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PAPER

Control of chemoselectivity in Dieckmann ring closures leading to tetramic acids

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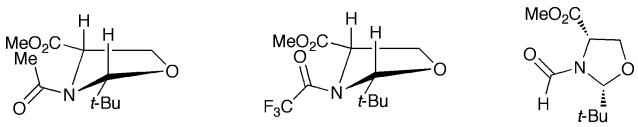
An efficient strategy for the control of the chemoselectivity in Dieckmann ring closures leading to tetramic acids derived from serine and α-methyl serine is reported, and this provides pathways to diversely substituted systems from a common starting material.

Diverted synthesis based on natural products possessing the desired biological activity is an attractive route for the discovery of new drugs;[1–4] the tetramic acid nucleus, found in various bioactive natural products such as reutericyclin and equisetin and their derivatives, provides an important scaffold for drug design.[5,6] In this regard, we have developed effective methodology for the enantioselective synthesis of highly functionalized tetramic acids *via* biomimetic Dieckmann or aldol ring closures; thus, the serine-derived oxazolidine **1a** may be acylated to *cis*-**2a**, and efficiently closed to tetramate **4a** (Scheme 1)[7–9] in a process in which the *t*-butyl group simultaneously controls chemo- and stereoselectivity.[10] However, along with the major product **4a** (73%), minor amounts of the alternative products **5a** (arising by C-2 epimerisation followed by Dieckmann ring closure (*vide infra*)) and of ***ent*-5a** (arising by Dieckmann ring closure of minor amounts of *trans*-**3a** (*vide infra*) present in *cis*-**2a**) were also obtained (12 and 3.5% respectively). Although these products were obtained with high stereocontrol, the yields of the minor products were clearly not synthetically useful and we sought to modify this route by changing the reagents, conditions and the substrates themselves to provide selective and efficient access to any of tetramates **4**, **5** or **6**, systems which we have recently shown to be of interest as templates for drug discovery.[11,12]

Firstly, in order to better understand the *N*-acylation of oxazolidine **1a**, its reaction with the less hindered acylating agents, acetyl chloride and trifluoroacetyl anhydride, at room temperature was examined; exclusive formation of the *cis*-oxazolidines **7** and **8a** (Fig. 1) was observed, the structures of which were confirmed by NOE analysis (Fig. 2). Room temperature VT and NOE analysis of *N*-acetyl **7** confirmed the structure as 2,5-*cis*- with



7 **8a** **9**

Fig. 1

no interconversion to the 2,5-*trans* isomer, although evidence for rotameric equilibrium around the *N*-acyl unit from peak broadening was observed; VT and NOE analysis at 60 °C in $CDCl_3$ and 90 °C in DMSO-d_6 suggested that the conformation shown in Fig. 1 was preferred, an arrangement which presumably minimises steric interactions. This outcome is similar to that reported for the *N*-formyl system **9**, in which only the *cis* isomer was reported.[13] However, if *N*-acylation of oxazolidine **1a** is conducted with TFAA at –40 °C, both *cis*- and *trans*-diastereomers **8a,b** were formed, and the stereochemistry of these were established by NOE analysis (Fig. 2). Equilibrium product ratios of between 9 : 1 and 99 : 1 correspond to energy differences of 1.3–2.7 kcal mol^{-1},[14] and this was confirmed by molecular modeling calculations (Spartan 04 for Windows, using DFT [B3LYP/6-31G*] basis set) which indicated that the *cis*/*trans* energy difference $\Delta E_{(cis\text{-}trans)}$ for the *N*-formyl, *N*-acetyl and *N*-trifluoroacetyl series was –0.9, –0.8 and –1.9 kcal mol^{-1} respectively (Table 1, entries 7–9), clearly favouring the *cis* outcome as observed experimentally. However, although full selectivity for the *trans*-*N*-acyloxazolidines was not possible, these results suggested that neither would their formation be impossible.

Next, we found that appropriate adjustment of the conditions enabled tetramate **6a** to be obtained directly from tetramate **4a**, itself available in high yield from oxazolidine **2a**, as shown in Scheme 1. Thus, hydrolysis of tetramate **4a** with sodium hydroxide gave the crude carboxylic acid **4c** in high yield, although this compound was found to be unstable to silica column chromatography. Decarboxylation of acid **4c** under various conditions such as refluxing in toluene with or without a catalytic amount (5 mol%) of *para*-toluenesulfonic acid, or refluxing in wet acetonitrile, gave tetramate **6a** in moderate yield (18–30%). However, hydrolysis of

