

## Mimics of Pramanicin derived from Pyroglutamic acid and their Antibacterial Activity

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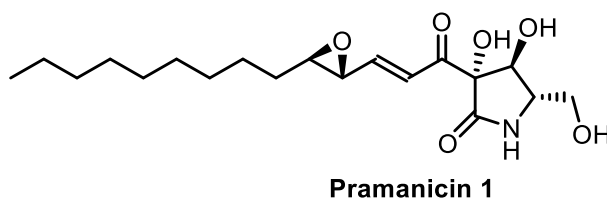
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**Abstract:** Mono and dihydroxypyrrolidinones are readily available by direct oxygenation of a pyroglutamate-derived bicyclic lactam with high diastereoselectivity, and these may be manipulated further in protected or unprotected form by Grignard addition to a pendant Weinreb amide to give acylhydroxypyrrolidinones, which are analogues of the natural product, pramanicin. Preliminary bioassay against *S. aureus* and *E. coli* indicated that some compounds exhibit selective Gram-negative antibacterial activity, and may offer promise for the development of novel systems suitable for antibacterial drug development.

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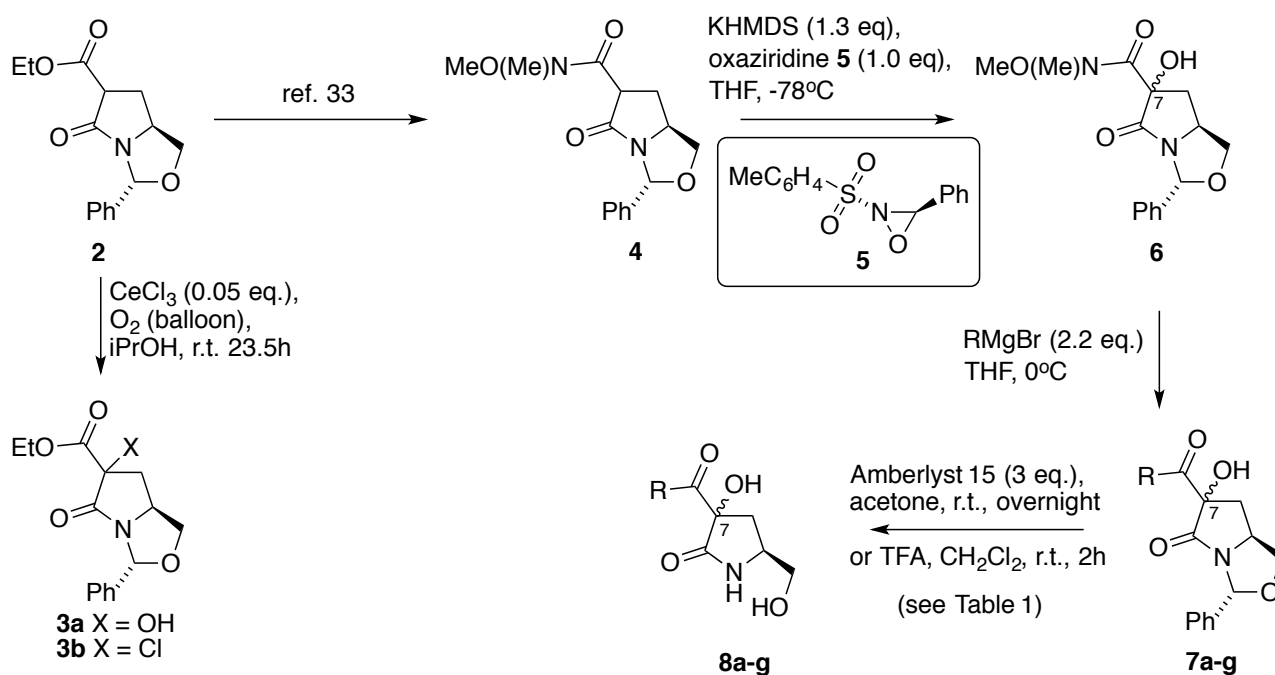
The critical importance of natural products in the development of pharmaceutically active compounds has been thoroughly documented, and although popularity of this approach has waned in recent years in favour of combinatorial and rational design, there have been strong calls for its reinvigoration.<sup>1-4</sup> These calls are particularly relevant for antibacterials, for which there is a serious

deficit of new candidates in the drug pipeline,<sup>5-8</sup> at a time when there is considerable urgency to expand therapeutics as a result of the rapid emergence of resistant bacterial strains.<sup>9-16</sup> The challenges peculiar to antibacterial drug discovery<sup>17-25</sup> mean that natural products often provide biologically validated start points suitable for immediate elaboration in the quest for new pharmaceutically useful agents. We have recently shown that small molecule mimics of streptolydigin<sup>26</sup> and kibelomycin<sup>27</sup> offer promise in that regard,<sup>28-30</sup> and we became interested in the exploration of pramanicin as a model start point using a similar strategy. Pramanicin **1** was isolated in 1994 and shown to exhibit antifungal activity and antibacterial activity,<sup>31</sup> but with significant human cytotoxicity.<sup>32</sup> We recently reported that epoxy analogues were readily available by elaboration of a pyroglutamate substrate, and that the derived compound libraries exhibited antibacterial activity against both Gram-positive and -negative bacteria.<sup>33</sup> We report here an extension of this work to include monohydroxy and dihydroxy derivatives, which complements the direct synthesis of the *cis*-dihydroxyl unit which has recently been reported,<sup>34</sup> providing access to libraries which exhibit antibacterial activity against *S. aureus* and/or *E. coli*.



## Results and Discussion

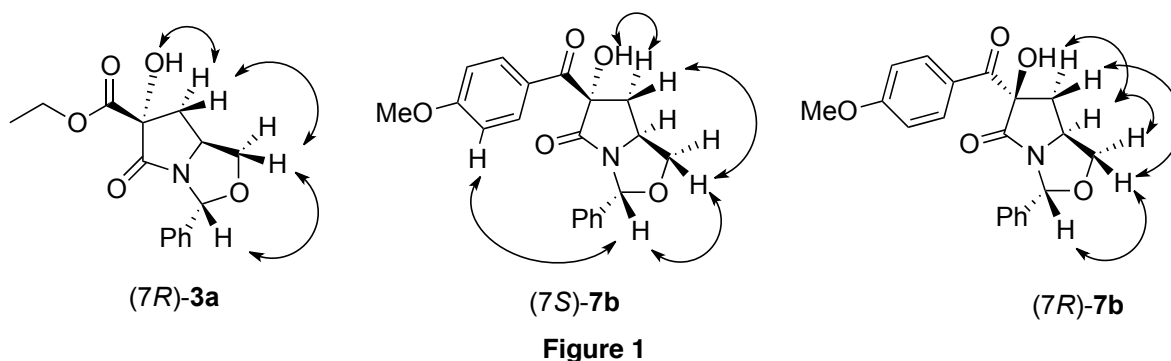
Our approach for access to such hydroxyl systems began with ester **2**, itself readily derived from pyroglutamic acid,<sup>33</sup> and the two diastereomers of the hydroxyl product **3a** were obtained using the procedure of Christoffers<sup>35</sup> and isolated separately in yields of 13% (7*S*) and 28% (7*R*). The stereochemistry of the hydroxyl-ester (7*R*)-**3a** was determined using nOeSY (Figure 1), and the (7*S*)-**3a** isomer was assigned via the analogous chemical shifts pattern of the H-6 protons known to be distinctive for such lactam scaffolds.<sup>36</sup> In addition,  $\alpha$ -chlorinated **3b** was isolated in lower yield from this reaction as a mixture of inseparable diastereomers. Given the low isolated yield of the desired product **3a**, an alternative hydroxylation approach was required.



Scheme 1

We therefore turned to the reported Weinreb amide **4**, readily prepared from ester **2**,<sup>33</sup> which was deprotonated with KHMDS and oxygenated with oxaziridine **5** to give hydroxyl derivative **6** in 57% yield and a diastereomeric ratio of 5.6:1 in favour of the *7R* *exo* diastereomer (Scheme 1), for which the stereochemistry was again assigned from the chemical shift and splitting of the two H-6 signals in the <sup>1</sup>H NMR spectrum.<sup>33, 36</sup> Amide **6** was successfully reacted with 2.2 eq. Grignard reagent to give the respective ketones **7a-g** in variable yields, even in the presence of the unprotected tertiary alcohol (Scheme 1 and Table 1); the selectivity of this process in such a functionally dense substrate is remarkable, and offers an alternative approach for the introduction of acyl residues to our recently published protocol based upon carbodiimide coupling of tetramates with carboxylates.<sup>37</sup> The efficiency of this conversion was found to be dependent upon the stereochemistry of lactam **6** at C-7, with (*7S*)-**6** being less efficient than (*7R*)-**6** (note that the *R,S* assignment changes due to the priority rule change upon conversion to the ketone **7**) probably as a result of greater steric hindrance in this *endo*- system. Both diastereomers of each of **7a-g** could be separated by chromatography, and the relative stereochemistry of **7b** was determined via NOESY analysis (Figure 1). As has been previously observed with this class of bicyclic lactam,<sup>33, 36, 38</sup> the chemical shift difference between the two H-6 protons also allows ready distinction of the

diastereomers, since when the tertiary C-7 hydroxyl group is at the *endo* position of the bicyclic system, the chemical shift difference between the two H-6 protons is significantly greater than the chemical shift difference between the two H-6 protons when the C-7 hydroxyl group is in the *exo* position. Although it has been noted that the bicyclic system generally exhibits *exo*-stereoselectivity in its reactions on the less hindered convex face as seen in this case and as might be expected,<sup>39</sup> it is nonetheless possible to favour *endo*-selectivity in the alkylations of the lactam enolates by use of acetophenone protected systems.<sup>40,41</sup> Overall, conversion of (7*S*)-**6** is best with alkynyl Grignard reagents, followed by aryl and alkyl Grignard reagents, with the bulky isobutyl Grignard reagent giving the lowest conversion, suggesting that the steric requirements in the vicinity of the *endo*-Weinreb amide dictate the course of the reaction, as might be expected. In order to probe this behaviour further, a competition reaction of **6** using phenylethynyl magnesium bromide and isobutyl magnesium bromide added simultaneously was conducted. No isobutyl product was obtained, and the ratio of (7*S*)-**7f** (*exo*-OH) to (7*R*)-**7f** (*endo*-OH) was 5:1, while the ratio of total ynone **7f** to recovered starting **6** was 10:1, suggesting good overall conversion to the ketone product. This outcome confirms that bulky Grignard reagents react more slowly with Weinreb amide **6**.



Products (7*S*)-**7a-g** could be deprotected under mildly acidic conditions (with Amberlyst 15) to give high yields of pyroglutaminols (2*S*)-**8a-g**, and alternative hydrolysis conditions (TFA 20 eq., CH<sub>2</sub>Cl<sub>2</sub>, r.t., 2 h) also gave good yields of (2*S*)-**8f,g**. However, of interest was that hydrolysis of the alternative diastereomer (7*R*)-**7a** with Amberlyst 15 (3 eq.) at r.t. overnight gave no conversion and starting material was recovered quantitatively, while hydrolysis under standard conditions with

excess TFA in THF/H<sub>2</sub>O gave a complex crude mixture. Overall, the Weinreb amide provided ready access to libraries of monohydroxyl pyroglutaminols.

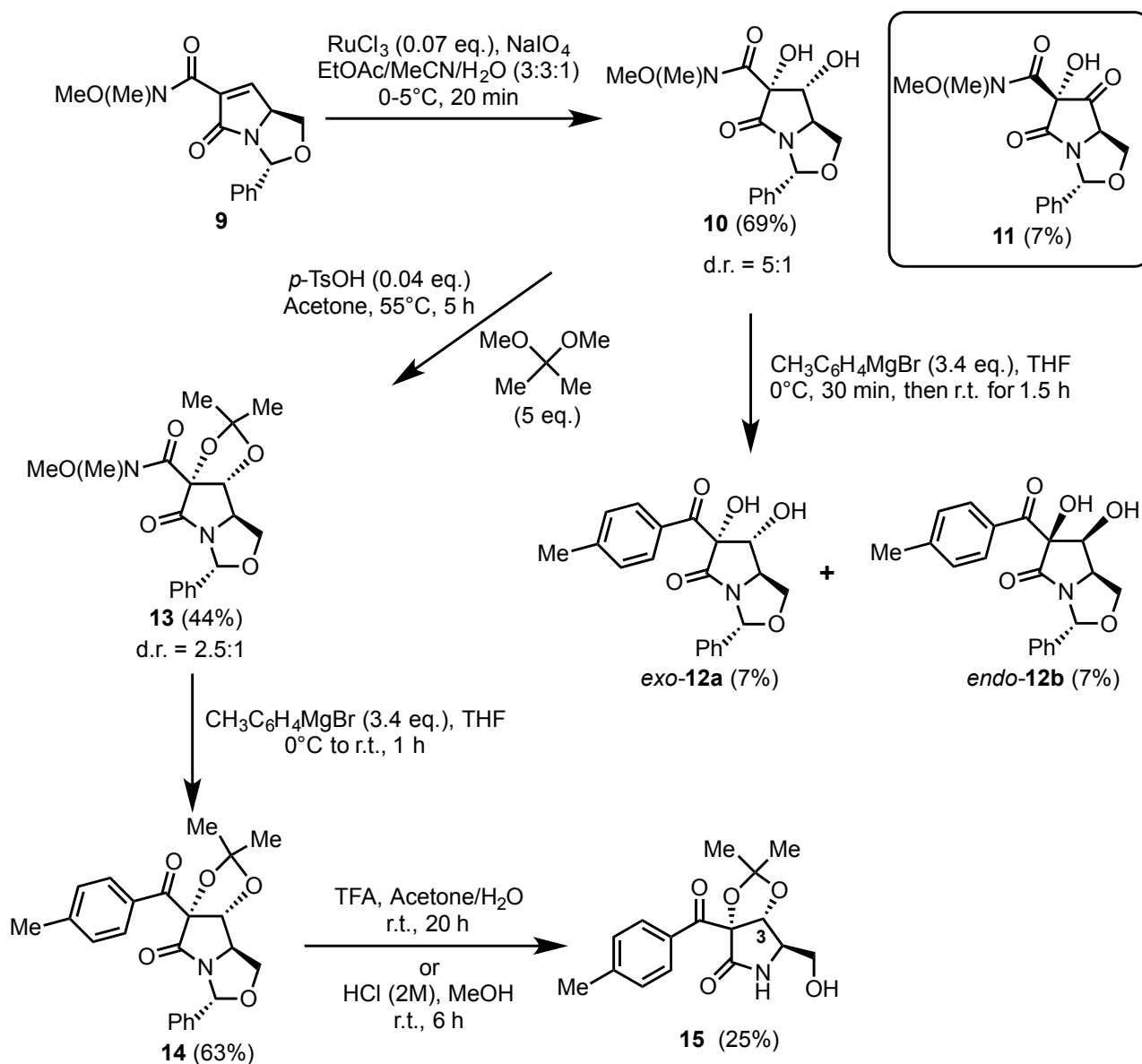
**Table 1:** Yields for the Grignard reaction of lactam **6** giving products **7** and **8**.

	d.r. of <b>6</b> used (-OH exo:endo)	<b>7</b> , Yield (%)		<b>8</b> , Yield (%)
<b>a</b> R =	5.9:1	7R	9	-
		7S	47	83
<b>b</b> R =	3.3:1	7R	17	-
		7S	35	89
<b>c</b> R =	5.6:1	7R	7	-
		7S	24	97
<b>d</b> R =	12.5:1	7R	3	-
		7S	35	91
<b>e</b> R =	5.6:1	7R	<4*	-
		7S	6	90
<b>f</b> R =	3:1	7R	22	-
		7S	49	85
<b>g</b> R =	3:1	7R	16	-
		7S	50	93

\*Isolated with impurities.

Lactam **4** may also be selenylated and eliminated to give the unsaturated derivative **9**,<sup>33</sup> since such  $\alpha,\beta$ -unsaturated lactams<sup>42</sup> are quite electrophilic and suitable for a variety of nucleophilic addition processes,<sup>43, 44</sup> and our earlier work had demonstrated efficient epoxidation of these systems,<sup>33</sup> an obvious question was its applicability to dihydroxylation processes, which in any case would provide a closer set of mimics to pramanicin **1**. However, although an earlier examination of a closely related ester had indicated successful dihydroxylation using osmium tetroxide or potassium permanganate was possible but that product isolation was problematic, application of the

ruthenium-mediated “flash dihydroxylation” procedure reported by Shing and co-workers<sup>45</sup> to **9** gave the desired *cis-exo*-diol **10** with an isolated yield of 69% (along with some *cis-endo*-diol **10**, d.r. of 5:1, as an inseparable mixture) as determined from the <sup>1</sup>H NMR spectrum (based on the corresponding H-2 resonances) (Scheme 2). A NOESY experiment suggested that the *exo*-diol was formed (Figure 2), and from nOe correlations between the lactam -OMe group with H-2 and H-4*endo*; that the Weinreb amide moiety was on the *endo* face of the bicycle was confirmed by X-ray crystal structural analysis (Figure 3).<sup>46</sup> This outcome was in agreement with the stereoselectivity observed with such bicyclic [3.3.0] scaffolds,<sup>43, 44, 47</sup> although noteworthy is a recent report indicating that *endo*- addition may be favoured in certain *N,O*-hemiaminal ether systems.<sup>48</sup> In addition, a single diastereomer of tetramic acid **11** (assigned by single crystal analysis, Figure 3) was also isolated, presumably arising from over-oxidation of **10** under the reaction conditions.<sup>45</sup>



Scheme 2

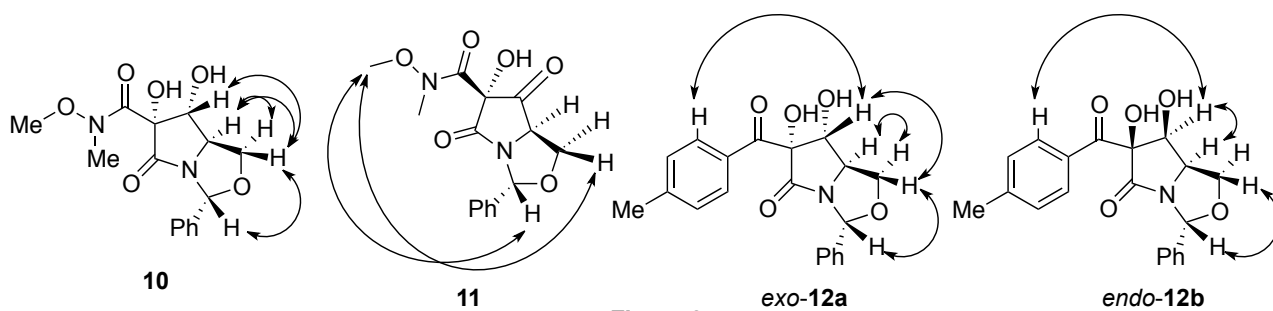
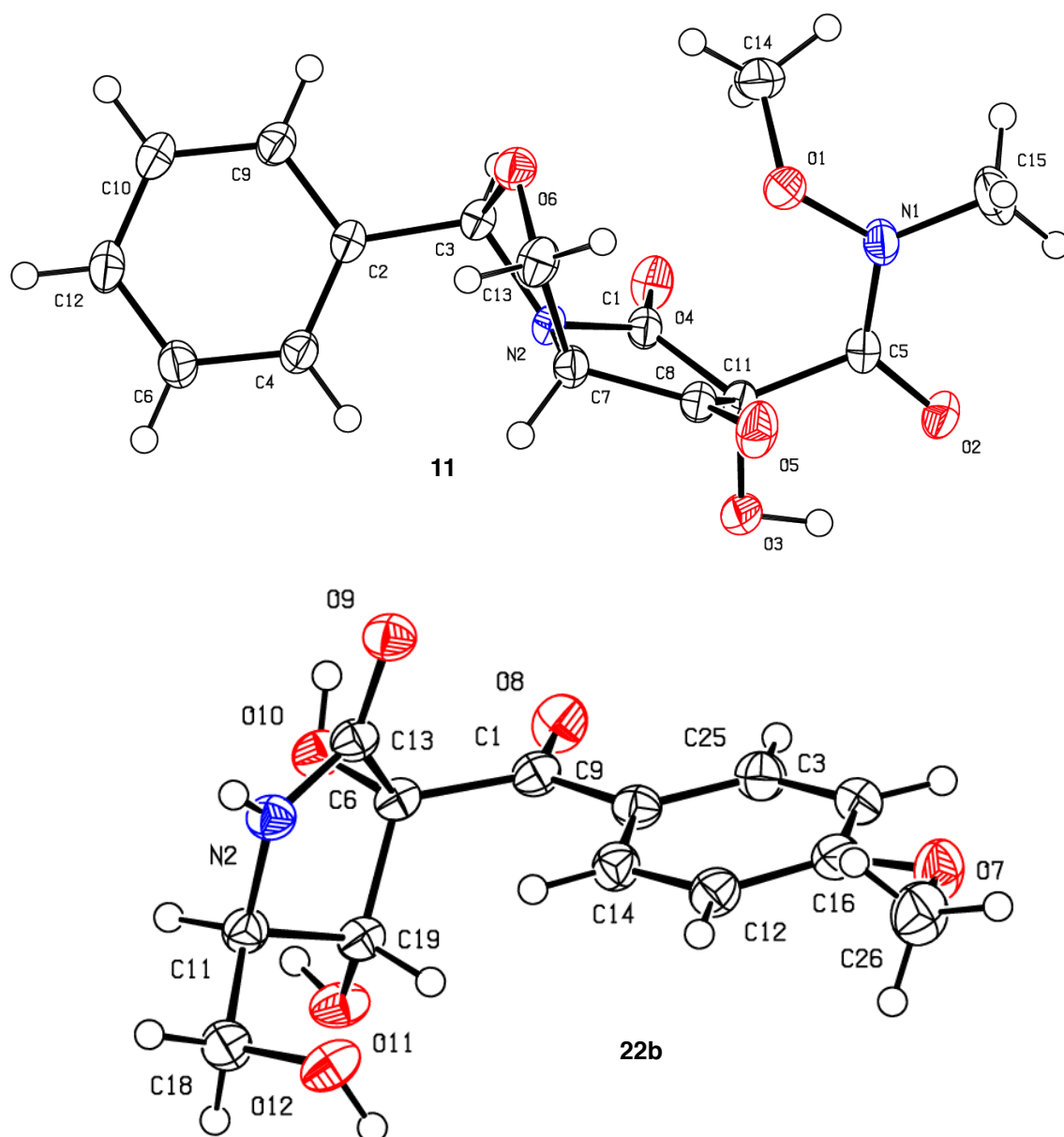


