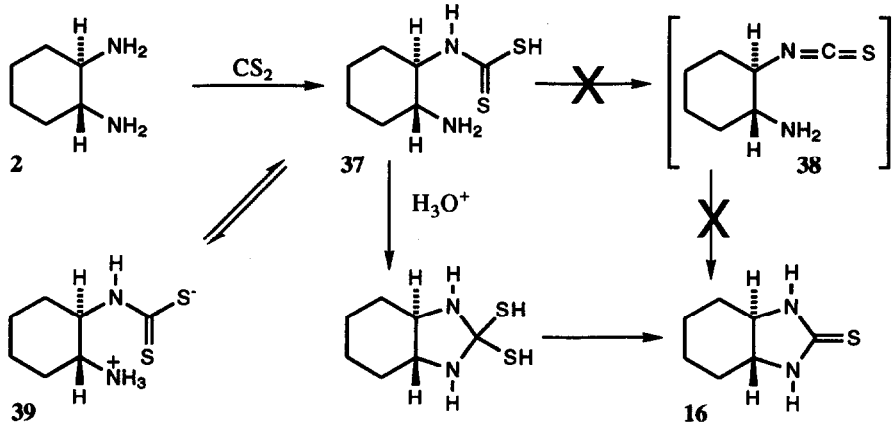
The enantiomeric purities of both these compounds were assessed from their ^{1}H n.m.r. spectra recorded in the presence of the chiral shift reagent (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol[30]. In the presence of seven equivalents of this reagent, racemic **28** showed clean splitting of the multiplets due to the propionyl methylene groups whilst racemic **32** showed clean splitting of the propionyl methyl triplets, with ten equivalents. As the samples prepared from homochiral diamines each showed signals due to just one enantiomer their enantiomeric excesses could be estimated at >99% (the methyl triplet due to (*R*,*R*)-**32** was at relatively low field and the methylene multiplets due to (*R*,*R*)-**28** were also at relatively low field).

Using this general synthetic method, octadecanoyl derivatives **35** and **36** were prepared due to interest in their use as zinc ionophores (Scheme 9)[31].



Scheme 9

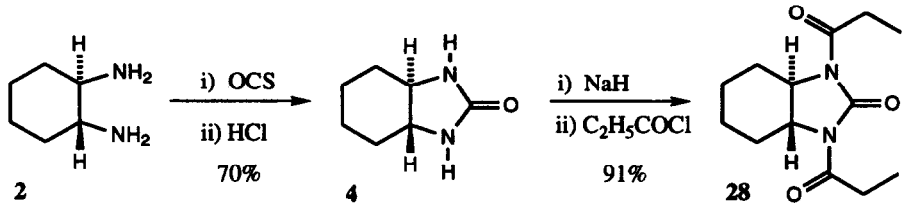
The mechanistic analysis used to rationalise why cyclisation of diamine **2** occurred with carbon disulphide, but not with phosgene or phosgene equivalents suggested that the role of the thiohydroxyl group as a nucleofuge in the cyclisation step was all important. As this is a poor leaving group, elimination from **37**, to give **38**, does not occur; this being further disadvantaged by the relative stability of **37** due its zwitterionic form **39**. On acidification, cyclisation of **37** occurs *via* direct attack on the carbonyl group rather than *via* attack on the isocyanate / isothiocyanate **38** which, it is proposed, cannot cyclise (Scheme 10).



Scheme 10

If this reasoning is correct, substitution of a carbonyl group for a thiocarbonyl group should not prevent cyclisation. Thus, reaction of **2** with carbonyl sulphide should give imidazolidin-2-one **4** directly[32]. Using gaseous carbonyl sulphide instead of carbon disulphide, in a method similar to that already described for the synthesis of **16** and **17**, gave **4** in a yield of 70%, after work-up. As some starting material was also recovered from this reaction, the yield may reflect the difficulty of adding precise volumes of toxic gases and could probably be optimised. Diacylation of **4** was possible with pyridine and propionyl chloride but the reaction was less convenient than when performed on the imidazolidine-2-thiones. However, by using sodium hydride as

the base, a much cleaner reaction took place and **28** could be obtained in a yield of 91%. This was found to be identical to a sample prepared by treatment of **19** with mercury (II) acetate (Scheme 11).



2 **4** **28**

Scheme 11

In summary, the work described above represents a simple and high-yielding route to 1,3-diacylimidazolidin-2-ones. In addition, the intermediate 1,3-diacylimidazolidine-2-thiones may themselves be used as chiral auxiliaries in asymmetric synthesis[33].

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 from chloroform solutions at the sodium D line using a Perkin-Elmer 241 polarimeter with values quoted in 10^{-1} deg $cm^2\ g^{-1}$.

Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen and dichloromethane distilled from calcium hydride under nitrogen. Butyllithium was used as a 1.6 mol dm^{-3} solution in hexane and other reagents were used as received or were purified by standard methods[34]. Flash chromatography was performed on silica gel (43-60 μm) under positive pressure. Cy-Cα refers to the methylene group of the cyclohexyl ring α- to the bridgehead, Cy-Cβ refers to that β- to the bridgehead.

N,N'-Diacetyl-trans-1,2-diaminocyclohexane **6** - Acetic anhydride (8.0ml, 84.8mmol) was added to a THF solution of *trans*-1,2-diaminocyclohexane **2** (4.5ml, 37.5mmol) at 0°C over a period of 5 min. The reaction was stirred at this temperature for a further 10 min before addition of triethylamine (15ml, 108mmol) over 5 min and then allowed to warm to ambient temperature over 3 h. The solvent was removed *in vacuo* and the solid residue taken up in dichloromethane (50ml). The organic solution was washed with water (2x50ml) and 0.1M hydrochloric acid (20ml), dried over $MgSO_4$ and evaporated to give **6** as a white amorphous solid, (an analytical sample was obtained by recrystallisation from ethanol-cyclohexane, 1:2), (6.15g, 83%), m.p. 261-263°C (Found; C, 60.2; H, 9.3; N, 14.0. $C_{10}H_{18}N_2O_2$ requires C, 60.6; H, 9.15; N, 14.1%); ν_{max} ($CHCl_3$)/cm^{-1} 3350br (N-H), 1659 (N-CO-CH_3) and 1520 (N-CO-CH_3); δ_H (300 MHz, $CDCl_3$) 5.99 (2H, br s, NH), 3.64 (2H, m, CHN), 2.03 (2H, m, Cy-C_α), 1.95 (6H, s, $COCH_3$), 1.74 (2H, m, Cy-C_α) and 1.31-1.19 (4H, m, Cy-C_β); δ_C (50 MHz, $CDCl_3$) 171.1, 53.8, 32.0, 24.5 and 23.2; m/z 199 (MH^+, 100%).

