Catalytic and stoichiometric approaches to the desymmetrisation of centrosymmetric piperazines by enantioselective acylation: a total synthesis of Dragmacidin A†

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The enantioselective desymmetrisation of centrosymmetric piperazines was investigated using both catalytic and stoichiometric asymmetric acylation approaches. The catalytic approach involved the desymmetrisation of 2,5-*trans*-dimethylpiperazine under the control of chiral DMAP analogues. With one equivalent of piperazine, relative to the acylating agent, low yields of products were obtained in up to 70% ee. It was shown that an inevitable 'proof reading' effect was occurring which increased the enantiomeric excess of the desymmetrised product through its kinetic resolution. The desymmetrisation of centrosymmetric piperazines with chiral acylating agents [(1*R*,2*R*)-*N*-formyl-1,2-bis(pentafluorobenzenesulfonamido)cyclohexane and (1*R*,2*R*)-*N*-acetyl-1,2-bis(trifluoromethanesulfonamido)-cyclohexane] was also studied. The yield and enantioselectivity of the process was highly dependent on the solvent used and the substitution of the piperazine. However, in some cases, good yields of enantiomerically enriched products could be obtained (up to 87% based on the limiting chiral reagent) in good enantiomeric excesses (up to 84% ee). The approach was exploited in the total synthesis of Dragmacidin A.

Introduction

The *trans*-2,5-dimethyl piperazine ring system may be regarded as a 'privileged'[1] fragment for ligand design. The ring system is present in over 3000 reported compounds described in over 900 papers and patents, of which approximately 600 describe studies of biological activity:‡ it is found in pharmaceutical leads for the treatment of a wide range of conditions including gastrointestinal[2] and immune system disorders,[3] inflammation[3] and HIV.[4] Examples of biologically active *trans*-2,5-dimethyl piperazines include the pyruvate dehydrogenase kinase inhibitor[5] **1** and the δ-opioid receptor agonist **2**.[6] In addition, many of the Dragmacidin and Hamacanthin alkaloids, including Dragacidin A (**3**) contain 2,5-disubstituted piperazine ring systems.

Despite the prevalence of the *trans*-2,5-dimethyl piperazine ring system in biologically active molecules, asymmetric syntheses of its *N*-substituted analogues are often highly unsatisfactory.[5,6] For example, allylation of *trans*-2,5-dimethyl piperazine gives a 50% yield of the inevitably racemic monoallylated product which must be subsequently resolved.[6] A six step procedure has, however, been developed to convert the unwanted, monoallylated enantiomer into its antipode in good yield.[7] Furthermore, despite the centrosymmetric fragments which embedded in the structures of a range of natural products,[8] this hidden symmetry has only been exploited in the synthesis of an early intermediate in a total synthesis of Hemibrevetoxin B.[9] Nonetheless, a few asymmetric reactions have now been exploited in the desymmetrisation of centrosymmetric molecules: asymmetric reduction,[10] enantioselective epoxide hydrolysis[9] and enzymatic acylation.[11]

An alternative approach to the synthesis of *N*-substituted *trans*-2,5-disubstituted piperazines could involve the desymmetrisation of the centrosymmetric ring system (Scheme 1): the nitrogen atoms of **4** and **5** are enantiotopic, and are 'coded' by the absolute configuration of their neighbouring stereogenic centres. Hence, enantioselective functionalisation of either **4** or **5** would remove the centre of symmetry, and could yield the corresponding *N*-substituted piperazines in high yield and enantiomeric excess. In this paper, we describe the desymmetrisation of centrosymmetric piperazines using both catalytic and stoichiometric methods to yield enantiomerically enriched *N*-acyl piperazines such as **6** and **7**. The synthetic strategy was then applied in an enantioselective total synthesis of the alkaloid, Dragmacidin A (**3**).

Synthesis of racemic samples

Racemic samples of potential desymmetrisation products were prepared using the reactions described in Scheme 2. Hence, the centrosymmetric piperazine **4** was reacted with one equivalent of methyl chloroformate, and subsequently derivatised with β-naphthoyl chloride: the chiral piperazine **10a**, and the centrosymmetric piperazines **9** and **11** were obtained in 31%, 32% and 26% yield respectively. The unsymmetrical piperazine **10a** could be easily resolved by chiral analytical HPLC.

The corresponding *N*-acetyl derivative **10b** was prepared in a similar way. Hence, monoprotection of the centrosymmeric piperazine **4** as its mono-Cbz derivative **12** was achieved in 36% yield. Acetylation (→**13**), hydrogenolytic removal of the Cbz

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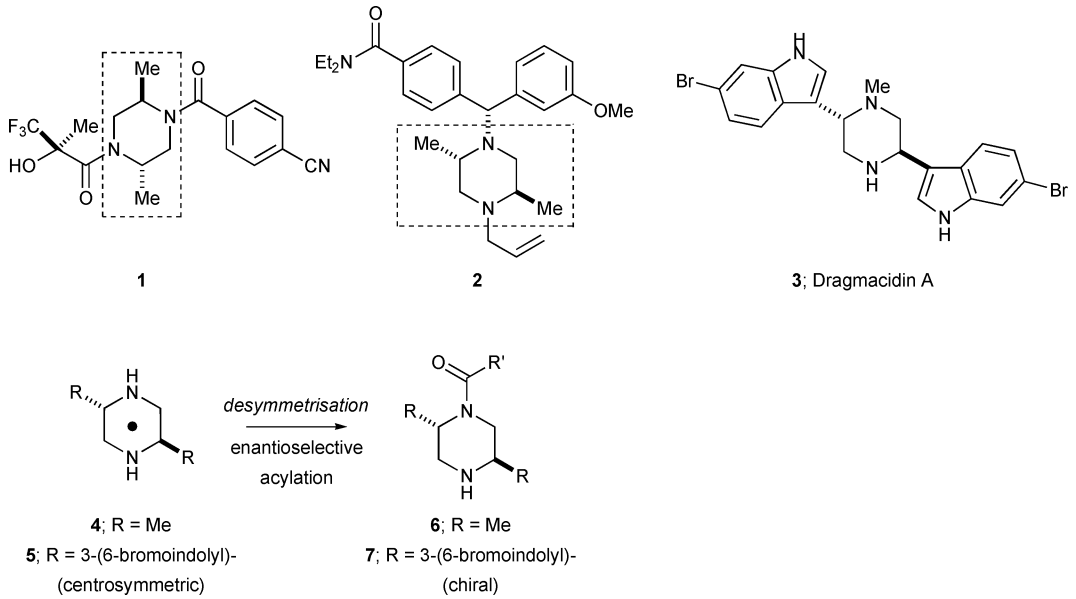
‡ These figures are based on a survey of the Scifinder Scholar Database in January 2006.



