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Formal synthesis of (+)-neooxazolomycin via a Stille cross-coupling/deconjugation route

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ABSTRACT

A formal synthesis of neooxazolomycin is described via the preparation of Kende's key intermediate in a longest linear sequence of 23 steps. This work is founded upon the union of three fragments: Moloney's lactam-derived triflate, a vinyl stannane and a Julia–Kocienski sulfone and encompasses three key steps: (i) a Stille cross-coupling to combine the triflate and vinyl stannane, (ii) a base-promoted enone deconjugation to derive the dihydroxylation precursor and (iii) our previously reported Julia–Kocienski methodology to assemble the pentadienyl amine side chain with the sulfone precursor.

1. Introduction

The first members of the oxazolomycin natural product family (Fig. 1), oxazolomycin A[1] and neooxazolomycin,[2] were isolated in 1985 from strains of *Streptomyces* by Uemura and co-workers. Since that time, several other members have also been isolated. Although there is structural variation within the family, all members adhere to a common template with a left-hand pyroglutamate core, central polyene and right-hand oxazole fragments. The left-hand fragment contains a glutamate core featuring a lactam fused to either a β- or γ-lactone. The central fragment comprises a pentadienyl amine, that is, common to all members of the family. Finally, the right-hand amide fragment comprises a triene featuring a secondary alcohol and oxazole terminating unit in the allylic positions; these fragments comprise a family of natural products in their own right—the inthomycins. Oxazolomycins A, B[3] and C[3] (**1**–**3**) are geometrical isomers differing only in the configuration of the triene. The other closely related members all possess extra substituents in addition to varied alkene stereochemistry with one unique exception, neooxazolomycin (**9**). For example, the curromycins[4,5] feature a C-13′ methyl group on the oxazole and 16-Me-oxazolomycin (**4**),[6,7] KSM-2690B (**7**)[8] and KSM-2690C (**8**)[8] feature a β-methyl group in the β-lactone (C-16). The unique structure of neooxazolomycin concerns the left-hand pyroglutamate core where a distinctive arrangement is observed; in contrast to the β-lactone observed in all other family members, a γ-lactone is present via connection through the C-4 hydroxyl, leaving a free primary alcohol in the C-16 position. There are several other derivative families of natural products with structural similarity to the oxazolomycins including the inthomycins/phthaloxazins,[9–11] lajollamycin[12] and clathrynamides,[13,14] which all contain fragments of the structure to a greater or lesser degree, but not all elements of the oxazolomycins.

The members of the oxazolomycin family possess widespread biological activity and a detailed study by Gräfe and co-workers[15] demonstrated in vitro antiviral activity against herpes simplex type I (HSV I), influenza A (WSN; H1N1), vaccinia (Lister) and Coxsackie A9 viruses. Moreover, anti-cancer activity in the form of in vivo Ehrlich ascites antitumour activity[2] and activity against P-388 leukaemia[1] have also been demonstrated. Finally, widespread activity against Gram positive bacteria has been demonstrated for all members of the family including neooxazolomycin. There has been interest in the mode of action of these compounds and this has been reflected in several studies.[16,17]

In contrast to the two reported syntheses of neooxazolomycin **9**, by Kende and co-workers (1990)[18] and Hatakeyama and co-workers (2007),[19] none of the β-lactone oxazolomycins have succumbed to total synthesis. There have been several reports describing approaches to key-elements of the core structure. We were

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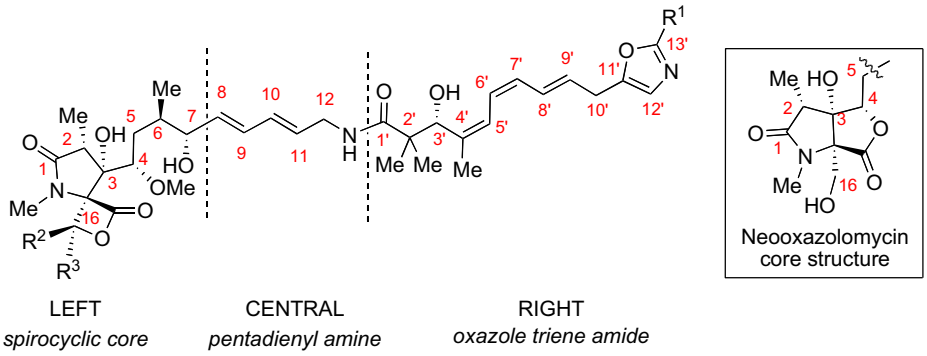


Oxazolomycin A **1,** R^1 = H, R^2 = H, R^3 = H, 4'*Z*, 6'*Z*, 8'*E*
Oxazolomycin B **2,** R^1 = H, R^2 = H, R^3 = H, 4'*E*, 6'*E*, 8'*E*
Oxazolomycin C **3,** R^1 = H, R^2 = H, R^3 = H, 4'*Z*, 6'*E*, 8'*E*
16-Me-oxazolomycin **4,** R^1 = H, R^2 = H, R^3 = Me, 4'*Z*, 6'*Z*, 8'*E*
Curromycin A **5,** R^1 = Me, R^2 = CH_2OMe, R^3 = H, 4'*Z*, 6'*Z*, 8'*E*
Curromycin B **6,** R^1 = Me, R^2 = H, R^3 = Me, 4'*Z*, 6'*Z*, 8'*E*
KSM-2690 B **7,** R^1 = H, R^2 = H, R^3 = Me, 4'*Z*, 6'*E*, 8'*E*
KSM-2690 C **8,** R^1 = H, R^2 = H, R^3 = Me, 4'*E*, 6'*E*, 8'*E*
Neooxazolomycin **9**, core structure on right, 4'*Z*, 6'*Z*, 8'*E*

Fig. 1. The oxazolomycin natural product family.

the first to disclose the successful construction of the left-hand β-lactone spirocyclic core of oxazolomycin via a Mitsunobu cyclisation to form the key four membered ring;[20] subsequent studies by the groups of Mohapatra,[21] Donohoe,[22] Pattenden,[23] Ohfune/Soloshonok[24] and Mondal[25] have also delineated alternative approaches. The central fragment has also been the subject of study and papers on the construction of pentadienyl amines from Kende[26] and Moloney,[27] along with our approach[28] using Julia–Kocienski chemistry, have been reported. With respect to the right-hand triene amide fragment, representing the inthomycin family of natural products, in addition to the complete syntheses by Kende[18] and Hatakeyama,[19] we have reported a route that allows access to any member of the inthomycin family via stereocontrolled olefination/Stille cross-coupling;[29,30] a similar racemic approach to inthomycin A has also been reported by Whiting and Henaff.[31,32]

Kende's synthesis[18] of neooxaozolomycin splits the molecule neatly into left- and right-hand fragments (Scheme 1). For the left-hand fragment a readily available sugar derivative, anhydrogalactoside **10**, is converted into **11**, which then undergoes cyclocondensation with **12** to afford **13**, which itself undergoes a key acid-promoted rearrangement/fragmentation to afford bicycle **14**. Further transformations including Takai olefination and then Stille cross-coupling provided intermediate **15**. The right-hand fragment was constructed in a linear sequence featuring a key Evans auxiliary controlled Reformatsky reaction to construct **16** that underwent further manipulation including Stille cross-coupling to afford acid **17**.

Hatakeyama and co-workers[19] used an essentially identical approach to Kende to prepare the right-hand fragment. However, a very different approach was employed to realise the left-hand fragment (Scheme 2). Intermediate **18**, derived from the common building block, methyl (3*S*)-hydroxy-2-methylpropanoate, underwent Tamao-type hydrosilylation/iodination to generate the (*E*)-olefin **19**, which in the key step was cyclised under palladium catalysis to dihydroxylation precursor **20**. Subsequent functionalisation and a Nozaki–Hiyama–Kishi (NHK) reaction installed the pentadienyl amine fragment.

Herein we describe our synthetic efforts towards the oxazolomycin family and the formal synthesis of neooxazolomycin.

