

# Antibacterial Mimics of Natural Products by Side Chain Functionalisation of Bicyclic Tetramic Acids

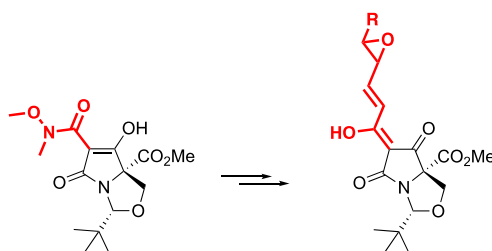
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**Abstract:** Tetramic acids with unsaturated acyl chains are widely found in natural products possessing a range of biological activities, and bicyclic tetramates represent a suitable scaffold to prepare simple mimics of such complex molecules. An efficient route to functionalise the C(6)-acyl group of a bicyclic tetramate was developed, and utilised to prepare a small chemical library with a range of saturated and unsaturated side-chains. The analogues with lipophilic residues possessed highly potent antibacterial activity, which was selective for Gram-positive bacteria, and the best compound was 37-fold more potent than the Cephalosporin C control and with an appropriate therapeutic window.

## Introduction

Natural products have long provided valuable sources of inspiration for drug design,<sup>1</sup> and may be considered to be ‘privileged structures’ possessing large chemical diversity with effective biological activity, suitable for therapies for a wide range of diseases.<sup>2,3</sup> In the area of anti-infectives, where the emergence of resistance to known antibiotics has pointed to the need for new systems, the use of natural products represents a promising

starting point for drug development. However, their long and low yielding synthetic routes which are frequently required has hindered their use in drug discovery programmes. An alternative approach, which avoids the total syntheses of the natural products, is to use their structure as inspiration to design simpler and more synthetically accessible small molecules.<sup>4–6</sup> Tetramic acids and hydroxylated pyrrolidinones are a widespread structural motif in nature.<sup>7–10</sup> Of interest are the 3-acyl substituted variants, and in particular dienoyl and polyenoyl derivatives, which have been reported to possess a range of biological properties including antibacterial, antifungal and anticancer activities (Figure 1). This has, in turn, generated significant interest in their synthesis, and approaches based upon Wittig-type or acylative homologation<sup>11–17</sup> or by late stage tetramisation<sup>18,19</sup> have been reported.

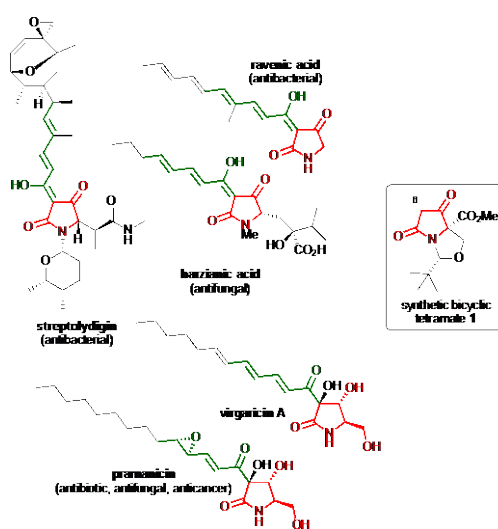
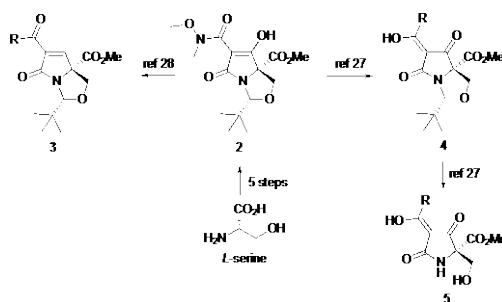


Figure 1. Structures and bioactivities of the natural products streptolydigin,<sup>20</sup> ravenic acid,<sup>21</sup> harzianic acid,<sup>22</sup> vigaricin A<sup>23,24</sup> and pramanicin.<sup>25,26</sup>

In the context of preparing simple versions of complex natural products, our group has identified bicyclic tetramate **1** as an easily accessible scaffold from which mimics of such natural tetramates and pyrrolidinones can be prepared. We have recently reported that functionalisation of the C(6) position of bicyclic tetramate **1** can be achieved via Grignard addition to Weinreb amide **2**, providing alkyl, aryl, alkenyl and alkynyl tricarbonyl compounds **4**, and identified conditions for subsequent *N,O*-acetal deprotection to **5** (Scheme 1).<sup>27</sup> Moreover, we have also shown that reduction of the C(7) ketone group is possible in high diastereoselectivity after hydrogenation with PtO<sub>2</sub> followed by elimination, leading to alkenes **3**.<sup>28</sup> Therefore, key to the synthesis of closer mimics of the natural products in Figure 1 is C(6)-side chain manipulation allowing the introduction of the dienoyl functionality, and we report here work which demonstrates that such side chain manipulation using a

general approach based upon organometallic substitution is feasible on densely functional tetramate skeletons, and that the derived products may exhibit antibacterial activity.

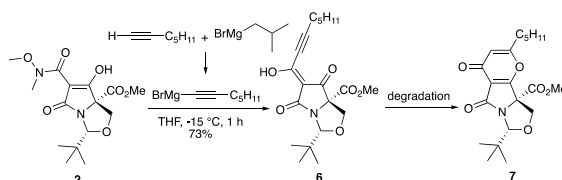


Scheme 1. Reported synthetic transformations of the bicyclic tetramate via Weinreb amide **2**.

## Results and Discussion

### Preparation of dienoyl-tetramates

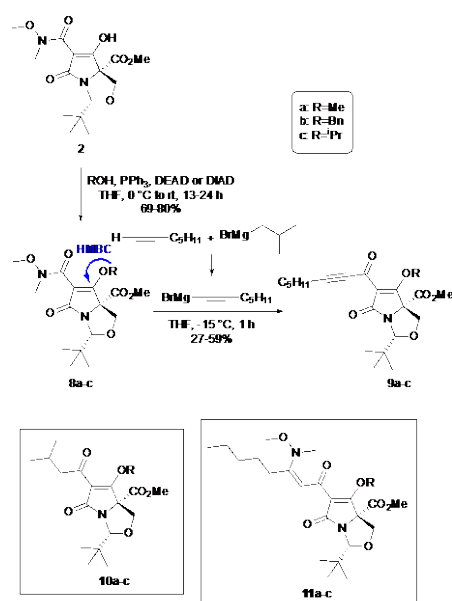
We envisaged that a *C*(6)-unsaturated chain could be introduced onto the bicyclic tetramate via isomerisation of the corresponding ynone. Trost *et al.* have shown that such a transformation is possible with both aromatic and aliphatic ketones, with the latter requiring higher temperatures.<sup>29</sup> To assess the feasibility of this approach, we treated Weinreb amide **2**, prepared using our reported procedure from *L*-serine,<sup>27,30</sup> with heptynylmagnesium bromide to form octynone **6** in good yield (Scheme 2). However, we found this compound to be unstable, and it fully converted to tricycle **7** within hours at room temperature. Such degradation had been observed for similar analogues,<sup>27</sup> but at lower rates probably due to the presence of aromatic groups instead of the alkyl chain of **6**, which lowered the reactivity of the alkyne. Unfortunately, attempted isomerisation of the crude alkynone did not give any desired product and only tricycle **7** was isolated.



Scheme 2. Grignard addition to Weinreb amide **2** and degradation product of **6**.

We suspected that protection of the enol would avoid the isomerisation path described above, and therefore Weinreb **2** was methylated via Mitsunobu-like conditions with methanol.<sup>27</sup> The expected methyl ether **8a** was

formed as a single regioisomer, as indicated by HMBC correlations (Scheme 3). Unfortunately, Grignard addition to the protected enolate was much less efficient than with enol **2**, and this was due to the formation of several by-products, including enol-deprotected amide **2** and alkynone **6**, as well as isobutyl **10a** and enamine **11a**. Even though the formation of the latter was unexpected, similar outcomes had already been observed in the addition of alkynes to Weinreb amides by Nielsen<sup>31</sup> and Choudhury,<sup>32</sup> who in fact did not obtain any of the desired alkynone. The deprotected enols were likely to have originated from attack of the Grignard reagent onto the methyl group, since the highly delocalised tricarbonyl system makes for a very good leaving group, and it was envisaged that this deprotection could be impeded by employing a bulkier protecting group. Indeed, an improvement was observed with the benzyl and isopropyl groups, but it was accompanied by a decrease in the yield of the initial protection step (Table 1). With bulkier groups such as benzhydryl or *tert*-butyl, there was low or no conversion. The use of the isopropoxy enol ether provided a good balance, where the protection could be achieved in acceptable yield and the Grignard addition proceeded with no detectable enol deprotection.



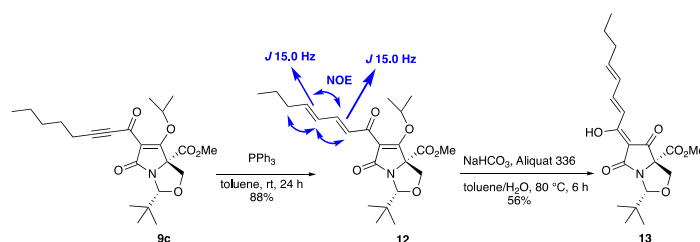
Scheme 3. Enol protection of **2** and subsequent Grignard addition.

Table 1. Screen of enol protecting groups to optimise the formation of alkynes **9a-c**.

R	Protection		Grignard	
	Time	Yield	Yield	Side products
Me	13 h	<b>8a</b> , 80%	<b>9a</b> , 27%	<b>2</b> , <b>6a</b> , <b>10a</b> , <b>11a</b>

<b>Bn</b>	18 h	<b>8b</b> , 71%	<b>9b</b> , 35%	<b>2, 6b, 10b, 11b</b>
<b><sup>i</sup>Pr</b>	24 h	<b>8c</b> , 69%	<b>9c</b> , 59%	<b>10c, 11c</b>
<b>CHPh<sub>2</sub></b>	24 h	21%	-	-
<b><sup>t</sup>Bu</b>	24 h	Recovered starting material		

With alkynone **9c** in hand, we were pleased to find that isomerisation to the dienone **12** occurred in high yields provided stoichiometric amounts of triphenylphosphine were used at room temperature (Scheme 4); diene **12** was obtained as a single (*E,E*)-regioisomer, evidenced by the large coupling constants and further confirmed by NOE correlations. For the deprotection of the isopropyl enol ether group of **12**, initial attempts with BBr<sub>3</sub> resulted in low yields, partly due to concurrent *N,O*-acetal deprotection. Alternatively, treatment with an excess of NaHCO<sub>3</sub> with stoichiometric Aliquat 336 under phase-transfer catalysis conditions successfully furnished tetramate **13**.

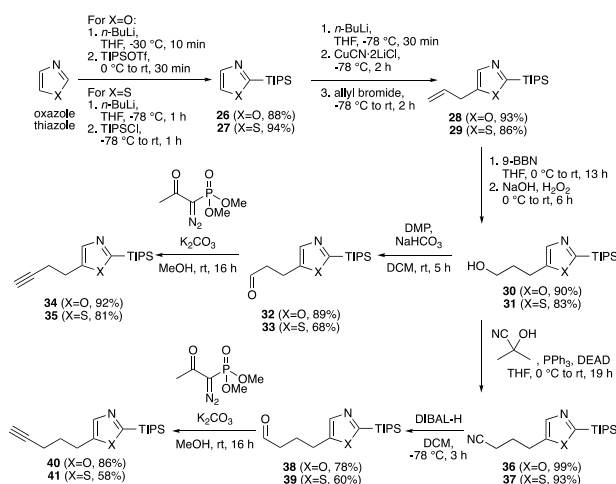


Scheme 4. Successful formation of dienoyl-tetramate **13** via isomerisation and enol deprotection.

This sequence provided a reliable route to dienone-tetramic acids, and was used to prepare analogues with different chain lengths **13**, **18**, **19** (Scheme 5). The carboxymethyl group, which is not present in the natural products, could also be removed via diastereoselective decarboxylation,<sup>27</sup> and gave analogue **20**. The deprotected tetramic acids exist a mixture of tautomers, a characteristic that has been found and extensively studied in related *C*(6)-substituted tetramates;<sup>27,33–35</sup> their double geometry was readily established by coupling constant and NOE analysis, and no double bond isomerism was detected. The corresponding saturated derivatives **21–23**, readily available via direct Grignard reaction of Weinreb amide **2**, were prepared to examine the role of the diene functionality in biological activity.

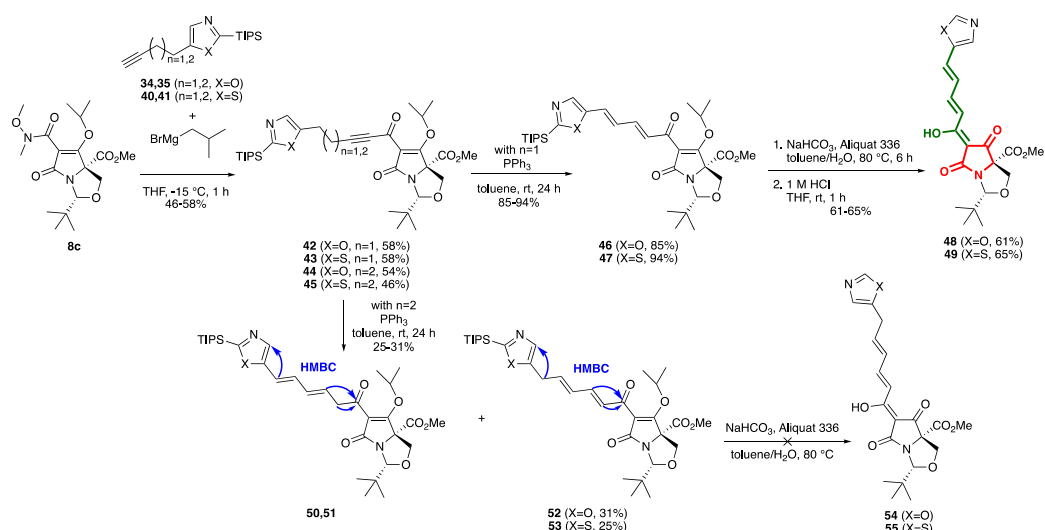


through oxidation to the aldehyde followed by Seyferth-Gilbert homologation. For the longer one, the additional carbon atom was introduced using a Mitsunobu-Wilk procedure<sup>38</sup> to substitute the hydroxyl by a nitrile group. Subsequent reduction with DIBAL-H and treatment with Bestmann reagent yielded alkyne **40**. The same sequence was employed to access thiazole alkynes **35** and **41**.



Scheme 7. Preparation of alkynes **34,35** and **40,41** starting from oxazole and thiazole.

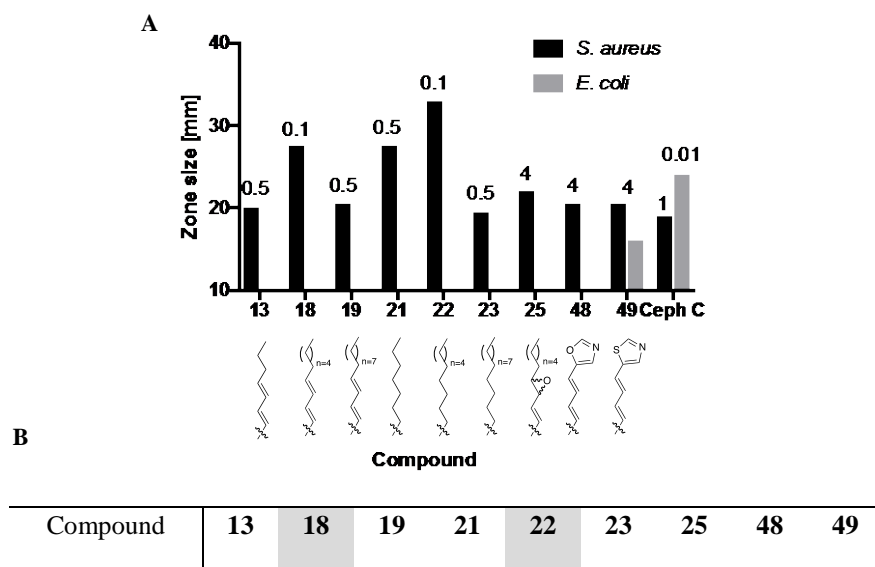
With the alkynes in hand, reaction with Weinreb amide **8c** gave the alkynoyl analogues **42-45**, along with the enamine side-product, which accounted for the moderate yields (Scheme 8). Interestingly, isomerisation of the alkynes was achieved in high yield with the short analogues (n=1), but when n=2, a 1:1 mixture of alkene isomers **50,52** and **51,53** was obtained. For the shorter systems **46** and **47**, deprotection of both isopropoxy and TIPS groups yielded the target diene-tetramates oxazole **48** and thiazole **49** without complication. Unfortunately, the analogues bearing the additional methylene (**52, 53**), experienced degradation upon deprotection of the enol group and no desired tetramate was isolated.



Scheme 8. Preparation of heterocyclic dienes **48,49** and unsuccessful formation of **54,55**.

### Antibacterial activity

To study the influence of the side chain on antibacterial activity, the synthesised *C*(6)-acyltetramates were tested using the hole-plate method.<sup>39</sup> Solutions of the compounds were loaded into 10 mm wells in agar plates inoculated with either Gram-negative *Escherichia coli* or Gram-positive *Staphylococcus aureus*. The plates were incubated for 20 h, and the resultant inhibition zones were measured and compared to the positive control (Cephalosporin C). The compounds were initially tested at 4 mg/mL, and the most active ones diluted to obtain a zone size smaller than 35 mm.





Relative potency	2.3	36.7	2.5	7.3	85.7	2.1	0.4	0.3	0.3
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Figure 2. Antibacterial activity of the synthesised C(6)-acyltetramates. (A) Zone size measured with the hole-plate method. The value above the bars indicates concentration of compound used in mg/mL; (B) Relative potency of the compounds compared to Cephalosporin C in *S. aureus*.

As indicated in Figure 2, the most active analogues against *S. aureus* were those with long lipophilic chains, while heterocycles **48** and **49** proved to be only weakly active. Epoxide **25** was also less active than the equivalent diene **18**. The length of the chain was also influential for activity, and interestingly both the 10-carbon analogues – diene **18** and saturated **22** – showed the biggest zone sizes at the lowest concentration (0.1 mg/mL). Remarkably, these were 37- and 86-fold more potent than the positive control respectively. Conversely, only thiazole **49** displayed weak inhibition of Gram-negative *E. coli*.

Given the high degree of unsaturation of the acyl chain in natural tetramic acids (Figure 1), the similar activities of both the dienoyl and the saturated analogues was unexpected. In fact, Schobert and co-workers have reported similar observations, that a high degree of unsaturation on the side chain of 3-acyltetramic acids is not a prerequisite for antibacterial activity, as a saturated analogue of the ravenic acid was equally active than the parent natural product (Figure 1).<sup>12</sup>

The selectivity of these compounds for Gram-positive *S. aureus* has also been observed for structurally related tetramates, with the less polar compounds found to be the most active against *S. aureus*.<sup>14,27</sup> The low activity against Gram-negative systems is likely to be due to poor cell penetration or efficient efflux pump removal. By comparison, the natural C(6)-acyltetramate, kibelomycin, was shown to inhibit DNA gyrase and topoisomerase enzymes from both *S. aureus* and *E. coli*, but this inhibition only correlated with whole-cell activity of the former; the efficacy of the latter was probably limited by poor cell membrane uptake or by the active efflux pump. In fact, the weakest C(6)-acyl analogue tested herein, thiazole **51**, was also the only one with some activity against Gram-negative *E. coli*, which could be ascribed to improved permeability.