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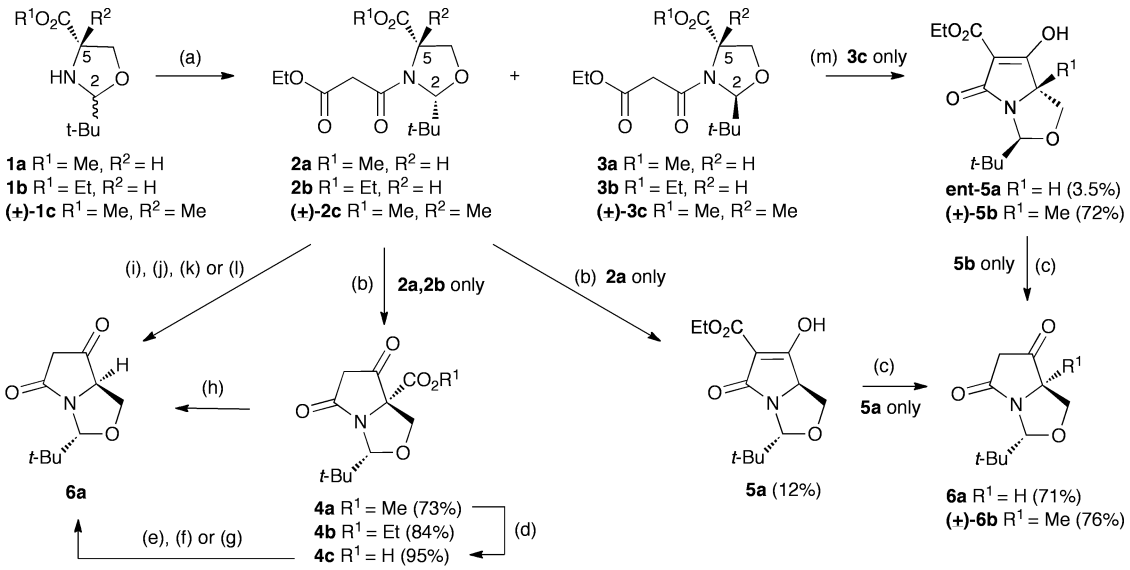

(a) *mono*-Ethyl malonate (1.1 eq), DCC (1.1 eq), DMAP (0.05 eq), CH_2Cl_2, r.t.; (b) K^{t}BuO (1.1 eq), dry ^{t}BuOH, reflux; (c) wet CH_3CN, reflux (70%); (d) NaOH (2.0 eq), THF/MeOH/H_2O (4:1:1), reflux; (e) PTSA (cat), toluene, reflux (22%); (f) toluene, reflux (18%); (g) wet CH_3CN, reflux (30%); (h) LiOH (2.0 eq), THF/ MeOH/ H_2O (4:1:1), reflux (30%); (i) KO^{t}Bu (2.2 eq), dry ^{t}BuOH, reflux (25%); (j) KO^{t}Bu (2.2 eq), wet ^{t}BuOH, reflux (40%); (k) KO^{t}Bu (3.3 eq), wet ^{t}BuOH, reflux (15%); (l) NaOMe (2.2 eq), benzene/MeOH, reflux (7%, along with **5a** (13%); (m) KO^{t}Bu (2.2 eq), dry THF, reflux (72%).

Scheme 1

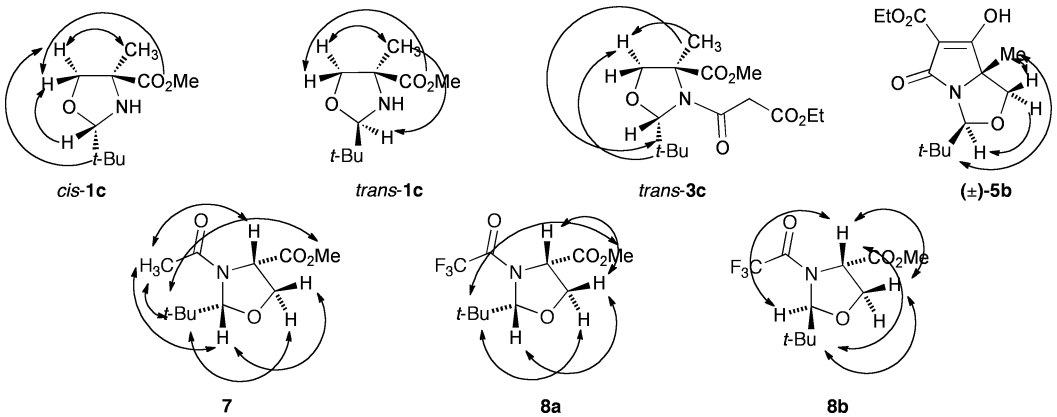

Fig. 2

Table 1 Compound ratio and energy differences of selected compounds (see Scheme 1 and Fig. 1)

			Calculated energy difference (kcal mol^{-1})[b]	
Entry	Compound	Observed *cis* : *trans* ratio[a]	AM1	PM3
1	**1a**	50 : 50	2.346[c]	1.616[c]
2	**1b**	40 : 60	4.250[c]	1.909[c]
3	**1c**	35 : 65	2.406[c]	1.409[c]
4	**2a** : **3a**	85 : 15	−1.622[c]	−2.531[c]
5	**2b** : **3b**	70 : 30	−1.994[c]	−1.642[c]
6	**2c** : **3c**	20 : 80	0.246[c]	1.948[c]
7	**7**	99 : 1	−1.608	−1.941
8	**8**	99 : 1	−1.968	−0.821
9	**9**	95 : 5	0.293	−0.904
10	(**4a** – **13**)	—	−3.042[d]	−6.248[d]
11	(**5a** – **14**)	—	−3.583[e]	−6.190[e]
12	(**4b** – **5a**)	—	−4.643[f]	−5.420[f]

[a] Determined by comparison of the integral of proton on C(2) in ^{1}H NMR spectrum. [b] Calculated by using semi-empirical AM1 and PM3 at ground state in Spartan 02. [c] Heat of formation (*cis* form- *trans* form). [d] Heat of formation difference between **4** and **13**. [e] Heat of formation difference between **5a** and **14**. [f] Heat of formation difference between **4b** and **5a**.