N,N'-Dipropionyl-trans-1,2-diaminocyclohexane **7** - Propionic anhydride (4.3ml, 33.9mmol) was added to a THF solution of *trans*-1,2-diaminocyclohexane **2** (2.0ml, 16.6mmol) at 0°C and the reaction allowed to stir for 10 min before addition of triethylamine (6.0ml, 43.0mmol). The reaction was allowed to warm to ambient temperature over 3 h before solvent evaporation *in vacuo*. The residue was taken up in dichloromethane (50ml), washed with water (2x50ml) and 0.1M hydrochloric acid (20ml), dried over $MgSO_4$ and evaporated to give **7** as a white amorphous solid, (3.45g, 92%), m.p. 212-214°C (Found; C, 63.6; H, 10.1; N, 12.3. $C_{12}H_{22}N_2O_2$ requires C, 63.7; H, 9.87; N, 12.4%); ν_{max} ($CHCl_3$)/cm^{-1} 3420br (N-H), 2940 (C-H), 1655 (N-CO-CH_3) and 1503 (N-CO-CH_3); δ_H (300 MHz, $CDCl_3$) 6.02 (2H, s, N<u>H</u>), 3.66 (2H, m, C<u>H</u>N), 2.15 (4H, dq, J 7.6, 2.4 Hz, COC<u>H</u>$_2$CH$_3$), 2.06 (2H, m, Cy-Cα), 1.75 (2H, m, Cy-Cα), 1.28 (4H, m, Cy-Cβ) and 1.14 (6H, t, J 7.6 Hz, COCH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 174.9, 53.5, 31.9, 29.6, 24.6 and 9.8; m/z 227 (MH^+, 100%).

N,N'-Dibutanoyl-trans-1,2-diaminocyclohexane **8** - Butyric anhydride (30ml, 183mmol) was added to a THF solution of *trans*-1,2-diamino-cyclohexane **2** (10ml, 83.3mmol) at 0°C and the reaction allowed to stir for 10 min before addition of triethylamine (36ml, 258mmol). The reaction was allowed to warm to ambient temperature over 3 h before solvent evaporation *in vacuo*. The residue was taken up in dichloromethane (100ml), washed with water (2x100ml) and 0.1M hydrochloric acid (20ml), dried over $MgSO_4$ and evaporated to give a yellow oil contaminated with butyric acid. This was redissolved in dichloromethane (100ml), washed with 10% aqueous potassium bicarbonate solution (2x100ml), dried over $MgSO_4$ and then evaporated to give **8** as a white crystalline solid, (8.06g, 45%), m.p. 208-210°C (Found; C, 66.2; H, 10.5; N, 10.9. $C_{14}H_{26}N_2O_2$ requires C, 66.1; H, 10.3; N, 11.0%); ν_{max} ($CHCl_3$)/cm^{-1} 3420br (N-H), 1651 (N-CO-CH_3) and 1498 (N-CO-CH_3); δ_H (300 MHz, $CDCl_3$) 5.95 (2H, s, N<u>H</u>), 3.66 (2H, m, C<u>H</u>N), 2.11 (4H, dt, J 7.5, 2.2 Hz, COC<u>H</u>$_2$), 2.04 (2H, m, Cy-Cα), 1.74 (2H, m, Cy-Cα), 1.63 (4H, m, COCH$_2$C<u>H</u>$_2$CH$_3$), 1.29 (4H, m, Cy-Cβ) and 0.93 (6H, t, J 7.4 Hz, COCH$_2$CH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 174.0, 53.5, 38.6, 32.1, 24.5, 19.0 and 13.5; m/z 255 (MH^+, 100%).

N,N'-Dimethyl-N,N'-dipropionyl-trans-1,2-diaminocyclohexane **9** - Butyllithium (1.60M in hexanes, 1.0ml, 1.60mmol) was added to a THF solution of diamide **7** (150mg, 0.66mmol) at -78°C and stirred for 1 h. Methyl iodide (0.3ml, excess) was added by syringe and the reaction allowed to warm to ambient temperature over 2 h. The solvent was evaporated *in vacuo* and the solid residue triturated with dichloromethane (3x5ml). The combined organic layers were decolourised by filtration through active charcoal, dried over $MgSO_4$ and evaporated to give **9** as a white crystalline solid, (143mg, 85%), m.p. 77-79°C (Found; C, 66.5; H, 10.5; N, 10.7. $C_{14}H_{26}N_2O_2$ requires C, 66.1; H, 10.3; N, 11.0%); ν_{max} ($CHCl_3$)/cm^{-1} 2940 (C-H) and 1628 (N-CO-CH_3); δ_H (300 MHz, $CDCl_3$) 4.63 (2H, m, C<u>H</u>N), 2.80 (6H, s, NC<u>H</u>$_3$), 2.27 (4H, q, J 7.4 Hz, COC<u>H</u>$_2$CH$_3$), 1.80-1.26 (8H, m, Cy-Cα, Cβ) and 1.10 (6H, t, J 7.5 Hz, COCH$_2$C<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 174.1, 53.5, 29.8, 29.2, 27.2, 24.9 and 9.2 (<u>C</u>H$_3$); m/z 255 (MH^+, 100%).

N,N'-Dimethyl-N,N'-dibutanoyl-trans-1,2-diaminocyclohexane **10** - Butyllithium (1.4M in hexanes, 10.8ml, 15.0mmol) was added to a THF solution (100ml) of diamide **8** (1.508g, 6.00mmol) at -78°C with stirring (2 h, -78°C). Methyl iodide (1.5ml, 24.0mmol) was added and the reaction allowed to warm to ambient temperature over 3 h. The solvent was removed *in vacuo* and the resulting residue triturated with dichloromethane (3x20ml), dried over $MgSO_4$ and evaporated down to a brown oil. Chromatography on silica

gel (eluting with diethyl ether) afforded **10** as a colourless oil which solidified on standing, (1.31g, 79%), m.p. 37-39°C (Found; C, 68.2; H, 11.0; N, 9.80. $C_{16}H_{30}N_2O_2$ requires C, 68.00; H, 10.70; N, 9.90%); ν_{max} ($CHCl_3$)/cm^{-1} 1628 (N-CO-CH_3); δ_H (300 MHz, $CDCl_3$) 4.63 (2H, m, C<u>H</u>N), 2.79 (6H, s, NC<u>H</u>$_3$), 2.22 (4H, t, J 7.5 Hz, COC<u>H</u>$_2$), 1.60 (4H, m, $COCH_2C\underline{H}_2CH_3$), 1.85-1.30 (8H, m, Cy-Cα, Cβ) and 0.93 (6H, t, J 7.4 Hz, $COCH_2CH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 173.3, 51.6, 35.8, 29.9, 29.2, 24.8, 18.4 and 13.7 (<u>C</u>H$_3$); m/z 283 (MH^+, 100%).