Of interest is also that isopropoxy-protected **17**, precursor of the most active diene **18**, was found to be completely inactive, suggesting that the tetramic acid scaffold is required for biological activity. However, the tetramate core itself is not sufficient for the antibacterial properties, as unsubstituted **1** and **2** are inactive, revealing that appropriate functionalisation is required to obtain potent compounds.

To support the results obtained with the hole-plate method, MIC values of the compounds were measured using a broth dilution assay (Table 2). For *S. aureus*, the lowest values were confirmed to be for those compounds with lipophilic side chains, and again only the most polar analogues displayed some inhibition against *E. coli*. Importantly, we observed a good correlation between the activity values obtained from both assays, namely hole-plate method and broth dilution (Figure 3); this is important, as the whole plate assay provides for a very convenient initial screen.

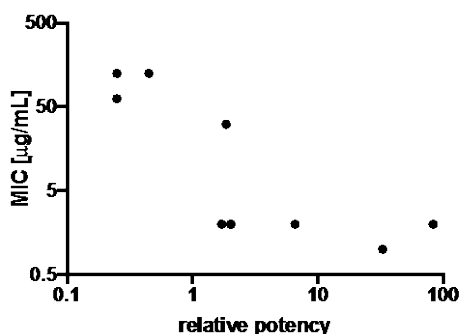


Figure 3. Correlation between the results obtained with the hole-plate method (quantified as relative potency to Cephalosporin C) and the broth dilution assay (MIC).

The most active analogues were also tested for antibacterial activity against Gram-positive *Enterococcus faecalis* and Gram-negative *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, and antifungal activity against *Candida albicans*, *Candida krusei* and *Aspergillus fumigatus*. Only activity against the bacterium *E. faecalis* was found, consistent with the selective Gram-positive activity noted above. With regards to antifungal activity, most analogues showed some inhibition, but in particular undecyl **22**.

Table 2. *In vitro* antibacterial and antifungal activity (MIC, μg/mL) of C(6)-acyltetramic acids.\*

	<i>E. coli</i>	<i>S. aureus</i>	<i>E. faecalis</i>	<i>S. pneumoniae</i>	<i>K. pneumoniae</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>	<i>C. krusei</i>	<i>A. fumigatus</i>
<b>13</b>	n.a.	31	16	31	n.a.	n.a.	250	250	250
<b>18</b>	n.a.	1	1	1	n.a.	250	250	250	62
<b>19</b>	n.a.	2	2	2	n.a.	n.a.	500	500	n.a.
<b>21</b>	n.a.	2	2	6	n.a.	500	500	500	200
<b>22</b>	n.a.	2	2	2	n.a.	n.a.	250	250	8
<b>23</b>	n.a.	2	2	2	n.a.	n.a.	250	250	250
<b>48</b>	250	125	–	125	–	–	–	–	–

**49**    250    62.5    –    62.5    –    –    –    –    –

\*n.a. = not active; – = not determined. Ciprofloxacin used as positive control.

The selectivity of the analogues to prokaryotic cells over mammalian cells was analysed by means of their EC<sub>50</sub> values against HaCaT, an immortalised keratinocyte human cell line (Table 3). The therapeutic window was estimated as the ratio of EC<sub>50</sub> (HaCaT) to MIC (*S. aureus*). The best compound in this regard was decadiene **18**, with an 88-fold selectivity, an excellent compromise between high potency and low toxicity. Therefore, despite the similar potencies of both the unsaturated and saturated analogues, this data suggests that the latter might suffer from bigger toxicities.

Table 3. Assessment of human toxicity: therapeutic ratio between MIC (*S. aureus*) and EC<sub>50</sub> (HaCat).

	<i>S. aureus</i>	HaCat	Therapeutic
	MIC [ $\mu\text{g/mL}$ ]	EC <sub>50</sub> [ $\mu\text{g/mL}$ ]	ratio
<b>13</b>	31	175	5.6
<b>18</b>	1	87.5	87.5
<b>19</b>	2	150	75.0
<b>21</b>	2	25	12.5
<b>22</b>	2	45	22.5
<b>23</b>	2	24	12.0

## Conclusion

With this work, we have developed methods to rapidly and efficiently access dienoyl-tetramates, a common moiety in several complex natural products; this complements alternative approaches.<sup>12</sup> We employed a simple bicyclic tetramate scaffold and prepared several analogues with different lipophilic C(6)-acyl chains, and we were able to regioselectively epoxidise the dienoyl analogues. We further applied our methodology to access more polar compounds, bearing heterocycles. These required the preparation of novel oxazole and thiazole alkynes, which were accessed efficiently in high yields. Overall, this provides a flexible route to a variety of mimics of pramanicin and of polyenoyl tetramates, some of which show antibacterial activity; although these mimics may be considered to be distant from their parent natural products, they nonetheless help to define the antibacterially active property space and, for example, the most active undecylidene **18** had an MIC value of 1

$\mu\text{g/mL}$ . This activity is comparable to that of known therapeutic systems,<sup>40,41</sup> and considering that MIC values of  $<16 \mu\text{g/mL}$  are acceptable as starting points for pharmaceutical development,<sup>42</sup> these compounds could be considered to be suitable for more detailed investigation.

The highly potent activity of some of the synthesised analogues demonstrates the suitability of tetramates as 3D-templates to prepare novel antibiotics and further supports the value of natural products as useful starting points for antibacterial drug discovery.

## Experimental section

### General methods

All reagents were obtained from commercial sources and used without further purification. Anhydrous solvents were dried by pre-storing them over activated 3 Å molecular sieves before being passed through an activated alumina column on a solvent tower under  $\text{N}_2$  pressure. Reactions were conducted in oven-dried glassware under an inert atmosphere of nitrogen. Concentrations ( $c$ ) in the general procedures refer to the limiting reagent and are given in  $\text{mmol/mL}$ . Analytical thin-layer chromatography (TLC) was carried out on Merck aluminium foil backed sheets precoated with 0.2 mm Kielselgel 60 F254. The spots were visualised by UV irradiation ( $\lambda$  254 nm) and by staining with a  $\text{KMnO}_4$  solution followed by heating. Flash column chromatography was performed on Kielselgel 60 silica gel (230-400 mesh particle size). Optical rotations were recorded at 25 °C on a polarimeter using the D line of sodium (589 nm) and a path length of 1 dm. Concentrations ( $c$ ) are given in  $\text{g}/100 \text{ mL}$  and specific rotations ( $[\alpha]_D^{20}$ ) are quoted in  $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ . Melting points were measured with a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an FT-IR spectrometer; absorption maxima ( $\nu_{\text{max}}$ ) are reported in wavenumbers ( $\text{cm}^{-1}$ ) and only selected peaks are reported.  $^1\text{H}$  NMR spectra were recorded 400 and 500 MHz, and  $^{13}\text{C}$  NMR spectra at 101 and 125 MHz. Chemical shifts ( $\delta_{\text{H}}$  and  $\delta_{\text{C}}$ ) are reported in parts per million (ppm) and are referenced to the residual solvent peak ( $\text{CDCl}_3$ :  $\delta$  7.26 for  $^1\text{H}$  NMR and  $\delta$  77.2 for  $^{13}\text{C}$  NMR;  $\text{C}_6\text{D}_6$ :  $\delta$  7.16 for  $^1\text{H}$  NMR and  $\delta$  128.1 for  $^{13}\text{C}$  NMR;  $\text{CD}_2\text{Cl}_2$ :  $\delta$  5.32 for  $^1\text{H}$  NMR and  $\delta$  54.0 for  $^{13}\text{C}$  NMR) and  $\text{CDCl}_3$ . Coupling constants ( $J$ ) are quoted in Hz. Two-dimensional COSY, NOE and HMBC experiments were recorded at 500 MHz. Low resolution mass spectra ( $m/z$ ) were recorded using electrospray ionisation (ESI); selected peaks are reported in Daltons and their intensities given as percentages of the base peak. High resolution mass spectra (HRMS) were recorded using TOF (ESI). In the

cases where the products exist as mixtures of tautomers or diastereomers, the ratio was calculated from the  $^1\text{H}$  NMR spectrum.

For  $^1\text{H}$  and  $^{13}\text{C}$  NMR assignments of tetramates, the conventional IUPAC numbering has been used for the bicyclic core; the C(6) side chain has been numbered with prime ('). For oxazoles and thiazoles, the prime ( ' or ' ') numbers correspond to the positions in the heterocycle.

Weinreb amide **2**,<sup>27</sup> oxazole **26**<sup>36</sup> and thiazole **27**<sup>43</sup> were prepared as reported.

#### *General procedure A: Alkylation of C(6)-acyltetramates*

Diethyl azodicarboxylate (1.1 eq) was added to a solution of C(6)-acyltetramate (1.0 eq), the required alcohol (1.1 eq) and triphenylphosphine (1.1 eq) in anhydrous THF (c 0.1) at 0 °C. The mixture was stirred at room temperature for 13-24 h and then concentrated under reduced pressure. The crude residue was purified by flash column chromatography to give the alkyl ether.

#### *General procedure B: Grignard reaction of enol-protected Weinreb amide with alkynyl Grignard reagents*

Isobutylmagnesium bromide (2 M in Et<sub>2</sub>O, 1.0 eq) was added dropwise to a solution of the 1-alkyne (1.1 eq) in anhydrous THF (c 0.7) at 0 °C. The suspension was then warmed to room temperature and heated at 40 °C for 5 h. The solution was used for the Grignard reaction directly at 40 °C.

The prepared Grignard reagent (2.5 eq) was added to enol-protected Weinreb amide (1.0 eq) in anhydrous THF dropwise at -15 °C. The reaction mixture was stirred at -15 °C for 1 h. The solution was quenched with saturated aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo* and purified by *flash* column chromatography to give the C(7)-alkynyl product.

#### *General procedure C: Isomerisation of alkynones*

Triphenylphosphine (1.0 eq, unless otherwise specified) was added to a solution of alkynone (1.0 eq) in anhydrous toluene (c 0.2). The reaction mixture was stirred at room temperature for 24 h, concentrated *in vacuo* and purified by *flash* column chromatography to give the dienone.

#### *General procedure D: Deprotection of isopropoxy enol ethers*

NaHCO<sub>3</sub> (60 eq) was added to a biphasic solution of the enol ether (1.0 eq) and Aliquat 336 (1.1 eq) in 1:1 toluene/H<sub>2</sub>O (c 0.05). The mixture was heated at 80 °C for 6 h, quenched with saturated aqueous NH<sub>4</sub>Cl,

extracted with EtOAc, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by *flash* column chromatography to give the deprotected tetramate.

*Methyl (3R,7aR)-3-(tert-butyl)-7-methoxy-6-(methoxy(methyl)carbamoyl)-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (8a)*

General procedure A with DIAD instead of DEAD (from **2**, with methanol, for 13 h); yield 80% (342 mg); colourless oil. *R*<sub>f</sub> (25% EtOAc in DCM) 0.41; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +74.6 (*c* 1.1, DCM);  $\nu_{\max}/\text{cm}^{-1}$  2959 (C-H), 1752 (C=O), 1719 (C=O), 1650 (C=O);  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>, 4:1 mixture of rotamers, major A and minor B) 0.89 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 3.29 (3H, s, NCH<sub>3</sub> A), 3.33 (3H, s, NCH<sub>3</sub> B), 3.51 (1H, d, *J* 8.5, C(1)*H*<sub>A</sub>*H*<sub>B</sub>), 3.71 (3H, s, NOCH<sub>3</sub> A), 3.79 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 3.87 (3H, s, NOCH<sub>3</sub> B), 3.93 (3H, s, C(7)OCH<sub>3</sub> A), 4.02 (3H, s, C(7)OCH<sub>3</sub> B), 4.70 (1H, s, C(3)*H*), 4.79 (1H, d, *J* 8.5, C(1)*H*<sub>A</sub>*H*<sub>B</sub>);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 24.7 (C(CH<sub>3</sub>)<sub>3</sub>), 32.5 (NCH<sub>3</sub>), 35.2 (C(CH<sub>3</sub>)<sub>3</sub>), 53.4 (CO<sub>2</sub>CH<sub>3</sub>), 60.2 (C(7)OCH<sub>3</sub>), 61.9 (NOCH<sub>3</sub>), 69.5 (C(1)), 74.4 (C(7a)), 97.3 (C(3)), 105.0 (C(6)), 163.0 (C(1')), 168.3 (CO<sub>2</sub>CH<sub>3</sub>), 169.7 (C(7)), 174.9 (C(5)); *m/z* (ESI<sup>+</sup>) 357.1 (MH<sup>+</sup>, 100%), 379.1 (MNa<sup>+</sup>, 51%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>25</sub>N<sub>2</sub>O<sub>7</sub> 357.1656; found 357.1651.

*Methyl (3R,7aR)-7-(benzyloxy)-3-(tert-butyl)-6-(methoxy(methyl)carbamoyl)-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (8b)*

*General procedure* General procedure A (from **2**, with benzyl alcohol, for 18 h); yield 71% (253 mg); yellow oil. *R*<sub>f</sub> (20% EtOAc in DCM) 0.57; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +29.2 (*c* 1.0, DCM);  $\nu_{\max}/\text{cm}^{-1}$  2957 (C-H), 1751 (C=O), 1718 (C=O), 1646 (C=O);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, 2:1 mixture of rotamers, major A and minor B) 0.89 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.88 (3H, s, NCH<sub>3</sub> B), 3.25 (3H, s, NCH<sub>3</sub> A), 3.42 (3H, s, NOCH<sub>3</sub> A), 3.57 (1H, d, *J* 8.6, C(1)*H*<sub>A</sub>*H*<sub>B</sub>), 3.77 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 3.80 (3H, s, NOCH<sub>3</sub> B), 4.68 (1H, s, C(3)*H*), 4.82 (1H, d, *J* 8.6, C(1)*H*<sub>A</sub>*H*<sub>B</sub>), 5.22 (1H, d, *J* 11.8, C(7)OCH<sub>A</sub>*H*<sub>B</sub> A), 5.31 (1H, d, *J* 11.8, C(7)OCH<sub>A</sub>*H*<sub>B</sub> A), 5.22 (1H, d, *J* 12.4, C(7)OCH<sub>A</sub>*H*<sub>B</sub> B), 5.31 (1H, d, *J* 12.4, C(7)OCH<sub>A</sub>*H*<sub>B</sub> B), 7.22-7.24 (2H, m, Ar), 7.34-7.37 (3H, m, Ar);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 24.7 (C(CH<sub>3</sub>)<sub>3</sub>), 32.3 (NCH<sub>3</sub>), 35.2 (C(CH<sub>3</sub>)<sub>3</sub>), 53.2 (CO<sub>2</sub>CH<sub>3</sub>), 61.3 (NOCH<sub>3</sub>), 68.0 (C(1)), 74.5 (C(7)OC), 74.6 (C(7a)), 97.2 (C(3)), 105.7 (C(6)), 127.9, 128.7, 129.0, 134.5 (Ar), 162.6 (C(1')), 168.2 (CO<sub>2</sub>CH<sub>3</sub>), 169.0 (C(7)), 174.7 (C(5)); *m/z* (ESI<sup>+</sup>) 433.1 (MH<sup>+</sup>, 58%), 455.1 (MNa<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>22</sub>H<sub>29</sub>N<sub>2</sub>O<sub>7</sub> 433.1969; found 433.1962.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-6-(methoxy(methyl)carbamoyl)-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (8c)*

General procedure A (from **2**, with 2-propanol, for 24 h); yield 69% (2.50 g); yellow oil.  $R_f$  (20% EtOAc in DCM) 0.57;  $[\alpha]_D^{20} +57.4$  ( $c$  1.0, DCM);  $\nu_{\max}/\text{cm}^{-1}$  2959 (C-H), 1752 (C=O), 1716 (C=O), 1641 (C=O);  $\delta_H$  (400 MHz,  $\text{CDCl}_3$ , 3:1 mixture of rotamers, major A and minor B) 0.90 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.20 (3H, d,  $J$  6.0,  $^i\text{Pr}$ ), 1.28-1.34 (3H, m,  $^i\text{Pr}$ ), 3.29 (3H, s,  $\text{NCH}_3$  A), 3.34 (3H, s,  $\text{NCH}_3$  B), 3.51 (1H, d,  $J$  8.5,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 3.73 (3H, s,  $\text{NOCH}_3$  A), 3.79 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 3.82 (3H, s,  $\text{NOCH}_3$  B), 4.72 (1H, s,  $\text{C}(3)\text{H}$ ), 4.72-4.77 (1H, m,  $^i\text{Pr}$ ), 4.81 (1H, d,  $J$  8.5,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ );  $\delta_C$  (100 MHz,  $\text{CDCl}_3$ ) 21.1 ( $^i\text{Pr}$ ), 22.2 ( $^i\text{Pr}$ ), 24.7 ( $\text{C}(\text{CH}_3)_3$ ), 32.4 ( $\text{NCH}_3$ ), 35.2 ( $\text{C}(\text{CH}_3)_3$ ), 53.2 ( $\text{CO}_2\text{CH}_3$ ), 61.8 ( $\text{NOCH}_3$ ), 69.4 ( $\text{C}(1)$ ), 74.9 ( $\text{C}(7\text{a})$ ), 76.8 ( $^i\text{Pr}$ ), 97.1 ( $\text{C}(3)$ ), 104.4 ( $\text{C}(6)$ ), 163.5 ( $\text{C}(1')$ ), 168.1, ( $\text{CO}_2\text{CH}_3$ ), 168.3 ( $\text{C}(7)$ ), 175.4 ( $\text{C}(5)$ );  $m/z$  ( $\text{ESI}^+$ ) 407.2 ( $\text{MNa}^+$ , 100%); HRMS ( $\text{ESI-TOF}$ )  $m/z$   $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{18}\text{H}_{29}\text{N}_2\text{O}_7$  385.1969; found 385.1964.

*Methyl (3R,7aR)-3-(tert-butyl)-7-methoxy-6-(oct-2-ynoyl)-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (9a)*

General procedure B (from **8a**, with 1-heptyne); yield 27% (13 mg); yellow oil.  $R_f$  (DCM) 0.48;  $[\alpha]_D^{20} +120.0$  ( $c$  1.0, DCM);  $\nu_{\max}/\text{cm}^{-1}$  2958 (C-H), 2213 ( $\text{C}\equiv\text{C}$ ), 1752 (C=O), 1720 (C=O), 1637 (C=O), 1604 (C=C);  $\delta_H$  (500 MHz,  $\text{CDCl}_3$ ) 0.90 (3H, t,  $J$  7.0,  $\text{C}(8')\text{H}_3$ ), 0.90 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.33 (2H, tq,  $J$  7.5, 7.0,  $\text{C}(7')\text{H}_2$ ), 1.39-1.45 (2H, m,  $\text{C}(6')\text{H}_2$ ), 1.63 (2H, tt,  $J$  7.5, 7.0,  $\text{C}(5')\text{H}_2$ ), 2.44 (2H, t,  $J$  7.0,  $\text{C}(4')\text{H}_2$ ), 3.47 (1H, d,  $J$  8.5,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 3.80 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.05 (3H, s,  $\text{C}(7)\text{OCH}_3$ ), 4.75 (1H, s,  $\text{C}(3)\text{H}$ ), 4.82 (1H, d,  $J$  8.5,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ );  $\delta_C$  (125 MHz,  $\text{CDCl}_3$ ) 14.0 ( $\text{C}(8')$ ), 19.6 ( $\text{C}(4')$ ), 22.3 ( $\text{C}(7')$ ), 24.8 ( $\text{C}(\text{CH}_3)_3$ ), 27.5 ( $\text{C}(5')$ ), 31.2 ( $\text{C}(6')$ ), 35.3 ( $\text{C}(\text{CH}_3)_3$ ), 53.6 ( $\text{CO}_2\text{CH}_3$ ), 63.5 ( $\text{C}(7)\text{OCH}_3$ ), 69.5 ( $\text{C}(1)$ ), 73.8 ( $\text{C}(7\text{a})$ ), 81.9 ( $\text{C}(2')$ ), 97.8 ( $\text{C}(3)$ ), 99.7 ( $\text{C}(3')$ ), 110.2 ( $\text{C}(6)$ ), 168.0 ( $\text{CO}_2\text{CH}_3$ ), 172.3 ( $\text{C}(1')$ ), 174.1 ( $\text{C}(5)$ ), 175.6 ( $\text{C}(7)$ );  $m/z$  ( $\text{ESI}^+$ ) 392.1 ( $\text{MH}^+$ , 42%), 414.1 ( $\text{MNa}^+$ , 100%); HRMS ( $\text{ESI-TOF}$ )  $m/z$   $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{21}\text{H}_{30}\text{NO}_6$  392.2068; found 392.2066.

