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Synthesis of fused tetramate-oxazolidine and -imidazolidine derivatives and their antibacterial activity†

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A chemoselective route which provides direct access to bicyclic tetramates, making use of Dieckmann cyclisation of functionalised oxazolidines and imidazolidines derived from an aminomalonate, is reported; calculations suggest that the observed chemoselectivity is kinetically controlled and leads to the thermodynamically most stable product. Some compounds in the library showed modest antibacterial activity against Gram-positive bacteria, and this activity is maximal in a well-defined region of chemical space ($554 < M_w < 722$ g mol^{-1}; $5.78 <$ cLogP < 7.16; $788 <$ MSA < 972 Å^2; $10.3 <$ rel. PSA < 19.08).

Introduction

The tetramate (pyrrolidine-2,4-dione) system occurs as the central scaffold in natural products with diverse bioactivity,[1,2] and is increasingly important as a synthetic skeleton in its own right.[3] Bicyclic derivatives may be accessed by a highly chemo-, diastereo- and enantioselective Dieckmann cyclisation of oxazolidine/thiazolidine templates **2a–g** derived from hydroxyalkyl- and thioalkyl side chain amino acids (serine **1a**, threonine **1b**, *allo*-threonine **1c**, cysteine **1d**, or *threo* **1e** and *allo*-phenylserines **1f**, Scheme 1).[4,5] Of importance is the identity of the aldehyde which is used to condense the amino acids to form the oxazolidine/thiazolidine heterocycle, which has generally been limited to pivaldehyde; this aldehyde gives a relatively stable oxazolidine/thiazolidine template **2a–g**, in which the bulky *t*-butyl group favours the most stable ring form in a ring-chain tautomeric equilibrium, and plays a significant role in the control of a subsequent diastereoselective *N*-acylation reaction and also directs the mode of the Dieckmann cyclisation towards bicyclic tetramates.[6]

For serine **1a**, threonines **1b,c** and cysteine **1d**, the Dieckmann cyclisation usually occurs from the 2,5-*cis*-malonyloxa(or thia)zolidines **2a–d** – which forms as the major product after *N*-acylation of oxazolidines – by closure from the C-5 enolate onto the side chain ethyl ester giving tetramates **4a–d** as the major product (Scheme 1, route A and inset A), placing the C-2 *t*-butyl group on the *exo*-face (that is, the less hindered convex face) of the newly generated bicyclic ring system. An alternative mode of cyclisation, starting from the 2,5-*trans*-malonyloxa(or thia)zolidines **3a–d** (which normally arise as a minor component by epimerisation at C-5 under the basic conditions of the cyclisation reaction) proceeds through closure of the more stabilised malonamide side chain enolate C7 onto the C-5 ester (Scheme 1, route B and inset A), also placing the C-2 *t*-butyl group on the *exo*-face, and which generates tetramates **5a–d** but typically only as minor products.[6] Route B closure can be achieved by adjusting reaction conditions[7] or by forcing ring closure by blocking the acidic α-position with a methyl group.[8] Such a process is not dissimilar to the biosynthesis of tetramate natural products.[9,10] We have also shown that *allo*-arylserines **1f** close by the conventional route A pathway[5] to give tetramate **4e** *via* the Dieckmann cyclisation of the major malonamide diastereomer **2g**, but interestingly, the minor 2,5-*trans* malonamide **2e** diastereomer derived from *threo*-aryl serines **1e** has been found to ring close by route B to give tetramate **5e**. The exclusive chemoselective formation of tetramates **4e** and **5e** can be explained *via* steric effects, in which the bulky C2-*t*-Bu and C4-aryl groups prefer to reside on the less hindered *exo*-face of the bicyclic lactam. On the other hand, the major 2,5-*cis* malonamide diastereomer **2f** derived from amino ester **1e** (inset B, Scheme 1) did not undergo the Dieckmann cyclisation as the C2-*t*-Bu and C4-aryl groups are