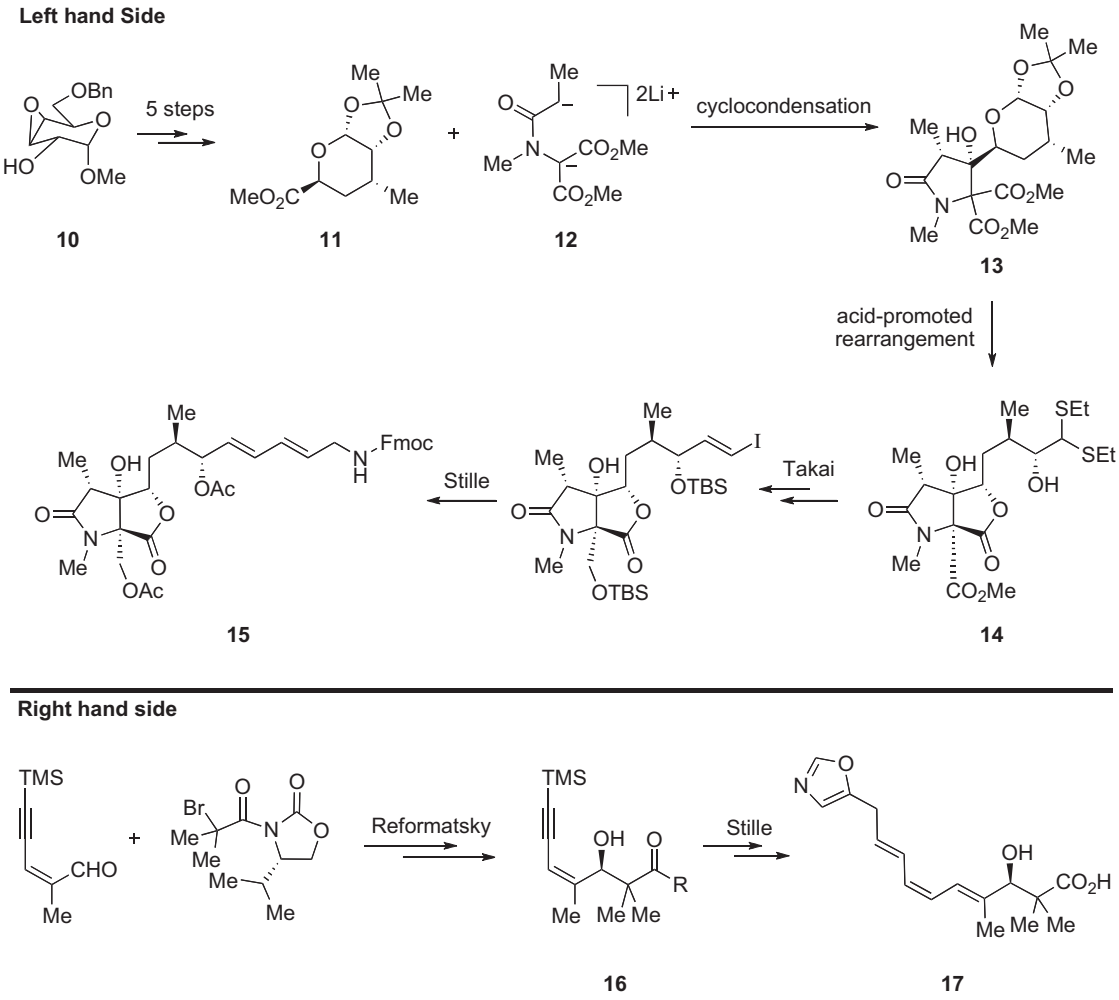
1.1. Retrosynthesis

Our synthetic plan to prepare neooxazolomycin (Scheme 3) envisaged the same late stage peptide coupling of fragments **15** and **17** also prepared by both Kende and Hatakeyama. Compound **17** itself was available as an intermediate from our previously reported synthesis of inthomycin A.[29,33] A convergent synthesis of amine **15** from three smaller building blocks: sulfone **22**, triflate **25** and stannane **26** defined our overall plan. Initially a Julia–Kocienski olefination between aldehyde **21** and sulfone **22** utilising our previously reported methodology[28] for the construction of pentadienyl amines would afford Kende's advanced intermediate **15**. The challenge then became the preparation of the highly functionalized spirocyclic lactam core **21**. We postulated that if the (*E*)-configured tri-substituted olefin **23** could be obtained then a dihydroxylation (with concomitant lactonisation) would lead to **12**. The difficulty in constructing this alkene stereoselectively via an olefination reaction led us to consider alternative possibilities. The preparation of enone **24** appeared facile via a cross-coupling strategy, thus a base-promoted deconjugation process, via a dienolate with a kinetic protonation, recommended itself. Stille disconnection then affords vinyl stannane **26** and tetramic acid derived core **25**. Vinyl stannane **26** should arise via a series of transformations featuring Sharpless asymmetric epoxidation (on allylic alcohol **29**) to set the C-7 centre and regioselective alanate opening of epoxide **28** to introduce the C-6 methyl group. Triflate **25** can be accessed via a straightforward triflation of bicyclic polyglutamate core **27** available via Moloney's elegant chemistry for the preparation of tetramic acids[34]—this strategy led back to D-serine.

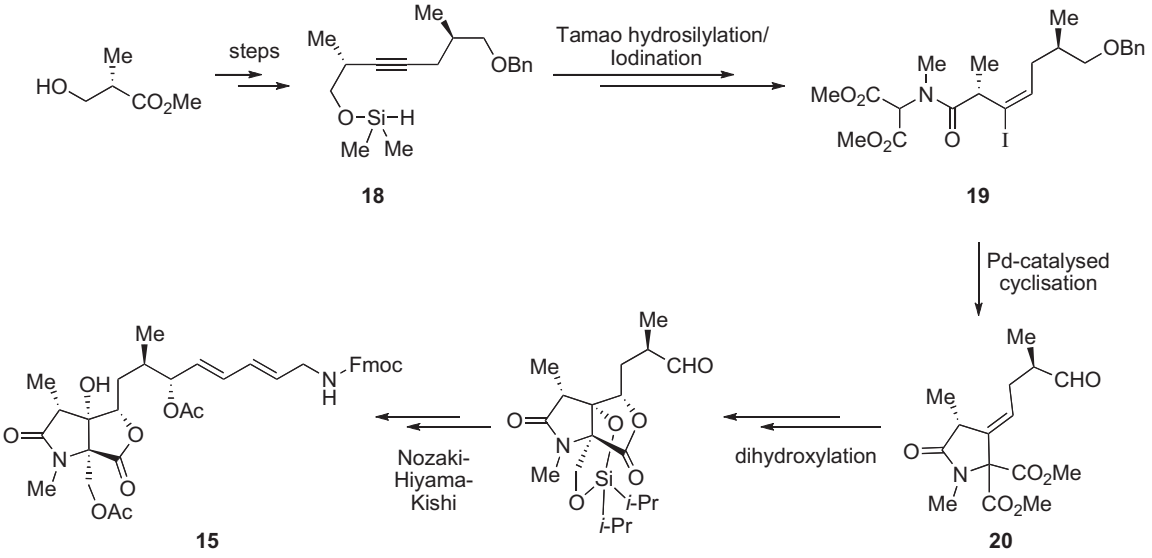
2. Results and discussion

2.1. The lactam core

Our inspiration for the left hand core was derived from the previous work reported by Moloney and co-workers for the synthesis of functionalised tetramic acids.[34] They described an approach based upon Seebach's self-regeneration of chirality principle[35] to construct the key quaternary centre present in the

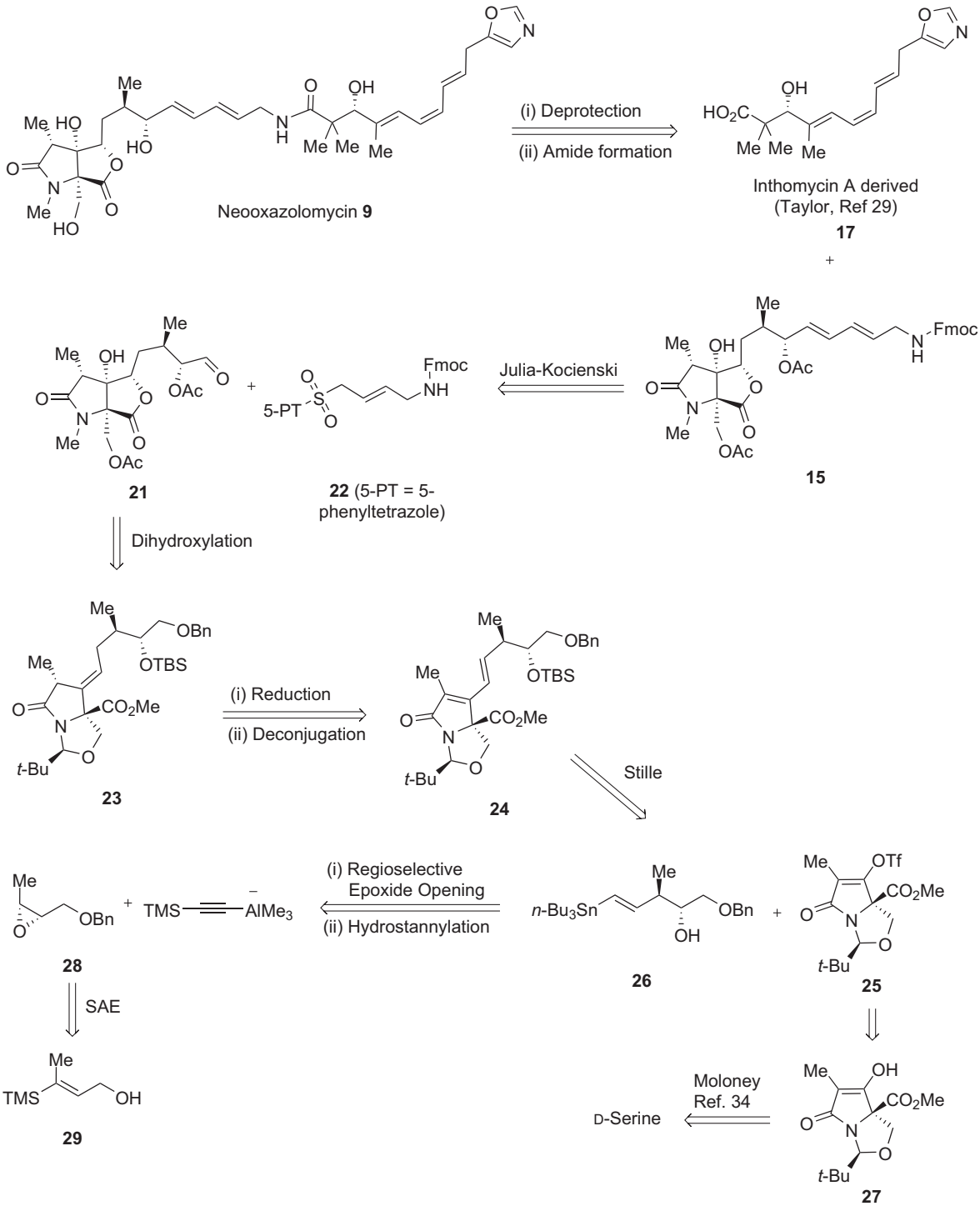


Scheme 1. Kende's synthesis of the neooxazolomycin fragments.