*Methyl (3R,7aR)-7-(benzyloxy)-3-(tert-butyl)-6-(oct-2-ynoyl)-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (9b)*

General procedure B (from **8b**, with 1-heptyne); yield 35% (18 mg); yellow oil.  $R_f$  (20% EtOAc in petrol) 0.58;  $[\alpha]_D^{20} +105.6$  ( $c$  0.7, DCM);  $\nu_{\max}/\text{cm}^{-1}$  2957 (C-H), 2210 ( $\text{C}\equiv\text{C}$ ), 1752 (C=O), 1721 (C=O), 1634 (C=O), 1598 (C=C);  $\delta_H$  (500 MHz,  $\text{CDCl}_3$ ) 0.90 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 0.91 (3H, t,  $J$  7.2,  $\text{C}(8')\text{H}_3$ ), 1.29-1.37 (2H, m,  $\text{C}(7')\text{H}_2$ ), 1.38-1.44 (2H, m,  $\text{C}(6')\text{H}_2$ ), 1.62 (2H, 77,  $J$  7.5, 7.0,  $\text{C}(5')\text{H}_2$ ), 2.44 (2H, t,  $J$  7.0,  $\text{C}(4')\text{H}_2$ ), 3.47 (1H, d,  $J$  8.6,

C(1) $H_AH_B$ ), 3.71 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.75 (1H, s, C(3) $H$ ), 4.81 (1H, d,  $J$  8.6, C(1) $H_AH_B$ ), 5.19 (1H, d,  $J$  12.0, C(7) $\text{OCH}_A\text{H}_B$ ), 5.50 (1H, d,  $J$  12.0, C(7) $\text{OCH}_A\text{H}_B$ ), 7.22-7.24 (2H, m, Ar), 7.35-7.37 (3H, m, Ar);  $\delta_c$  (125 MHz,  $\text{CDCl}_3$ ) 14.0 (C(8')), 19.7 (C(4')), 22.3 (C(7')), 24.8 (C( $\text{CH}_3$ )<sub>3</sub>), 27.5 (C(5')), 31.2 (C(6')), 35.3 (C( $\text{CH}_3$ )<sub>3</sub>), 53.4 ( $\text{CO}_2\text{CH}_3$ ), 69.6 (C(1)), 74.2 (C(7a)), 77.8 (C(7)OC), 81.9 (C(2')), 97.8 (C(3)), 100.0 (C(3')), 110.6 (C(6)), 128.3, 128.9, 129.3, 134.1 (Ar), 168.0 ( $\text{CO}_2\text{CH}_3$ ), 172.6 (C(1')), 174.1 (C(5)), 174.6 (C(7));  $m/z$  (ESI<sup>+</sup>) 468.3 ( $\text{MH}^+$ , 66%), 490.2 ( $\text{MNa}^+$ , 100%); HRMS (ESI-TOF)  $m/z$  [ $\text{M}+\text{H}$ ]<sup>+</sup> Calcd for  $\text{C}_{27}\text{H}_{34}\text{NO}_6$  468.2381; found 468.2369.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-6-(oct-2-ynoyl)-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (9c)*

General procedure B (from **8c**, with 1-heptyne); yield 59% (657 mg); light yellow solid; m.p. 63-65 °C.  $R_f$  (DCM) 0.43;  $[\alpha]_D^{20}$  +117.3 ( $c$  1.0, DCM);  $\nu_{\text{max}}/\text{cm}^{-1}$  2958 (C-H), 2211 (C $\equiv$ C), 1754 (C=O), 1720 (C=O), 1634 (C=O), 1587 (C=C);  $\delta_H$  (500 MHz,  $\text{CDCl}_3$ ) 0.90 (3H, t,  $J$  7.2, C(8') $H_3$ ), 0.91 (9H, s, C( $\text{CH}_3$ )<sub>3</sub>), 1.17 (3H, d,  $J$  6.0,  $i\text{Pr}$ ), 1.30-1.37 (2H, m, C(7') $H_2$ ), 1.32 (3H, d,  $J$  6.0,  $i\text{Pr}$ ), 1.39-1.45 (2H, m, C(6') $H_2$ ), 1.63 (2H, tt,  $J$  7.5, 7.0, C(5') $H_2$ ), 2.45 (2H, t,  $J$  7.0, C(4') $H_2$ ), 3.45 (1H, d,  $J$  8.5, C(1) $H_AH_B$ ), 3.79 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.77 (1H, s, C(3) $H$ ), 4.82 (1H, d,  $J$  8.5, C(1) $H_AH_B$ ), 5.20 (1H, sept,  $J$  6.0,  $i\text{Pr}$ );  $\delta_c$  (125 MHz,  $\text{CDCl}_3$ ) 14.0 (C(8')), 19.7 (C(4')), 21.1 ( $i\text{Pr}$ ), 22.3 (C(7')), 22.3 ( $i\text{Pr}$ ), 24.8 (C( $\text{CH}_3$ )<sub>3</sub>), 27.5 (C(5')), 31.2 (C(6')), 35.3 (C( $\text{CH}_3$ )<sub>3</sub>), 53.4 ( $\text{CO}_2\text{CH}_3$ ), 69.6 (C(1)), 74.4 (C(7a)), 79.7 ( $i\text{Pr}$ ), 81.9 (C(2')), 97.8 (C(3)), 99.3 (C(3')), 109.4 (C(6)), 168.1 ( $\text{CO}_2\text{CH}_3$ ), 172.7 (C(1')), 173.9 (C(5)), 174.6 (C(7));  $m/z$  (ESI<sup>+</sup>) 420.2 ( $\text{MH}^+$ , 61%), 442.2 ( $\text{MNa}^+$ , 100%); HRMS (ESI-TOF)  $m/z$  [ $\text{M}+\text{H}$ ]<sup>+</sup> Calcd for  $\text{C}_{23}\text{H}_{34}\text{NO}_6$  420.2381; found 420.2371.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-6-(3-methylbutanoyl)-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (10c)*

Side-product from the reaction of isopropoxy Weinreb amide **8c** with alkynyl Grignard reagents, yellow oil.  $R_f$  (DCM) 0.40;  $[\alpha]_D^{20}$  +104.2 ( $c$  1.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2958 (C-H), 1754 (C=O), 1712 (C=O), 1681 (C=O), 1588 (C=C);  $\delta_H$  (400 MHz,  $\text{CDCl}_3$ ) 0.90 (9H, s, C( $\text{CH}_3$ )<sub>3</sub>), 0.93 (3H, d,  $J$  6.7, C(4'<sub>A</sub>) $H_3$ ), 0.95 (3H, d,  $J$  6.6, C(4'<sub>B</sub>) $H_3$ ), 1.10 (3H, d,  $J$  6.1,  $\text{O}^i\text{Pr}$ ), 1.30 (3H, d,  $J$  6.1,  $\text{O}^i\text{Pr}$ ), 2.19 (1H, n,  $J$  6.7, C(3') $H$ ), 2.77 (1H, dd,  $J$  17.7, 6.7, C(2') $H_AH_B$ ), 3.02 (1H, dd,  $J$  17.7, 6.7, C(2') $H_AH_B$ ), 3.45 (1H, d,  $J$  8.4, C(1) $H_AH_B$ ), 3.77 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.73 (1H, s, C(3) $H$ ), 4.80 (1H, d,  $J$  8.4, C(1) $H_AH_B$ ), 5.16 (1H, sept,  $J$  6.1,  $\text{O}^i\text{Pr}$ );  $\delta_c$  (100 MHz,  $\text{CDCl}_3$ ) 21.0 ( $\text{O}^i\text{Pr}$ ), 22.3 ( $\text{O}^i\text{Pr}$ ), 22.7 (C(4'<sub>B</sub>)), 22.8 (C(4'<sub>A</sub>)), 24.1 (C(3')), 24.8 (C( $\text{CH}_3$ )<sub>3</sub>), 35.3 (C( $\text{CH}_3$ )<sub>3</sub>), 51.3 (C(2')), 53.3



(CO<sub>2</sub>CH<sub>3</sub>), 69.6 (C(1)), 74.7 (C(7a)), 78.9 (O<sup>i</sup>Pr), 97.6 (C(3)), 110.1 (C(6)), 168.2 (CO<sub>2</sub>CH<sub>3</sub>), 173.1 (C(7)), 176.2 (C(5)), 198.2 (C(1')); *m/z* (ESI<sup>+</sup>) 382.23 (MH<sup>+</sup>, 18%), 404.2 (MNa<sup>+</sup>, 74%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>20</sub>H<sub>32</sub>NO<sub>6</sub> 382.2224; found 382.2226.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-6-((Z)-3-(methoxy(methyl)amino)tetradec-2-enoyl)-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (11c')*

Side-product (24%, 79 mg) from the Grignard reaction of isopropoxy Weinreb amide **8c** and 1-tridecyne, General procedure B; colourless oil. *R<sub>f</sub>* (20% EtOAc in petrol) 0.51; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +114.1 (*c* 1.0, CHCl<sub>3</sub>);  $\nu_{\max}/\text{cm}^{-1}$  2925 (C-H), 1753 (C=O), 1708 (C=O), 1635 (C=O), 1585 (C=C);  $\delta_{\text{H}}$  (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 0.86-0.89 (3H, m, C(14')H<sub>3</sub>), 0.88 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.12 (3H, d, *J* 6.0, <sup>i</sup>Pr), 1.26 (3H, d, *J* 6.0, <sup>i</sup>Pr), 1.25-1.33 (14H, m, C(7'-13')H<sub>2</sub>), 1.40 (2H, tt, *J* 7.5, 6.5, C(6')H<sub>2</sub>), 1.46-1.52 (2H, m, C(5')H<sub>2</sub>), 2.79 (1H, dt, *J* 12.4, 7.4, C(4')H<sub>A</sub>H<sub>B</sub>), 2.94 (1H, dt, *J* 12.4, 8.1, C(4')H<sub>A</sub>H<sub>B</sub>), 3.20 (3H, s, NCH<sub>3</sub>), 3.47 (1H, d, *J* 8.5, C(1)H<sub>A</sub>H<sub>B</sub>), 3.67 (3H, s, NOCH<sub>3</sub>), 3.76 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.68 (1H, s, C(3)H), 4.75 (1H, d, *J* 8.5, C(1)H<sub>A</sub>H<sub>B</sub>), 5.13 (1H, sept, *J* 6.0, <sup>i</sup>Pr), 5.73 (1H, s, C(10')H);  $\delta_{\text{C}}$  (125 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 14.4 (C(14')), 21.5 (<sup>i</sup>Pr), 22.6 (<sup>i</sup>Pr), 23.3 (C(13')), 25.0 (C(CH<sub>3</sub>)<sub>3</sub>), 28.7 (C(5')), 28.9 (C(4')), 29.9, 30.0, 30.1, 30.2, 30.2, 30.3 (C(6'-11')), 32.5 (C(12)), 35.6 (C(CH<sub>3</sub>)<sub>3</sub>), 37.2 (NCH<sub>3</sub>), 53.4 (CO<sub>2</sub>CH<sub>3</sub>), 60.4 (NOCH<sub>3</sub>), 70.2 (C(1)), 74.8 (C(7a)), 77.4 (<sup>i</sup>Pr), 96.0 (C(2')), 97.7 (C(3)), 113.7 (C(6)), 164.7 (C(3')), 169.4 (CO<sub>2</sub>CH<sub>3</sub>), 169.8 (C(7)), 177.4 (C(5)), 183.7 (C(1')); *m/z* (ESI<sup>+</sup>) 565.4 (MH<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>31</sub>H<sub>53</sub>N<sub>2</sub>O<sub>7</sub> 565.3847; found 565.3840.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-6-((2E,4E)-octa-2,4-dienoyl)-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (12)*

General procedure C (from **9c**); yield 88% (574 mg); yellow oil. *R<sub>f</sub>* (DCM) 0.39; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +129.7 (*c* 1.0, DCM);  $\nu_{\max}/\text{cm}^{-1}$  2960 (C-H), 1754 (C=O), 1712 (C=O), 1652 (C=O), 1591 (C=C);  $\delta_{\text{H}}$  (500 MHz, C<sub>6</sub>D<sub>6</sub>) 0.71 (3H, t, *J* 7.4, C(8')H<sub>3</sub>), 0.87 (3H, d, *J* 6.0, <sup>i</sup>Pr), 1.02 (3H, d, *J* 6.0, <sup>i</sup>Pr), 1.11 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.13 (2H, sext, *J* 7.4, C(7')H<sub>2</sub>), 1.76 (2H, q, *J* 7.4, C(6')H<sub>2</sub>), 3.05 (1H, d, *J* 8.4, C(1)H<sub>A</sub>H<sub>B</sub>), 3.29 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.84 (1H, d, *J* 8.4, C(1)H<sub>A</sub>H<sub>B</sub>), 4.88 (1H, s, C(3)H), 5.41 (1H, sept, *J* 6.0, <sup>i</sup>Pr), 5.76 (1H, dt, *J* 15.0, 7.4, C(5')H), 5.99 (1H, dd, *J* 15.0, 11.0, C(4')H), 7.17 (1H, d, *J* 15.0, C(2')H), 7.59 (1H, dd, *J* 15.0, 11.0, C(3')H);  $\delta_{\text{C}}$  (125 MHz, C<sub>6</sub>D<sub>6</sub>) 13.8 (C(8')), 20.7 (<sup>i</sup>Pr), 22.0 (<sup>i</sup>Pr), 22.0 (C(7')), 25.1 (C(CH<sub>3</sub>)<sub>3</sub>), 35.3 (C(6')), 35.5 (C(CH<sub>3</sub>)<sub>3</sub>), 52.6 (CO<sub>2</sub>CH<sub>3</sub>), 69.7 (C(1)), 75.2 (C(7a)), 78.5 (<sup>i</sup>Pr), 97.8 (C(3)), 110.5 (C(6)), 128.4 (C(2')), 129.9 (C(4')), 144.1 (C(3')), 146.1

(C(5')), 168.6 (CO<sub>2</sub>CH<sub>3</sub>), 173.5 (C(7)), 176.3 (C(5)), 186.7 (C(1')); *m/z* (ESI<sup>+</sup>) 420.3 (MH<sup>+</sup>, 47%), 442.2 (MNa<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>23</sub>H<sub>34</sub>NO<sub>6</sub> 420.2381; found 420.2371.

*Methyl (3R,7aR,Z)-3-(tert-butyl)-6-((2E,4E)-1-hydroxyocta-2,4-dien-1-ylidene)-5,7-dioxodihydro-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (13)*

*Method 1:* BBr<sub>3</sub> (1 M in DCM, 150  $\mu$ L, 0.150 mmol) was added dropwise to a solution of isopropoxy **12** (63 mg, 0.15 mmol) in anhydrous DCM (1.5 mL). The solution was stirred at room temperature for 1 h, quenched with H<sub>2</sub>O and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by *flash* column chromatography (EtOAc), and the product obtained was dissolved in EtOAc, washed with 2 M aqueous HCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give dienoyltetramate **13** (21 mg, 0.055 mmol, 37%).

*Method 2:* General procedure D (from **12**); yield 56% (29 mg).

Orange oil; 3.5:1 mixture of tautomers. *R<sub>f</sub>* (EtOAc) 0.42; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +73.4 (*c* 0.4, CHCl<sub>3</sub>);  $\nu_{\max}$ /cm<sup>-1</sup> 2960 (C-H), 1752 (C=O), 1712 (C=O), 1654 (C=O), 1612 (C=C), 1557 (C=C);  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) major tautomer: 0.91-0.94 (3H, m, C(8')H<sub>3</sub>), 0.93 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.48 (2H, sext, *J* 7.5, C(7')H<sub>2</sub>), 2.22 (2H, q, *J* 7.5, C(6')H<sub>2</sub>), 3.50 (1H, d, *J* 8.9, C(1)H<sub>A</sub>H<sub>B</sub>), 3.77 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.82 (1H, s, C(3)H), 4.85 (1H, d, *J* 8.9, C(1)H<sub>A</sub>H<sub>B</sub>), 6.32-6.40 (2H, m, C(4')H + C(5')H), 7.03 (1H, d, *J* 15.2, C(2')H), 7.55-7.60 (1H, m, C(3')H);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) major tautomer: 13.8 (C(8')), 21.9 (C(7')), 24.8 (C(CH<sub>3</sub>)<sub>3</sub>), 35.3 (C(CH<sub>3</sub>)<sub>3</sub>), 35.6 (C(6')), 53.4 (CO<sub>2</sub>CH<sub>3</sub>), 68.5 (C(1)), 78.4 (C(7a)), 98.4 (C(3)), 99.6 (C(6)), 119.0 (C(2')), 129.8 (C(4')), 148.3 (C(3')), 150.4 (C(5')), 167.9 (CO<sub>2</sub>CH<sub>3</sub>), 177.4 (C(1')), 180.9 (C(5)), 188.0 (C(7)); *m/z* (ESI<sup>+</sup>) 378.2 (MH<sup>+</sup>, 100%), 400.2 (MNa<sup>+</sup>, 66%), *m/z* (ESI<sup>-</sup>) 376.1 (M-H<sup>-</sup>, 100%); HRMS (ESI-TOF) *m/z* [M-H]<sup>-</sup> Calcd for C<sub>20</sub>H<sub>26</sub>NO<sub>6</sub> 376.1766; found 376.1779.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-(undec-2-ynoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (14)*

General procedure B (from **8c**, with 1-decyne); yield 54% (156 mg); yellow oil. *R<sub>f</sub>* (DCM) 0.42; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +99.3 (*c* 0.7, DCM);  $\nu_{\max}$ /cm<sup>-1</sup> 2957 (C-H), 2929 (C-H), 2211 (C $\equiv$ C), 1754 (C=O), 1721 (C=O), 1634 (C=O), 1586 (C=C);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 0.84 (3H, t, *J* 6.9, C(11')H<sub>3</sub>), 0.87 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.13 (3H, d, *J* 6.0, <sup>i</sup>Pr), 1.21-1.27 (8H, m, C(7'-10')H<sub>2</sub>), 1.29 (3H, d, *J* 6.0, <sup>i</sup>Pr), 1.35-1.42 (2H, m, C(6')H<sub>2</sub>), 1.65 (2H, quint, *J* 7.2, C(5')H<sub>2</sub>), 2.42 (2H, t, *J* 7.2, C(4')H<sub>2</sub>), 3.42 (1H, d, *J* 8.5, C(1)H<sub>A</sub>H<sub>B</sub>), 3.75 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.73 (1H, s, C(3)H), 4.78 (1H, d, *J* 8.5, C(1)H<sub>A</sub>H<sub>B</sub>), 5.17 (1H, sept, *J* 6.0, <sup>i</sup>Pr);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 14.2 (C(11')), 19.6 (C(4')), 21.0

