Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 3472

www.rsc.org/obc

PAPER

Biomimetic synthesis, antibacterial activity and structure–activity properties of the pyroglutamate core of oxazolomycin†

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Received 6th January 2012, Accepted 28th February 2012
DOI: 10.1039/c2ob00042c

Biomimetic intramolecular aldol reactions on oxazolidine templates derived from serine may be used to generate densely functionalised pyroglutamates, which are simpler mimics of the right hand side of oxazolomycin. Some of the compounds from this sequence exhibit *in vivo* activity against *S. aureus* and *E. coli*, suggesting that pyroglutamate scaffolds may be useful templates for the development of novel antibacterials, and cheminformatic analysis has been used to provide some structure–activity data.

The oxazolomycin class of natural products (Fig. 1), which includes oxazolomycins A–C **1a–c**, 16-methyloxazolomycin **1d**, curromycin A and B **1e–f** and KSM2690 **1g–h** and lajollamycin, is of interest for its structural uniqueness and wide biological activity[1] (lajollamycin, for instance, exhibits potent antibacterial activity against both drug-sensitive and -resistant Gram-positive strains (MIC values < 20 μg mL^{-1}),[2] and 16-methyloxazolomycin is active against *B. subtilis* at 5 μg mL^{-1} although this drops to 50 μg mL^{-1} for KSM-2690B[1]) and significant progress in the understanding of their biosynthesis has recently been reported.[3,4] Although several total syntheses have now been achieved,[5–7] the highly functionalised-γ-lactam ring portion remains a particular synthetic challenge. Access to the lactam–lactone spirocyclic system has been the focus of some attention, and Mohapatra has recently reported the use of auxiliary-controlled aldol chemistry to construct the substituted pyroglutamate ring,[8] while Taylor has reported an approach based upon modification of proline.[9] However, the synthesis of an intermediate suitable for incorporation of the middle fragment, by including the necessary chiral quaternary centre at C-3 (oxazolomycin numbering), has proved to be much more challenging, and in addition to our own work in this area,[10–12] the groups of Donohoe,[13] Pattenden,[14] Ohfune and Soloshonok[15] and Wang[16] have all made important contributions. We report here the successful achievement of an intramolecular aldol reaction on a functionalised oxazolidine, leading directly to highly functionalised pyroglutamates with three contiguous chiral centres and which are simpler mimics of the more complex spirolactam–lactone system of the oxazolomycins. Seebach's concept of self-reproduction of stereocentres is used as a key element to control the chemo- and stereo-selectivity of the reaction.[17] Other groups have also found merit in a similar strategy based on aldol closure for the synthesis of salinosporamide A and its analogues,[18,19] by direct adaptation of our original report.[12]

At the outset, we required an entry to γ-alkoxymalonamides, a compound class for which there is a surprising paucity of effective synthetic methodology. Our first attempt to access these systems is outlined in Scheme 1; although conversion of glycolic acid **2** to the corresponding silyl ethers **3** could be achieved in good yield under standard conditions (RCl, imidazole, DMF) (**3**, R = TBDMS (98%), TBDPS (80%), TIPS (64%)), their further conversion according to Scheme 1 proved to be problematic. Thus, apart from the reaction of the PMB protected material (**3**, R = PMB), which was quantitative, the silyl ethers **3** did not give good conversion to the corresponding β-ketoesters **4** (yield, R = TBDMS (19%), TBDPS (0%), TIPS (29%)). Deprotection of both the PMB and TIPS systems was possible (yield **5**, R = PMB (65%), TIPS (11%)), but only the TIPS acid **5** allowed access to the desired oxazolidine **6** (R = TIPS) by DCC–DMAP coupling, and even then in poor yield (11%). Although this multi-step sequence offered considerable flexibility, given the low yields, an alternative was required.

Of recent approaches leading to functionalised β-ketoesters,[20] methods for the synthesis of functional acetoacetates by condensation of 3,3-dimethylacryloyl chloride[21] or methoxyacetyl chloride[22] with Meldrum's acid **7a** were of particular interest; Meldrum's acid is enjoying a renaissance of interest as a nucleophile.[23] We found that acylation of methyl Meldrum's acid **7b** using 3,3-dimethylacryloyl and methoxyacetyl chlorides proceeded efficiently (Scheme 2), but we could not open either of the products **8a** or **8b** with alcohols under a variety of conditions. Suspecting that the bulk of the α-methyl substituent was likely to be the source of the problem, we examined acylation of Meldrum's acid **7a** using methoxyacetyl chloride. We found in this case that acylation also efficiently generated the desired

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†Electronic supplementary information (ESI) available. CCDC 860455 and 860456. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob00042c

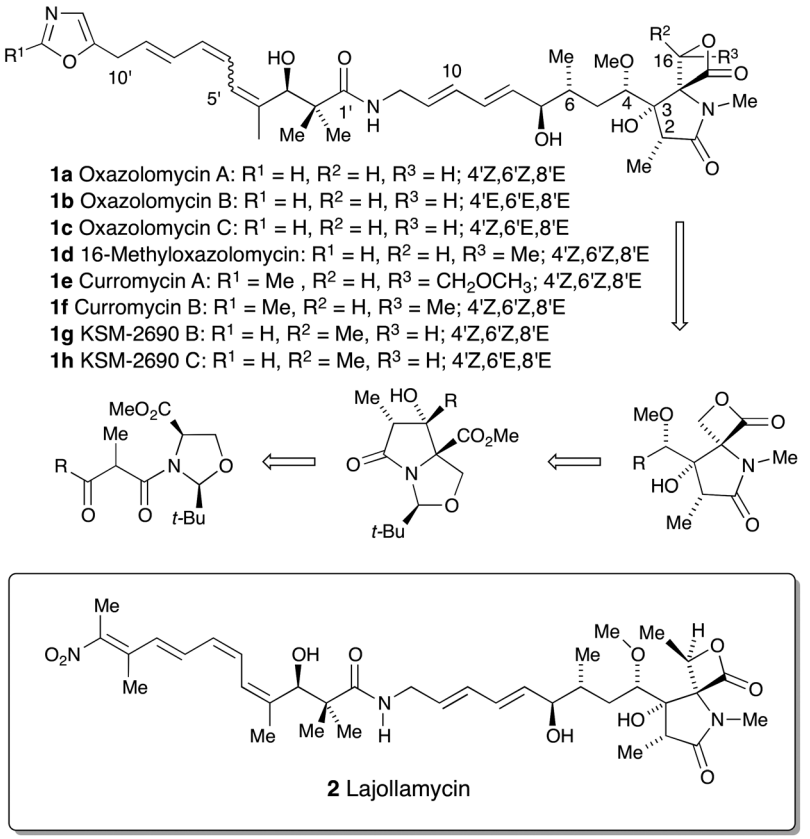
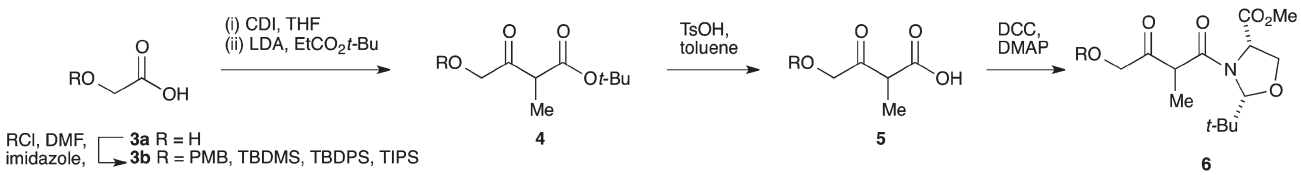