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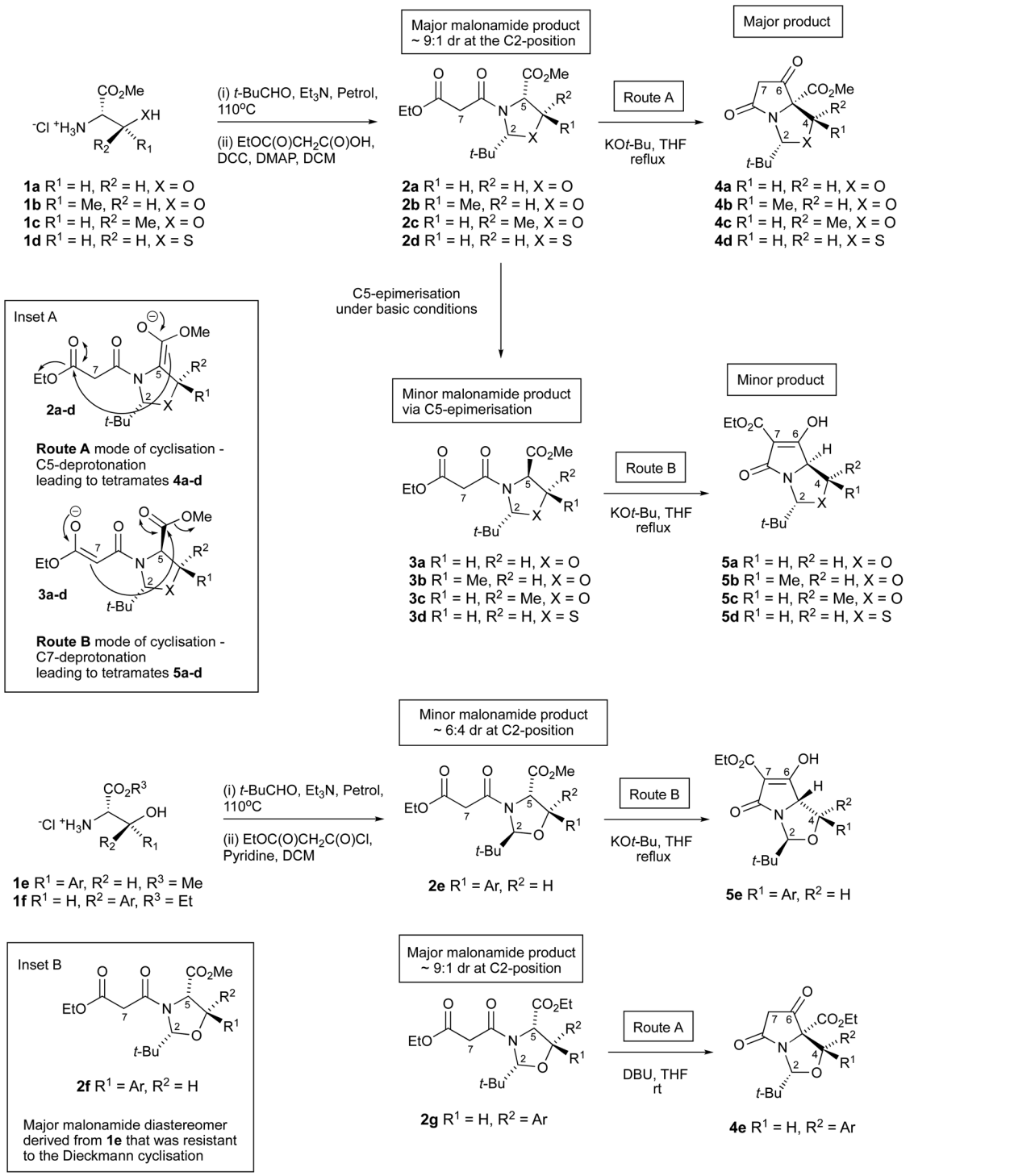
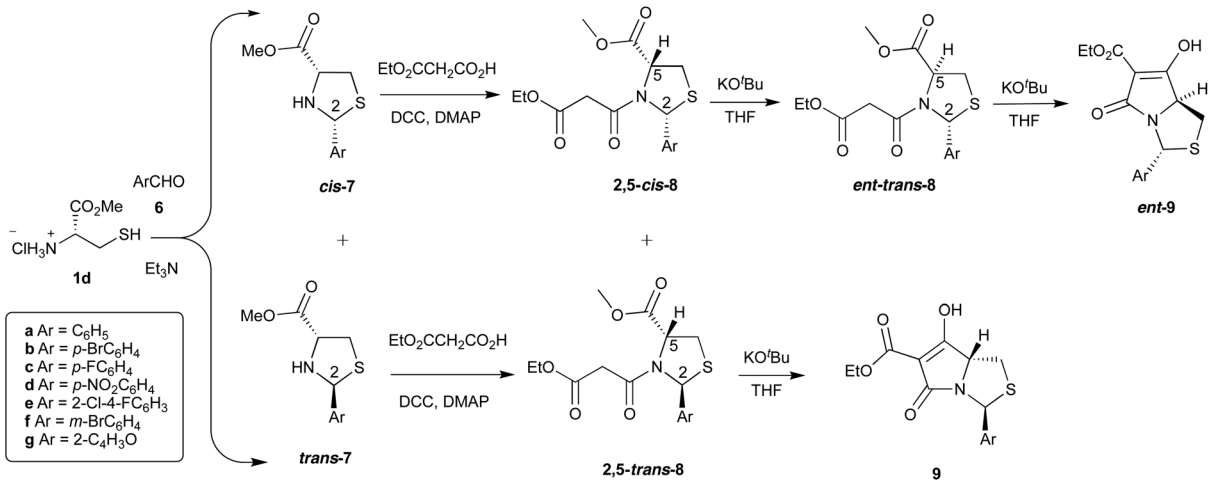


Scheme 1 Dieckmann ring closures in malonyloxazolidines and -thiazolidines.

placed on the more hindered *endo*-face of the bicyclic lactam regardless of which cyclisation route is taken.

Although cyclic *N*,*O*-hemiaminal ethers derived from aldehydes and ketones are stable provided that the N-heteroatom is acylated,[11–14] aldehydes other than pivaldehyde were initially found to be unsuitable in the process shown in Scheme 1. However, more recently, thiazolidine substrates derived from cysteine **1d** using aromatic aldehydes were found to give hemiaminal thioether systems *cis*- and *trans*-**7**, and Dieckmann cyclisation successfully gave the corresponding tetramate products **9** and *ent*-**9** but in a different sense of chemoselectivity, by route B (Schemes 1 and 2).[8,15] Thus, it became clear that