Scheme 2. Hatakeyama's approach to the left-hand fragment **15**.

bicyclic core **25** via a regioselective, counter-intuitive, Dieckmann cyclisation. The synthesis of lactam core **25** commenced with D-serine, which was converted into its methyl ester (Fieser conditions) before condensation with pivaldehyde in the presence of triethylamine to afford oxazolidine **30** in 95% yield and a 1:1 *cis*/*trans*-ratio. *N*-Acylation with racemic acid chloride **31** in the presence of pyridine afforded the acyl oxazolidine **32**, the cyclisation precursor in 92% yield (as a 1:1 mixture of diastereomers at the

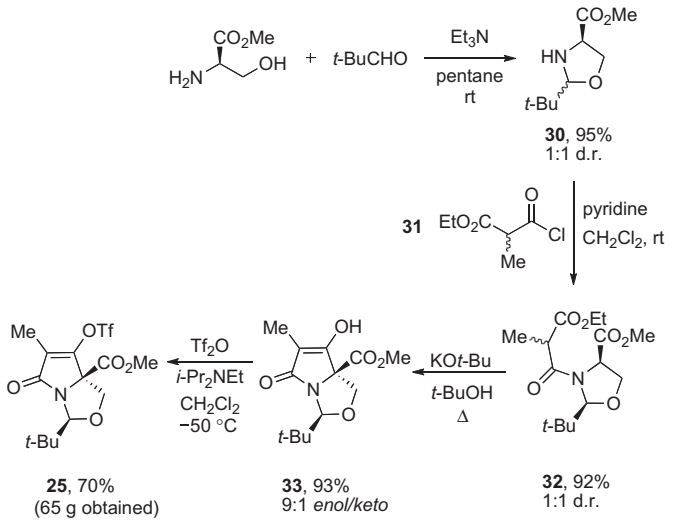


Scheme 3. Retrosynthetic analysis.

malonate centre); the oxazolidine C-2 centre is set with *cis*-stereochemistry relative to the inherent stereocentre according to the previous precedent.[36] Regioselective Dieckmann condensation to the bicyclic oxazolidine core promoted by potassium *tert*-butoxide afforded the desired **33** in 93% yield and as a single diastereomer, albeit as a 9:1 mixture of enol/keto tautomers. The unexpected Dieckmann cyclisation occurs via the less stable enolate rather than the more stable 'malonate enolate'. This has been rationalized by the consideration that the product derived from the more stable enolate is too sterically hindered to form because it places a *tert*-butyl group on the *endo*-face of the product. With Moloney's derivative **33** in hand, it was necessary only for it to be converted into crystalline triflate **25** (Tf_2O, *i*-Pr_2NEt) in 70% yield. Thus, in five linear steps from chiral pool material, the Stille partner **25** was assembled in 60% yield. The crystalline nature of **25** allowed the material to be obtained on a large scale (65 g) without the need for chromatography (Scheme 4).

2.2. The stannane cross-coupling partner

The required (*E*)-tri-substituted alkene **29**, was readily prepared in two-steps from (trimethylsilyl)propargyl alcohol according to

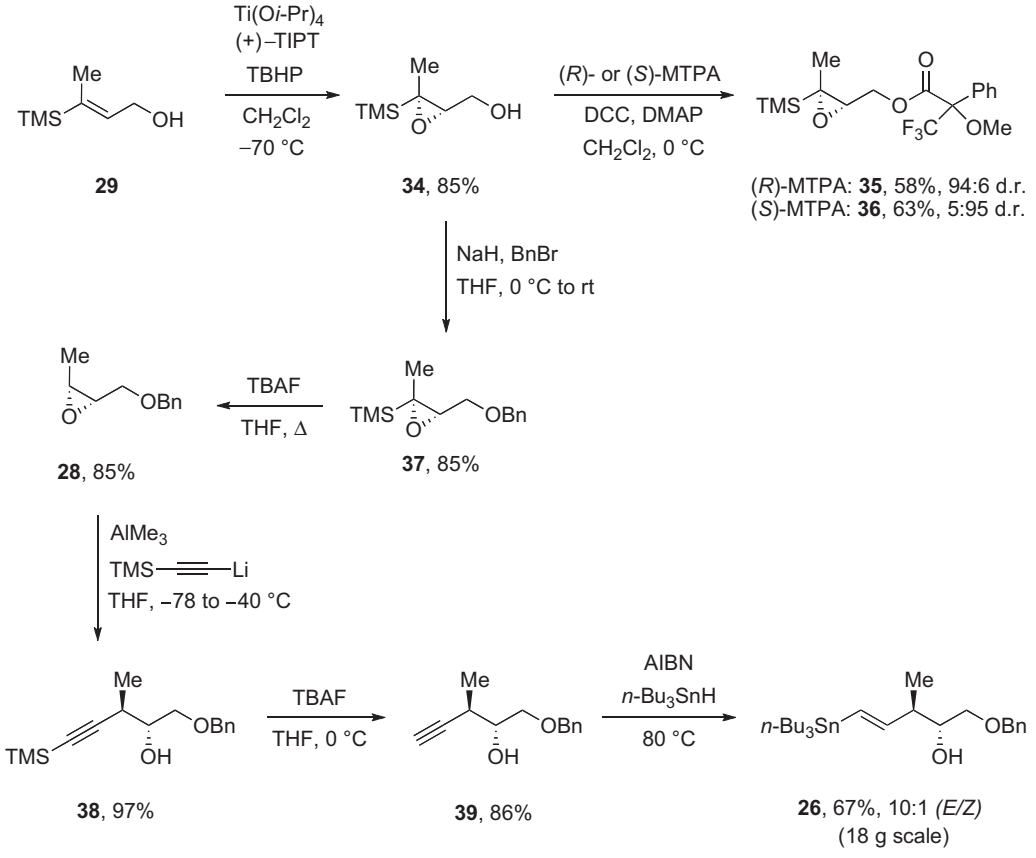


Scheme 4. Moloney's tetramic acid chemistry and further elaboration.

the robust procedure of Denmark and co-workers.[37] Sharpless epoxidation of alkene **29** proved to be somewhat troublesome and rigorously anhydrous conditions were required. The use of *tert*-butylhydroperoxide in decane or toluene solution as the oxidant led to successful oxidation but in moderate enantioselectivity (2:1 er). However, the preparation of a solution of TBHP in methylene chloride gave a major improvement. Presumably the improvement in selectivity arises from the elimination of traces of water in the TBHP in toluene when prepared according to the procedure of Sharpless and co-workers from aqueous TBHP.[38] Thus, epoxide **34** was obtained in 85% yield and 95:5 er with (+)-DIPT; the enantioselectivity of the epoxidation was determined by Mosher's ester formation with both (*S*)- and (*R*)-MTPA-Cl and ^{1}H NMR analysis. Subsequent benzyl protection of the alcohol and desilylation of the epoxide **37**, both under standard conditions, afforded (2*R*,3*S*)-epoxide **28**. Regioselective epoxide opening at the C-3 position was achieved under Lewis acidic conditions with the alanate reagent derived from lithium trimethylsilylacetylide and trimethylaluminium.[39] At −40 °C in Et_2O, a 9:1 mixture of regioisomers in favour of the desired alcohol **38** was obtained; the control of temperature in this reaction was essential to ensure high regioselectivity. Ultimately, the minor regioisomer was readily removed after desilylation of the alkyne with TBAF in THF at 0 °C to afford alkyne **39** in 83% yield over the two-steps. Finally, radical hydrostannylation with *n*-Bu_3SnH at 80 °C afforded the Stille cross-coupling partner **26** in 67% yield as a 10:1 mixture of (*E*/*Z*)-isomers. Ultimately, we were able to perform the asymmetric epoxidation on a 65 mmol scale without deleterious effect on either the enantioselectivity or yield; this material was then converted into more than 18 g of stannane **26** (Scheme 5).