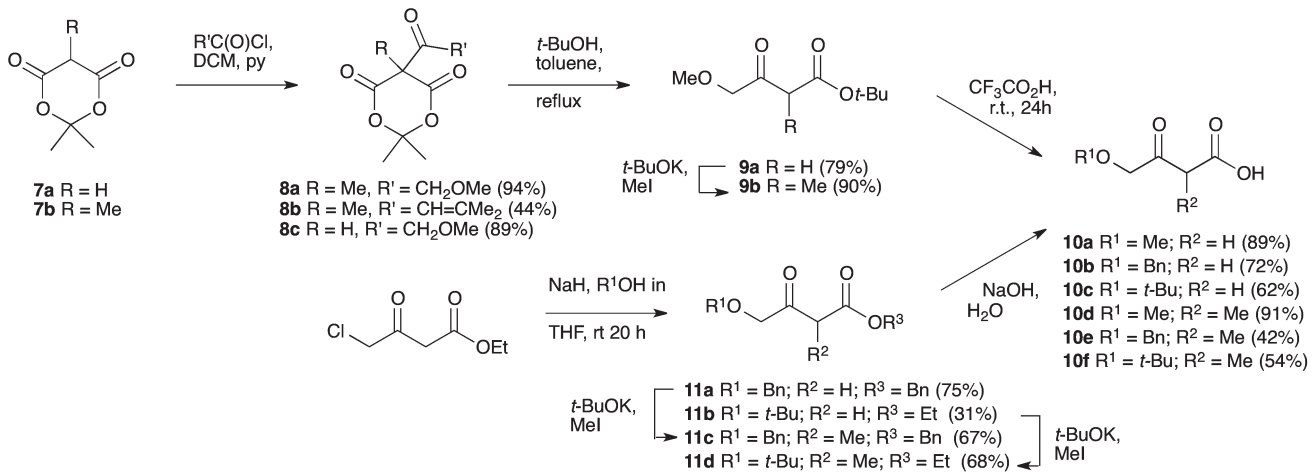
Fig. 1



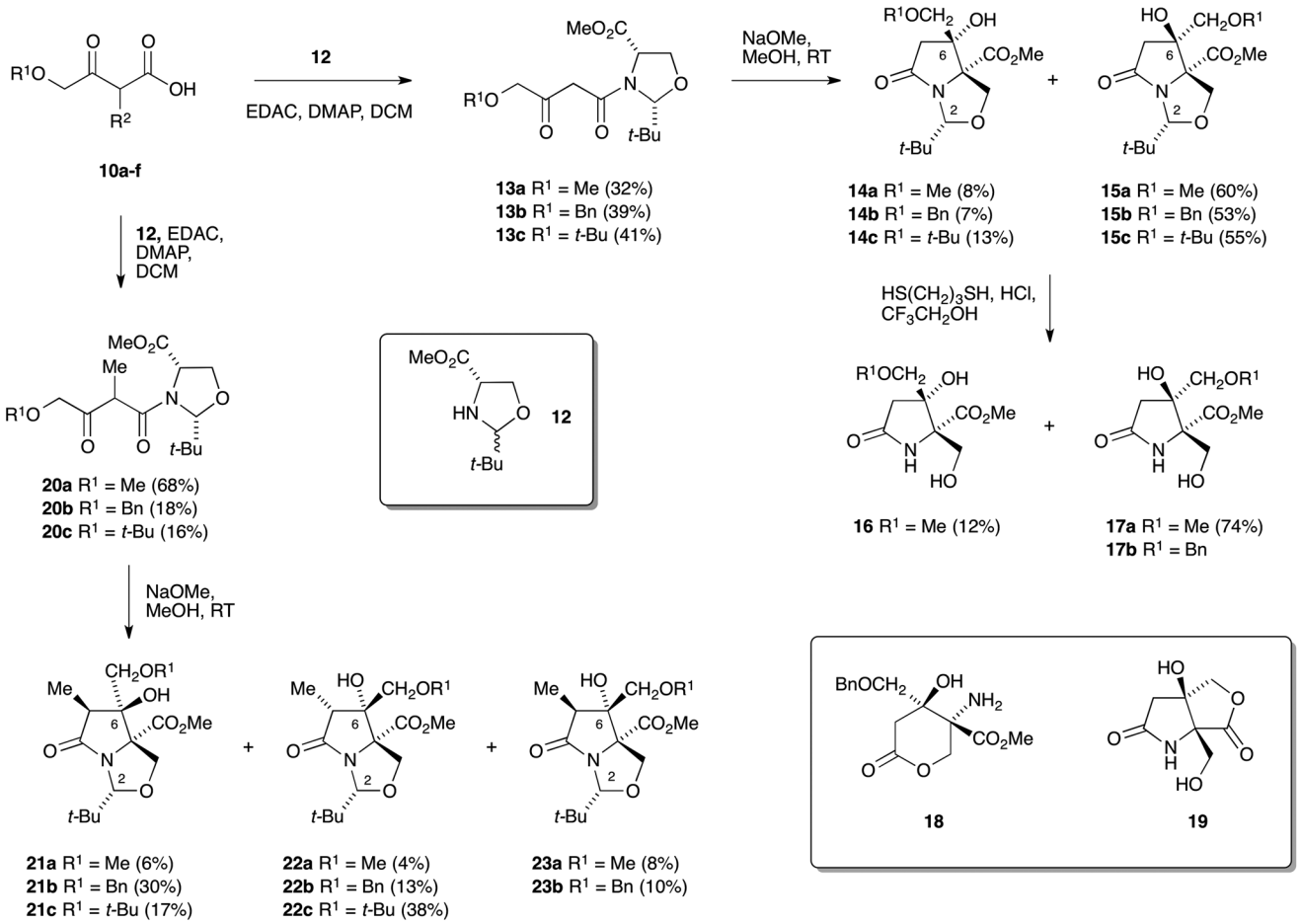
Scheme 1

product **8c**, predominantly as the enol form (keto–enol = 1 : 4), and that this material was not fully stable to silica purification; in keeping with the literature report,[22] it was in fact readily converted using *tert*-butanol in toluene at reflux to the *tert*-butyl ester **9a** in 79% yield. This material was easily deprotected using trifluoroacetic acid, to give the corresponding acid **10a** predominantly in the keto form (keto–enol = 4 : 1) in 89% yield. In order to conveniently vary the alkoxy substituent, we used a literature procedure for the direct substitution of alkoxides on the enolate derived from ethyl 4-chloroacetoacetate (Scheme 2).[24–27] By this means, we were able to access acetoacetates **11a,b** in good yields (in the case of **11a**, concomitant transesterification was obtained), which were found to exist as a mixture of keto–enol tautomers, and these were readily saponified (NaOH, H_2O) to the β-ketoacids **10b,c** in good yield (Scheme 2).

These acids were used to acylate oxazolidine **12**, prepared from L-serine methyl ester hydrochloride and pivaldehyde according to the Seebach protocol,[28,29] with EDAC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide) in the presence of a catalytic amount of DMAP, to the *cis*-oxazolidines **13a–c** (Scheme 3). Reaction of these half-malonamides with sodium methoxide efficiently gave the aldol products **14a–c** and **15a–c**, typically as a mixture of epimers, in favour of the diastereomer in which the more bulky alkoxymethyl group was located in the *exo*-position at C-6. The stereochemistry of the major products **15a–c** was readily established by nOe analysis (Fig. 2).[30] We believe that the chemoselectivity of this process results from initial deprotonation at the malonamide residue, which equilibrates with the C-5 position prior to ring closure, leading to a bicyclic system in which the bulky substituent resides on the less hindered convex *exo*-face;[12,31,32] this is consistent with the outcomes in related reports.[18,19] These materials were easily deprotected using the Corey–Reichard protocol,[33] to give the inseparable pyroglutaminols **16** and **17a** in 86% yield (ratio 1 : 6). Deprotection of **15b** gave the desired lactam **17b** along with **18** which could not be separated (3 : 2 ratio) in a yield of 82%. In the case of **15c**, concomitant *tert*-butyl ether deprotection was also observed, and the resulting diol underwent intramolecular lactonisation to give lactone–lactam **19**, whose structure was assigned by careful HMBC analysis; this



Scheme 2



Scheme 3

compound is of interest since it comprised the core structure of neooxazolomycin.[34] The major diastereomers **15a–c** from this sequence possess the correct relative stereochemistry for oxazolomycin **1**, and this outcome effectively demonstrated that the presence of the additional alkoxy functionality in malonamides **13a–c**, even with inclusion of quite bulky groups such as the *tert*-butyl group, did not impede the desired aldol reaction. However, critical to the further development of this strategy was the incorporation of the C-2 methyl group (Fig. 1) which is invariably present in all known members of the oxazolomycin family.

On the basis of earlier work,[11,32] we expected that deprotonation of acetoacetates **9a**, **11a**, and **11b** with potassium *tert*-butoxide followed by reaction with methyl iodide would permit

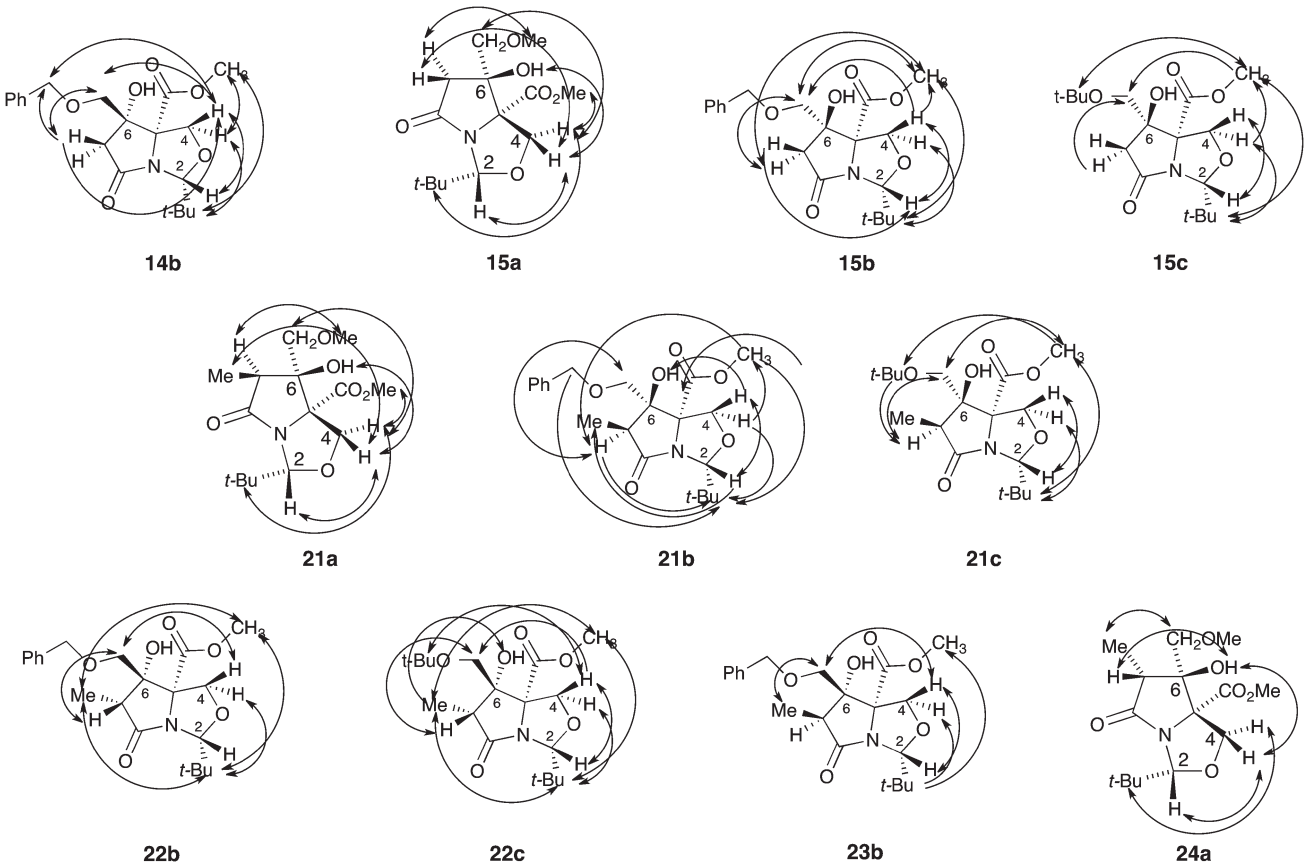
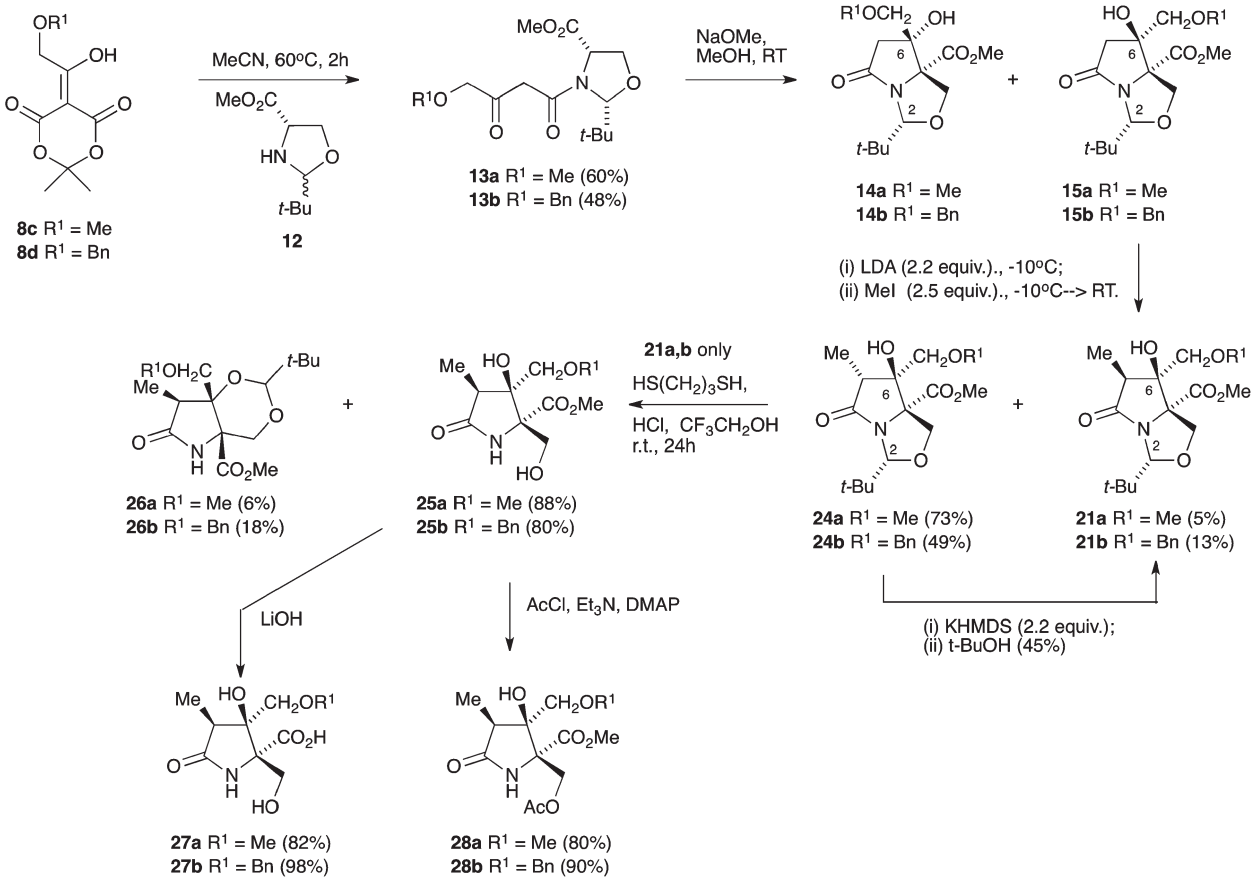


Fig. 2

methylation to give methylacetoacetates **9b**, **11c**, and **11d**, and this strategy in fact worked very efficiently (Scheme 2). Deprotection under appropriate conditions gave the corresponding acids **10d–f**. Repetition of the sequence outlined above (Scheme 3) gave the corresponding oxazolidines **20a–c** as a mixture diastereoisomers, albeit in lower yield in two cases than the desmethyl series, probably as a result of the additional steric bulk in this system, but these products were again readily cyclised by aldol reaction using sodium methoxide in dry methanol; this reaction proceeded most efficiently for the benzyl **20b** and *tert*-butyl **20c** systems. In all cases, more than one diastereomer was formed, not all of which were separable, for which the stereochemistry of most was readily assigned by nOe analysis (Fig. 2). However, in the case of the cyclisation of oxazolidine **20a**, the several product diastereomers **21a**, **22a** and **23a** which were formed could only be assigned by reference to chemical shift patterns. Thus, it was noted that in the ^{1}H NMR spectrum of diastereomers **21b**, **21c** and **23b**, all possessing the 7*S*-stereochemistry as established by nOe analysis, that the C(7) methine protons had relatively higher chemical shifts (both δ 3.2) while the C(7) methyl groups had relatively lower chemical shifts (both δ 1.1). On the other hand, diastereomers **22b** and **22c** with the 7*R*-stereochemistry, exhibited the C(7) methine proton with a relatively low chemical shift (δ 2.4) while the C(7) methyl group had a relatively higher chemical shift (δ 1.4); this outcome corresponds with the less highly functionalised systems examined earlier,[12] and provides a useful, if indirect, method for assigning stereochemistry in these systems. On this basis, the isomers **22a** (minor) with C(7)Me at 1.41 and C(7)H at 2.43, and **23a** (major), with C(7)Me at 1.06 and C(7)H at 3.50, were assigned as shown in Scheme 3. This approach provides direct access to polysubstituted pyroglutamates related to the right hand side of oxazolomycin. That the additional methyl substituent has such a pronounced effect on the diastereoselectivity of the ring closing process (at least compared to the outcome for the desmethyl series **13**) is a reflection of the congested nature of the bicyclic system, which possess three contiguous chiral centres, two of which are quaternary. We did not examine equilibration phenomena of the diastereomeric products, and whether the product distribution is a result of kinetic and thermodynamic control is therefore not clear.