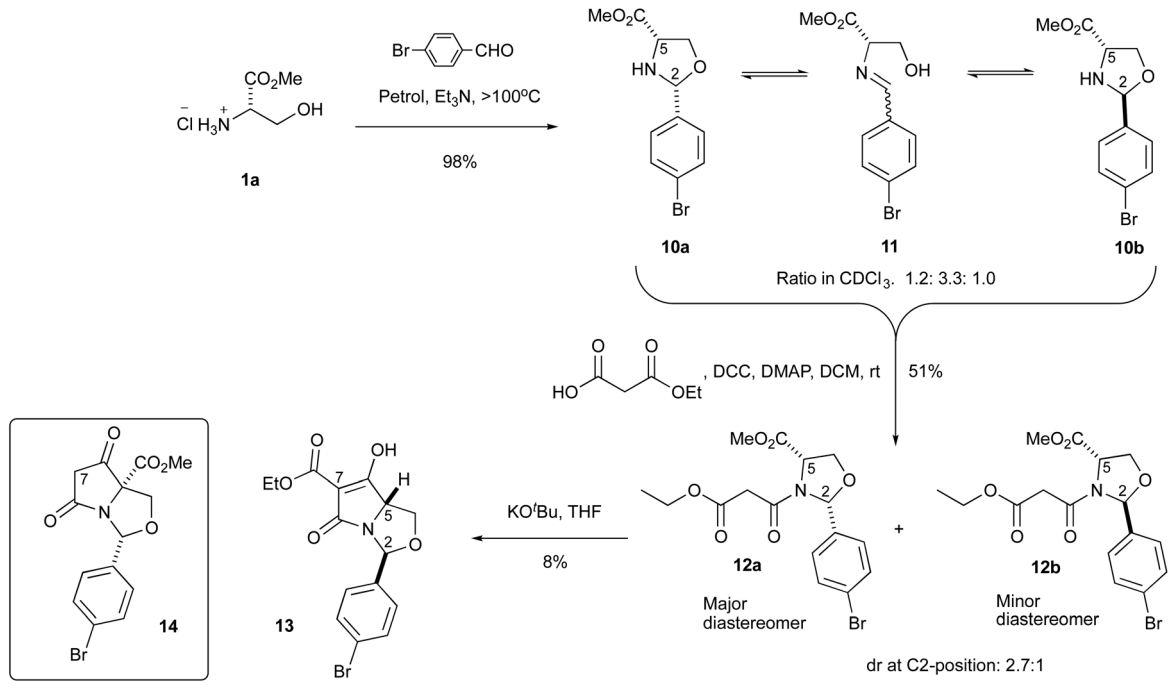


Scheme 2 Dieckmann ring closures in arylthiazolidine templates.

the chemo- and stereoselective outcomes in the oxazolidine and thiazolidine series differed, and we report here a more detailed examination of the reactions of hemiaminal and aminal –NCH(Ar)X– (X = O, NR) heterocycles in this Dieckmann cyclisation.

Results and discussion

An initial examination demonstrated that L-serine methyl ester hydrochloride **1a** could be condensed with *p*-bromobenzaldehyde to form oxazolidines **10a,b** that were obtained only as minor unstable products, along with the ring-opened imine **11** as the major product, readily distinguished in the NMR spectrum of the crude reaction mixture (δ_H for H-2 (ppm): **10a : 11 : 10b** = 5.27; 8.28; 5.64 in the ratio 1.2 : 3.3 : 1.0) (Scheme 3). The open chain form (B) was observed to be the predominant form (Table S1, ESI†). This contrasted with the equivalent condensation using pivaldehyde, in which the oxazolidine was obtained exclusively in the ring-closed form.[16,17] However, it was found that reaction of the oxazolidine **10a,b** with ethyl hydrogen malonate by DCC/DMAP coupling drove the equilibrium between the oxazolidine **10a,b** and imine **11** towards the formation of the oxazolidine ring system, giving

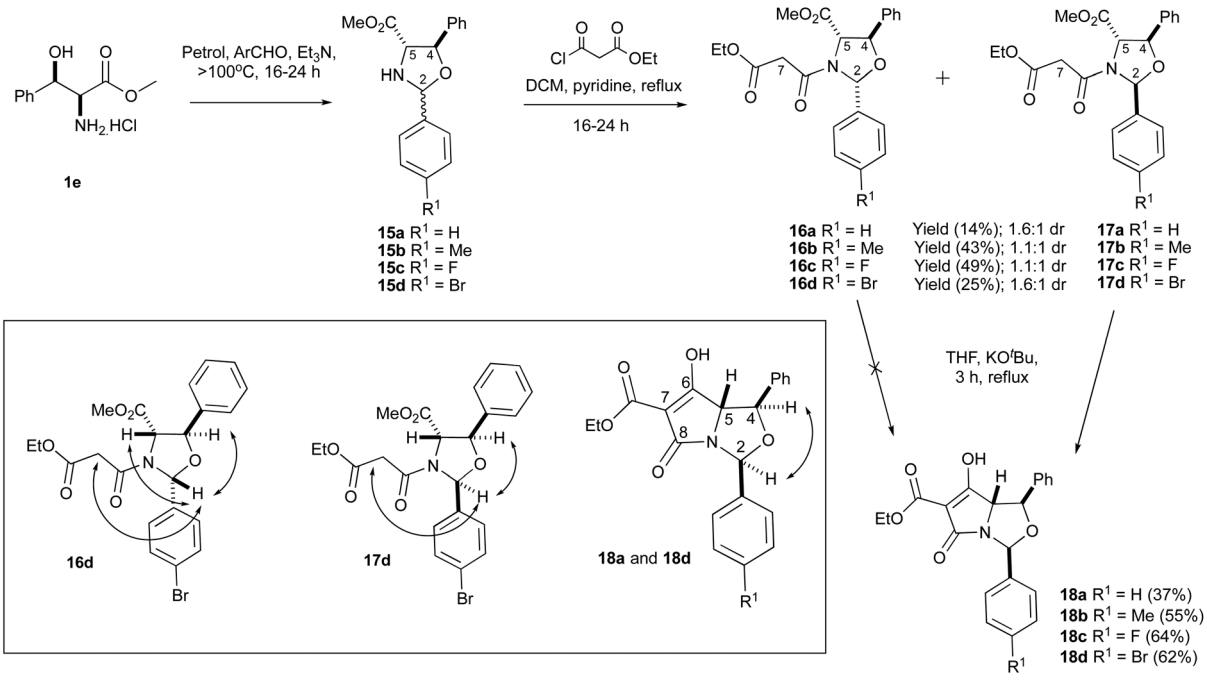


Scheme 3 Dieckmann ring closures in aryloxazolidines.