Scheme 1

group, and β-naphthoylation gave the unsymmetrical piperazine **10b**; **10b** could also be easily resolved by chiral analytical HPLC.

An alternative approach was used in the preparation of the racemic *N*-formyl piperazine **10c**. Hence, treatment of the piperazine **4** with two equivalents of butyllithium, and one equivalent of β-naphthoyl chloride, gave the monosubstituted piperazine **15** in 42% yield; formylation of **15** provided a racemic standard of the *N*-formyl piperazine **10c** which could also be resolved by analytical chiral HPLC.

Desymmetrisation of centrosymmetric piperazines by catalytic asymmetric acylation

The catalytic asymmetric acylation of amines is challenging because the reactivity of the acylating agent needs to be tuned such that it reacts more rapidly with the nucleophilic catalyst than (unselectively) with the amine reactant. The only example of a non-enzymatic catalytic enantioselective acylation of amines has been described by Fu:[12a] a range of racemic amines have been kinetically resolved using a chiral DMAP derivative in conjunction with the *O*-methoxycarbonylated azlactone **19**. Fu's optimised system involved the use of 10 mol% of the chiral catalyst in chloroform at −50 °C, and selectivity factors in the range of $S = 12–27$ were observed in the kinetic resolution of a series of substituted α-methyl benzylamines.[12a]

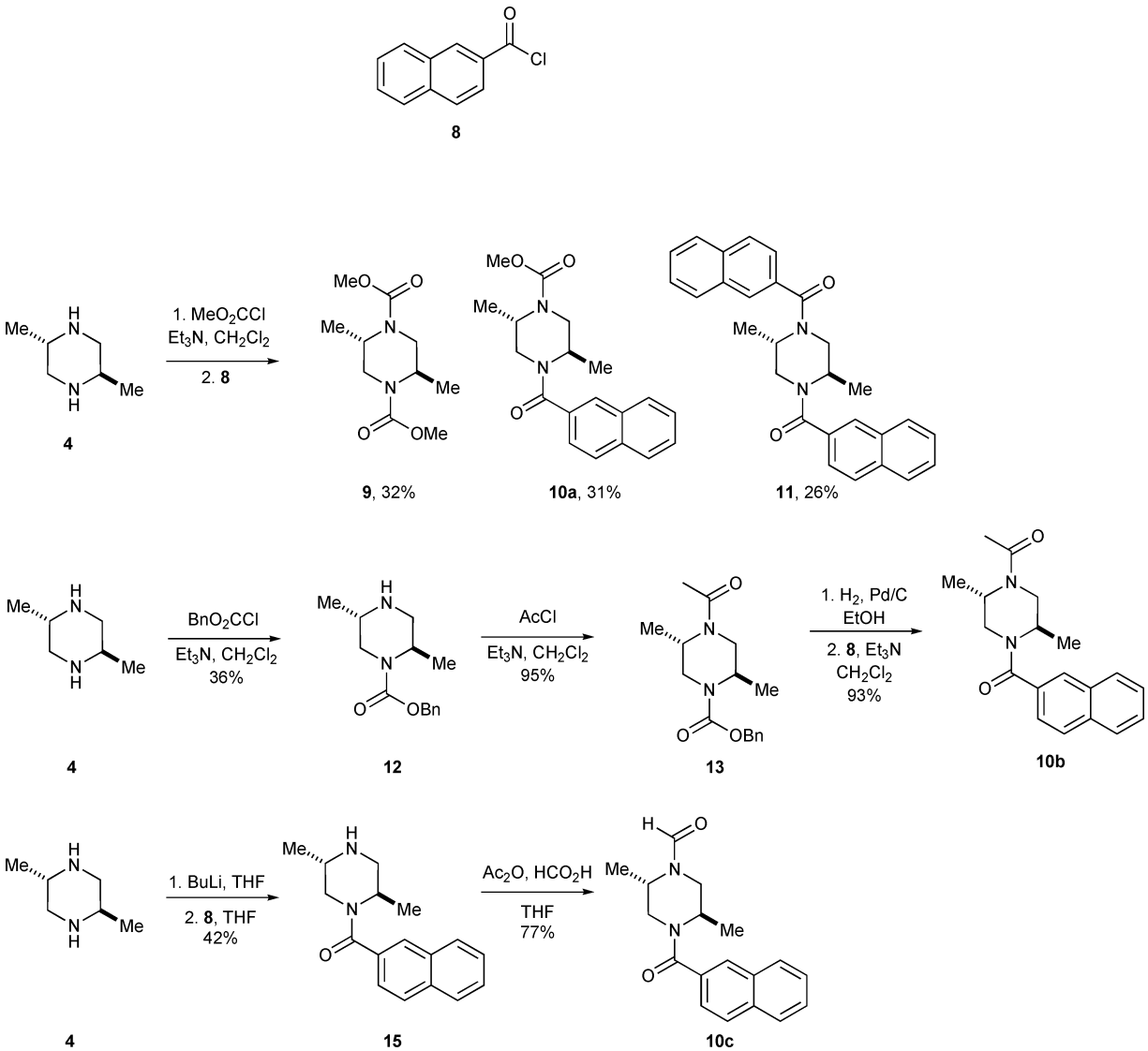
The catalytic asymmetric acylation of the centrosymmetric piperazine **4** was investigated using the chiral DMAP analogues[12] (*R*)-**16**,[13] (*S*)-**17**[14] and (*R*)-**18**.[15] In each experiment, the piperazine **4** was treated with the acylating agent **19** in chloroform in the presence of a catalytic quantity of DMAP analogue (Scheme 3); the initial products were acylated with β-naphthoyl chloride, and the ratio of the desymmetrised product **10a** and the centrosymmetric bis-amide **11** (derived from acylation of any unreacted starting material) was determined by analytical HPLC. The enantiomeric excess of the desymmetrised product **10a** was determined by chiral analytical HPLC. The conditions screened, and our results, are summarised in Table 1.