Having demonstrated the feasibility of conducting efficient aldol reactions according to Fig. 1, it was of interest to improve this approach, and on the basis of recently published work,[35–37] we expected that direct opening of acylated Meldrum's acids **8c, d** with oxazolidine **12** should be possible; if so, this would remove two steps from the synthesis. In the event, when the two starting materials **8c** or **8d** and **12** were simply heated at 60 °C in acetonitrile for 2 h, the desired amides **13a,b** were readily formed and in good yield. In keeping with earlier observations, aldol cyclisation of the ketoamides **13a,b** proceeded smoothly at r.t. in the presence of 1.5 equiv. of sodium methoxide in methanol, giving the products as mixtures of diastereoisomers **14a,b** and **15a,b** (**14a** : **15a** = 1 : 4 and **14b** : **15b** = 1 : 5), the



Scheme 4

major ones **15a,b** having the correct relative stereochemistry for oxazolomycin (Scheme 3) as determined on the basis of NOE experiments (Fig. 2).

Having successfully prepared the desired lactams **15a,b**, we investigated the introduction of a methyl group by double deprotonation and diastereoselective enolate alkylation. Initial reaction of **15a** with 2 equiv. LDA followed by 1 equiv. of iodomethane which gave the desired *C*-methylated products **21a** and **24a** with high diastereoselectivity, but only in moderate yield, and no competing *O*-methylation was observed. However, by using an excess of the alkylating reagent (3 equiv.), the yield of the *C*-alkylated products was significantly improved (60–80%) and no *O*-alkylation was observed (Scheme 3). This process could be easily replicated with the benzyl substrate **15b**, although in both these reactions, 15–30% of unreacted starting materials **15a,b** was recovered. The stereochemical outcome of this process was determined on the basis of NOE experiments (Fig. 2) and showed that the electrophilic attack occurs predominantly from the less hindered convex side of the bicyclic system, as might be expected; we have previously shown that alkylation, nucleophilic additions and reductions in these bicyclic systems is strongly influenced by the concave nature of the substrate.[38–40] Although the configuration of the major products **24a,b** is incorrect for the natural product, the high diastereoselectivity of the enolate alkylation suggested that it may be possible to invert the configuration through double deprotonation and subsequent proton delivery from the less hindered face. Indeed, treatment of **24a,b** with 2 equiv KHMDS followed by *t*-BuOH gave nearly clean **21a,b** in 45 and 46% isolated yield respectively (Scheme 4), and identical to the material prepared by direct aldol reaction (Scheme 3). This represents a significant improvement over the direct cyclisation, and not least in significantly enhanced diastereoselectivity. In the ^{1}H NMR spectrum of diastereomers **21a,b** and **24a,b**, NMR patterns were consistent with those described above; thus, for **21a,b**, both possessing the 7*S*-stereochemistry, the C(7) methine protons had relatively higher chemical shifts (both δ 3.2) while the C(7) methyl groups had relatively lower chemical shifts (δ 1.1–1.2). On the other hand, diastereomers **24a** and **24b** with the 7*R*-stereochemistry, exhibited the C(7) methine proton with a lower chemical shift (δ 2.8) while the C (7) methyl group had a relatively higher chemical shift (δ 1.4).

With **21a,b** in hand, we proceeded with their deprotection using Corey–Reichard aminal cleavage[33] to give the corresponding acids **25a,b** in good yield (80 and 88% respectively) along with minor amounts of acetals **26a,b** (up to 20%) (Scheme 4). The stereochemical assignments were confirmed by single-crystal X-ray diffraction of the intermediate **25a**,[41] which indicated a conformation in which the relatively more bulky C(4) Me, C(3)CH_2OMe and C(2)CH_2OH groups occupy pseudoequatorial positions (Fig. 3). That selective manipulation of **21a,b** was possible was demonstrated by ester hydrolysis (LiOH) which gave pyroglutamates **27a,b**, with the opposite absolute

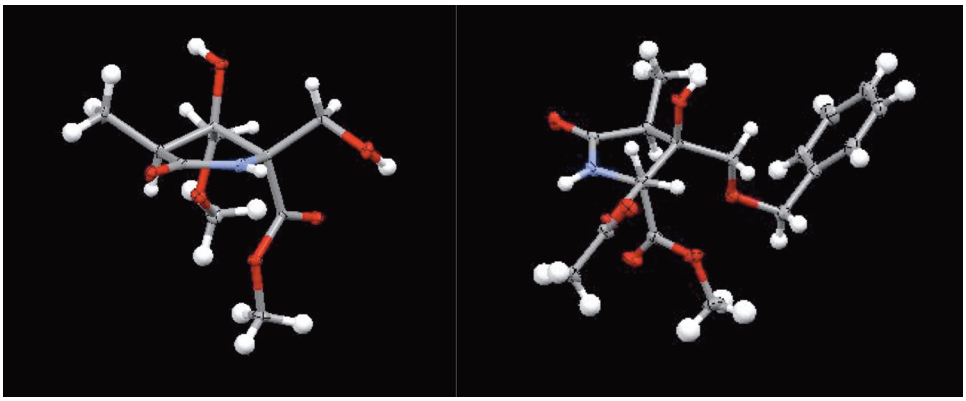


Fig. 3 X-ray structures for **25a** and **28a** (thermal ellipsoids shown at 25% probability level).

Table 1 Cheminformatic[a] and bioassay[b] of compounds **14–19** and **21–28** against *S. aureus* and *E. coli*

				Bioactivity[b]			
				S. aureus		*E. coli*	
Compound	Log*P*[a]	PSA	%PSA	Zone size/mm	Relative potency[c]	Zone size/mm	Relative potency[c]
1a	1.61	171.7	17.9	—	—	—	—
1b	1.61	171.7	17.9	—	—	—	—
1c	1.61	171.7	17.9	—	—	—	—
1d	2.03	171.7	17.1	—	—	—	—
1e	1.72	180.1	16.6	—	—	—	—
1f	2.10	171.7	16.5	—	—	—	—
1g	2.03	171.7	17.1	—	—	—	—
1h	2.03	171.7	17.1	—	—	—	—
Lajollamycin	2.66	191.5	18.4	—	—	—	—
14a/15a	0.24	85.3	17.6	Inactive	—	12	0.038
14b	1.97	85.3	14.4	15	3.8	18	0.087
14b	1.97	85.3	14.4	Inactive[e]	—	14[e]	0.095
15a	0.40	85.3	17.6	Inactive	—	Inactive	—
15b	2.14	85.3	14.4	13	0.91	19	0.08
15c	1.30	85.3	14.6	Inactive	—	Inactive	—
16a/17a	−2.40	105	30.3	Inactive	—	Inactive	—
17b+18	—	—	—	Inactive	—	Inactive	—
19	−2.52	—	39.2	Inactive	—	Inactive	—
21a	0.79	85.3	16.6	Inactive	—	Inactive	—
21b	2.69	85.3	13.8	Inactive	—	12	—
21c	1.84	85.3	14.0	11[d]	1.7	12[d]	0.035
22a/23a	0.79	85.3	16.6	Inactive	—	Inactive	—
22b	2.51	85.3	13.8	13	2.6	18	0.087
22b	2.51	85.3	13.8	Inactive	—	14[e]	0.095
22c	1.84	85.3	14.0	11[d]	1.7	12[d]	0.035
23b	2.51	85.3	13.8	15	3.8	15	0.055
23b	2.51	85.3	13.8	Inactive[e]	—	12[e]	0.070
24a	0.95	85.3	16.7	Inactive	—	Inactive	—
24b	2.69	85.3	13.8	Inactive	—	Inactive	—
25a	−1.74	105.1	27.9	Inactive	—	11	—
25b	−0.01	105.1	21.8	11	—	18	0.06
27a	−1.91	116.1	34.1	Inactive	—	20.5	0.06
28b	0.45	111.2	20.4	13	0.88	18	0.07

[a] Log*P*, PSA and MSA calculated using Marvin; %PSA = (PSA/MSA) × 100.[48] [b] Hole plate bioassay using 100 μL of 4 mg mL^{-1} solution (6 : 4 DMSO–H_2O) unless otherwise indicated.[49] [c] Expressed as zone size per mg ml^{-1}, relative to cephalosporin C standard. [d] Halo only. [e] Concentration 2 mg mL^{-1} (6 : 4 DMSO–H_2O).

but the correct relative configuration for the right-hand fragment of oxazolomycin, or alternatively acetylation of **25a,b** gave esters **28a,b** in excellent yield. Confirmation of the structure of lactam **28b** was confirmed by single-crystal X-ray diffraction (Fig. 3).[41] Despite the hindered nature of **21a,b** and **25a,b**, noteworthy is the efficiency with which both of these processes proceeded.