2.3. Stille cross-coupling and subsequent modification

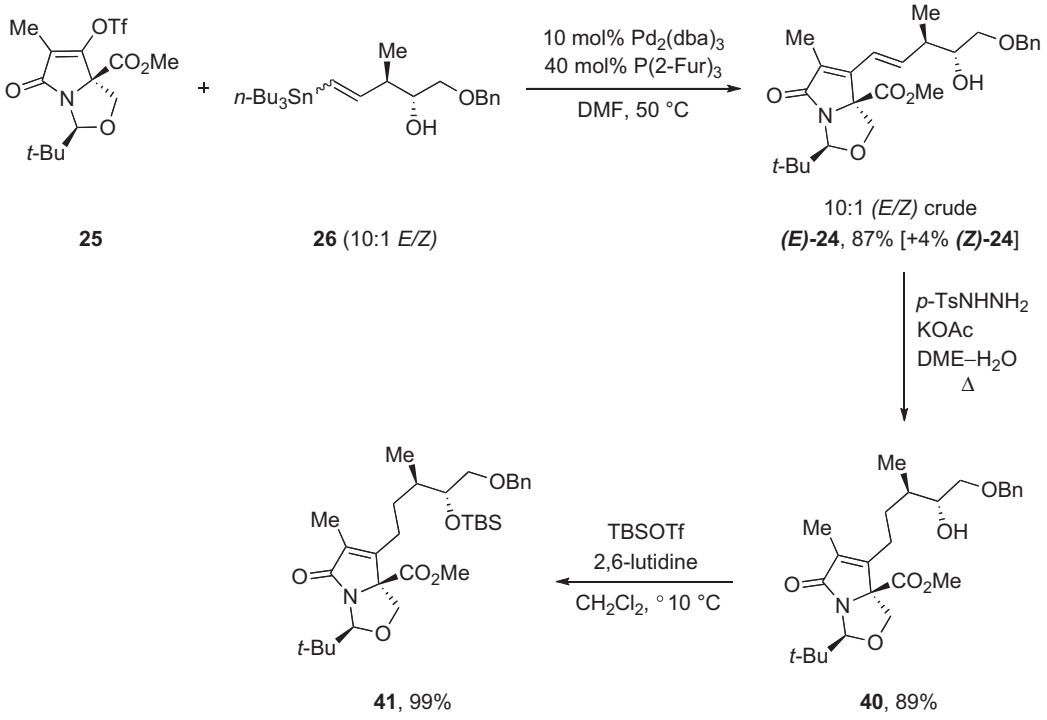
The union of two of the key fragments, **25** and **26**, was accomplished via Stille coupling [$Pd_2(dba)_3$/P(2-fur)$_3$] in DMF at 50 °C for 6 h. Control of the temperature was essential in this reaction; if the reaction was run at higher temperatures the persistent formation of an unwanted isomer was observed. This being the case, unified diene **24** was obtained in 87% yield with the same crude ratio of (*E*/*Z*)-isomers as present in the stannane precursor; chromatography afforded 87% of pure (*E*)-**24** and 4% of pure (*Z*)-**24**. Selective



Scheme 5. Preparation of the key stannane cross-coupling partner.

reduction of the di-substituted alkene **24** was accomplished with diimide (generated in situ from *p*-tosylhydrazine with sodium acetate). The hindered nature of the alkene was evident from the difficulty of the reduction and this necessitated the use of a vast excess of diimide (25 equiv) to ensure complete conversion. It is noteworthy that the (*E*)-alkene proved to be much easier to reduce than the (*Z*)-isomer; if fewer equivalents of reagent were applied then the (*Z*)-isomer was recovered and this compound could not then be removed at a later stage. Subsequent silylation proved facile (TBSOTf, 2,6-lutidine) and afforded the key deconjugation precursor **41** in 88% yield over the two steps. Perhaps unsurprisingly, if the order of the last two steps was reversed then the troublesome (*Z*)-isomer could be removed after silylation but then diimide reduction of the remaining (*E*)-isomer proved to be impossible (Scheme 6).

To our disappointment, when the same conditions were applied to substrate **41**, no isomerisation occurred and only starting material was recovered. Through a series of experiments we identified that the desired reaction could be accomplished with KHMDS and a rapid quench by pouring into stirred water. Though not ideal, this afforded a 10:1 mixture of α-**23** and β-**23** in 50% and 5% yield, respectively,—the remainder of the mixture was recovered starting material (Scheme 8). The configuration of the α-centre was assigned by NOE studies[41] and the tri-substituted alkene geometry was also assigned the (*E*)-configuration by NOE studies;[42] it should be noted that the formation of an (*E*)-alkene is also in accord with observations of Kende and Toder from their studies on the deconjugation of α,β-unsaturated esters for the synthesis of the litsenolide natural product family.[43] Furthermore, if a longer reaction time or more base was applied then none of the desired deconjugation

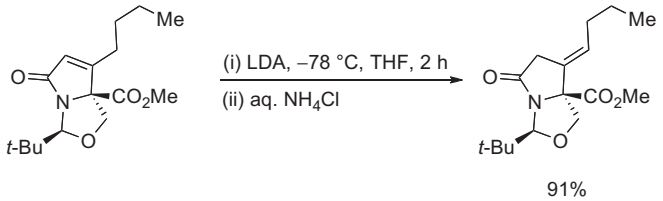


25 **26** (10:1 *E/Z*) **41**, 99% **40**, 89%

Scheme 6. Stille cross-coupling and subsequent elaboration.

2.4. Deconjugation

In order to introduce the necessary oxygenation, the deconjugation of α,β-unsaturated lactam **41** to give the non-conjugated lactam **23** was required; this step was the cornerstone of our strategy. We anticipated that deconjugation could be realised via dienolate formation and kinetic protonation in the α-position to afford the (*E*)-alkene **23**. To our delight, model studies[40] on simple analogues without the α-methyl group showed this could be readily accomplished in high yield (Scheme 7); the structure of the product was also secured by X-ray crystallography,[40] confirming the (*E*)-alkene configuration.

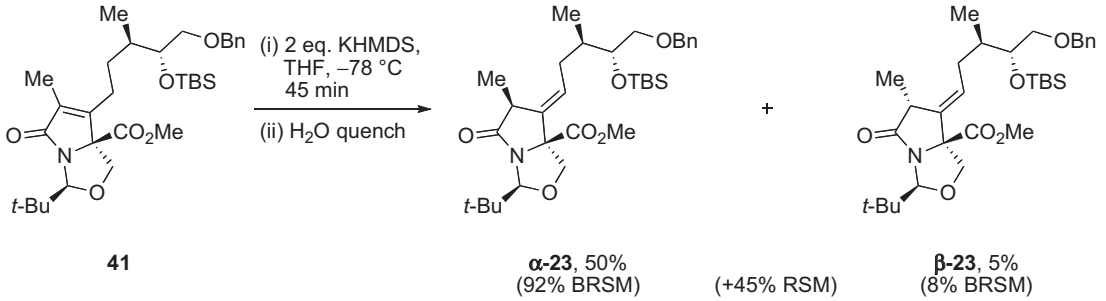


Scheme 7. Model system for deconjugation.

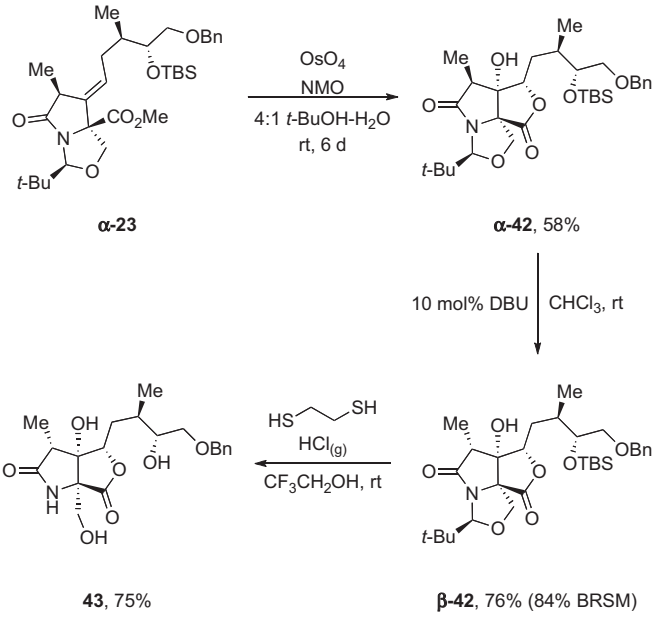
product was obtained. Initially, the result of this deconjugation appeared disheartening with the major product bearing the wrong configuration at the α-methyl centre. However, subsequent osmylation studies showed this to be a serendipitous result.