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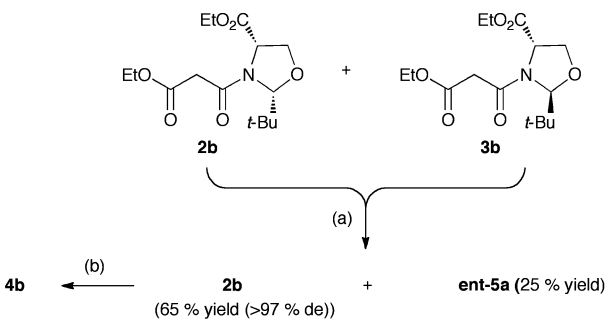
tetramate **4a** with lithium hydroxide gave tetramate **6a** directly in 30% yield, without isolation of acid **4c**. The yield *via* this route (26% over 2 steps from **1a**) is significantly improved over our initial report.[8,15] Moreover, we found that cyclisation of oxazolidine **2a** with 2.2 equivalents of potassium *tert*-butoxide in dry butanol also gave tetramate **6a** directly in 25% yield, in a sequence in which the Dieckmann cyclisation, hydrolysis and decarboxylation all occurred in one pot. When wet butanol was used as solvent, the yield increased even further to 40%.[8] Further excess amounts (3.3 equivalents) of potassium *tert*-butoxide or 2.2 equivalents of sodium methoxide instead of potassium *tert*-butoxide, however, gave poorer yields of 15 and 7% respectively. Nonetheless, this yield for tetramate **6a** (35% yield overall from **1a**) is improved by more than 4-fold over our initial report.[8]

In order to develop this process further, we sought to control the diastereoselectivity of the initial acylation of the key oxazolidine **1a** (Scheme 1) by modifying the steric bulk of the C-5 ester function, expecting improved 2,5-*trans* selectivity which would in turn provide access to tetramates of type **5**. Although oxazolidine **1a** is formed as a 1 : 1 mixture of diastereomers, acylation with *mono*-methyl malonate using dicyclohexylcarbodiimide (DCC) in the presence of a catalytic amount of dimethylaminopyridine (DMAP) gives the acylated oxazolidine (88% yield) as an 85 : 15 mixture of *cis*-**2a** and *trans*-**3a** isomers (Scheme 1).[7–9] However, for the slightly more bulky ethyl ester **1b**, acylation with ethyl malonyl chloride in the presence of triethylamine gave oxazolidines **2b** and **3b** (75% yield) only as a 70 : 30 mixture in favour of the *cis* isomer (Scheme 2).[16] Treatment of this mixture with DMAP at room temperature gave not only tetramate ***ent*-5a** (arising by cyclisation of the minor isomer *trans*-**3b**) by precipitation in a solution of ethyl acetate and petroleum ether with improved yield (25%) but also *cis*-oxazolidine **2b** by column chromatography of the extraction residue (>97% de) (Scheme 2). As expected, the pure *cis*-**2b** could be readily converted to tetramate **4b** using the standard cyclisation methodology (Scheme 2). This outcome confirms that although oxazolidines **1** can freely equilibrate, after *N*-acylation, the products *cis*-**2b** and *trans*-**3b** cannot interconvert and will cyclise with different chemoselectivities, giving isomeric tetramates **4b** or ***ent*-5a** respectively.

In an attempt to bias the *trans* selectivity of this process even further, an α-methyl analogue was examined (Scheme 1). Thus, a 35 : 65 *cis* and *trans* mixture of oxazolidine (±)-**1c** was prepared from commercially available α-methyl-DL-serine *via* esterification with thionyl chloride in methanol, followed by condensation of pivalaldehyde in the presence of triethylamine. Acylation of oxazolidine (±)-**1c** with DCC and DMAP gave oxazolidines (±)-**2c** and (±)-**3c** with a *cis* to *trans* ratio of 20 : 80, an outcome which is inverted relative to **1a,b**. This material when treated with potassium *tert*-butoxide in dry THF at reflux gave only tetramate (±)-**5b** in 72% yield, and of interest is that no other diastereomers of this product could be isolated from the reaction mixture. The relative stereochemistries of key compounds were established by ^{1}H NOE experiments (Fig. 2). Tetramate (±)-**5b** could be readily converted to (±)-**6b** by hydrolysis and decarboxylation in 76% yield.

In order to explain the above results, the energy difference of the heat of formation of *cis*- and *trans*-oxazolidines was calculated using semi-empirical AM1 and PM3 in Spartan 04 (Table 1). In the calculation results for oxazolidines **1a–c**, which exist in equilibrium between the *cis* and *trans* forms in solution, the *trans* form was found to be more stable than the *cis* form (Table 1, entries 1–3), but for acylated oxazolidines *cis*-**2a–c** and *trans*-**3a–c**, although *cis*-**2a** and **2b** are more stable than the corresponding *trans* isomers, for the α-methyl serine derivative, it is *trans*-**3c** which is more stable (entries 4–6), consistent with experimental observations. The preferred *cis* stereochemical outcome for oxazolidines **2a–b** permits an all-*trans* configuration of the five membered ring (as shown in Fig. 3, and assuming the envelope conformations as indicated in Fig. 1), in which the nitrogen is slightly pyramidalised, and which places all three contiguous bulky groups in pseudoequatorial arrangements which minimise steric interactions; however, for the 1,3-*trans* products **3a,b**, adjacent pairs of *cis* substituents cannot avoid steric interactions in both possible conformers. The switch to preference for *trans*-**3c** is a result of the presence of the additional methyl group (R^1 = R^2 = Me) (Fig. 3) whose bulk can then be more readily accommodated on the oxazolidine ring. These calculations indicate that in the acylation reaction of oxazolidines **1a–c**, the favoured products are also the thermodynamically more stable ones; the facile equilibrium between *cis*- and *trans*-**1a–c** is critical in this outcome, and it has been recently reported that this equilibrium is catalysed by water.[17] On the other hand, configurationally stable related 2-trifluoromethyl-1,3-oxazolidines derived from serine have recently been reported and exploited as unusual pseudoprolines.[18]

In the subsequent Dieckmann cyclisation of *cis*-oxazolidines **2a–c** using potassium *tert*-butoxide, an equilibrium of enolates **10–12** is established after deprotonation (Fig. 3), with the closure of enolate **11** leading to tetramates **4a,b** and the closure of enolate



(a) Ethyl malonyl chloride (1.1 eq), triethylamine (1.2 eq), CH_2Cl_2, 0 °C; (b) DMAP (1.1 eq), CH_2Cl_2, r.t.; (c) KO^{t}Bu (1.1 eq), dry THF, reflux.