N,N'-Dipropyl-trans-1,2-diaminocyclohexane **14** - *trans*-1,2-Diaminocyclohexane **2** (12ml, 100mmol) was added dropwise to solution of propanal (15ml, 210mmol) in THF at 0°C containing activated molecular sieves. After addition the reaction was allowed to warm to ambient temperature and stir for a further 18 h. The reaction mixture was then added, without further purification, to a THF solution of lithium aluminium hydride (6.1g, 160mmol) at 0°C *via* cannula. Again the reaction was stirred at ambient temperature for 1 h and then cooled to 0°C and quenched by addition of water (10ml). Celite was added and the reaction mixture filtered, the residue being washed with dichloromethane (4x50ml), before the combined washings were evaporated to give **14** as a clear oil, (14.92g, 75%), (Found; C, 72.5; H, 13.1; N, 14.1. $C_{12}H_{26}N_2$ requires C, 72.7; H, 13.2; N, 14.1%); ν_{max} ($CHCl_3$)/cm^{-1} 3200 (N-H) and 2900 (C-H); δ_H (300 MHz, $CDCl_3$) 2.68 (2H, m, C<u>H</u>$_2$N), 2.39 (2H, m, C<u>H</u>$_2$N), 2.08 (2H, m, C<u>H</u>N), 2.08 (2H, bs, N<u>H</u>), 1.68 (4H, m, Cy-Cα), 1.47 (4H, q, J 7.3 Hz, $NCH_2C\underline{H}_2CH_3$), 1.20 (2H, m, Cy-C$\beta$), 0.96 (2H, m, Cy-C$\beta$) and 0.92 (6H, t, J 7.4 Hz, $NCH_2CH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 61.6, 48.8, 31.2, 24.9, 23.4 and 11.6 (<u>C</u>H$_3$); m/z 199 (MH^+, 100%).

1,3-Dipropyl-trans-4,5-tetramethyleneimidazolidin-2-one **15** - 1,1'-Carbonyl di-imidazole (2.76g, 17.0mmol) and diamine **14** (3.00g, 15.1mmol) were heated in THF solution (100ml) at reflux for 2 h. The reaction was allowed to cool, the solvent was removed *in vacuo* and the crude product taken up in dichloromethane (50ml). The organic layer was washed with 1.0M hydrochloric acid (100ml), dried over $MgSO_4$ and evaporated down to a yellow oil which was distilled (b.p. 150°C / 1.0mmHg). The product was found to be contaminated with imidazole which could be removed by chromatography on silica gel (eluting with dichloromethane) to give **15** as a colourless oil, (2.55g, 75%), (Found; C, 69.66%; H, 11.22%. $C_{13}H_{24}N_2O$ requires C, 69.60%; H, 10.78%); ν_{max} ($CHCl_3$)/cm^{-1} 1677 (N-CO); δ_H (300 MHZ, $CDCl_3$) 3.16, 3.03 (4H, ABX_2 system, J_{AB} 7.3 Hz, J_{AX} 7.3 Hz, J_{BX} 7.4 Hz, C<u>H</u>$_2$N), 2.73 (2H, m, C<u>H</u>N), 2.04 (2H, m, Cy-Cα), 1.85 (2H, m, Cy-Cα), 1.49 (4H, q, J 7.4 Hz, $NCH_2C\underline{H}_2CH_3$), 1.36 (4H, m, Cy-C$\beta$) and 0.89 (6H, t, J 7.4 Hz, $NCH_2CH_2C\underline{H}_3$); δ_C (50 MHZ, $CDCl_3$) 164.6, 62.1, 44.4, 28.5, 24.1, 21.4 and 11.3; m/z 225 (MH^+, 100%).

trans-4,5-Tetramethyleneimidazolidine-2-thione **16** - *trans*-1,2-Diaminocyclohexane **2** (6.0ml, 50.0mmol), water (12ml) and ethanol (12ml) were placed in a 100ml RB flask fitted with a reflux condenser and with a pressure-equalising dropping funnel on top of that. The apparatus was placed in an oil-bath and the dropping funnel was charged with carbon disulphide (3.5ml, 58.2mmol). Approximately 20% of the carbon disulphide was added causing a rapid exothermic reaction. The oil-bath was then heated to 80°C and the remainder of the carbon disulphide added dropwise ensuring that the product did not start precipitating out of solution. At the end of the addition the reaction was heated at reflux for 1 h and then acidified with 5.0M hydrochloric acid (0.5ml) and allowed to reflux for 12 h. On cooling, the desired product precipitated out from

solution and could be collected by filtration. Washing with a little cold ethanol removed some of the beige colour and gave **16** as a white fluffy solid, (7.32g, 94%), m.p. 148-150°C (Found; C, 53.85; H, 7.8; N, 17.9. $C_7H_{12}N_2S$ requires C, 53.8; H, 7.7; N, 17.9%); ν_{max} ($CHCl_3$)/cm^{-1} 3430br (N-H), 2940 (C-H), 1580 (N-CS-N) and 1350 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 6.24 (2H, bs, NH), 3.31 (2H, m, CHN), 2.06 (2H, m, Cy-Cα), 1.85 (2H, m, Cy-Cα) and 1.57-1.30 (4H, m, Cy-Cβ); δ_C (50 MHz, $CDCl_3$) 187.5, 64.7, 28.8 and 23.7; m/z 157 (MH^+, 100%).

trans-4,5-Diphenylimidazolidine-2-thione **17** - Racemic 1,2-diphenyl-1,2-diaminoethane **3** (stilbene diamine) (21.2g, 100mmol) was reacted with carbon disulphide (7.0ml, 116mmol) in a water-ethanol solvent system (1:1 - 100ml), under identical conditions to those described above for the formation of **16**, to give *trans*-4,5-diphenylimidazolidine-2-thione **17** as a cream solid, (22.90g, 90%), m.p. 212-214°C (Found; C, 71.1; H, 5.5; N, 11.4. $C_{15}H_{14}N_2S$ requires C, 70.8; H, 5.55; N, 11.0%); ν_{max} ($CHCl_3$)/cm^{-1} 3440br (N-H), 2955 (C-H), 1490 (N-CS-N) and 1168 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 7.39 (6H, m, Ph), 7.28 (4H, m, Ph), 6.39 (2H, bs, NH) and 4.82 (2H, s, PhCH); δ_C (50 MHz. $CDCl_3$) 183.8, 139.2, 129.2, 128.9, 126.5 and 70.1; m/z 255 (MH^+, 100%).

1,3-Diacetyl-trans-4,5-tetramethyleneimidazolidine-2-thione **18** - To a solution of *trans*-4,5-tetramethyleneimidazolidine-2-thione **16** (4.00g, 25.6mmol) in dichloromethane (100ml) at ambient temperature was added 4-(dimethylamino)pyridine (~20mg, cat.) and pyridine (5.0ml, 62.1mmol). The reaction was allowed to stir for 5 min before cautious addition of acetyl chloride (5.0ml, 70.3mmol) which caused a vigorous exothermic reaction resulting in the reaction being brought to reflux. After the addition had been completed (~10 min) the reaction was allowed to stir at ambient temperature for 12 h before the reaction was quenched by addition of water (100ml). The organic layer was separated and the combined organic layers were dried over $MgSO_4$ before solvent evaporation gave a yellow solid. This was recrystallised from cyclohexane to give **18** as a white crystalline solid, (4.40g, 71%), m.p. 119-120°C (Found; C, 54.7; H, 6.8; N, 11.45. $C_{11}H_{16}N_2O_2S$ requires C, 55.0; H, 6.7; N, 11.7%); ν_{max} ($CHCl_3$)/cm^{-1} 2940 (C-H), 1705 (N-CO), and 1309 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 3.52 (2H, m, CHN), 2.76 (6H, s, $COCH_3$), 2.78 (2H, m, Cy-Cα), 1.92 (2H, m, Cy-Cα) and 1.51-1.26 (4H, m, Cy-Cβ); δ_C (50 MHz, $CDCl_3$) 181.1, 174.4, 64.0, 28.5, 28.4 and 24.2; m/z 241 (MH^+, 100%).