In order to assess the likely intervention of the uncatalysed pathway, the direct reaction between the piperazine **4** and the acylating agent **19** was studied. The reaction between **4** and **19** in dichloromethane was complete within 5 minutes at room temperature, suggesting that the background reaction was likely to be significant under these conditions. In contrast, no reaction between **4** and **19** was detected after 4 hours at −42 °C in chloroform,§ and attention was, therefore, focused on catalysed reactions under these conditions.

With 5 mol% DMAP, the acylating agent **19** was completely consumed within 2 hours at −42 °C in chloroform. After β-naphthoylation, yields of the desymmetrised product **10a** and the acylated starting material (**11**), determined by analytical HPLC, were 25% and 40% respectively (entry 1, Table 1). We were surprised to isolate a worse than statistical yield of the desymmetrised product.

Our initial results with the chiral DMAP analogues (*R*)-**16**, (*S*)-**17** and (*R*)-**18** are described in Table 1 (see entries 2a–b, 3a and 4a). With 20 mol% of Fu's catalyst, (*R*)-**16**, no reaction was observed after 7 hours at −42 °C in chloroform (data not shown).¶ It was clear that the catalyst (*R*)-**16** was considerably less active than DMAP, presumably because 2-substituents reduce the catalyst's nucleophilicity.[16] At −18 °C, with the reagent added in three equal batches 48 hours apart, the acylating agent **19** was completely consumed after 7 days; after β-naphthoylation, the desymmetrised product **10a** was obtained in 25% isolated yield and 44% ee (entry 2a). The sense of enantioselectivity observed is unknown, and the absolute configuration of the desymmetrised product is drawn arbitrarily. At 0 °C, the reaction was considerably faster, though less enantioselective: after 16 hours, with the acylating agent **19** added in two portions eight hours apart, the piperazine **10a** was obtained, after β-naphthoylation, in 23% isolated yield and 33% ee

§ Under these conditions, all components of the reaction were completely soluble at a reasonable (0.12 M) concentration of the reactants **4** and **19**.
¶ In this experiment, the acylation agent **19** was added in two equal batches.



Scheme 2

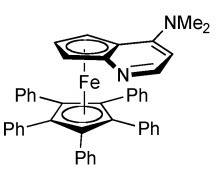
(entry 2b). Under these conditions, it is likely that the uncatalysed pathway intervenes significantly.

Spivey's catalyst (*S*)-**17** and Vedejs' catalyst (*R*)-**18** were much more active than Fu's catalyst (*R*)-**16**. With both (*S*)-**17** and (*R*)-**18**, the acylating reagent **19** was consumed within a reasonable timeframe at −42 °C. With 5 mol% (*S*)-**17**, the desymmetrised product was obtained in rather low yield and 70% ee after 7 hours and subsequent β-naphthoylation (entry 3a, Table 1); the sense of enantioselectivity was the opposite to that observed with (*R*)-**16**. The catalyst (*R*)-**18** was rather less active than (*S*)-**17** and,

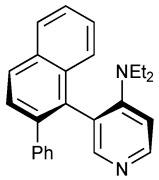
Table 1 Desymmetrisation of the centrosymmetric piperazine **4** by catalytic enantioselective methoxycarbonylation (see Scheme 3)

					10a		**11**
Entry	Catalyst (mol%[a])	Eq. **4**[a]	Temp./°C	Time/h	Yield[b] (%)	Ee[c]	Yield[b] (%)
1	DMAP	1	−42	2	25	–	40
2a	(*R*)-**16** (20)	1	−18	164[d]	25[e]	44	39[e]
2b		1	0	16[f]	23[e]	33	37[e]
3a	(*S*)-**17** (5)	1	−42	7	20	−70	43
3b		10	−42	4	43[g]	−26	[h]
4a	(*R*)-**18** (5)	1	−42	14	22	64	34
4b		10	−42	7	49[g]	23	[h]

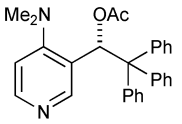
[a] Relative to the reagent **19**. [b] Unless otherwise stated, determined by analytical HPLC by calibration against external standards. [c] Determined by chiral analytical HPLC; negative values indicate that the sense of asymmetric induction was reversed. [d] The reagent was added in three batches. [e] Yield of isolated product obtained after flash column chromatography. [f] The reagent was added in two batches. [g] Yield based on the reagent **19**. [h] Not detected.