Figure 2



**Figure 3: ORTEP plots for structures 11 and 22b**

When the Grignard reaction with the Weinreb function using tolylmagnesium bromide was attempted with the unprotected diol **10**, a very low conversion to the desired products **12a,b** was obtained (which further confirmed the existence of **10** as a mixture of *cis-exo* and *cis-endo* isomers), in contrast to the reaction of lactam **6**, and their very similar chromatographic retention factors made purification difficult (Scheme 2); stereochemistry was assigned by NOESY experiment (Figure 2). In order to improve the chemical yield by removing the acidic hydroxylic functionality, the diol was protected as acetonide **13** (44% yield, major *cis-exo* and minor *cis-endo*) under standard conditions, which when followed by Grignard reaction as above gave ketone **14** in a much

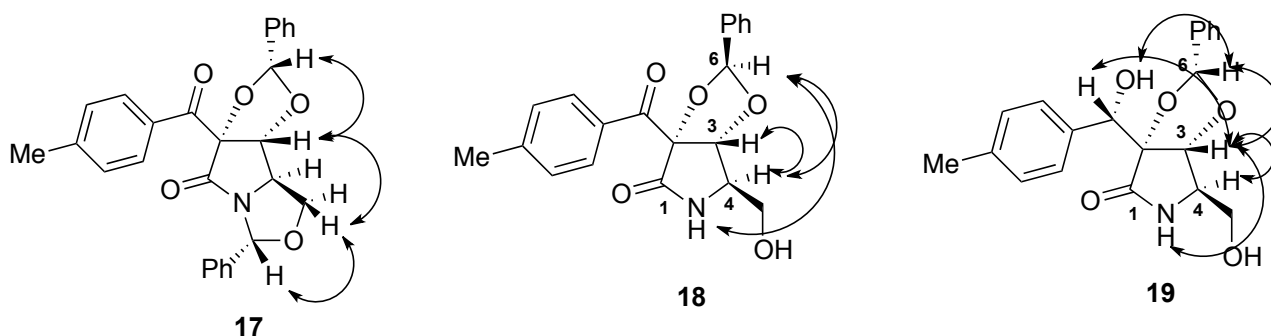
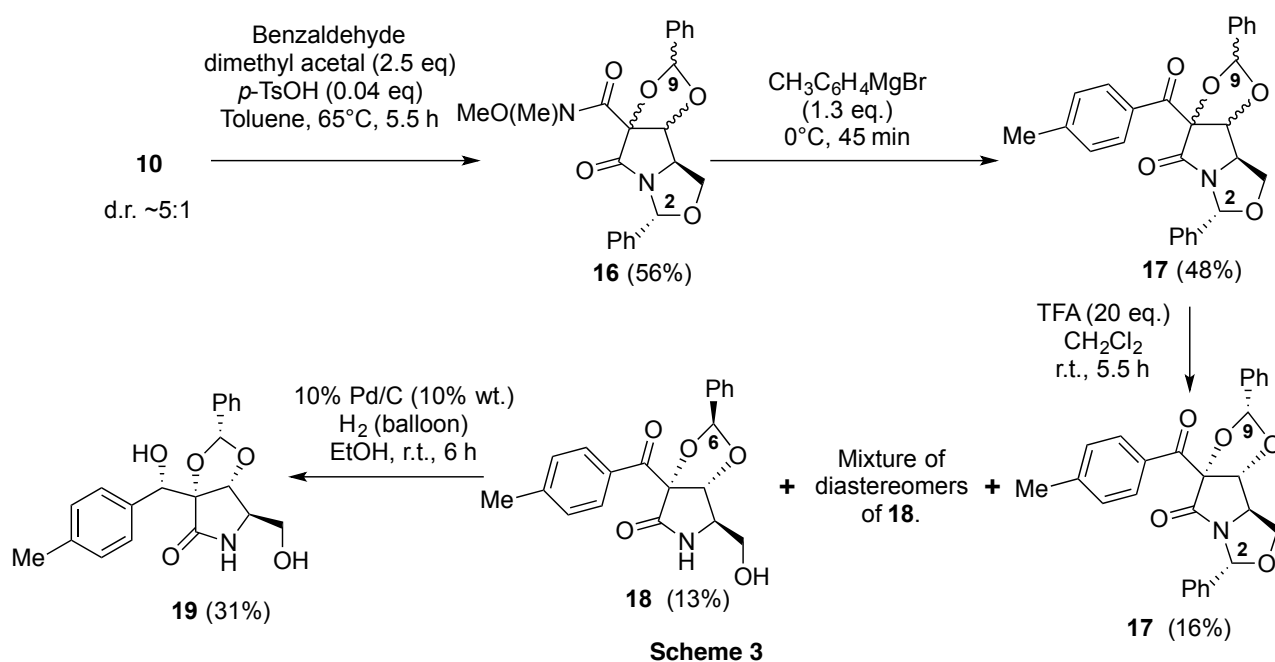


improved yield of 63% yield as a mixture of diastereomers (*exo* diol: *endo* diol 2.5:1). Although a single spot was observed by TLC analysis of **14**, its  $^1\text{H}$  NMR spectrum contained two sets of H-6 signals, with some of the other signals being broad. A variable temperature  $^1\text{H}$  and  $^{13}\text{C}$  NMR experiment at 65°C (338K) improved the resolution of the broad peaks, but the ratio of these two forms remained essentially unchanged, suggesting their identity as diastereomers and not rotamers, thereby confirming the formation of *cis-exo* and *cis-endo* products, but as an inseparable mixture. However, various acidic hydrolysis conditions failed to simultaneously deprotect both the oxazolidine and the acetonide functions, and strong acidic conditions (2 M aq. HCl (4 eq.)) MeOH, r.t., 6 h gave the *cis-exo* diastereomer of **15** in 25% yield.

Given this difficult deprotection, other more acid-labile diol protecting groups were investigated, beginning with a benzylideneacetal protecting group (Scheme 3), notwithstanding the possible complications resulting from the new stereogenic centre. Acetal **16** (as a mixture of diastereomers) was readily prepared in good yield and elaborated to ketone **17** as before. However, again, on attempted hydrolysis with TFA, only the oxazolidine was hydrolysed (Scheme 3) and after purification, both **18** and unreacted **17** were isolated each as a single diastereomer, in 13 and 16% yield respectively. The relative stereochemistry of recovered **17** was readily determined via NOESY (Figure 4). For **18**, NOESY gave correlations between H6-NH, H6-H4, H3-H4 but this data was insufficient to assign the stereochemistry of the protected diol relative to the pyrrolidinone. In order to establish this, MM2-minimised molecular modelling was used to generate the most stable conformers of all four possible diastereomers of **18**, and this suggested that only one diastereomer could have the H-6 oriented in close proximity to both -NH- and H-4, enabling its assignment as shown in Scheme 3 and Figure 4.

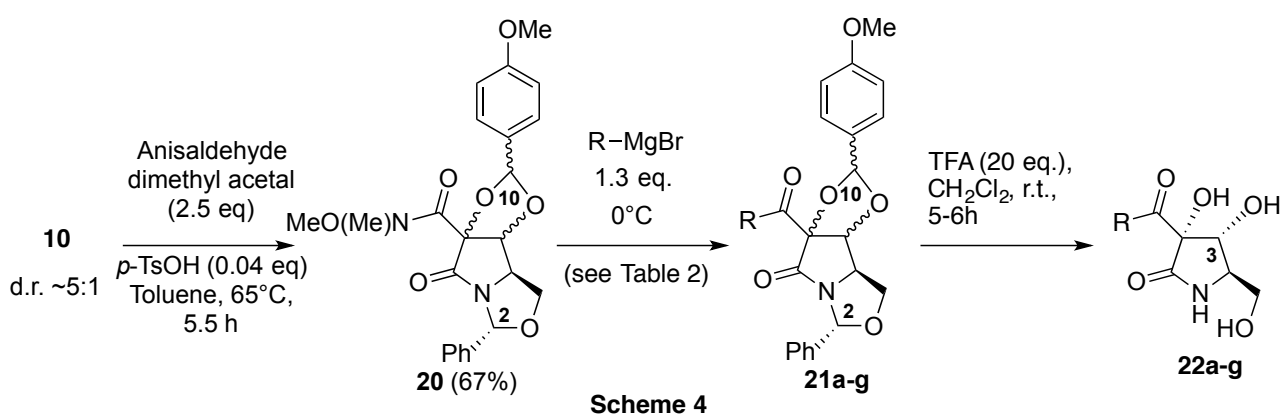
Given the stability of the benzylidene acetal towards Bronsted acid, deprotection under reductive conditions was investigated. When a mixture of diastereomers of **18** was treated with hydrogen gas in the presence of Pd/C catalyst, reduction of the ketone to the hydroxyl occurred, rather than hydrogenolysis, giving pyroglutaminol **19** in 31% yield as a single diastereomer. The

stereochemistry of the protected diol, benzylidene and newly formed hydroxyl group were assigned using nOe correlations (Figure 4), and this outcome would appear to arise from least hindered attack by hydrogen, again as might be expected.

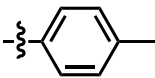
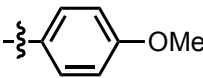
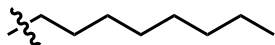
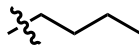
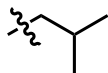
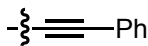
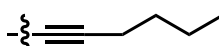


Taken together, these results seemed to indicate that acetals in this system might be more stable to acidic hydrolysis than expected. For this reason, the more acid-labile *p*-methoxyphenyl (PMP) benzylidene diol protecting group was examined.<sup>49</sup> Protection of the diol **10** with anisaldehyde dimethylacetal gave **20** in 67% yield, again as a mixture of diastereomers (Scheme 4). When **20** was reacted with the respective Grignard reagent, the ketones **21a-g** were obtained in modest yield (Table 2); this may again be attributed to the steric bulk in the vicinity of the Weinreb amide due to the PMP benzylidene acetal. Treatment with TFA/CH<sub>2</sub>Cl<sub>2</sub> gave global deprotection and the desired 2,3-dihydroxypyrrolidinones **22a-g** were obtained in good yields (Table 2). Some

of these derivatives were isolated as a mixture of diastereomers (about the diol), and it was observed that the minor diastereomer had a larger  $J_{\text{H3-H4}}$  value and that the H-3 signal resonated further downfield compared to the major diastereomer. On the basis of earlier reactions, it was assumed that the major diastereomer was the *exo*-diol, and in order to confirm this, *exo*-**12a** which had been earlier prepared and isolated as a single diastereomer (see Scheme 2) was subjected to standard acidic hydrolysis conditions; the product thus obtained had the same  $J_{\text{H3-H4}}$  value of 6.4 Hz as that of **22a** obtained via the PMP protected intermediate, confirming their identity. In addition, X-ray crystallography of **22b** prepared via the PMP-protected intermediate confirmed its *exo*-stereochemistry (Figure 3).<sup>46</sup>

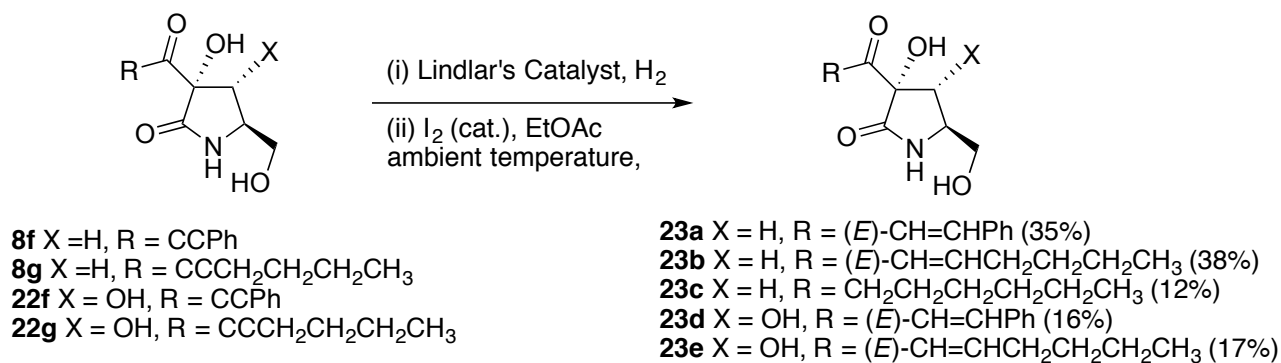


**Table 2:** Yields of ketones **21** and triols **22**.

	21, Yield (%)	22	
		Yield (%)	$J_{\text{H3-H4}}$
<b>a</b> R = 	45	48	6.4 Hz
<b>b</b> R = 	44	52	6.4 Hz
<b>c</b> R = 	30	41; d.r. 5:1	6.1 Hz (Major) 6.7 Hz (Minor)
<b>d</b> R = 	19	58; d.r. 2:1	6.1 Hz (major) 6.8 Hz (minor)
<b>e</b> R = 	27	31	6.1 Hz
<b>f</b> R = 	51	48; d.r. 3.3:1	6.7 Hz (major) 7.0 Hz (minor)
<b>g</b> R = 	34*	72; d.r. 1:1	6.8 Hz (major) 7.2 Hz (minor)

\*nOeSY shows exo-diol but ~1:1 epimeric mixture about H-10

With the ynones **8f,g** and **22f,g** in hand, of interest was the synthesis of the corresponding enones; it was expected that a sequence using Lindlar's catalyst/hydrogen for the partial reduction of ynones followed by isomerisation of the *cis*-enones in the presence of catalytic amount of iodine would provide the *trans*-enones.<sup>50</sup> In the event (Scheme 5), the reduction was found to proceed with poor (*E*)/(*Z*) selectivity, but isomerization with iodine cleanly gave the (*E*) isomer with none of the (*Z*) isomer detectable by NMR analysis, although in low chemical yield over the two steps. No deoxygenated or over-reduced by-products were isolated from this sequence.

**Scheme 5**

## Antibacterial Activity

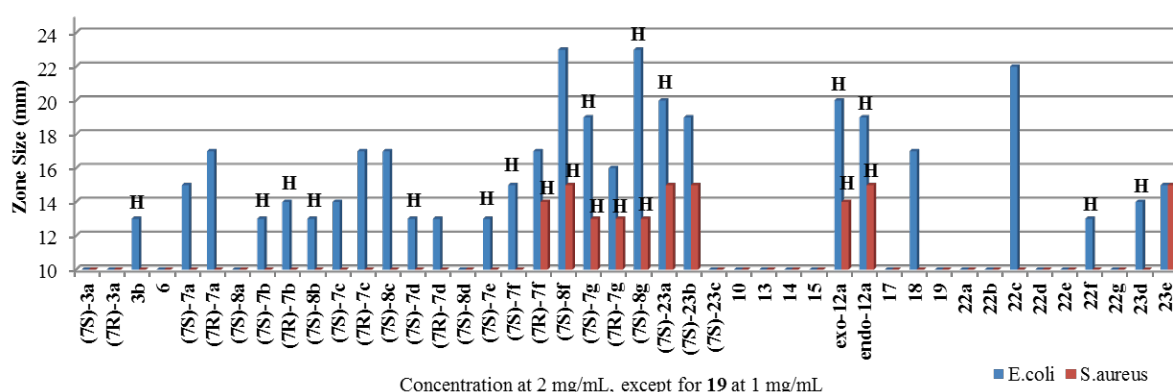
In order to assess whether any members of the above chemical libraries, which might be considered to be mimics of pramanicin **1**, exhibited antibacterial activity, assays were performed using the hole-plate method against either *Staphylococcus aureus* DS267 (Gram-positive) or *Escherichia coli* X580 (Gram-negative), using Cephalosporin C (CephC) as a standard (Table 3 and Figure 4).<sup>51</sup> It was found that 2-hydroxypyrrolidinones with a C-7 carboxamido substituent **6** or a C-7 carboxylate substituent **3a** did not exhibit antibacterial activity, while 2-chloro-carboxylpyrrolidinone **3b** exhibited some activity with *E. coli*. By contrast, 2-hydroxy-ketopyrrolidinones **7a-f**, **8a-i,k** generally exhibited antibacterial activity, and with high selectivity towards *E.coli* over *S.aureus*. However, lower selectivity was observed for derivatives with Michael acceptor functionalities (for example ynones or enones) on their side-chain, due to their better activity with *S.aureus*. For some derivatives, the minor hydroxyl diastereomer ((*7R*)-**7a-c**, (*7R*)-**7f**) exhibited greater activity towards *E.coli* as compared to the major hydroxyl diastereomer ((*7S*)-**7a-c**, (*7R*)-**7f**).

**Table 3:** Antibacterial Bioactivity and Physicochemical Parameters for Selected Compounds.<sup>a,b</sup>

Compound	Conc. (mg/mL)	Zone Size/mm		MW	clogD <sub>7.4</sub>	PSA	MSA	%PSA
		<i>S. Aureus</i>	<i>E. Coli</i>					
Monohydroxypyroglutaminols								
(7S)-3a	2	10	10	291.3	0.95	76.07	415.03	18.3
(7R)-3a	2	10	10	291.3	0.95	76.07	415.03	18.3
3b	2	10	13 (H)	309.75	2.31	55.84	419.69	13.3
6	2	10	10	306.32	0.24	79.31	434.74	18.2
(7S)-7a	2	10	15	337.38	2.72	66.84	473.47	14.1
(7R)-7a	2	10	17	337.38	2.72	66.84	473.47	14.1
(7S)-8a	2	10	10	249.27	-0.03	86.63	356.52	24.3
(7S)-7b	2	10	13 (H)	353.37	2.05	76.07	489.55	15.5
(7R)-7b	2	10	14 (H)	353.37	2.05	76.07	489.55	15.5
(7S)-8b	2	10	13 (H)	265.27	-0.7	95.86	372.33	25.7
(7S)-7c	2	10	14	359.47	4.15	66.84	581.86	11.5
(7R)-7c	2	10	17	359.47	4.15	66.84	581.86	11.5
(7S)-8c	2	10	17	271.36	1.4	86.63	465.38	18.6
(7S)-7d	2	10	13 (H)	303.36	2.37	66.84	459.34	14.6
(7R)-7d	2	10	13	303.36	2.37	66.84	459.34	14.6
(7S)-8d	2	10	10	215.25	-0.38	86.63	343.14	25.2
(7S)-7e	2	10	13 (H)	303.36	2.21	66.84	458.66	14.6
(7S)-7f	2	10	15 (H)	347.37	3.16	66.84	460.85	14.5

(7R)-7f	2	14 (H)	17	347.37	3.16	66.84	460.85	14.5
(7S)-8f	2	15 (H)	23	259.26	0.41	86.63	344.82	25.1
(7S)-7g	2	13 (H)	19 (H)	327.38	3.35	66.84	477.76	14.0
(7R)-7g	2	13 (H)	16	327.38	3.35	66.84	477.76	14.0
(7S)-8g	2	13 (H)	23 (H)	239.27	0.61	86.63	361.88	23.9
(7S)-8h	2	15	20 (H)	261.28	0.39	86.63	357.08	24.3
(7S)-23b	2	15	19	241.29	0.51	86.63	374.28	23.1
(7S)-23c	2	10	10	243.3	0.51	86.63	404.93	21.4
Dihydroxypyroglutaminols								
10	2	10	10	322.32	-0.45	99.54	442.29	22.5
13	2	10	10	362.38	1.25	77.54	524.64	14.8
14	2	10	10	393.44	3.73	65.07	563.65	11.5
15	2	10	10	305.33	0.98	84.86	447.05	19.0
exo-12a	2	14 (H)	20 (H)	353.37	2.03	87.07	481.29	18.1
endo-12a	2	15 (H)	19 (H)	353.37	2.03	87.07	481.29	18.1
17	2	10	10	441.48	5.19	65.07	601.88	10.8
18	2	10	17	353.37	2.45	84.86	484.25	17.5
19	1	10	10	355.39	2.45	84.86	485.7	17.5
22a	2	10	10	265.27	-0.72	106.86	364.45	29.3
22b	2	10	10	281.26	-1.39	116.09	380.84	30.5
22c	2	10	22	287.36	0.71	106.86	474	22.5
22d	2	10	10	231.25	-1.07	106.86	350.48	30.5
22e	2	10	10	231.25	-1.22	106.86	348.4	30.7
22f	2	10	13 (H)	275.26	-0.28	106.86	352.34	30.3
22g	2	10	10	255.27	-0.08	106.86	368.82	29.0
23d	2	10	14 (H)	277.28	-0.3	106.86	364.8	29.3
23e	2	15	15	257.29	-0.18	106.86	382.12	28.0

<sup>a</sup> (H) – represents that the zone exists as a “halo”, where an area of reduced bacteria density was observed instead of a distinct clear zone; <sup>b</sup> For a concise summary of structures relevant to this table, see Figure (ESI).