Scheme 2

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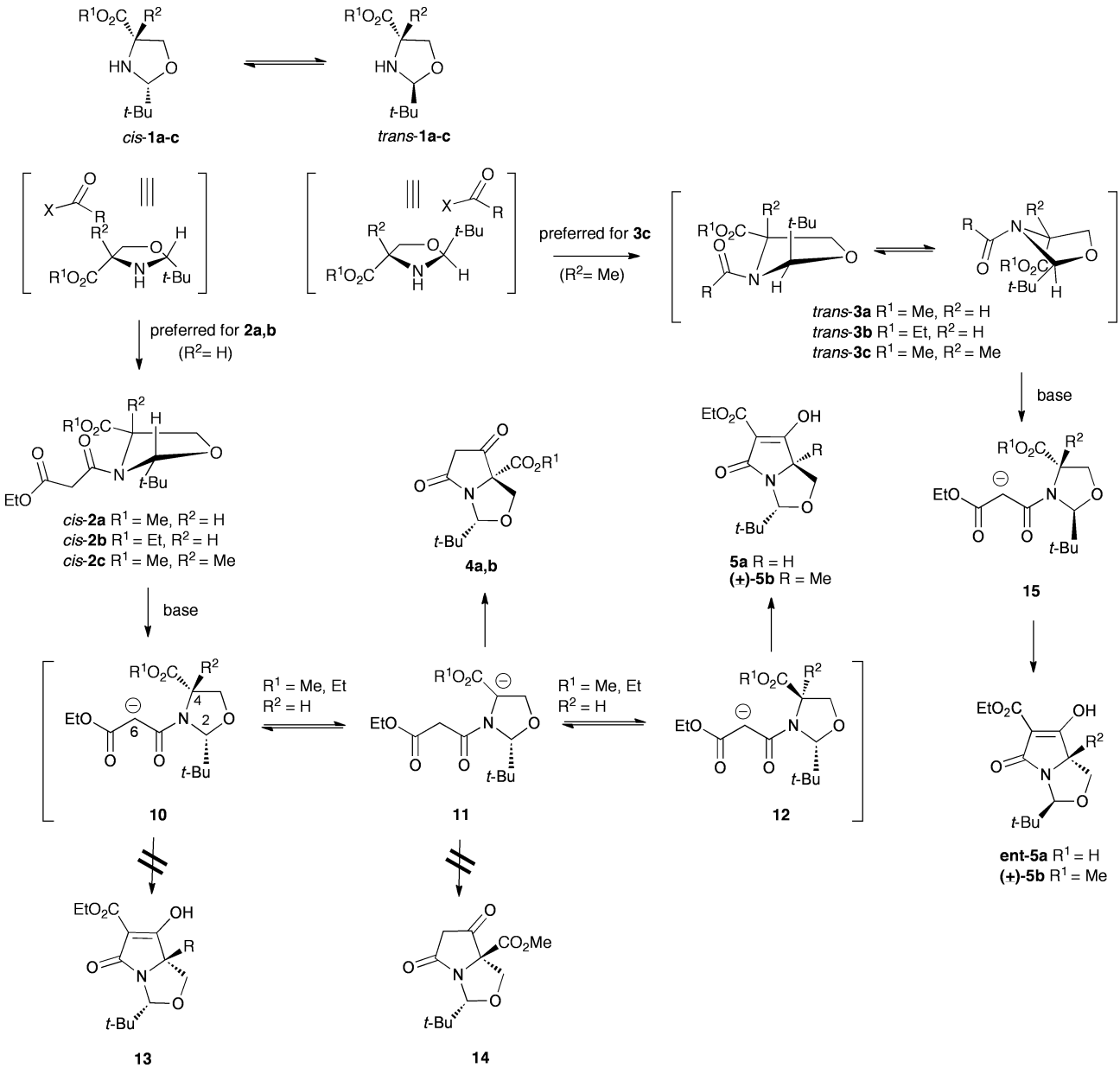

Fig. 3

12 to the alternative system **5**. The cyclised tetramates **13** (R = H) and **14** are much less stable by about 3–6 kcal mol^{-1} than the corresponding tetramates **4a** and **5a** (Table 1, entries 10 and 11), since the bulky *t*-butyl group ends up on the more hindered concave *endo*-face of the bicyclic system, and therefore **13** and **14** are not formed by closure of enolates **10** and **11** respectively. However, of interest is that tetramate **4b** is more stable than tetramate **5a** by 4.6 kcal mol^{-1} (entry 12), consistent with the experimental observation that it is formed preferentially from oxazolidine **2b**, although both tetramates **4a** and **5a** as the major and minor forms respectively are formed from oxazolidine **2a** where the energy difference between them is much lower. When DMAP is used as a mild base in the closure of *cis*-**2b** and *trans*-**3b**, only the most acidic C(6) position is deprotonated, giving enolates **12** and **15** and cyclisation forms the more stable **5a** and ***ent*-5a** respectively (Fig. 3). Although the reactions leading to tetramate products are unlikely to be thermodynamically controlled (for example, **4a** and **5a** do not equilibrate under basic conditions), the magnitude of the relative rate constants of the ring closures are likely to be reflected in the calculated stabilities of the products shown in Table 1. In the case of *trans*-oxazolidines **3a–c**, formation of enolate **15** is followed by ring closure to give the tetramates of type **5**, in which the bulky *t*-butyl group naturally ends up on the *exo*-face of the bicyclic ring, but now as the enantiomeric series; for **3c**, this is the only possible course.