2.5. Oxidation/epimerisation

The next step was to introduce the required C-3/C-4 oxygenation and form the γ-lactone ring; this proved to be more challenging than expected as a result of the crowded steric environment around the tri-substituted olefin (Scheme 9). In fact, β-**23** possessing the correct configuration at the C-2 methine centre proved to be inert to dihydroxylation under any of the conditions examined and we recovered solely the starting material. In contrast, although α-**23** also displayed retarded reactivity, we were able to obtain tricyclic lactone core α-**42** in 58% yield via classical stoichiometric dihydroxylation with concomitant lactonisation; even then, six days at rt were required to ensure complete reaction. In this respect, the failure of all the catalytic conditions we attempted is unsurprising.[44] Dihydroxylation proved to be entirely facially selective, yielding a single oxidation product derived from



Scheme 8. Deconjugation to afford the dihydroxylation precursor **23**.



Scheme 9. Dihydroxylation and epimerisation.

attack on the concave face of alkene α-**23**; although perhaps counter-intuitive, this can be clearly inferred from the diagram shown in Fig. 2.

Successful oxidation of the α-**23** epimer necessitated inversion of the configuration of the centre adjacent to the carbonyl group. In this respect, we found that a catalytic amount of DBU (10 mol %) was sufficient to effect epimerisation in an equilibrium process. This isomerisation process was studied by ^{1}H NMR spectroscopy on discrete lactam core α-**42** and proved to be a slow equilibrium process proceeding to >95% conversion over 24 h (Fig. 3)—of interest was the observation that increasing the mol % of DBU used served only to attenuate the desired reaction.

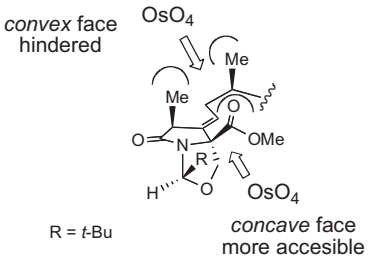


Fig. 2. Model for dihydroxylation of alkene α-**23**.

Synthetically, epimerisation could be accomplished under these conditions in 76% yield to afford β-**42** (with 10% recovered starting material α-**42**). Having achieved the correct oxidation level and rectified the stereochemistry of the α-centre, the remaining challenges were to methylate the lactam nitrogen and reveal the aldehyde necessary for Julia–Kocienski coupling with sulfone **22**. Because of the requirement to perform several protecting group manipulations, we examined several sequences to divine how best this might be achieved with respect to the order of the steps. The first step in all these sequences was acidic deprotection of the oxazolidine moiety (under standard Corey conditions[45]) to afford the poorly soluble triol **43** in 75% yield (Scheme 9).

2.6. Lactam methylation

We examined several strategies for the lactam methylation with the intention of accomplishing methylation without the need for protecting some (or indeed all) of the hydroxyl groups. Unfortunately, we found that competitive methylation was unavoidable with the 1°/2° alcohols. Although it was possible to perform *N*-methylation without 3° alcohol protection, we found that the diminished yields and skeletal rearrangements did not recommend this approach. Our aspiration to effect an early introduction of the acetate protecting groups present in **15** (and accomplish methylation on such a derivative) proved unsuccessful; thus, a strategy involving the preparation of a tris-silyl derivative, preferably in a single step, evolved. This process was complicated by the poor solubility of triol **43** in anything but methanol or DMF. Attempted TBS protection, even with an excess of TBSOTf, afforded only monosilyl derivative **44** (in 55% yield), presumably due to steric hindrance; application of the less hindered TESOTf led to double silylation and the formation of **45** in 90% yield. In order to protect the 3° alcohol functionality in **45** it was necessary to use a TMS group and forcing conditions. Thus, 25 equiv of TMSOTf at ambient temperature for 24 h afforded **46** as an approximately 3:1 mixture of compounds **46**/**47** in 84% yield. The metathesis of one of the TES groups with a TMS group proved unavoidable, since the use of fewer equivalents of TMSOTf led to the reaction stalling. Though the mixture of silyl isomers could be separated by careful chromatography, this proved to be unnecessary. Methylation of the mixed silylated lactam (*n*-BuLi/MeI/THF/−78 °C), subsequent global silyl deprotection with HCl and standard acetylation (Py/Ac_2O) afforded diacetate **50** in 69% yield over a straightforward three-step sequence (Scheme 10).

2.7. Aldehyde reveal/Julia–Kocienski

The required Julia–Kocienski partner **22** was obtained in three steps from sulfide **51**, an intermediate in our methodological study of the synthesis of pentadienyl amines.[28] Thus, in a facile fashion, sequential acidic Boc cleavage (TFA) afforded amine **52** in 90% yield

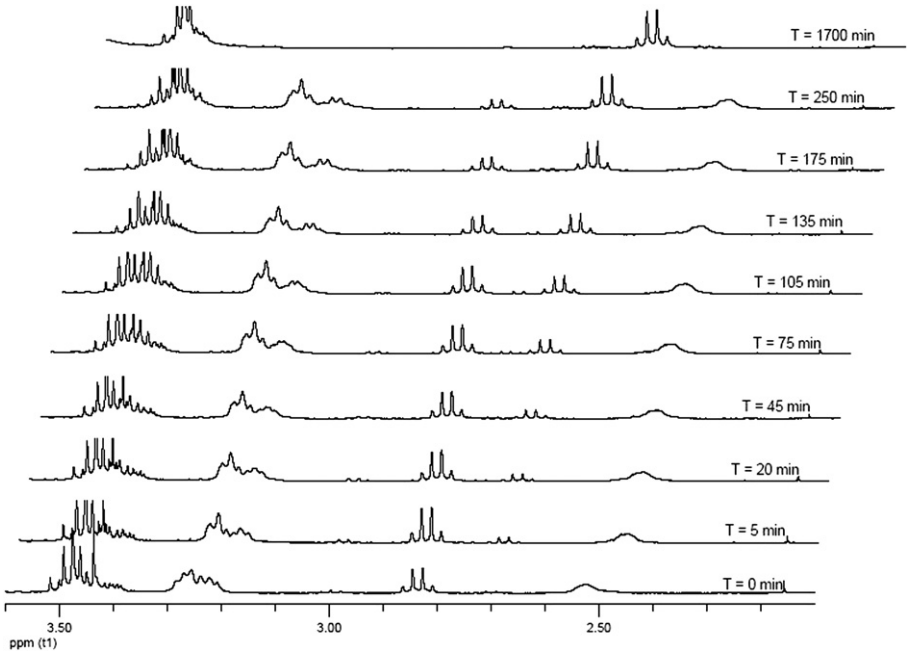
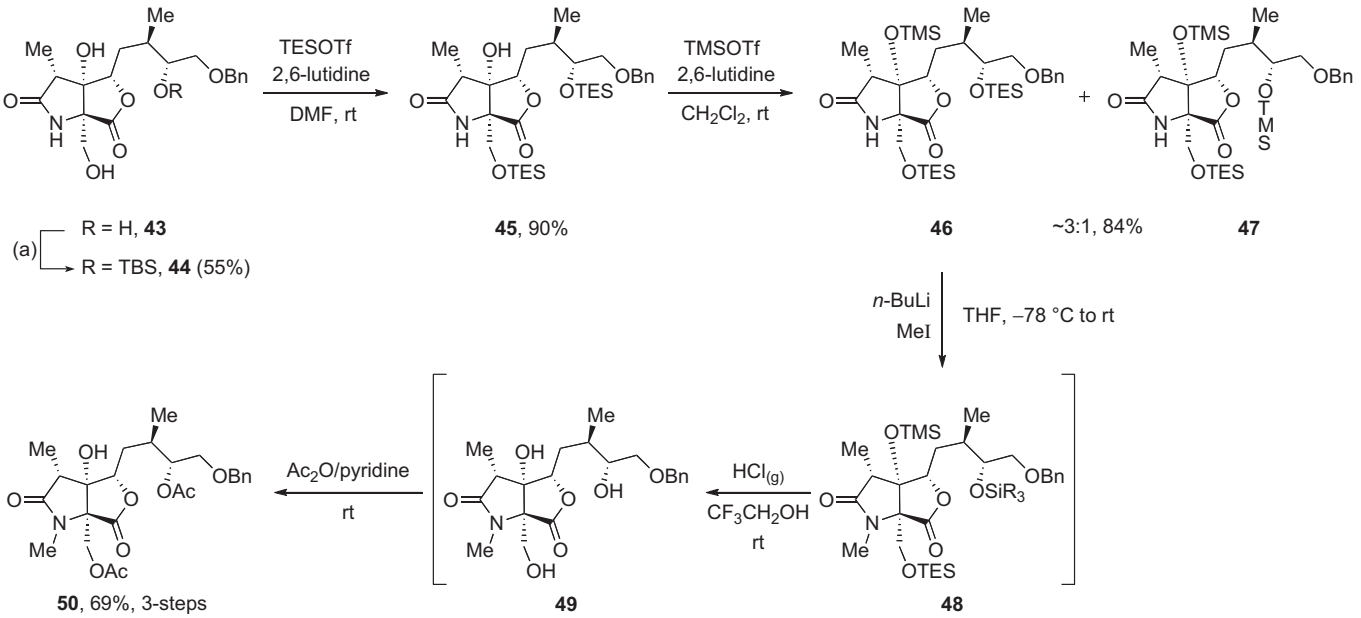