Bioassay of these compound libraries against *S. aureus* and *E. coli* using the hole-plate method gave the activities indicated in Table 1; although not giving quantitative MIC values, these

in vivo assays give outcomes enabling rapid assessment of the effect of structural variations of the fragment modification. The value of such forward chemical genetic (phenotypic) screens in these cell based systems is that hits are automatically selected for their combination of activity and cell-permeability properties, and without any bias or pre-selection of the most optimal target of a pathway, although it of course gives no information about mode of action or target identity.[42,43] Of significance is that only a few compounds in this library showed antibacterial activity against *S. aureus*, although more were active against *E. coli*. Alkoxy derivatives **14b**, **15b**, **21c**, **22b,c**, **25b** and **28b** were the only ones with activity against *S. aureus*, and of the compounds with the correct relative configuration for oxazolomycin, only **21c**, **25b** and **28b** were active. All the active compounds have *c*Log*P* values in the range 1.8–2.5, and %PSA values close to 14, and with a potency of some 1–4% relative to the cephalosporin reference standard. However, **25b** and **28b** are clearly different, being very much more polar, with *c*Log*P* values in the range −0.01 to 0.5, and %PSA values close to 21. For *E. coli*, different diastereomers exhibited different activities, and in some cases these were very marked, especially for the benzyloxymethyl systems **21b**, **22b**, **23b** and **24b**; actives had *c*Log*P* values in the range 1.8–2.7 and %PSA values in the range 13.8–17.6, although their potencies were also substantially lower than the cephalosporin C control. However, compounds **25a,b** and **28b** are clearly different, being very much more polar and generally significantly more active, with *c*Log*P* values in the range −1.9 to 0.5, and %PSA values as high as 34. The methoxymethyl compounds **14a**, **15a**, **21a**, **22a** and **23a**, which might be considered to mimic structurally most closely the oxazolomycin right hand side, were all inactive or only weakly active, with *c*Log*P* values in the range 0.24–0.79 and %PSA values of 16.6–17.6, that is, outside the range of identified actives above, and we have recently reported that other pyroglutamate systems are similarly inactive, unless conjugated to a longer middle fragment mimic which attenuates *c*Log*P*.[44,45] Of interest is that the most active compounds had cheminformatic values which correlated with the corresponding values for oxazolomycins **1a–h**, which have *c*Log*P* values in the range 1.7–2.1 and %PSA values in the range 16.5–17.9 (Table 1). The better activity of the benzyloxymethyl systems **14b**, **15b**, **21b**, **22b** and **23b**, which also exhibit higher *c*Log*P* values than the methoxymethyl and *tert*-butyloxymethyl systems, is probably as a result of improved cell membrane permeability, and it would seem likely that introduction of significant bioactivity into compounds like **21a** with the correct relative configuration for oxazolomycin will require adjustment of their *c*Log*P* values at least. That this might be feasible is illustrated by the fact that the highly polar deprotected systems **16–18** were inactive, but the less highly polar **25b** and **28a,b**, all of which possess the correct relative stereochemistry for oxazolomycin, exhibit strong bioactivity against *E. coli*. The polar surface area parameter (PSA), which correlates the presence of polar atoms with membrane permeability and therefore gives an indication of drug transport properties,[46] has been reported to have an optimal value of 70 < PSA < 120 Å^2 for a non-CNS orally absorbable drug,[47] and of interest is that the active compounds **14**, **15**, **21**, **22**, **23**, **25** and **28** had values in the range 85–116. Two-fold dilution (to 2 mg mL^{-1}) of the most active compounds **14b**, **22b**, and **23b** still gave activity for *E. coli*, although not for *S. aureus*. However, it is important to note that the compounds reported herein belong to the enantiomeric series relative to the natural product, and therefore conclusions about the pharmacophoric grouping responsible for antibacterial activity cannot be made.

The efficiency of the biomimetic aldol ring closures disclosed herein is remarkable,[3] and although this synthesis has resulted in the construction of the opposite enantiomeric series relative to oxazolomycin, the correct absolute configuration would be available using D-serine as a precursor. We have recently demonstrated that the intrinsic antibacterial activity of simple pyroglutamates[50,51] and tetramates is low,[52] but that homologation to longer chain side-units restores activity.[44,45,53] We have also shown that a change as small as the introduction of a methyl substituent, achieved using threonine as the starting amino acid, improves bioactivity in tetramates,[11] and it would therefore appear from the work described here that bioactivity may be critically dependent on appropriate functionality around the pyroglutamate ring periphery. Moreover, the absence of the β-lactone unit does not fully abolish activity, and work to establish the biological effect of its introduction is currently underway. Given the difficulties in the development of antibacterials[54] and the recently discussed urgent need for the identification of novel strategies for expanding the antibacterial drug development pipeline,[55,56] particularly using fragment-based approaches,[57] and the renaissance of interest in natural product lead structures,[58–69] the oxazolomycins may offer inspiration for unusual chiral fragments for antibacterial development, in much the same way as we have shown for simpler pyrrolidinones.[70]

Experimental

(2*R*,5*R*,6*R*)-1-Aza-2-(*tert*-butyl)-6-hydroxy-6-(methoxymethyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]octane 15a

The ketoamide **13a** (3.02 g, 10 mmol) was dissolved in MeOH (100 mL) and to the solution was added NaOMe (0.81 g, 15 mmol). The mixture was stirred overnight at r.t. under nitrogen; the reaction was quenched with sat. aq. NH_4Cl (200 mL) and extracted with Et_2O (4 × 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give 2.72 g of 4 : 1 mixture of **15a** and **14a**. Column chromatography on silica gel with petrol–Et_2O 1 : 1 (increasing polarity to 1 : 2) allowed partial separation of the diastereoisomers and gave 1.44 g of **15a** as white crystalline solid, and 1.3 g mixed fraction which was re-columned with the next batch. R_f 0.30 (Et_2O); $[\alpha]_D^{25}$ = +37.4° (*c* = 1, MeOH); m. p. 110–112 °C; ν_{max} (film) 1733, 1699; δ_H (400 MHz, $CDCl_3$) 0.88 (9H, s, *t*-Bu), 2.41 (1H, d, *J* = 16, C(7)H*H*), 3.19 (1H, d, *J* = 16 Hz, C(7)H*H*), 3.35 (5H, m, CH_2OCH_3), 3.46 (1H, s, OH), 3.79 (3H, s, $COOCH_3$), 4.21 (1H, d, *J* = 8 Hz, C(4)*H*H), 4.53 (1H, d, *J* = 8 Hz, C(4)*H*H), 4.92 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 24.9, 36.3, 45.6, 52.6, 59.4, 67.8, 74.2, 79.1, 96.2, 171.4, 175.6; *m*/*z* (ESI$^+$) 324 ([M + Na]$^+$, 25%) 625 ([2M + Na]$^+$, 100%); HRMS: found 324.1407 for $C_{14}H_{23}NNaO_6$ [M + Na]$^+$, calculated 324.1418.

(2*R*,5*R*,6*S*)-1-Aza-2-(*tert*-butyl)-6-hydroxy-6-(benzyloxymethyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]octane 14b and (2*R*,5*R*,6*R*)-1-aza-2-(*tert*-butyl)-6-hydroxy-6-(benzyloxymethyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]octane 15b

The ketoamide **13b** (2.70 g, 7.15 mmol) was dissolved in MeOH (75 mL) and to the solution was added NaOMe (0.58 g, 10.72 mmol). The mixture was stirred overnight at r.t. under nitrogen. The reaction was quenched with sat. aq. NH_4Cl (150 mL) and extracted with Et_2O (3 × 75 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give 2.51 g of crude 5 : 1 mixture of **15b** and **14b**. Column chromatography on silica gel with 3 : 1 petrol–EtOAc (increasing polarity to 2 : 1) allowed partial separation of the diastereoisomers and gave 1.40 g of **15b**, 0.65 g mixed fraction and 0.15 g of **14b**. R_f 0.20 (petrol–EtOAc 2 : 1); m.p. 114–116 °C; ν_{max} (film) 3367, 2951, 1747, 1698; δ_H (400 MHz, $CDCl_3$) 0.88 (9H, s, *t*-Bu), 2.41 (1H, d, J = 16 Hz, C(7)H*H*), 3.19 (1H, d, J = 16 Hz, C(7)H*H*), 3.34 (1H, s, OH), 3.43 (2H, s, CH_2OBn), 3.67 (3H, s, COOCH_3), 4.21 (1H, d, J = 8 Hz, C(4)*H*H), 4.50 (2H, AB quartet, J = 12 Hz, OCH_2Ph), 4.59 (1H, d, J = 8 Hz, C(4)*H*H), 4.91 (1H, s, C(2)*H*), 7.27–7.40 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 24.9, 36.3, 45.6, 52.6, 67.8, 71.8, 73.8, 79.2, 96.1, 127.9, 128.2, 128.6, 136.7, 171.3, 175.4; HRMS: found 400.1716 for $C_{20}H_{27}NNaO_6^+$ $[M + Na]^+$, requires 400.1731. **Data for 14b**: R_f 0.15 (petrol–EtOAc 2 : 1) m.p. 104–106 °C; ν_{max} (cm^{-1}, neat): 3365, 2960, 1731, 1692; δ_H (400 MHz, $CDCl_3$) 0.89 (9H, s, *t*-Bu), 2.37 (1H, d, J = 16 Hz, C(7)H*H*), 3.22 (1H, s, OH), 3.37 (1H, d, J = 16 Hz, C(7)H*H*), 3.38 (1H, d, J = 8 Hz, CH_2OBn), 3.59 (1H, d, J = 8 Hz, CH_2OBn), 3.73 (1H, d, J = 8 Hz, CH_2O), 3.81 (3H, s, COOCH_3), 4.56 (2H, AB quartet, J = 12 Hz, OCH_2Ph), 4.73 (1H, d, J = 8 Hz, CH_2O), 4.80 (1H, d, J = 8 Hz, CH_2O), 7.27–7.40 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 25.0, 36.1, 45.2, 52.5, 69.67, 72.4, 73.77, 79.3, 95.5, 128.1, 128.5, 128.7, 136.2, 153.7, 171.0, 173.3; HRMS: found 400.1725 for $C_{20}H_{27}NNaO_6^+$ $[M + Na]^+$, requires 400.1731.

(2*R*,5*R*,6*R*)-1-Aza-2-(*tert*-butyl)-6-hydroxy-6-(*tert*-butoxymethyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0] octane 15c and (2*R*,5*R*,6*S*)-1-aza-2-(*tert*-butyl)-6-hydroxy-6-(*tert*-butoxymethyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0] octane 14c

To a solution of oxazolidine **13c** (0.46 g, 1.34 mmol) in dry methanol (10 mL) was added NaOMe (0.073 g, 1.35 mmol) and solution was stirred for 24 h at r.t. and then partitioned between diethyl ether (20 mL) and aq. NH_4Cl (20 mL). The diethyl ether layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo* to give crude product as a light brown sticky oil (0.35 g), which was purified by flash column chromatography (3 : 1 petrol–EtOAc) to give a mixture of epimeric alcohols **15c** (0.25 g, 55%) and **14c** (0.062 g, 13%) as white solid and colourless thick oil, respectively. **Data for 15c**: R_f 0.40 (2 : 1 petrol–EtOAc); ν_{max} (film)/cm^{-1} 3253, 2976, 1682, 1366, 1192, 1086; δ_H (400 MHz; $CDCl_3$) 0.86 (9H, s, C(CH_3)$_3$), 1.14 (9H, s, C(CH_3)$_3$), 2.39 (1H, d, J = 15.6 Hz, C(7)H*H*), 3.16 (1H, d, J = 15.6 Hz, C(7)H*H*), 3.31 (2H, AB quartet, J = 9.0 Hz, CH_2OC(CH$_3$)$_3$), 3.75 (3H, s, COOCH_3), 4.13 (1H, d, J = 8.8 Hz, C(4)*H*H), 4.54 (1H, d, J = 8.8 Hz, C(4)H*H*) and 4.88 (1H, s, C(2)*H*); δ_C (100 MHz; $CDCl_3$) 24.9 (C(*C*H$_3$)$_3$), 27.2 (C(*C*H$_3$)$_3$), 36.3 (*C*(CH$_3$)$_3$), 45.5 (C(7)), 52.5 (COO*C*H$_3$), 63.7 (*C*H$_2$OC(CH$_3$)$_3$), 67.7 (C(4)), 74.0 (C(6)), 79.2 (C(5)), 95.82 (C(2)), 171.4 and 175.5 (2 × *C*═O); m/z (ESI$^+$) 709 ([2M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{29}NNaO_6^+$ requires 366.1887, found 366.1884; $[\alpha]_D^{20}$ + 31.2 (c = 0.88 in MeOH). **Data for 14c**: R_f 0.25 (2 : 1 petrol–EtOAc); δ_H (400 MHz; $CDCl_3$) 0.90 (9H, s, C(CH_3)$_3$), 1.22 (9H, s, C(CH_3)$_3$), 2.37 (1H, d, J = 16.2, C(7)H*H*), 3.23 (1H, br, s, O*H*), 3.29 (1H, d, J = 9.4 Hz, C*H*HOC(CH$_3$)$_3$), 3.41 (1H, d, J = 16.2 Hz, C(7)H*H*), 3.53 (1H, d, J = 9.4 Hz, CH*H*OC(CH$_3$)$_3$), 3.81 (3H, s, COOCH_3), 3.84 (1H, d, J = 9.7 Hz, C(4)*H*H), 4.69 (1H, d, J = 9.7 Hz, C(4)H*H*), 4.83 (1H, s, C(2)*H*).