(<sup>i</sup>Pr), 22.2 (<sup>i</sup>Pr), 22.7 (C(10')), 24.7 (C(CH<sub>3</sub>)<sub>3</sub>), 27.7 (C(5')), 29.0 (C(6')), 29.1, 29.2 (C(7'), C(8')), 31.9 (C(9')), 35.2 (C(CH<sub>3</sub>)<sub>3</sub>), 53.3 (CO<sub>2</sub>CH<sub>3</sub>), 69.5 (C(1)), 74.3 (C(7a)), 79.6 (<sup>i</sup>Pr), 81.8 (C(2')), 97.7 (C(3)), 99.2 (C(3')), 109.3 (C(6)), 168.0 (CO<sub>2</sub>CH<sub>3</sub>), 172.5 (C(1')), 173.8 (C(7)), 174.5 (C(5)); *m/z* (ESI<sup>+</sup>) 462.3 (MH<sup>+</sup>, 67%), 484.3 (MNa<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>26</sub>H<sub>40</sub>NO<sub>6</sub> 462.2850; found 462.2835.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-(tetradec-2-ynoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (15)*

General procedure B (from **8c**, with 1-tridecyne); yield 47% (141 mg); light yellow oil. *R<sub>f</sub>* (20% EtOAc in petrol) 0.52; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +93.3 (*c* 1.0, CHCl<sub>3</sub>);  $\nu_{\max}$ /cm<sup>-1</sup> 2925 (C-H), 2211 (C≡C), 1754 (C=O), 1721 (C=O), 1633 (C=O), 1583 (C=C);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 0.85 (3H, t, *J* 6.8, C(14')H<sub>3</sub>), 0.90 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.15 (3H, d, *J* 6.0, <sup>i</sup>Pr), 1.22-1.29 (14H, m, C(7'-13')H<sub>2</sub>), 1.31 (3H, d, *J* 6.0, <sup>i</sup>Pr), 1.41 (2H, quint, *J* 7.2, C(6')H<sub>2</sub>), 1.61 (2H, quint, *J* 7.2, C(5')H<sub>2</sub>), 2.44 (2H, t, *J* 7.2, C(4')H<sub>2</sub>), 3.44 (1H, d, *J* 8.5, C(1)H<sub>A</sub>H<sub>B</sub>), 3.78 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.75 (1H, s, C(3)H), 4.80 (1H, d, *J* 8.5, C(1)H<sub>A</sub>H<sub>B</sub>), 5.19 (1H, sept, *J* 6.0, <sup>i</sup>Pr);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 14.2 (C(14')), 19.7 (C(4')), 21.1 (<sup>i</sup>Pr), 22.3 (<sup>i</sup>Pr), 22.8 (C(13')), 24.8 (C(CH<sub>3</sub>)<sub>3</sub>), 27.8 (C(5')), 29.1 (C(6')), 29.2, 29.5, 29.6, 29.7, 29.7 (C(7'-11')), 32.0 (C(12')), 35.3 (C(CH<sub>3</sub>)<sub>3</sub>), 53.3 (CO<sub>2</sub>CH<sub>3</sub>), 69.6 (C(1)), 74.4 (C(7a)), 79.7 (<sup>i</sup>Pr), 81.8 (C(2')), 97.8 (C(3)), 99.3 (C(3')), 109.4 (C(6)), 168.1 (CO<sub>2</sub>CH<sub>3</sub>), 172.6 (C(1')), 173.9 (C(7)), 174.6 (C(5)); *m/z* (ESI<sup>+</sup>) 526.3 (MNa<sup>+</sup>, 31%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>29</sub>H<sub>46</sub>NO<sub>6</sub> 504.3320; found 504.3320.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-((2E,4E)-undeca-2,4-dienoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (16)*

General procedure C (from **14**); yield 81% (129 mg); orange oil. *R<sub>f</sub>* (10% EtOAc in petrol) 0.28; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +126.0 (*c* 0.4, DCM);  $\nu_{\max}$ /cm<sup>-1</sup> 2957 (C-H), 2929 (C-H), 1755 (C=O), 1713 (C=O), 1663 (C=O), 1626 (C=C), 1591 (C=C);  $\delta_{\text{H}}$  (500 MHz, C<sub>6</sub>D<sub>6</sub>) 0.87 (3H, d, *J* 6.0, <sup>i</sup>Pr), 0.89 (3H, t, *J* 7.2, C(11')H<sub>3</sub>), 1.02 (3H, d, *J* 6.0, <sup>i</sup>Pr), 1.07-1.17 (6H, m, C(8'-10')H<sub>2</sub>), 1.12 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.21-1.26 (2H, m, C(7')H<sub>2</sub>), 1.82 (2H, q, *J* 6.8, C(6')H<sub>2</sub>), 3.04 (1H, d, *J* 8.4, C(1)H<sub>A</sub>H<sub>B</sub>), 3.29 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.85 (1H, d, *J* 8.4, C(1)H<sub>A</sub>H<sub>B</sub>), 4.89 (1H, s, C(3)H), 5.43 (1H, sept, *J* 6.0, <sup>i</sup>Pr), 5.80 (1H, dt, *J* 15.2, 6.8, C(5')H), 6.03 (1H, dd, *J* 15.2, 11.0, C(4')H), 7.20 (1H, d, *J* 15.2, C(2')H), 7.61 (1H, dd, *J* 15.2, 11.0, C(3')H);  $\delta_{\text{C}}$  (100 MHz, C<sub>6</sub>D<sub>6</sub>) 14.2 (C(11')), 20.7 (<sup>i</sup>Pr), 22.0 (<sup>i</sup>Pr), 22.9 (C(10')), 25.1 (C(CH<sub>3</sub>)<sub>3</sub>), 28.9, 29.2, 32.0 (C(7'-9')), 33.4 (C(6')), 35.5 (C(CH<sub>3</sub>)<sub>3</sub>), 52.5 (CO<sub>2</sub>CH<sub>3</sub>), 69.7 (C(1)), 75.2 (C(7a)), 78.5 (<sup>i</sup>Pr), 97.9 (C(3)), 110.5 (C(6)), 128.0 (C(2')), 129.7 (C(4')), 144.2 (C(3')), 146.3 (C(5')),

168.6 (CO<sub>2</sub>CH<sub>3</sub>), 173.6 (C(7)), 176.3 (C(5)), 186.7 (C(1')); *m/z* (ESI<sup>+</sup>) 462.3 (MH<sup>+</sup>, 100%), 484.3 (MNa<sup>+</sup>, 79%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>26</sub>H<sub>40</sub>NO<sub>6</sub> 462.2850; found 462.2853.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-((2E,4E)-tetradeca-2,4-dienoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (17)*

General procedure C (from **15**); yield 75% (80 mg); orange oil. *R<sub>f</sub>* (DCM) 0.32;  $[\alpha]_D^{20}$  +120.3 (*c* 1.0, DCM);  $\nu_{\max}/\text{cm}^{-1}$  2957 (C-H), 2926 (C-H), 1755 (C=O), 1714 (C=O), 1663 (C=O), 1626 (C=C), 1591 (C=C);  $\delta_{\text{H}}$  (400 MHz, C<sub>6</sub>D<sub>6</sub>) 0.87 (3H, d, *J* 6.0, <sup>i</sup>Pr), 0.93 (3H, t, *J* 7.0, C(14')H<sub>3</sub>), 1.02 (3H, d, *J* 6.0, <sup>i</sup>Pr), 1.11 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.13-1.35 (14H, m, C(7'-13')H<sub>2</sub>), 1.84 (2H, q, *J* 6.8, C(6')H<sub>2</sub>), 3.04 (1H, d, *J* 8.4, C(1)H<sub>A</sub>H<sub>B</sub>), 3.29 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.85 (1H, d, *J* 8.4, C(1)H<sub>A</sub>H<sub>B</sub>), 4.89 (1H, s, C(3)H), 5.43 (1H, sept, *J* 6.0, <sup>i</sup>Pr), 5.82 (1H, dt, *J* 15.2, 6.8, C(5')H), 6.04 (1H, dd, *J* 15.2, 11.2, C(4')H), 7.20 (1H, d, *J* 15.2, C(2')H), 7.64 (1H, dd, *J* 15.2, 11.2, C(3')H);  $\delta_{\text{C}}$  (100 MHz, C<sub>6</sub>D<sub>6</sub>) 14.4 (C(14')), 20.6 (<sup>i</sup>Pr), 22.0 (<sup>i</sup>Pr), 23.1 (C(13')), 25.1 (C(CH<sub>3</sub>)<sub>3</sub>), 28.9, 29.6, 29.8, 29.9, 30.0, 32.3 (C(7'-12')), 33.4 (C(6')), 35.5 (C(CH<sub>3</sub>)<sub>3</sub>), 52.6 (CO<sub>2</sub>CH<sub>3</sub>), 69.6 (C(1)), 75.2 (C(7a)), 78.5 (<sup>i</sup>Pr), 97.8 (C(3)), 110.5 (C(6)), 128.0 (C(2')), 129.7 (C(4')), 144.2 (C(3')), 146.4 (C(5')), 168.6 (CO<sub>2</sub>CH<sub>3</sub>), 173.5 (C(7)), 176.3 (C(5)), 186.7 (C(1')); *m/z* (ESI<sup>+</sup>) 504.4 (MH<sup>+</sup>, 100%), 526.3 (MNa<sup>+</sup>, 43%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>29</sub>H<sub>46</sub>NO<sub>6</sub> 504.3320; found 504.3322.

*Methyl (3R,7aR,Z)-3-(tert-butyl)-6-((2E,4E)-1-hydroxyundeca-2,4-dien-1-ylidene)-5,7-dioxodihydro-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (18)*

General procedure D (from **16**); yield 48% (14 mg); orange oil; 1.9:1 mixture of tautomers. *R<sub>f</sub>* (50% EtOAc in petrol) 0.16;  $[\alpha]_D^{20}$  +62.9 (*c* 0.9, CHCl<sub>3</sub>);  $\nu_{\max}/\text{cm}^{-1}$  2960 (C-H), 1753 (C=O), 1712 (C=O), 1651 (C=O), 1613 (C=C), 1558 (C=C);  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) major tautomer: 0.88 (3H, t, *J* 6.9, C(11')H<sub>3</sub>), 0.94 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.24-1.35 (6H, m, C(8'-10')H<sub>2</sub>), 1.42-1.48 (2H, m, C(7')H<sub>2</sub>), 2.22-2.27 (2H, m, C(6')H<sub>2</sub>), 3.51 (1H, d, *J* 8.9, C(1)H<sub>A</sub>H<sub>B</sub>), 3.78 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.83 (1H, d, *J* 8.9, C(1)H<sub>A</sub>H<sub>B</sub>), 4.86 (1H, s, C(3)H), 6.32-6.40 (2H, m, C(4')H + C(5')H), 7.03 (1H, d, *J* 15.3, C(2')H), 7.58 (1H, dd, *J* 15.3, 10.2, C(3')H);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) major tautomer: 14.2 (C(11')), 22.7 (C(10')), 24.8 (C(CH<sub>3</sub>)<sub>3</sub>), 28.6 (C(7')), 29.0 (C(8')), 29.9 (C(9')), 33.7 (C(6')), 35.4 (C(CH<sub>3</sub>)<sub>3</sub>), 53.4 (CO<sub>2</sub>CH<sub>3</sub>), 68.5 (C(1)), 78.4 (C(7a)), 98.4 (C(3)), 99.6 (C(6)), 118.9 (C(2')), 129.7 (C(4')), 148.4 (C(3')), 150.8 (C(5')), 167.9 (CO<sub>2</sub>CH<sub>3</sub>), 177.4 (C(1')), 181.0 (C(5)), 188.0 (C(7)); *m/z* (ESI<sup>+</sup>) 418.1 (M-H<sup>-</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>23</sub>H<sub>34</sub>NO<sub>6</sub> 420.2381; found 420.2381.

*Methyl (3R,7aR,Z)-3-(tert-butyl)-6-((2E,4E)-1-hydroxytetradeca-2,4-dien-1-ylidene)-5,7-dioxodihydro-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (19)*

General procedure D (from **17**); yield 41% (30 mg); orange oil; 2.6:1 mixture of tautomers.  $R_f$  (70% EtOAc in petrol) 0.26;  $[\alpha]_D^{20} +76.6$  ( $c$  1.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2924 (C-H), 1754 (C=O), 1710 (C=O), 1654 (C=O), 1613 (C=C), 1556 (C=C);  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) major tautomer: 0.88 (3H, t,  $J$  6.6,  $\text{C}(14')\text{H}_3$ ), 0.93 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.20-1.33 (12H, m,  $\text{C}(8'-13')\text{H}_2$ ), 1.40-1.48 (2H, m,  $\text{C}(7')\text{H}_2$ ), 2.24 (2H, q,  $J$  6.3,  $\text{C}(6')\text{H}_2$ ), 3.51 (1H, d,  $J$  8.8,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 3.78 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.83 (1H, d,  $J$  8.8,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 4.86 (1H, s,  $\text{C}(3)\text{H}$ ), 6.32-6.40 (2H, m,  $\text{C}(4')\text{H} + \text{C}(5')\text{H}$ ), 7.03 (1H, d,  $J$  15.2,  $\text{C}(2')\text{H}$ ), 7.58 (1H, dd,  $J$  15.2, 9.7,  $\text{C}(3')\text{H}$ );  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) major tautomer: 14.3 ( $\text{C}(14')$ ), 22.8 ( $\text{C}(13')$ ), 24.8 ( $\text{C}(\text{CH}_3)_3$ ), 28.6 ( $\text{C}(7')$ ), 29.3, 29.4, 29.5, 29.6 ( $\text{C}(8'-11')$ ), 32.0 ( $\text{C}(12')$ ), 33.7 ( $\text{C}(6')$ ), 35.4 ( $\text{C}(\text{CH}_3)_3$ ), 53.4 ( $\text{CO}_2\text{CH}_3$ ), 68.5 ( $\text{C}(1)$ ), 78.5 ( $\text{C}(7\text{a})$ ), 98.4 ( $\text{C}(3)$ ), 99.6 ( $\text{C}(6)$ ), 118.9 ( $\text{C}(2')$ ), 129.7 ( $\text{C}(4')$ ), 148.3 ( $\text{C}(3')$ ), 150.8 ( $\text{C}(5')$ ), 167.9 ( $\text{CO}_2\text{CH}_3$ ), 177.4 ( $\text{C}(1')$ ), 180.9 ( $\text{C}(5)$ ), 188.0 ( $\text{C}(7)$ );  $m/z$  ( $\text{ESI}^+$ ) 462.3 ( $\text{MH}^+$ , 19%), 484.2 ( $\text{MNa}^+$ , 100%); HRMS ( $\text{ESI-TOF}$ )  $m/z$   $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{26}\text{H}_{40}\text{NO}_6$  462.2850; found 462.2849.

*(3R,7aR,Z)-3-(tert-Butyl)-6-((2E,4E)-1-hydroxyundeca-2,4-dien-1-ylidene)dihydro-3H,5H-pyrrolo[1,2-c]oxazole-5,7(6H)-dione (20)*

Methyl ester **18** (41 mg, 0.098 mmol) and  $\text{LiOH}\cdot\text{H}_2\text{O}$  (20 mg, 0.50 mmol) in a 4:1:1 mixture of THF/MeOH/ $\text{H}_2\text{O}$  (1.4 mL) were heated at reflux for 8 h and then cooled to room temperature. The mixture was diluted with brine, acidified with 2 M aqueous HCl, extracted with EtOAc, dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The residue was dissolved in MeCN and heated at reflux for 5 h, then cooled to room temperature. The mixture was diluted with brine, acidified with 2 M aqueous HCl, extracted with EtOAc, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude residue was purified by *flash* column chromatography and the product thus obtained was dissolved in EtOAc, washed with 2 M aqueous HCl, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to give the decarboxylated acyltetramate **20** (18 mg, 0.050, 51%) as an orange oil; 2.2:1 mixture of tautomers.  $R_f$  (80% EtOAc in petrol) 0.18;  $[\alpha]_D^{20} +136.4$  ( $c$  0.5,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2957 (C-H), 2927 (C-H), 1708 (C=O), 1650 (C=O), 1613 (C=O), 1557 (C=C);  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) major tautomer: 0.86-0.90 (3H, m,  $\text{C}(11')\text{H}_3$ ), 0.97 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.25-1.34 (6H, m,  $\text{C}(8'-10')\text{H}_2$ ), 1.45 (2H, tt,  $J$  7.0, 6.5,  $\text{C}(7')\text{H}_2$ ), 2.23 (2H, td,  $J$  7.0, 6.0,  $\text{C}(6')\text{H}_2$ ), 3.45 (1H, dd,  $J$  9.5, 8.3,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 4.15 (1H, dd,  $J$  9.5, 7.0,  $\text{C}(7\text{a})\text{H}$ ), 4.26 (1H, dd,  $J$  8.3, 7.0,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 4.95 (1H, s,  $\text{C}(3)\text{H}$ ), 6.32-6.40 (2H, m,  $\text{C}(4')\text{H} +$

C(5')H), 7.07 (1H, d, *J* 15.5, C(2')H), 7.53 (1H, dd, *J* 15.5, 10.0, C(3')H);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) major tautomer: 14.2 (C(11')), 22.7 (C(10')), 24.9 (C(CH<sub>3</sub>)<sub>3</sub>), 28.6 (C(7')), 29.0 (C(8')), 31.8 (C(9')), 33.6 (C(6')), 36.1 (C(CH<sub>3</sub>)<sub>3</sub>), 67.0 (C(1)), 67.3 (C(7a)), 96.0 (C(3)), 101.1 (C(6)), 119.2 (C(2')), 129.7 (C(4')), 147.2 (C(3')), 149.7 (C(5')), 176.0 (C(1')), 179.9 (C(5)), 191.8 (C(7)); *m/z* (ESI<sup>+</sup>) 360.2 (M-H<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M-H]<sup>+</sup> Calcd for C<sub>21</sub>H<sub>30</sub>NO<sub>4</sub> 360.2180; found 360.2180.