1,3-Dipropionyl-trans-4,5-tetramethyleneimidazolidine-2-thione **19** - In an analogous manner to that described above for the synthesis of **18**, treatment of *trans*-4,5-tetramethyleneimidazolidine-2-thione **16** (16.5g, 106mmol) with pyridine (21.5ml, 267mmol) and propionyl chloride (24.5ml, 282mmol) in dichloromethane (240ml) in the presence of a catalytic amount of 4-(dimethylamino)pyridine gave **19** as a white, highly crystalline solid (an analytical sample was obtained by recrystallisation from ethanol-cyclohexane, 1:1), (24.5g, 87%), m.p. 87-89°C (Found; C, 58.3; H, 7.7; N, 10.2. $C_{13}H_{20}N_2O_2S$ requires C, 58.2; H, 7.5; N, 10.4%); ν_{max} ($CHCl_3$)/cm^{-1} 2940 (C-H), 1702 (N-CO), 1460 (N-CS-N) and 1309 (N-CS-N); δ_H 3.50 (300 MHz, $CDCl_3$) (2H, m, CHN), 3.42, 2.96 (4H, ABX_3 system, J_{AB} 17.0 Hz, J_{AX} 7.4 Hz, J_{BX} 7.3 Hz, $COCH_2$), 2.68 (2H, m, Cy-Cα), 1.88 (2H, m, Cy-Cα), 1.50-1.20 (4H, m, Cy-Cβ) and 1.20 (6H, t, J 7.3 Hz, $COCH_2CH_3$); δ_C (50 MHz, $CDCl_3$) 180.9, 178.8, 64.0, 33.6, 28.4, 24.1 and 9.1; m/z 269 (MH^+, 100%).

1,3-Dibutanonyl-trans-4,5-tetramethyleneimidazolidine-2-thione **20** - In an analogous manner to that described above for the synthesis of **18**, treatment of *trans*-4,5-tetramethyleneimidazolidine-2-thione (**16**) (2.70g, 17.3mmol) with pyridine (3.0ml, 37.2mmol) and butanonyl chloride (3.0ml, 35.0mmol) in dichloromethane (100ml) in the presence of a catalytic amount of 4-(dimethylamino)pyridine gave a brown oil as the crude product. Chromatography on silica gel (eluting with dichloromethane) gave a yellow oil which solidified on standing to give **20** as a white crystalline solid, (3.50g, 83%), m.p. 75-77°C (Found; C, 60.5; H, 8.4; N, 9.2. $C_{15}H_{24}N_2O_2S$ requires C, 60.8; H, 8.2; N, 9.45%); ν_{max} ($CHCl_3$)/cm^{-1} 1699 (N-CO), 1458 (N-CS-N) and 1304 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 3.50 (2H, m, C<u>H</u>N), 3.22, 3.09 (4H, ABXY system, J_{AB} 16.1 Hz, J_{AX} 8.1 Hz, J_{AY} 6.4 Hz, J_{BX} 7.0 Hz, J_{BY} 7.0 Hz, COC<u>H</u>$_2$), 2.68 (2H, m, Cy-Cα), 1.88 (2H, m, Cy-Cα), 1.74 (4H, m, $COCH_2C\underline{H}_2CH_3$), 1.45-1.28 (4H, m, Cy-Cβ) and 0.97 (6H, t, J 7.4 Hz, $COCH_2CH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 180.8, 178.0, 64.0, 41.9, 28.3, 24.1, 18.7 and 13.4; m/z 297 (MH^+, 100%).

1,3-Di(3-phenylpropionyl)-trans-4,5-tetramethyleneimidazolidine-2-thione **21** - In an analogous manner to that described above for the synthesis of **18**, treatment of *trans*-4,5-tetramethyleneimidazolidine-2-thione **16** (4.0g, 25.6mmol) with pyridine (5.0ml, 62.1mmol) and 3-phenylpropionyl chloride (9.0ml, 60.6mmol) in dichloromethane (100ml) in the presence of a catalytic amount of 4-(dimethylamino)pyridine gave a beige solid which, on recrystallisation from ethanol, gave **21** as a white crystalline solid, (8.11g, 75%), m.p. 132-134°C (Found; C, 71.75; H, 6.7; N, 6.9. $C_{25}H_{28}N_2O_2S$ requires C, 71.4; H, 6.7; N, 6.7%); ν_{max} ($CHCl_3$)/cm^{-1} 2940 (C-H), 1699 (N-CO), 1450 (N-CS-N) and 1303 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 7.32-7.18 (10H, m, Ph), 3.58-3.40 (4H, m, COC<u>H</u>$_2$), 3.38 (2H, m, C<u>H</u>N), 3.14-2.95 (4H, m, PhC<u>H</u>$_2$), 2.54 (2H, m, Cy-Cα), 1.80 (2H, m, Cy-Cα), 1.36 (2H, m, Cy-Cβ) and 1.01 (2H, m, Cy-Cβ); δ_C (50 MHz, $CDCl_3$) 180.3, 177.0, 140.5, 128.6, 128.5, 126.4, 64.1, 41.4, 31.2, 28.0 and 24.1; m/z 421 (MH^+, 100%).

1,3-Diacetyl-trans-4,5-diphenylimidazolidine-2-thione **22** - To a solution of *trans*-4,5-diphenylimidazolidine-2-thione **17** (1.00g, 3.93mmol) in dichloromethane (25ml) at ambient temperature was added 4-(dimethylamino)pyridine (~5mg, cat.) and pyridine (0.9ml, 11.2mmol). The reaction was allowed to stir for 5 min before cautious addition of acetyl chloride (1.0ml, 14.1mmol), which caused a vigorous exothermic reaction resulting in the reaction being brought to reflux. After the addition had been completed (~10 min) the reaction was allowed to stir at ambient temperature for 18 h before the reaction was quenched by addition of water (25ml). The organic layer was separated, the aqueous layer was extracted with dichloromethane (2x20ml) and the combined organic layers were dried over Na_2SO_4 before solvent evaporation gave a yellow solid (1.25g, 94%). This was recrystallised from chloroform-ethanol (1:3) to give **22** as a crystalline white solid, (974mg, 73%), m.p. 134-135°C (Found; C, 67.5; H, 5.4; N, 8.15. $C_{19}H_{18}N_2O_2S$ requires C, 67.4; H, 5.4; N, 8.3%); ν_{max} ($CHCl_3$)/cm^{-1} 1696 (N-CO), 1452 (N-CS-N) and 1350 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 7.43-7.35 (6H, m, Ph), 7.27-7.23 (4H, m, Ph), 5.40 (2H, s, PhC<u>H</u>) and 2.86 (6H, s, COC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 178.4, 171.8, 139.4, 129.5, 128.8, 125.2, 66.6 and 27.6; m/z 339 (MH^+, 100%).