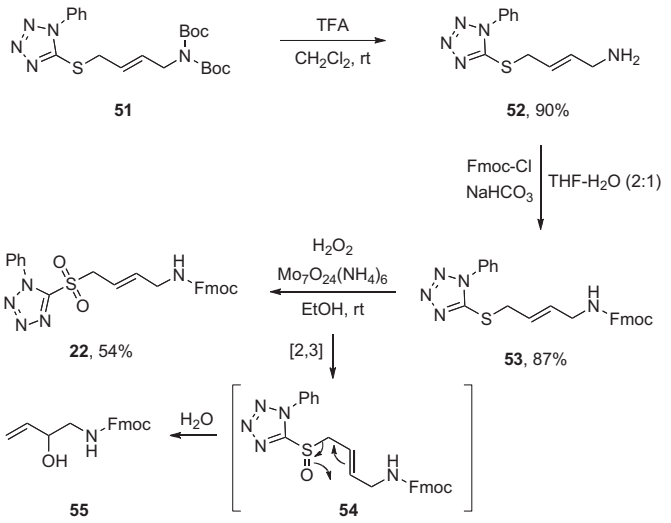
Fig. 3. ^{1}H NMR study of the epimerisation of α-**42** to β-**42**.

and then Fmoc re-protection (Fmoc-Cl) in aqueous THF afforded Fmoc sulfide **53** in 87% yield. Oxidation of this precursor proved frustratingly difficult, surprisingly so given our previous success with similar substrates. The problem proved to be the formation of side-product **55** via [2,3]-sigmatropic rearrangement[46] of the intermediate allylic sulfoxide **54** and subsequent hydrolysis. Ultimately, this problem was circumvented by the use of a polyoxometallate-catalysed[47] oxidation using high concentration with a vast excess of hydrogen peroxide (30 equiv) to increase the rate of the second oxidation relative to the undesired [2,3]-sigmatropic rearrangement; this afforded 54% of the desired sulfone **22** (Scheme 11).

The end-game sequence commenced with careful deprotection of the benzyl group [$Pd(OH)_2$–C/H_2/1 h] to afford primary alcohol **56**. If the reaction was left to proceed for longer periods a process of acetate migration from the secondary to primary alcohol commenced, but none of this could be detected after 1 h. The primary alcohol was then oxidised to the corresponding aldehyde **21** in 51% yield via a DMP oxidation. Although this reaction proved problematic, the product rapidly decomposes under other oxidation conditions, e.g., Swern, Ley-Griffith, success was ultimately achieved with an excess of DMP (3.3 equiv) and a short reaction time (45 min). The product obtained from rapid chromatography was then subjected to the key Julia–Kocienski olefination step.[28] Treatment of sulfone **22** with a single equivalent of NaHMDS at −78 °C and then addition of aldehyde **21** afforded after 1 h at −78 °C a 4.5:1 mixture of (4*E*,6*E*)/(4*Z*,6*E*) isomers. Careful chromatography afforded the desired Kende intermediate, (4*E*,6*E*)-**15**, in 63% yield along with 14% of the isomer (4*Z*,6*E*)-**15**. The data obtained corresponded well to those reported by Kende, e.g., $[\alpha]_D$



Scheme 10. Lactam methylation. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, DMF, rt.



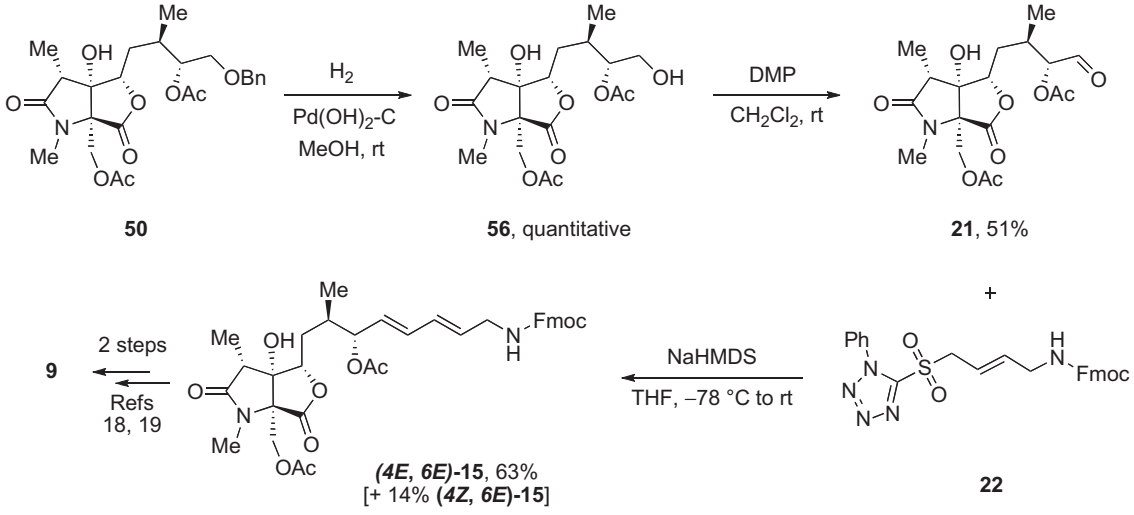
Scheme 11. Preparation of the Julia–Kocienski sulfone.

+2.0, lit.[18] +3.6; ν_{max} 1771, 1728 cm^{-1}, lit.[18] 1780, 1730 cm^{-1}; δ_H ($CDCl_3$) 5.56 (1H, dd, *J* 15.0, 7.0 Hz, H-8), lit.[18] 5.59 (1H, dd, *J* 14.6, 6.9 Hz, H-8); and the majority of the data reported by Hatakeyama.[19] Significantly, our ^{13}C NMR data were different in several respects to Hatakeyama's although through careful 2D analysis and assignment of all the signals we were confident in the fidelity of our data—Professor Hatakeyama subsequently confirmed there were errors in his published ^{13}C NMR data (Scheme 12).[48]

4. Experimental

4.1. General experimental detail

^1H NMR and ^{13}C NMR spectra were recorded on either a JEOL ECX400 spectrometer operating at 400 MHz and 100 MHz, respectively, or a Bruker AV500 spectrometer operating at 500 MHz and 125 MHz, respectively. All spectral data was acquired at 295 K. Chemical shifts are quoted in parts per million (ppm) using the residual solvent peak as an internal standard (^1H NMR 7.26 ppm for $CHCl_3$ and ^{13}C NMR 77.0 ppm for $CDCl_3$; ^1H NMR 4.84 (s), 3.31 (quintuplet) and ^{13}C NMR 49.05 (septuplet) for D_3COD). Coupling constants (*J*) are reported in Hertz to the nearest 0.1 Hz. Signal assignments were accomplished via analysis of COSY, NOESY, HSQC and HMBC experiments where necessary. Infrared spectra were recorded on a ThermoNicolet IR100 spectrometer using NaCl plates. Low and high-resolution mass spectra were obtained for all novel compounds. Electrospray ionization (ESI) spectra were measured on a Bruker MicrOTOF spectrometer and electron ionization (EI) spectra on a Waters GCT Premier Spectrometer. Melting points were determined using Gallenkamp apparatus and are uncorrected. Thin layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} pre-coated aluminium-backed plates. The compounds were visualized using UV light (254 nm) and the stain specified. Flash chromatography was performed at medium pressure using slurry packed Fluka silica gel 35–70 μm, 60 Å with the eluant specified. Petrol refers to the fraction of petroleum ether with bp 40–60 °C. Tetrahydrofuran was distilled from sodium-benzophenone ketyl immediately before use. Anhydrous toluene and dichloromethane were obtained from an MBraun SPS solvent



Scheme 12. The neooxazolomycin end-game.

3. Conclusion

We have completed a 23-step formal synthesis of neooxazolomycin with the preparation of Kende's key intermediate **15**. In contrast to the previously reported approaches by Kende[18] and Hatakeyama[19] who used mid-stage cyclisation events to form the lactam, our distinct approach commenced with the formation of the lactam via Moloney's tetramic acid chemistry and features a modular route to achieve the union of three key fragments via key Stille coupling and Julia–Kocienski olefination. The elaboration of the Stille adduct was accomplished with a strategic deconjugation/dihydroxylation sequence to achieve the stereoselective construction of the bicyclic core.

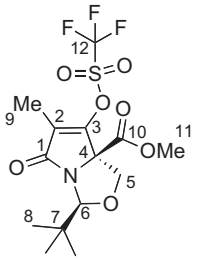
purification system. Water refers to deionised water. All numbering on the structures below is for the benefit of structural assignment and does not conform to IUPAC rules.