**Figure 5:** Bioactivity of monohydroxy and dihydroxypyroglutaminols

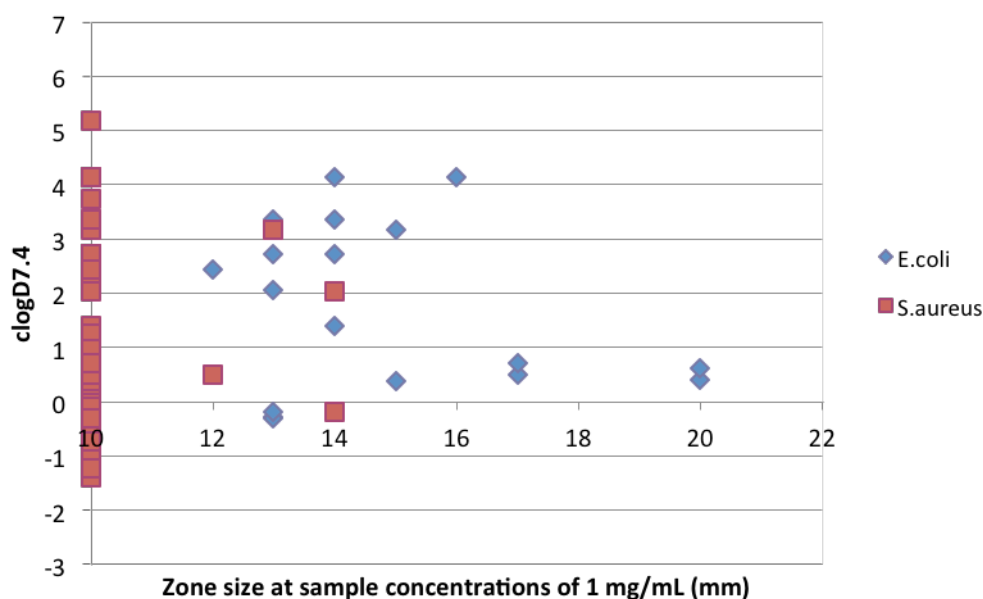
Analysis of the bioactivity of protected 2,3-dihydroxypyrrolidinones suggested that the exocyclic ketone at C-7, together with the presence of the free hydroxyl groups at C-6 and C- 7, were important for activity (Figure 4 and Table 5). Absence of the oxazolidine group (compare **15** with **14**) did not alter

the antibacterial activity, but absence of the acetonide (compare **14** with **12a**) resulted in a significant increase in antibacterial activity. From a comparison of **15** with **14**, **17** might have been expected to have similar antibacterial activity after oxazolidine hydrolysis to **18**. However, **18** was observed to have significant activity with *E. coli*, perhaps due to the different stereochemistry of the benzylidene group. Interestingly, 2,3-dihydroxypyrrolidinones **22a-i**, all possessing a scaffold that is most structurally similar to pramamicin, did not show strong antibacterial effects. Only four out of the nine derivatives exhibited any antibacterial activity, with good antibacterial activity towards *E. coli* being observed for **22c**. These results suggest that either a long hydrophobic side-chain (**22c**) or one that contains a Michael acceptor (**22f**, **22g-h**) plays an important role in the observation of antibacterial activity.

Optimal bioactivity for the different molecular scaffolds correlated with their respective clogP and %PSA ranges, and the data are summarised in Table 4 and Figure 5.<sup>52</sup> It was observed that compounds active towards *E. coli* only are more polar than compounds active towards *S. aureus* only, as shown by lower clogD<sub>7.4</sub> or higher %PSA values, while compounds active towards both *E. coli* and *S. aureus* generally have intermediate clogD<sub>7.4</sub> and %PSA values, and this is likely to be related to their ability to penetrate the bacterial cell wall.<sup>53</sup> Antibacterial drugs are generally more polar than other drugs, and a certain degree of polarity is required for bactericidal molecules as the cell walls of both Gram-positive and Gram-negative bacteria are charged.<sup>54, 55</sup> This contrasts with Lipinski's "rule of five" (good absorption predicted if H-bond donors < 5; H-bond acceptors < 10; molecular weight < 500; clogP < 5) which is applicable for the prediction of good oral absorption in mammalian systems.<sup>56</sup>

**Table 4:** cLogP and %PSA ranges of compounds with optimal bioactivity against *S. aureus* and *E. coli*.

Molecular Scaffold	<i>S. aureus</i> activity			<i>E. coli</i> activity		
	Zone size range/mm	clogP range	%PSA range	Zone size range	clogP range	%PSA range
2-Hydroxypyrrolidinones <b>7</b>	13	3.16	14.5	13-16	2.05-4.15	11.5-15.5
2-Hydroxypyrrolidinones <b>8</b>	Nil	-	-	14-20	0.41-1.4	18.6-25.1
2,3-Dihydroxypyrrolidinones <b>22</b> and <b>23</b>	12-14	-0.18-0.51	23.1-28.0	13-17	-0.3-0.71	22.5-30.3



**Figure 5.** Correlation of  $\text{clogD}_{7.4}$  (polarity) with the zone sizes (antibacterial activity) of pyroglutamate-derived.

## Conclusion

Mild and facile hydroxylation conditions have been identified, which along with a protocol exploiting the Grignard addition to a Weinreb amide, permits the direct and rapid construction of mono- and dihydroxypyrrolidinones from a pyroglutamate scaffold. An assessment of their antibacterial properties showed that the compounds most active against *E. coli* are those with higher polarity ( $\text{cLogP}$  values  $<1$  and  $\% \text{PSA} >22$ ) probably as a result of their greater bacterial cell wall permeability.<sup>57</sup> However, it is clear that appropriate ring functionalisation is critically important for antibacterial activity, especially since unsubstituted systems show little activity.<sup>58</sup> This work shows that pyroglutamates can provide useful structurally well-defined 3D building blocks with large  $\text{Fsp3}$  values,<sup>59, 60</sup> generating novel structures suitable for inclusion in the antibacterial drug discovery process.<sup>61-63</sup>

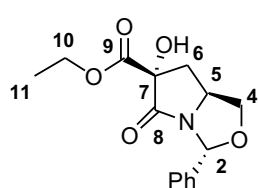
## Experimental

### Ce(III)-mediated $\alpha$ -hydroxylation of 2



Lactam **2** (50 mg, 0.182 mmol, 1.0 eq.) was added to a solution of  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (3.4 mg, 0.009 mmol, 0.05 eq.) in  $i\text{PrOH}$  (1 mL). The reaction mixture was first bubbled through with  $\text{O}_2$  (balloon) to saturate the solvent, and left to stir with  $\text{O}_2$  balloon attached. The reaction was stirred at r.t. for 25 h, and filtered over a pad of silica gel followed by washing with EtOAc. The solvent was evaporated to give the crude which was purified on via silica gel flash column chromatography (Eluent: 10% to 20% EtOAc/PE) to give the following:

**(2*R*, 5*S*, 7*R*)-7-Ethoxycarbonyl-7-hydroxy-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane, (7*R*)-3a**

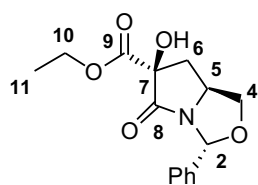


$R_f = 0.35$  (1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23} = +128.8$  ( $c = 0.5$  in MeCN);

$\nu_{\text{max}} / \text{cm}^{-1}$  (film) 3422 (br, ), 1744 (s, C=O), 1711 (s, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.45-7.48 (m, 2H, PhH), 7.33-7.40 (m, 3H, PhH), 6.29 (s, 1H, H-2),

4.34 (q,  $J = 7.1$  Hz, 2H, H-10), 4.27-4.33 (m, 2H, H-5 and H-4), 3.64-3.70 (m, 1H, H-4'), 2.55 (dd,  $J = 4.8, 14.2$  Hz, 1H, H-6), 2.47 (dd,  $J = 7.2, 14.2$  Hz, 1H, H-6'), 1.35 (t,  $J = 7.1$  Hz, 3H, H-11);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 172.62 (C-8), 171.03 (C-9), 137.83, 128.82, 128.50, 125.95 (PhC), 87.09 (C-2), 82.23 (C-7), 71.36 (C-4), 63.31 (C-10), 55.94 (C-5), 35.20 (C-6), 14.03 (C-11);  $m/z$  (ESI+) 314.25 ( $[\text{M}+\text{Na}]^+$ , 40%); HRMS (ESI+) calculated for  $\text{C}_{15}\text{H}_{17}\text{NNaO}_5$  ( $[\text{M}+\text{Na}]^+$ ) 314.0999, found 314.1000.

**(2*R*, 5*S*, 7*S*)-7-Ethoxycarbonyl-7-hydroxy-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0] octane, (7*S*)-3a**



$R_f = 0.28$  (1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23} = +98.8$  ( $c = 0.80$  in MeCN);

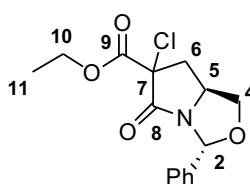
$\nu_{\text{max}} / \text{cm}^{-1}$  (film) 3423 (br, ), 1745 (s, C=O), 1712 (s, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.35-7.44 (m, 5H, PhH), 6.33 (s, 1H, H-2), 4.24-4.35 (m, 4H, H-10,

H-5 and H-4), 3.63 (t,  $J = 8.0$  Hz, 1H, H-4'), 2.94 (dd,  $J = 6.7, 13.3$  Hz, 1H, H-6), 2.12 (dd,  $J = 7.0, 13.3$  Hz, 1H, H-6'), 1.30 (t,  $J = 7.1$  Hz, 3H, H-11);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 171.25 (C-8), 170.57 (C-9), 137.58, 128.94, 128.55, 126.02 (PhC), 86.99 (C-2), 82.10 (C-7), 72.26 (C-4), 63.01 (C-10),

55.28 (C-5), 37.45 (C-6), 14.01 (C-11);  $m/z$  (ESI+) 314.22 ( $[M+Na]^+$ , 70%); HRMS (ESI+) calculated for  $C_{15}H_{17}NNaO_5$  ( $[M+Na]^+$ ) 314.0999, found 314.1005.

**(2R, 5S, 7RS)-7-Chloro-7-ethoxycarbonyl-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0] octane,**

**3b**



$R_f$  = 0.63 (1:1 EtOAc:PE); colorless oil;  $\nu_{max}$  /  $cm^{-1}$  (film) 1758 (s, C=O),

1722 (s, C=O);  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.33-7.47 (m, 5H, PhH), 6.38 (s, 0.5H,

H-2a), 6.32 (s, 0.5H, H-2b), 4.27-4.40 (m, 4H, H-4a, H-4b, H-5b, H-10a, H-

10b), 4.13-4.20 (m, 0.5H, H-5a), 3.66-3.76 (m, 1H, H-4'a, H-4'b), 3.37 (dd,  $J$  = 6.5, 13.4 Hz, 0.5H,

H-6a), 2.93 (dd,  $J$  = 6.7, 14.1 Hz, 0.5H, H-6b), 2.75 (dd,  $J$  = 6.2, 14.1 Hz, 0.5H, H-6'b), 2.37 (dd,  $J$

= 7.0, 13.4 Hz, 0.5H, H-6'a), 1.37 (t,  $J$  = 7.1 Hz, 1.5H, H-11b), 1.31 (t,  $J$  = 7.1 Hz, 1.5H, H-11a);  $\delta_C$

(100 MHz,  $CDCl_3$ ) 169.09 (C-8b), 167.86 (C-8a), 166.48 (C-9a), 166.14 (C-9b), 137.25, 137.23,

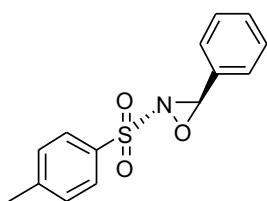
129.00, 128.98, 128.61, 128.56, 125.98 (PhC), 87.74 (C-2a), 87.10 (C-2b), 71.68 (C-4a), 71.00 (C-

4b), 70.76 (C-7b), 70.43 (C-7a), 63.70, 63.63 (C-10), 56.12 (C-5b), 55.51 (C-5a), 41.17 (C-6a),

40.75 (C-6b), 14.00, 13.88 (C-11);  $m/z$  (ESI+) 332.19 ( $[M+Na]^+$ , 90%); HRMS (ESI+) calculated

for  $C_{15}H_{16}ClNNaO_4$  ( $[M+Na]^+$ ) 332.0660, found 332.0677.

**3-Phenyl-2-*p*-tolylsulfonyloxaziridine, 5**



(*E*)-*N*-Benzylidene-4-methylbenzenesulfonamide (1 g, 3.856 mmol, 1.0 eq.)

in  $CH_2Cl_2$  (10 mL) was added to the white suspension of 77% *m*-CPBA

(950.6 mg, 4.242 mmol, 1.1 eq.) and powdered KOH (757.3 mg, 13.50

mmol, 13.5 eq.) in 10 mL  $CH_2Cl_2$ . (prepared at 0°C on adding *m*-CPBA to KOH and warmed to r.t.

prior use). After 15 min, the reaction crude is then filtered over Celite and the solvent evaporated to

give the pure oxaziridine (824 mg, 78%).  $R_f$  = 0.40 (20% EtOAc/PE); white solid, mp = 89-91°C

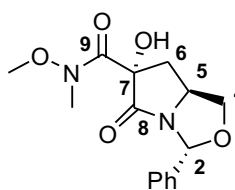
[lit. <sup>64</sup> 87-89°C];  $\nu_{max}$  /  $cm^{-1}$  (film) 3068, 2930, 1350, 1168;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.93 (d,  $J$  = 8.3

Hz, 2H, ArH), 7.40-7.47 (m, 7H, ArH), 5.45 (s, 1H), 2.50 (s, 3H);  $\delta_C$  (100 MHz,  $CDCl_3$ ) 146.36,

131.60, 131.35, 130.60, 130.03, 129.42, 128.71, 128.22, 76.33, 21.81;  $m/z$  (ESI-) 274.26 ( $[M-H]^-$ , 65%).

**(2*R*, 5*S*, 7*S*) and (2*R*, 5*S*, 7*R*)-1-Aza-7-hydroxy-7-(*N,O*-dimethylcarbamoyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, 6**

To a 1 M THF solution of KHMDS (1.36 mL, 1.357 mmol, 1.3 eq.) at  $-78^\circ\text{C}$  was added **73** (303 mg, 1.044 mmol, 1.0 eq.) in THF (4 mL). The solution was stirred at  $-78^\circ\text{C}$  for 40 min, after which oxaziridine **5** (287.4 mg, 1.044 mmol, 1.0 eq.) in THF (3 mL) was added. After stirring at  $-78^\circ\text{C}$  for 35 min, the reaction was quenched with sat. aq.  $\text{NH}_4\text{Cl}$ , extracted with EtOAc. The combined organic layers dried with  $\text{MgSO}_4$ , filtered and evaporated to give the crude, which was purified on silica gel (Eluent 0% to 10% EtOAc/ $\text{CH}_2\text{Cl}_2$ ) to give the desired product (182 mg, 57%, d.r. = 1:0.2).



$R_f = 0.54$  (1:1 EtOAc: $\text{CH}_2\text{Cl}_2$ ); colourless solid;  $\nu_{\text{max}} / \text{cm}^{-1}$  (film) 3404 (br, -

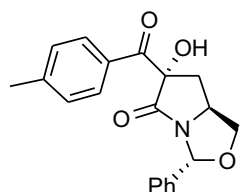
OH), 1710 (s, C=O), 1655 (s, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{MeCN-d}_3$ ) 7.36-7.49 (m, 5H, PhH), 6.20, 6.19 (s, 1H, H-2), 4.84, 4.82 (s, 1H, -OH), 4.33-4.40 (m,

0.75H, H-5), 4.28-4.32 (m, 1H, H-4), 4.06-4.13 (m, 0.25H, H-5), 3.68, 3.44 (s, 3H, -NMe), 3.54 (t,  $J = 8.2$  Hz, 1H, H-4), 3.28, 3.23 (s, 3H, -OMe), 2.86 (dd,  $J = 7.9, 14.3$  Hz, 0.6H, H-6b), 2.50 (dd,  $J = 5.5, 14.1$  Hz, 0.4H, H-6a), 2.22 (dd,  $J = 7.6, 14.0$  Hz, 0.4H, H-6a'), 2.00 (dd,  $J = 3.8, 14.3$  Hz, 0.6H, H-6b');  $\delta_{\text{C}}$  (100 MHz,  $\text{MeCN-d}_3$ ) 175.12, 173.31 (C-8), 171.28, 171.00 (C-9), 140.26, 139.87, 129.84, 129.75, 129.70, 129.66, 129.59, 129.51, 129.49, 129.48, 127.17, 127.09 (PhC), 89.57, 87.84 (C-2), 83.19, 81.94 (C-7), 73.01, 72.74 (C-4), 61.58, 61.08 (-NMe), 57.36, 56.78 (C-5), 37.32, 36.20 (C-6), 33.97, 33.61 (-OMe);  $m/z$  (ESI+) 329.24 ( $[M+\text{Na}]^+$ , 95%); HRMS (ESI+) calculated for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{NaO}_5$  ( $[M+\text{Na}]^+$ ) 329.1108, found 329.1121.

**General procedure for Grignard reaction of hydroxy Weinreb amide 6**

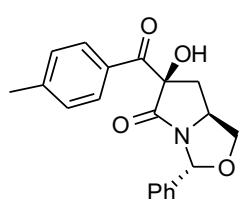
The Grignard reagent in THF (2.2 eq. based on amount of **6** used) was added to **6** (1.0 eq.) in THF at 0°C. The reaction was stirred at 0°C to r.t. over a period of 3-4 h, after which it was quenched with sat. aq. NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic layers were dried with anhydrous MgSO<sub>4</sub>, filtered and the solvents removed *in vacuo* to give the crude product. Purification via silica gel flash column chromatography (Eluent: EtOAc/PE) gave the respective product as two separate diastereomers about C-7.

**(2*R*, 5*S*, 7*S*)-1-Aza-7-hydroxy-7-(4'-methylphenylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, (7*S*)-7a**



Scale of reaction: 87 mg (0.284 mmol), product 45 mg, 47%;  $R_f = 0.51$  (1:1 EtOAc:PE); colourless crystals, mp = 145-146°C;  $[\alpha]_D^{23} = +143.0$  ( $c = 0.93$  in CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max} / \text{cm}^{-1}$  (film) 3405 (br, -OH), 1709 (s, C=O), 1673 (s, C=O);  $\delta_H$  (400 MHz, MeCN-d<sub>3</sub>) 7.85 (d,  $J = 8.3$  Hz, 2H, ArH), 7.48-7.53 (m, 2H, PhH), 7.38-7.47 (m, 3H, PhH), 7.36 (d,  $J = 8.0$  Hz, 2H, ArH), 6.30 (s, 1H, H-2), 5.03 (s, 1H, -OH), 4.48 (ddt,  $J = 6.1, 6.9, 8.5$  Hz, 1H, H-5), 4.33 (dd,  $J = 6.2, 8.4$  Hz, 1H, H-4' exo), 3.69 (t,  $J = 8.5$  Hz, 1H, H-4' endo), 2.68 (dd,  $J = 6.1, 14.4$  Hz, 1H, H-6' endo), 2.42 (s, 3H, Ar-Me), 2.40 (dd,  $J = 7.0, 14.4$  Hz, 1H, H-6' exo);  $\delta_C$  (100 MHz, MeCN-d<sub>3</sub>) 198.95 (C-8), 174.27 (C-9), 145.88, 139.54, 131.77, 130.78, 130.23, 129.98, 129.63, 127.23 (ArC), 88.38 (C-7), 88.12 (C-2), 72.72 (C-4), 58.02 (C-5), 39.08 (C-6), 21.77 (Ar-Me);  $m/z$  (ESI+) 360.27 ( $[M+Na]^+$ , 65%); HRMS (ESI+) calculated for C<sub>20</sub>H<sub>19</sub>NNaO<sub>4</sub> ( $[M+Na]^+$ ) 360.1206, found 360.1222.

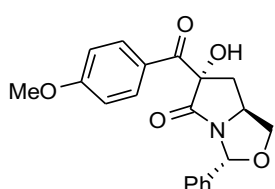
**(2*R*, 5*S*, 7*R*)-1-Aza-7-hydroxy-7-(4'-methylphenylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, (7*R*)-7a**



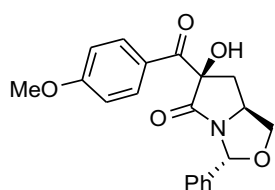
Product: 9 mg, 9%;  $R_f = 0.38$  (1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23} = +152.3$  ( $c = 1.03$  in CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max} / \text{cm}^{-1}$  (film) 3345 (br, -OH), 1702 (s, C=O), 1672 (s, C=O);  $\delta_H$  (400 MHz, MeCN-d<sub>3</sub>) 8.10 (d,  $J = 8.3$  Hz, 2H, ArH), 7.35-7.42 (m,

5H, PhH), 7.29 (d,  $J = 8.1$  Hz, 2H, ArH), 6.20 (s, 1H, H-2), 4.72 (s, 1H, -OH), 4.32 (dd,  $J = 6.1, 8.2$  Hz, 1H, H-4), 4.14 (apparent dq,  $J = 6.5, 8.3$  Hz, 1H, H-5), 3.63 (t,  $J = 8.3$  Hz, 1H, H-4'), 3.13 (dd,  $J = 6.5, 13.1$  Hz, 1H, H-6), 2.15 (s, 3H, Ar-Me), 2.12 (dd,  $J = 7.1, 13.2$  Hz, 1H, H-6' partially obscured by Ar-Me);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 197.86 (C-9), 173.89 (C-8), 145.59, 139.56, 132.38, 131.24, 129.93, 129.92, 129.56, 127.23, 127.01 (ArC), 89.29 (C-7), 88.12 (C-2), 73.43 (C-4), 56.34 (C-5), 40.05 (C-6), 21.74 (Ar-Me);  $m/z$  (ESI+) 360.26 ( $[M+Na]^+$ , 95%); HRMS (ESI+) calculated for  $C_{20}H_{19}NNaO_4$  ( $[M+Na]^+$ ) 360.1206, found 360.1218.