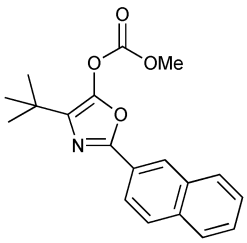
(*R*)-**16**



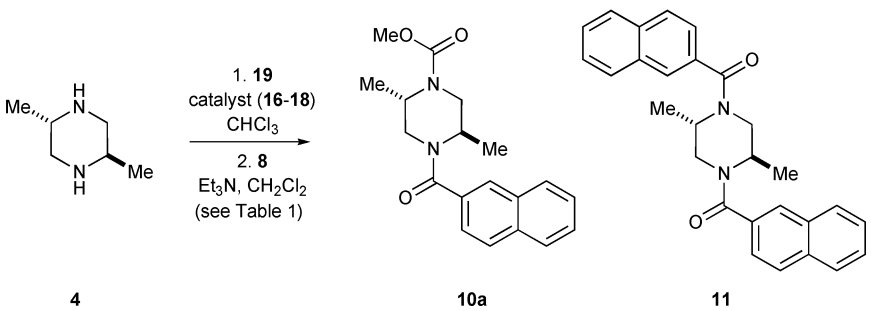
(*S*)-**17**



(*R*)-**18**



19



4 **10a** **11**

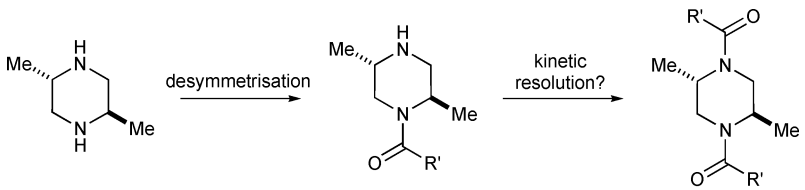
Scheme 3

under the same conditions, the reaction required 14 hours to reach completion. After β-naphthoylation, the desymmetrised product **10a** was obtained in similar enantiomeric excess (64% ee) though the sense of asymmetric induction was reversed (entry 4a). The yield (22%) of **10a** was, however, disappointing.

'Proof-reading' in the catalytic asymmetric desymmetrisation reaction

The low yields of the desymmetrised product **10a** obtained with the chiral catalysts **16–18** stemmed from further reaction of the required product with the acylating agent (**19**) under the conditions of the reaction (entries 2a–b, 3a and 4a). We reasoned that this process may have increased the enantiomeric excess of the desymmetrised product by the selective destruction (kinetic resolution) of its minor enantiomer. This type of 'proof reading' effect, described in Scheme 4, has been previously recognised, for example in the desymmetrisation of divinyl carbinols by Sharpless asymmetric epoxidation.[17]

To investgate the possibility of a 'proof reading' effect, the reactions catalysed by (*S*)-**17** and (*R*)-**18** were repeated using ten equivalents of the centrosymmetric piperazine **4** relative to the acylating agent **19**. Under these conditions, it was expected that the second acylation would be suppressed, and the genuine enantioselectivity of the desymmetrisation step could be determined. In each case, the desymmetrisation product **10a** was



4 **6** improved ee through proof reading? **20**

Scheme 4

Table 2 Desymmetrisation of the centrosymmetric piperazine **4** by enantioselective acylation with the chiral reagents **21** and **22** (see Scheme 5)

			4	Et_3N	**11**	Monoacylated product		
Entry	Reagent	Solvent	Eq.[a]	Eq.[a]	Yield[b] (%)	Product	Yield[b] (%)	Ee[c] (%)
1	**21**	DMPU	1	—	[d]	**10b**	[d]	57
2a	**21**	DMF	1	—	41	**10b**	20	75
2b	**21**	DMF	2	—	—	**10b**	48[e]	84
2c	**21**	DMF	10	—	—	**10b**	87[e]	73
3a	**21**	DMF	1	3	37	**10b**	31	84
3b	**21**	DMF	2	10	—	**10b**	51[e]	81
4	**22**	$CDCl_3$	1	—	[df]	**10c**	66	28
5	**22**	DMSO-d_6	1	—	[d]	**10c**	<10[g]	28
6	**22**	DMF	1	—	[d]	**10c**	[d]	35
7	**22**	Dioxane	1	—	[d]	**10c**	48[g]	−10

[a] Relative to the reagent **21** or **22**. [b] Unless otherwise stated, isolated yield of purified compound. [c] Determined by chiral analytical HPLC; negative values indicate that the sense of asymmetric induction was reversed. [d] Not determined. [e] Yield based on the reagent **19**. [f] The yield of the diacylated product **23c**, determined by 300 Hz ^{1}H NMR spectroscopic analysis of the crude reaction mixture, was <10%. [g] Determined by 300 Hz ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

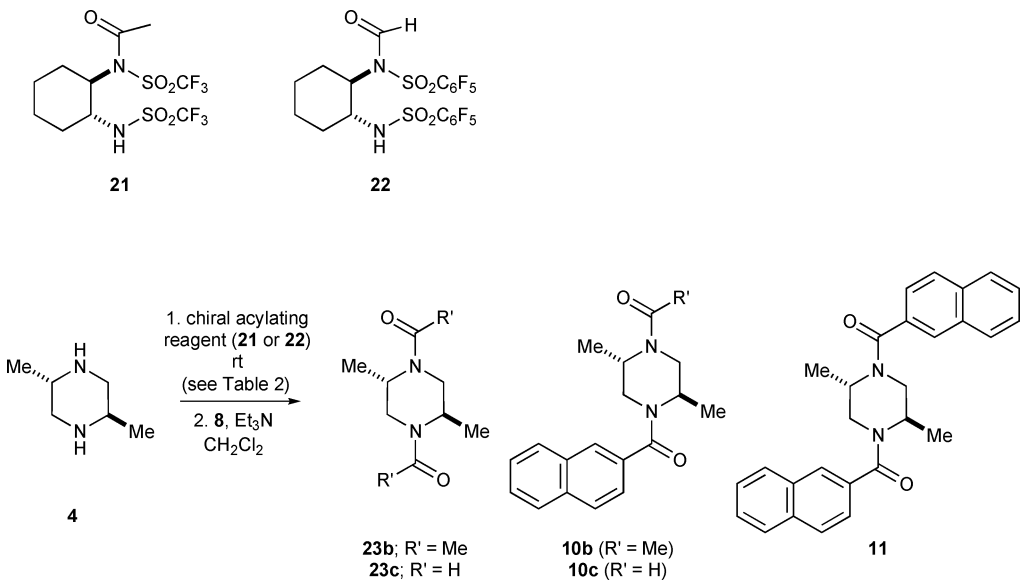
obtained, after β-naphthoylation, in higher yield (based on the reagent **19**) but with reduced enantiomeric excess (compare entry 3b with entry 3a, and entry 4b with entry 4a). With both (*S*)-**17** and (*R*)-**18**, and one equivalent of the acylating agent **19**, enhancement of the enantiomeric excess of the desymmetrised product did occur at the expense of yield. Unfortunately, the 'proof reading' effect was an inevitable consequence of the relative rates of the two acylation steps: the experimenter is not, therefore, able to choose an appropriate compromise between the yield and enantiomeric excess of the product. However, with a cheap and available centrosymmetric piperazine, such as **4**, low (20–25%) yields of desymmetrised products may be obtained with reasonable enantiomeric excess.