Except where specified, all reagents were purchased from commercial sources and were used without further purification. (*E*)-3-(Trimethylsilyl)but-2-en-1-ol **29** was prepared according to the procedure of Denmark and co-workers.[37] The solution of *tert*-butylhydroperoxide in dichloromethane was obtained from an anhydrous solution of *tert*-butylhydroperoxide in toluene (prepared according to the Sharpless protocol[38]) by careful concentration and re-dissolution of the neat *tert*-butylhydroperoxide in dichloromethane. (*E*)-Di-*tert*-butyl (4-(1-phenyl-1*H*-tetrazol-5-ylthio)but-2-enyl)iminodicarbonate **51** was synthesised according

to our previous procedure.[28] Compounds **30**–**33** were prepared according to the report of Moloney and co-workers.[34]

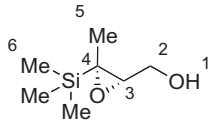
4.2. Specific compound procedures

*4.2.1. (3S,7aS)-Methyl 3-tert-butyl-6-methyl-5-oxo-7-(trifluoromethylsulfonyloxy)-1,3,5,7a-tetrahydropyrrolo[1,2-c]oxazole-7a-carboxylate **25**.*



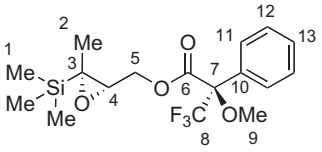
To a solution of lactam **33** (62.3 g, 231 mmol) in CH_2Cl_2 (1.5 L) was added, via syringe, *i*-Pr_2NEt (44.4 mL, 254 mmol). The resultant solution was cooled to −50 °C and triflic anhydride (42.0 mL, 254 mmol) added via syringe pump over 1 h 15 min. Once the addition was complete, the reaction mixture was stirred at −50 °C for 15 min then warmed to rt and transferred to a separating funnel containing CH_2Cl_2 (2.0 L). The organic layers were washed with water (3×500 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was passed twice through a plug of silica (CH_2Cl_2), then recrystallised (pentane) to afford the title compound (**16**) (65.0 g, 70%) as a cream coloured microcrystalline solid; mp 60–62 °C; R_f (9:1 petrol/Et_2O) 0.28; ν_{max} 1754, 1733, 1689, 1436, 1230, 1137, 1110, 819 cm^{-1}; $[\alpha]_D^{21}$ −106.5 (*c* 1.25, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.79 (1H, d, *J* 8.5 Hz, CH_2(5a)), 4.71 (1H, s, CH(6)), 3.79 (3H, s, CH_3(11)), 3.48 (1H, d, *J* 8.5 Hz, CH_2(5b)), 1.91 (3H, s, CH_3(9)), 0.93 (9H, s, CH_3(8)); δ_C (100 MHz, $CDCl_3$) 173.7 (C=O(10)), 166.7 (C=O(1)), 154.8 (C(3)), 127.2 (C(2)), 118.2 (d, J_{CF} 319 Hz, CF_3(12)), 96.7 (CH(6)), 74.1 (C(4)), 70.6 (CH_2(5)), 53.6 (CH_3(11)), 35.1 (C(7)), 24.6 (CH_3(8)), 8.1 (CH_3(9)); *m*/*z* (ESI): 402 (MH^+); HRMS (ESI): MH^+, found 402.0841. $C_{14}H_{19}F_3NO_7S$ requires 402.0834 (1.5 ppm error).

*4.2.2. [(2S,3S)-3-Methyl-3-(trimethylsilyl)oxiranyl]methanol **34**.*



A solution of allylic alcohol **19** (5.86 g, 40.6 mmol) in CH_2Cl_2 (90 mL) (pre-stirred with 3 Å molecular sieves (3 g) for 30 min), was cooled to −20 °C and (+)-diisopropyl L-tartrate (0.57 mL, 2.40 mmol) then Ti(O*i*-Pr)$_4$ (0.57 mL, 2.00 mmol), (both of which were pre-dried over 3 Å molecular sieves) added via syringe. The reaction mixture was stirred for 1.5 h before the addition of *tert*-butylhydroperoxide ([3.50 M in CH_2Cl_2], 12.0 mL, 6.50 mmol) added and then stirred for a further 21 h, maintaining at −20 °C. At this time the reaction mixture was warmed to rt and quenched with a solution of citric acid (463 mg, 2.40 mmol) in EtOAc/Me_2CO (9:1, 50 mL). The quenched solution was stirred at rt for 2 h and then concentrated in vacuo. The residue was dissolved in EtOAc (100 mL) and filtered through Celite® rinsing with EtOAc (2×100 mL). Water (300 mL) was added, the layers separated and the aqueous extracted with EtOAc (6×200 mL). The combined organics were stirred for 1 h with a solution of saturated aqueous sodium sulfite (300 mL) to destroy residual *tert*-butylhydroperoxide. The layers were separated, the aqueous extracted with EtOAc (4×300 mL), the combined organics washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (SiO_2, 4:1 petrol/EtOAc) to afford the title compound, **34**, (5.50 g, 85%) as a colourless oil. R_f (3:1 petrol/EtOAc) 0.16; $[\alpha]_D^{23}$ −13.9 (*c* 1.00, $CHCl_3$); ν_{max} 3437, 2958, 1743, 1250, 1105, 1028, 843, 752 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.82 (1H, dd, *J* 12.0, 4.0 Hz, CH_2(2a)), 3.69 (1H, dd, *J* 12.0, 6.5 Hz, CH_2(2b)), 2.98 (1H, dd, *J* 6.5, 4.0 Hz, CH(3)), 1.21 (3H, s, CH_3(5)), 0.00 (9H, s, CH_3(6)); δ_C (100 MHz, $CDCl_3$) 61.2 (CH_2(2)), 60.0 (CH(3)), 54.9 (C(4)), 14.7 (CH_3(5)), −4.3 (CH_3(6)); *m*/*z* (ESI): 161 (MH^+), 183 (MNa^+); HRMS (ESI): MNa^+, found 183.0814. $C_7H_{16}NaO_2Si$ requires 183.0812 (1.2 ppm error).

*4.2.3. [(2S,3S)-3-Methyl-3-(trimethylsilyl)oxiranyl]methyl (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **35**.*

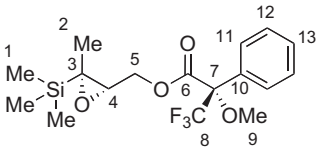


To a stirred solution of epoxide **34** (11.0 mg, 68.0 μmol), DMAP (1 mg, 8.0 μmol) and (*R*)-(−)-MTPA (19 mg, 81.0 μmol) in CH_2Cl_2 (1 mL) at 0 °C was added DCC (17 mg, 82.0 μmol). The mixture was stirred for 30 min at 0 °C and then the volatiles were evaporated in vacuo. The residue was taken up in Et_2O (5 mL) and filtered through a small SiO_2 plug. The resultant residue was then purified by flash silica column chromatography (SiO_2, 19:1 petrol/EtOAc) to afford the title compound, **25**, (15 mg, 40.0 μmol, 58%) as a colourless oil and an inseparable 94:6 mixture of diastereomers. R_f (9:1 petrol/Et_2O) 0.29; $[\alpha]_D^{20}$ +33.3 (*c* 0.73, $CHCl_3$); ν_{max} 2958, 1753, 1251, 1171, 1122, 1022, 841, 719 cm^{-1}; *m*/*z* (CI, NH_3): 394 (MNH_4^+, 52), 377 (MH^+, 50), 90 (100%).

Major diastereomer: δ_H (400 MHz, C_6D_6) 7.65 (2H, dd, *J* 7.5, 1.0 Hz, CH(11)), 6.95–7.08 (m, 3H, CH(12 and 13)), 4.25 (1H, dd, *J* 12.0, 6.5 Hz, CH_2(5a)), 4.08 (1H, dd, *J* 12.0, 5.0 Hz, CH_2(5b)), 3.39 (s, 3H, CH3(9)), 2.83 (1H, dd, *J* 6.5, 5.0 Hz, CH(4)), 0.97 (3H, s, CH_3(2)), −0.18 (9H, s, CH_3(1)).

Minor diastereomer: Same as above except, δ_H (C_6D_6) 4.17 (1H, d, *J* 6.0 Hz, CH_2(5a)), 4.16 (1H, d, *J* 6.0 Hz, CH_2(5b)), 3.38 (3H, s, CH_3(9)), 2.90 (1H, dd, *J* 6.0, 6.0 Hz, CH(4)), 0.97 (3H, s, CH_3(2)), −0.17 (9H, s, CH_3(1)).

*4.2.4. [(2S,3S)-3-Methyl-3-(trimethylsilyl)oxiranyl]methyl (2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **36**.*



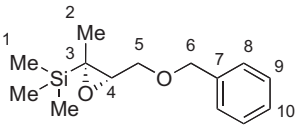
To a stirred solution of epoxide **34** (12.0 mg, 75.0 μmol), DMAP (1 mg, 8.0 μmol) and (*S*)-(−)-MTPA (21 mg, 90.0 μmol) in CH_2Cl_2 (1 mL) at 0 °C was added DCC (19 mg, 92.0 μmol). The mixture was stirred for 30 min at 0 °C and then the volatiles were evaporated in vacuo. The residue was taken up in Et_2O (5 mL) and filtered through a small SiO_2 plug. The resultant residue was then purified by flash silica column chromatography (SiO_2, 19:1 petrol/EtOAc) to afford the title compound, **26**, (18 mg, 48.0 μmol, 90%) as a colourless oil and an inseparable 95:5 mixture of diastereomers. R_f (9:1 petrol/Et_2O) 0.29; $[\alpha]_D^{20}$ −49.4 (*c* 0.85, $CHCl_3$); ν_{max} 2958, 1753, 1251, 1171, 1122, 1022, 841, 754 cm^{-1}; HRMS (ESI): MH^+, found 377.1403. $C_{17}H_{24}F_3O_4Si$ requires 377.1396 (1.9 ppm error).