1,3-Dipropionyl-trans-4,5-diphenylimidazolidine-2-thione **23** - In an analogous manner to that described above for the synthesis of **22**, treatment of *trans*-4,5-diphenylimidazolidine-2-thione **17** (5.0g, 19.7mmol)

with pyridine (4.0ml, 50.0mmol) and propionyl chloride (5.0ml, 57.6mmol) in dichloromethane (100ml) in the presence of a catalytic amount of 4-(dimethylamino)pyridine gave **23** as a white crystalline solid (an analytical sample was recrystallised from ethanol-cyclohexane, 1:1), (6.18g, 88%), m.p. 92-94°C (found; C, 68.5; H, 6.3; N, 7.5. $C_{21}H_{22}N_2O_2S$ requires C, 68.8; H, 6.05; N, 7.6%); ν_{max} ($CHCl_3$)/cm^{-1} 1694 (N-CO), 1452 (N-CS-N) and 1342 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 7.43-7.32 (6H, m, Ph), 7.26-7.23 (4H, m, Ph), 5.38 (2H, s, PhC<u>H</u>), 3.43, 3.30 (4H, ABX_3 system, J_{AB} 18.1 Hz, J_{AX} 7.3 Hz, J_{BX} 7.3 Hz, $COC\underline{H}_2$) and 1.15 (6H, t, J 7.3 Hz, $COCH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 177.7, 175.8, 139.8, 129.5, 128.7, 128.7, 66.8, 32.9 and 8.6; m/z 367 (MH^+, 100%).

1,3-Dibutanoyl-trans-4,5-diphenylimidazolidine-2-thione **24** - In an analogous manner to that described above for the synthesis of **22**, treatment of *trans*-4,5-diphenylimidazolidine-2-thione **17** (320mg, 1.26mmol) with pyridine (0.3ml, 3.72mmol) and butanoyl chloride (0.5ml, 48.1mmol) in dichloromethane (10ml) in the presence of a catalytic amount of 4-(dimethylamino)pyridine gave a yellow oil which solidified on standing. Chromatography on silica gel (eluting with dichloromethane) gave **24** as a white crystalline solid, (436mg, 88%), m.p. 57-59°C (Found; C, 70.0; H, 6.8; N, 7.2. $C_{23}H_{26}N_2O_2S$ requires C, 70.0; H, 6.6; N, 7.1%); ν_{max} ($CHCl_3$)/cm^{-1} 1692 (N-CO), 1451 (N-CS-N) and 1353 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 7.42-7.32 (6H, m, Ph), 7.26-7.22 (4H, m, Ph), 5.36 (2H, s, PhC<u>H</u>), 3.35, 3.27 (4H, ABXY system, J_{AB} 17.0 Hz, J_{AX} 8.1 Hz, J_{AY} 6.5 Hz, J_{BX} 8.0 Hz, J_{BY} 6.7 Hz, $COC\underline{H}_2$), 1.68 (4H, m, $COCH_2C\underline{H}_2$) and 0.93 (6H, t, J 7.4 Hz, $COCH_2CH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 177.7, 174.9, 139.7, 129.4, 128.7, 125.2, 66.8, 40.8, 18.0 and 13.4; m/z 395 (MH^+, 100%).

1,3-Di(3-phenylpropionyl)-trans-4,5-diphenylimidazolidine-2-thione **25** - Pyridine (0.25ml, 3.11mmol), 4-(dimethylamino)pyridine (5mg, cat.) and 3-phenyl-propionyl chloride (601mg, 3.56mmol) were added to a solution of *trans*-4,5-diphenylimidazolidine-2-thione **17** (300mg, 1.18mmol) in dichloromethane (40ml) at ambient temperature. The reaction was heated under reflux for 36 h before being quenched by addition of water (20ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (2x25ml). The combined organic layers were dried over $MgSO_4$ and evaporated down to a yellow solid which was chromatographed on silica gel (eluting with dichloromethane) to give **25** as a cream solid, (418mg, 68%), m.p. 97-99°C (Found; C, 76.4; H, 6.1; N, 5.1. $C_{33}H_{30}N_2O_2S$ requires C, 76.4; H, 5.8; N, 5.4%); ν_{max} ($CHCl_3$)/cm^{-1} 1692 (N-CO), 1452 (N-CS-N), 1358 (N-CS-N) and 699 (Ph, C-H); δ_H (300 MHz, $CDCl_3$) 7.47-7.24 (20H, m, Ph), 6.62 (2H, bs, N<u>H</u>), 5.45 (2H, s, PhC<u>H</u>), 3.74 (4H, m, $COC\underline{H}_2$) and 3.04 (4H, m, $COCH_2C\underline{H}_2$); δ_C (50 MHz, $CDCl_3$) 177.6, 174.2, 140.6, 139.5, 129.5, 128.8, 128.7, 128.6, 126.4, 125.3, 66.9, 40.5 and 30.5; m/z 519 (MH^+, 100%).

2-Thiomethoxy-trans-4,5-tetramethylene-4,5-dihydroimidazole **26** - Methyl iodide (0.5ml, excess) was added to *trans*-4,5-tetramethyleneimidazolidine-2-thione **16** (230mg, 1.47mmol) in dichloromethane (2ml) and the resulting solution stirred at ambient temperature for 12 h. Excess methyl iodide was removed *in vacuo* to give a white crystalline solid identified as the hydrogen iodide salt. The free base was liberated by dissolving the salt in diethyl ether (10ml) and washing with a saturated aqueous solution of sodium bicarbonate (25ml). Separation of the organic phase, drying over $MgSO_4$ and solvent evaporation afforded **26** as a white crystalline solid, (247mg, 96%), m.p. 122-123°C (Found; C, 56.5; H, 8.6; N, 16.5. $C_8H_{14}N_2S$ requires C, 56.4; H,

8.3; N, 16.45%); ν_{max} ($CHCl_3$)/cm^{-1} 3100 (N-H), 2950 (C-H) and 1356 (C-S); δ_H (300 MHz, $CDCl_3$) 4.40 (1H, br s, NH), 3.21 (2H, m, CHN), 2.64 (3H, s, SCH_3), 2.21 (2H, m, Cy-C_α), 1.84 (2H, m, Cy-C_α) and 1.53-1.29 (4H, m, Cy-C_β); δ_C (50 MHz, $CDCl_3$) 170.0, 68.1, 29.7, 24.2 and 14.2; m/z 171 (MH^+, 100%).

1,3-Diacetyl-trans-4,5-tetramethyleneimidazolidin-2-one **27** - To a solution of 1,3-diacetyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **18** (500mg, 2.08mmol) in dichloromethane (10ml) at ambient temperature was added mercury (II) acetate (750mg, 2.35mmol). The reaction was allowed to stir for 12 h before the reaction mixture was filtered through celite (washed with dichloromethane) and then stirred with fresh mercury (II) acetate (350mg, 1.10mmol) for 12 h more. 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. As this solid could not be readily purified by recrystallisation it was sublimed *in vacuo* (s.p. 60°C / 0.7mmHg) to give **27** as a white crystalline solid, (356mg, 76%), m.p. 83-85°C (Found; C, 58.6; H, 7.5; N, 12.25. $C_{11}H_{16}N_2O_3$ requires C, 58.9; H, 7.2; N, 12.5%); ν_{max} ($CHCl_3$)/cm^{-1} 2940 (C-H), 1751 (N-CO-N), 1701 (N-CO) and 1369 (N-CO-CH_2); δ_H (300 MHz, $CDCl_3$) 3.37 (2H, m, CHN), 2.89 (2H, m, Cy-C_α), 2.50 (6H, s, $COCH_3$), 1.87 (2H, m, Cy-C_α) and 1.52-1.33 (4H, m, Cy-C_β); δ_C (50 MHz, $CDCl_3$) 172.9, 154.7, 60.5, 28.7, 25.3 and 24.1; m/z 225 (MH^+, 100%).

