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Efficient enantioselective synthesis of tetramic acids and lactams from threonine

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Abstract—Regioselective Dieckmann and aldol cyclisations using an *N*-acyloxazolidine derived from threonine give substituted tetramic acids and pyroglutamates in high yield and enantioselectivity. These are easily deprotected under mild conditions to give products, some of which exhibit antibacterial activity.

Tetramic acids and their derivatives form a particularly important sub-group of natural products, and are well known for their potent antibiotic, antiviral and antifungal as well as cytotoxic activity;[1] new examples continue to be discovered.[2] Those which contain structural units derived from *N*-methylserine or *N*-methylthreonine are of current interest,[3] and include the equisetins,[4] the oxazolomycins,[5] the salinosporamides[6] and the cinnabaramides.[7] The synthesis of this key structural motif continues to attract interest,[3,8–10] and the development of rapid and effective synthetic methodology has implications for fragment-based drug design.[11] Our contribution in this area stems not only from the finding that pyroglutamate provides a useful template for structural modification,[12–14] but also that suitable serine-derived oxazolidine templates can be used for highly chemo- and diasteroselective ring closure reactions leading to tetramic acid[15] and pyroglutamate derivatives,[16,17] a process which has found recent application to the large scale synthesis of salinosporamide.[18] Due to the emergence of related methyl substituted natural products, it became desirable to investigate the counterpart of this reaction, which uses threonine as the starting material, and we report our preliminary results here.

According to the method developed by Seebach and coworkers,[19] L- or DL-threonine methyl ester hydrogen chloride **1** was condensed with pivaldehyde in the presence of triethylamine with continuous removal of water to give oxazolidine **2** as a 1:1 mixture of *cis* and *trans* isomers in 74% yield (Scheme 1). This compound was readily acylated with the required carboxylic acid in the presence of DCCI and DMAP in DCM, or by reaction with the corresponding acid chloride, to give *N*-acylated oxazolidines predominantly as the *cis*-2,4-diastereomer;[20] the stereochemistry was readily shown by NOE analysis. In this way, the malonamides **3a**–**c**, the amides **4a**, **b** and the β-ketoamides **5a**, **b** were readily obtained in good yields.[21]

Dieckmann ring closure of oxazolidine **3a** to the corresponding tetramic acid using our reported conditions (KO^tBu in ^tBuOH for 3 h) **15** was not successful, but longer reactions times (potassium *tert*-butoxide for 8 h at reflux) gave tetramic acid **6** in 43% yield along with 7% of decarboxylated tetramic acid **7** (Scheme 2).[22] The treatment of oxazolidine **3b** with potassium *tert*-butoxide in *tert*-butanol at reflux gave tetramic acid **8** in 43% yield, which existed in equilibrium with its enol form, and similar ring closure of *N*-acyl oxazolidine **3c** (KO^tBu in HO^tBu at reflux) gave bicycle **9** in 67% yield, obtained exclusively in the enolic form. Tetramic acid **9** was hydrolysed with 1 M NaOH by heating at reflux and decarboxylated by heating in vacuo to give tetramic acid **10** in 53% yield with complete retention of stereochemistry at C-5. When oxazolidine **4a** was treated with sodium methoxide in refluxing methanol, the only compound obtained was tetramic acid **10** in 51% yield, identical in structure to the material obtained from **3c**. When nitrile ester **4b** was treated with sodium methoxide in