Desymmetrisation of centrosymmetric piperazines with chiral acylating reagents

We turned our attention to the use of chiral acylating reagents for the desymmetrisation of the centrosymmetric piperazine **4**. We focused on the acetylation reagent[18] **21**, and the formylating reagent **22**, prepared by formylation of the corresponding bis-sulfonamide. Our results are summarised in Scheme 5 and Table 2.

Dipolar aprotic solvents, such as DMPU, DMF and HMPA, have been previously shown to be most effective in the kinetic resolution of chiral primary amines by acetylation with the reagent **21**. We therefore studied the reaction of the centrosymmetric piperazine **4** with one equivalent of the chiral acetylating agent **21** (entries 1 and 2a, Table 2). In DMPU, the desymmetrised product **10b** was obtained, after β-naphthoylation, in extremely low yield and 57% ee (entry 1). In DMF, the results were also disappointing, and a 20% yield of **10b** was obtained, albeit with 75% ee (entry 2a).

A comparison of the estimated[19] pK_a value of the deacetylated bis-sulfonamide (pK_a: 5.6 ± 0.4) with the estimated[19] pK_{aH} values of the piperazine **4** (pK_{aH}: 10.0 ± 0.6) and the monoacetylated product (pK_{aH}: 8.1 ± 0.7) suggested that, as the reaction proceeded, the concentration of the piperazine **4** was being unnecessarily depleted by its selective protonation. Such an effect would selectively reduce the rate of the first acetylation and, hence,



Scheme 5

the yield of the required product. Addition of three equivalents of triethylamine (pK_{aH}: 10.65,[20] 10.6 ± 0.3[19]) to the acetylation reaction increased the yield of desymmetrised product to 31%, suggesting that this effect was significant (compare entry 3a with entry 2a, Table 1).

Nevertheless, the yield of the required product was still rather low, and it was possible that the enantiomeric excess of the products was being enhanced once more through an inevitable 'proof reading' mechanism. The desymmetrisation reaction was, therefore, repeated with both two and ten equivalents of the piperazine: in each case, the second acetylation reaction was suppressed, and the yield of the desymmetrised product (relative to the limiting reagent **21**) increased dramatically (compare entries 2b and 2c with entry 2a, Table 2). However, in each case, the enantiomeric excess of the desymmetrised product was similar to that obtained with one equivalent of reagent. This observation indicated that, although the yield of the product was less diminished by a competing, second acetylation, it is the first acetylation that is enantioselective. 'Proof reading' does not, therefore, occur. Increasing the number of equivalents of the piperazine **4**, relative to the acetylation reagent **21**, does not, therefore, reduce the enantiomeric excess of the required, desymmetrised product. Indeed, with 10 equivalents of triethylamine and two equivalents of the piperazine **4**, relative to the acetylation reagent **21**, a reasonable yield (51% based on the limiting reagent) of the desymmetrised product was obtained in 81% ee (entry 3b).

With the chiral formylating reagent **22**, the nature of the solvent had a profound effect on the distribution of products (entries 4–7, Table 2). In deuterated chloroform, the major product was, after β-naphthoylation, the required desymmetrised product **10c**, and only a trace of the disubstituted piperazine **23c** was detected (entry 4). In contrast, in the dipolar aprotic solvents DMSO-d_6 (entry 5) and DMF (entry 6), only small amounts of the desymmetrised product were obtained, together with substantial amounts of the diformylated product **23c**. Under these conditions, the second formylation step was much faster than the first. In each case, the enantiomeric excess of the desymmetrised product **10c** was determined by chiral analytical HPLC. Unfortunately, disappointing enantiomeric excesses were observed, with a very low, though reversed, sense of asymmetric induction in dioxane (entry 7). Previously, the sense and magnitude of asymmetric induction in the kinetic resolution of chiral primary amines with the reagent **21** has been shown to be highly dependent on the nature of the solvent used.[18]