1,3-Dipropionyl-trans-4,5-tetramethyleneimidazolidin-2-one **28** - In a manner analogous to that described for the synthesis of **27**, treatment of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **19** (24.5g, 91.3mmol) with two batches of mercury (II) acetate (29.8g, 93.5mmol and 11.2g, 35.1mmol) in dichloromethane (2x200ml) gave a cream solid. Chromatography through a short plug of silica gel (eluting with dichloromethane) gave **28** as a white crystalline solid (an analytical sample was recrystallised from ethanol-cyclohexane, 1:1), (20.32g, 88%), m.p. 65-67°C (Found; C, 61.8; H, 7.9; N, 11.1. $C_{13}H_{20}N_2O_3$ requires C, 61.9; H, 8.0; N, 11.1%); ν_{max} ($CHCl_3$)/cm^{-1} 1746 (N-CO-N) and 1702 (N-CO); δ_H (300 MHz, $CDCl_3$) 3.39 (2H, m, CHN), 3.04, 2.77 (4H, ABX_3 system, J_{AB} 17.6 Hz, J_{AX} 7.4 Hz, J_{BX} 7.3 Hz, $COCH_2$), 2.89 (2H, m, Cy-C_α), 1.88 (2H, m, Cy-C_α), 1.53-1.33 (4H, m, Cy-C_β) and 1.16 (6H, t, J 7.3 Hz, $COCH_2CH_3$); δ_C (50 MHz, $CDCl_3$) 176.9, 154.6, 60.6, 30.7, 28.8, 24.2 and 8.3; m/z 253 (MH^+, 100%).

1,3-Dibutanoyl-trans-4,5-tetramethyleneimidazolidin-2-one **29** - In a manner analogous to that described above for the synthesis of **27**, treatment of 1,3-dibutanoyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **20** (7.75g, 26.1mmol) with two batches of mercury (II) acetate (9.0g, 28.2mmol and 1.50g, 4.70mmol) in diethyl ether (2x75ml) gave a cream solid. Chromatography through a short plug of silica gel (eluting with dichloromethane) gave **29** as a white crystalline solid (an analytical sample was recrystallised from ethanol), (5.13g, 70%), m.p. 53-54°C (Found; C, 64.2; H, 8.9; N, 9.8. $C_{15}H_{24}N_2O_3$ requires C, 64.3; H, 8.6; N, 10.0%); ν_{max} ($CHCl_3$)/cm^{-1} 2940 (C-H), 1743 (N-CO-N) and 1698 (N-CO); δ_H (300 MHz, $CDCl_3$) 3.38 (2H, m, CHN), 2.96-2.75 (4H, m, $COCH_2$), 2.89 (2H, m, Cy-C_α), 1.87 (2H, m, Cy-C_α), 1.73-1.62 (4H, m, $COCH_2CH_2CH_3$), 1.52-1.31 (4H, m, Cy-C_β) and 0.98 (6H, t, J 7.4 Hz, $COCH_2CH_2CH_3$); δ_C (50 MHz, $CDCl_3$) 176.1, 154.6, 60.5, 39.2, 28.8, 24.2, 17.8 and 13.5; m/z 281 (MH^+, 100%).

1,3-Di(3-phenylpropionyl)-trans-4,5-tetramethyleneimidazolidin-2-one **30** - In a manner analogous to that described above for the synthesis of **27**, treatment of 1,3-di(3-phenylpropionyl)-*trans*-4,5-

tetramethyleneimidazolidine-2-thione **21** (2.00g, 4.76mmol) with two batches of mercury (II) acetate (2.00g, 6.28mmol and 0.80g, 2.51mmol) in dichloromethane (2x50ml) gave a cream solid. Chromatography through a short plug of silica gel (eluting with dichloromethane) gave **30** as a white crystalline solid (an analytical sample was recrystallised from ethanol), (1.58g, 82%), m.p. 133-135°C (Found; C, 74.35; H, 7.2; N, 6.7. $C_{25}H_{28}N_2O_3$ requires C, 74.2; H, 7.0; N, 6.9%); ν_{max} ($CHCl_3$)/cm^{-1} 1747 (N-CO-N) and 1699 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.31-7.17 (10H, m, Ph), 3.35 (2H, m, C<u>H</u>N), 3.29, 3.13 (4H, ABXY system, J_{AB} 17.2 Hz, J_{AX} 9.0 Hz, J_{AY} 6.1 Hz, J_{BX} 8.3 Hz, J_{BY} 6.8 Hz, COC<u>H</u>$_2$), 2.99 (4H, m, PhC<u>H</u>$_2$), 2.86 (2H, m, Cy-Cα), 1.87 (2H, m, Cy-Cα) and 1.50-1.27 (4H, m, Cy-Cβ); δ_C (50 MHz, $CDCl_3$) 175.2, 152.4, 140.8, 128.6, 128.5, 126.3, 60.6, 38.9, 30.4, 28.7 and 24.2; m/z 405 (MH^+, 100%).

1,3-Diacetyl-trans-4,5-diphenylimidazolidin-2-one **31** - In a manner analogous to that described above for the synthesis of **27**, treatment of 1,3-diacetyl-*trans*-4,5-diphenylimidazolidine-2-thione **22** (501mg, 1.48mmol) with two batches of mercury (II) acetate (550mg, 1.73mmol and 200mg, 0.63mmol) in dichloromethane (2x25ml) gave a cream solid. Chromatography through a short plug of silica gel (eluting with dichloromethane) gave **31** as a white crystalline solid, (444mg, 93%), m.p. 130-132°C (Found; C, 70.9; H, 5.8; N, 8.7. $C_{19}H_{18}N_2O_3$ requires C, 70.8; H, 5.6; N, 8.7%); ν_{max} ($CHCl_3$)/cm^{-1} 1751 (N-CO-N) and 1720 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.43-7.34 (6H, m, Ph), 7.26-7.23 (4H, m, Ph), 5.16 (2H, s, PhC<u>H</u>) and 2.62 (6H, s, COC<u>H</u>$_3$); δ_C (50 MHz, $CDCl_3$) 170.2, 152.5, 139.7, 129.4, 128.8, 125.3, 62.3 and 24.5; m/z 323 (MH^+, 100%).

1,3-Dipropionyl-trans-4,5-diphenylimidazolidin-2-one **32** - In a manner analogous to that described above for the synthesis of **27**, treatment of 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidine-2-thione **23** (3.80g, 10.4mmol) with two batches of mercury (II) acetate (4.80g, 15.1mmol and 1.20g, 3.80mmol) in dichloromethane (2x50ml) gave a cream solid. Chromatography through a short plug of silica gel (eluting with dichloromethane) gave **32** as a white crystalline solid, (3.30g, 91%), m.p. 112-114°C (Found; C, 71.8; H, 6.4; N, 8.1. $C_{21}H_{22}N_2O_3$ requires C, 72.0; H, 6.3; N, 8.0%); ν_{max} ($CHCl_3$)/cm^{-1} 1750 (N-CO-N) and 1694 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.43-7.34 (6H, m, Ph), 7.26-7.23 (4H, m, Ph), 5.16 (2H, s, PhC<u>H</u>), 3.05 (4H, q, J 7.3 Hz, COC<u>H</u>$_2$) and 1.17 (6H, t, J 7.3 Hz, $COCH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 174.1, 152.4, 139.9, 129.4, 128.7, 125.3, 62.4, 30.0 and 8.1; m/z 351 (MH^+, 100%).