(2*R*,3*R*)-Methyl 3-hydroxy-2-(hydroxymethyl)-3-(methoxymethyl)-5-oxopyrrolidine-2-carboxylate 17a and (2*R*,3*S*)-methyl 3-hydroxy-2-(hydroxymethyl)-3-(methoxymethyl)-5-oxopyrrolidine-2-carboxylate 16

To a solution of **15a** (0.090 g, 0.30 mmol) in 2% HCl in trifluoroethanol (3 mL) was added 1,3-propanedithiol (0.030 mL, 0.30 mmol). The mixture was left to stir overnight and then the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (increasing polarity from petrol (40–60)–ethyl acetate 1 : 1 to ethyl acetate–methanol 4 : 1), affording **16** and **17a** in 6 : 1 dr as a colourless oil (0.06 g, 86%); R_f = 0.52 (EtOAc–MeOH, 4 : 1); ν_{max} (film) 3662, 2961, 1748; **Data for 17a**: δ_H (400 MHz; $CDCl_3$) 2.36 (1H, d, J = 17.2 Hz, C(5)*H*), 2.69 (1H, d, J = 17.2 Hz, C(5)*H*) 3.30 (3H, s, CH$_2$OCH_3), 3.33 (2H, m, CH_2OCH$_3$), 3.76 (3H, s, CO$_2$CH_3), 3.90 (1H, d, J = 11.4 Hz, CH_2OH), 4.10 (1H, d, J = 11.4 Hz, CH_2OH); δ_C (100 MHz; MeOD) 42.0 (*C*(5)), 51.9 (CO$_2$CH_3), 58.4 (*C*H$_2$OH), 64.2 (CH$_2$OCH_3), 72.4 (*C*(3)), 74.8 (*C*(2)), 79.1 (*C*H$_2$OCH$_3$), 171.7 (*C*O$_2$Me), 177.7 (*C*(5)); **Data for 16**: δ_H (400 MHz; MeOD) 2.30 (1H, d, J = 17.2 Hz, C(5)*H*), 2.79 (1H, d, J = 17.2 Hz, C(5)*H*) 3.31 (3H, s, CH$_2$OCH_3), 3.42 (2H, m, CH_2OCH$_3$), 3.58 (1H, d, J = 9.6 Hz, CH_2OH), 3.70 (1H, d, J = 9.6 Hz, CH_2OH), 3.77 (3H, s, CO$_2$CH_3); δ_C (100 MHz; $CDCl_3$) 42.0 (*C*(5)), 51.9 (CO$_2$CH_3), 58.4 (*C*H$_2$OH), 64.2 (CH$_2$OCH_3), 72.4 (*C*(3)), 74.8 (*C*(2)), 79.1 (*C*H$_2$OCH$_3$), 171.7 (*C*O$_2$Me), 177.7 (*C*(5)); m/z (ESI$^+$) 234 ([M + H]$^+$, 80%) 467 ([2M + H]$^+$, 100%); HRMS (ESI$^+$) Found 256.0794 for $C_9H_{15}NNaO_6^+$ $[M + Na]^+$, requires 256.0792.

(2*R*,3*R*)-Methyl 3-hydroxy-2-(hydroxymethyl)-3-(benzyloxymethyl)-5-oxopyrrolidine-2-carboxylate 17b and (3*R*,4*R*)-methyl 3-amino-4-benzyloxymethyl-4-hydroxy-6-oxotetrahydro-2H-pyran-3-carboxylate 18

To a solution of alcohol **15b** (0.13 g, 0.33 mmol) in 2% HCl in trifluoroethanol (2 mL) was added 1,3-propanedithiol (0.036 g, 0.33 mmol) and mixture was stirred for 20 h at r.t. The solvent was then evaporated *in vacuo* to give mixture of **17b** and **18** (0.088 g, 85%) in a ratio of 3 : 2, respectively, as a pale brown thick oil: R_f 0.72 (4 : 1 EtOAc–MeOH with a drop of AcOH); ν_{max} (film)/cm^{-1} 2925, 2361, 2329, 1736, 1682, 1313, 1235, 1461, 1377, 722;); m/z (ESI$^+$) 332 ([M + Na]$^+$, 99%); HRMS

(ESI$^+$) $C_{15}H_{19}NNaO_6^+$ requires 332.1105, found 332.1106; **Data for 17b**: δ_H (400 MHz; D_2O) 2.50–2.60 (2H, AB quartet, J = 17.4 Hz, C(4)*HH*), 3.38–3.41 (2H, AB quartet, J = 10.1 Hz, C(3)C*HH*), 3.52 (3H, s, COOCH_3), 3.82 (1H, d, J = 11.7 Hz, C*H*HOH), 3.98 (1H, d, J = 11.7 Hz, C*H*HOH), 4.37–4.41 (2H, AB quartet, J = 12.0 Hz, OC*HH*Ph) and 7.24–7.33 (Ar*H*); δ_C (100 MHz; D_2O) 41.9 (C(4)), 53.4 (COO*C*H$_3$), 63.2 (C(2)*C*H$_2$), 72.5 (C(3)*C*H$_2$), 73.6 (O*C*H$_2$Ph), 79.5 (C(3)), 128.6 (*para*-*C*H), 128.7 and 129.0 (*ortho*- and *meta*-*C*H), 137.4 (*ipso*-*C*H), 172.5 and 177.5 (2 × *C*═O); **Data for 18**: δ_H (400 MHz; D_2O) 2.26 (1H, d, J = 17.7 Hz, C(4)*H*H), 2.73 (1H, d, J = 17.7 Hz, C(4)H*H*), 3.38–3.41 (2H, AB quartet, J = 10.1 Hz, C(3)C*HH*), 3.69 (3H, s, COOCH_3), 3.64–3.75 (2H, m, C(7)*HH*), 4.34–4.41 (2H, m, OC*HH*Ph); δ_C (100 MHz; D_2O) 42.2 (C(4)), 53.4 (COO*C*H$_3$), 59.2 (C(2)), 64.0 (C(7)), 72.5 (C(3)*C*H$_2$), 73.3 (C(3)), 73.6 (O*C*H$_2$Ph), 128.6 (*para*-*C*H), 128.7 and 129.0 (*ortho*- and *meta*-*C*H), 137.4 (*ipso*-*C*H), 171.5 and 177.5 (2 × *C*═O).

(1*R*, 5*R*)-2-Aza-5-hydroxy-1-hydroxymethyl-3,8-dioxo-7-oxabicyclo[3.3.0]octane 19

To a solution of alcohol **15c** (0.075 g, 0.22 mmol) in 2% HCl in trifluoroethanol (1.5 mL) was added 1,3-propanedithiol (0.024 g, 0.22 mmol) and the mixture stirred for 20 h at r.t. The solvent was then evaporated *in vacuo* to give **19** (0.034 g, 83%) as a pale yellow thick oil: R_f 0.66 (4 : 1 EtOAc–MeOH with a drop of AcOH); ν_{max} (film)/cm^{-1} 2924, 2854, 1779, 1692, 1461, 1377, 1273, 723; δ_H (500.3 MHz; acetone-d) 2.65–2.72 (2H, AB quartet, J = 17.2 Hz, C(7)*HH*), 3.95 (2H, s, C(2)C*H*$_2$), 4.38 (1H, d, J = 9.5 Hz, C(5)*HH*), 4.42 (1H, d, J = 9.5 Hz, C(5)*HH*), 5.28 (br, s, C(6)O*H*); δ_C (125 MHz; acetone-d) 43.5 (C(7)), 59.9 (C(2)*C*H$_2$), 67.5 (C(2)), 76.7 (C(5)), 78.5 (C(6)), 173.9 (C(3)) and 175.3 (C(8)); *m*/*z* (ESI$^+$) 210 ([M + Na]$^+$, 70%); HRMS (ESI$^+$) $C_7H_9NNaO_5^+$ requires 210.0378, found 210.0380.

(2*R*,5*R*)-Methyl 2-(*tert*-butyl)-1-(4′-methoxy-2′-methyl-3′-oxobutanoyl)oxazolidine-5-carboxylate 20a

To a solution of oxazolidine **12**[29] (1.19 g, 6.4 mmol) in DCM (30 mL) was added DMAP (0.053 g, 0.43 mmol) and EDC·HCl (1.22 g, 6.4 mmol). The mixture was stirred for 15 min at 0 °C and a solution of acid **10d** (0.927 g, 6.35 mmol) in DCM (10 mL) was added dropwise. The mixture was stirred at 0 °C for a further 15 min and then at r.t. for 3 h. The reaction mixture was washed with sat. aq. NaH_2PO_4 (3 × 30 mL) and the aqueous layer extracted with DCM (3 × 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*, affording **20a** (1.34 g, 68%) as an orange oil, which was used without further purification.

(2*R*,5*S*)-Methyl 1-(4′-(benzyloxy)-2′-methyl-3′-oxobutanoyl)-2-(*tert*-butyl)oxazolidine-5-carboxylate 20b

To a stirred solution of oxazolidine **12**[29] (0.098 g, 0.53 mmol), DMAP (0.0057 g, 0.046 mmol), EDAC (0.12 g, 0.63 mmol) in DCM (7 mL) at 0 °C was added a solution of 4-(benzyloxy)-2-methyl-3-oxobutanoic acid **11c** (0.14 g, 0.63 mmol) in DCM (3 mL). The reaction mixture was stirred at 0 °C for 15 min and then at r.t. for 5 h. The crude reaction mixture was partitioned between DCM (20 mL) and aq. NH_4Cl (20 mL) and the organic layer was dried over $MgSO_4$, filtered and concentrated to give a brown oil (0.18 g). Purification by column chromatography (3 : 1 petrol–EtOAc) gave *cis*-oxazolidine **20b**, (0.044 g, 18%) as a pale yellow thick oil: R_f 0.29 (3 : 1 petrol–EtOAc); δ_H (400 MHz; $CDCl_3$) 0.89 (9H, s, C(CH_3)$_3$), 1.34 (3H, d, CH_3), 3.71–3.80 (4H, m, COOCH_3 and C(2)′*H*), 4.02–4.10 and 4.30 and 4.50–4.65 (4H, m, C(4)*HH* and C(4)′H_2), 4.28 (2H, s, C(6)′H_2), 5.32 (1H, s, C(2)*H*), 7.27–7.34 (5H, m, Ar*H*); δ_C (100 MHz; $CDCl_3$) 12.8 (*C*H$_3$), 25.7 (C(*C*H$_3$)$_3$), 37.7 (*C*(CH$_3$)$_3$), 52.8 (COO*C*H$_3$), 67.9 (C(4)), 72.9 (C(4)′), 73.4 (C(6)′), 96.9 (C(2)), 127.7 (*para*-*C*H), 128.3, 128.5 (*ortho*- and *meta*-*C*H), 136.8 (*ipso*-*C*H), 169.7, 171.8 and 202.4 (3 × *C*═O); *m*/*z* (ESI$^+$) 805 ([2M + Na]$^+$, 99%); HRMS (ESI$^+$) $C_{21}H_{29}NNaO_6^+$ requires 414.1887 found 414.1887.