**(2*R*, 5*S*, 7*S*)-1-Aza-7-hydroxy-7-(4'-methoxyphenylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, (7*S*)-7b**



$R_f = 0.32$  (1:1 EtOAc:PE); colourless crystals, mp = 145-147°C;  $[\alpha]_D^{23} = +100.9$  ( $c = 0.83$  in  $CH_2Cl_2$ );  $\nu_{max} / cm^{-1}$  (film) 3404 (br, -OH), 1707 (s, C=O), 1665 (s, C=O), 1599;  $\delta_H$  (400 MHz, MeCN- $d_3$ ) 7.96 (d,  $J = 9.1$  Hz, 2H, ArH), 7.48-7.54 (m, 2H, PhH), 7.36-7.47 (m, 3H, PhH), 7.05 (d,  $J = 9.1$  Hz, 2H, ArH), 6.29 (s, 1H, H-2), 5.04 (s, 1H, -OH), 4.48 (ddt,  $J = 6.1, 7.0, 8.5$  Hz, 1H, H-5), 4.34 (dd,  $J = 6.3, 8.3$  Hz, 1H, H-4 exo), 3.88 (s, 3H, -OMe), 3.71 (t,  $J = 8.5$  Hz, 1H, H-4' endo), 2.69 (dd,  $J = 6.1, 14.4$  Hz, 1H, H-6 endo), 2.40 (dd,  $J = 7.0, 14.4$  Hz, 1H, H-6' exo);  $\delta_C$  (100 Mhz, MeCN- $d_3$ ) 197.41 (C-9), 174.36 (C-8), 165.04, 139.57, 133.28, 129.99, 129.65, 127.25, 126.80, 114.90 (ArC), 88.17 (C-7), 88.13 (C-2), 72.76 (C-4), 58.01 (C-5), 56.47 (-OMe), 39.30 (C-6);  $m/z$  (ESI+) 376.27 ( $[M+Na]^+$ , 55%); HRMS (ESI+) calculated for  $C_{20}H_{19}NNaO_5$  ( $[M+Na]^+$ ) 376.1155, found 376.1151.

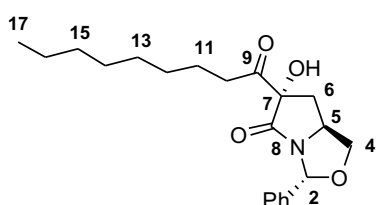


**(2*R*, 5*S*, 7*R*)-1-Aza-7-hydroxy-7-(4'-methoxyphenylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, (7*R*)-7b**

$R_f = 0.24$  (1:1 EtOAc:PE); colourless crystals, mp = 140-142°C;  $[\alpha]_D^{23} = +94.0$  ( $c = 0.51$  in  $CH_2Cl_2$ );  $\nu_{max} / cm^{-1}$  (film) 3404 (br, -OH), 1707 (s, C=O), 1665 (s, C=O), 1599;  $\delta_H$  (400 MHz, MeCN- $d_3$ ) 8.23 (d,  $J = 9.1$  Hz, 2H, ArH), 7.29-7.46 (m, 5H, PhH), 6.98 (d,  $J = 9.1$

Hz, 2H, ArH), 6.20 (s, 1H, H-2), 4.71 (s, 1H, -OH), 4.32 (dd,  $J = 6.0, 8.2$  Hz, 1H, H-4 exo), 4.14 (ddt,  $J = 6.2, 7.0, 8.4$  Hz, 1H, H-5), 3.86 (s, 3H, -OMe), 3.62 (t,  $J = 8.5$  Hz, 1H, H-4' endo), 3.14 (dd,  $J = 6.5, 13.0$  Hz, 1H, H-6 exo), 2.11 (dd,  $J = 7.1, 13.0$  Hz, 1H, H-6' endo);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 196.26 (C-9), 174.04 (C-8), 164.90, 139.58, 133.76, 129.91, 129.56, 127.54, 127.23, 114.53 (ArC), 89.26 (C-7), 88.12 (C-2), 73.46 (C-4), 56.37 (C-5), 56.35 (-OMe), 40.15 (C-6);  $m/z$  (ESI+) 376.26 ( $[M+Na]^+$ , 80%); HRMS (ESI+) calculated for  $C_{20}H_{19}NNaO_5$  ( $[M+Na]^+$ ) 376.1155, found 376.1165.

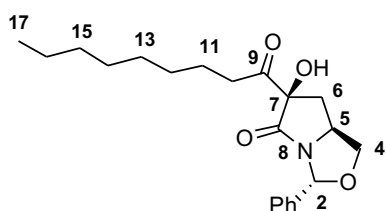
**(2*R*, 5*S*, 7*S*)-1-Aza-7-hydroxy-7-(octylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, (7*S*)-7c**



Scale of reaction: 90 mg (0.294 mmol), product: 25 mg, 24%;  $R_f = 0.53$  (1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23} = +106.6$  ( $c = 0.91$  in  $CH_2Cl_2$ );  $\nu_{max}$  /  $cm^{-1}$  (film) 3403 (br, -OH), 1719 (s, C=O), 1703 (s, C=O);

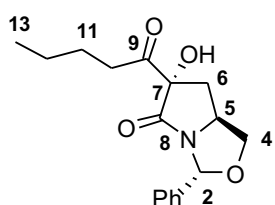
$\delta_H$  (400 MHz, MeCN- $d_3$ ) 7.38-7.47 (m, 5H, PhH), 6.12 (s, 1H, H-2), 4.67 (s, 1H, -OH), 4.30-4.39 (m, 2H, H-5, H-4), 3.63 (t,  $J = 8.1$  Hz, 1H, H-4'), 2.69 (dt,  $J = 7.2, 18.1$  Hz, 1H, H-10), 2.67 (dt,  $J = 7.2, 18.1$  Hz, 1H, H-10'), 2.51 (dd,  $J = 5.4, 14.3$  Hz, 1H, H-6), 2.24 (dd,  $J = 6.8, 14.2$  Hz, 1H, H-6'), 1.54-1.59 (m, 2H, H-11), 1.26-1.35 (m, 10H, H-12, H-13, H-14, H-15, H-16), 0.89 (t,  $J = 7.0$  Hz, 3H, H-17);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 210.13 (C-9), 174.17 (C-8), 139.74, 129.90, 129.57, 127.19 (PhC), 88.65 (C-7), 87.82 (C-2), 72.71 (C-4), 57.67 (C-5), 38.47 (C-10), 36.75 (C-6), 32.61, 30.11, 29.61, 29.77, 24.10 (C-11), 23.39 (C-12, C-13, C-14, C-15, C-16), 14.38 (C-17);  $m/z$  (ESI+) 382.38 ( $[M+Na]^+$ , 70%); HRMS (ESI+) calculated for  $C_{21}H_{29}NNaO_4$  ( $[M+Na]^+$ ) 382.1989, found 382.1996.

**(2*R*, 5*S*, 7*R*)-1-Aza-7-hydroxy-7-(octylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, (7*R*)-7c**



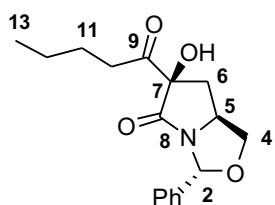
Product: 7 mg, 7%;  $R_f = 0.38$  (1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23} = +190.1$  ( $c = 0.73$  in  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}} / \text{cm}^{-1}$  (film) 3373 (br, -OH), 1694 (s, br with shoulder towards larger wavenumber, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{MeCN-d}_3$ ) 7.37-7.43 (m, 5H, PhH), 6.16 (s, 1H, H-2), 4.48 (s, 1H, -OH), 4.32 (dd,  $J = 6.0$ , 8.2 Hz, 1H, H-4), 4.13-4.20 (m, 1H, H-5), 3.57 (t,  $J = 8.4$  Hz, 1H, H-4'), 2.85 (dd,  $J = 6.8$ , 13.4 Hz, 1H, H-6), 2.67 (t,  $J = 7.2$  Hz, 2H, H-10), 1.97 (dd, 1H, H-6', partially obscured by  $\text{MeCN-d}_3$  signal), 1.48-1.55 (m, 2H, H-11), 1.19-1.34 (m, 10H, H-12, H-13, H-14, H-15, H-16), 0.87 (t,  $J = 7.0$  Hz, 3H, H-17);  $\delta_{\text{C}}$  (100 MHz,  $\text{MeCN-d}_3$ ) 209.29 (C-9), 173.26 (C-8), 139.62, 129.93, 129.57, 127.19 (PhC), 88.96 (C-7), 88.01 (C-2), 73.61 (C-4), 56.40 (C-5), 37.91 (C-6), 37.33 (C-10), 32.55, 30.02, 29.88, 29.71 (C-13, C-14, C-15, C-16), 24.02 (C-11), 23.36 (C-12), 14.38 (C-17);  $m/z$  (ESI+) 382.39 ( $[\text{M}+\text{Na}]^+$ , 70%); HRMS (ESI+) calculated for  $\text{C}_{21}\text{H}_{29}\text{NNaO}_4$  ( $[\text{M}+\text{Na}]^+$ ) 382.1989, found 382.1989.

**(2R, 5S, 7S)-1-Aza-7-(butylcarbonyl)-7-hydroxy-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, (7S)-7d**



Scale of reaction: 108 mg (0.353 mmol), product: 37 mg, 35%  $R_f = 0.53$  (1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23} = +137.0$  ( $c = 1.06$  in  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}} / \text{cm}^{-1}$  (film) 3405 (br, -OH), 1719 (s, C=O), 1701 (s, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{MeCN-d}_3$ ) 7.34-7.49 (m, 5H, PhH), 6.12 (s, 1H, H-2), 4.68 (s, 1H, -OH), 4.35-4.41 (m, 1H, H-5), 4.32 (dd,  $J = 6.1$ , 7.6 Hz, 1H, H-4), 3.63 (t,  $J = 8.1$  Hz, 1H, H-4'), 2.71 (dt,  $J = 7.2$ , 18.1 Hz, 1H, H-10), 2.69 (dt,  $J = 7.2$ , 18.1 Hz, 1H, H-10'), 2.51 (dd,  $J = 5.5$ , 14.3 Hz, 1H, H-6), 2.24 (dd,  $J = 6.9$ , 14.3 Hz, 1H, H-6'), 1.52-1.60 (m, 2H, H-11), 1.28-1.39 (m, 2H, H-12), 0.92 (t,  $J = 7.3$  Hz, 3H, H-13);  $\delta_{\text{C}}$  (100 MHz,  $\text{MeCN-d}_3$ ) 210.15 (C-9), 174.18 (C-8), 139.75, 129.91, 129.58, 127.20 (PhC), 88.67 (C-7), 87.82 (C-2), 72.71 (C-4), 57.67 (C-5), 38.20 (C-10), 36.76 (C-6), 26.11 (C-11), 22.88 (C-12), 14.16 (C-13);  $m/z$  (ESI+) 326.30 ( $[\text{M}+\text{Na}]^+$ , 50%); HRMS (ESI+) calculated for  $\text{C}_{17}\text{H}_{21}\text{NNaO}_4$  ( $[\text{M}+\text{Na}]^+$ ) 326.1363, found 326.1371.

**(2*R*, 5*S*, 7*R*)-1-Aza-7-(butylcarbonyl)-7-hydroxy-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, (7*R*)-7d**

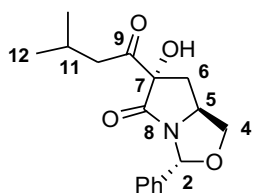


Product: 3 mg, 3%;  $R_f = 0.39$  (1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23} = +156.2$

( $c = 0.66$  in  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}} / \text{cm}^{-1}$  (film) 3383 (br, -OH), 1696 (s, br shoulder towards larger wavenumber, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{MeCN-d}_3$ ) 7.34-7.44 (m,

5H, PhH), 6.16 (s, 1H, H-2), 4.49 (s, 1H, -OH), 4.32 (dd,  $J = 6.0, 8.2$  Hz, 1H, H-4), 4.16 (apparent dq,  $J = 6.8, 8.5$  Hz, 1H, H-5), 3.57 (t,  $J = 8.4$  Hz, 1H, H-4'), 2.85 (dd,  $J = 6.8, 13.4$  Hz, 1H, H-6), 2.68 (t,  $J = 7.2$  Hz, 2H, H-10), 1.95 (dd,  $J = 6.9$  Hz, 1H, H-6', partially obscured by  $\text{MeCN-d}_3$  signal), 1.44-1.55 (m, 2H, H-11), 1.19-1.31 (m, 2H, H-12), 0.85 (t,  $J = 7.4$  Hz, 3H, H-13);  $\delta_{\text{C}}$  (100 MHz,  $\text{MeCN-d}_3$ ) 209.36 (C-9), 173.27 (C-8), 139.61, 130.56, 129.93, 129.58, 127.20 (PhC), 88.96 (C-7), 88.01 (C-2), 73.60 (C-4), 56.40 (C-5), 37.95 (C-6), 37.08 (C-10), 26.13 (C-11), 22.83 (C-12), 14.08 (C-13);  $m/z$  (ESI+) 326.26 ( $[\text{M}+\text{Na}]^+$ , 65%); HRMS (ESI+) calculated for  $\text{C}_{17}\text{H}_{21}\text{NNaO}_4$  ( $[\text{M}+\text{Na}]^+$ ) 326.1363, found 326.1373.

**(2*R*, 5*S*, 7*S*)-1-Aza-7-hydroxy-7-(isobutylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, (7*S*)-7e**



Scale of reaction: 86 mg (0.281 mmol), product: 5 mg, 6%;  $R_f = 0.57$  (1:1

EtOAc/PE); colourless oil;  $[\alpha]_D^{23} = +180.3$  ( $c = 0.57$  in  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}} / \text{cm}^{-1}$

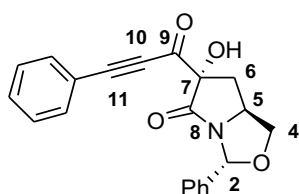
(film) 3404 (br, -OH), 1718 (s, C=O), 1700 (s, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{MeCN-d}_3$ )

7.35-7.49 (m, 5H, PhH), 6.12 (s, 1H, H-2), 4.66 (s, 1H, -OH), 4.29-4.40 (m, 2H, H-5, H-4), 3.63 (t,  $J = 8.0$  Hz, 1H, H-4'), 2.64 (dd,  $J = 6.7, 17.9$  Hz, 1H, H-10), 2.56 (dd,  $J = 6.7, 17.9$  Hz, 1H, H-10'), 2.50 (dd,  $J = 5.5, 14.3$  Hz, 1H, H-6), 2.23 (dd,  $J = 6.9, 14.3$  Hz, 1H, H-6'), 2.13-2.18 (m, 1H, H-11), 0.94 (d,  $J = 3.5$  Hz, 3H, H-12), 0.92 (d,  $J = 3.5$  Hz, 3H, H-12');  $\delta_{\text{C}}$  (100 MHz,  $\text{MeCN-d}_3$ ) 209.63 (C-9), 174.08 (C-8), 139.77, 129.90, 129.58, 127.20 (PhC), 88.65 (C-7), 87.82 (C-2), 72.71 (C-4), 57.63 (C-5), 47.15 (C-10), 36.69 (C-6), 24.73 (C-11), 22.75, 22.68 (C-12, C-12');  $m/z$  (ESI+)



326.31 ( $[M+Na]^+$ , 100%); HRMS (ESI+) calculated for  $C_{17}H_{21}NNaO_4$  ( $[M+Na]^+$ ) 327.1396, found 327.1415.

**(2*R*, 5*S*, 7*S*)-1-Aza-7-hydroxy-7-(phenylacetylenecarbonyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, (7*S*)-7f**



Scale of reaction: 99 mg (0.323 mmol), product: 55 mg, 49%;  $R_f$  = 0.54

(1:1 EtOAc:PE); white solid, mp = 154-156°C;  $[\alpha]_D^{23}$  = +151.1 ( $c$  = 1.12 in

$CH_2Cl_2$ );  $\nu_{max}$  /  $cm^{-1}$  (film) 3405 (br, -OH), 2195 (s, alkyne), 1710 (s,

C=O), 1675 (s, C=O);  $\delta_H$  (400 MHz,  $MeCN-d_3$ ) 7.66-7.71 (m, 2H, PhH), 7.57-7.63 (m, 1H, PhH),

7.36-7.56 (m, 7H, PhH), 6.24 (s, 1H, H-2), 4.85 (s, 1H, -OH), 4.46 (ddt,  $J$  = 5.6, 6.7, 8.1 Hz, 1H, H-

5), 4.39 (dd,  $J$  = 6.1, 7.9 Hz, 1H, H-4), 3.73 (t,  $J$  = 8.3 Hz, 1H, H-4'), 2.83 (dd,  $J$  = 5.4, 14.7 Hz,

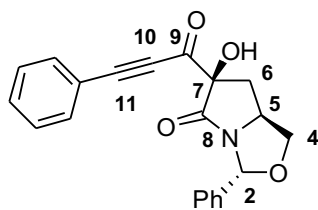
1H, H-6), 2.44 (dd,  $J$  = 7.0, 14.6 Hz, 1H, H-6');  $\delta_C$  (100 MHz,  $MeCN-d_3$ ) 186.07 (C-9), 173.34 (C-

8), 139.51, 134.26, 132.85, 130.09, 129.99, 129.62, 127.19, 119.78 (PhC), 97.87 (C-11), 89.92 (C-

7), 88.13 (C-2), 85.99 (C-10), 72.96 (C-4), 57.73 (C-5), 36.98 (C-6);  $m/z$  (ESI+) 370.29 ( $[M+Na]^+$ ,

100%); HRMS (ESI+) calculated for  $C_{21}H_{18}NO_4$  ( $[M+H]^+$ ) 348.1230, found 348.1224.

**(2*R*, 5*S*, 7*R*)-1-Aza-7-hydroxy-7-(phenylacetylenecarbonyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, (7*R*)-7f**



Product: 25 mg, 22%;  $R_f$  = 0.39 (1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23}$  =

+42.9 ( $c$  = 1.08 in  $CH_2Cl_2$ );  $\nu_{max}$  /  $cm^{-1}$  (film) 3404 (br, -OH), 2195 (s,

alkyne), 1715 (s, C=O), 1666 (s, C=O);  $\delta_H$  (400 MHz,  $MeCN-d_3$ ) 7.52-

7.58 (m, 1H, PhH), 7.39-7.48 (m, 6H, PhH), 7.28-7.34 (m, 3H, PhH),

6.25 (s, 1H, H-2), 4.74 (s, 1H, -OH), 4.30-4.46 (m, 2H, H-4, H-5), 3.66 (t,  $J$  = 7.8 Hz, 1H, H-4'),

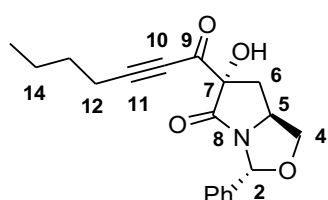
3.07 (dd,  $J$  = 7.0, 14.0 Hz, 1H, H-6), 2.17 (dd,  $J$  = 6.6, 14.0 Hz, 1H, H-6');  $\delta_C$  (100 MHz,  $MeCN-d_3$ )

185.02 (C-9), 171.58 (C-8), 139.60, 134.15, 132.76, 129.99, 129.96, 129.58, 127.10, 119.60 (PhC),

97.05 (C-11), 90.10 (C-7), 87.91 (C-2), 85.08 (C-10), 73.72 (C-4), 56.45 (C-5), 37.17 (C-6);  $m/z$

(ESI+) 370.31 ( $[M+Na]^+$ , 100%); HRMS (ESI+) calculated for  $C_{21}H_{18}NO_4$  ( $[M+H]^+$ ) 348.1230, found 348.1232.

**(2*R*, 5*S*, 7*S*)-1-Aza-7-hydroxy-7-(butylacetylenecarbonyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, (7*S*)-7g**



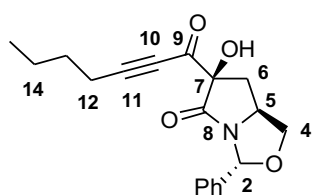
Scale of reaction: 100 mg (0.326 mmol), product: 53 mg, 50%;  $R_f$  = 0.51

(1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23}$  = +176.9 ( $c$  = 1.28 in  $CH_2Cl_2$ );  $\nu_{max}$

/  $cm^{-1}$  (film) 3416 (br, -OH), 2211 (s, alkyne), 1712 (s, C=O), 1680 (s,

C=O);  $\delta_H$  (400 MHz,  $MeCN-d_3$ ) 7.37-7.49 (m, 5H, PhH), 6.15 (s, 1H, H-2), 4.71 (d,  $J$  = 0.9 Hz, 1H, -OH), 4.34-4.46 (m, 2H, H-5, H-4), 3.65 (t,  $J$  = 7.8 Hz, 1H, H-4'), 2.74 (dd,  $J$  = 4.9, 14.6 Hz, 1H, H-6), 2.51 (t,  $J$  = 7.0 Hz, 2H, H-12), 2.35 (dd,  $J$  = 7.1, 14.6 Hz, 1H, H-6'), 1.54-1.65 (m, 2H, H-13), 1.39-1.51 (m, 2H, H-14), 0.95 (t,  $J$  = 7.3 Hz, 3H, H-15);  $\delta_C$  (100 MHz,  $MeCN-d_3$ ) 185.89 (C-9), 173.23 (C-8), 139.55, 129.98, 129.61, 127.17 (PhC), 103.23 (C-11), 89.90 (C-7), 88.07 (C-2), 78.75 (C-10), 72.94 (C-4), 57.78 (C-5), 36.76 (C-6), 30.22 (C-13), 22.70 (C-14), 19.36 (C-12), 13.75 (C-15);  $m/z$  (ESI+) 350.30 ( $[M+Na]^+$ , 100%); HRMS (ESI+) calculated for  $C_{19}H_{21}NNaO_4$  ( $[M+Na]^+$ ) 350.1363, found 350.1356.