*Methyl (3R,7aR,Z)-3-(tert-butyl)-6-(1-hydroxyoctylidene)-5,7-dioxodihydro-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (21)*

General procedure B (from **2**, with 2 eq of 1-bromoheptane); yield 60% (124 mg); orange oil; 3.4:1 mixture of tautomers. *R<sub>f</sub>* (EtOAc) 0.40;  $[\alpha]_D^{20}$  +67.4 (*c* 1.0, DCM);  $\nu_{\max}/\text{cm}^{-1}$  2958 (C-H), 2930 (C-H), 1758 (C=O), 1718 (C=O), 1657 (C=O), 1602 (C=C);  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) major tautomer: 0.84-0.89 (3H, m, C(8')H<sub>3</sub>), 0.92 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.24-1.30 (8H, m, C(4'-7')H<sub>2</sub>), 1.66 (2H, quint, *J* 7.6, C(3')H<sub>2</sub>), 2.83 (2H, app td, *J* 7.6, 2.5, C(2')H<sub>2</sub>), 3.48 (1H, d, *J* 8.9, C(1)H<sub>A</sub>H<sub>B</sub>), 3.78 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.81 (1H, d, *J* 8.9, C(1)H<sub>A</sub>H<sub>B</sub>), 4.84 (1H, s, C(3)H);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) major tautomer: 14.2 (C(8')), 22.7 (C(7')), 24.8 (C(CH<sub>3</sub>)<sub>3</sub>), 26.0 (C(3')), 28.9, 29.3 ((C(4')), C(5')), 31.7 (C(6')), 33.2 (C(2')), 35.3 (C(CH<sub>3</sub>)<sub>3</sub>), 53.4 (CO<sub>2</sub>CH<sub>3</sub>), 68.4 (C(1)), 78.4 (C(7a)), 98.4 (C(3)), 101.2 (C(6)), 167.6 (CO<sub>2</sub>CH<sub>3</sub>), 180.4 (C(5)), 187.9 (C(7)), 192.6 (C(1')); *m/z* (ESI<sup>+</sup>) 382.2 (MH<sup>+</sup>, 81%), 404.3 (MNa<sup>+</sup>, 100%), *m/z* (ESI<sup>+</sup>) 380.2 (M-H<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M-H]<sup>+</sup> Calcd for C<sub>20</sub>H<sub>30</sub>NO<sub>6</sub> 380.2079; found 380.2092.

*Methyl (3R,7aR,Z)-3-(tert-butyl)-6-(1-hydroxyundecylidene)-5,7-dioxodihydro-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (22)*

General procedure B (from **2**, with 2 eq of 1-bromodecane); yield 61% (119 mg); orange oil; 6:1 mixture of tautomers. *R<sub>f</sub>* (EtOAc) 0.35;  $[\alpha]_D^{20}$  +64.6 (*c* 1.0, DCM);  $\nu_{\max}/\text{cm}^{-1}$  2926 (C-H), 2856 (C-H), 1758 (C=O), 1719 (C=O), 1658 (C=O), 1602 (C=C);  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) major tautomer: 0.86 (3H, t, *J* 6.8, C(11')H<sub>3</sub>), 0.91 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.24-1.37 (14H, m, C(4'-10')H<sub>2</sub>), 1.65 (2H, quint, *J* 7.5, C(3')H<sub>2</sub>), 2.81-2.84 (2H, m, C(2')H<sub>2</sub>), 3.48 (1H, d, *J* 8.8, C(1)H<sub>A</sub>H<sub>B</sub>), 3.77 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.81 (1H, d, *J* 8.8, C(1)H<sub>A</sub>H<sub>B</sub>), 4.83 (1H, s, C(3)H);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) major tautomer: 14.2 (C(11')), 22.8 (C(10')), 24.8 (C(CH<sub>3</sub>)<sub>3</sub>), 26.0 (C(3')), 29.3, 29.3, 29.4, 29.5, 29.6 (C(4'-8')), 32.0 (C(9')), 33.2 (C(2')), 35.3 (C(CH<sub>3</sub>)<sub>3</sub>), 53.4 (CO<sub>2</sub>CH<sub>3</sub>), 68.5 (C(1)), 78.4 (C(7a)), 98.3 (C(3)), 101.1 (C(6)), 167.6 (CO<sub>2</sub>CH<sub>3</sub>), 180.4 (C(5)), 187.9 (C(7)), 192.6 (C(1')); *m/z* (ESI<sup>+</sup>) 424.3 (MH<sup>+</sup>, 100%),

446.3 (MNa<sup>+</sup>, 76%), *m/z* (ESI<sup>-</sup>) 422.2 (M-H<sup>-</sup>, 100%); HRMS (ESI-TOF) *m/z* [M-H]<sup>-</sup> Calcd for C<sub>23</sub>H<sub>36</sub>NO<sub>6</sub> 422.2537; found 422.2545.

*Methyl (3R,7aR,Z)-3-(tert-butyl)-6-(1-hydroxytetradecylidene)-5,7-dioxodihydro-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (23)*

General procedure B (from **2**, with 2 eq of 1-bromotridecane); yield 66% (102 mg); orange oil; 4.3:1 mixture of tautomers. *R<sub>f</sub>* (EtOAc) 0.46; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +62.0 (*c* 1.0, DCM);  $\nu_{\max}/\text{cm}^{-1}$  2924 (C-H), 2854 (C-H), 1758 (C=O), 1719 (C=O), 1658 (C=O), 1603 (C=C);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) major tautomer: 0.87 (3H, t, *J* 7.0, C(14')H<sub>3</sub>), 0.92 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.24-1.30 (18H, m, C(5'-13')H<sub>2</sub>), 1.33-1.39 (2H, m, C(4')H<sub>2</sub>), 1.66 (2H, quint, *J* 7.5, C(3')H<sub>2</sub>), 2.82-2.85 (2H, m, C(2')H<sub>2</sub>), 3.49 (1H, d, *J* 8.9, C(1)H<sub>A</sub>H<sub>B</sub>), 3.78 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.82 (1H, d, *J* 8.9, C(1)H<sub>A</sub>H<sub>B</sub>), 4.84 (1H, s, C(3)H);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) major tautomer: 14.3 (C(14')), 22.8 (C(13')), 24.8 (C(CH<sub>3</sub>)<sub>3</sub>), 26.0 (C(3')), 29.3, 29.3, 29.5, 29.5, 29.7, 29.8, 29.8, 29.8 (C(4'-11')), 32.1 (C(12')), 33.2 (C(2')), 35.3 (C(CH<sub>3</sub>)<sub>3</sub>), 53.4 (CO<sub>2</sub>CH<sub>3</sub>), 68.4 (C(1)), 78.5 (C(7a)), 98.4 (C(3)), 101.2 (C(6)), 167.6 (CO<sub>2</sub>CH<sub>3</sub>), 180.4 (C(5)), 187.9 (C(7)), 192.7 (C(1')); *m/z* (ESI<sup>-</sup>) 464.3 (M-H<sup>-</sup>, 100%); HRMS (ESI-TOF) *m/z* [M-H]<sup>-</sup> Calcd for C<sub>26</sub>H<sub>42</sub>NO<sub>6</sub> 464.3007; found 464.3013.

*Methyl (3R,7aR)-3-(tert-butyl)-6-((E)-3-(3-hexyloxiran-2-yl)acryloyl)-7-isopropoxy-5-oxo-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (24)*

*m*CPBA (80%, 88 mg, 0.41 mmol) was added portionwise to a solution of diene **16** (64 mg, 0.14 mmol) in anhydrous DCM (700  $\mu$ L) at 0 °C. The mixture was stirred at room temperature for 5 h and quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The aqueous phase was extracted with DCM, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by *flash* column chromatography (10% EtOAc in petrol) to give a 1:1 unseparable diastereomeric mixture of epoxide **24** (43 mg, 0.089 mmol, 64%) as a light yellow oil. *R<sub>f</sub>* (10% EtOAc in petrol) 0.19;  $\nu_{\max}/\text{cm}^{-1}$  2960 (C-H), 2931 (C-H), 1754 (C=O), 1711 (C=O), 1671 (C=O), 1618 (C=C), 1585 (C=C);  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>, 1:1 mixture of diastereomers A and B) 0.88 (6H, t, *J* 6.8, C(11')H<sub>3</sub> A + B), 0.91 (9H, s, C(CH<sub>3</sub>)<sub>3</sub> A), 0.91 (9H, s, C(CH<sub>3</sub>)<sub>3</sub> B), 1.09 (3H, d, *J* 6.0, <sup>i</sup>Pr A), 1.09 (3H, d, *J* 6.0, <sup>i</sup>Pr B), 1.25-1.37 (12H, m, C(8'-10')H<sub>2</sub> A + B), 1.31 (3H, d, *J* 6.0, <sup>i</sup>Pr A), 1.32 (3H, d, *J* 6.0, <sup>i</sup>Pr B), 1.40-1.49 (4H, m, C(7')H<sub>2</sub> A + B), 1.56-1.62 (4H, m, C(6')H<sub>2</sub> A + B), 2.94-2.97 (2H, m, C(5')H A + B), 3.27-3.29 (2H, m, C(4')H A + B), 3.48 (1H, d, *J* 8.5, C(1)H<sub>A</sub>H<sub>B</sub> A), 3.48 (1H, d, *J* 8.5, C(1)H<sub>A</sub>H<sub>B</sub> B), 3.78 (3H, s,

CO<sub>2</sub>CH<sub>3</sub> A), 3.79 (3H, s, CO<sub>2</sub>CH<sub>3</sub> B), 4.74 (2H, s, C(3)H A + B), 4.82 (1H, d, *J* 8.5, C(1)H<sub>A</sub>H<sub>B</sub> A), 4.82 (1H, d, *J* 8.5, C(1)H<sub>A</sub>H<sub>B</sub> B), 5.16 (1H, sept, *J* 6.0, <sup>i</sup>Pr A), 5.17 (1H, sept, *J* 6.0, <sup>i</sup>Pr B), 6.59 (1H, dd, *J* 15.6, 8.0, C(3')H A), 6.65 (1H, dd, *J* 15.6, 7.3, C(3')H B), 7.16 (1H, dd, *J* 15.6, 0.5, C(2')H A), 7.23 (1H, dd, *J* 15.6, 0.5, C(2')H B); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 14.2 (C(11') A + B), 20.9 (<sup>i</sup>Pr A), 21.0 (<sup>i</sup>Pr B), 22.3 (<sup>i</sup>Pr A), 22.3 (<sup>i</sup>Pr B), 22.7 (C(10') A + B), 24.8 (C(CH<sub>3</sub>)<sub>3</sub> A + B), 25.9 (C(7') A + B), 29.2 (C(8') A + B), 31.8 (C(9') A + B), 32.1 (C(6') A), 32.1 (C(6') B), 35.3 (C(CH<sub>3</sub>)<sub>3</sub> A + B), 53.4 (CO<sub>2</sub>CH<sub>3</sub> A + B), 56.9 (C(4') A), 57.1 (C(4') B), 61.6 (C(5') A), 62.0 (C(5') B), 69.6 (C(1) A + B), 74.9 (C(7a) A), 74.9 (C(7a) B), 79.2 (C(12') A), 79.3 (C(12') B), 97.7 (C(3) A), 97.7 (C(3) B), 109.0 (C(6) A), 109.0 (C(6) B), 130.3 (C(2') A), 130.7 (C(2') B), 144.5 (C(3') A), 144.7 (C(3') B), 168.1 (CO<sub>2</sub>CH<sub>3</sub> A + B), 174.2 (C(7) A), 174.3 (C(7) B), 176.1 (C(5) A), 176.2 (C(5) B), 185.5 (C(1') A), 185.8 (C(1') B); *m/z* (ESI<sup>+</sup>) 478.3 (MH<sup>+</sup>, 93%), 500.3 (MNa<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>26</sub>H<sub>40</sub>NO<sub>7</sub> 478.2799; found 478.2796.

*Methyl (3R,7aR,Z)-3-(tert-butyl)-6-((E)-3-(3-hexyloxiran-2-yl)-1-hydroxyallylidene)-5,7-dioxodihydro-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (25)*

General procedure D (from **24**); yield 77% (43 mg); orange oil. R<sub>f</sub> (80% EtOAc in petrol) 0.32; ν<sub>max</sub>/cm<sup>-1</sup> 2958 (C-H), 2930 (C-H), 1753 (C=O), 1715 (C=O), 1645 (C=O), 1616 (C=C), 1574 (C=C); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>, 1:1 mixture of diastereomers A and B) 0.85-0.90 (6H, m, C(11')H<sub>3</sub> A + B), 0.93 (18H, s, C(CH<sub>3</sub>)<sub>3</sub> A + B), 1.23-1.36 (12H, m, C(8'-10')H<sub>2</sub> A + B), 1.42-1.48 (4H, m, C(7')H<sub>2</sub> A + B), 1.60-1.66 (4H, m, C(6')H<sub>2</sub> A + B), 2.95-3.00 (2H, m, C(5')H A + B), 3.31-3.34 (2H, m, C(4')H A + B), 3.51 (1H, d, *J* 8.8, C(1)H<sub>A</sub>H<sub>B</sub> A), 3.52 (1H, d, *J* 8.8, C(1)H<sub>A</sub>H<sub>B</sub> B), 3.79 (3H, s, CO<sub>2</sub>CH<sub>3</sub> A), 3.79 (3H, s, CO<sub>2</sub>CH<sub>3</sub> B), 4.84 (2H, d, *J* 8.8, C(1)H<sub>A</sub>H<sub>B</sub> A + B), 4.87 (2H, s, C(3)H A + B), 6.94 (1H, dd, *J* 15.6, 7.6, C(3')H A), 6.95 (1H, dd, *J* 15.6, 7.6, C(3')H B), 7.34 (2H, d, *J* 15.6, C(2')H A + B); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 14.2 (C(11') A + B), 22.6 (C(10') A + B), 24.8 (C(CH<sub>3</sub>)<sub>3</sub> A + B), 25.9 (C(7') A + B), 29.1 (C(8') A + B), 31.8 (C(9') A + B), 32.1 (C(6') A + B), 35.3 (C(CH<sub>3</sub>)<sub>3</sub> A + B), 53.5 (CO<sub>2</sub>CH<sub>3</sub> A), 53.5 (CO<sub>2</sub>CH<sub>3</sub> B), 57.0 (C(4') A), 57.0 (C(4') B), 62.3 (C(5') A), 62.4 (C(5') B), 68.3 (C(1) A + B), 78.4 (C(7a) A + B), 98.5 (C(3) A), 98.5 (C(3) B), 100.4 (C(6) A + B), 122.6 (C(2') A), 122.7 (C(2') B), 148.5 (C(3') A + B), 167.5 (CO<sub>2</sub>CH<sub>3</sub> A), 167.6 (CO<sub>2</sub>CH<sub>3</sub> B), 175.2 (C(1') A + B), 180.3 (C(5) A + B), 187.8 (C(7) A + B); *m/z* (ESI<sup>-</sup>) 434.2 (M-H<sup>-</sup>, 100%); HRMS (ESI-TOF) *m/z* [M-H]<sup>-</sup> Calcd for C<sub>23</sub>H<sub>32</sub>NO<sub>7</sub> 434.2184; found 434.2188.



#### 5-Allyl-2-(triisopropylsilyl)oxazole (**28**)

CuCN (495 mg, 5.52 mmol) and LiCl (485 mg, 11.4 mmol) were stirred at 130 °C under vacuum for 5 h. After cooling to room temperature, anhydrous THF (10 mL) was added and stirring was continued for further 30 min. To a solution of TIPS-protected oxazole **26** (1.08 g, 4.80 mmol) in anhydrous THF (12 mL) was added *n*-BuLi (1.6 M in hexanes, 3.3 mL, 5.3 mmol) dropwise at -78 °C. After stirring at this temperature for 30 min, the CuCN·2LiCl solution was added by cannula (with another 2 mL of anhydrous THF) and the mixture was stirred at -78 °C for 2 h. Allyl bromide (630 µL, 7.28 mmol) was then added and the solution was stirred at -78 °C for 30 min and at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl, extracted with Et<sub>2</sub>O and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified by *flash* column chromatography (5% EtOAc in petrol) to give a 13:1 inseparable mixture of alkene **28** and remaining starting material (1.21 g, 4.48 mmol, 93%) as a light yellow oil. *R*<sub>f</sub> (5% EtOAc in petrol) 0.38; *v*<sub>max</sub>/cm<sup>-1</sup> 2944 (C-H), 2867 (C-H), 1464 (C=C); *δ*<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.12 (18H, d, *J* 7.4, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.39 (3H, sept, *J* 7.4, SiCH(CH<sub>3</sub>)<sub>2</sub>), 3.45 (2H, app dq, *J* 6.4, 1.2, C(1)*H*<sub>2</sub>), 5.11-5.13 (1H, m, C(3)*H*<sub>A</sub>*H*<sub>B</sub>), 5.14-5.16 (1H, m, C(3)*H*<sub>A</sub>*H*<sub>B</sub>), 5.87-5.97 (1H, m, C(2)*H*), 6.83 (1H, t, *J* 1.2, C(4')*H*); *δ*<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 11.1 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.5 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 30.2 (C(1)), 117.5 (C(3)), 123.0 (C(4')), 133.0 (C(2)), 152.6 (C(5')), 167.9 (C(2')); *m/z* (ESI<sup>+</sup>) 266.2 (MH<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>28</sub>NOSi 266.1935; found 266.1935.

#### 5-Allyl-2-(triisopropylsilyl)thiazole (**29**)

CuCN (782 mg, 8.73 mmol) and LiCl (752 mg, 17.7 mmol) were stirred at 130 °C under vacuum for 5 h. After cooling to room temperature, anhydrous THF (15 mL) was added and stirring was continued for further 30 min. To a solution of protected oxazole **27** (1.92 g, 7.94 mmol) in anhydrous THF (20 mL) was added *n*-BuLi (1.6 M in hexanes, 5.5 mL, 8.8 mmol) dropwise at -78 °C. After stirring at this temperature for 30 min, the CuCN·2LiCl solution was added by cannula (with another 5 mL of anhydrous THF) and the mixture was stirred at -78 °C for 2 h. Allyl bromide (1.0 mL, 12 mmol) was then added and the solution was stirred at -78 °C for 30 min and at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl, extracted with Et<sub>2</sub>O and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified by *flash* column chromatography (5% EtOAc in petrol) to give alkene **29** (1.92 g, 6.83 mmol, 86%) as an orange oil. *R*<sub>f</sub> (5% EtOAc in petrol) 0.37; *v*<sub>max</sub>/cm<sup>-1</sup> 2943 (C-H), 2866 (C-H), 1462 (C=C); *δ*<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.13 (18H, d, *J* 7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.42 (3H, sept, *J* 7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 3.63 (2H, d, *J* 6.6, C(1)*H*<sub>2</sub>), 5.09-5.19 (2H, m, C(3)*H*<sub>2</sub>), 5.98 (1H, ddt, *J* 16.8, 10.0, 6.6, C(2)*H*), 7.80 (1H, s, C(4')*H*); *δ*<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 11.8 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.7

(SiCH(CH<sub>3</sub>)<sub>2</sub>), 31.2 (C(1)), 116.8 (C(3)), 136.1 (C(2)), 139.5 (C(5')), 143.3 (C(4')), 169.4 (C(2')); *m/z* (ESI<sup>+</sup>) 282.1 (MH<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>28</sub>NSSi 282.1706; found 282.1704.