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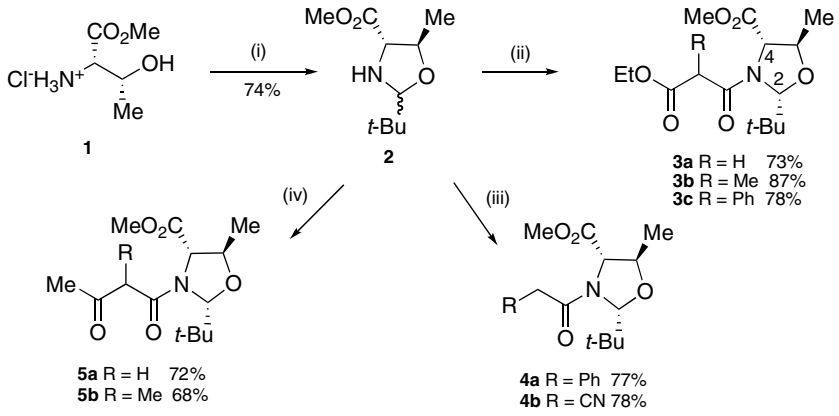
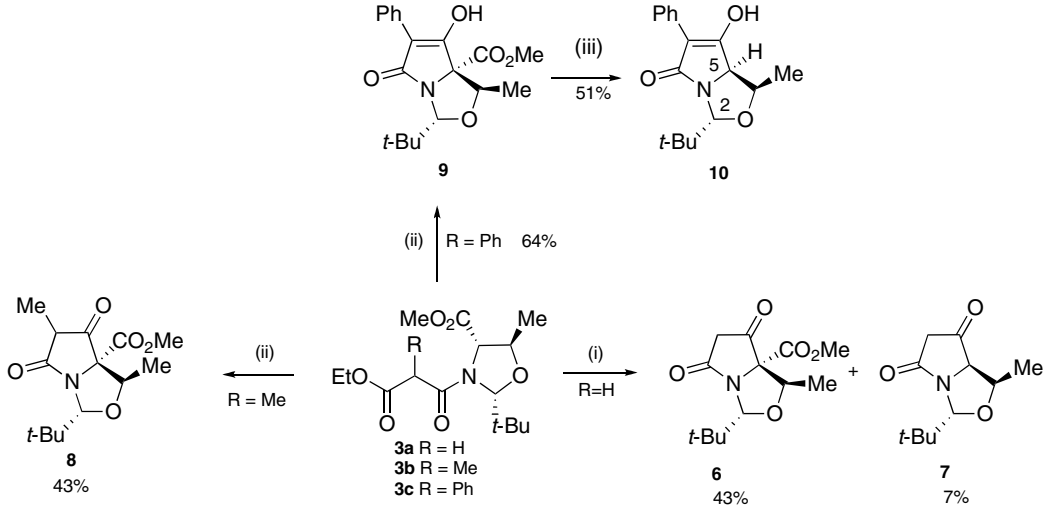


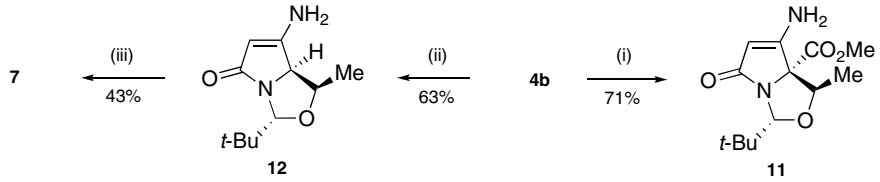
Scheme 1. Reagents and conditions: (i) Me_3CCHO, petrol (40/60), Et_3N, reflux, 16–20 h; (ii) DCCI, DMAP, $EtO_2CCH_2CO_2H$, DCM, 4 h; or ethyl α-methylmalonyl chloride, pyridine, DCM, rt, 5 h; or $EtO_2CCH(Ph)CO_2H$, DCCI, DMAP, DCM, rt, 4 h; (iii) $NCCH_2CO_2H$, DCCI, DMAP, DCM, CH_3CN, rt, 4 h; or $PhCH_2COCl$, pyridine, DCM, rt, 4 h; (iv) $CH_3C(O)CH_2CO_2H$, DCCI, DMAP, DCM, rt, 4 h; or $CH_3C(O)CH(Me)CO_2H$, EDAC, DMAP, DCM, rt, 4 h.



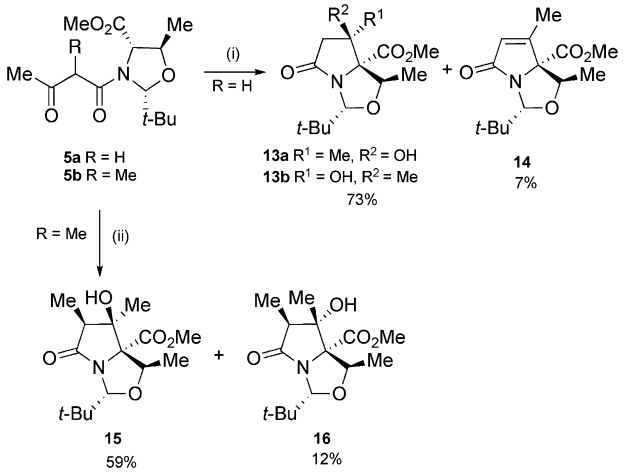
Scheme 2. Reagents and conditions: (i) KO^{t}Bu, *t*-BuOH, reflux, 8 h; (ii) KO^{t}Bu, *t*-BuOH, reflux, 3 h; (iii) 1 N NaOH, reflux, 5 h.

methanol, it underwent Thorpe–Ziegler reaction to give enamine **11** in 71% yield (Scheme 3). On the other hand, when this reaction was carried out with potassium *tert*-butoxide in *tert*-butanol, enamine **12** was obtained as the major product (63%), along with lactam **11** as a minor product (11%), and this reaction was more effective when wet *tert*-butanol was used, presumably due to improved in situ ester hydrolysis and decarboxylation. Enamine **12** on basic hydrolysis gave tetramic acid **7** in 43% yield. The relative stereochemistry of each of these products was readily established by NOE analysis; generally, irradiation of H-2 gave an enhancement to the methyl at C-4 and irradiation of the methyl of CO_2Me gave an enhancement to the *tert*-butyl group, thus indicating that the methyl ester and *tert*-butyl groups are on the *exo* face of the bicyclic system.