(2*R*,5*S*)-Methyl 1-(4′-(*tert*-butoxy)-2′-methyl-3′-oxobutanoyl)-2-(*tert*-butyl)oxazolidine-5-carboxylate 20c

To a stirred solution of oxazolidine **12**[29] (0.26 g, 1.41 mmol), DMAP (0.015 g, 0.12 mmol), EDAC (0.32 g, 1.69 mmol) in DCM (7 mL) at 0 °C was added a solution of 4-(*tert*-butoxy)-2-methyl-3-oxobutanoic acid **10f** (0.32 g, 1.69 mmol) in DCM (3 mL). The reaction mixture was stirred at 0 °C for 15 min and then at r.t. for 5 h. The crude reaction mixture was partitioned between DCM (30 mL) and aq. NH_4Cl (30 mL) and the organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo* to give brown oil (0.43 g). Purification by column chromatography (3 : 1 petrol–EtOAc) gave *cis*-oxazlidine **20c** (0.095 g, 16%) as a pale yellow thick oil: R_f 0.4 (2 : 1 petrol–EtOAc); ν_{max} (film)/cm^{-1} 2975, 2361, 1745, 1667, 1366, 1192, 1104, 894; δ_H (400 MHz; $CDCl_3$) 0.94 (9H, s, C(CH_3)$_3$), 1.22 (9H, s, C(CH_3)$_3$), 1.25 (3H, m, CH_3), 3.78 (3H, s, COOCH_3), 3.87–4.10 (2H, m) and 4.10–4.30 (2H, m) and 4.40–4.62 (2H, m, C(5)*H*, C(2)′*H*, C(4)′H_2 and C(4)*HH*), 5.35 (1H, s, C(2)*H*); δ_C (100 MHz; $CDCl_3$) 25.7 (C(*C*H$_3$)$_3$), 27.4 (C(*C*H$_3$)$_3$), 52.8 (COO*C*H$_3$), 68.0 (C(4)), 97.0 (C(2)); *m*/*z* (ESI$^+$) 737 ([2M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{31}NNaO_6^+$ requires 380.2044, found 380.2044.

(2*R*,5*R*,6*R*,7*S*)-Methyl 2-(*tert*-butyl)-6-hydroxy-6-(methoxymethyl)-7-methyl-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]octane 21a and (2*R*,5*R*)-Methyl 2-(*tert*-butyl)-6-hydroxy-6-(methoxymethyl)-7-methyl-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]octane 22a/23a

To a solution of crude **20a** (1.34g, 4.24 mmol) in dry methanol (30 mL) was added NaOMe (0.34 g, 6.34 mmol). The reaction mixture was left to stir at r.t. for 24 h. The contents were then poured into sat. aq. NH_4Cl (50 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*, affording the crude product. The crude product was purified *via* column chromatography on silica gel (petrol (40–60)–EtOAc, 3 : 1), first affording **21a** (0.079 g, 6%) as a white solid and then **22a**/**23a** (0.16 g, 12%) in a 2 : 1 dr as a

colourless solid; **Data for 21a**: R_f 0.46 (Et_2O); $[\alpha]_D^{25}$ = +16.4° (c = 1, MeOH); m.p. 146–148 °C; ν_{max} (cm^{-1}, neat) 3345, 2966, 1736, 1696; δ_H (200 MHz; $CDCl_3$) 0.88 (9H, s, C(CH_3)$_3$), 1.12 (3H, d, J = 7.2 Hz, CH_3), 3.20 (1H, q, J = 7.2 Hz, C(7)*H*), 3.34 (1H, br s, C(6)(O*H*)), 3.35 (3H, s, CH_2OCH_3), 3.36 (2H, m, CH_2OCH_3), 3.78 (3H, s, CO_2CH_3), 4.15 (1H, d, J = 8.5 Hz, C(4)*H*), 4.55 (1H, d, J = 8.5 Hz, C(4)*H*), 4.90 (1H, s, C(2)*H*); δ_H (400 MHz, C_6D_6) 1.16 (9H, s, *t*-Bu), 1.27 (3H, d, J = 8 Hz, CH_3CH), 2.74 (1H, s, OH), 2.86 (3H, s, CH_3O), 2.95 (2H, AB quartet, J = 8 Hz, CH_2OCH_3), 3.21 (1H, q, J = 8 Hz, CH_3CH), 3.38 (3H, s, $COOCH_3$), 4.29 (1H, d, J = 8 Hz, C(4)*H*), 4.82 (1H, d, J = 8 Hz, C(4)*H*), 5.24 (1H, s, C(2)*H*); δ_C (100 MHz; $CDCl_3$) 7.2 (CH_3), 24.9 (C(CH_3)$_3$), 36.3 (C(CH_3)$_3$, 45.8 (C(7)), 52.6 (CO_2CH_3), 59.4 (CH_2OCH_3), 68.2 (C(4)), 73.6 (CH_2OCH_3), 78.0 (C(6)), 81.1 (C(5)), 96.2 (C(2)), 171.6 (CO_2Me), 178.0 (C(8)O); δ_C (100 MHz, C_6D_6) 7.58 (CH_3), 25.28 (C(CH_3)$_3$), 36.61 (C(CH_3)$_3$, 45.95 (C(7)), 51.85 (CO_2CH_3), 58.70 (CH_2OCH_3), 68.62 (C(4)), 73.51 (CH_2OCH_3), 78.32 (C(6)), 81.11 (C(5)), 96.61 (C(2)), 171.82 (CO_2Me), 177.60 (C(8)O); m/z (ESI)$^+$ 338 ([M + Na]+, 50%) 658 ([[M + Na]+, 100%); HRMS (ESI$^+$) Found 338.1574 for $C_{15}H_{25}NNaO_6^+$ [M + Na]$^+$, requires 338.1574; **Data for 22a/23a** (major isomer); R_f = 0.13 (petrol (40–60)–EtOAc, 3 : 1); ν_{max} (film) 3440, 2973, 1655; δ_H (400 MHz; $CDCl_3$) 0.89 (9H, s, CC(CH_3)$_3$), 1.06 (3H, d, J = 7.6 Hz, CH_3), 3.37 (2H, m, CH_2OCH_3), 3.38 (3H, s, CH_2OCH_3), 3.50 (1H, m, C(7)*H*), 3.68 (1H, d, J = 9.6 Hz, C(4)*H*), 3.79 (3H, s, CO_2CH_3), 4.72 (1H, d, C(4)*H*), 4.82 (1H, s, C(2)*H*); δ_C (100 MHz; $CDCl_3$) 7.62 (CH_3), 25.0 (C(CH_3)$_3$), 36.1 (C(CH_3)$_3$), 47.4 (C(7)), 52.5 (CO_2CH_3) 59.0 (CH_2OCH_3) 65.3 (C(4)H), 71.6 (CH_2OCH_3), 77.3 (C(6)), 79.7 (C(5)), 95.4 (C(2)), 171.1 (CO_2CH_3), 175.7 (C(8)O); **Data for 22a/23a** (minor isomer) R_f = 0.13 δ_H (400 MHz; $CDCl_3$) 0.91 (9H, s, C(CH_3)$_3$), 1.41 (3H, d, J = 7.8 Hz, CH_3), 2.43 (1H, q, J = 7.8 Hz, C(7)*H*), 3.27 (1H, d, J = 9.9 Hz, CH_2OCH_3), 3.39 (3H, s, CH_2OCH_3), 3.43 (1H, d, J = 9.9 Hz, CH_2OCH_3), 3.78 (3H, s, CO_2CH_3) 3.94 (1H, d, J = 14.4 Hz, C(4)H), 4.11 (1H, d, J = 14.4 Hz, C(4)*H*), 4.72 (1H, s, C(2)*H*); δ_C (100 MHz; $CDCl_3$) 12.1 (CH_3), 25.1 (C(CH_3)$_3$), 35.6 (C(CH_3)$_3$), 49.4 (C(7)), 52.4 (CO_2CH_3) 59.0 (CH_2OCH_3) 62.0 (C(4)H), 76.0 (CH_2OCH_3), 77.0 (C(6)), 80.3 (C(5)), 96.1 (C(2)), 171.1 (CO_2CH_3), 175.7 (C(8)O); m/z (ESI)$^+$ 338 ([M + Na]+, 65%) 658 ([2M + Na]$^+$, 100%); HRMS (ESI$^+$) Found 338.1575 for $C_{15}H_{25}NNaO_6^+$ [M + Na]$^+$, requires 338.1574.

(2*R*,5*R*,6*R*,7*S*), (2*R*,5*R*,6*S*,7*R*)- And (2*R*,5*R*,6*S*,7*S*)-1-Aza-2-(*tert*-butyl)-6-hydroxy-7-methyl-6-(benzyloxymethyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]octane 21b, 22b and 23b

To a solution of oxazolidine **20b** (0.048 g, 0.12 mmol) in dry methanol (5 mL) was added NaOMe (0.0067 g, 0.12 mmol) and solution was stirred for 24 h at r.t. and then partitioned between diethyl ether (10 mL) and aq. NH_4Cl (10 mL). The ether layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo* to give crude product as a light brown sticky oil (0.052 g), which was purified by flash column chromatography (5 : 1 petrol–EtOAc) to give a mixture of isomers **21b**, (0.014 g, 30%) as white solid, **22b** (0.0062 g, 13%) as a thick colourless oil and **23b** (0.0047g, 10%) as thick colourless oil. **Data for 21b**: R_f 0.30 (petrol–EtOAc 2 : 1); m.p. 100–102 °C; ν_{max} (film) 3406, 2952, 1746, 1703; δ_H (400 MHz, $CDCl_3$) 0.88 (9H, s, *t*-Bu), 1.11 (3H, d, J = 7 Hz, CH_3CH), 2.97 (1H, s, OH), 3.22 (1H, q, J = 7 Hz, CH_3CH), 3.45 (2H, AB quartet, J = 10 Hz, CH_2OBn), 3.66 (3H, s, $COOCH_3$), 4.16 (1H, d, J = 9 Hz, CH_2O), 4.46 (1H, d, J = 12 Hz, CH_2Ph), 4.55 (1H, d, J = 12 Hz, CH_2Ph), 4.61 (1H, d, J = 9 Hz, CH_2O), 4.89 (1H, s, NCHO), 7.27–7.40 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 7.3 (CH_3), 24.9 (C(CH_3)$_3$), 36.3 (C(CH_3)$_3$, 45.9 (C(7)), 52.5 (CO_2CH_3), 68.3 (C(4)), 71.2, 73.9 (CH_2OCH_3), 78.1 (C(6)), 81.2 (C(5)), 96.2 (C(2)), 127.9, 128.2, 128.6, 136.7, 171.5 (CO_2Me), 177.9 (C(8)); HRMS: found 414.1876 for $C_{21}H_{29}NNaO_6^+$ [M + Na]$^+$, requires 414.1887. **Data for 22b**: R_f 0.53 (1 : 1 petrol–EtOAc); δ_H (500.3 MHz; C_6D_6) 1.23 (9H, s, C(CH_3)$_3$), 1.60 (3H, d, J = 7.5 Hz, C(7) CH_3), 2.32 (1H, q, J = 7.5 Hz, C(7)*H*), 2.94 (br, s, O*H*), 2.85 (1H, d, J = 9.8 Hz, C*HH*OCH$_2$Ph), 3.04 (1H, d, J = 9.8 Hz, C*HH*OCH$_2$Ph), 3.44 (1H, d, J = 9.1 Hz, C(4)*H*H), 3.48 (3H, s, $COOCH_3$), 4.06 (2H, s, OCH_2Ph), 5.00 (1H, d, J = 9.1 Hz, C(4) H*H*), 5.02 (1H, s, C(2)*H*), 7.13–7.25 (5H, m, Ar*H*); δ_C (125 MHz; $CDCl_3$) 12.3 (C(7)CH_3), 25.6 (C(CH_3)$_3$), 36.0 (C(CH_3)$_3$), 49.5 (C(7)), 51.9 ($COOCH_3$), 71.2 (C(4)), 73.3 (CH_2OCH_2Ph), 80.0 (OCH_2Ph), 96.9 (C(2)), 127.8 (*para*-CH), 128.6, 128.7 (*ortho*- and *meta*-CH), 137.5 (*ipso*-C), 171.4 and 179.1 (2 × *C*=O); m/z (ESI$^+$) 805 ([2M + Na]$^+$, 99%); HRMS (ESI$^+$) $C_{21}H_{29}NNaO_6^+$ requires 414.1887, found 414.1891. **Data for 23b**: R_f 0.47 (1 : 1 petrol–EtOAc); δ_H (500 MHz; C_6D_6) 1.08 (3H, d, J = 7.4 Hz, CH_3), 1.19 (9H, s, C(CH_3)$_3$), 3.11 (2H, s, CH_2OCH_2Ph), 3.53 (3H, s, $COOCH_3$), 3.65 (1H, q, J = 7.4 Hz, C(7)*H*), 3.73 (1H, d, J = 9.4 Hz, C(4)*H*H), 4.00 (1H, d, J = 11.9 Hz, OC*HH*Ph), 4.02 (1H, d, J = 11.9 Hz, OC*HH*Ph), 5.02 (1H, d, J = 9.4 Hz, C(4)H*H*), 5.09 (1H, s, C(2)*H*), 7.13–7.24 (5H, m, Ar*H*); δ_C (125 MHz; $CDCl_3$) 7.9 (CH_3), 25.4 (C(CH_3)$_3$), 36.5 (C(CH_3)$_3$), 47.7 (C(7)), 52.0 ($COOCH_3$), 69.6 (C(4)), 70.5 (CH_2OCH_2Ph), 73.4 (OCH_2Ph), 95.9 (C(2)), 127.9 (*para*-C), 128.7, 128.8 (*ortho*- and *meta*-CH), 137.5 (*ipso*-C), 171.3 and 175.3 (2 × *C*=O); m/z (ESI$^+$) 805 ([2M + Na]$^+$, 99%); HRMS (ESI$^+$) $C_{21}H_{29}NNaO_6^+$ requires 414.1887, found 414.1892.