Total synthesis of Dragmacidin A

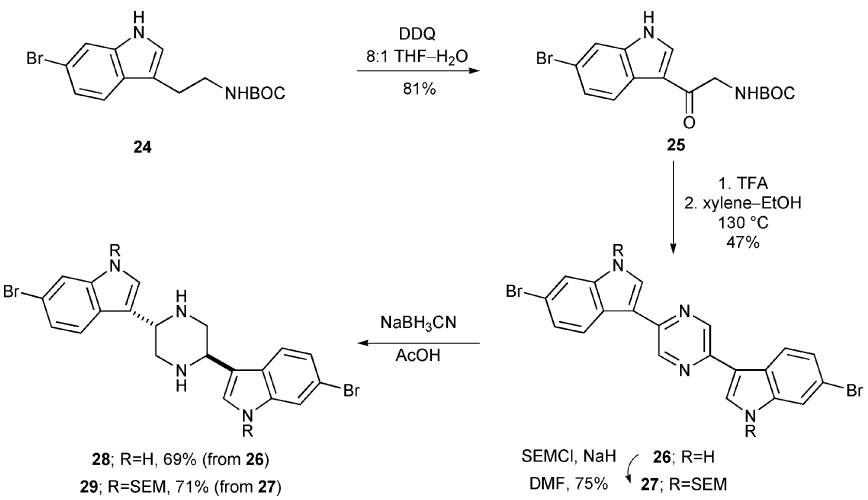
The desymmetrisation of a centrosymmetric piperazine was exploited in a total synthesis of Dragmacidin A (**3**). The protected 6-bromo tryptamine derivative[21] **24** was oxidized to yield the amino ketone derivative **25**, which was deprotected and condensed to yield the pyrazine **26** (Scheme 6).[6] SEM-protection (→**27**) and diastereoselective reduction[6] (90 : 10 *trans–cis*) gave the required centrosymmetric piperazine **29**.

A range of solvents were screened for the key desymmetrisation step (see Scheme 7 and Table 3). Treatment of the centrosymmetric piperzine **29** with the reagent **22** in chloroform gave the desymmetrised product **30** in 61% yield (entry 1, Table 3); however, although these conditions give good yield of the desymmetrised product (compare entry 1, Table 3 with entry 4, Table 2), its enantiomeric excess was very low. Of the other solvents screened (entries 2–8, Table 3), the best result was obtained in dioxane:

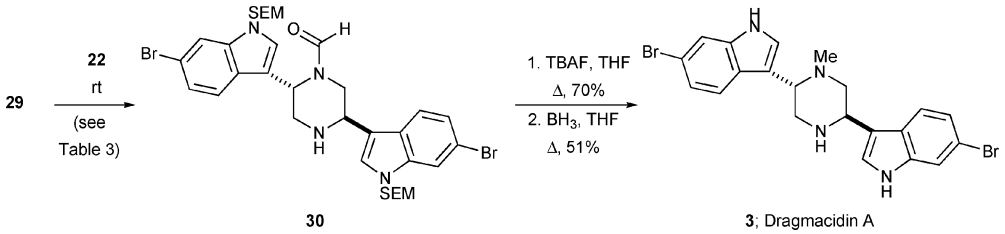
Table 3 Desymmetrisation of the centrosymmetric piperazine **29** by enantioselective formylation with the reagent **22** (see Scheme 7)

		Product **30**	
Entry	Solvent	Yield[a] (%)	Ee[b] (%)
1	$CDCl_3$	61	−12
2	DMF	46	0
3	THF	70	19
4	Toluene	50[c]	−13
5	Acetone[d]	24[c]	1
6	EtOAc[d]	31[c]	6
7	Cl_3CCH_2OH	62	−3
8	Dioxane	66	48

[a] Isolated yield of purified compound. [b] Determined by chiral analytical HPLC; negative values indicate that the sense of asymmetric induction was reversed. [c] The reaction did not reach completion. [d] The piperazine **29** was only sparingly soluble under the reaction conditions.



Scheme 6



Scheme 7

under these conditions, the required desymmetrised product, **30**, was obtained in 66% yield and 48% ee (entry 8).

The enantiomerically enriched formamide **30** was converted into Dragmacidin A (Scheme 7). Removal of the SEM groups with TBAF, and reduction with borane, gave the *N*-methyl piperazine, which was spectroscopically identical to the natural product.[22] A sample of Dragmacidin A, prepared by Jiang *et al.*,[23] was reported to have 96% ee and an optical rotation of +4.0 in chloroform. The sample which we prepared had 48% ee and a rotation of +5.9 (in chloroform) or +5.8 (in acetone). The piperazine **3** is believed to have the same absolute configuration as that previously prepared by Jiang,[23] although the reasons for the discrepancy in the magnitude of the optical rotation measurement are unclear.

Summary

The enantioselective desymmetrisation of centrosymmetric piperazines was investigated using both catalytic and stoichiometric asymmetric approaches. The catalysts (*S*)-**17** and (*R*)-**18**, developed by Spivey and Vedejs respectively, were used for the first time in the enantioselective acylation of amines. In the catalytic approach investigated, an inevitable 'proof reading' effect was found to increase to enantiomeric excesses of the desymmetrised products at the expense of yield.

The reaction of centrosymmetric piperazines with chiral acylating agents yielded the corresponding desymmetrised products. The yield and enantioselectivity of the process was highly dependent on the solvent used and the substitution of the piperazine. However, in some cases, good yields of enantiomerically enriched products could be obtained, particularly if the acylating agent was used as the limiting reagent. The approach was applied in the total synthesis of Dragmacidin A.

Experimental

General procedure for desymmetrisation of *trans*-2,5-dimethylpiperazine with chiral DMAP analogues and the reagent 19

A solution of the reagent[12] **19** (97 mg, 0.298 mmol) in chloroform (0.5 mL) was added to a solution of *trans*-2,5-dimethylpiperazine (32 mg, 0.284) and the chiral catalyst (0.014 mmol) in chloroform (2.0 mL) at −42 °C. After complete consumption of the reagent **19** was observed by TLC, the reaction was warmed to 0 °C and triethylamine (125 μL, 0.90 mmol) was added. A solution of 2-naphthoyl chloride (125 mg, 0.66 mmol) in chloroform (1.0 mL) was added and the mixture stirred for 30 min. Water (25 mL) and dichloromethane (25 mL) were added, and the aqueous layer separated and extracted with dichoromethane (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, a mixture of the piperazines **10a** and **11** were separated from the residue by flash chromatography (gradient elution 9 : 1 → 1 : 1 petrol–EtOAc). The yields of **10a** and **11**, relative to an external standard, and the enantiomeric excess of **10a** were determined by chiral analytical HPLC (Chiralcel® OD) monitoring at $\lambda = 250$ nm; eluting with 9 : 1 hexane–IPA, 1 mL min^{-1} over 60 min, then 3 : 2 hexane–IPA, 1 mL min^{-1} over 30 min; retention times: **10a**, 24.1 min and 32.5 min; **11**, 68.4 min (see ESI†).