Aldol reaction of *cis*-oxazolidine **5a** was found to be particularly effective using our reported conditions, **17** and on treatment with sodium methoxide in methanol at room temperature, two aldol products **13a** and **13b** were formed in 73% yield in a 5:1 ratio (Scheme 4),



Scheme 3. Reagents and conditions: (i) NaOMe, MeOH, rt, 15 h; (ii) KO^{t}Bu, *t*-BuOH (wet) then H_2O, rt, 2 h; (iii) $NaOH/H_2O$, heat, rt, 18 h.



Scheme 4. Reagents and conditions: (i) NaOMe, MeOH, 18 h, rt; (ii) NaOMe, MeOH, 20 h, rt.

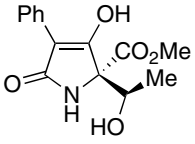
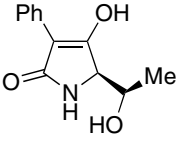
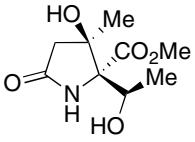
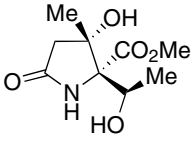
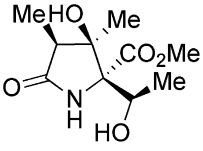
which were readily separated by flash column chromatography, and their relative stereochemistry easily assigned by NOE. At elevated reaction temperatures, unsaturated lactam **14** was also obtained.[23] Cyclisation of *cis*-oxazolidine **5b** gave only two diastereomers on reaction with sodium methoxide in methanol (Scheme 4), and purification by column chromatography gave major diastereomer **15** in 59% yield and minor diastereomer **16** in 12% yield. The relative stereochemistry of these epimers was easily determined by NOE analysis.

The Corey and Reichard[24] protocol (2% HCl w/v in trifluoroethanol at room temperature for 5–20 h) was applied for the deprotection of some representative examples **9**, **10**, **13a**, **b** and **15** (Table 1).[25] The products were purified by partitioning the reaction mixture between ethyl acetate and water. The organic extracts were dried over $MgSO_4$ and evaporated in vacuo to give the free amido alcohols in good yields as shown in Table 1. The deprotected compounds **19**–**21** were readily purified by flash column chromatography eluting with ethyl acetate and methanol (4:1).

The *N*-acyl oxazolidines derived from DL-threonine, and tetramic acids and other nitrogen heterocycles obtained by the cyclisation of these *N*-acyl oxazolidines were tested for their bioactivity against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis* at a concentration of 4 mg/ml using the hole plate method. Compounds **7**, **13a** and **18** were found to be active only against *S. aureus*, but compound **15** was active against *S. aureus* and *B. subtilis*, and compound **19a** was active against *S. aureus*, *B. subtilis* and *E. coli*. Compounds obtained from L-threonine were tested against *S. aureus*; only compound **13a** was found to be active at a concentration of 2 mg/ml.

Thus, we have demonstrated that L-threonine methyl ester may be transformed to tetramic acids by Dieckmann cyclisation and Thorpe–Ziegler cyclisation. Aldol cyclisation of *N*-acyl oxazolidines gave highly functionalised bicyclic products with three contiguous chiral centres.

Table 1. Deprotection of heterocycles

Starting material	Product	Reaction time (h)	Yield (%)
9	 **17**	7	78
10	 **18**	7.5	82
13a	 **19**	5	85
13b	 **20**	5	71
15	 **21**	7	89

These products may be deprotected to give amido alcohols, some of which display biocidal activity against *E. coli*, *S. aureus* and *B. subtilis*.