1,3-Dibutanoyl-trans-4,5-diphenylimidazolidin-2-one **33** - In a manner analogous to that described above for the synthesis of **27**, treatment of 1,3-dibutanoyl-*trans*-4,5-diphenylimidazolidine-2-thione **24** (3.15g, 8.00mmol) with two batches of mercury (II) acetate (3.35g, 10.5mmol and 1.10g, 3.45mmol) in dichloromethane (2x75ml) gave an oily solid. Chromatography through a short plug of silica gel (eluting with dichloromethane) gave **33** as a white crystalline solid, (2.61g, 87%), m.p. 74-75°C (Found; C, 73.1; H, 7.2; N, 7.1. $C_{23}H_{26}N_2O_3$ requires C, 73.0; H, 6.9; N, 7.4%); ν_{max} ($CHCl_3$)/cm^{-1} 1744 (N-CO-N) and 1692 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.42-7.34 (6H, m, Ph), 7.26-7.22 (4H, m, Ph), 5.15 (2H, s, PhC<u>H</u>), 3.35, 3.27 (4H, ABX_2 system, J_{AB} 12.8 Hz, J_{AX} 7.6 Hz, J_{BX} 8.5 Hz, COC<u>H</u>$_2$), 1.68 (4H, sextet, J 7.4 Hz, $COCH_2C\underline{H}_2$) and 0.96 (6H, t, J 7.4 Hz, $COCH_2CH_2C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 173.3, 152.3, 139.9, 129.4, 128.7, 125.3, 62.3, 38.3, 17.6 and 13.5; m/z 379 (MH^+, 100%).

1,3-Di(3-phenylpropionyl)-trans-4,5-diphenylimidazolidin-2-one **34** - In a manner analogous to that described above for the synthesis of **27**, treatment of 1,3-di(3-phenylpropionyl)-*trans*-4,5-diphenylimidazolidine-2-thione **25** (350mg, 0.68mmol) with two batches of mercury (II) acetate (300mg, 0.94mmol and 100mg, 0.31mmol) in dichloromethane (2x50ml) gave a colourless oil. This was crystallised by allowing an ether solution of the oil to slowly evaporate which gave **34** as a white crystalline solid, (314mg, 93%), m.p. 91-93°C (Found; C, 78.9; H, 6.4; N, 5.5. $C_{33}H_{30}N_2O_3$ requires C, 78.9; H, 6.0; N, 5.6%); ν_{max} ($CHCl_3$)/cm^{-1} 1750 (N-CO-N) and 1699 (N-CO); δ_H (300 MHz, $CDCl_3$) 7.26-7.20 (4H, m, Ph), 7.18-7.14 (4H, m, Ph), 7.18-7.14 (6H, m, Ph), 7.02-7.00 (4H, m, Ph), 6.58-6.54 (2H, m, Ph), 5.19 (2H, s, PhC<u>H</u>), 2.92 (4H, m, $COCH_2$) and 2.47 (4H, m, $COCH_2CH_2$); δ_C (50 MHz, $CDCl_3$) 172.5, 152.2, 140.5, 139.7, 129.4, 128.7, 128.6, 127.1, 126.3, 125.3, 62.4, 37.9 and 30.1; m/z 503 (MH^+, 100%).

(R,R)-(+)-trans-4,5-tetramethyleneimidazolidine-2-thione **(*R*,*R*)-(+)-16** - In a manner entirely analogous to the preparation of racemic **16**, (R,R)-(-)-*trans*-1,2-diaminocyclohexane **(*R*,*R*)-(-)-2** (824mg, 7.22mmol) was reacted with carbon disulphide (0.55ml, 9.11mmol) in a mixture of water (2ml) and ethanol (2ml). At the end of the reaction, the precipitate was collected by filtration (661mg), the filtrate was evaporated to dryness, triturated with dichloromethane (2x20ml) and the resulting organic solution evaporated down to a white solid (141mg). The combined yield of **(*R*,*R*)-(+)-16** was thus 802mg (71%); all spectroscopic data were in agreement with that obtained from racemic samples; $[\alpha]_D^{20}$ +54.2 (c = 1.10, $CHCl_3$).

(R,R)-(-)-1,3-Dipropionyl-trans-4,5-tetramethyleneimidazolidine-2-thione **(*R*,*R*)-(-)-19** - In an analogous manner to that described above for the synthesis of racemic **19**, treatment of (R,R)-(+)-*trans*-4,5-tetramethyleneimidazolidine-2-thione **(*R*,*R*)-(+)-16** (700mg, 4.48mmol) with pyridine (0.90ml, 11.1mmol) and propionyl chloride (1.20ml, 13.8mmol) in dichloromethane (15ml) in the presence of a catalytic amount of 4-(dimethylamino)pyridine gave **(*R*,*R*)-(-)-19** as a white crystalline solid after chromatography on silica gel with dichloromethane as eluent (981mg, 82%); all spectroscopic data were in agreement with that obtained from racemic samples; $[\alpha]_D^{20}$ -183 (c = 0.30, $CHCl_3$).

(R,R)-(-)-1,3-Dipropionyl-trans-4,5-tetramethyleneimidazolidin-2-one **(*R*,*R*)-(-)-28** - In an analogous manner to that described above for the synthesis of **27**, treatment of (R,R)-(-)-1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **(*R*,*R*)-(-)-19** (950mg, 3.54 mmol) with two batches of mercury (II) acetate (1.10g, 3.45mmol and 320mg, 1.00mmol) in dichloromethane (2x35ml) gave a white amorphous solid, (871mg, 98%). Chromatography on silica gel with dichloromethane as eluent gave **(*R*,*R*)-(-)-28** as a white crystalline solid (773mg, 87%). All spectroscopic data were in agreement with that obtained from racemic samples; $[\alpha]_D^{20}$ -151.3 (c = 0.23, $CHCl_3$).

(R,R)-(+)-trans-4,5-diphenylimidazolidine-2-thione **(*R*,*R*)-(+)-17** - In a manner entirely analogous to the preparation of racemic **17**, (R,R)-(+)-1,2-diphenyl-1,2-diaminoethane **(*R*,*R*)-(+)-3**[29,35] (4.20g, 19.8mmol) was reacted with carbon disulphide (1.45ml, 24.0mmol) in a mixture of water (10ml) and ethanol (10ml). At the end of the reaction, the precipitate was collected by filtration to give **(*R*,*R*)-(+)-17** as cream needles (3.64g, 71%). All spectroscopic data were in agreement with that obtained from racemic samples; $[\alpha]_D^{20}$ +65 (c = 0.25, $CHCl_3$).