General procedure for desymmetrisation of *trans*-2,5-dimethylpiperazine with the acetylating agent 21

A solution of the acetylating agent[18] **21** (120 mg, 0.286 mmol) in dimethylformamide (0.75 mL) was added to a solution of the *trans*-2,5-dimethylpiperazine (32 mg, 0.284 mmol) in dimethylformamide (2.0 mL). After 40 hours, triethylamine (180 μL, 1.29 mmol) was added, followed by a solution of 2-naphthoyl chloride (180 mg, 0.94 mmol) in dichloromethane (1.0 mL). The mixture was stirred for 30 min, concentrated under reduced pressure and the residue subjected to flash chromatography (gradient elution 9 : 1 → 0 : 1 petrol–EtOAc to give the disubstituted piperazine **11**.

Also obtained was the substituted piperazine **10b**, whose enantiomeric excess was determined by chiral analytical HPLC (Chiralcel® OD) monitoring at $\lambda = 225$ nm; eluting with 7 : 3 hexane–IPA, 1 mL min^{-1} over 40 min; retention times: 12.0 min and 16.3 min (see ESI†).

General procedure for desymmetrisation of *trans*-2,5-dimethylpiperazine with the formylating agent 22

The formylating agent **22** (75 mg, 0.125 mmol) was added to a solution of the *trans*-2,5-dimethylpiperazine (13 mg, 0.114 mmol) in a an appropriate solvent (2.0 mL). After 72 hours, sodium hydrogen carbonate (30 mg, 0.35 mmol) was added, followed by a solution of 2-naphthoyl chloride (48 mg, 0.25 mmol) in dichloromethane (1.0 mL). The mixture was stirred for 30 min, concentrated under reduced pressure and the residue subjected to flash chromatography (gradient elution 9 : 1 → 0 : 1 petrol–EtOAc to give the substituted piperazine **10c**, whose enantiomeric excess was determined by chiral analytical HPLC (Chiralcel® OD–RH) monitoring at $\lambda = 225$ nm (gradient elution: 7 : 3 → 1 : 1 water–MeCN), 1 mL min^{-1} over 40 min; retention times: 10.6 min and 12.6 min (see ESI†).

(2*R*,5*S*)-1-Formyl-2,5-bis[6-bromo-1′-(2″-trimethylsilanylethoxymethyl) indol-3′-yl]piperazine 30

The formylating agent **22** (246 mg, 0.408 mmol) was added to a solution of the piperazine **29** in dioxane (6.5 mL). After 16 days the

mixture was concentrated under reduced pressure and subjected to flash chromatography eluting with dichloromethane to remove the disulfonamide (200 mg, 81%). The elution was continued (gradient: 199 : 1 → 99 : 1 CH_2Cl_2–MeOH/NH_3) to give the *formamide* **30** (206 mg, 66%) as a pale yellow glass, R_f 0.60 (97 : 3 CH_2Cl_2–MeOH/NH_3); $[\alpha]_D$ +10.4 (*c* 1.0 in acetone); ν_{max}/cm^{-1} (film) 2955, 2924, 2855, 1736 and 1658; δ_H (300 MHz; $CDCl_3$) 7.97 (1H, s, CHO), 7.70 (1H, d, *J* 8.5, 4′-H), 7.69 (1H, d, *J* 1.5, 7′-H), 7.65 (1H, d, *J* 1.5, 7′-H), 7.50 (1H, d, *J* 8.5, 4′-H), 7.27 (4H, m, 2′-H and 5′-H), 5.45 (2H, s, 1′-NCH_2), 5.41 (2H, s, 1′-NCH_2), 4.79 (1H, dd, *J* 9.5 and 3.2, 2-H), 4.59 (1H, dd, *J* 13.1 and 3.1, 6-H_AH_B), 4.24 (1H, dd, *J* 9.6 and 3.1, 5-H), 3.48 (5H, m, 2 × 1″-H and 3-H_AH_B), 3.32 (1H, dd, *J* 11.9 and 3.2, 3-H_AH_B), 3.18 (1H, dd, *J* 13.1 and 9.6, 6-H_AH_B), 0.91 (2H, t, *J* 8.1, 2″-H), 0.91 (2H, t, *J* 8.1, 2″-H) and −0.03 (18H, s, $SiMe_3$); δ_C (75 MHz; $CDCl_3$) 161.4, 137.7, 137.6, 127.6, 126.2, 126.1, 125.9, 124.2, 123.4, 121.0, 120.9, 116.9, 116.3, 115.8, 114.4, 113.4, 110.3, 75.8, 75.8, 66.3, 66.1, 53.9, 52.4, 51.3, 46.4, 17.7, 17.7, −1.42 and −1.42; *m*/*z* (CI) 765 (4%, MH^+), 763 (5), 761 (3), 647 (57), 645 (100), 643 (53), 567 (60), 565 (53) and 487 (48); *m*/*z* (ES) (Found: $(M–C_5H_{13}OSi)^+$, 643.0728; $C_{28}H_{33}N_4O_2BrSi$ requires 643.0734). The sample was shown to have 48% ee by chiral analytical HPLC (Chiralcel® OD–RH) monitoring at $\lambda = 225$ nm (gradient elution: 23 : 77 → 1 : 4 water–MeCN), 1 mL min^{-1} over 30 min; retention times: 23.7 min and 26.7 min (see ESI†).