(2*R*,5*R*,6*R*,7*S*) And (2*R*,5*R*,6*S*, 7*R*)-1-aza-2-(*tert*-butyl)-6-hydroxy-7-methyl-6-(*tert*-butoxymethyl)-5-methoxycarbonyl-3-oxa-8-oxobicyclo[3.3.0]octane 21c and 22c

To a solution of oxazolidine **20c** (0.071 g, 0.20 mmol) in dry methanol (5 mL) was added NaOMe (0.011 g, 0.200 mmol) and solution was stirred for 24 h at r.t. and then partitioned between diethyl ether (10 mL) and NH_4Cl (10 mL). The diethyl ether layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo* to give crude product as a light brown sticky oil (0.052 g), which was purified by flash column chromatography (5 : 1 petrol–EtOAc) to give a mixture of isomers **21c** (0.012 g, 17%) and **22c** (0.027 g, 38%) both as white solid. **Data for 21c**: R_f 0.34 (3 : 1 petrol–EtOAc); δ_H (500 MHz; $CDCl_3$) 0.88 (9H, s, C(CH_3)$_3$), 1.12 (3H, d, J = 7.2 Hz, C(7)CH_3), 1.17 (9H, s, C(CH_3)$_3$), 3.04 (br, s, O*H*), 3.23 (1H, q, J = 7.2 Hz, C(7)*H*), 3.34 (2H, s, $CH_2OC(CH_3)_3$), 3.76 (3H, s, $COOCH_3$), 4.10 (1H, d, J = 8.8 Hz, C(4)*H*H), 4.57

(1H, d, J = 8.8 Hz, C(4)H*H*), 4.88 (1H, s, C(2)*H*); δ_C (125 MHz; $CDCl_3$) 7.4 (*C*H_3), 24.9 (C(*C*H_3)$_3$), 25.6 (CH_2OC(*C*H_3)$_3$), 36.3 (*C*(CH$_3$)$_3$), 46.1 (C(7)), 52.1 (COO*C*H_3), 63.1 (*C*H_2OC(CH$_3$)$_3$), 68.0 (C(4)), 95.9 (C(2)), 171.6 and 178.0 (2 × *C*═O); m/z (ESI$^+$) 737 ([2M + Na]$^+$, 98%); HRMS (ESI$^+$) $C_{18}H_{31}NNaO_6^+$ requires 380.2044, found 380.2040. **Data for 22c**: R_f 0.20 (3 : 1 petrol–EtOAc); δ_H (500.3 MHz; C_6D_6) 0.88 (9H, s, $CH_2OC(CH_3)_3$), 1.29 (9H, s, C(C*H*$_3$)$_3$), 1.73 (3H, d, J = 7.7 Hz, C(7)C*H*$_3$), 2.46 (1H, q, J = 7.7 Hz, C(7)*H*), 2.91 (1H, d, J = 9.4 Hz, C*H*HOC(CH$_3$)$_3$), 3.13 (1H, d, J = 9.4 Hz, CH*H*OC(CH$_3$)$_3$), 3.15 (br, s, O*H*), 3.53 (3H, s, COOC*H*$_3$), 3.63 (1H, d, J = 9.2 Hz, C(4)*H*H), 5.04 (1H, d, J = 9.2 Hz, C(4)H*H*), 5.15 (1H, s, C(2)*H*); δ_C (125 MHz; C_6D_6) 12.5 (*C*H$_3$), 25.7 (C(*C*H$_3$)$_3$), 27.0 (C(*C*H$_3$)$_3$), 36.4 (*C*(CH$_3$)$_3$), 49.8 (C(7)), 51.8 (COO*C*H$_3$), 66.0 (*C*H_2OC(CH$_3$)$_3$), 71.4 (C(4)), 96.8 (C(2)), 171.5 and 179.2 (2 × *C*═O); m/z (ESI$^+$) 737 ([2M + Na]$^+$, 35%); HRMS (ESI$^+$) $C_{18}H_{31}NNaO_6^+$ requires 380.2044, found 380.2039.

(2*R*,5*R*,6*R*,7*R*)-2-(*tert*-Butyl)-6-hydroxy-6-(methyloxymethyl)-5-methoxycarbonyl-7-methyl-3-oxa-8-oxobicyclo[3.3.0]octane 24a

A solution of **15a** (1.22 g, 4.05 mmol) in THF (40 mL) under nitrogen was cooled to −10 °C in a methanol–ice bath and LDA (4.95 mL of a 1.8 mol l^{-1} solution, 8.91 mmol) was slowly added. The mixture was stirred for 30 min and then iodomethane (0.63 mL, 10.13 mmol) was added. The reaction mixture was left to stir for 90 more minutes, gradually reaching r.t. The reaction was quenched with sat. aq. NH_4Cl and extracted with diethyl ether (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The residue was re-dissolved in small amount of diethyl ether and dry-loaded onto silica gel. Column chromatography with 1 : 1 petrol–Et_2O, increasing polarity to neat Et_2O, gave a mixed fraction of **24a** and **21a** (10 : 4 by NMR)(213 mg), **24a** (780 mg) and the starting material **15a** (180 mg). Data for **24a**: R_f 0.40 (Et_2O); $[\alpha]_D^{25}$ = +36.3° (c = 1, MeOH); m.p. 102–104 °C; ν_{max} (film) 3420, 2958, 1740, 1716; δ_H (400 MHz, C_6D_6) 1.20 (9H, s, *t*-Bu), 1.43 (3H, d, J = 8 Hz, C*H*$_3$CH), 2.79 (1H, q, J = 8 Hz, CH$_3$C*H*), 2.89 (3H, s, CH$_3$O), 3.05 (1H, s, OH), 3.08 (1H, d, J = 9 Hz, C*H*$_2$OCH$_3$), 3.18 (1H, d, J = 9 Hz, C*H*$_2$OCH$_3$), 3.33 (3H, s, CO$_2$CH$_3$), 4.39 (1H, d, J = 9 Hz, C(4)*H*), 4.75 (1H, d, J = 9 Hz, C(4)*H*), 5.22 (1H, s, C(2)*H*); δ_C (100 MHz, C_6D_6) 12.9 (*C*H$_3$), 25.5 (C(*C*H$_3$)$_3$), 36.1 (*C*(CH$_3$)$_3$, 51.7 (CO$_2$*C*H$_3$), 54.0, 58.7 (CH$_2$O*C*H$_3$), 69.4 (C(4)), 73.0 (*C*H$_2$O*C*H$_3$), 78.6 (*C*(6)), 97.2 (C(2)), 171.9 (*C*O$_2$Me), 179.7 (*C*(8)); HRMS: found 338.1570 for $C_{15}H_{25}NNaO_6^+$, [M + Na]$^+$ requires 338.1574.

(2*R*,5*R*,6*R*,7*S*)-2-(*tert*-Butyl)-6-hydroxy-6-(methoxymethyl)-5-methoxycarbonyl-7-methyl-3-oxa-8-oxobicyclo[3.3.0]octane 21a

A solution of **24a** (927 mg, 2.9 mmol) in THF (60 mL) under nitrogen was cooled to 0 °C in a water–ice bath and KHMDS (12.9 mL of a 0.5 mol l^{-1} solution, 6.47 mmol) was added over a period of 3–5 min while stirring. The cooling bath was removed and the mixture was left to stir for 15 more minutes. *t*-BuOH (0.5 mL) was added, followed by sat. aq. NH_4Cl (50 mL). The mixture was extracted with Et_2O (3 × 50 mL), the combined organic layers were dried ($MgSO_4$) and the solvents were evaporated under reduced pressure to give crude material containing **21a** and **24a** in 20 : 1 ratio (by NMR). Column chromatography on silica gel with 2 : 1 Et_2O–petrol as the eluent gave **21a** (430 mg, 46%) as crystalline solid. Data as above.

(2*R*,5*R*,6*R*,7*R*)-2-(*tert*-Butyl)-6-hydroxy-6-(benzyloxymethyl)-5-methoxycarbonyl-7-methyl-3-oxa-8-oxobicyclo[3.3.0]octane 24b

A solution of **15b** (1.38 g, 3.65 mmol) in THF (40 mL) under nitrogen was cooled to −10 °C in methanol–ice bath and LDA (4.46 mL of a 1.8 mol l^{-1} solution, 8.03 mmol) was slowly added. The mixture was stirred for 30 min and then iodomethane (0.57 mL, 9.20 mmol) was added. The reaction mixture was left to stir for 90 more minutes, gradually reaching r.t., quenched with sat. aq. NH_4Cl and extracted with diethyl ether (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The residue was re-dissolved in small amount of diethyl ether and dry-loaded onto silica gel. Column chromatography with 3 : 1 petrol–EtOAc, increasing polarity to 2 : 1, gave 475 mg of mixed fraction of **24b** and **21b** (5 : 2 by NMR), **24b** (415 mg) as viscous oil and the starting material **15b** (410 mg). R_f 0.26 (petrol–EtOAc 2 : 1); ν_{max} (film) 3418, 2957, 1730, 1716; δ_H (400 MHz, C_6D_6) 1.18 (9H, s, *t*-Bu), 1.44 (3H, d, J = 8 Hz, C*H*$_3$CH), 2.85 (1H, q, J = 8 Hz, CH$_3$C*H*), 3.26 (1H, d, J = 9, C*H*$_2$OBn), 3.29 (3H, s, COOCH$_3$), 3.40 (1H, d, J = 9 Hz, C*H*$_2$OBn), 3.44 (1H, s, OH), 4.18 (2H, AB quartet, J = 12 Hz, CH$_2$Ph), 4.42 (1H, d, J = 9 Hz, C(4)*H*), 4.78 (1H, d, J = 9 Hz, C(4)*H*), 5.20 (1H, s, C(2)*H*), 7.20–7.35 (5H, m, Ph); δ_C (100 MHz, C_6D_6) 13.0 (*C*H$_3$), 25.5 (C(*C*H$_3$)$_3$), 36.1 (*C*(CH$_3$)$_3$, 51.7 (CO$_2$*C*H$_3$), 54.1 (CH$_2$O*C*H$_3$), 69.4 (C(4)), 71.1 (*C*H$_2$O*C*H$_3$), 73.7, 78.8 (C(6)), 78.9 (*C*(6)), 97.0 (C(2)), 137.6, 172.0 (*C*O$_2$Me), 179.9 (*C*(8)); HRMS: found 414.1874 for $C_{21}H_{29}NNaO_6^+$ [M + Na]$^+$, requires 414.1887.