malonamides **12a,b** in 51% yield as a mixture of diastereomers, in which the 2,5-*cis* diastereomer was the major product (2.7 : 1 dr). The change in diastereomeric ratio in favour of the *cis*-diastereomer upon *N*-acylation indicates that the ring-chain tautomerism allows equilibration to the more stable product, where both substituents are (presumably) pseudoequatorial. Although it seems likely that this 2,5-*cis* diastereomer is the more stable, the diastereoselectivity was much lower than pivaldehyde-derived systems, in which malonamide **2a** was obtained almost exclusively as the single 2,5-*cis*-diastereomer.[16,17] Each diastereomer **12a,b** existed as a rotameric pair (δ_H for H-2 (ppm) *cis*-**12a** (6.04 and 6.16 ppm) and *trans*-**12b** (6.29 and 6.42 ppm) (major and minor rotamers respectively)) and the relative stereochemistry of C-2 and C-5 substituents across the ring was confirmed by NOE experiments (Fig. S1, ESI†). NMR resonances for H-2 signals were distinct and for both rotamers, H-2 of the *trans*-diastereomer appeared more downfield than the *cis*-diastereomer. The malonamides **12a,b** were subjected to the Dieckmann cyclisation using KO^{t}Bu, to give the bicyclic tetramate **13**, and although **14** was not isolated, it could be detected by mass spectrometry in the crude reaction mixture. This is in contrast to the observed reactivity of malonamide **2a** with a *t*-Bu at C-2 position, where the major product of cyclisation was the methyl ester **4a** (Scheme 1). However, during acidic work up of the cyclisation reaction, the product proved to be extremely unstable. Thus, the crude reaction mixture was directly purified by column chromatography on silica gel run with 1% Et_3N, but the desired product **13** was isolated in only 8% yield. Thus, it became apparent that the stability of these compounds was a significant drawback, derived from the lability of the hemiaminal ether system, at least compared to the thioether system.[15]

Of interest was whether *threo*-phenylserines, possessing an additional phenyl substituent on the hydroxyalkyl side chain, might prove to be more stable. *threo*-Phenylserine methyl ester hydrochloride **1e** was condensed with benzaldehyde and *para*-substituted benzaldehydes to form oxazolidines **15a–d** using the established protocols (Scheme 4). These compounds were not purified by column chromatography due to the possibility of retro-aldol decomposition on silica gel[18] but excess aldehyde was always detected in the NMR spectra of the crude products, consistent with poor conversion to the desired products. Oxazolidines **15a–d** were therefore used in crude form and were immediately *N*-acylated under basic conditions to form malonamides **16a–d** and **17a–d** (Table S2, ESI†), with the 2,5-*cis* diastereomer being slightly more favoured. This was consistent with earlier reports.[4] The yields obtained were moderate and was calculated over two steps from amino ester **1e**. In the ^{1}H-NMR data, the H2 signals were invariably more downfield for malonamides **16a–d**/**17a–d** than for malonamides derived from *threo*-phenylserines **1e** that were condensed with pivaldehyde **2e–f**. nOe analysis was used to determine the relative stereochemistry for compounds **16a,d** and **17a,d** (Scheme 4) and was further confirmed from a single-crystal X-ray structure of compounds **16c** and **17c** (Fig. S2, ESI†).[19] Based on these X-ray crystal structures and the similarities in the NMR data for the compound series (Table S2, ESI†), the relative stereochemistry of malonamides **16a–d** and **17a–d** was assumed to be similar.

Unlike the C2-^{t}Bu series,[4] these malonamide diastereomers **16a–d**/**17a–d** were easier to separate by chromatographic purification and could be obtained in gram-scale quantities. Interestingly, however, the NMR spectra for malonamides **17a–d** in comparison to malonamides **2e** that had a ^{t}Bu substituent