*3-(2-(Triisopropylsilyl)oxazol-5-yl)propan-1-ol (30)*

9-BBN (0.5 M in THF, 24 mL, 12 mmol) was added dropwise to a solution of alkene **28** (1.14 g, 3.98 mmol) in anhydrous THF (16 mL) at 0 °C and the solution was stirred at room temperature for 13 h. The mixture was then cooled to 0 °C and water (2.2 mL), aqueous NaOH (2 M, 20 mL, 40 mmol) and H<sub>2</sub>O<sub>2</sub> (35% w/w, 3.4 mL, 40 mmol) were added dropwise. The biphasic mixture was stirred at room temperature for 6 h, diluted with brine and extracted with EtOAc, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The crude product was purified by *flash* column chromatography (30% EtOAc in DCM) to give alcohol **30** (1.02 g, 3.59 mmol, 90%) as a colourless oil. *R*<sub>f</sub> (20% EtOAc in petrol) 0.33; *v*<sub>max</sub>/cm<sup>-1</sup> 3340 (O-H), 2944 (C-H), 2867 (C-H), 1464 (C=C); *δ*<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.11 (18H, d, *J* 7.4, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.37 (3H, sept, *J* 7.4, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.90 (2H, tt, *J* 7.4, 6.4, C(2)H<sub>2</sub>), 1.96 (1H, br s, OH), 2.79 (2H, t, *J* 7.4, C(3)H<sub>2</sub>), 3.68 (2H, t, *J* 6.4, C(1)H<sub>2</sub>), 6.81 (1H, s, C(4')H); *δ*<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 11.1 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.5 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 22.1 (C(3)), 30.8 (C(2)), 61.8 (C(1)), 122.5 (C(4')), 154.3 (C(5')), 167.7 (C(2')); *m/z* (ESI<sup>+</sup>) 284.2 (MH<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>30</sub>NO<sub>2</sub>Si 284.2040; found 284.2041.

*3-(2-(Triisopropylsilyl)thiazol-5-yl)propan-1-ol (31)*

9-BBN (0.5 M in THF, 41 mL, 20 mmol) was added dropwise to a solution of alkene **29** (1.92 g, 6.83 mmol) in anhydrous THF (27 mL) at 0 °C and the solution was stirred at room temperature for 13 h. The mixture was then cooled to 0 °C and water (3.8 mL), aqueous NaOH (2 M, 34 mL, 68 mmol) and H<sub>2</sub>O<sub>2</sub> (35% w/w, 5.8 mL, 68 mmol) were added dropwise. The biphasic mixture was stirred at room temperature for 6 h, diluted with brine and extracted with EtOAc, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The crude product was purified by *flash* column chromatography (20% EtOAc in DCM) to give alcohol **31** (1.69 g, 5.65 mmol, 83%) as a yellow oil. *R*<sub>f</sub> (20% EtOAc in DCM) 0.22; *v*<sub>max</sub>/cm<sup>-1</sup> 3348 (O-H), 2942 (C-H), 2866 (C-H), 1462 (C=C); *δ*<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.12 (18H, d, *J* 7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.41 (3H, sept, *J* 7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.90 (1H, br s, OH), 1.95 (2H, tt, *J* 7.6, 6.4, C(2)H<sub>2</sub>), 2.99 (2H, t, *J* 7.6, C(3)H<sub>2</sub>), 3.69 (2H, t, *J* 6.4, C(1)H<sub>2</sub>), 7.80 (1H, s, C(4')H); *δ*<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 11.7 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.6 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 23.2 (C(3)), 34.5 (C(2)), 61.7 (C(1)), 141.3 (C(5')), 143.1 (C(4')), 168.9 (C(2')); *m/z* (ESI<sup>+</sup>) 300.2 (MH<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>30</sub>NOSSi 300.1812; found 300.1811.

### 3-(2-(Triisopropylsilyl)oxazol-5-yl)propanal (**32**)

To a solution of alcohol **30** (346 mg, 1.22 mmol) and NaHCO<sub>3</sub> (115 mg, 1.37 mmol) in anhydrous DCM (6.1 mL) was added portionwise Dess-Martin periodinane (767 mg, 1.81 mmol) at 0 °C. After stirring at room temperature for 5 h, a 1:1 mixture of saturated aqueous NaHCO<sub>3</sub> and saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added and the organic layer was extracted with Et<sub>2</sub>O, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by *flash* column chromatography (5% EtOAc in DCM) to give aldehyde **32** (303 mg, 1.08 mmol, 89%) as a yellow oil. R<sub>f</sub> (5% EtOAc in DCM) 0.36;  $\nu_{\max}/\text{cm}^{-1}$  2944 (C-H), 2867 (C-H), 1728 (C=O), 1465 (C=C);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.10 (18H, d, *J* 7.4, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.36 (3H, sept, *J* 7.4, SiCH(CH<sub>3</sub>)<sub>2</sub>), 2.80 (2H, t, *J* 7.6, C(2)H<sub>2</sub>), 3.02 (2H, t, *J* 7.6, C(3)H<sub>2</sub>), 6.83 (1H, s, C(4')H), 9.82 (1H, s, C(1)H);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 11.0 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.5 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.5 (C(3)), 41.7 (C(2)), 122.8 (C(4')), 152.7 (C(5')), 168.0 (C(2')), 200.3 (C(1)); *m/z* (ESI<sup>+</sup>) 282.1 (MH<sup>+</sup>, 5%); HRMS (ESI-TOF) *m/z* [M+Na]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>27</sub>NNaO<sub>2</sub>Si 304.1703; found 304.1703.

### 3-(2-(Triisopropylsilyl)thiazol-5-yl)propanal (**33**)

To a solution of alcohol **31** (358 mg, 1.19 mmol) and NaHCO<sub>3</sub> (111 mg, 1.32 mmol) in anhydrous DCM (6 mL) was added portionwise Dess-Martin periodinane (766 mg, 1.81 mmol) at 0 °C. After stirring at room temperature for 5 h, a 1:1 mixture of saturated aqueous NaHCO<sub>3</sub> and saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added and the organic layer was extracted with Et<sub>2</sub>O, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by *flash* column chromatography (2% EtOAc in DCM) to give aldehyde **33** (242 mg, 0.813 mmol, 68%) as a yellow oil. R<sub>f</sub> (2% EtOAc in DCM) 0.24;  $\nu_{\max}/\text{cm}^{-1}$  2943 (C-H), 2865 (C-H), 2722 (C-H), 1727 (C=O), 1462 (C=C);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.12 (18H, d, *J* 7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.41 (3H, sept, *J* 7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 2.87 (2H, td, *J* 7.4, 1.0, C(2)H<sub>2</sub>), 3.23 (2H, td, *J* 7.4, 0.8, C(3)H<sub>2</sub>), 7.82 (1H, t, *J* 0.8, C(4')H), 9.83 (1H, t, *J* 1.0, C(1)H);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 11.8 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.6 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 19.5 (C(3)), 45.3 (C(2)), 139.7 (C(5')), 143.4 (C(4')), 169.6 (C(2')), 200.4 (C(1)); *m/z* (ESI<sup>+</sup>) 298.1 (MH<sup>+</sup>, 4%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>28</sub>NOSSi 298.1655; found 298.1654.

### 5-(But-3-yn-1-yl)-2-(triisopropylsilyl)oxazole (**34**)

Potassium carbonate (300 mg, 2.17 mmol) and a solution of the Bestmann reagent (250 mg, 1.30 mmol) in MeOH (1.5 mL) were added to a solution of aldehyde **32** (295 mg, 1.05 mmol) in MeOH (9 mL). After stirring

at room temperature for 14 h, the suspension was cooled to 0 °C, quenched with saturated aqueous NaHCO<sub>3</sub> and extracted with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by *flash* column chromatography (5% EtOAc in petrol) to give alkyne **34** (267 mg, 0.963 mmol, 92%) as a colourless oil. R<sub>f</sub> (5% EtOAc in petrol) 0.24;  $\nu_{\text{max}}/\text{cm}^{-1}$  3313 (C-H), 2944 (C-H), 2867 (C-H), 2123 (C≡C), 1465 (C=C);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.12 (18H, d, *J* 7.4, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.38 (3H, sept, *J* 7.4, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.97 (1H, t, *J* 2.6, C(4)*H*), 2.53 (2H, td, *J* 7.4, 2.6, C(2)*H*<sub>2</sub>), 2.93 (2H, td, *J* 7.4, 0.8, C(1)*H*<sub>2</sub>), 6.90 (1H, t, *J* 0.8, C(4')*H*);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 11.1 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 17.7 (C(2)), 18.5 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 25.2 (C(1)), 69.4 (C(4)), 82.7 (C(3)), 123.1 (C(4')), 152.7 (C(5')), 167.9 (C(2')); *m/z* (ESI<sup>+</sup>) 278.2 (MH<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>28</sub>NOSi 278.1935; found 278.1933.

#### 5-(But-3-yn-1-yl)-2-(triisopropylsilyl)thiazole (**35**)

Potassium carbonate (192 mg, 1.39 mmol) and a solution of the Bestmann reagent (160 mg, 0.835 mmol) in MeOH (2.0 mL) were added to a solution of aldehyde **33** (204 mg, 0.685 mmol) in MeOH (4.9 mL). After stirring at room temperature for 15 h, the suspension was cooled to 0 °C, quenched with saturated aqueous NaHCO<sub>3</sub> and extracted with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by *flash* column chromatography (5% EtOAc in petrol) to give alkyne **35** (164 mg, 0.557 mmol, 81%) as a colourless oil. R<sub>f</sub> (5% EtOAc in petrol) 0.26;  $\nu_{\text{max}}/\text{cm}^{-1}$  3311 (C-H), 2943 (C-H), 2866 (C-H), 2122 (C≡C), 1463 (C=C);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.12 (18H, d, *J* 7.6, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.42 (3H, sept, *J* 7.6, SiCH(CH<sub>3</sub>)<sub>2</sub>), 2.02 (1H, t, *J* 2.6, C(4)*H*), 2.54 (2H, td, *J* 7.4, 2.6, C(2)*H*<sub>2</sub>), 3.12 (2H, t, *J* 7.4, C(1)*H*<sub>2</sub>), 7.87 (1H, s, C(4')*H*);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 11.8 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.6 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 21.2 (C(2)), 26.3 (C(1)), 69.9 (C(4)), 82.9 (C(3)), 139.4 (C(5')), 143.5 (C(4')), 169.4 (C(2')); *m/z* (ESI<sup>+</sup>) 294.2 (MH<sup>+</sup>, 100%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>28</sub>NSSi 294.1706; found 294.1707.

#### 4-(2-(Triisopropylsilyl)oxazol-5-yl)butanenitrile (**36**)

Triphenylphosphine (1.67 g, 6.37 mmol) and acetone cyanohydrin (580  $\mu$ L, 6.35 mmol) were added to a solution of alcohol **30** (723 mg, 2.55 mmol) in anhydrous THF (10 mL). After stirring at room temperature for 10 min, the solution was cooled to 0 °C and diethyl azodicarboxylate (1.0 mL, 6.4 mmol) in anhydrous THF (3 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h and for further 18 h at room temperature. The solvent was then evaporated and the crude product was purified by *flash* column chromatography (10% to 20% EtOAc in petrol) to give nitrile **36** (737 mg, 2.52 mmol, 99%) as a light yellow oil. R<sub>f</sub> (20% EtOAc in petrol)

0.30;  $\nu_{\max}/\text{cm}^{-1}$  2944 (C-H), 2867 (C-H), 2247 (C $\equiv$ N), 1464 (C=C);  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 1.12 (18H, d,  $J$  7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.39 (3H, sept,  $J$  7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 2.03 (2H, quint,  $J$  7.5, C(3) $H_2$ ), 2.38 (2H, t,  $J$  7.5, C(2) $H_2$ ), 2.88 (2H, td,  $J$  7.5, 1.0, C(4) $H_2$ ), 6.89 (1H, t,  $J$  1.0, C(4') $H$ );  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 11.1 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 16.6 (C(2)), 18.5 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 24.0 (C(3)), 24.5 (C(4)), 119.0 (C(1)), 123.4 (C(4')), 152.1 (C(5')), 168.4 (C(2'));  $m/z$  (ESI<sup>+</sup>) 293.2 (MH<sup>+</sup>, 100%), 315.2 (MNa<sup>+</sup>, 14%); HRMS (ESI-TOF)  $m/z$  [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>29</sub>N<sub>2</sub>OSi 293.2044; found 293.2042.

#### 4-(2-(Triisopropylsilyl)thiazol-5-yl)butanenitrile (**37**)

Triphenylphosphine (2.29 g, 8.74 mmol) and acetone cyanohydrin (800  $\mu$ L, 8.76 mmol) were added to a solution of alcohol **31** (1.05 g, 3.50 mmol) in anhydrous THF (12 mL). After stirring at room temperature for 5 min, the solution was cooled to 0 °C and diethyl azodicarboxylate (1.4 mL, 8.9 mmol) in anhydrous THF (5 mL) was added dropwise. The mixture was stirred for 1 h at 0 °C and for further 18 h at room temperature. The solvent was then evaporated and the crude product was purified by *flash* column chromatography (DCM) to give nitrile **37** (1.00 g, 3.25 mmol, 93%) as a light yellow oil.  $R_f$  (DCM) 0.35;  $\nu_{\max}/\text{cm}^{-1}$  2943 (C-H), 2866 (C-H), 2247 (C $\equiv$ N), 1462 (C=C);  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 1.13 (18H, d,  $J$  7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.42 (3H, sept,  $J$  7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 2.05 (2H, quint,  $J$  7.2, C(3) $H_2$ ), 2.39 (2H, t,  $J$  7.2, C(2) $H_2$ ), 3.07 (2H, td,  $J$  7.2, C(4) $H_2$ ), 7.83 (1H, s, C(4') $H$ );  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 11.7 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 16.6 (C(2)), 18.6 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 25.7 (C(4)), 27.3 (C(3)), 119.1 (C(1)), 138.8 (C(5')), 143.7 (C(4')), 170.0 (C(2'));  $m/z$  (ESI<sup>+</sup>) 309.2 (MH<sup>+</sup>, 100%), 331.1 (MNa<sup>+</sup>, 3%); HRMS (ESI-TOF)  $m/z$  [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>29</sub>N<sub>2</sub>SSi 309.1815; found 309.1815.

#### 4-(2-(Triisopropylsilyl)oxazol-5-yl)butanal (**38**)

DIBAL-H (1 M in toluene, 3.7 mL, 3.7 mmol) was added dropwise to a solution of nitrile **36** (363 mg, 1.24 mmol) in anhydrous DCM (12 mL) at -78 °C. After stirring at this temperature for 3 h, EtOAc was added followed by a saturated solution of Rochelle's salt. After stirring at room temperature for 1 h, the aqueous layer was extracted with EtOAc, washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by *flash* column chromatography (20% EtOAc in petrol) to give aldehyde **38** (286 mg, 0.969 mmol, 78%) as a colourless oil.  $R_f$  (20% EtOAc in petrol) 0.34;  $\nu_{\max}/\text{cm}^{-1}$  2944 (C-H), 2867 (C-H), 1726 (C=O), 1464 (C=C);  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 1.13 (18H, d,  $J$  7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.40 (3H, sept,  $J$  7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 2.00 (2H, quint,  $J$  7.2, C(3) $H_2$ ), 2.50 (2H, td,  $J$  7.2, 1.2, C(2) $H_2$ ), 2.76 (2H, td,  $J$  7.2, 0.7, C(4) $H_2$ ), 6.86 (1H, s, C(4') $H$ ), 9.78 (1H, t,  $J$  1.2, C(1) $H$ );  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 11.1 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.5

(SiCH(CH<sub>3</sub>)<sub>2</sub>), 20.4 (C(3)), 24.9 (C(4)), 43.0 (C(2)), 122.8 (C(4')), 153.6 (C(5')), 168.0 (C(2')), 201.6 (C(1)); *m/z* (ESI<sup>+</sup>) 296.2 (MH<sup>+</sup>, 13%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>30</sub>NO<sub>2</sub>Si 296.2040; found 296.2042.

*4-(2-(Triisopropylsilyl)thiazol-5-yl)butanal (39)*

DIBAL-H (1 M in cyclohexanes, 9.1 mL, 9.1 mmol) was added dropwise to a solution of nitrile **37** (939 mg, 3.04 mmol) in anhydrous DCM (30 mL) at -78 °C. After stirring at this temperature for 3 h, EtOAc was added followed by a saturated solution of Rochelle's salt. After stirring at room temperature for 1 h, the aqueous layer was extracted with Et<sub>2</sub>O, washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by *flash* column chromatography (15% EtOAc in petrol) to give aldehyde **39** (566 mg, 1.82 mmol, 60%) as a yellow oil. *R<sub>f</sub>* (15% EtOAc in petrol) 0.29; *v*<sub>max</sub>/cm<sup>-1</sup> 2943 (C-H), 2865 (C-H), 2718 (C-H), 1725 (C=O), 1462 (C=C); *δ*<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 1.13 (18H, d, *J* 7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.42 (3H, sept, *J* 7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 2.02 (2H, quint, *J* 7.2, C(3)*H*<sub>2</sub>), 2.52 (2H, td, *J* 7.2, 1.2, C(2)*H*<sub>2</sub>), 2.94 (2H, t, *J* 7.2, C(4)*H*<sub>2</sub>), 7.80 (1H, s, C(4')*H*), 9.78 (1H, t, *J* 1.2, C(1)*H*); *δ*<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 11.8 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.6 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 24.1 (C(3)), 26.2 (C(4)), 43.1 (C(2)), 140.6 (C(5')), 143.3 (C(4')), 169.3 (C(2')), 201.7 (C(1)); *m/z* (ESI<sup>+</sup>) 312.1 (MH<sup>+</sup>, 7%); HRMS (ESI-TOF) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>30</sub>NOSSi 312.1812; found 312.1813.

*5-(Pent-4-yn-1-yl)-2-(triisopropylsilyl)oxazole (40)*

Potassium carbonate (324 mg, 1.68 mmol) and a solution of the Bestmann reagent (278 mg, 1.44 mmol) in MeOH (2 mL) were added to a solution of aldehyde **38** (342 mg, 1.16 mmol) in MeOH (10 mL). After stirring at room temperature for 16 h, the suspension was cooled to 0 °C, quenched with saturated aqueous NaHCO<sub>3</sub> and extracted with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by *flash* column chromatography (5% EtOAc in petrol) to give alkyne **40** (291 mg, 0.999 mmol, 86%) as a colourless oil. *R<sub>f</sub>* (5% EtOAc in petrol) 0.27; *v*<sub>max</sub>/cm<sup>-1</sup> 3312 (C-H), 2944 (C-H), 2867 (C-H), 2120 (C≡C), 1464 (C=C); *δ*<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.12 (18H, d, *J* 7.4, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.38 (3H, sept, *J* 7.4, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.88 (2H, quint, *J* 7.2, C(2)*H*<sub>2</sub>), 1.98 (1H, t, *J* 2.6, C(5)*H*), 2.24 (2H, td, *J* 7.2, 2.6, C(3)*H*<sub>2</sub>), 2.82 (2H, td, *J* 7.2, 0.8, C(1)*H*<sub>2</sub>), 6.84 (1H, t, *J* 0.8, C(4')*H*); *δ*<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 11.1 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.0 (C(3)), 18.5 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 24.6 (C(2)), 26.7 (C(1)), 69.2 (C(5)), 83.5 (C(4)),

122.8 (C(4')), 153.8 (C(5')), 167.7 (C(2'));  $m/z$  (ESI<sup>+</sup>) 292.2 (MH<sup>+</sup>, 100%); HRMS (ESI-TOF)  $m/z$  [M+H]<sup>+</sup> Calcd for C<sub>17</sub>H<sub>30</sub>NOSi 292.2091; found 292.2092.