(2*R*,5*R*,6*R*,7*S*)-2-(*tert*-Butyl)-6-hydroxy-6-(benzyloxymethyl)-5-methoxycarbonyl-7-methyl-3-oxa-8-oxobicyclo[3.3.0]octane 21b

A solution of **24b** (445 mg, 1.14 mmol) in THF (15 mL) under nitrogen was cooled to 0 °C in a water–ice bath. The solution was magnetically stirred and KHMDS (5 mL of a 0.5 mol l^{-1} solution, 2.5 mmol) was added over a period of 2–3 min and the mixture left to stir for 15 more minutes. *t*-BuOH (0.5 mL) was added, followed by sat. aq. NH_4Cl (20 mL). The mixture was extracted with Et_2O (3 × 30 mL), the combined organic layers were dried ($MgSO_4$) and the solvents were evaporated under reduced pressure to give 320 mg of crude material containing **21b** and **24b** in 20 : 1 ratio (by NMR analysis). Column chromatography on silica gel with 2 : 1 petrol–EtOAc as the eluent gave 200 mg of **21b** (45%) as crystalline solid. Data as above.

(2*R*,3*R*,4*S*)-3-Hydroxy-2-hydroxymethyl-3-methoxymethyl-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid methyl ester 25a

To a solution of **21a** (460 mg, 1.46 mmol) in 2,2,2-trifluoroethanol (15 mL) was added 1,3-propanedithiol (0.22 mL, 2.2 mmol)

and conc. aq. HCl (0.18 mL, 2.2 mmol). The mixture was left to stir at r.t. and after 24 h the solvent was removed under reduced pressure. The residue was re-dissolved in small amount of DCM and dry-loaded onto silica gel. Column chromatography on silica gel with Et_2O, increasing polarity to 10 : 1 Et_2O–MeOH, gave 30 mg (6%) of **26a** (eluted with Et_2O) and 320 mg (88%) of **25a** (eluted with 10 : 1 Et_2O–MeOH). R_f 0.23 (Et_2O–MeOH 10 : 1). $[\alpha]_D^{25} = -60.5°$ (c = 1, MeOH); m.p. 157–159 °C; ν_{max} (cm^{-1}, neat) 3315, 3270, 1710, 1650; δ_H (400 MHz, CD_3OD) 1.05 (3H, d, J = 7 Hz, CH_3CH), 2.77 (1H, q, J = 7 Hz, CH_3CH), 3.28 (1H, d, J = 10 Hz, CH_2OCH_3), 3.29 (3H, s, OCH_3), 3.47 (1H, d, J = 10 Hz, CH_2OCH_3), 3.74 (3H, s, $COOCH_3$), 3.83 (1H, d, J = 11 Hz, CH_2OH), 4.20 (1H, d, J = 11 Hz, CH_2OH); δ_C (100 MHz, CD_3OD) 6.4, 42.0, 52.0, 58.2, 63.7, 72.2, 72.5, 80.4, 172.2, 179.8; HRMS: found 270.0948 for $C_{10}H_{17}NNaO_6^+$ $[M + Na]^+$, requires 270.0948.

(2*R*,3*R*,4*S*)-3-Benzyloxymethyl-3-hydroxy-2-hydroxymethyl-4-methyl-5-oxopyrrolidine-2-carboxylic acid methyl ester 25b

To a solution of **21b** (300 mg, 0.77 mmol) in 2,2,2-trifluoroethanol (10 mL) was added 1,3-propanedithiol (0.12 mL, 1.16 mmol) and conc. aq. HCl (0.10 mL, 1.16 mmol). The mixture was left to stir at r.t. and after 24 h the solvent was removed under reduced pressure. The residue was re-dissolved in small amount of DCM and dry-loaded onto silica gel. Column chromatography with Et_2O, increasing polarity to 10 : 1 Et_2O–MeOH, gave 56 mg (18%) of **26b** (eluted with Et_2O) and 200 mg (80%) of **25b** (eluted with 10 : 1 Et_2O–MeOH). R_f 0.38 (Et_2O–MeOH 10 : 1); ν_{max} (film) 3324, 2950, 1730, 1688; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, J = 7 Hz, CH_3CH), 2.84 (1H, q, J = 7 Hz, CH_3CH), 3.42 (1H, d, J = 12 Hz, CH_2OBn), 3.56 (3H, s, $COOCH_3$), 3.56 (1H, d, J = 12 Hz, CH_2OBn), 4.00 (1H, app t, J = 8 Hz, CH_2OH), 4.09 (1H, dd, J = 12, 8 Hz, CH_2OH), 4.17 (1H, dd, J = 12, 8 Hz, CH_2OH), 4.32 (1H, s, OH), 4.48 (2H, AB quartet, J = 12 Hz, CH_2Ph), 7.18 (1H, s, NH), 7.27–7.37 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 7.1, 42.3, 52.7, 63.2, 70.3, 71.3, 73.4, 81.2, 127.6, 127.9, 128.5, 137.2, 171.7, 179.1; HRMS: found 346.1252 for $C_{16}H_{21}NNaO_6^+$ $[M + Na]^+$, requires 346.1261.

(2*R*,3*R*,4*S*)-3-Hydroxy-2-hydroxymethyl-3-methoxymethyl-4-methyl-5-oxopyrrolidine-2-carboxylic acid 27a

To a solution of **25a** (440 mg, 1.78 mmol) in 1 : 1 : 1 THF–MeOH–H_2O (30 mL) was added $LiOH{\cdot}H_2O$ (150 mg, 3.56 mmol) and the mixture was stirred overnight at r.t. The solvents were evaporated under reduced pressure and to the viscous aqueous residue was added sat. aq. soln. of NaCl (20 mL). The pH was then brought to 2–3 by careful addition of conc. HCl and the acidic solution was extracted with THF (5 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give a highly viscous oily residue, which was stirred for one night in Et_2O. The amorphous residue was dried under reduced pressure to give **27a** as solid foam (340 mg, 82%). R_f 0.3 (EtOAc–MeOH 1 : 1); $[\alpha]_D^{25} = -42.1°$ (c = 1, MeOH); m.p. 110–120 °C (dec.); ν_{max} (film) 3293, 2939, 1682; δ_H (400 MHz, acetone-d_6) 1.05 (3H, d, J = 5 Hz, CH_3CH), 2.68 (1H, q, J = 5 Hz, CH_3CH), 3.28 (3H, s, OCH_3), 3.47 (1H, d, J = 9 Hz, CH_2OCH_3), 3.54 (1H, d, J = 9 Hz, CH_2OCH_3), 3.95 (1H, d, J = 12 Hz, CH_2OH), 4.20 (1H, d, J = 12 Hz, CH_2OH), 7.09 (1H, s, NH); δ_C (100 MHz, acetone-d_6) 7.4, 42.6, 58.4, 63.8, 71.4, 73.9, 80.4, 173.0, 177.9; HRMS: found 232.0819 for $C_9H_{14}NO_6^-$ $[M - H]^-$, requires 232.0827.

(2*R*,3*R*,4*S*)-3-Benzyloxymethyl-3-hydroxy-2-hydroxymethyl-4-methyl-5-oxopyrrolidine-2-carboxylic acid 27b

To a solution of **25b** (180 mg, 0.56 mmol) in 1 : 1 : 1 THF–MeOH–H_2O (15 mL) was added $LiOH{\cdot}H_2O$ (47 mg, 1.11 mmol) and the mixture was stirred for 36 h at r.t. The solvents were evaporated under reduced pressure and to the viscous aqueous residue was added sat. aq. soln. of NaCl (20 mL). The pH was then brought to 2–3 by careful addition of conc. HCl and the acidic solution was extracted with EtOAc (5 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give **27b** as solid foam (170 mg, 98%). m.p. 90–100 °C (dec.). ν_{max} (film) 3295, 2946, 1687; δ_H (400 MHz, CD_3OD) 1.07 (3H, d, J = 8 Hz, CH_3CH), 2.83 (1H, q, J = 8 Hz, CH_3CH), 3.48 (1H, d, J = 8 Hz, CH_2OBn), 3.65 (1H, d, J = 8 Hz, CH_2OBn), 3.88 (1H, d, J = 10 Hz, CH_2Ph), 4.23 (1H, d, J = 10 Hz, CH_2Ph), 4.44 (1H, d, J = 12 Hz, CH_2OH), 4.57 (1H, d, J = 12 Hz, CH_2OH), 7.27–7.36 (5H, m, Ph); δ_C (100 MHz, CD_3OD) 6.9, 42.9, 63.8, 71.1, 72.4, 73.2, 80.4, 127.6, 127.7, 128.3, 138.3, 173.3, 179.9; HRMS: found 308.1136 for $C_{15}H_{18}NO_6^-$ $[M - H]^-$, requires 308.1140.

(2*R*,3*R*,4*S*)-2-Acetoxymethyl-3-hydroxy-3-methoxymethyl-4-methyl-5-oxopyrrolidine-2-carboxylic acid methyl ester 28a

To a magnetically stirred solution of **25a** (400 mg, 1.62 mmol), Et_3N (0.24 mL, 1.7 mmol) and DMAP (12 mg, 0.1 mmol) in THF (50 mL) was added acetyl chloride (0.12 mL, 1.7 mmol) and the mixture was left to stir at r.t. After 40 min there was still starting material visible on the TLC, so additional amount of Et_3N–DMAP–AcCl (0.24 mL, 12 mg and 0.12 mL respectively) were added and 30 min later the reaction was quenched with aq. soln. of NH_4Cl and a few drops of conc. HCl. The mixture was extracted with ethyl acetate, the combined organic layers were dried ($MgSO_4$) and the solvents were evaporated under reduced pressure to give crude **28a**, which was purified by column chromatography on silica gel with 20 : 1 Et_2O–MeOH as the eluent. Pure product **28a** was obtained as a solid foam (375 mg, 80%) along with 40 mg of the starting material **25a**. ν_{max} (film) 3302, 1730, 1698; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, J = 7 Hz, CH_3CH), 2.06 (3H, s, $COCH_3$), 2.67 (1H, q, J = 7 Hz, CH_3CH), 3.32 (1H, d, J = 10 Hz, CH_2OCH_3), 3.32 (3H, s, OCH_3), 3.42 (1H, d, J = 10 Hz, CH_2OCH_3), 3.71 (1H, s, OH), 3.75 (3H, s, $COOCH_3$), 4.42 (1H, d, J = 11 Hz, CH_2OAc), 4.73 (1H, d, J = 11 Hz, CH_2OAc), 6.82 (1H, s, NH); δ_C (100 MHz, $CDCl_3$) 7.3, 20.8, 42.0, 52.9, 59.1, 66.4, 70.1, 72.8, 80.5, 170.7, 178.0; HRMS: found 312.1055 for $C_{12}H_{19}NNaO_7^+$ $[M + Na]^+$, requires 312.1054.

(2*R*,3*R*,4*S*)-2-Acetoxymethyl-3-benzyloxymethyl-3-hydroxy-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid methyl ester 28b

To a stirred solution of **25a** (130 mg, 0.4 mmol), Et_3N (0.14 mL, 1 mmol) and DMAP (12 mg, 0.1 mmol) in DCM (10 mL) at r.t. was added acetyl chloride (0.07 mL, 1 mmol). After 15 min, the reaction mixture was washed with dilute aq. HCl. The aqueous layer was extracted once with DCM, the combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give practically clean **28b** as a crystalline solid. Yield (132 mg, 90%). R_f 0.13 (Et_2O); m.p. 146–148 °C; ν_{max} (film) 3340, 1741, 1707; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, J = 6 Hz, CH_3CH), 2.06 (3H, s, COCH_3), 2.23 (1H, s, OH), 2.71 (1H, q, J = 6 Hz, CH$_3$CH), 3.42 (1H, d, J = 10 Hz, CH_2OBn), 3.50 (1H, d, J = 10 Hz, CH_2OBn), 3.61 (3H, s, COOCH_3), 4.44 (1H, d, J = 11 Hz, CH_2OAc), 4.51 (2H, AB quartet, J = 12 Hz, CH_2Ph), 4.77 (1H, d, J = 11 Hz, CH_2OAc), 6.91 (1H, s, NH), 7.27–7.38 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 7.4, 20.8, 42.3, 52.9, 66.3, 70.3, 70.7, 73.6, 80.5, 127.8, 128.1, 128.6, 136.9, 170.7, 178.1; HRMS: found 388.1357 for $C_{18}H_{23}NNaO_7^+$ $[M + Na]^+$, requires 388.1367.

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