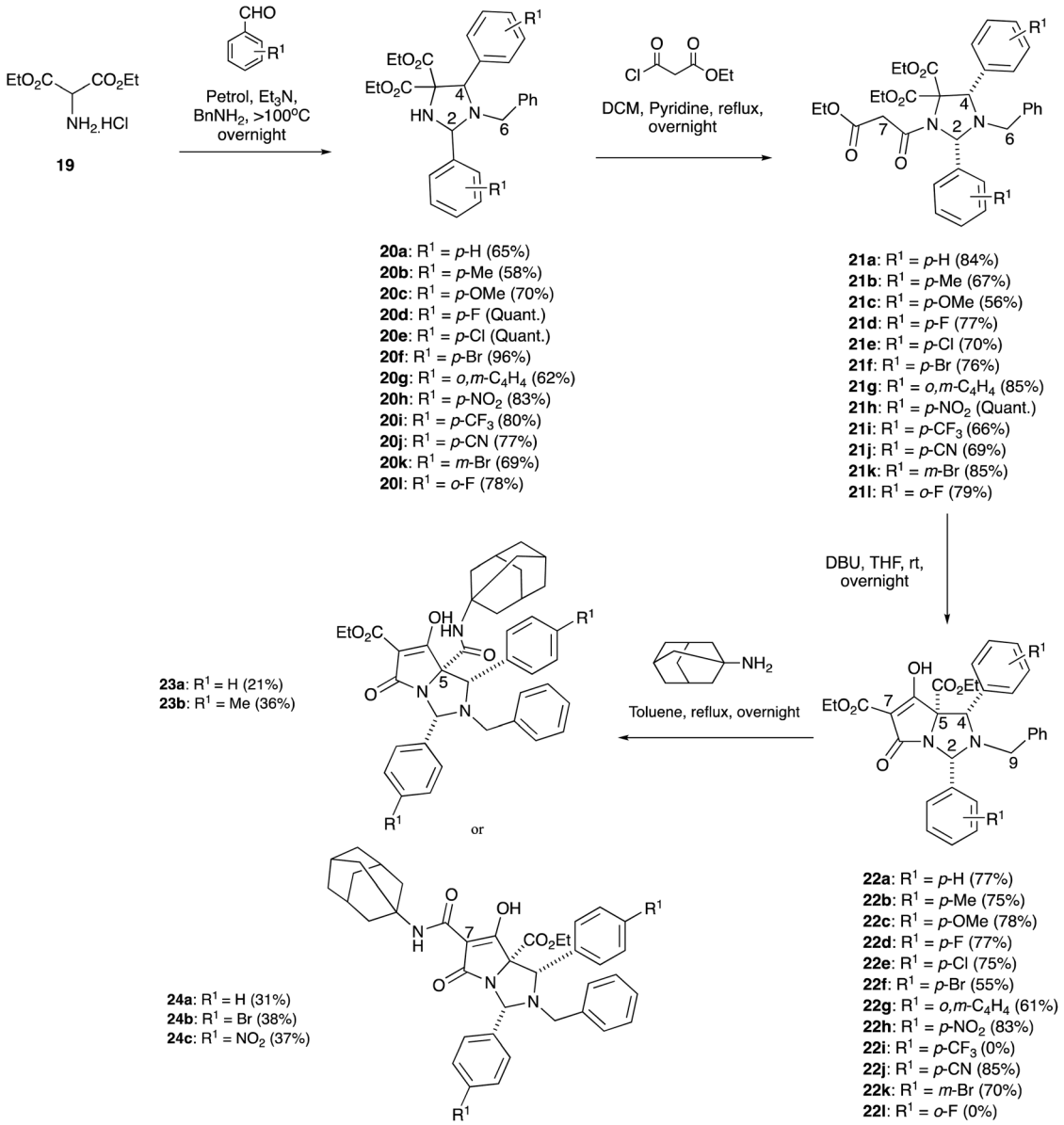
Scheme 4 Dieckmann ring closures in variously substituted aryloxazolidines.

at the C2-position were very different. In the case of malonamides **17a–d**, the NMR peaks were all sharp (Fig. S3, ESI†), but the presence of rotamers could not be found in the 2-D NOESY spectrum, whereas the NMR peaks for malonamides **2e** – particularly the oxazolidine ring protons – were very broad at room temperature but could be sharpened using low temperature VT-NMR experiments.[4] The bulky ^{t}Bu group at the C2-position for compounds **2e** was probably giving rise to this conformational dynamic, which was not seen for the planar aromatic ring substituents attached at the C2-position for malonamides **17a–d**. Moreover, malonamides **16a–d** clearly existed as a pair of rotamers around the *N*-malonyl bond, unlike **17a–d**. This was chiefly detected in the 2D-NOESY spectrum where chemical exchange processes were detected. Analogues 2,5-*cis*-malonamides **2a–b,d** derived from the methyl ester derivatives of L-serine **1a**, L-threonine **1b** and L-cysteine **1d** have all been reported to exist as pairs of rotamers.[17]

2,5-*cis* Malonamides **16a,d** were subjected to the Dieckmann cyclisation using KO^{t}Bu in THF (Scheme 4), but none of the desired product was detected by ^{1}H-NMR spectroscopy or mass spectrometry. This was consistent with earlier findings that the major 2,5-*cis* malonamide diastereomer **2f** derived from *threo*-arylserine **1e** was resistant to the Dieckmann cyclisation.[4] However, the 2,5-*trans* malonamides **17a–d** readily reacted with KO^{t}Bu to give the desired tetramates **18a–d** in acceptable yields – typically between 37–64% – as the sole products (Table S3, ESI†). These compounds were not purified on silica gel due to the stability problems encountered earlier for tetramates **5e**, but in any case, the crude products were pure enough for direct NMR analysis (Fig. S4, ESI†). The chemoselectivity of the Dieckmann cyclisation and the lack of diastereoselectivity of the *N*-acylation reaction of oxazolidines **15a–d** was consistent with that seen for the C2-^{t}Bu series for *threo*-phenylserine derived bicyclic tetramates **5e**.[4] The relative stereochemistry of tetramates **18a–d** was assigned using nOe spectroscopy. The formation of tetramates **18a–d** is noteworthy since they proved to be isolable after acidic workup and were obtained in better yields than C2-functionalised tetramates **13** derived from L-serine **1a**, although they were very unstable upon short-term storage in their solid/oil form. Moreover, the H2-signal for tetramates **18a–d** was invariably more downfield in comparison to the C2-^{t}Bu series **5e**.[4] Attempted aminolysis of tetramate **18a,d** with 1-adamantylamine using toluene as a solvent – a reaction which had reliably generated the corresponding C7-carboxamide in related systems[4] – did not give the corresponding C7-carboxamide, most likely due to steric bulk in the bicyclic system, or the breakdown of the starting material at high temperatures – potentially due to the lability of the *N*,*O*-acetal. This work showed that –OCH(Ar)N– hemiaminal ether systems were accessible, provided sufficient stability was provided by substituents on the tetramate ring.