*5-(Pent-4-yn-1-yl)-2-(triisopropylsilyl)thiazole (41)*

Potassium carbonate (505 mg, 3.65 mmol) and a solution of the Bestmann reagent (421 mg, 2.19 mmol) in MeOH (6 mL) were added to a solution of aldehyde **39** (566 mg, 1.82 mmol) in MeOH (12 mL). After stirring at room temperature for 15 h, the suspension was cooled to 0 °C, quenched with saturated aqueous NaHCO<sub>3</sub> and extracted with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by *flash* column chromatography (5% EtOAc in petrol) to give alkyne **41** (322 mg, 1.05 mmol, 58%) as a colourless oil.  $R_f$  (5% EtOAc in petrol) 0.24;  $\nu_{\max}/\text{cm}^{-1}$  3311 (C-H), 2943 (C-H), 2866 (C-H), 2120 (C≡C), 1462 (C=C);  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 1.12 (18H, d,  $J$  7.2, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.42 (3H, sept,  $J$  7.2, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.90 (2H, quint,  $J$  7.5, C(2)H<sub>2</sub>), 1.98-2.01 (1H, m, C(5)H), 2.25 (2H, td,  $J$  7.5, 2.4, C(3)H<sub>2</sub>), 2.82 (2H, t,  $J$  7.5, C(1)H<sub>2</sub>), 7.81 (1H, s, C(4')H);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 11.8 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.0 (C(3)), 18.6 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 25.7 (C(1)), 30.3 (C(2)), 69.3 (C(5)), 83.5 (C(4)), 140.7 (C(5')), 143.3 (C(4')), 169.0 (C(2'));  $m/z$  (ESI<sup>+</sup>) 308.2 (MH<sup>+</sup>, 100%); HRMS (ESI-TOF)  $m/z$  [M+H]<sup>+</sup> Calcd for C<sub>17</sub>H<sub>30</sub>NSSi 308.1863; found 308.1864.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-(5-(2-(triisopropylsilyl)oxazol-5-yl)pent-2-ynoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (42)*

General procedure B (from **8c**, with **34**); yield 58% (93 mg); light yellow oil.  $R_f$  (20% EtOAc in petrol) 0.26;  $[\alpha]_D^{20}$  +65.1 ( $c$  1.0, CHCl<sub>3</sub>);  $\nu_{\max}/\text{cm}^{-1}$  2947 (C-H), 2868 (C-H), 2215 (C≡C), 1755 (C=O), 1721 (C=O), 1635 (C=O), 1587 (C=C);  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 0.89 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.09 (18H, d,  $J$  7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.13 (3H, d,  $J$  6.1, <sup>i</sup>Pr), 1.29 (3H, d,  $J$  6.1, <sup>i</sup>Pr), 1.40 (3H, sept,  $J$  7.5, SiCH(CH<sub>3</sub>)<sub>2</sub>), 2.79 (2H, t,  $J$  7.5, C(4')H<sub>2</sub>), 3.04 (2H, t,  $J$  7.5, C(5')H<sub>2</sub>), 3.43 (1H, d,  $J$  8.5, C(1)H<sub>A</sub>H<sub>B</sub>), 3.77 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.74 (1H, s, C(3)H), 4.80 (1H, d,  $J$  8.5, C(1)H<sub>A</sub>H<sub>B</sub>), 5.18 (1H, sept,  $J$  6.1, <sup>i</sup>Pr), 6.90 (1H, s, C(4'')H);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 11.0 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.5 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 18.7 (C(4')), 21.1 (<sup>i</sup>Pr), 22.3 (<sup>i</sup>Pr), 24.4 (C(5')), 24.7 (C(CH<sub>3</sub>)<sub>3</sub>), 35.3 (C(CH<sub>3</sub>)<sub>3</sub>), 53.3 (CO<sub>2</sub>CH<sub>3</sub>), 69.5 (C(1)), 74.4 (C(7a)), 80.0 (<sup>i</sup>Pr), 82.1 (C(2')), 96.1 (C(3')), 97.8 (C(3)), 109.1 (C(6)), 123.2 (C(4'')), 152.1 (C(5'')), 168.0 (CO<sub>2</sub>CH<sub>3</sub>), 168.1 (C(2'')), 172.1 (C(1')), 174.4 (C(7)), 174.5 (C(5));  $m/z$  (ESI<sup>+</sup>) 601.4 (MH<sup>+</sup>, 100%), 623.3 (MNa<sup>+</sup>, 14%); HRMS (ESI-TOF)  $m/z$  [M+H]<sup>+</sup> Calcd for C<sub>32</sub>H<sub>49</sub>N<sub>2</sub>O<sub>7</sub>Si 601.3304; found 601.3301.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-(5-(2-(triisopropylsilyl)thiazol-5-yl)pent-2-ynoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (43)*

General procedure B (from **8c**, with **35**); yield 58% (67 mg); light yellow oil.  $R_f$  (25% EtOAc in petrol) 0.42;  $[\alpha]_D^{20} +70.2$  ( $c$  0.6,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2945 (C-H), 2867 (C-H), 2215 ( $\text{C}\equiv\text{C}$ ), 1755 (C=O), 1722 (C=O), 1636 (C=O), 1585 (C=C);  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 0.89 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.10 (18H, d,  $J$  7.6,  $\text{SiCH}(\text{CH}_3)_2$ ), 1.13 (3H, d,  $J$  6.1,  $^i\text{Pr}$ ), 1.29 (3H, d,  $J$  6.1,  $^i\text{Pr}$ ), 1.39 (3H, sept,  $J$  7.6,  $\text{SiCH}(\text{CH}_3)_2$ ), 2.80 (2H, t,  $J$  7.6,  $\text{C}(4')\text{H}_2$ ), 3.22 (2H, t,  $J$  7.6,  $\text{C}(5')\text{H}_2$ ), 3.44 (1H, d,  $J$  8.8,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 3.77 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.74 (1H, s,  $\text{C}(3)\text{H}$ ), 4.80 (1H, d,  $J$  8.8,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 5.19 (1H, sept,  $J$  6.1,  $^i\text{Pr}$ ), 7.86 (1H, s,  $\text{C}(4'')\text{H}$ );  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 11.7 ( $\text{SiCH}(\text{CH}_3)_2$ ), 18.6 ( $\text{SiCH}(\text{CH}_3)_2$ ), 21.1 ( $^i\text{Pr}$ ), 22.1 ( $\text{C}(4')$ ), 22.2 ( $^i\text{Pr}$ ), 24.7 ( $\text{C}(\text{CH}_3)_3$ ), 25.4 ( $\text{C}(5')$ ), 35.3 ( $\text{C}(\text{CH}_3)_3$ ), 53.4 ( $\text{CO}_2\text{CH}_3$ ), 69.5 ( $\text{C}(1)$ ), 74.4 ( $\text{C}(7\text{a})$ ), 79.9 ( $^i\text{Pr}$ ), 82.4 ( $\text{C}(2')$ ), 96.2 ( $\text{C}(3')$ ), 97.8 ( $\text{C}(3)$ ), 109.1 ( $\text{C}(6)$ ), 138.8 ( $\text{C}(5'')$ ), 143.6 ( $\text{C}(4'')$ ), 168.0 ( $\text{CO}_2\text{CH}_3$ ), 169.6 ( $\text{C}(2'')$ ), 172.1 ( $\text{C}(1')$ ), 174.3, 174.5 ( $\text{C}(7)$ ,  $\text{C}(5)$ );  $m/z$  ( $\text{ESI}^+$ ) 617.3 ( $\text{MH}^+$ , 100%); HRMS (ESI-TOF)  $m/z$   $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{32}\text{H}_{49}\text{N}_2\text{O}_6\text{SSi}$  617.3075; found 617.3071.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-(6-(2-(triisopropylsilyl)oxazol-5-yl)hex-2-ynoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (44)*

General procedure B (from **8c**, with **40**); yield 54% (81 mg); light yellow oil.  $R_f$  (20% EtOAc in petrol) 0.24;  $[\alpha]_D^{20} +58.2$  ( $c$  1.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2947 (C-H), 2868 (C-H), 2215 ( $\text{C}\equiv\text{C}$ ), 1755 (C=O), 1721 (C=O), 1635 (C=O), 1587 (C=C);  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.91 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.12 (18H, d,  $J$  7.5,  $\text{SiCH}(\text{CH}_3)_2$ ), 1.17 (3H, d,  $J$  6.0,  $^i\text{Pr}$ ), 1.33 (3H, d,  $J$  6.0,  $^i\text{Pr}$ ), 1.38 (3H, sept,  $J$  7.5,  $\text{SiCH}(\text{CH}_3)_2$ ), 1.99 (2H, quint,  $J$  7.2,  $\text{C}(5')\text{H}_2$ ), 2.51 (2H, t,  $J$  7.2,  $\text{C}(4')\text{H}_2$ ), 2.90 (2H, td,  $J$  7.2, 2.7,  $\text{C}(6')\text{H}_2$ ), 3.46 (1H, d,  $J$  8.5,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 3.79 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.76 (1H, s,  $\text{C}(3)\text{H}$ ), 4.82 (1H, d,  $J$  8.5,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 5.24 (1H, sept,  $J$  6.0,  $^i\text{Pr}$ ), 6.87 (1H, s,  $\text{C}(4'')\text{H}$ );  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 11.1 ( $\text{SiCH}(\text{CH}_3)_2$ ), 18.5 ( $\text{SiCH}(\text{CH}_3)_2$ ), 19.0 ( $\text{C}(4')$ ), 21.1 ( $^i\text{Pr}$ ), 22.3 ( $^i\text{Pr}$ ), 24.6 ( $\text{C}(6')$ ), 24.8 ( $\text{C}(\text{CH}_3)_3$ ), 25.9 ( $\text{C}(5')$ ), 35.3 ( $\text{C}(\text{CH}_3)_3$ ), 53.4 ( $\text{CO}_2\text{CH}_3$ ), 69.6 ( $\text{C}(1)$ ), 74.5 ( $\text{C}(7\text{a})$ ), 80.0 ( $^i\text{Pr}$ ), 82.3 ( $\text{C}(2')$ ), 97.4 ( $\text{C}(3')$ ), 97.8 ( $\text{C}(3)$ ), 109.2 ( $\text{C}(6)$ ), 123.0 ( $\text{C}(4'')$ ), 153.5 ( $\text{C}(5'')$ ), 167.8 ( $\text{C}(2'')$ ), 168.1 ( $\text{CO}_2\text{CH}_3$ ), 172.4 ( $\text{C}(1')$ ), 174.3 ( $\text{C}(7)$ ), 174.6 ( $\text{C}(5)$ );  $m/z$  ( $\text{ESI}^+$ ) 615.4 ( $\text{MH}^+$ , 100%), 637.3 ( $\text{MNa}^+$ , 14%); HRMS (ESI-TOF)  $m/z$   $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{33}\text{H}_{51}\text{N}_2\text{O}_7\text{Si}$  615.3460; found 615.3456.



*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-(6-(2-(triisopropylsilyl)thiazol-5-yl)hex-2-ynoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (45)*

General procedure B (from **8c**, with **41**); yield 46% (93 mg); light yellow oil.  $R_f$  (20% EtOAc in petrol) 0.30;  $[\alpha]_D^{20} +58.3$  ( $c$  1.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2945 (C-H), 2867 (C-H), 2213 ( $\text{C}\equiv\text{C}$ ), 1755 (C=O), 1721 (C=O), 1635 (C=O), 1583 (C=C);  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 0.88 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.10 (18H, d,  $J$  7.6,  $\text{SiCH}(\text{CH}_3)_2$ ), 1.15 (3H, d,  $J$  6.1,  $^i\text{Pr}$ ), 1.30 (3H, d,  $J$  6.1,  $^i\text{Pr}$ ), 1.39 (3H, sept,  $J$  7.6,  $\text{SiCH}(\text{CH}_3)_2$ ), 1.99 (2H, quint,  $J$  6.9,  $\text{C}(5')\text{H}_2$ ), 2.50 (2H, t,  $J$  6.9,  $\text{C}(4')\text{H}_2$ ), 3.05-3.10 (2H, m,  $\text{C}(6')\text{H}_2$ ), 3.44 (1H, d,  $J$  8.8,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 3.76 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.74 (1H, s,  $\text{C}(3)\text{H}$ ), 4.80 (1H, d,  $J$  8.8,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 5.22 (1H, sept,  $J$  6.1,  $^i\text{Pr}$ ), 7.81 (1H, s,  $\text{C}(4'')\text{H}$ );  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 11.7 ( $\text{SiCH}(\text{CH}_3)_2$ ), 18.6 ( $\text{SiCH}(\text{CH}_3)_2$ ), 18.9 ( $\text{C}(4')$ ), 21.1 ( $^i\text{Pr}$ ), 22.3 ( $^i\text{Pr}$ ), 24.7 ( $\text{C}(\text{CH}_3)_3$ ), 25.7 ( $\text{C}(5')$ ), 29.5 ( $\text{C}(6')$ ), 35.2 ( $\text{C}(\text{CH}_3)_3$ ), 53.3 ( $\text{CO}_2\text{CH}_3$ ), 69.5 ( $\text{C}(1)$ ), 74.4 ( $\text{C}(7\text{a})$ ), 79.9 ( $^i\text{Pr}$ ), 82.4 ( $\text{C}(2')$ ), 97.4 ( $\text{C}(3')$ ), 97.7 ( $\text{C}(3)$ ), 109.2 ( $\text{C}(6)$ ), 140.3 ( $\text{C}(5'')$ ), 143.4 ( $\text{C}(4'')$ ), 167.8 ( $\text{C}(2'')$ ), 168.0 ( $\text{CO}_2\text{CH}_3$ ), 169.0 ( $\text{C}(1')$ ), 174.2 ( $\text{C}(7)$ ), 174.5 ( $\text{C}(5)$ );  $m/z$  ( $\text{ESI}^+$ ) 631.4 ( $\text{MH}^+$ , 100%); HRMS ( $\text{ESI-TOF}$ )  $m/z$   $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{33}\text{H}_{51}\text{N}_2\text{O}_6\text{SSi}$  631.3232; found 631.3229.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-((2E,4E)-5-(2-(triisopropylsilyl)oxazol-5-yl)penta-2,4-dienoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (46)*

General procedure C (from **42**); yield 94% (53 mg); yellow oil.  $R_f$  (20% EtOAc in petrol) 0.27;  $[\alpha]_D^{20} +118.2$  ( $c$  1.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2956 (C-H), 2868 (C-H), 1755 (C=O), 1713 (C=O), 1657 (C=O), 1588 (C=C);  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.92 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.10 (3H, d,  $J$  6.0,  $^i\text{Pr}$ ), 1.15 (18H, d,  $J$  7.5,  $\text{SiCH}(\text{CH}_3)_2$ ), 1.32 (3H, d,  $J$  6.0,  $^i\text{Pr}$ ), 1.42 (3H, sept,  $J$  7.5,  $\text{SiCH}(\text{CH}_3)_2$ ), 3.49 (1H, d,  $J$  9.0,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 3.78 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.75 (1H, s,  $\text{C}(3)\text{H}$ ), 4.83 (1H, d,  $J$  9.0,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 5.24 (1H, sept,  $J$  6.0,  $\text{C}(6')\text{H}$ ), 6.80 (1H, d,  $J$  15.0,  $\text{C}(5')\text{H}$ ), 6.92 (1H, dd,  $J$  15.0, 11.2,  $\text{C}(4')\text{H}$ ), 7.13 (1H, d,  $J$  15.0,  $\text{C}(2')\text{H}$ ), 7.21 (1H, s,  $\text{C}(4'')\text{H}$ ), 7.41 (1H, dd,  $J$  15.0, 11.2,  $\text{C}(3')\text{H}$ );  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 11.1 ( $\text{SiCH}(\text{CH}_3)_2$ ), 18.5 ( $\text{SiCH}(\text{CH}_3)_2$ ), 20.9 ( $^i\text{Pr}$ ), 22.3 ( $^i\text{Pr}$ ), 24.8 ( $\text{C}(\text{CH}_3)_3$ ), 35.3 ( $\text{C}(\text{CH}_3)_3$ ), 53.3 ( $\text{CO}_2\text{CH}_3$ ), 69.6 ( $\text{C}(1)$ ), 74.9 ( $\text{C}(7\text{a})$ ), 79.1 ( $\text{C}(6')$ ), 97.7 ( $\text{C}(3)$ ), 109.6 ( $\text{C}(6)$ ), 125.3 ( $\text{C}(5')$ ), 127.9 ( $\text{C}(4')$ ), 128.3 ( $\text{C}(4'')$ ), 129.7 ( $\text{C}(2')$ ), 142.6 ( $\text{C}(3')$ ), 151.2 ( $\text{C}(5'')$ ), 168.2 ( $\text{CO}_2\text{CH}_3$ ), 170.4 ( $\text{C}(2'')$ ), 174.0 ( $\text{C}(7)$ ), 176.5 ( $\text{C}(5)$ ), 186.1 ( $\text{C}(1')$ );  $m/z$  ( $\text{ESI}^+$ ) 601.4 ( $\text{MH}^+$ , 100%), 623.2 ( $\text{MNa}^+$ , 21%); HRMS ( $\text{ESI-TOF}$ )  $m/z$   $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{32}\text{H}_{49}\text{N}_2\text{O}_7\text{Si}$  601.3304; found 601.3302.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-((2E,4E)-5-(2-(triisopropylsilyl)thiazol-5-yl)penta-2,4-dienoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (47)*

General procedure C (from **43**); yield 85% (57 mg); orange oil.  $R_f$  (25% EtOAc in petrol) 0.50;  $[\alpha]_D^{20} +130.9$  ( $c$  1.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2946 (C-H), 2867 (C-H), 1754 (C=O), 1712 (C=O), 1656 (C=O), 1585 (C=C);  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 0.91 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.11 (3H, d,  $J$  6.1,  $^i\text{Pr}$ ), 1.13 (18H, d,  $J$  7.6,  $\text{SiCH}(\text{CH}_3)_2$ ), 1.32 (3H, d,  $J$  6.1,  $^i\text{Pr}$ ), 1.44 (3H, sept,  $J$  7.6,  $\text{SiCH}(\text{CH}_3)_2$ ), 3.49 (1H, d,  $J$  8.4,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 3.79 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.75 (1H, s,  $\text{C}(3)\text{H}$ ), 4.83 (1H, d,  $J$  8.4,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 5.22 (1H, sept,  $J$  6.1,  $\text{C}(6')\text{H}$ ), 6.79 (1H, dd,  $J$  15.2, 11.0,  $\text{C}(4')\text{H}$ ), 7.05 (1H, d,  $J$  15.2,  $\text{C}(2')\text{H}$ ), 7.15 (1H, d,  $J$  15.2,  $\text{C}(5')\text{H}$ ), 7.40 (1H, dd,  $J$  15.2, 11.0,  $\text{C}(3')\text{H}$ ), 8.06 (1H, s,  $\text{C}(4'')\text{H}$ );  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 11.7 ( $\text{SiCH}(\text{CH}_3)_2$ ), 18.5 ( $\text{SiCH}(\text{CH}_3)_2$ ), 20.9 ( $^i\text{Pr}$ ), 22.3 ( $^i\text{Pr}$ ), 24.8 ( $\text{C}(\text{CH}_3)_3$ ), 35.3 ( $\text{C}(\text{CH}_3)_3$ ), 53.3 ( $\text{CO}_2\text{CH}_3$ ), 69.6 ( $\text{C}(1)$ ), 74.8 ( $\text{C}(7\text{a})$ ), 79.1 ( $\text{C}(6')$ ), 97.7 ( $\text{C}(3)$ ), 109.5 ( $\text{C}(6)$ ), 130.5 ( $\text{C}(4')$ ), 130.9 ( $\text{C}(5')$ ), 129.3 ( $\text{C}(2')$ ), 139.1 ( $\text{C}(5'')$ ), 142.8 ( $\text{C}(3')$ ), 146.4 ( $\text{C}(4'')$ ), 168.2 ( $\text{CO}_2\text{CH}_3$ ), 172.5 ( $\text{C}(2'')$ ), 173.9 ( $\text{C}(7)$ ), 176.3 ( $\text{C}(5)$ ), 186.3 ( $\text{C}(1')$ );  $m/z$  ( $\text{ESI}^+$ ) 617.3 ( $\text{MH}^+$ , 100%); HRMS ( $\text{ESI-TOF}$ )  $m/z$   $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{32}\text{H}_{49}\text{N}_2\text{O}_6\text{SSi}$  617.3075; found 617.3071.