Acknowledgements

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20. An exception to this outcome was the formation of (2*S*,4*S*,5*R*′)-*epi*-**3b** as the major isomer.
21. All new compounds gave satisfactory spectroscopic and high resolution mass spectrometric or analytical data.
22. To a solution of oxazolidine **3a** (0.2 g, 0.64 mmol) in ^{t}BuOH (15 ml) was added KO^{t}Bu (78 mg, 0.70 mmol) and the solution was heated at reflux for 7 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 ether (2 × 20 ml). The organic extracts were washed with brine, dried over $MgSO_4$ and evaporated in vacuo to give a brown oil, which was purified by flash column chromatography (EtOAc–petrol, 1:1 increasing polarity to neat EtOAc) to give pure tetramic acid **6** as a light yellow solid (72 mg, 43% yield) and dicarbonyl **7** (11 mg, 7%) as a white solid.
Compound **6**: mp 69–71 °C $R_f = 0.22$ (EtOAc–petrol, 1:1); $[\alpha]_D^{22}$ +47.2 (*c* 1.5 in MeOH); ν_{max}/cm^{-1} ($CHCl_3$) 2960 (m), 1750 (s), 1730 (s) and 1665 (s); δ_H (400 MHz, $CDCl_3$) 0.91 (9H, s, C(C*H*$_3$)$_3$), 1.06 (3H, d, *J* 6.7 Hz, C(4)HC*H*$_3$), 3.15 (1H, d, *J* 21.7 Hz, C(7)*H*H), 3.65 (1H, d, *J* 21.7 Hz, C(7)H*H*), 3.81 (3H, s, CO_2CH_3), 5.10 (1H, q, *J* 6.7 Hz, C*H*CH$_3$), 5.13 (1H, s, C(2)*H*); δ_C (100.6 MHz, $CDCl_3$) 15.1 (CH*C*H$_3$), 24.7 (C(*C*H$_3$)$_3$), 35.4 (*C*(CH$_3$)$_3$), 45.2 (*C*(7)), 53.6 (CO_2CH_3), 73.9 (*C*(5)), 75.0 (*C*(4)), 95.8 (*C*(2)), 162.7, 173.4 and 199.5 (carbonyls); *m*/*z* (ES^-) 268 ($(M-H)^-$, 35%), 201 (100); HRMS ($M-H^-$). Found 268.1179, $C_{13}H_{18}NO_5$ requires 268.1185.
Compound **7**: mp 98 °C $R_f = 0.17$ (EtOAc); $[\alpha]_D^{22}$ +95.4 (*c* 1.5 in MeOH); ν_{max} 2970 (m), 1775 (s), 1720 (s), 1370 (s), 1360 (s), 1245 (s); δ_H (400 MHz, $CDCl_3$) 0.96 (9H, s, C(C*H*$_3$)$_3$), 1.02 (3H, d, *J* 6.6 Hz, CHC*H*$_3$), 3.10 (1H, d, *J* 22.1 Hz, COC*H*H), 3.39 (1H, d, *J* 22.1 Hz, COCH*H*), 4.37 (1H, d, *J* 6.2 Hz, C*H*CO), 4.53 (1H, q, *J* 6.6 Hz, C*H*CH$_3$), 5.20 (1H, s, C(2)*H*); δ_C (100.6 MHz) 15.7 (CH*C*H$_3$), 24.7 (C(*C*H$_3$)$_3$), 36.2 (*C*(CH$_3$)$_3$), 45.4 (*C*(7)), 71.8 (*C*(5)), 73.6 (*C*(4)), 94.2 (*C*(2)), 172.9 (N*C*O) and 203.6 (*C*(6)); *m*/*z* (ES^-) 211 ($(M-H)^-$, 100%).
23. To a solution of oxazolidine **5a** (0.45 g, 1.58 mmol) in dry methanol was added NaOMe (86 mg, 1.59 mmol) and the solution was stirred for 24 h at room temperature and then partitioned between ether (15 ml) and NH_4Cl (aq) (15 ml). The ether layer was washed with brine (15 ml), dried over $MgSO_4$ and evaporated in vacuo to give a crude product, which was purified by flash column chromatography (EtOAc–petrol, 1:2) to give alcohol **13a** (0.27 g, 61%) as a crystalline white solid and alcohol **13b** (0.05 g, 12%) as a white solid.