**(2*R*, 5*S*, 7*R*)-1-Aza-7-hydroxy-7-(butylacetylenecarbonyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, (7*R*)-7g**



Product: 17 mg, 16%;  $R_f$  = 0.37 (1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23}$  =

+122.0 ( $c$  = 0.95 in  $CH_2Cl_2$ );  $\nu_{max}$  /  $cm^{-1}$  (film) 3420 (br, -OH), 2210 (s,

alkyne), 1718 (s, C=O), 1670 (s, C=O);  $\delta_H$  (400 MHz,  $MeCN-d_3$ ) 7.34-

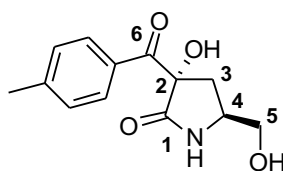
7.48 (m, 5H, PhH), 6.21 (s, 1H, H-2), 4.60 (s, 1H, -OH), 4.37 (dd,  $J$  = 6.0, 8.0 Hz, 1H, H-4), 4.22 (apparent dq,  $J$  = 6.7, 8.7 Hz, 1H, H-5), 3.62 (t,  $J$  = 8.4 Hz, 1H, H-4'), 2.96 (dd,  $J$  = 7.0, 13.9 Hz, 1H, H-6), 2.38 (t,  $J$  = 7.1 Hz, 2H, H-12), 2.10 (dd,  $J$  = 6.6, 14.0 Hz, 1H, H-6'), 1.41-1.50 (m, 2H, H-13), 1.26-1.39 (m, 2H, H-14), 0.85 (t,  $J$  = 7.3 Hz, 3H, H-15);  $\delta_C$  (100 MHz,  $MeCN-d_3$ ) 185.08

(C-9), 171.68 (C-8), 139.64, 129.96, 129.60, 127.11 (PhC), 102.49 (C-11), 89.90 (C-7), 87.96 (C-2), 77.77 (C-10), 73.61 (C-4), 56.45 (C-5), 37.07 (C-6), 30.17 (C-13), 22.71 (C-14), 19.34 (C-12), 13.69 (C-15);  $m/z$  (ESI+) 350.31 ( $[M+Na]^+$ , 100%); HRMS (ESI+) calculated for  $C_{19}H_{21}NNaO_4$  ( $[M+Na]^+$ ) 350.1363, found 350.1372.

### General procedure for acidic oxazolidine hydrolysis to 2-hydroxypyrrolidinones (2S)-8a-g

To a stirred solution of (7S)-91/7a-g (1.0 eq.) in acetone (approx. concentration 0.06 M, with one small drop of water) at r.t. was added Amberlyst 15 (3.0 eq.). After stirring at r.t. for 22-24 h, the reaction mixture was filtered and the resin rinsed with acetone. The solvent was evaporated to give the crude, which was purified via silica gel flash column chromatography (Eluent: EtOAc, then 5% MeOH/EtOAc) to give the respective product.

### (2S, 4R)-2-Hydroxy-2-(4'-methylphenylcarbonyl)-4-hydroxymethyl-1-oxo-pyrrolidinone, (2S)-8a



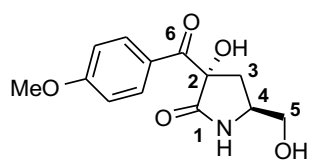
Scale of reaction: 37 mg (0.110 mmol), product: 23 mg, 83%;  $R_f$  = 0.19

(EtOAc); white solid, mp = 179-180°C;  $[\alpha]_D^{23}$  = +17.4 ( $c$  = 0.95 in MeOH);

$\nu_{max}$  /  $cm^{-1}$  (film) 3496 (br, -NH-), 3276 (br, -OH), 1685 (s, C=O), 1673 (s,

C=O);  $\delta_H$  (400 MHz, Acetone- $d_6$ ) 8.02 (d,  $J$  = 8.3 Hz, 2H, ArH), 7.41 (br s, 1H, -NH-), 7.30 (d,  $J$  = 7.9 Hz, 2H, ArH), 5.30 (s, 1H, -OH), 4.13 (t,  $J$  = 5.4 Hz, 1H, -CH<sub>2</sub>OH), 3.90-4.01 (m, 1H, H-4), 3.72 (dd,  $J$  = 4.6, 10.9 Hz, 1H, H-5), 3.58 (dt,  $J$  = 4.6, 10.8 Hz, 1H, H-5'), 2.64 (dd,  $J$  = 6.6, 13.9 Hz, 1H, H-3), 2.40 (s, 3H, Ar-Me), 2.23 (dd,  $J$  = 7.3, 13.9 Hz, 1H, H-3');  $\delta_C$  (100 MHz, Acetone- $d_6$ ) 199.70 (C-6), 174.96 (C-1), 144.83, 132.25, 130.88, 129.74 (ArC), 83.54 (C-2), 64.85 (C-5), 54.49 (C-4), 38.03 (C-3), 21.58 (Ar-Me);  $m/z$  (ESI+) 272.22 ( $[M+Na]^+$ , 65%); HRMS (ESI+) calculated for  $C_{13}H_{16}NO_4$  ( $[M+H]^+$ ) 250.1074, found 250.1086.

**(2*S*, 4*R*)-2-Hydroxy-4-hydroxymethyl-2-(4'-methoxyphenylcarbonyl)-1-oxo-pyrrolidinone, (2*S*)-8b**



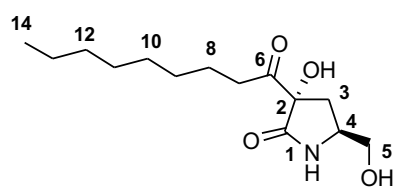
Scale of reaction: 15 mg (0.0424 mmol), product: 10 mg, 89%;  $R_f = 0.14$

(EtOAc); white solid, mp = 153-154°C;  $[\alpha]_D^{23} = -23.5$  ( $c = 0.56$  in MeCN);

$\nu_{\max} / \text{cm}^{-1}$  (film) 3481 (br, -NH-), 3285 (br, -OH), 1687 (s, C=O), 1667

(s, C=O);  $\delta_H$  (400 MHz, MeCN- $d_3$ ) 8.05 (d,  $J = 9.1$  Hz, 2H, ArH), 7.00 (d,  $J = 9.1$  Hz, 2H, ArH), 6.74 (br s, 1H, -NH-), 4.86 (s, 1H, -OH), 3.89-3.97 (m, 1H, H-4), 3.87 (s, 3H, -OMe), 3.66 (ddd,  $J = 3.9, 5.1, 11.4$  Hz, 1H, H-5), 3.46 (dt,  $J = 6.0, 11.6$  Hz, 1H, H-5'), 3.13 (dd,  $J = 5.1, 6.4$  Hz, 1H, -CH<sub>2</sub>OH), 2.53 (dd,  $J = 7.0, 14.1$  Hz, 1H, H-3), 2.18 (dd,  $J = 7.0, 14.3$  Hz, 1H, H-3', partially obscured by water signal);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 198.21 (C-6), 175.51 (C-1), 165.00, 133.19, 126.74, 114.77 (ArC), 83.18 (C-2), 64.30 (C-5), 56.42 (-OMe), 54.64 (C-4), 38.00 (C-3);  $m/z$  (ESI+) 288.23 ( $[M+Na]^+$ , 100%); HRMS (ESI+) calculated for C<sub>13</sub>H<sub>15</sub>NNaO<sub>5</sub> ( $[M+Na]^+$ ) 288.0842, found 288.0857.

**(2*S*, 4*R*)-2-Hydroxy-4-hydroxymethyl-2-(octylcarbonyl)-1-oxo-pyrrolidinone, (2*S*)-8c**



Scale of reaction: 15 mg (0.417 mmol), product: 11 mg, 97%;  $R_f =$

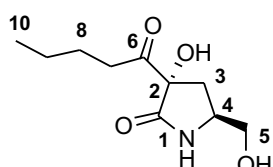
0.28 (EtOAc); colourless crystals, mp = 101-103°C;  $[\alpha]_D^{23} = +31.0$

( $c = 1.22$  in MeOH);  $\nu_{\max} / \text{cm}^{-1}$  (film) 3298 (br), 1716 (s, C=O),

1689 (s, C=O);  $\delta_H$  (400 MHz, MeCN- $d_3$ ) 6.61 (br s, 1H, -NH-), 4.42 (s, 1H, -OH), 3.77-3.83 (m, 1H, H-4), 3.61 (dt,  $J = 4.4, 11.3$  Hz, 1H, H-5), 3.44 (dt,  $J = 6.1, 11.1$  Hz, 1H, H-5'), 3.02 (dd,  $J = 5.1, 6.3$  Hz, 1H, -CH<sub>2</sub>OH), 2.68 (dt,  $J = 7.6, 17.9$  Hz, 1H, H-7), 2.56 (dt,  $J = 7.2, 17.9$  Hz, 1H, H-7'), 2.32 (dd,  $J = 6.3, 14.2$  Hz, 1H, H-3), 2.03 (dd,  $J = 7.6, 14.2$  Hz, 1H, H-3'), 1.50-1.57 (m, 2H, H-8), 1.25-1.31 (m, 10H, H-9, H-10, H-11, H-12, H-13), 0.89 (t,  $J = 7.0$  Hz, 3H, H-14);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 210.92 (C-6), 174.68 (C-1), 84.01 (C-2), 65.03 (C-5), 53.84 (C-4), 37.91 (C-7), 35.61 (C-3), 32.59, 30.09, 29.90, 29.79, 24.19 (C-8), 23.38 (C-9, C-10, C-11, C-12, C-13), 14.38

(C-14);  $m/z$  (ESI+) 294.30 ( $[M+Na]^+$ , 85%); HRMS (ESI+) calculated for  $C_{14}H_{26}NO_4$  ( $[M+H]^+$ ) 272.1856, found 272.1862.

**(2*S*, 4*R*)-2-(Butylcarbonyl)-2-hydroxy-4-hydroxymethyl-1-oxo-pyrrolidinone, (2*S*)-8d**

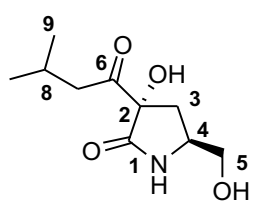


Scale of reaction: 37 mg (0.122 mmol), product: 24 mg, 91%;  $R_f$  = 0.19

(EtOAc); colourless oil;  $[\alpha]_D^{23}$  = +50.9 ( $c$  = 1.07 in MeOH);  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film)

3311 (br), 1716 (s, C=O), 1690 (s, C=O);  $\delta_H$  (400 MHz, MeCN- $d_3$ ) 6.81 (br s, 1H, -NH-), 4.57 (s, 1H, -OH), 3.77-3.84 (m, 1H, H-4), 3.61 (ddd,  $J$  = 4.1, 5.1, 11.2 Hz, 1H, H-5), 3.44 (dt,  $J$  = 6.3, 11.2 Hz, 1H, H-5'), 3.14 (dd,  $J$  = 5.1, 6.3 Hz, 1H, -CH<sub>2</sub>OH), 2.69 (dt,  $J$  = 7.3, 17.9 Hz, 1H, H-7), 2.58 (dt,  $J$  = 7.3, 18.0 Hz, 1H, H-7'), 2.31 (dd,  $J$  = 6.2, 14.2 Hz, 1H, H-3), 2.04 (dd,  $J$  = 7.6, 14.2 Hz, 1H, H-3'), 1.47-1.58 (m, 2H, H-8), 1.24-1.36 (m, 2H, H-9), 0.89 (t,  $J$  = 7.4 Hz, 3H, H-10);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 211.01 (C-6), 174.98 (C-1), 84.07 (C-2), 65.04 (C-5), 53.92 (C-4), 37.67 (C-7), 35.64 (C-3), 26.28 (C-8), 22.89 (C-9), 14.15 (C-10);  $m/z$  (ESI+) 238.23 ( $[M+Na]^+$ , 40%); HRMS (ESI+) calculated for  $C_{10}H_{18}NO_4$  ( $[M+H]^+$ ) 216.1230, found 216.1241.

**(2*S*, 4*R*)-2-Hydroxy-4-hydroxymethyl-2-(isobutylcarbonyl)-1-oxo-pyrrolidinone, (2*S*)-8e**



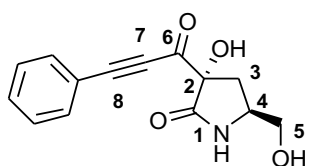
Scale of reaction: 5 mg (0.0165 mmol), product: 3 mg, 90%;  $R_f$  = 0.16

(EtOAc); colourless oil;  $[\alpha]_D^{23}$  = +50.9 ( $c$  = 0.70 in MeOH);  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film)

3295 (br), 1716 (s, C=O), 1690 (s, C=O);  $\delta_H$  (400 MHz, MeCN- $d_3$ ) 6.66 (br s, 1H, -NH-), 4.46 (br s, 1H, -OH), 3.80-3.86 (m, 1H, H-4), 3.64 (dd,  $J$  = 4.2, 11.2 Hz, 1H, H-5), 3.47 (dd,  $J$  = 6.2, 11.2 Hz, 1H, H-5'), 3.12 (br s, 1H, -OH), 2.62 (dd,  $J$  = 6.7, 17.7 Hz, 1H, H-7), 2.49 (dd,  $J$  = 6.8, 17.7 Hz, 1H, H-7'), 2.34 (dd,  $J$  = 6.3, 14.2 Hz, 1H, H-3), 2.11-2.17 (m, 1H, H-8, partially obscured by water signal), 2.06 (dd,  $J$  = 6.3, 14.2 Hz, 1H, H-3'), 0.93 (d,  $J$  = 6.7 Hz, 3H, H-9), 0.92 (d,  $J$  = 6.7 Hz, 3H, H-9);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 210.39 (C-6), 174.61 (C-1), 84.04 (C-2), 65.05 (C-5), 53.83 (C-4), 46.66 (C-7), 35.52 (C-3), 24.76 (C-8), 22.74, 22.67 (C-9);  $m/z$  (ESI-)

214.22 ( $[M-H]^-$ , 55%); HRMS (ESI+) calculated for  $C_{10}H_{17}NNaO_4$  ( $[M+Na]^+$ ) 238.1050, found 238.1057.

**(2S, 4R)-2-Hydroxy-4-hydroxymethyl-2-(phenylacetylenecarbonyl)-1-oxo-pyrrolidinone, (2S)-8f**



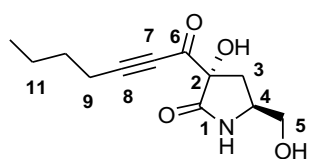
Scale of reaction: 82 mg (0.236 mmol), product: 52 mg, 85%;  $R_f$  = 0.27

(EtOAc); white solid, mp = 158-160°C;  $[\alpha]_D^{23}$  = -25.0 ( $c$  = 1.13 in MeOH);

$\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 3259 (br), 2195 (s, alkyne), 1697 (s, C=O), 1678 (s,

C=O);  $\delta_H$  (400 MHz,  $\text{MeCN-d}_3$ ) 7.63-7.70 (m, 2H, PhH), 7.53-7.60 (m, 1H, PhH), 7.44-7.51 (m, 2H, PhH), 6.78 (br s, 1H, -NH-), 4.61 (br s, 1H, -OH), 3.85-3.91 (m, 1H, H-4), 3.70 (ddd,  $J$  = 4.1, 5.0, 11.3 Hz, 1H, H-5), 3.52 (dt,  $J$  = 6.3, 11.3 Hz, 1H, H-5'), 3.13 (dd,  $J$  = 5.1, 6.4 Hz, 1H, -CH<sub>2</sub>OH), 2.69 (ddd,  $J$  = 1.0, 6.7, 14.3 Hz, 1H, H-3), 2.19 (ddd,  $J$  = 0.8, 7.3, 14.3 Hz, 1H, H-3');  $\delta_C$  (100 MHz,  $\text{MeCN-d}_3$ ) 187.33 (C-6), 173.62 (C-1), 134.24, 132.66, 130.00, 120.00 (PhC), 97.35 (C-8), 85.92 (C-7), 85.51 (C-2), 65.03 (C-5), 54.06 (C-4), 35.74 (C-3);  $m/z$  (ESI-) 258.20 ( $[M-H]^-$ , 70%); HRMS (ESI+) calculated for  $C_{14}H_{14}NO_4$  ( $[M+H]^+$ ) 260.0917, found 260.0911.

**(2S, 4R)-2-Hydroxy-4-hydroxymethyl-2-(butylacetylenecarbonyl)-1-oxo-pyrrolidinone, (2S)-8g**



Scale of reaction: 87 mg (0.266 mmol), product: 59 mg, 93%;  $R_f$  = 0.29

(EtOAc); colourless crystals, mp = 120-122°C;  $[\alpha]_D^{23}$  = +18.5 ( $c$  = 1.14 in

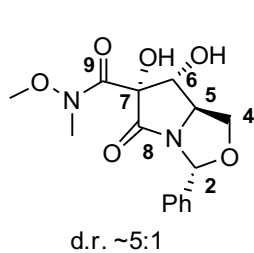
MeOH);  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 3328 (peak with broad base), 2209 (s, alkyne), 1698 (s, C=O), 1686 (s, C=O);  $\delta_H$  (400 MHz,  $\text{MeCN-d}_3$ ) 6.71 (br s, 1H, -NH-), 4.45 (br s, 1H, -OH), 3.76-3.88 (m, 1H, H-4), 3.63 (dt,  $J$  = 4.3, 11.0 Hz, 1H, H-5), 3.47 (dt,  $J$  = 6.1, 10.9 Hz, 1H, H-5'), 3.05 (t,  $J$  = 5.6 Hz, 1H, -CH<sub>2</sub>OH), 2.53 (dd,  $J$  = 6.8, 14.3 Hz, 1H, H-3), 2.47 (t,  $J$  = 7.0 Hz, 2H, H-9), 2.12 (dd,  $J$  = 7.3, 14.3 Hz, 1H, H-3'), 1.52-1.62 (m, 2H, H-10), 1.37-1.46 (m, 2H, H-11), 0.92 (t,  $J$  = 7.3 Hz, 3H, H-12);  $\delta_C$  (100 MHz,  $\text{MeCN-d}_3$ ) 187.27 (C-6), 173.54 (C-1), 102.59 (C-8), 85.30 (C-2), 78.59 (C-7),

65.48 (C-5), 54.04 (C-4), 35.88 (C-3), 30.26 (C-10), 22.67 (C-11), 19.34 (C-9), 13.74 (C-12);  $m/z$  (ESI<sup>+</sup>) 262.22 ([M+Na]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) calculated for C<sub>12</sub>H<sub>18</sub>NO<sub>4</sub> ([M+H]<sup>+</sup>) 240.1230, found 240.1241.

### Ru-catalysed dihydroxylation

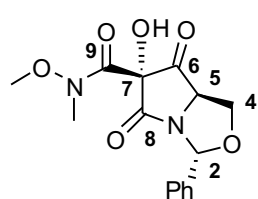
To a vigorously stirred solution of **9** (662 mg, 2.297 mmol, 1.0 eq.) in EtOAc/MeCN (1:1) (10 mL) at 0°C was added a solution of RuCl<sub>3</sub>.xH<sub>2</sub>O (33 mg, 0.161 mmol, 0.07 eq.) and NaIO<sub>4</sub> (737 mg, 3.45 mmol, 1.5 eq.) in distilled water (5 mL). The biphasic mixture was stirred vigorously for 20 min and quenched with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with EtOAc. The combined organic layers was dried with anhydrous MgSO<sub>4</sub>, filtered and the solvents removed *in vacuo* to give the crude. Purification via silica gel flash column chromatography (Eluent: 10% to 80% EtOAc/PE) gave diol **10** (513 mg, 69%) as a mixture diastereomers, and tetramic acid **11** (51 mg, 7%) as a single diastereomer.

### (2*R*, 5*S*, 6*R*, 7*R*)-1-Aza-6,7-dihydroxy-7-(*N,O*-dimethylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, **10**



$R_f$  = 0.49 (EtOAc); colourless oil;  $\nu_{\max}$  / cm<sup>-1</sup> (film) 3386 (br, -OH), 1716 (s, C=O), 1659 (s, C=O); Major diastereomer (*cis*-diol on *exo* face)  $\delta_H$  (400 MHz, MeCN-d<sub>3</sub>) 7.34-7.51 (m, 5H, PhH), 6.21 (s, 1H, H-2), 4.81 (br s, 1H, -OH C-7), 4.45 (d,  $J$  = 5.1 Hz, 1H, H-6), 4.38 (ddd,  $J$  = 0.6, 6.5, 8.5 Hz, 1H, H-4<sub>exo</sub>), 4.00 (ddd,  $J$  = 5.1, 6.5, 7.8 Hz, 1H, H-5), 3.75 (t,  $J$  = 8.0 Hz, 1H, H-4'<sub>endo</sub>), 3.68 (s, 3H, -OMe), 3.62 (br s, 1H, -OH C-6) 3.29 (s, 3H, -NMe);  $\delta_C$  (100 Mhz, MeCN-d<sub>3</sub>) 171.55 (C-8), 169.86 (C-9), 139.34, 129.95, 129.63, 127.15 (PhC), 88.00 (C-2), 83.12 (C-7), 73.71 (C-6), 71.22 (C-4), 66.29 (C-5), 61.17 (-OMe), 33.61 (-NMe);  $m/z$  (ESI<sup>+</sup>) 345.27 ([M+Na]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) calculated for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>6</sub> ([M+Na]<sup>+</sup>) 345.1057, found 345.1069.