Although *N*,*O*- and *N*,*S*-hemiaminal ethers have been examined in some detail, the corresponding *N*,*N*-bicyclic tetramic acids have not. As thiazolidines are known to be more stable than oxazolidine derivatives,[11,20] where imidazolidine derivatives might fit in this spectrum was of interest. Although we had earlier demonstrated that *N*,*N*-bicyclic tetramates could be derived from imidazolidine scaffolds *via* 1,3-dipolar cycloaddition[21] by modification of a literature approach,[22] the resulting tetramic acids possessed numerous ethyl ester substituents that did not allow for chemoselective elaboration for aminolysis reactions. Instead, diethyl aminomalonate hydrochloride **19**, along with 2 eq. of substituted benzaldehydes and benzylamine, was reacted under basic conditions and heated to more than 100 °C in a Dean–Stark trap to form imidazolidines **20a–l** (Scheme 5), as either a single diastereomer or as a mixture of diastereomers (Table S4, ESI†), by a one-pot, three component 1,3-dipolar cycloaddition using a modification of the work of Nagao *et al.*[23] In the case of imidazolidine **20a**, a single crystal X-ray structure was obtained which confirmed the relative stereochemistry of the major diastereomer that had been assigned by nOe studies – in which the relative stereochemistry was assigned to be 2,4-*cis* (Fig. S2, ESI†).[19] Additionally, the spectroscopic data for **20a** matched literature data from the work of Nagao *et al.*[23] This enabled the spectroscopic data for the rest of the 2,4-*cis* imidazolidine series to be assigned based upon comparison with imidazolidine **20a** (Table S4, ESI†). NMR data and the X-ray crystal structures of imidazolidines **20b,e–f** also confirmed the presence of the 2,4-*trans* diastereomer (Fig. S2, ESI†).[19]

Imidazolidines **20a–l** were stable to chromatographic purification, unlike the corresponding oxazolidine series, although their diastereoisomers were often inseparable. Interestingly, in the ^{1}H-NMR data, the H-2 and H-4 signals with electron-withdrawing ring substituents were more downfield than the electron-donating substituents, and the signals of the 2,4-*trans* diastereomers were invariably more downfield compared with the 2,4-*cis* diastereomers (Table S4, ESI†). The methylene ethyl ester peaks were all clearly diastereotopic in the ^{1}H-NMR spectra (Fig. S5, ESI†). Imidazolidines **20a–l** were then *N*-acylated with ethyl malonyl chloride to form malonamides **21a–l** as single diastereomers in good to excellent yields (Scheme 5 and Table S5, ESI†), demonstrating that Seebach's "*cis* effect" (*i.e.* formation of a single *cis*-2,4-diastereomer upon *N*-acylation of the oxazolidine substrate[24]) applied in this case. The relative stereochemistry of **21a–d,f** and **h** was established by nOe studies and this was confirmed with various X-ray crystal structures of malonamides **21a,c–d** and **l** (Fig. S2, ESI†).[19] As a result, it was assumed that the rest of the malonamide series had the same relative stereochemistry due to consistencies in the NMR spectra (Table S5, ESI†). It was observed that one of the diastereotopic methylene malonyl protons at the H7-position had a very broad doublet peak, whereas the other proton had a sharp doublet peak at room temperature (Fig. S6(a), ESI†), and this observation was seen in all but two cases – malonamides **21h** and **j** – both of which contained an electron withdrawing group, in which their respective methylene protons were both relatively broad. In the case of malonamide **21a**, use of low-temperature VT-NMR experiments (193 K) sharpened the broad doublet peak (Fig. S6(b), ESI†), indicating that conformational dynamics were operating within this monocyclic system.



Scheme 5 Dieckmann ring closures in malonylimidazolidines.

Malonamides **21a–l** were subjected to the usual Dieckmann cyclisation using DBU in THF to form tetramates **22a–h**, **j–k** in good yields with high levels of chemoselectivity and in which only a single diastereomer was isolated (Scheme 5). These compounds were not purified by column chromatography as they were found to be unstable in solution, giving C7-decarboxylation over time. However, the crude material was relatively pure for NMR structural analysis (Fig. S7, ESI†). The relative stereochemistry – determined from nOe studies – clearly showed a 2,4-*cis* relationship across the bicyclic core **22a–d**, indicating that no epimerisation had occurred at the C2 and C4-positions under basic conditions. Moreover, as the chemical shifts and coupling constants of **22a–d** were consistent across the series (Table S6, ESI†), it was assumed that all tetramates had the same relative stereochemistry. The C5-ethyl ester stereochemistry was initially assigned as being on the same face as the C2 and C4-aryl substituents, similar to reported tetramates **4e**, placing the C5-ethyl ester on the less hindered *exo*-face of the bicyclic lactam. This was later supported with DFT calculations (*vide infra*) which identified the most stable product. It was assumed that reaction with 1-adamantylamine would proceed by chemoselective attack at the C7-ethyl ester but in the event, indiscriminate attack at both the C5 and C7-ethyl ester positions was observed to form both C5-**23a** and C7-**24a** carboxamides (Scheme 4). The assignment of structure to these by NMR analysis using NOESY or HMBC analysis was difficult, but a comparison of chemical shift information with the structures of previously reported analogues[4,5] enabled tentative assignment of the C5-carboxamide **23a** and C7-carboxamide **24a** (Fig. S8, ESI†) as the C7-ethyl ester tetra-