Compound **13a**: mp 136–138 °C; $R_f = 0.32$ (EtOAc–petrol, 1:4); $[\alpha]_D^{20}$ +38.2 (*c* 1.5 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3400 (w), 2960 (m), 1750 (s), 1730 (s) and 1665 (s); δ_H (400 MHz, $CDCl_3$) 0.87 (9H, s, C(C*H*$_3$)$_3$), 1.33 (3H, s, CC*H*$_3$), 1.68 (3H, d, *J* 6.6 Hz, CHC*H*$_3$), 2.30 (1H, d, *J* 15.9 Hz, C(7)*H*H), 3.05 (1H, d, *J* 15.8 Hz, C(7)H*H*), 3.77 (3H, s, CO_2CH_3), 4.74 (1H, q, *J* 6.5 Hz, C(4)*H*), 5.03 (1H, s, C(2)*H*); δ_C (100.6 MHz, $CDCl_3$) 15.1 (CH*C*H$_3$), 22.9 (C(OH)*C*H$_3$), 25.7 (C(*C*H$_3$)$_3$), 37.4 (*C* (CH$_3$)$_3$), 49.5 (*C*(7)), 52.7 (CO_2CH_3), 78.4 (*C*(4)), 80.5 and 82.2 [*C*(5) and *C*(6)], 96.0 (*C*(2)), 172.2, 179.0 (carbonyls), *m*/*z* (ES) 284 ($(M-H)^-$, 100%), 198 (95); HRMS ($(M-H)^-$). Found 284.1490, $C_{14}H_{22}NO_5$ requires 284.1498.
Compound **13b**: $R_f = 0.27$ (EtOAc–petrol, 1:4); $[\alpha]_D^{20}$ +29.0 (*c* 1.35 in $CHCl_3$); ν_{max}/cm^{-1} 3420 (w), 3370 (br w), 2960 (m), 1740 (s), 1710 (s), 1115 (s); δ_H (400 MHz, $CDCl_3$) 0.93 (9H, s, C(C*H*$_3$)$_3$), 1.38 (3H, s, C(OH)C*H*$_3$), 1.71 (3H, d, *J* 6.6 Hz, CHC*H*$_3$), 2.29 (1H, d, *J* 15.8 Hz, C(7)*H*H), 2.69 (1H, br s, O*H*), 3.10 (1H, d, *J* 15.8 Hz, C(7)H*H*), 3.81 (3H, s, CO_2CH_3), 4.77 (1H, q, *J* 6.6 Hz, C*H*CH$_3$), 5.31 (1H, s, C(2)*H*); δ_C (100.6 MHz, $CDCl_3$)15.1 (CH*C*H$_3$), 22.8 (C(OH)*C*H$_3$), 25.8 (C(*C*H$_3$)$_3$), 37.4 (*C*(CH$_3$)$_3$), 49.6 (*C*(7)), 52.7 (CO_2CH_3),78.3 (*C*(4)), 80.2 and 82.3 [*C*(5) and *C*(6)], 96.5 (*C*(2)), 171.9 and 178.8 (ester and amide carbonyls); *m*/*z* (ES^-) 284 ($(M-H)^-$, 100%), 198 (95); HRMS ($(M-H)^-$). Found 284.1494, $C_{14}H_{22}NO_5$ requires 284.1498.
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25. To a solution of alcohol **13b** (0.37 g, 1.3 mmol) in 2% HCl in trifluoroethanol (5 ml) was added 1,3-propanedithiol (0.13 ml, 1.3 mmol) and the mixture was stirred for 7 h at room temperature. The solvent was then evaporated in vacuo and the residue was purified by flash column chromatography (EtOAc–MeOH, 4:1) to give **20** (0.20 g, 73%) as a white solid. Mp 158–160 °C; $R_f = 0.34$ (MeOH: EtOAc, 1:4); $[\alpha]_D^{20}$ +79.6 (*c* 1.7 in MeOH); ν_{max}/cm^{-1} 3428 (w), 2597 (w), 2039 (s), 1704 (s), 1563 (s), 1257 (s), 720 (s); δ_H (400 MHz, CD_3OD) 1.30 (3H, d, *J* 6.3 Hz, CHC*H*$_3$), 1.33 (3H, s, C(OH)C*H*$_3$), 2.30 (1H, d, *J* 17.0 Hz, C(4)*H*H), 2.66 (1H, d, *J* 17.0 Hz, C(4)H*H*), 3.80 (3H, s, CO_2CH_3), 4.48 (1H, q, *J* 6.2 Hz, C*H*CH$_3$); δ_C (100.6 MHz, $CDCl_3$) 17.7 (CH*C*H$_3$), 26.6 (C(OH)*C*H$_3$), 46.3 (*C*(4)), 51.6 (CO_2CH_3), 70.4 (*C*HCH$_3$), 75.5 and 77.7 [*C*(2) and *C*(3)], 172.3 and 176.1 (amide and ester carbonyls); *m*/*z* (ES^-) 216 ($(M-H)^-$, 100%); HRMS ($(M-H)^-$). Found 216.0871, $C_9H_{14}NO_5$ requires 216.0872.