(R,R)-(-)-1,3-Dipropionyl-trans-4,5-diphenylimidazolidin-2-one **(*R*,*R*)-(-)-32** - In an analogous manner to that described above for the synthesis of racemic **23**, treatment of (R,R)-(+)-*trans*-4,5-diphenylimidazolidine-2-thione **(*R*,*R*)-(+)-17** (199mg, 0.78mmol) with pyridine (0.15ml, 1.86mmol) and propionyl chloride (0.40ml, 4.60mmol) in dichloromethane (5ml) in the presence of a catalytic amount of 4-(dimethylamino)pyridine gave a white solid 161mg, 56%). This was not isolated but treated with two batches of mercury (II) acetate (154mg, 0.48mmol and 60mg, 0.19mmol) in dichloromethane (2x5ml) to give **(*R*,*R*)-(-)-32** as a white amorphous solid, after chromatography on silica gel with dichloromethane as eluent (122mg, 79%). All spectroscopic data were in agreement with that obtained from racemic samples; $[\alpha]_D^{20}$ -101.5 (c = 1.00, $CHCl_3$).

1,3-Dioctadecanoyl-trans-4,5-tetramethyleneimidazolidine-2-thione **35** - *trans*-4,5-Tetramethyleneimidazolidine-2-thione **16** (1.00g, 6.40mmol) was stirred with pyridine (1.30ml, 14.0mmol) and octadecanoyl chloride (4.90g, 16.0mmol) in dichloromethane (35ml) in the presence of a catalytic amount of 4-(dimethylamino)pyridine for 12 h at ambient temperature. The reaction was quenched by addition of water (75ml), hexane (35ml) was added and the solid material collected by suction filtration. The product was washed with water (2x25ml) and diethyl ether (20ml) to give **35** as a white crystalline solid, (4.27g, 97%), m.p. 71-73°C (Found; C, 74.8; H, 12.0; N, 3.8. $C_{43}H_{80}N_2O_2S$ requires C, 74.9; H, 11.7; N, 4.1%); ν_{max} $(CHCl_3)/cm^{-1}$ 1701 (N-CO), 1461 (N-CS-N) and 1302 (N-CS-N); δ_H (300 MHz, $CDCl_3$) 3.48 (2H, m, C<u>H</u>N), 3.21, 3.11 (4H, ABX_2 system, J_{AB} 15.2 Hz, J_{AX} 6.8 Hz, J_{BX} 6.8 Hz, $COC\underline{H}_2$) 2.67 (2H, m, Cy-Cα), 1.89 (2H, m, Cy-Cα), 1.68 (4H, m, $COCH_2C\underline{H}_2$), 1.44 (2H, m, Cy-Cβ), 1.26 (2H, m, Cy-Cβ) 1.26 (56H, m, $COCH_2CH_2(C\underline{H}_2)_n$) and 0.89 (6H, t, J 6.7 Hz, $C\underline{H}_3$); δ_C (50 MHz, $CDCl_3$) 181.0 (<u>C</u>=S), 178.2, 64.0, 40.1, 28.3, 24.2, 31.8-22.5 and 13.9; m/z 690 (MH^+, 100%).

1,3-Dioctadecanoyl-trans-4,5-tetramethyleneimidazolidin-2-one **36** - In a manner analogous to that described above for the synthesis of **27**, treatment of 1,3-dioctadecanoyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **35** (320mg, 0.46mmol) with two batches of mercury (II) acetate (155mg, 0.49mmol and 60mg, 0.19mmol) in chloroform (12ml) gave **36** as a white amorphous solid, after chromatography through a short plug of silica gel (eluting with dichloromethane), (302mg, 97%), m.p. 49-51°C, (Found; C, 76.9; H, 12.0; N, 4.3. $C_{43}H_{80}N_2O_3$ requires C, 76.7; H, 12.0; N, 4.2%); ν_{max} $(CHCl_3)/cm^{-1}$ 1745 (N-CO-N) and 1702 (N-CO-CH_2); δ_H (300 MHz, $CDCl_3$) 3.38 (2H, m, C<u>H</u>N), 2.89 (4H, m, $COC\underline{H}_2$), 2.89 (2H, m, Cy-Cα), 1.87 (2H, m, Cy-Cα), 1.62 (4H, m, $COCH_2C\underline{H}_2$), 1.48 (2H, m, Cy-Cβ), 1.26 (2H, m, Cy-Cβ) 1.26 (56H, m, $COCH_2CH_2(C\underline{H}_2)_n$) and 0.89 (6H, t, J 6.7 Hz, $C\underline{H}_3$); ^{13}C n.m.r. δ_C 176.3, 154.8, 60.5, 37.3, 28.8, 24.2, 34.2-22.5 and 13.9; m/z 674 (MH^+, 100%).

trans-4,5-Tetramethyleneimidazolidin-2-one **4** - *trans*-1,2-Diaminocyclohexane **2** (2.01ml, 16.7mmol), ethanol (10ml) and water (10ml) were placed in a 50ml RB flask fitted with a gas inlet and reflux condenser, the top of which was connected to two Drechsel bottles filled with 4.0M aqueous potassium hydroxide solution. The reaction was allowed to stir at ambient temperature and a slow stream of carbonyl sulphide was introduced from a lecture bottle causing an exothermic reaction and a slight change of colour to yellow, over 10 min. The reaction was stirred at ambient temperature for a further 30 min (during which time a solid began to

precipitate out of solution) and then heated to reflux and acidified with 5.0M hydrochloric acid (0.2ml). The reaction was heated under reflux for 12 h, cooled, evaporated *in vacuo* and the residue triturated with chloroform (2x40ml). The organic layers were dried over $MgSO_4$ and evaporated to a brown solid. Washing a dichloromethane solution of this solid with 0.5M hydrochloric acid followed by drying and solvent evaporation gave **4** as a white flaky solid, (1.64g, 70%), m.p. 229-231°C (Found; C, 59.7; H, 8.95; N, 20.1. $C_7H_{12}N_2O$ requires C, 60.0; H, 8.6; N, 20.0%); ν_{max} ($CHCl_3$)/cm^{-1} 3430br (N-H), 2940 (C-H) and 1706 (N-CO-N); δ_H (300 MHz, $CDCl_3$) 4.61 (2H, bs, NH), 3.16 (2H, m, CHN), 1.97 (2H, m, Cy-C_α), 1.82 (2H, m, Cy-C_α) and 1.48-1.32 (4H, m, Cy-C_β); δ_C (50 MHz, $CDCl_3$) 166.2, 61.0, 29.3 and 23.8; m/z 141 (MH^+, 100%).

1,3-Dipropionyl-trans-4,5-tetramethyleneimidazolidin-2-one **28** - Sodium hydride (60% dispersion in mineral oil) (24mg, 0.60mmol) was added to a THF solution of *trans*-4,5-tetramethyleneimidazolidin-2-one **4** (30mg, 0.21mmol) at ambient temperature and allowed to stir for 1 h. Propionyl chloride (0.2ml, excess) was added and the reaction stirred for a further 3 h before the reaction was quenched by addition of water (0.5ml). The THF was removed *in vacuo* and the resulting aqueous phase extracted with dichloromethane (3x5ml), dried over $MgSO_4$ and evaporated to give **28** as a white amorphous solid, (49mg, 91%). This was identical to a sample prepared by treatment of **19** with mercury (II) acetate.

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