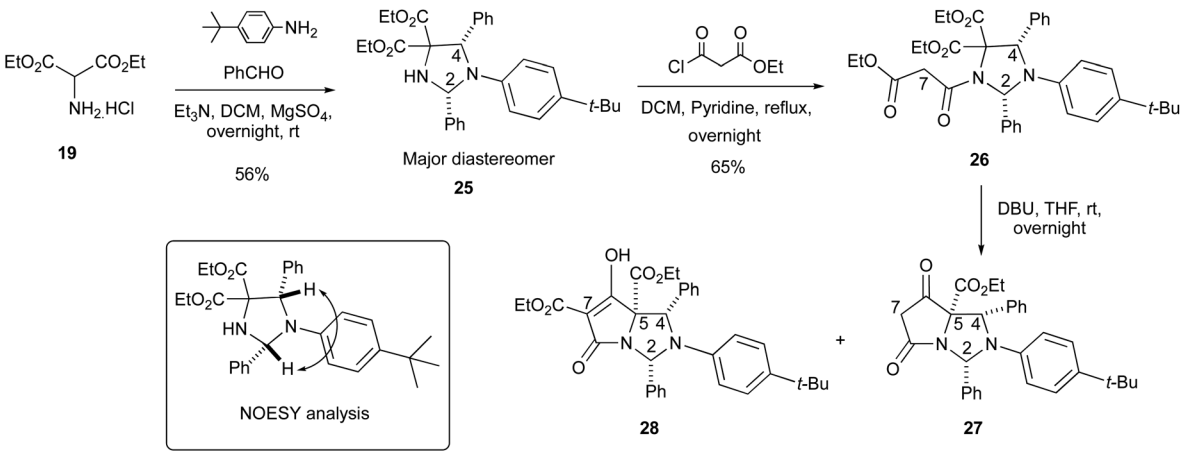
mate **5e** tended to be more downfield in comparison to the C5-ethyl ester tetramate **4e** – and as a result it was assumed the same was true for tetramates **22**.

It was further possible to show – taking inspiration from the work of Liu *et al.*[25] – that when diethyl aminomalonate **19** was reacted with 2 eq. of benzaldehyde and 4-*tert*-butylaniline under basic conditions, imidazolidine **25** could be formed in 56% yield with an acceptable level of diastereoselectivity (4 : 1 dr), with the major diastereomer being the 2,4-*cis* diastereomer as established by NOESY (Scheme 6). Additionally, it was shown that a temperature of 100 °C under a Dean–Stark trap was not necessary for the cycloaddition reaction to occur and that O'Shaughnessy's reaction conditions (anhydrous $MgSO_4$) enabled these reactions to occur under much milder conditions.[21] Imidazolidine **25** was *N*-acylated with ethyl malonyl chloride to form malonamide **26** in 65% yield as a single diastereomer. The relative stereochemistry of **26** was confirmed from a single-crystal X-ray structure and showed a 2,4-*cis* relationship, consistent with the *N*-acylation of imidazolidines **20a–l** (Fig. S2, ESI†).[19] Surprisingly, the NMR peaks for the methylene malonyl protons at the H7-position for **26** were both relatively sharp, which was in contrast to the *N*-benzyl malonamides **21a–l**, again suggesting that conformational dynamics and substituents attached around the periphery of the imidazolidine ring system at the C2, N3 and C4-positions could have a pronounced effect on the H7-protons (Fig. S9, ESI†).

Malonamide **26** was subjected to the Dieckmann cyclisation, but the extraction process for this reaction, as well as for benzyl tetramates **20i** was complicated by the formation of emulsions. However, an inseparable mixture of tetramate **28** along with C7-decarboxylated tetramate **27** could be obtained in low yield, whose structures were confirmed by ^{1}H-NMR and mass spectroscopy. Moreover, an aldehyde signal at ~10 ppm was detected in the NMR spectrum after the Dieckmann cyclisation for some products, suggesting that the *N*,*N*-aminal was not as stable as the *N*,*O*-hemiaminal formed by condensation with pivaldehyde; this is unsurprising given the basicity of the N3-amine in the bicyclic system.

In order to understand the chemo- and diastereoselectivity of this process, DFT calculations were conducted (Fig. 1), and these showed that this reaction was governed by kinetic and thermodynamic control, in which the favoured reaction pathway (route A) – highlighted in red – had a considerably lower E_a than route B – highlighted in blue – by 9.1 kcal mol^{-1}, to give a tetrahedral alkoxide which was more stable in the case of route A (by 4.9 kcal mol^{-1}). In both the transition state and the product, this stability is likely to arise from an arrangement in which most bulky substituents are located on the *exo*-(convex) face of the bicyclic system; the close proximity of the malonyl enolate to the reacting ethoxycarbonyl group will also assist the kinetics of the ring closure process. This outcome further confirmed that the C5-ethyl ester was most likely to be on the same face as the C2 and C4-aryl substituents, which is consistent with Dieckmann cyclisations of similar bicyclic tetramate derivatives.[4,5] Moreover, this work also showed that –NCH(Ar)N– aminal systems are accessible, and whose better stability relative to –NCH(Ar)O– hemiaminal ether systems was likely assisted by the electronic withdrawing properties of the tetramate ring.

Evaluation of the antibacterial activity of C7-ethyl ester tetramates derived from imidazolidine scaffolds **22a**, **22c** and **22h** showed no antibacterial activity against MRSA and *E. coli*, although some activity was seen against MRSA for compounds **22b** and **22f** at concentrations of 31.25 μg mL^{-1}. This indicated that appropriate functionalisation around the C2 and C4-aromatic ring systems allowed antibacterial activity to be restored. C5-carboxamide **23b** showed good bioactivity against MRSA at MIC = 3.9 μg mL^{-1} and C7-carboxamide **24a** showed good antibacterial activity against MRSA (MIC = 3.9 μg mL^{-1}), although this was far less potent than that of the C7-adamantylcarboxamide-*N*,*O*-bicyclic tetramates which typically had MICs of 0.25 μg mL^{-1}.[4,5] Tetramate **24c** was far less potent than **24a** (MIC = 15.6 μg mL^{-1}) and tetramate **24b** showed no antibacterial activity against MRSA (Table 1). Unsurprisingly, none of these carboxamides **23b** and **24a–c** were active against *E. coli*, in keeping with the known activity profiles of tetramates.