**(2*R*, 5*S*, 7*R*)-1-Aza-2-(phenyl)-7-hydroxy-7-(*N,O*-dimethylcarbamoyl)-6,8-dioxo-3-oxabicyclo[3.3.0]-octane, **11****

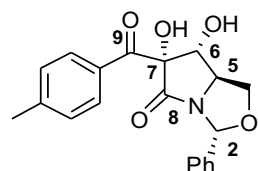


$R_f$  = 0.71 (EtOAc); colourless crystals, mp = 141-143°C;  $[\alpha]_D^{23}$  = +134.3 ( $c$  = 1.12 in  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  (film) 3350 (br, -OH), 1786 (s, C=O), 1718 (s, C=O), 1677 (s, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{MeCN-d}_3$ ) 7.36-7.53 (m, 5H, Ph), 6.69 (s, 1H, H-2), 5.34 (s, 1H, -OH), 4.74 (dd,  $J$  = 6.4, 8.8 Hz, 1H, H-5), 4.22 (apparent t,  $J$  = 8.7 Hz, 1H, H-4), 4.01 (dd,  $J$  = 6.4, 8.5 Hz, 1H, H-4'), 3.65 (s, 3H, -OMe), 3.25 (s, 3H, -NMe);  $\delta_{\text{C}}$  (100 MHz,  $\text{MeCN-d}_3$ ) 201.32 (C-6), 171.46 (C-8), 166.54 (C-9), 138.11, 130.10, 129.77, 126.95 (PhC), 89.24 (C-2), 79.18 (C-7), 66.93 (C-4), 65.23 (C-5), 61.68 (-OMe), 33.58 (-NMe);  $m/z$  (ESI-) 319.57 ( $[\text{M-H}]^-$ , 100%); HRMS (ESI-) calculated for  $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_6$  ( $[\text{M-H}]^-$ ) 319.0936, found 319.0937.

**Grignard reaction of unprotected diol **10****

Tolyl magnesium bromide (3.4 eq.) was reacted with the Weinreb lactam **10** according to the General Procedure and the reaction mixture was stirred at 0°C for 30 min, then r.t. for 1.5 h. Each of the *exo*- and *endo*-diastereomers of **97a/12a** was isolated (7% yield each).

**(2*R*, 5*S*, 6*R*, 7*S*)-1-Aza-6,7-dihydroxy-7-(4'-methylphenylcarbonyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, *exo* -**12a****



Scale of reaction: 52 mg (0.161 mmol), product: 4 mg, 7%;  $R_f$  = 0.50 (1:1

EtOAc:PE); white waxy oil;  $[\alpha]_D^{23}$  = +120.0 ( $c$  = 0.70 in  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$

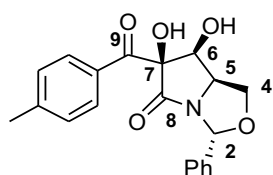
(film) 3359 (br, -OH), 1728 (s, C=O), 1669 (s, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{MeCN-d}_3$ )

7.80 (d,  $J$  = 8.0 Hz, 2H, ArH), 7.39-7.53 (m, 5H, PhH), 7.36 (d,  $J$  = 8.0 Hz, 2H, ArH), 6.31 (s, 1H, H-2), 4.96 (br s, 1H, -OH), 4.72 (d,  $J$  = 5.9 Hz, 1H, H-6), 4.39 (ddd,  $J$  = 0.6, 6.4, 8.7 Hz, 1H, H-4<sub>exo</sub>), 4.17 (dt,  $J$  = 6.1, 7.2 Hz, 1H, H-5), 3.95 (dd,  $J$  = 7.3, 8.7 Hz, 1H, H-4<sub>endo</sub>), 3.88 (br s, 1H, -OH), 2.43 (s, 3H, Ar-Me);  $\delta_{\text{C}}$  (100 MHz,  $\text{MeCN-d}_3$ ) 198.03 (C-9), 172.51 (C-8), 146.04, 139.03, 132.19, 130.97, 130.20, 130.07, 129.66, 127.29 (ArC), 88.96 (C-7), 88.11 (C-2), 76.31 (C-6), 70.93



(C-4), 65.07 (C-5), 21.77 (Ar-Me);  $m/z$  (ESI+) 376.27 ( $[M+Na]^+$ , 35%); HRMS (ESI+) calculated for  $C_{20}H_{19}NNaO_5$  ( $[M+Na]^+$ ) 376.1155, found 376.1140.

**(2*R*, 5*S*, 6*S*, 7*S*)-1-Aza-6,7-dihydroxy-7-(4'-methylphenylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, *endo* -12a**



Product: 4 mg, 7%;  $R_f$  = 0.38 (1:1 EtOAc:PE); white solid, mp = 163°C

decomposes to brown liquid;  $[\alpha]_D^{23}$  = +138.9 ( $c$  = 0.70 in  $CH_2Cl_2$ );  $\nu_{max}$  /  $cm^{-1}$

(film) 3362 (br, -OH), 1709 (s, C=O), 1669 (s, C=O);  $\delta_H$  (400 MHz, MeCN-

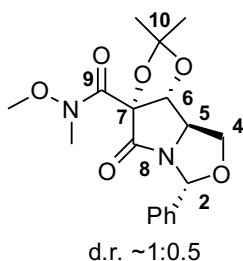
$d_3$ ) 8.15 (d,  $J$  = 8.0 Hz, 2H, ArH), 7.33-7.39 (m, 5H, PhH), 7.31 (d,  $J$  = 8.0 Hz, 2H, ArH), 6.22 (s, 1H, H-2), 4.69 (d,  $J$  = 4.0 Hz, 1H, H-6), 4.37 (dt,  $J$  = 4.0, 7.0 Hz, 1H, H-5), 4.17 (dd,  $J$  = 6.8, 8.5 Hz, 1H, H-4<sub>endo</sub>), 4.07 (dd,  $J$  = 7.2, 8.4 Hz, 1H, H-4<sub>exo</sub>), 2.40 (s, 3H, Ar-Me);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 196.26 (C-9), 173.30 (C-8), 145.86, 139.27, 133.06, 131.45, 129.88, 129.84, 129.55, 127.14 (ArC), 90.35 (C-7), 88.08 (C-2), 72.79 (C-6), 66.02 (C-4), 61.42 (C-5), 21.77 (Ar-Me);  $m/z$  (ESI+) 376.35 ( $[M+Na]^+$ , 50%); HRMS (ESI+) calculated for  $C_{20}H_{19}NNaO_5$  ( $[M+Na]^+$ ) 376.1155, found 376.1141.

**(2*R*, 5*S*, 6*R*, 7*R*)-1-Aza-6,7-(isopropylidene)dioxy-7-(*N,O*-dimethylcarbamoyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, 13**

To a solution of **10** (176 mg, 0.546 mmol, 1.0 eq.) in acetone (8 ml), were added 2,2-dimethoxypropane (0.34 mL, 2.730 mmol, 5 eq.), and *p*-TsOH·H<sub>2</sub>O (4 mg, 0.0218 mmol, 0.04 eq.) at r.t.. The mixture was stirred at 55°C for 6 h. The reaction solvent was evaporated give the crude.

Purification via silica gel flash column chromatography (Eluent: 10% to 50% EtOAc/PE) gave the acetone **13** as a colourless oil (86 mg, 44%), and unreacted **10** was recovered

(33 mg, d.r. = 1:0.5).  $R_f$  = 0.35 (1:1 EtOAc/PE); colourless oil;  $\nu_{max}$  /  $cm^{-1}$



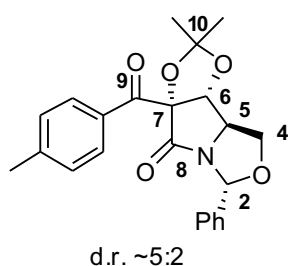
(film) 1721 (s, C=O), 1687 (s, C=O);  $\delta_H$  (400 MHz, MeCN- $d_3$ , 303K) 7.34-

7.50 (m, 5H, PhH), 6.33 (br s, 0.7H, H-2), 6.16 (s, 0.3H, H-2), 5.03 (br s, 0.7H,

d.r. ~1:0.5

H-6), 4.95 (d,  $J = 4.9$  Hz, 0.3H, H-6), 4.33 (t,  $J = 7.8$  Hz, 1H, H-4), 4.20 (dd,  $J = 6.7, 8.1$  Hz, 0.3H, H-4'), 4.05-4.15 (m, 1H, H-5), 3.69 (t,  $J = 8.3$  Hz, 0.7H, H-4'), 3.64 (s, 2H, -OMe), 3.43 (br s, 1H, -OMe), 3.24 (br s, 3H, -NMe), 1.51 (s, 3H, -CMe), 1.44 (s, 2H, -CMe), 1.37 (s, 1H, -CMe);  $\delta_C$  (100 MHz, MeCN- $d_3$ , 303K) 172.26 (v br, C-8), 168.39 (v br, C-9), 139.66, 139.43, 129.97, 129.82, 129.71, 129.67, 129.56, 127.28, 126.78 (PhC), 115.43 (C-10), 92.00 (C-7), 88.42, 88.34 (C-2), 82.76, 78.92 (br, C-6), 69.50, 66.58 (C-4), 66.10 (br, C-5), 60.73, 60.00 (-OMe), 33.66 (v br, -NMe), 28.35, 27.88, 27.30, 25.79 (Me of acetonide);  $\delta_H$  (400 MHz, MeCN- $d_3$ , 338K) 7.34-7.51 (m, 5H, PhH), 6.33 (s, 0.7H, H-2), 6.17 (s, 0.3H, H-2), 5.03 (d,  $J = 1.6$  Hz, 0.7H, H-6), 4.95 (d,  $J = 4.8$  Hz, 0.3H, H-6), 4.33 (t,  $J = 7.7$  Hz, 1H, H-4), 4.21 (dd,  $J = 6.8, 8.3$  Hz, 0.3H, H-4'), 4.05-4.14 (m, 1H, H-5), 3.72 (t,  $J = 8.3$  Hz, 0.7H, H-4'), 3.66 (s, 2H, -OMe), 3.50 (s, 1H, -OMe), 3.28 (s, 3H, -NMe), 1.52 (s, 3H, -CMe), 1.46 (s, 2H, -CMe), 1.41 (s, 1H, -CMe);  $\delta_C$  (100 MHz, MeCN- $d_3$ , 338K) 173.07, 170.97 (C-8), 168.63 (C-9), 139.98, 139.74, 130.10, 129.97, 129.88, 129.83, 129.73, 127.44, 126.99 (PhC), 117.43, 115.75 (C-10), 93.79, 92.34 (C-7), 88.83, 88.67 (C-2), 82.89, 79.47 (C-6), 69.65, 66.74 (C-4), 66.23, 61.83 (C-5), 61.01, 60.16 (-OMe), 34.31 (v br, -NMe), 28.46, 27.82, 27.61, 26.15 (Me of acetonide);  $m/z$  (ESI+) 385.23 ( $[M+Na]^+$ , 60%); HRMS (ESI+) calculated for  $C_{18}H_{22}N_2NaO_6$  ( $[M+Na]^+$ ) 385.1370, found 385.1387.

**(2R, 5S, 6R, 7S)-1-Aza-6,7-(isopropylidene)dioxy-7-(4'-methylphenylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, 14**



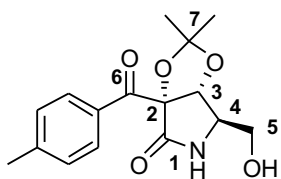
Tolyl magnesium bromide and the Grignard reaction were synthesised and carried out as described on p. 165. 1.3 eq. of the Grignard reagent was used and the reaction mixture was stirred at 0°C to r.t. over 1 h. Scale of reaction: 70 mg (0.198 mmol), product: 48 mg, 63%;  $R_f = 0.45$  (30% EtOAc/PE);

colourless oil;  $\nu_{max}$  /  $cm^{-1}$  (film) 1719 (s, C=O), 1666 (s, C=O); Major diastereomer:  $\delta_H$  (400 MHz, MeCN- $d_3$ ) 8.13 (d,  $J = 8.3$  Hz, 2H, ArH), 7.31-7.48 (m, 7H, PhH and ArH), 6.15 (s, 1H, H-2), 5.14 (s, 1H, H-6), 4.42 (dd,  $J = 6.6, 8.1$  Hz, 1H, H-4), 4.07-4.25 (m, 1H, H-5), 3.80 (dd,  $J =$

8.1, 10.0 Hz, 1H, H-4'), 2.43 (s, 3H, Ar-Me), 1.53 (s, 3H, C-Me), 1.13 (s, 3H, C-Me);  $\delta_c$  (100 MHz, MeCN-d<sub>3</sub>) 199.15 (C-9), 174.44 (C-8), 146.21, 139.64, 133.33, 131.90, 129.91, 129.64, 126.94 (ArC), 115.84 (C-10), 96.24 (C-7), 89.19 (C-2), 80.14 (C-6), 68.51 (C-4), 64.52 (C-5), 26.88, 25.73 (2x C-Me), 21.84 (Ar-Me);  $m/z$  (ESI+) 416.39 ([M+Na]<sup>+</sup>, 65%); HRMS (ESI+) calculated for C<sub>23</sub>H<sub>23</sub>NNaO<sub>5</sub> ([M+Na]<sup>+</sup>) 416.1468, found 416.1453.

**(2*S*, 3*R*, 4*R*)-2,3-(isopropylidene)dioxy-2-(4'-methylphenylcarbonyl)-4-hydroxymethyl-1-oxo-pyrrolidinone, **15****

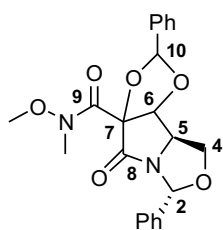
Condition A: TFA (5  $\mu$ L, 0.635 mmol, 10 eq.) was added to a solution of **14** (25 mg, 0.0635 mmol, 1.0 eq.) in THF (1.5 mL with a drop of water) at r.t. and the reaction mixture stirred for 20 h. Solvent was evaporated to give the crude, followed by purification via silica gel flash column chromatography (eluent: EtOAc/PE, 10% to 50%) gave **15** (6.5 mg, 34%, d.r. ~ 1:0.3 about the diol).



Condition B: A solution of **14** (17.5 mg, 0.0445 mmol, 1.0 eq.), 2 M aq. HCl (88  $\mu$ L, 0.089 mmol, 4 eq.) and MeOH (1 mL) was stirred at r.t. for 6 h. Solvents were evaporated to give the crude, followed by purification via

silica gel flash column chromatography (Eluent: EtOAc/PE, 10% to 50%) gave **15** (3 mg, 25%, one diastereomer).  $R_f$  = 0.21 (1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23}$  = -91.0 ( $c$  = 0.50 in CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}$  / cm<sup>-1</sup> (film) 3319 (br, -OH), 1708 (s, C=O), 1666 (s, C=O);  $\delta_H$  (400 MHz, MeCN-d<sub>3</sub>) 8.14 (d,  $J$  = 8.3 Hz, 2H, ArH), 7.33 (d,  $J$  = 8.0 Hz, 2H, ArH), 6.65 (br s, 1H, -NH-), 4.85 (s, 1H, H-3), 3.58-3.74 (m, 3H, H-4 and H-5), 2.42 (s, 3H, Ar-Me), 1.49 (s, 3H, C-Me), 1.13 (s, 3H, C-Me);  $\delta_c$  (100 MHz, MeCN-d<sub>3</sub>) 199.03 (C-6), 171.59 (C-1), 145.87, 133.57, 131.96, 129.74 (ArC), 114.45 (C-7), 92.89 (C-2), 82.19 (C-3), 63.51 (C-5), 60.45 (C-4), 26.92, 25.38 (2x C-Me), 21.81 (Ar-Me);  $m/z$  (ESI+) 328.26 ([M+Na]<sup>+</sup>, 70%); HRMS (ESI+) calculated for C<sub>16</sub>H<sub>19</sub>NNaO<sub>5</sub> ([M+Na]<sup>+</sup>) 328.1155, found 328.1164.

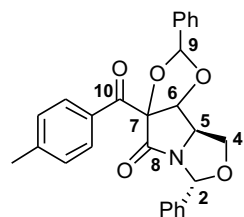
**(2R, 5S)-1-Aza-6,7-(phenylidene)dioxy-7-(*N,O*-dimethylcarbamoyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, **16****



To a solution of **10** (136 mg, 0.422 mmol, 1.0 eq.) in toluene (6 mL), were added benzaldehyde dimethyl acetal (158  $\mu$ L, 1.055 mmol, 2.5 eq.), and *p*-TsOH·H<sub>2</sub>O (3.2 mg, 0.0169 mmol, 0.04 eq.) at r.t.. The mixture was stirred at 65°C for 5.5 h, and the solvents evaporated to give crude. Purification via silica gel flash

column chromatography (Eluent: 10% to 45% EtOAc/PE) gave **16** (96.1 mg, 56%).  $R_f$  = 0.47 and 0.54 (2:1 EtOAc:PE); colourless oil;  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 1718 (s, C=O), 1683 (s, C=O);  $m/z$  (ESI+) 411.37 ( $[\text{M}+\text{H}]^+$ , 100%); HRMS (ESI+) calculated for  $\text{C}_{22}\text{H}_{22}\text{N}_2\text{NaO}_6$  ( $[\text{M}+\text{Na}]^+$ ) 433.1370, found 433.1384.

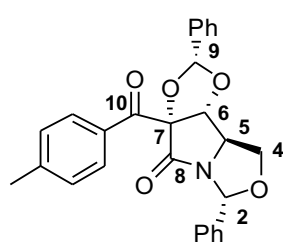
**(2R, 5S)-1-Aza-6,7-(phenylidene)dioxy-7-(4'-methylphenylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, **17****



Tolyl magnesium bromide and the Grignard reaction were synthesised and carried out as described on p. 165. The Grignard reagent in THF (1.3 eq., 0.304 mmol) was added to **16** (96 mg, 0.234 mmol, 1.0 eq.) in THF (2 mL) at 0°C.

The reaction mixture was stirred at 0°C for 45 min. It was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The combined organic layers were dried with anhydrous  $\text{MgSO}_4$ , filtered and the solvents removed *in vacuo* to give the crude product. Purification via silica gel flash column chromatography (Eluent: 5% to 45%, EtOAc/PE) gave **17** (50 mg, 48%).  $R_f$  = 0.46 (2:1 EtOAc:PE); colourless oil;  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 1718 (s, C=O), 1666 (s, C=O);  $m/z$  (ESI+) 442.66 ( $[\text{M}+\text{H}]^+$ , 100%); HRMS (ESI+) calculated for  $\text{C}_{27}\text{H}_{23}\text{NNaO}_5$  ( $[\text{M}+\text{Na}]^+$ ) 464.1468, found 464.1475.

**(2R, 5S, 6R, 7S, 9R)-1-Aza-6,7-(phenylidene)dioxy-7-(4'-methylphenylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, **17****



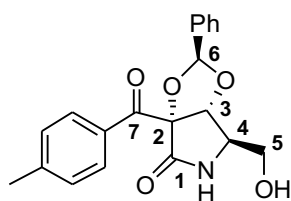
$R_f = 0.46$  (2:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23} = +320.7$  ( $c = 1.0$  in  $\text{CH}_2\text{Cl}_2$ );

$\nu_{\text{max}} / \text{cm}^{-1}$  (film) 1720 (s, C=O), 1666 (s, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{MeCN-d}_3$ )

8.17 (d,  $J = 8.3$  Hz, 2H, ArH), 7.46-7.57 (m, 5H, ArH), 7.29-7.45 (m, 7H, ArH), 6.31 (s, 1H, H-2), 6.13 (s, 1H, H-9), 5.20 (d,  $J = 4.4$  Hz, 1H, H-6),

4.58 (dt,  $J = 4.4, 7.2$  Hz, 1H, H-5), 4.23 (dd,  $J = 7.1, 8.3$  Hz, 1H, H-4), 4.16 (dd,  $J = 7.4, 8.6$  Hz, 1H, H-4'), 2.40 (s, 3H, Ar-Me);  $\delta_{\text{C}}$  (100 MHz,  $\text{MeCN-d}_3$ ) 195.14 (C-10), 171.38 (C-8), 146.63, 138.80, 136.79, 133.06, 131.70, 131.36, 130.09, 130.04, 139.66, 128.27, 127.18 (ArC), 108.25 (C-9), 98.15 (C-7), 88.36 (C-2), 81.52 (C-6), 66.21 (C-4), 59.52 (C-5), 21.87 (Ar-Me);  $m/z$  (ESI+) 442.64 ( $[\text{M}+\text{H}]^+$ , 100%); HRMS (ESI+) calculated for  $\text{C}_{27}\text{H}_{23}\text{NNaO}_5$  ( $[\text{M}+\text{Na}]^+$ ) 464.1468, found 464.1475.

**(2S, 3R, 4R, 6S)-2,3-(phenylidene)dioxy-2-(4'-methylphenylcarbonyl)-4-hydroxymethyl-1-oxo-pyrrolidinone, 18**

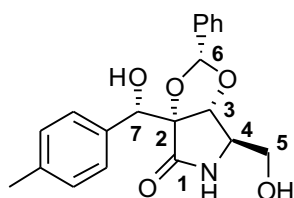


TFA (18  $\mu\text{L}$ , 2.265 mmol, 20 eq.) was added to **17** (50 mg, 0.113 mmol, 1 eq.) in  $\text{CH}_2\text{Cl}_2$  (1.5 mL) and the resulting pale yellow solution was stirred at r.t. for 5.5 h. The solvents were removed *in vacuo* to give the crude

which was purified via silica gel column chromatography (Eluent: 10% to 60% EtOAc/PE) to give a one fraction containing a diastereomeric mixture of **18** (13 mg) and one pure diastereomer of **18** (5 mg, 13%). One diastereomer of **17** was recovered (16%).  $R_f = 0.13$  (1:1 EtOAc:PE); colourless oil;  $[\alpha]_D^{23} = +23.4$  ( $c = 0.63$  in  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}} / \text{cm}^{-1}$  (film) 1714 (s, C=O), 1669 (s, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{MeCN-d}_3$ ) 8.09 (d,  $J = 8.3$  Hz, 2H, ArH), 7.32-7.48 (m, 5H, ArH), 7.30 (d,  $J = 8.3$  Hz, 2H, ArH), 6.97 (br s, 1H, -NH-), 6.15 (s, 1H, H-6), 4.97 (s, 1H, H-3), 3.81 (tt,  $J = 1.2, 6.4$  Hz, 1H, H-4), 3.60-3.72 (m, 2H, H-5 and H-5') 3.26 (dt,  $J = 1.3, 5.7$  Hz, 1H, -OH), 2.39 (s, 3H, Ar-Me);  $\delta_{\text{C}}$  (100 MHz,  $\text{MeCN-d}_3$ ) 196.51 (C-7), 170.62 (C-1), 145.96, 136.52, 133.46, 131.60, 130.98, 129.81, 129.47, 127.84 (ArC), 106.05 (C-6), 92.92 (C-2), 82.05 (C-3), 63.61 (C-4), 61.26 (C-5), 21.79 (Ar-

Me);  $m/z$  (ESI+) 376.56 ( $[M+Na]^+$ , 100%); HRMS (ESI+) calculated for  $C_{22}H_{19}NNaO_5$  ( $[M+Na]^+$ ) 376.1155, found 376.1172.