(2*R*,5*S*)-1-Formyl-2,5-bis[6-bromoindol-3′-yl]piperazine

Tetrabutylammonium fluoride (2.62 mL, 1 M solution in tetrahydrofuran, 2.62 mmol), was added to a stirred mixture of the formamide **30** (100 mg, 0.131 mmol) and ground 4 Å molecular sieves in tetrahydrofuran (2 mL). The reaction mixture was heated at reflux for 6 hours, cooled, filtered, diluted with acetone (10 mL), water (10 mL) and ethyl acetate (20 mL). The mixture was washed with water (3 × 10 mL) and the combined aqueous washes were washed with ethyl acetate (15 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give a crude product which was purified by flash chromatography (gradient elution: 49 : 1 → 24 : 1 CH_2Cl_2–MeOH/NH_3) to give the title compound (46 mg, 70%) as a pale yellow glass, R_f 0.31 (23 : 2 CH_2Cl_2–MeOH/NH_3); $[\alpha]_D$ +12.8 (*c* 1.0 in acetone); ν_{max}/cm^{-1} (film) 3273, 2916, 1696 and 1642; δ_H (500 MHz; acetone-d_6) 10.57 (1H, br s, 1′-NH), 10.26 (1H, br s, 1′-NH), 7.78 (1H, s, COH), 7.65 (1H, d, *J* 8.5, 4′-H), 7.55 (1H, d, *J* 1.3, 7′-H), 7.51 (1H, d, *J* 8.5, 4′-H), 7.48 (1H, d, *J* 1.3, 7′-H), 7.45 (1H, s, 2′-H), 7.28 (1H, s, 2′-H), 7.09 (1H, dd, *J* 8.5 and 1.3, 5′-H), 7.03 (1H, dd, *J* 8.5 and 1.3, 5′-H), 4.74 (1H, dd, *J* 10.1 and 3.0, 2-H), 4.35 (1H, dd, *J* 12.7 and 3.0, 6-H_AH_B), 4.09 (1H, dd, *J* 9.6 and 3.0, 5-H), 3.33 (1H, dd, *J* 11.7 and 10.1, 3-H_AH_B), 3.15 (1H, dd, *J* 11.7 and 3.0, 3-H_AH_B), 3.04 (1H, dd, *J* 12.7 and 9.6, 6-H_AH_B); δ_C (75 MHz; acetone-d_6) 161.8, 139.2, 139.0, 126.9, 126.8, 124.6, 123.9, 123.0, 122.4, 122.1, 117.4, 117.4, 116.4, 116.0, 115.8, 115.6, 111.6, 55.1, 53.8, 52.6 and 47.6; *m*/*z* (ES) 505 (54%, MH^+), 505 (100) and 503 (50); *m*/*z* (ES) (Found: MH^+, 502.9908; $C_{21}H_{19}N_4OBr_2$ requires MH, 502.9905).

(2*R*,5*S*)-1-Methyl-2,5-bis[6-bromoindol-3′-yl]piperazine 3, Dragmacidin A[22,23]

Borane–tetrahydrofuran complex (239 μL, 1 M solution in tetrahydrofuran, 0.239 mmol) was added to a stirred solution of (2*R*,5*S*)-1-formyl-2,5-bis[6-bromoindol-3′-yl]piperazine (40 mg, 0.0796 mmol) in tetrahydrofuran (4 mL). The reaction mixture was heated at reflux for 2 hours, cooled, quenched with methanol (10 mL), diluted with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a crude product which was purified by flash chromatography (gradient elution: 49 : 1 → 24 : 1 CH_2Cl_2–MeOH/NH_3) to give Dragmacidin A **3** (20 mg, 51%) as a pale yellow glass, R_f 0.56 (23 : 2 CH_2Cl_2–MeOH/NH_3); $[\alpha]_D$ +5.8 (*c* 1.0 in acetone), +5.9 (*c* 0.20 in $CHCl_3$) [lit.[23] +4.0 (*c* 0.20 in $CHCl_3$)]; ν_{max}/cm^{-1} (film) 3413, 2849, 1695, 1615, 1543 and 1454; δ_H (500 MHz; acetone-d_6) 10.29 (2H, br s, 1′-NH), 7.91 (1H, d, *J* 8.5, 4′-H), 7.80 (1H, d, *J* 8.5, 4′-H), 7.60 (2H, s, 7′-H), 7.37 (1H, d, *J* 1.9 2′-H), 7.33 (1H, d, *J* 2.1 2′-H), 7.16 (2H, d, *J* 8.5, 5′-H), 4.40 (1H, dd, *J* 10.4 and 2.6, 5-H), 3.36 (1H, dd, *J* 10.4 and 3.0, 2-H), 3.27 (1H, dd, *J* 11.7 and 10.4, 3-H_AH_B), 3.16 (1H, dd, *J* 11.0 and 2.6, 6-H_AH_B), 3.06 (1H, dd, *J* 11.7 and 3.0, 3-H_AH_B), 2.34 (1H, dd, *J* 11.0 and 10.4, 6-H_AH_B); δ_C (75 MHz; acetone-d_6) 139.1, 139.0, 126.9, 125.3, 125.1, 124.1, 123.9, 123.1, 122.8, 122.5, 119.1, 117.6, 115.7, 115.6, 115.5, 115.4, 64.9, 63.7, 55.1, 54.8 and 44.7; *m*/*z* (CI) 491 (50%, MH^+), 489 (100), 477 (57), 411 (52) and 409 (60); *m*/*z* (ES) (Found: MH^+, 487.0129; $C_{21}H_{20}N_4Br_2$ requires MH, 487.0127).

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