In conclusion, closure of *cis*-oxazolidines **2** to tetramates of type **4** is most readily achieved in good yield using the Dieckmann reaction conditions (KO*t*-Bu (1.1 eq), dry *t*-BuOH, reflux), while use of alternate conditions (KO*t*-Bu (2.2 eq), wet *t*-BuOH, reflux) gives the simple bicyclic tetramate **6** directly. On the other hand,

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tetramates of type **5** are obtainable in good yield from *trans*-oxazolidines **3** by the use of similar conditions (KO*t*-Bu (1.1 eq), dry THF, reflux). Thus, by exploiting steric effects around the periphery of an oxazolidine template derived from serine, it is possible to control chemoselectivity and therefore the pathway of competing Dieckmann cyclisation reactions, giving efficient synthetic routes to variously functionalised tetramic acids from a common starting material.

Experimental

Oxazolidines **1a–c**, **2a–c** and **3a–c** were prepared using the published procedures.[8,19]

(±)-Methyl 2-(*tert*-butyl)-5-methyloxazolidine-5-carboxylate 1c

To α-methyl-DL-serine ester hydrochloride (2.0 g, 11.8 mmol) in petrol (100 ml) was added triethylamine (2.46 ml, 17.7 mmol) and pivaldehyde (1.54 ml, 14.2 mmol). The mixture was heated at reflux for 20 h with continuous removal of water using a Dean–Stark head then filtered and washed with ether (30 ml). The combined filtrates were concentrated *in vacuo* to give a crude 35 : 65 *cis* and *trans* mixture of oxazolidine (±)-**1c** (1.6 g, 68%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) major isomer; 0.97 (9H, s, $C(CH_3)_3$), 1.45 (3H, s, CCH_3), 3.49 (1H, d, *J* 8.5 Hz, CH*H*), 3.75 (3H, s, CO_2CH_3), 3.94 (1H, d, *J* 8.5 Hz, C*H*H), 4.15 (1H, s, C*H**t*-Bu). minor isomer; 0.92 (9H, s, $C(CH_3)_3$), 1.42 (3H, s, CCH_3),3.52 (1H, d, *J* 8.2 Hz, CH*H*), 3.74 (3H, s, CO_2CH_3), 4.09 (1H, d, *J* 8.2 Hz, C*H*H), 4.29 (1H, s, C*H**t*-Bu). δ_C (100 MHz, $CDCl_3$) major isomer; 23.3 (CH_3), 25.0 $C(CH_3)_3$), 33.9 $C(CH_3)_3$), 52.4 (CO_2CH_3), 65.1 (*C*-5), 75.0 (*C*-4), 98.7 (*C*-2), 175.2 (CO_2); minor isomer; 23.0 (CH_3), 24.6 $C(CH_3)_3$), 33.0 $C(CH_3)_3$), 52.2 (CO_2CH_3), 65.2 (*C*-5), 74.6 (*C*-4), 98.7 (*C*-2), 175.4 (CO_2); *m*/*z* (ES^+) 202.16 ($M + H^+$), 224.14 ($M + Na^+$); HRMS ($M + H^+$) Found 202.1446, calculated for $C_{10}H_{20}NO_3$ 202.1438.

(±)-(2*S**,5*S**)- and (±)-(2*S**,5*R**)-Methyl 2-(*tert*-butyl)-1-(3-ethoxy-3-oxopropanoyl)-5-methyloxazolidine-5-carboxylate (2c and 3c)