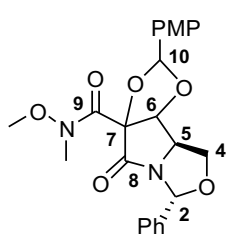
**(2*S*, 3*R*, 4*R*, 6*R*, 7*S*)-2,3-(phenylidene)dioxy-2-(hydroxymethyl-4'-methylphenylcarbonyl)-4-hydroxymethyl-1-oxo-pyrrolidinone, 19**



10% Pd/C (1.5 mg) was added to a diastereomeric mixture of **18** (13 mg, 0.0368 mmol) in EtOH (3 mL). The suspension was stirred at r.t. with bubbling of  $H_2$  (balloon) for 6 h, after which it was filtered over Celite and the residue rinsed with EtOAc. The solvent was evaporated to give the crude which was purified via silica gel flash column chromatography (Eluent: 10% to 60% EtOAc/PE) to give **19** (4 mg, 31%).  $R_f$  = 0.63 (EtOAc); fine white crystals, mp = 156-158°C;  $[\alpha]_D^{23}$  = +26.0 ( $c$  = 0.68 in MeOH);  $\nu_{max}$  /  $cm^{-1}$  (film) 3329 (br), 1695 (s, C=O);  $\delta_H$  (400 MHz, MeCN- $d_3$ ) 7.39-7.45 (m, 5H, PhH), 7.33 (d,  $J$  = 8.1 Hz, 2H, ArH), 7.19 (d,  $J$  = 7.9 Hz, 2H, ArH), 6.37 (br s, 1H, -NH-), 5.98 (s, 1H, H-6), 5.25 (d,  $J$  = 3.3 Hz, 1H, H-7), 4.55 (s, 1H, H-3), 4.25 (d,  $J$  = 3.3 Hz, 1H, C7 -OH), 3.42-3.46 (m, 1H, H-4), 2.86 (t,  $J$  = 5.6 Hz, 1H, C5 -OH), 2.49 (ddd,  $J$  = 5.5, 6.9, 10.9 Hz, 1H, H-5), 2.43 (ddd,  $J$  = 5.5, 6.9, 10.9 Hz, 1H, H-5'), 2.34 (s, 3H, Ar-Me);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 173.46 (C-1), 138.96, 137.82, 136.23, 130.71, 129.78, 129.40, 128.17, 127.81 (ArC), 107.28 (C-6), 90.00 (C-2), 79.27 (C-3), 73.22 (C-7), 62.64 (C-5), 60.27 (C-4), 21.22 (Ar-Me);  $m/z$  (ESI+) 354.65 ( $[M-H]^-$ , 100%); HRMS (ESI+) calculated for  $C_{20}H_{21}NNaO_5$  ( $[M+Na]^+$ ) 378.1312, found 378.1323.

**(2*R*, 5*S*)-1-Aza-6,7-(4'-methoxyphenylidene)dioxy-7-(*N,O*-dimethylcarbamoyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, 20**

To a solution of **10** (513 mg, 1.592 mmol 1.0 eq.) in toluene (12 mL), were added anisaldehyde dimethyl acetal (680  $\mu$ L, 3.98 mmol, 2.5 eq.), and  $p$ -TsOH $\cdot$ H $_2$ O (12.2 mg, 0.064 mmol, 0.04 eq.) at r.t.. The mixture was stirred at 65°C for 5.5 h, and the solvents evaporated to give crude. Purification via silica gel flash column chromatography (Eluent: 5% to 40% EtOAc/PE) gave **20**

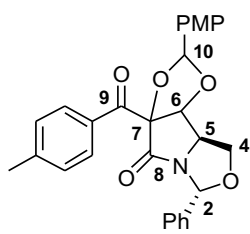


(468 mg, 67%) as a mixture of diastereomers.  $R_f = 0.37$  and  $0.45$  (2:1 EtOAc:PE);  $\nu_{\max} / \text{cm}^{-1}$  (film) 1721 (s, C=O), 1683 (s, C=O);  $m/z$  (ESI+) 441.35 ( $[M+H]^+$ , 100%); HRMS (ESI+) calculated for  $C_{23}H_{24}N_2NaO_7$  ( $[M+Na]^+$ ) 463.1476, found 463.1484.

### General procedure for Grignard reaction of Weinreb amide **20**

The Grignard reagent in THF (1.3 eq. based on amount of **20** used) was added to **20** (1.0 eq.) in THF at  $0^\circ\text{C}$ . The reaction was stirred at  $0^\circ\text{C}$  to r.t. over a period of 45 min to 1 h, after which it was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The combined organic layers were dried with anhydrous  $\text{MgSO}_4$ , filtered and the solvents removed *in vacuo* to give the crude product. Purification via silica gel flash column chromatography (Eluent: EtOAc/PE) gave the respective product as mixture of diastereomers about the protected diol.

### (2*R*, 5*S*)-1-Aza-6,7-(4'-methoxyphenylidene)dioxo-7-(4'-methylphenylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, **21a**

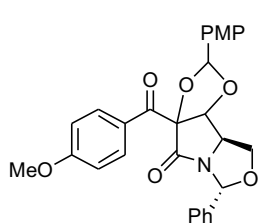


Scale of reaction: 77 mg (0.175 mmol), product: 37 mg, 45%;  $R_f = 0.53$  (30% EtOAc/PE); colourless oil;  $\nu_{\max} / \text{cm}^{-1}$  (film) 1718 (s, C=O), 1667 (s, C=O);  $\delta_H$  (400 MHz,  $\text{MeCN-d}_3$ ) 8.16 (d,  $J = 8.2$  Hz, Ar-H), 8.14 (d,  $J = 8.2$  Hz, Ar-H), 8.06 (d,  $J = 8.3$  Hz, Ar-H), 7.51-7.56 (m, ArH), 7.00 (d,  $J = 8.8$  Hz, Ar-H),

6.93 (d,  $J = 8.8$  Hz, Ar-H), 6.88 (d,  $J = 8.9$  Hz, Ar-H), 6.32, 6.23, 6.17 (3x s, H-2), 6.20, 6.08, 5.95 (3x s, H-10), 5.30 (d,  $J = 1.2$  Hz, H-6), 5.20 (s, H-6), 5.17 (d,  $J = 4.4$  Hz, H-6), 4.56 (dt,  $J = 4.4$ , 7.2 Hz, H-5), 4.50 (dd,  $J = 6.5$ , 8.3 Hz, H-4), 4.43 (dd,  $J = 6.6$ , 8.1 Hz, H-4), 4.31 (ddd,  $J = 1.2$ , 6.5, 9.8 Hz, H-5), 4.19-4.27 (m, H-4), 4.14 (dd,  $J = 7.4$ , 8.6 Hz, H-4), 3.83, 3.79, 3.76 (3x s, 3H, Ar-OMe), 2.42, 2.40, 2.39 (3x s, 3H, Ar-Me);  $\delta_C$  (100 MHz,  $\text{MeCN-d}_3$ ) 198.47, 196.69, 195.22 (C-9), 173.60, 173.36, 171.52 (C-8), 162.31, 162.20, 162.17, 146.57, 146.43, 146.18, 139.50, 139.45, 138.79, 133.31, 133.05, 131.78, 131.67, 131.65, 130.05, 130.01, 129.91, 129.89, 129.83, 129.80, 129.63, 129.31, 128.72, 128.36, 127.73, 127.22, 127.16, 127.14, 126.94, 118.29, 114.96, 114.91, 114.80

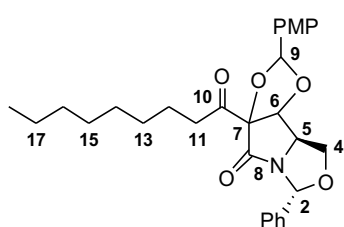
(ArC), 108.22, 107.89, 106.57 (C-10), 97.98, 96.06, 95.75 (C-7), 89.45, 89.29, 88.32 (C-2), 81.33, 80.65, 80.20 (C-6), 69.21, 68.39, 66.17 (C-4), 64.77, 64.00, 59.48 (C-5), 56.11, 56.06, 56.03 (Ar-OMe), 21.85, 21.81 (Ar-Me);  $m/z$  (ESI+) 494.33 ( $[M+Na]^+$ , 100%); HRMS (ESI+) calculated for  $C_{28}H_{25}NNaO_6$  ( $[M+Na]^+$ ) 495.1607, found 495.1588.

**(2R, 5S)-1-Aza-6,7-(4'-methoxyphenylidene)dioxy-7-(4'-methoxyphenylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, 21b**



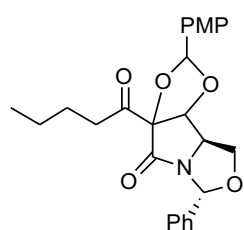
Scale of reaction: 98 mg (0.222 mmol), product: 48 mg, 44%;  $R_f$  = 0.22 (30% EtOAc/PE); colourless oil;  $\nu_{max}$  /  $cm^{-1}$  (film) 1718 (s, C=O), 1661 (s, C=O);  $m/z$  (ESI+) 510.41 ( $[M+Na]^+$ , 100%); HRMS (ESI+) calculated for  $C_{28}H_{25}NNaO_7$  ( $[M+Na]^+$ ) 511.1556, found 511.1634.

**(2R, 5S)-1-Aza-6,7-(4'-methoxyphenylidene)dioxy-7-(octylcarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, 21c**



Scale of reaction: 128 mg (0.291 mmol), product: 43 mg, 30%;  $R_f$  = 0.42 (30% EtOAc/PE); colourless oil;  $\nu_{max}$  /  $cm^{-1}$  (film) 1726 (s, C=O), 1709 (s, C=O);  $m/z$  (ESI+) 494.48 ( $[M+H]^+$ , 100%); HRMS (ESI+) calculated for  $C_{29}H_{36}NO_6$  ( $[M+H]^+$ ) 494.2537, found 494.2543.

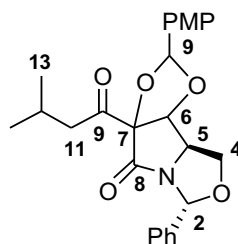
**(2R, 5S)-1-Aza-7-(butylcarbonyl)-6,7-(4'-methoxyphenylidene)dioxy-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, 21d**



Scale of reaction: 135 mg (0.307 mmol), product: 33 mg, 19%;  $R_f$  = 0.28 (30% EtOAc/PE); colourless oil;  $\nu_{max}$  /  $cm^{-1}$  (film) 1724 (s, C=O), 1708 (s, C=O);  $m/z$  (ESI+) 438.42 ( $[M+H]^+$ , 100%); HRMS (ESI+) calculated for  $C_{25}H_{27}NNaO_6$  ( $[M+Na]^+$ ) 460.1731, found 460.1734.

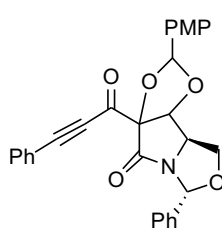


**(2*R*, 5*S*)-1-Aza-7-(isobutylcarbonyl)-6,7-(4'-methoxyphenylidene)dioxy-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, 21e**



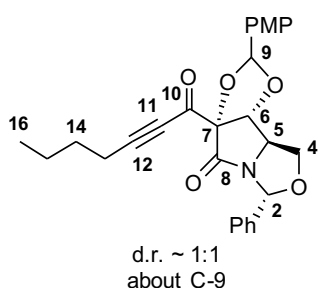
Scale of reaction: 140 mg (0.318 mmol), product: 37 mg, 27%;  $R_f$  = 0.33 (30% EtOAc/PE); colourless oil;  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 1707 (s, C=O, with shoulder towards longer wave number);  $m/z$  (ESI+) 438.39 ( $[\text{M}+\text{H}]^+$ , 25%); HRMS (ESI+) calculated for  $\text{C}_{25}\text{H}_{27}\text{NO}_6$  ( $[\text{M}+\text{H}]^+$ ) 438.1911, found 438.1927.

**(2*R*, 5*S*)-1-Aza-6,7-(4'-methoxyphenylidene)dioxy-7-(phenylacetylenecarbonyl)-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, 21f**



Scale of reaction: 130 mg (0.295 mmol), product: 72 mg, 51%;  $R_f$  = 0.68 (1:1 EtOAc/PE); pale yellow oil;  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 2192 (s, alkyne), 1722 (s, C=O), 1661 (s, C=O);  $m/z$  (ESI+) 482.48 ( $[\text{M}+\text{H}]^+$ , 55%); HRMS (ESI+) calculated for  $\text{C}_{29}\text{H}_{23}\text{NNaO}_6$  ( $[\text{M}+\text{Na}]^+$ ) 504.1418, found 504.1431.

**(2*R*, 5*S*, 6*R*, 7*S*)-1-Aza-7-(butylacetylenecarbonyl)-6,7-(4'-methoxyphenylidene)dioxy-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]octane, 21g**



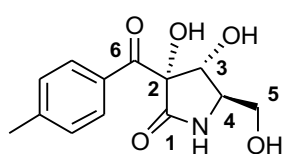
Scale of reaction: 135 mg (0.307 mmol), product: 48 mg, 34%;  $R_f$  = 0.22 (30% EtOAc/PE); colourless oil;  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 2212 (s, alkyne), 1724 (s, C=O), 1665 (s, C=O);  $\delta_{\text{H}}$  (400 MHz,  $\text{MeCN-d}_3$ ) 7.49-7.54 (m, 2H, ArH), 7.37-7.48 (m, 5H, PhH), 6.92-7.01 (m, 2H, ArH), 6.28 (s, 0.5H, H-2), 6.25 (s, 0.5 H, H-2), 6.15 (s, 0.5 H, H-9), 6.11 (s, 0.5 H, H-9), 5.10 (d,  $J$  = 1.4 Hz, 0.5H, H-6), 4.97 (s, 0.5H, H-6), 4.48 (dd,  $J$  = 6.5, 8.4 Hz, 0.5H, H-4), 4.40 (dd,  $J$  = 6.7, 8.2 Hz, 0.5H, H-4), 4.19-4.31 (m, 1H, H-5), 3.81 and 3.80 (s, 3H, Ar-OMe), 3.68 (ddd,  $J$  = 4.6, 8.4, 9.7 Hz, 1H, H-4), 2.53 (dt,  $J$  = 7.0, 15.1 Hz, 2H, H-13), 1.52-1.66 (m, 2H, H-14), 1.35-1.50 (m, 2H, H-15), 0.86-0.96 (m, 3H, H-16);  $\delta_{\text{C}}$  (100 MHz,  $\text{MeCN-d}_3$ ) 184.23, 182.61 (C-10), 172.53, 172.40 (C-8), 162.29, 162.25 (ArC quart), 139.31, 139.26, 130.07, 129.98, 129.92, 129.65, 129.39, 127.94, 127.67, 127.21, 126.95, 114.92, 114.83 (ArC), 108.87, 106.87 (C-9), 104.32, 103.84 (C-12), 95.21, 94.91 (C-7), 89.35, 89.28 (C-2), 80.60, 80.46 (C-11), 79.64, 79.43 (C-6), 69.55, 68.60 (C-4), 64.83,

64.17 (C-5), 56.08, 55.33 (Ar-OMe), 30.22, 30.19 (C-14), 22.68 (C-15), 19.48, 19.47 (C-13), 13.76, 13.75 (C-16);  $m/z$  (ESI+) 462.38 ( $[M+H]^+$ , 15%); HRMS (ESI+) calculated for  $C_{27}H_{28}NO_6$  ( $[M+H]^+$ ) 462.1911, found 462.1917.

### General procedure for acidic oxazolidine hydrolysis to 2,3-dihydroxypyrrolidinones **22a-g**

TFA (20 eq.) was added to a solution of **21a-g** in  $CH_2Cl_2$  at r.t.. The reaction mixture was stirred at r.t. for 5-6.5 h and the solvents evaporated to give the crude. Purification via silica gel flash column chromatography (Eluent: 0% to 10% MeOH/EtOAc) gave the respective 2,3-dihydroxypyrrolidinones.

#### (2*S*, 3*R*, 4*R*)-2,3-Dihydroxy-2-(4'-methylphenylcarbonyl)-4-hydroxymethyl-1-oxo-pyrrolidinone, **22a**



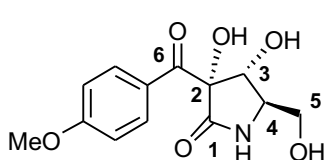
Scale of reaction: 35 mg (0.0742 mmol), product: 9 mg, 45%;  $R_f$  = 0.23

(EtOAc); white solid, mp = 154-156°C;  $[\alpha]_D^{23}$  = -33.4 ( $c$  = 1.35 in MeOH);

$\nu_{max}$  /  $cm^{-1}$  (film) 3452 (br, -NH-), 1692 (s, C=O), 1663 (s, C=O);  $\delta_H$  (400

MHz, MeCN- $d_3$ ) 7.92 (d,  $J$  = 8.3 Hz, 2H, ArH), 7.32 (d,  $J$  = 8.3 Hz, 2H, ArH), 6.76 (br s, 1H, -NH-), 4.85 (br s, 1H, -OH), 4.55 (d,  $J$  = 6.4 Hz, 1H, H-3), 3.96 (br s, 1H, -OH), 3.80 (dd,  $J$  = 3.1, 11.8 Hz, 1H, H-5), 3.74 (br s, 1H, -OH), 3.61 (dd,  $J$  = 4.6, 11.8 Hz, 1H, H-5'), 3.53 (ddd,  $J$  = 2.2, 5.2, 7.3 Hz, 1H, H-4), 2.41 (s, 3H, Ar-Me);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 198.62 (C-6), 173.05 (C-1), 146.21, 131.57, 130.75, 130.24 (ArC), 83.75 (C-2), 72.94 (C-3), 62.59 (C-4), 61.13 (C-5), 21.76 (Ar-Me);  $m/z$  (ESI+) 288.18 ( $[M+Na]^+$ , 85%); HRMS (ESI+) calculated for  $C_{13}H_{15}NNaO_5$  ( $[M+Na]^+$ ) 288.0842, found 288.0843.

#### (2*S*, 3*R*, 4*R*)-2,3-Dihydroxy-4-hydroxymethyl-2-(4'-methoxyphenylcarbonyl)-1-oxo-pyrrolidinone, **22b**

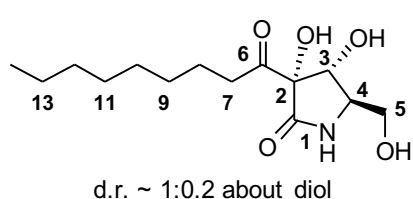


Scale of reaction: 48 mg (0.0985 mmol), product: 15 mg, 52%;  $R_f$  =

0.14 (EtOAc); white solid, mp = 145-147°C;  $[\alpha]_D^{23}$  = -27.3 ( $c$  = 1.21 in

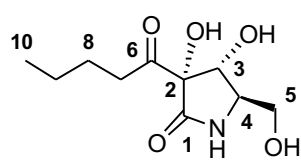
MeOH);  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 3304 (br, -NH-), 1688 (s, C=O), 1677 (s, C=O);  $\delta_{\text{H}}$  (400 MHz, MeCN- $\text{d}_3$ ) 8.03 (d,  $J = 9.0$  Hz, 2H, ArH), 7.01 (d,  $J = 9.0$  Hz, 2H, ArH), 6.81 (br s, 1H, -NH-), 4.55 (d,  $J = 6.4$  Hz, 1H, H-3), 3.87 (s, 3H, -OMe), 3.81 (dd,  $J = 3.1, 11.8$  Hz, 1H, H-5), 3.62 (dd,  $J = 4.6, 11.8$  Hz, 1H, H-5'), 3.51-3.57 (m, 1H, H-4);  $\delta_{\text{C}}$  (100 MHz, MeCN- $\text{d}_3$ ) 197.10 (C-6), 173.28 (C-1), 165.27, 133.23, 126.67, 114.89 (ArC), 83.47 (C-2), 73.06 (C-3), 62.67 (C-4), 61.14 (C-5), 56.47 (-OMe);  $m/z$  (ESI+) 304.21 ( $[\text{M}+\text{Na}]^+$ , 100%); HRMS (ESI+) calculated for  $\text{C}_{13}\text{H}_{15}\text{NNaO}_6$  ( $[\text{M}+\text{Na}]^+$ ) 304.0792, found 304.0800.