*Methyl (3R,7aR,Z)-3-(tert-butyl)-6-((2E,4E)-1-hydroxy-5-(oxazol-5-yl)penta-2,4-dien-1-ylidene)-5,7-dioxodihydro-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (48)*

$\text{NaHCO}_3$  (690 mg, 8.21 mmol) was added to a biphasic solution of enol ether **46** (81 mg, 0.14 mmol) and Aliquat 336 (61 mg, 0.15 mmol) in 1:1 toluene/ $\text{H}_2\text{O}$  ( $c$  0.05). The mixture was heated at 80 °C for 6 h, quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ , extracted with EtOAc, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was dissolved in THF (2.7 mL), and aqueous HCl (1 M, 1.1 mL, 1.1 mmol) was added. The mixture was stirred at room temperature for 1 h, diluted with brine, extracted with EtOAc, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The crude product was purified by *flash* column chromatography (80% EtOAc in petrol to 5% MeOH in EtOAc), and the product thus obtained was dissolved in EtOAc, washed with 2 M aqueous HCl, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to give deprotected tetramate **48** (33 mg, 0.083 mmol, 61%) as an orange solid; m.p. 98 °C; 3:1 mixture of tautomers.  $R_f$  (5% MeOH in EtOAc) 0.20;  $[\alpha]_D^{20} +49.3$  ( $c$  0.4,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2960 (C-H), 2917 (C-H), 1752 (C=O), 1706 (C=O), 1654 (C=O), 1632 (C=C), 1603 (C=C), 1571 (C=C);  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) major tautomer: 0.94 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 3.53 (1H, d,  $J$  8.9,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 3.80 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.85 (1H, d,  $J$  8.9,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 4.88 (1H, s,  $\text{C}(3)\text{H}$ ), 6.86 (1H, d,  $J$  15.5,  $\text{C}(5')\text{H}$ ), 6.98 (1H, dd,  $J$  15.5, 11.0,  $\text{C}(4')\text{H}$ ), 7.25 (1H, s,  $\text{C}(4'')\text{H}$ ), 7.27 (1H, d,  $J$  15.2,  $\text{C}(2')\text{H}$ ), 7.66 (1H, dd,  $J$  15.2, 11.0,  $\text{C}(3')\text{H}$ ), 7.93 (1H, s,  $\text{C}(2'')\text{H}$ );  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) major tautomer: 24.8

(C(CH<sub>3</sub>)<sub>3</sub>), 35.4 (C(CH<sub>3</sub>)<sub>3</sub>), 53.5 (CO<sub>2</sub>CH<sub>3</sub>), 68.5 (C(1)), 78.5 (C(7a)), 98.5 (C(3)), 100.4 (C(6)), 122.6 (C(2')), 126.3 (C(5')), 127.7 (C(2'')), 128.1 (C(4')), 128.8 (C(4'')), 145.5 (C(3')), 149.4 (C(5')), 167.8 (CO<sub>2</sub>CH<sub>3</sub>), 175.9 (C(1')), 180.5 (C(5)), 188.0 (C(7)); *m/z* (ESI) 401.1 (M-H<sup>-</sup>, 100%); HRMS (ESI-TOF) *m/z* [M-H]<sup>-</sup> Calcd for C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>7</sub> 401.1354; found 401.1357.

*Methyl (3R,7aR,Z)-3-(tert-butyl)-6-((2E,4E)-1-hydroxy-5-(thiazol-5-yl)penta-2,4-dien-1-ylidene)-5,7-dioxodihydro-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (49)*

NaHCO<sub>3</sub> (423 mg, 5.04 mmol) was added to a biphasic solution of enol ether **47** (51 mg, 0.083 mmol) and Aliquat 336 (36 mg, 0.089 mmol) in 1:1 toluene/H<sub>2</sub>O (1.7 mL). The mixture was heated at 80 °C for 12 h, quenched with saturated aqueous NH<sub>4</sub>Cl, extracted with EtOAc, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in THF (1.7 mL), and aqueous HCl (1 M, 660 µL, 0.660 mmol) was added. The mixture was stirred at room temperature for 1 h, diluted with brine, extracted with EtOAc, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by *flash* column chromatography (80% EtOAc in petrol to 5% MeOH in EtOAc), and the product thus obtained was dissolved in EtOAc, washed with 2 M aqueous HCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give deprotected tetramate **49** (22 mg, 0.053 mmol, 65%) as an orange solid; m.p. 152 °C; 4:1 mixture of tautomers. *R*<sub>f</sub> (5% MeOH in EtOAc) 0.26; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +69.7 (*c* 0.5, CHCl<sub>3</sub>);  $\nu_{\max}$ /cm<sup>-1</sup> 2959 (C-H), 1752 (C=O), 1705 (C=O), 1654 (C=O), 1617 (C=C), 1601 (C=C), 1556 (C=C);  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) major tautomer: 0.94 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 3.52 (1H, d, *J* 9.0, C(1)*H*<sub>A</sub>*H*<sub>B</sub>), 3.79 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.84 (1H, d, *J* 9.0, C(1)*H*<sub>A</sub>*H*<sub>B</sub>), 4.87 (1H, s, C(3)*H*), 6.81 (1H, dd, *J* 15.2, 11.0, C(4')*H*), 7.22 (1H, d, *J* 15.0, C(2')*H*), 7.22 (1H, d, *J* 15.0, C(5')*H*), 7.67 (1H, dd, *J* 15.0, 11.0, C(3')*H*), 7.95 (1H, s, C(4'')*H*), 8.79 (1H, s, C(2'')*H*);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) major tautomer: 24.8 (C(CH<sub>3</sub>)<sub>3</sub>), 35.4 (C(CH<sub>3</sub>)<sub>3</sub>), 53.4 (CO<sub>2</sub>CH<sub>3</sub>), 68.4 (C(1)), 78.4 (C(7a)), 98.4 (C(3)), 100.3 (C(6)), 121.9 (C(2')), 130.0 (C(4')), 132.7 (C(5')), 145.3 (C(4'')), 145.7 (C(3')), 154.4 (C(2'')), 136.7 (C(5'')), 167.8 (CO<sub>2</sub>CH<sub>3</sub>), 176.0 (C(1')), 180.5 (C(5)), 187.9 (C(7)); *m/z* (ESI) 417.1 (M-H<sup>-</sup>, 100%); HRMS (ESI-TOF) *m/z* [M-H]<sup>-</sup> Calcd for C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>6</sub>S 417.1126; found 417.1126.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-((3E,5E)-6-(2-(triisopropylsilyl)thiazol-5-yl)hexa-3,5-dienoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (51)*

Side-product (29%, 30 mg) from the isomerisation of alkyne **45** with General procedure C, isolated together with other impurities; orange oil. *R*<sub>f</sub> (15% EtOAc in petrol) 0.27;  $\nu_{\max}$ /cm<sup>-1</sup> 2948 (C-H), 2868 (C-H), 1753

(C=O), 1711 (C=O), 1683 (C=O), 1588 (C=C);  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.91 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.11 (3H, d,  $J$  6.0,  $^i\text{Pr}$ ), 1.13 (18H, d,  $J$  7.5,  $\text{SiCH}(\text{CH}_3)_2$ ), 1.30 (3H, d,  $J$  6.0,  $^i\text{Pr}$ ), 1.42 (3H, sept,  $J$  7.5,  $\text{SiCH}(\text{CH}_3)_2$ ), 3.45 (1H, d,  $J$  8.5,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 3.76-3.81 (1H, m,  $\text{C}(2')\text{H}_\text{A}\text{H}_\text{B}$ ), 3.77 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 3.93 (1H, dd,  $J$  18.7, 7.2,  $\text{C}(2')\text{H}_\text{A}\text{H}_\text{B}$ ), 4.75 (1H, s,  $\text{C}(3)\text{H}$ ), 4.82 (1H, d,  $J$  8.5,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 5.20 (1H, sept,  $J$  6.0,  $^i\text{Pr}$ ), 5.96 (1H, dt,  $J$  15.0, 7.2,  $\text{C}(3')\text{H}$ ), 6.27 (1H, dd,  $J$  15.0, 10.0,  $\text{C}(4')\text{H}$ ), 6.59 (1H, dd,  $J$  15.5, 10.0,  $\text{C}(5')\text{H}$ ), 6.67 (1H, d,  $J$  15.5,  $\text{C}(6')\text{H}$ ), 7.90 (1H, s,  $\text{C}(4'')\text{H}$ );  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 11.7 ( $\text{SiCH}(\text{CH}_3)_2$ ), 18.6 ( $\text{SiCH}(\text{CH}_3)_2$ ), 21.1 ( $^i\text{Pr}$ ), 22.3 ( $^i\text{Pr}$ ), 24.8 ( $\text{C}(\text{CH}_3)_3$ ), 35.3 ( $\text{C}(\text{CH}_3)_3$ ), 46.1 ( $\text{C}(2')$ ), 53.4 ( $\text{CO}_2\text{CH}_3$ ), 69.6 ( $\text{C}(1)$ ), 74.8 ( $\text{C}(7\text{a})$ ), 79.5 ( $^i\text{Pr}$ ), 97.7 ( $\text{C}(3)$ ), 109.1 ( $\text{C}(6)$ ), 121.2 ( $\text{C}(6')$ ), 127.2 ( $\text{C}(3')$ ), 132.4 ( $\text{C}(5')$ ), 133.8 ( $\text{C}(4')$ ), 140.0 ( $\text{C}(5'')$ ), 144.0 ( $\text{C}(4'')$ ), 168.0 ( $\text{CO}_2\text{CH}_3$ ), 169.4 ( $\text{C}(2'')$ ), 174.2 ( $\text{C}(7)$ ), 176.0 ( $\text{C}(5)$ ), 195.5 ( $\text{C}(1')$ );  $m/z$  ( $\text{ESI}^+$ ) 631.3 ( $\text{MH}^+$ , 100%); HRMS ( $\text{ESI-TOF}$ )  $m/z$   $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{33}\text{H}_{51}\text{N}_2\text{O}_6\text{SSi}$  631.3232; found 631.3228.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-((2E,4E)-6-(2-(triisopropylsilyl)oxazol-5-yl)hexa-2,4-dienoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (52)*

General procedure C (from **44**); yield 31% (59 mg); orange oil.  $R_f$  (15% EtOAc in petrol) 0.13;  $[\alpha]_{\text{D}}^{20} +68.6$  ( $c$  1.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2956 (C-H), 2868 (C-H), 1755 (C=O), 1713 (C=O), 1665 (C=O), 1629 (C=C), 1593 (C=C);  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.90 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.09 (3H, d,  $J$  6.0,  $^i\text{Pr}$ ), 1.12 (18H, d,  $J$  7.5,  $\text{SiCH}(\text{CH}_3)_2$ ), 1.30 (3H, d,  $J$  6.0,  $^i\text{Pr}$ ), 1.38 (3H, sept,  $J$  7.5,  $\text{SiCH}(\text{CH}_3)_2$ ), 3.48 (1H, d,  $J$  8.5,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 3.59 (2H, d,  $J$  6.5,  $\text{C}(6')\text{H}_2$ ), 3.78 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 4.73 (1H, s,  $\text{C}(3)\text{H}$ ), 4.82 (1H, d,  $J$  8.5,  $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$ ), 5.17 (1H, sept,  $J$  6.0,  $^i\text{Pr}$ ), 6.26 (1H, dt,  $J$  15.0, 6.5,  $\text{C}(5')\text{H}$ ), 6.36 (1H, dd,  $J$  15.0, 10.5,  $\text{C}(4')\text{H}$ ), 6.86 (1H, s,  $\text{C}(4'')\text{H}$ ), 6.88 (1H, d,  $J$  15.2,  $\text{C}(2')\text{H}$ ), 7.28 (1H, dd,  $J$  15.2, 10.5,  $\text{C}(3')\text{H}$ );  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 11.1 ( $\text{SiCH}(\text{CH}_3)_2$ ), 18.5 ( $\text{SiCH}(\text{CH}_3)_2$ ), 20.9 ( $^i\text{Pr}$ ), 22.3 ( $^i\text{Pr}$ ), 24.8 ( $\text{C}(\text{CH}_3)_3$ ), 29.5 ( $\text{C}(6')$ ), 35.3 ( $\text{C}(\text{CH}_3)_3$ ), 53.3 ( $\text{CO}_2\text{CH}_3$ ), 69.6 ( $\text{C}(1)$ ), 74.8 ( $\text{C}(7\text{a})$ ), 79.0 ( $\text{C}(6')$ ), 97.7 ( $\text{C}(3)$ ), 109.5 ( $\text{C}(6)$ ), 123.4 ( $\text{C}(4'')$ ), 128.6 ( $\text{C}(2')$ ), 131.5 ( $\text{C}(4')$ ), 139.1 ( $\text{C}(5')$ ), 143.2 ( $\text{C}(3')$ ), 151.2 ( $\text{C}(5'')$ ), 168.2 ( $\text{CO}_2\text{CH}_3$ ), 168.4 ( $\text{C}(2'')$ ), 173.7 ( $\text{C}(7)$ ), 176.3 ( $\text{C}(5)$ ), 186.9 ( $\text{C}(1')$ );  $m/z$  ( $\text{ESI}^+$ ) 615.4 ( $\text{MH}^+$ , 94%), 637.4 ( $\text{MNa}^+$ , 13%); HRMS ( $\text{ESI-TOF}$ )  $m/z$   $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{33}\text{H}_{51}\text{N}_2\text{O}_7\text{Si}$  615.3460; found 615.3458.

*Methyl (3R,7aR)-3-(tert-butyl)-7-isopropoxy-5-oxo-6-((2E,4E)-6-(2-(triisopropylsilyl)thiazol-5-yl)hexa-2,4-dienoyl)-1H,3H-pyrrolo[1,2-c]oxazole-7a(5H)-carboxylate (53)*

General procedure C (from **45**); yield 25% (26 mg); yellow oil.  $R_f$  (15% EtOAc in petrol) 0.19;  $[\alpha]_{\text{D}}^{20} +74.7$  ( $c$  1.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2959 (C-H), 2867 (C-H), 1755 (C=O), 1713 (C=O), 1665 (C=O), 1629 (C=C), 1592

(C=C);  $\delta_H$  (500 MHz,  $CDCl_3$ ) 0.91 (9H, s,  $C(CH_3)_3$ ), 1.10 (3H, d,  $J$  6.0,  $iPr$ ), 1.13 (18H, d,  $J$  7.5,  $SiCH(CH_3)_2$ ), 1.31 (3H, d,  $J$  6.0,  $iPr$ ), 1.42 (3H, sept,  $J$  7.5,  $SiCH(CH_3)_2$ ), 3.48 (1H, d,  $J$  8.5,  $C(1)H_AH_B$ ), 3.77 (2H, d,  $J$  6.5,  $C(6')H_2$ ), 3.78 (3H, s,  $CO_2CH_3$ ), 4.74 (1H, s,  $C(3)H$ ), 4.82 (1H, d,  $J$  8.5,  $C(1)H_AH_B$ ), 5.18 (1H, sept,  $J$  6.0,  $iPr$ ), 6.29-6.40 (2H, m,  $C(4')H + C(5')H$ ), 6.91 (1H, d,  $J$  15.0,  $C(2')H$ ), 7.29 (1H, dd,  $J$  15.0, 10.2,  $C(3')H$ ), 7.81 (1H, s,  $C(4'')H$ );  $\delta_C$  (125 MHz,  $CDCl_3$ ) 11.8 ( $SiCH(CH_3)_2$ ), 18.6 ( $SiCH(CH_3)_2$ ), 20.9 ( $iPr$ ), 22.3 ( $iPr$ ), 24.8 ( $C(CH_3)_3$ ), 30.5 ( $C(6')$ ), 35.3 ( $C(CH_3)_3$ ), 53.3 ( $CO_2CH_3$ ), 69.6 ( $C(1)$ ), 74.9 ( $C(7a)$ ), 79.0 ( $iPr$ ), 97.7 ( $C(3)$ ), 109.5 ( $C(6)$ ), 128.6 ( $C(2')$ ), 130.8 ( $C(4')$ ), 138.0 ( $C(5'')$ ), 142.0 ( $C(5')$ ), 143.2 ( $C(3')$ ), 143.6 ( $C(4'')$ ), 168.2 ( $CO_2CH_3$ ), 170.1 ( $C(2'')$ ), 173.7 ( $C(7)$ ), 176.3 ( $C(5)$ ), 186.8 ( $C(1')$ );  $m/z$  (ESI $^+$ ) 631.3 ( $MH^+$ , 100%); HRMS (ESI-TOF)  $m/z$   $[M+H]^+$  Calcd for  $C_{33}H_{51}N_2O_6SSi$  631.3232; found 631.3228.

### Hole plate method

Agar plates were inoculated with Gram-positive *Staphylococcus aureus* DS267 and Gram-negative *Escherichia coli* X580. Tested compounds were prepared as 4 mg/mL solutions in 1:1 MeOH/DMSO, and diluted to lower concentrations where necessary (when zone size was bigger than 35 mm). A 100  $\mu$ L aliquot of each solution was loaded into wells of 10 mm of diameter in agar plates and incubated at 37 °C for 16-20 h. The diameters of the resultant inhibition zones were then measured along two perpendicular axes and averaged to obtain the zone of inhibition. The assays were repeated in duplicate, and a negative control was run with solvent alone. Cephalosporin C (CephC) was used as a standard. Calibration curves were performed at 2-100  $\mu$ g/mL for *E. coli* and 200-1000  $\mu$ g/mL for *S. aureus*, and these were collected for each set of bioassays performed.

### Broth dilution assay

MIC values were determined with a broth dilution method. The extracts were tested in a primary 96 well plate screening assay. The substances were diluted in MHB for bacterial screening to a stock solution of 1000  $\mu$ g/mL or 1% serial diluted and overlaid with a microbe solution in a concentration of 104 CFU/mL. The plates were incubated at 35 °C for 24 h. All the compounds were tested against Gram-negative *Escherichia coli* and Gram-positive MRSA and *Streptococcus pneumoniae*. Some compounds were also tested for antibacterial activity against Gram-negative *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, Gram-positive *Enterococcus faecalis*, and antifungal activity against *Candida albicans*, *Candida krusei* and *Aspergillus fumigatus*. Ciprofloxacin was used as a positive control.

## Cytotoxicity

Toxicity of selected compounds was evaluated via determination of their inhibitory activity against mammalian HaCaT keratinocytes and HUVEC (human umbilical vein endothelial cell) cell lines in a primary 96 well plate screening assay. In the assay, cells were seeded in the well with cell density of around 60% confluency and incubated for 24-48 hours with the compounds to measure cytotoxic potential. The read out was standardized with Resazurin Cell Viability Assay (Alamar Blue).

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## Supporting information

The supporting Information is available free of charge on the ACS Publications website at DOI: xxxx

Copies of  $^1\text{H}$  and  $^{13}\text{C}$  spectra of new compounds (PDF)

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