To a solution of (±)-methyl 2-(*tert*-butyl)-4-methyloxazolidine-4-carboxylate **1c** (0.74 g, 3.7 mmol), DCCI (0.84 g, 4.1 mmol) and DMAP (24 mg, 0.20 mmol) in DCM (15 ml) at 0 °C was added ethyl hydrogen malonate (0.54 g, 4.05 mmol) in DCM (10 ml). The mixture was stirred at 0 °C for 15 min and then at room temperature for 4 h. The reaction mixture was filtered, the residue was washed with DCM (3 × 10 ml). The combined filtrates were evaporated *in vacuo* and purified by flash column chromatography (EtOAc : petrol, 1 : 3) to give the oxazolidines (±)-**2c** and **3c** (0.84 g, 72% yield) in a ratio of 1 : 4 as a colourless oil. δ_H (400 MHz, $CDCl_3$) major isomer; 0.67–0.95 (9H, s, $C(CH_3)_3$), 1.17 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.60 (3H, s, CH_3), 3.28 (1H, d, *J* 15.5 Hz, CH*H*), 3.40 (1H, d, *J* 15.5 Hz, C*H*H), 3.63–3.78 (4H, m, CH*H* and CO_2CH_3), 4.08 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.32 (1H, br d, *J* 6.4 Hz, C*H*H), 5.48 (1H, br s, C*H**t*-Bu); minor isomer; 1.62 (3H, s, CH_3), 0.92 (9H, s, $C(CH_3)_3$), 1.42 (3H, s, CCH_3),3.52 (1H, d, *J* 8.2 Hz, CH*H*), 3.74 (3H, s, CO_2CH_3), 4.09 (1H, d, *J* 8.2 Hz, C*H*H), 4.29 (1H, s, C*H**t*-Bu). δ_C (100 MHz, $CDCl_3$) major isomer; 13.9 (CH_2CH_3), 20.5 (CCH_3), 26.4 $C(CH_3)_3$), 38.9 $C(CH_3)_3$), 43.1 ($NCOCH_2$), 52.8 (CO_2CH_2), 61.2 (CH_2CH_3), 65.8 (*C*-5), 78.5 (*C*-4), 98.3 (*C*-2), 166.9 (NCO), 167.7 (CO_2CH_3), 173.6 (CO_2CH_3); minor isomer; 13.9 (CH_2CH_3), 21.5 (CCH_3), 27.1 $C(CH_3)_3$), 39.2 $C(CH_3)_3$), 43.5 ($NCOCH_2$), 53.4 (CO_2CH_2), 61.3 (CH_2CH_3), 66.1 (*C*-5), 78.5 (*C*-4), 98.7 (*C*-2), 167.4 (NCO), 167.7 (CO_2CH_3), 172.0 (CO_2CH_3); *m*/*z* (ES^+) 338.19 ($M + Na^+$); HRMS ($M + Na^+$) Found for $C_{15}H_{25}NO_6Na$ 338.1576, calculated 338.1572.

(±)-(3*S**,7a*S**)-Ethyl 3-(*tert*-butyl)-7-hydroxy-7a-methyl-5-oxo-1,3,5,7a-tetrahydropyrrolo[1,2-*c*]oxazole-6-carboxylate (±)-5b

To a solution of oxazolidine (±)-**3c** (1.2 g, 3.6 mmol) in dry THF (25 ml) was added KO^{t}Bu (0.42 g, 3.73 mmol) and solution was heated at reflux for 4 h, cooled to room temperature and partitioned between ether (15 ml) and water (2 × 15 ml). The aqueous layer was acidified with 2 M HCl and extracted with ethyl acetate (3 × 20 ml). The combined ethyl acetate extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : MeOH, 6 : 1) giving (±)-**5b** as a light yellow solid (0.78 g, 72% yield). δ_H (400 MHz, $CDCl_3$) 0.97 (9H, s, $C(CH_3)_3$), 1.34 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.55 (3H, s, CH_3), 3.39 (1H, d, *J* 8.1 Hz, CH*H*), 3.86 (1H, d, *J* 8.1 Hz, C*H*H), 4.33 (2H, q, *J* 7.1 Hz, CH_2CH_3), 4.64 (1H, br s, C*H**t*-Bu). δ_C (100 MHz, $CDCl_3$) 14.1, 20.8, 25.5, 34.6, 61.6, 71.0, 72.2, 97.5, 167.3, 189.3, 206.1. *m*/*z* (ES^+) 306.16 ($M + Na^+$) HRMS ($M + Na^+$) Found for $C_{14}H_{21}NO_5Na$ 306.1315, calculated 306.1312.

Synthesis of (2*R*,5*R*)-2-*tert*-butyl-7-ethoxycarbonyl-6-hydroxy-8-oxo-1-aza-3-oxabicyclo[3.3.0]oct-6-ene (*ent*-5a) and (2*R*,5*S*)-2-*tert*-butyl-1-ethoxycarbonylacetyl-4-ethoxycarbonyl-1,3-oxazolidine (*cis*-2b) (Scheme 2)

To a mixture of *cis*-**2b** and *trans*-**3b** (ratio of *cis* : *trans* = 70 : 30, 6.0 g, 19.0 mmol) in dichloromethane (50 ml) was added 4-(dimethylamino)pyridine (2.3 g, 19.0 mmol) at 0 °C. The mixture was stirred for 1 day at room temperature. The crude reaction mixture was washed with acidic water (1 N HCl) and the organic layer was dried by using $MgSO_4$. After removing dichloromethane, the crude was dissolved in ethyl acetate and slowly added petrol. The white solid *ent*-**5a** (1.3 g, 4.76 mmol, 25% yield) was obtained by filtration. The filtered solution was concentrated *in vacuo* followed by flash column chromatography gave *cis*-**2b** (3.9 g, 65% yield).

Synthesis of (2*R*,5*R*)-2-*tert*-butyl-6,8-dioxo-1-aza-3-oxabicyclo-[3.3.0]octane 6a from 4a

A mixture of ester **4a** (260 mg, 1.02 mmol) and lithium hydroxide monohydrate (85 mg, 2.04 mmol) in tetrahydrofuran (12 ml), methanol (3 ml) and water (3 ml) was heated at reflux for 15 h then cooled to room temperature. The mixture was extracted with ethyl acetate and acidic water (1 N HCl) then the organic layer was dried by using $MgSO_4$ and evaporated *in vacuo*. The purification by flash column chromatography gave tetramic acid **6a** (60 mg, 30% yield).