**(2*S*, 3*R*, 4*R*)-2,3-Dihydroxy-4-hydroxymethyl-2-(octylcarbonyl)-1-oxo-pyrrolidinone, 22c**



Scale of reaction: 42 mg (0.851 mmol), product: 10 mg, 41%;  $R_f$  = 0.18 (EtOAc); colourless oil;  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 3317 (br, -OH), 1691 (s, C=O); Major diastereomer  $\delta_{\text{H}}$  (400 MHz, MeCN- $\text{d}_3$ ) 6.61 (br s, 1H, -NH-), 4.29 (d,  $J = 6.1$  Hz, 1H, H-3), 3.76 (dd,  $J = 3.5, 11.6$  Hz, 1H, H-5), 3.56 (dd,  $J = 5.5, 11.6$  Hz, 1H, H-5'), 3.43 (dt,  $J = 3.5, 5.8$  Hz, 1H, H-4), 2.53-2.72 (m, 2H, H-7), 1.48-1.60 (m, 2H, H-8), 1.21-1.36 (m, 10H, H-9, H-10, H-11, H-12, H-13), 0.88 (t,  $J = 7.3$  Hz, 3H, H-14);  $\delta_{\text{C}}$  (100 MHz, MeCN- $\text{d}_3$ ) 210.78 (C-6), 172.44 (C-1), 84.06 (C-2), 71.64 (C-3), 61.96 (C-5), 61.93 (C-4), 38.72 (C-7), 32.59, 30.11, 29.91, 29.80, 23.92 (C-8), 23.38 (C-9, C-10, C-11, C-12, C-13), 14.39 (C-14);  $m/z$  (ESI+) 288.37 ( $[\text{M}+\text{H}]^+$ , 35%); HRMS (ESI+) calculated for  $\text{C}_{14}\text{H}_{25}\text{NNaO}_5$  ( $[\text{M}+\text{Na}]^+$ ) 310.1625, found 310.1635.

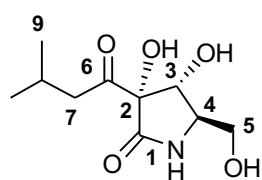
**(2*S*, 3*R*, 4*R*)-2-(Butylcarbonyl)-2,3-dihydroxy-4-hydroxymethyl-1-oxo-pyrrolidinone, 22d**



Scale of reaction: 30 mg (0.0686 mmol), product: 9 mg, 58%;  $R_f$  = 0.20 (EtOAc); colourless oil;  $[\alpha]_{\text{D}}^{23} = +40.1$  ( $c = 0.67$  in MeOH);  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 3291 (br, -NH-), 1680 (s, C=O);  $\delta_{\text{H}}$  (400 MHz, MeCN- $\text{d}_3$ ) 6.68 (br s, 1H, -NH-), 4.30 (d,  $J = 6.1$  Hz, 1H, H-3), 3.76 (dd,  $J = 3.5, 11.6$  Hz, 1H, H-5), 3.57 (dd,  $J = 5.6, 11.6$  Hz, 1H, H-5'), 3.45 (dt,  $J = 3.5, 5.8$  Hz, 1H, H-4), 2.54-2.76 (m, 2H, H-7, partially obscured by broad water signal), 1.48-1.59 (m, 2H, H-8), 1.26-1.37 (m, 2H, H-9), 0.90 (t,  $J = 7.3$  Hz, 3H, H-

10);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 210.76 (C-6), 172.56 (C-1), 84.10 (C-2), 71.64 (C-3), 62.01 (C-4), 61.96 (C-5), 38.44 (C-7), 26.03 (C-8), 22.90 (C-9), 14.15 (C-10);  $m/z$  (ESI+) 254.21 ( $[M+Na]^+$ , 90%); HRMS (ESI+) calculated for  $C_{10}H_{17}NNaO_5$  ( $[M+Na]^+$ ) 254.0999, found 254.1010.

**(2*S*, 3*R*, 4*R*)-2,3-Dihydroxy-4-hydroxymethyl-2-(isobutylcarbonyl)-1-oxo-pyrrolidinone, 22e**



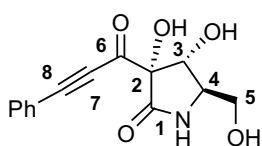
Scale of reaction: 37 mg (0.0846 mmol), product: 6 mg, 31%;  $R_f$  = 0.18

(EtOAc); colourless oil;  $[\alpha]_D^{23}$  = +45.5 ( $c$  = 0.8 in MeOH);  $\nu_{max}$  /  $cm^{-1}$  (film)

3355 (br, -OH), 1680 (s, C=O);  $\delta_H$  (400 MHz, MeCN- $d_3$ ) 6.68 (br s, 1H, -

NH-), 4.29 (d,  $J$  = 6.0 Hz, 1H, H-3), 3.77 (dd,  $J$  = 3.6, 11.6 Hz, 1H, H-5), 3.57 (dd,  $J$  = 5.6, 11.7 Hz, 1H, H-5'), 3.44 (dt,  $J$  = 3.5, 5.8 Hz, 1H, H-4), 2.59 (dd,  $J$  = 6.8, 17.8 Hz, 1H, H-7), 2.48 (dd,  $J$  = 6.7, 17.8 Hz, 1H, H-7'), 2.09-2.19 (m, 1H, H-8), 0.91 (d,  $J$  = 6.7 Hz, 6H, H-9);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 210.23 (C-6), 172.49 (C-1), 84.09 (C-2), 71.52 (C-3), 62.02 (C-4), 61.97 (C-5), 47.39 (C-7), 24.61 (C-8), 22.72 (C-9);  $m/z$  (ESI+) 232.23 ( $[M+H]^+$ , 20%); HRMS (ESI+) calculated for  $C_{10}H_{17}NNaO_5$  ( $[M+Na]^+$ ) 254.0999, found 254.1003.

**(2*S*, 3*R*, 4*R*)-2,3-Dihydroxy-4-hydroxymethyl-2-(phenylacetylenecarbonyl)-1-oxo-pyrrolidinone, 22f**



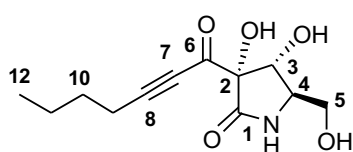
Scale of reaction: 70 mg (0.145 mmol), product: 19 mg, 48%;  $R_f$  = 0.17

(EtOAc); white solid, mp = 149-150°C;  $\nu_{max}$  /  $cm^{-1}$  (film) 3299 (br, -OH),

d.r. ~ 1:0.3 about diol 2193 (s, alkyne), 1699 (s, C=O), 1674 (s, C=O); Major diastereomer:  $\delta_H$  (400

MHz, MeCN- $d_3$ ) 7.63-7.71 (m, 2H, PhH), 7.54-7.62 (m, 1H, PhH), 7.44-7.52 (m, 2H, PhH), 6.69 (br s, 1H, -NH-), 4.74 (d,  $J$  = 6.7 Hz, 1H, H-3), 3.84 (dd,  $J$  = 3.0, 11.9 Hz, 1H, H-5), 3.64 (dd,  $J$  = 4.8, 11.9 Hz, 1H, H-5'), 3.50 (ddd,  $J$  = 3.0, 4.8, 6.7 Hz, 1H, H-4);  $\delta_C$  (100 MHz, MeCN- $d_3$ ) 186.86 (C-6), 171.34 (C-1), 134.34, 132.73, 130.00, 119.95 (PhC), 97.73 (C-8), 86.09 (C-2), 85.87 (C-7), 72.16 (C-3), 61.71 (C-4), 61.30 (C-5);  $m/z$  (ESI+) 276.48 ( $[M+H]^+$ , 35%); HRMS (ESI+) calculated for  $C_{14}H_{13}NNaO_5$  ( $[M+Na]^+$ ) 298.0686, found 298.0698.

**(2*S*, 3*R*, 4*R*)-2,3-Dihydroxy-4-hydroxymethyl-2-(butylacetylenecarbonyl)-1-oxo-pyrrolidinone, 22g**



Scale of reaction: 45 mg (0.0975 mmol), product: 18 mg, 72%;  $R_f =$

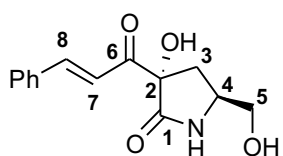
0.21 (EtOAc); white solid, mp = 123-125°C;  $[\alpha]_D^{23} = +37.7$  ( $c = 1.33$  in MeOH);  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 3356 (br, -NH-), 2211 (s, alkyne), 1701 (s, C=O), 1682 (s, C=O);  $\delta_{\text{H}}$  (400 MHz, MeCN- $\text{d}_3$ ) 6.67 (br s, 1H, -NH-), 4.57 (d,  $J = 6.8$  Hz, 1H, H-3), 3.81 (dd,  $J = 3.2, 11.7$  Hz, 1H, H-5), 3.57 (dd,  $J = 5.5, 11.7$  Hz, 1H, H-5'), 3.46 (ddd,  $J = 3.1, 5.5, 6.8$  Hz, 1H, H-4), 2.47 (t,  $J = 7.0$  Hz, 2H, H-9) (overlapping broad water signal at baseline), 1.51-1.63 (m, 2H, H-10), 1.36-1.49 (m, 2H, H-11), 0.92 (t,  $J = 7.3$  Hz, 3H, H-12);  $\delta_{\text{C}}$  (100 MHz, MeCN- $\text{d}_3$ ) 186.67 (C-6), 171.36 (C-1), 103.00 (C-8), 85.69 (C-2), 78.77 (C-7), 72.39 (C-3), 61.85 (C-5), 61.79 (C-4), 30.27 (C-10), 22.66 (C-11), 19.38 (C-9), 13.77 (C-12);  $m/z$  (ESI+) 256.26 ( $[\text{M}+\text{H}]^+$ , 15%); HRMS (ESI+) calculated for  $\text{C}_{12}\text{H}_{18}\text{NO}_5$  ( $[\text{M}+\text{H}]^+$ ) 256.1179, found 256.1175.

**General procedure for partial reductive hydrogenation-isomerisation of ynones 8f,g and 22f,g**

To an EtOAc solution (approx. 0.02-0.05 M) of the ynone (between 0.07-0.1 mmol scale) was added Lindlar's catalyst (5% Pd/CaCO<sub>3</sub> (poisoned with Pb), 10-15% wt. of ynone). Quinoline (1  $\mu\text{L}$ ) was added for the reduction of all butylethynyl derivatives. The suspension was stirred at r.t. with H<sub>2</sub> gas (balloon) bubbled through the mixture and the progress of the reaction was monitored using LRMS analysis. The suspension was then filtered over Celite, rinsed with EtOAc and the solvent removed *in vacuo* to give the crude product. The crude from the above reduction was dissolved in EtOAc (approx. 0.02 M), with one drop of dilute I<sub>2</sub>/EtOAc solution added. The solution irradiated using a 500W halogen lamp with stirring for 5-6 h. The reaction was quenched with aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and extracted with EtOAc. The combined organic layers were dried with anhydrous MgSO<sub>4</sub>, filtered and the solvents removed *in vacuo* to give the crude. Purification of the crude was done via reverse-phase preparative HPLC on an Agilent 1200 series system with

Phenomenex® Luna C18(2) column (10.0 × 100 mm, 5 µm) using the elution gradient with a MeCN-H<sub>2</sub>O mobile phase at a flow rate of 5 mL/min and detection at λ<sub>210</sub> and 254 nm.

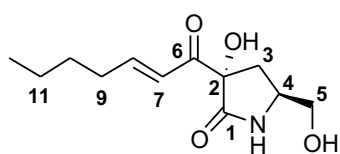
**(2*S*, 4*R*)-2-Hydroxy-4-hydroxymethyl-2-[(*E*)-phenylvinlenecarbonyl]-1-oxo-pyrrolidinone, (*E*)-23a**



Retention time: 17.204 min; white crystals, mp = 107-109°C;  $[\alpha]_{\text{D}}^{23} = -47.2$

( $c = 1.16$  in MeOH);  $\nu_{\text{max}} / \text{cm}^{-1}$  (film) 3278 (br, -OH), 1687 (br s, C=O);  $\delta_{\text{H}}$  (400 MHz, MeCN- $\text{d}_3$ ) 7.77 (d,  $J = 15.9$  Hz, 1H, H-8), 7.64-7.71 (m, 2H, PhH), 7.39-7.51 (m, 3H, PhH), 7.32 (d,  $J = 15.9$  Hz, 1H, H-7), 6.84 (br s, 1H, -NH-), 4.75 (br s, 1H, -OH), 3.86-3.91 (m, 1H, H-4), 3.69 (dd,  $J = 3.8, 11.4$  Hz, 1H, H-5), 3.51 (dd,  $J = 5.5, 11.4$  Hz, 1H, H-5'), 2.50 (dd,  $J = 6.1, 14.4$  Hz, 1H, H-3), 2.14 (dd,  $J = 7.8, 14.4$  Hz, 1H, H-3');  $\delta_{\text{C}}$  (100 MHz, MeCN- $\text{d}_3$ ) 198.60 (C-6), 174.84 (C-1), 145.48 (C-8), 135.46, 132.02, 130.06, 129.78 (PhC), 121.15 (C-7), 83.70 (C-2), 64.68 (C-5), 53.96 (C-4), 35.59 (C-3);  $m/z$  (ESI+) 262.53 ( $[\text{M}+\text{H}]^+$ , 98%); HRMS (ESI+) calculated for  $\text{C}_{14}\text{H}_{16}\text{NO}_4$  ( $[\text{M}+\text{H}]^+$ ) 262.1074, found 262.1076.

**(2*S*, 4*R*)-2-Hydroxy-4-hydroxymethyl-2-[(*E*)-butylvinlenecarbonyl]-1-oxo-pyrrolidinone, (*E*)-23b**



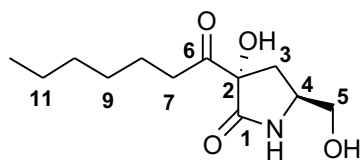
Retention time: 17.98 min; colourless oil;  $[\alpha]_{\text{D}}^{23} = +45.3$  ( $c = 1.07$  in

$\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}} / \text{cm}^{-1}$  (film) 3303 (br, -OH), 1702 (br s, C=O; with shoulder towards smaller wavenumber);  $\delta_{\text{H}}$  (400 MHz, MeCN- $\text{d}_3$ ) 7.07

(dt,  $J = 7.0, 15.5$  Hz, 1H, H-8), 6.76 (br s, 1H, -NH-), 6.56 (dt,  $J = 1.6, 15.5$  Hz, 1H, H-7), 4.60 (br s, 1H, -OH), 3.79-3.90 (m, 1H, H-4), 3.64 (dd,  $J = 3.9, 11.3$  Hz, 1H, H-5), 3.45 (dd,  $J = 5.9, 11.3$  Hz, 1H, H-5'), 2.35 (dd,  $J = 6.4, 14.3$  Hz, 1H, H-3), 2.24-2.29 (m, 2H, H-9) (partially obscured by water signal), 2.06 (dd,  $J = 7.6, 14.3$  Hz, 1H, H-3'), 1.41-1.51 (m, 2H, H-10), 1.28-1.40 (m, 2H, H-11), 0.91 (t,  $J = 7.3$  Hz, 3H, H-12);  $\delta_{\text{C}}$  (100 MHz, MeCN- $\text{d}_3$ ) 198.28 (C-6), 174.80 (C-1), 151.75 (C-8), 124.49 (C-7), 83.30 (C-2), 64.82 (C-5), 54.03 (C-4), 35.73 (C-3), 32.98 (C-9), 30.78 (C-10),

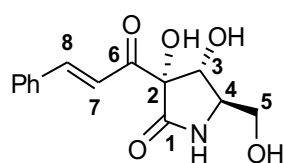
23.01 (C-11), 14.12 (C-12);  $m/z$  (ESI+) 264.58 ( $[M+Na]^+$ , 100%); HRMS (ESI+) calculated for  $C_{12}H_{19}NNaO_4$  ( $[M+Na]^+$ ) 264.1206, found 264.1206.

**(2*S*, 4*R*)-2-(Hexylcarbonyl)-2-hydroxy-4-hydroxymethyl-1-oxo-pyrrolidinone, 23c**



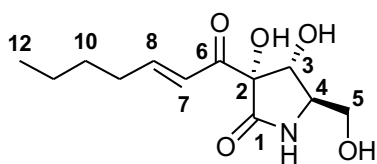
Retention time: 22.20 min; colourless oil;  $[\alpha]_D^{23} = +75.0$  ( $c = 0.84$  in  $CH_2Cl_2$ );  $\nu_{max} / cm^{-1}$  (film) 3289 (br, -OH), 1715 (br s, C=O), 1690 (br s, C=O);  $\delta_H$  (400 MHz,  $MeCN-d_3$ ) 6.67 (br s, 1H, -NH-), 4.47 (br s, 1H, -OH), 3.74-3.87 (m, 1H, H-4), 3.61 (dd,  $J = 4.2, 11.2$  Hz, 1H, H-5), 3.44 (dd,  $J = 6.3, 11.2$  Hz, 1H, H-5'), 2.68 (dd,  $J = 7.3, 17.9$  Hz, 1H, H-7), 2.57 (dd,  $J = 7.3, 17.9$  Hz, 1H, H-7'), 2.32 (dd,  $J = 6.3, 14.2$  Hz, 1H, H-3), 2.04 (dd,  $J = 7.6, 14.2$  Hz, 1H, H-3'), 1.47-1.60 (m, 2H), 1.26-1.32 (m, 6H) (H-8, H-9, H-10, H-11), 0.88 (t,  $J = 7.3$  Hz, 3H, H-12);  $\delta_C$  (100 MHz,  $MeCN-d_3$ ) 211.01 (C-6), 174.76 (C-1), 84.05 (C-2), 65.09 (C-5), 53.90 (C-4), 37.96 (C-7), 35.67 (C-3), 32.36, 29.48, 24.17, 23.25 (C-8, C-9, C-10, C-11), 14.35 (C-12);  $m/z$  (ESI+) 244.58 ( $[M+H]^+$ , 85%); HRMS (ESI+) calculated for  $C_{12}H_{22}NO_4$  ( $[M+H]^+$ ) 244.1543, found 244.1544.

**(2*S*, 3*R*, 4*R*)-2,3-Dihydroxy-4-hydroxymethyl-2-[(*E*)-phenylvinyl]enecarbonyl-1-oxo-pyrrolidinone, (*E*)-23d**



Retention time: 10.91 min; white solid, mp = decomposes at 175°C;  $[\alpha]_D^{23} = -36.2$  ( $c = 1.09$  in MeOH);  $\nu_{max} / cm^{-1}$  (film) 3250 (br, -OH), 1706 (C=O), 1697 (C=O);  $\delta_H$  (400 MHz,  $MeCN-d_3$ ) 7.79 (d,  $J = 15.9$  Hz, 1H, H-8), 7.66-7.73 (m, 2H, PhH), 7.40-7.50 (m, 3H, PhH), 7.23 (d,  $J = 15.9$  Hz, 1H, H-7), 6.63 (br s, 1H, -NH-), 4.41 (d,  $J = 6.2$  Hz, 1H, H-3), 3.81 (dd,  $J = 3.4, 11.7$  Hz, 1H, H-5), 3.62 (dd,  $J = 5.4, 11.6$  Hz, 1H, H-5'), 3.50 (ddd,  $J = 3.4, 5.4, 6.2$  Hz, 1H, H-4);  $\delta_C$  (100 MHz,  $MeCN-d_3$ ) 198.28 (C-6), 172.3 (C-1), 145.58 (C-8), 135.41, 132.10, 130.07, 129.82 (PhC), 121.17 (C-7), 83.73 (C-2), 71.89 (C-3), 62.22 (C-4), 62.11 (C-5);  $m/z$  (ESI+) 278.65 ( $[M+H]^+$ , 100%); HRMS (ESI+) calculated for  $C_{14}H_{16}NO_5$  ( $[M+H]^+$ ) 278.1023, found 278.1024.

**(2*S*, 3*R*, 4*R*)-2,3-Dihydroxy-4-hydroxymethyl-2-[(*E*)-butylvinylencarbonyl]-1-oxo-pyrrolidinone, (*E*)-23e**



Retention time: 15.31 min; colourless oil;  $[\alpha]_D^{23} = +37.2$  ( $c = 0.68$  in MeOH);  $\nu_{\max}$  /  $\text{cm}^{-1}$  (film) 3346 (br, -OH), 1701 (br s, C=O with shoulder towards smaller wavenumber);  $\delta_{\text{H}}$  (400 MHz,  $\text{MeCN-d}_3$ )

7.09 (dt,  $J = 7.0, 15.5$  Hz, 1H, H-8), 6.54 (br s, 1H, -NH-), 6.50 (dt,  $J = 1.6, 15.6$  Hz, 1H, H-7), 4.54 (s, 1H, -OH C2), 4.31 (dd,  $J = 6.3, 8.6$  Hz, 1H, H-3), 3.73-3.83 (m, 1H, H-5), 3.58 (ddd,  $J = 5.1, 6.6, 11.7$  Hz, 1H, H-5'), 3.51 (d,  $J = 8.6$  Hz, 1H, -OH C3), 3.42-3.48 (m, 1H, H-4), 3.05 (dd,  $J = 5.1, 6.6$  Hz, 1H, -OH C5), 2.27 (apparent dq,  $J = 1.6, 7.1$  Hz, 2H, H-9), 1.41-1.55 (m, 2H, H-10), 1.28-1.41 (m, 2H, H-11), 0.91 (t,  $J = 7.3$  Hz, 3H, H-12);  $\delta_{\text{C}}$  (100 MHz,  $\text{MeCN-d}_3$ ) 197.71 (C-6), 172.24 (C-1), 152.07 (C-8), 124.62 (C-7), 83.33 (C-2), 71.77 (C-3), 62.20 (C-4), 61.87 (C-5), 33.04 (C-9), 30.79 (C-10), 23.02 (C-11), 14.11 (C-12);  $m/z$  (ESI+) 258.86 ( $[\text{M}+\text{H}]^+$ , 75%); HRMS (ESI+) calculated for  $\text{C}_{12}\text{H}_{20}\text{NO}_5$  ( $[\text{M}+\text{H}]^+$ ) 258.1336, found 258.1334.

## Acknowledgements

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**Electronic Supplementary Supporting Information.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of all compounds.

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