Scheme 6 Dieckmann ring closures in malonyl-*N*-arylimidazolidines.

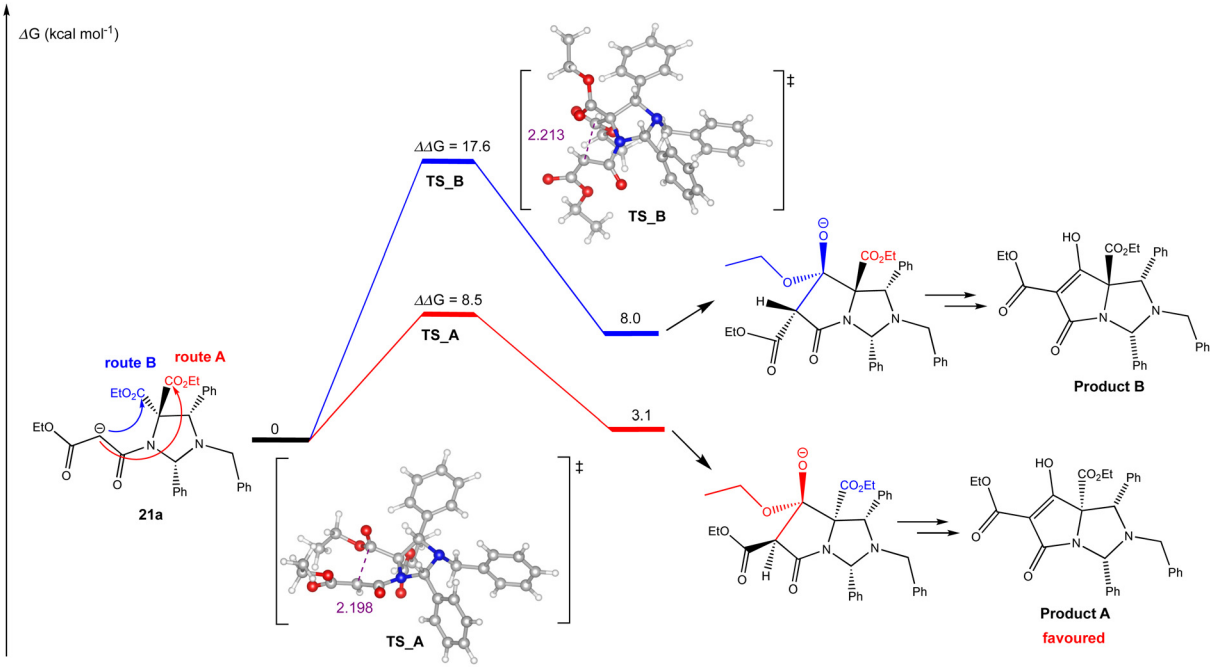


Fig. 1 DFT calculated reaction energy profile for the Dieckmann cyclisation of malonamide **21a**, using M06-2X/def2-TZVP method level of theory with SMD solvation (THF) and zero-point energy correction (Table S7, ESI†). All energies (Gibbs free energy) are reported in kcal mol^{-1} and are referenced to the lowest energy carbanion generated after initial deprotonation. Distances are in angstrom (Å).

Table 1 MIC values of tetramates **22a–c**, **22f,h**, **23b** and **24a–c** against MRSA, EC_{50} values against various cell lines and selected therapeutic ratio used to assess toxicity. Therapeutic ratio = [EC_{50}(CaCo) (μg mL^{-1})]/[MIC against MRSA (μg mL^{-1})]

		Cell lines EC_{50} (μg mL^{-1})				
Compound	MIC against MRSA (μg mL^{-1})	HeLa EC_{50}	HEK-293	CaCo	MDCK	Therapeutic ratio
22a	Not active	—	—	—	—	—
22b	31.25	31.3	31.3	62.5	31.3	2
22c	Not active	—	—	—	—	—
22f	31.25	31.3	31.3	62.5	31.3	2
22h	Not active	31.3	62.5	125.0	31.3	—
23b	3.9	15.6	62.5	125.0	62.5	32
24a	3.9	31.3	62.5	62.5	62.5	16
24b	Not active	62.5	62.5	62.5	125.0	—
24c	15.6	62.5	62.5	62.5	125.0	4

A toxicity study was completed and interestingly, compounds **23b** and **24a** had a therapeutic ratio of 32 and 16 respectively against CaCo cell lines (Table 1). This was a promising starting point, as antibacterial drug candidates should have >10-fold higher antibacterial activity over cytotoxicity.[26] Moreover, Brown *et al.*[27] had demonstrated that high lipophilicity tended to correlate with increased cytotoxicity, however, these bicyclic tetramates, although being quite lipophilic (Table S8, ESI†), were generally non-toxic. Moreover, although these *N*,*N*-bicyclic tetramates were less potent than their *N*,*O*-bicyclic counterparts against MRSA,[4,5] they were also less toxic in comparison, thus demonstrating that manipulation of C2, N3, C4, C5 and C7 all give scope for control of antibacterial activity. Additionally, physicochemical properties of the most active compounds correspond to a distinct chemical space; 554 < M_w < 722 g mol^{-1}; 5.78 < cLogP < 7.16; 788 < MSA < 972 $Å^2$; 10.3 < rel. PSA < 19.08.

Conclusion

We have shown here that Dieckmann ring closure of hemiaminal ether and imidazolidine substrates effectively gives bicyclic substrates in a chemoselective ring closure, in a process which is kinetically controlled; hemiaminal and aminal –NCH(Ar)X– (X = O, NR) heterocyclic systems are available. These systems display good levels of antibacterial activity, at least against Gram positive organisms, and this activity is maximal in a well-defined region of chemical space.

Conflicts of interest

There are no conflicts to declare.

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