Synthesis of (2*R*,5*R*)-2-*tert*-butyl-6,8-dioxo-1-aza-3-oxabicyclo[3.3.0]octane 6a *via* 4c

A mixture of ester **4a** (500 mg, 1.96 mmol) and sodium hydroxide (40 mg, 4.00 mmol) in tetrahydrofuran (20 ml), methanol (5 ml)

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and water (5 ml) was heated at reflux for 8 h then cooled to room temperature. The mixture was extracted with ethyl acetate and acidic water (1 N HCl) then the organic layer was dried by using $MgSO_4$. Evaporation *in vacuo* gave crude carboxylic acid **4c** (460 mg, 1.91 mmol, 97% yield). A solution of crude carboxylic acid **4c** (460 mg, 1.91 mmol) in wet CH_3CN (15 ml) was heated at reflux for 5 h then cooled to room temperature. The mixture was extracted with ethyl acetate and acidic water (1 N HCl) then the organic layer was dried by using $MgSO_4$ and evaporated *in vacuo*. Purification by flash column chromatography gave tetramic acid **6a** (115 mg, 0.57 mmol, 30% yield). Tetramic acid **6a** was also obtained in toluene with (22% yield) or without (18% yield) catalytic amount (5.0 mol%) of *p*-toluenesulfonic acid monohydrate from crude carboxylic acid **4c**.

Synthesis of (2*R*,5*R*)-2-*tert*-butyl-6,8-dioxo-1-aza-3-oxabicyclo-[3.3.0]octane 6a from 2a

A solution of oxazolidine **2a** (1.0 g, 3.32 mmol) and $KOBu^t$ (0.82 g, 7.31 mmol) in wet Bu^tOH (40 ml) was heated at reflux for 15 h then cooled to room temperature. The mixture was extracted with ethyl acetate and acidic water (1 N HCl) then the organic layer was dried by using $MgSO_4$. Purification by flash column chromatography gave tetramic acid **6a** (260 mg, 1.33 mmol, 40% yield). Tetramic acid **6a** was also obtained with 2.2 equivalents of $KOBu^t$ in dry Bu^tOH (25% yield), 3.3 equivalents of $KOBu^t$ in wet Bu^tOH (15% yield) and 2.2 equivalents of NaOMe in benzene and methanol (7% yield along with 13% yield of **4a**) from oxazolidine **2a**.

(2*R*,5*R*)-2-*tert*-Butyl-5-methyl-6,8-dioxo-1-aza-3-oxabicyclo[3.3.0]octane (±)-6b

A solution of tetramic acid (±)-**5b** (0.21 g, 0.74 mmol) in wet CH_3CN (10 ml) was heated at reflux for 18 h, cooled to room temperature and partitioned between EtOAc (20 ml) and 2 M HCl (20 ml). The aqueous layer was extracted with EtOAc (20 ml) and the combined organic extracts were washed with brine (25 ml), dried over $MgSO_4$ and evaporated *in vacuo*. The was purified by flash column chromatography (EtOAc : petrol; 1 : 1) increasing polarity to EtOAc giving (±)-**6b** as a white solid (0.12 g, 76% yield). m.p. 95 °C; δ_H (400 MHz, $CDCl_3$) 1.00 (s, 9H, CMe_3). 1.56 (s, 3H, CH_3), 3.14 (d, J = 11.5 Hz, C7), 3.54 (d, J = 7.5 Hz, C4), 3.57 (d, J = 11.5 Hz, C7), 3.84 (d, J = 7.5 Hz, C4), 4.98 (s, 1H, C2); δ_C (100 MHz, $CDCl_3$); δ 22.4 (CH_3), 25.6 ((CH_3)$_3$), 34.9 (CMe_3), 44.8 (C7), 71.1 (C4), 75.1 (C5), 95.8 (C2), 173.1 (C8), 206.2 (C6); m/z (ES^-); 210.13 ($M - H^-$); HRMS ($M - H^-$); calculated for $C_{11}H_{16}NO_3$; 210.1136; found; 210.1134.

(2*R*,5*S*)-Methyl 1-acetyl-2-(*tert*-butyl)-oxazolidine-5-carboxylate 7

To a solution of the oxazolidine (100 mg, 0.53 mmol, 1.0 eq.) in CH_2Cl_2 was added a solution of acetyl chloride (57 µl, 0.80 mmol, 1.5 eq.) and pyridine (130 µl, 1.60 mmol, 3.eq.) at r.t. The reaction mixture was stirred at r.t. for 3.5 h, after which it was quenched with water, washed with 10% aq. HCl and extracted with CH_2Cl_2. The combined organic layer was dried with anhydrous $MgSO_4$, filtered and solvents evaporated to give the crude material, which was purified on silica gel *via* flash column chromatography (eluent: ethyl acetate–CH_2Cl_2, 2% to 5%) to afford the product as a colourless oil (111 mg, 91% yield). R_f 0.37 (EA : CH_2Cl_2, 1 : 9); $[\alpha]_D^{20}$ −33.2 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1744 (s, C═O), 1667 (s, C═O); δ_H (400 MHz, $CDCl_3$, at r.t.) 0.91 (s, br, 9H, C(CH_3)$_3$), 2.19 (s, 3H, H-9), 3.79 (s, br, 3H, CO_2CH_3), 4.08 (s, br, 1H, CH*H*), 4.46 (s, br, 1H, CH*H*), 4.54 (s, br, 1H, 1H, CH(CO_2CH_3)), 5.32 (s, br, 1H, C*H*′Bu); δ_H (500 MHz, $CDCl_3$, at 67 °C) 0.98 (s, 9H, C(CH_3)$_3$), 2.22 (s, 3H, H-9), 3.83 (s, 3H, CO_2Me), 4.14 (t, J = 8.5 Hz, 1H, CH*H*), 4.49 (dd, J = 3.8, 8.5 Hz, 1H, CH*H*), 4.68 (s, br, 1H, H-5), 5.33 (s, 1H, H-2); δ_H(500 MHz, DMSO-d_6, at 90 °C) 0.86 (s, 9H, *t*-Bu), 2.13 (s, 3H, H-9), 3.73 (s, 3H, CO_2Me), 4.06 (t, J = 8. Hz, 1H, CH*H*), 4.33 (dd, J = 3.2, 8.5 Hz, 1H, CH*H*), 4.96 (dd, J = 3.5, 7.9 Hz, 1H, H-5), 5.18 (s, 1H, C*H*t-Bu); δ_C (125 MHz, $CDCl_3$, at r.t.) 23.49 (C-9), 25.69 (*t*-Bu), 37.55 (*Ct*-Bu), 52.68 (C-7), 59.88 (C-5), 68.08 (C-4), 96.62 (C-2), 170.22, 171.87; m/z (ESI+) 252.12 ($[M + Na]^+$, 94%); HRMS (FI+) calculated for $C_{11}H_{19}NO_4$ ($[M + Na]^+$) 229.1314, found 229.1319.

(2*R*,5*S*)-Methyl 2-(*tert*-butyl)-1-(2,2,2-trifluoroacetyl)-oxazolidine-5-carboxylate 8a

At r.t.: To a solution of the oxazolidine **1a** (50 mg, 0.27 mmol, 1.0 eq.) in CH_2Cl_2 was added a solution of TFAA (56 µl, 0.40 mmol, 1.5 eq.) and pyridine (65 µl, 0.80 mmol, 3.eq.) at r.t. The reaction mixture was stirred at r.t for 3.5 h, after which it was quenched with water, washed with 10% aq. HCl and extracted with CH_2Cl_2. The combined organic layer was dried with anhydrous $MgSO_4$, filtered and solvents evaporated to give the crude material which was purified on silica gel *via* flash column chromatography (eluent: 20% ethyl acetate–petroleum ether) to afford the product as a colourless oil (60 mg, 80% yield).

At −40 °C: To a solution of the oxazolidine **1a** (50 mg, 0.27 mmol, 1.0 eq.) in CH_2Cl_2 was added a solution of TFAA (56 µl, 0.40 mmol, 1.5 eq.) and pyridine (65 µl, 0.80 mmol, 3.eq.) at −40 °C. The reaction mixture was stirred at −40 °C overnight, quenched with water, washed with 10% aq. HCl and extracted with CH_2Cl_2. The combined organic layer was dried with anhydrous $MgSO_4$, filter and solvents evaporated to give the crude product, which was purified on silica gel *via* flash column chromatography (eluent: 20% ethyl acetate–petroleum ether) to afford the pure *cis*-isomer (25 mg, 33% isolated yield) and *trans*-isomer (23 mg, 31% isolated yield). R_f 0.58 (PE : EA, 4 : 1); colourless oil; $[\alpha]_D^{20}$ −15.6 (*c* 0.4 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1758 (s, C═O), 1707 (s, C═O); δ_H(400 MHz, $CDCl_3$) 0.98 (s, 9H, C(CH_3)$_3$), 3.81 (s, 3H, CO_2CH_3), 4.06 (t, J = 8.3 Hz, 1H, CH*H*), 4.56 (dd, J = 2.3, 9.1 Hz, 1H, CH*H*), 4.76 (d, J = 6.3 Hz, 1H, CH(CO_2CH_3)), 5.32 (s, 1H, C*H*t-Bu); δ_C (100 MHz, $CDCl_3$) 25.80 (*t*-Bu), 37.30 (-*Ct*-Bu), 52.89 (-CO_2Me), 58.44 (C-5), 69.13 (C-4), 98.82 (C-2), 115.79 ($^1J_{C-F}$ = 286.3 Hz, C-9), 158.93 ($^2J_{C-F}$ = 36.3 Hz, C-8), 168.70 (C-6); m/z (ESI+) 306.09 ($[M + Na]^+$, 100%); HRMS (ESI+) calculated for $C_{11}H_{16}F_3NO_4Na$ ($[M + Na]^+$) 306.0924, found 306.0922.

(2*R*,5*S*)-Methyl 2-(*tert*-butyl)-1-(2,2,2-trifluoroacetyl)oxazolidine-5-carboxylate 8b

R_f 0.52 (PE : EA, 4 : 1); Colourless oil; $[\alpha]_D^{20}$ −33.5 (*c* = 0.6 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1753 (s, C═O), 1704 (s, C═O); δ_H(400 MHz, $CDCl_3$) 0.98 (s, 9H, C(CH_3)$_3$), 3.82 (s, 3H, CO_2CH_3), 4.27 (dd, J = 1.5, 9.3 Hz, 1H, CH*H*), 4.50 (dd, J = 7.3, 9.3 Hz, 1H, CH*H*), 4.76 (dt, J = 1.8, 7.1 Hz, 1H, CH(CO_2CH_3)), 5.63 (s, 1H,

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C*Ht*-Bu); δ_C (125 MHz, $CDCl_3$) 26.21 (*t*-Bu), 39.57 (-*Ct*-Bu), 53.46 (-CO_2*Me*), 60.04 (C-5), 71.39 (C-4), 97.72 (C-2), 115.88 ($^1J_{C-F}$ = 286.3 Hz, C-9), 158.12 ($^2J_{C-F}$ = 36.3 Hz, C-8), 170.83 (C-6); *m/z* (ESI+) 306.09 ([M + Na]$^+$, 100%); HRMS (ESI+) calculated for $C_{11}H_{16}F_3NO_4Na$ ([M + Na]$^+$) 306.0924, found 306.0917.

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