Major diastereomer: δ_H (400 MHz, C_6D_6) 7.65 (2H, d, *J* 7.5 Hz, CH(11)), 6.94–7.08 (m, 3H, CH(12 and 13)), 4.17 (1H, d, *J* 6.0 Hz, CH_2(5a)), 4.16 (1H, d, *J* 6.0 Hz, CH_2(5b)), 3.38 (3H, s, CH_3(9)), 2.90 (1H, dd, *J* 6.0, 6.0 Hz, CH(4)), 0.97 (3H, s, CH_3(2)), −0.17 (9H, s, CH_3(1)).

Minor diastereomer: Same as above except, δ_H (C_6D_6) 4.25 (1H, dd, *J* 12.0, 6.5 Hz, CH_2(5a)), 4.08 (1H, dd, *J* 12.0, 5.0 Hz, CH_2(5b)), 3.39 (s, 3H, CH_3(9)), 2.83 (1H, dd, *J* 6.5, 5.0 Hz, CH(4)), −0.18 (9H, s, CH_3(1)).

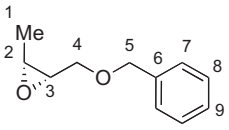
The er of the epoxide **34** was therefore determined to be 95:5.

*4.2.5. (2S,3S)-3-[(Benzyloxy)methyl]-2-methyloxiranyl(trimethyl)silane **37**.*



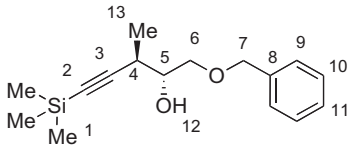
To a stirred solution of epoxide **34** (15.3 g, 95.4 mmol, 1.0 equiv) in THF (250 mL) at 0 °C was added in four portions sodium hydride (60% dispersion in mineral oil, 4.80 g, 120 mmol, 1.25 equiv). The solution was stirred at 0 °C for 1 h then benzyl bromide (12.9 mL, 109 mmol, 1.1 equiv) and tetrabutylammonium iodide (1.85 g, 5.00 mmol, 0.05 equiv) were added. The reaction was stirred for 16 h warming from 0 °C to rt then quenched with aqueous saturated ammonium chloride (250 mL). The resultant solution was transferred to a separating funnel containing water (250 mL) and Et_2O (500 mL), the layers separated and the aqueous extracted with Et_2O (3×500 mL). The combined organic layers were washed with brine (250 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford the title compound (**37**) (20.4 g, 81.1 mmol, 85%) as an orange oil contaminated with residual benzyl bromide (6.8 g). A sample was purified for characterisation by flash chromatography (SiO_2, 9:1 petrol/Et_2O) to afford **37** as a colourless oil. R_f (9:1 petrol/Et_2O) 0.26; $[\alpha]_D^{22}$ −4.1 (*c* 2.85, $CHCl_3$); ν_{max} 2956, 2858, 1454, 1248, 1101, 840, 748, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27–7.31 (5H, m, CH(8, 9 and 10)), 4.65 (1H, d, *J* 12.0 Hz, CH_2(6a)), 4.54 (1H, d, *J* 12.0 Hz, CH_2(6b)), 3.77 (1H, dd, *J* 11.0, 4.5 Hz, CH_2(5a)), 3.60 (1H, dd, *J* 11.0, 6.0 Hz, CH_2(5b)), 3.04 (1H, dd, *J* 6.0, 4.5 Hz, CH(4)), 1.21 (3H, s, CH_3(2)), 0.05 (9H, s, CH_3(1)); δ_C (100 MHz, $CDCl_3$) 138.0 (C(7)), 128.4 (CH(8)), 127.7 (CH(9)), 127.7 (CH(10)), 73.1 (CH_2(6)), 68.9 (CH_2(5)), 58.3 (CH(4)), 53.5 (C(3)), 14.8 (CH_3(2)), −4.2 (CH_3(1)); *m*/*z* (ESI): 251 (MH^+), 273 (MNa^+); HRMS (ESI): MNa^+ found 273.1276. $C_{14}H_{22}NaO_2Si$ requires 273.1281 (1.9 ppm error).

*4.2.6. (2S,3R)-2-[(Benzyloxy)methyl]-3-methyloxirane **28**.*



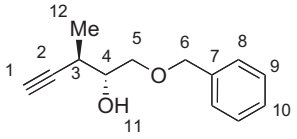
To epoxide **37** (19.8 g, 79.2 mmol, 1.0 equiv) in THF (250 mL) was added tetra-*n*-butylammonium fluoride ([1.0 M in THF], 95.0 mL, 95.0 mmol, 1.2 equiv) and the reaction mixture heated to reflux for 4 h. At this time, the mixture was concentrated in vacuo and the crude purified by flash chromatography (SiO_2, 4:1 petrol/Et_2O) to afford the title compound, **28**, (12.0 g, 67.3 mmol, 85%) as a colourless oil. R_f (4:1 petrol/Et_2O) 0.25; $[\alpha]_D^{21}$ +15.5 (*c* 2.20, $CHCl_3$), lit.[50] +17.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.26–7.39 (5H, m, CH(7, 8 and 9)), 4.65 (1H, d, *J* 12.0 Hz, CH_2(6a)), 4.54 (1H, d, *J* 12.0 Hz, CH_2(6b)), 3.69 (1H, dd, *J* 11.0, 4.5 Hz, CH_2(5a)), 3.57 (1H, dd, *J* 11.0, 6.0 Hz, CH_2(5b)), 3.18 (1H, ddd, *J* 6.0, 4.5, 4.5 Hz, CH(3)), 3.10 (1H, qd, *J* 5.5, 4.5 Hz, CH(2)), 1.27 (3H, d, *J* 5.5 Hz, CH_3(1)); δ_C (100 MHz, $CDCl_3$) 137.8 (C(6)), 128.3 (CH(7)), 127.6 (CH(8)), 127.6 (CH(9)), 73.1 (CH_2(5)), 68.0 (CH_2(4)), 54.9 (CH(3)), 51.6 (CH(2)), 13.2 (CH_3(1)); *m*/*z* (ESI): 179 (MH^+), 201 (MNa^+); HRMS (ESI): MNa^+ found 201.0887. $C_{11}H_{14}NaO_2$ requires 201.0886 (0.3 ppm error). The spectral data were consistent with those reported.[49]

*4.2.7. (2R,3R)-1-[(Benzyloxy)-3-methyl-5-trimethylsilylpent-4-yn-2-ol **38**.*



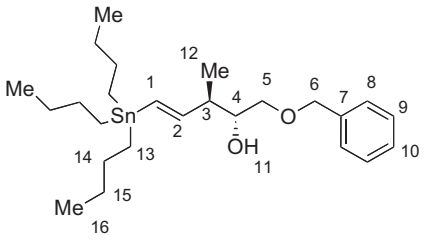
To a solution of trimethylsilylacetylene (8.2 mL, 58.1 mmol, 1.07 equiv) in Et_2O (300 mL) at −78 °C was added dropwise via syringe over 10 min *n*-butyllithium [1.57 M in hexanes] (37.0 mL, 58.1 mmol, 1.07 equiv). The reaction mixture was stirred at −78 °C for 40 min then trimethylaluminium [2.0 M in hexanes] (29.1 mL, 58.1 mmol, 1.07 equiv) added via syringe pump over 60 min. The reaction mixture was then warmed to −40 °C and stirred for 1 h, after which time it was re-cooled to −78 °C. Epoxide **28** (9.68 g, 54.3 mmol, 1.00 equiv) in Et_2O (25 mL) was added via cannula over 25 min and the mixture stirred for 15 min then $_3{\cdot}OEt_2$ (8.0 mL, 65.2 mmol, 1.2 equiv) added via syringe pump over 15 min. Once addition was complete the solution was stirred for 15 min then quenched with saturated aqueous ammonium chloride (250 mL) and allowed to warm to rt. The layers were separated, the aqueous extracted with Et_2O (5×250 mL), the combined organics washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford the title compound, **38**, (14.6 g, 53.0 mmol, 97%) as a yellow oil in a 15:1 inseparable mixture of regioisomers. R_f (1:1 petrol/Et_2O) 0.37; $[\alpha]_D^{22}$ +28.5 (*c* 1.30, $CHCl_3$); ν_{max} 3455, 3031, 2960, 2900, 2873, 2167, 1453, 1368, 1250, 1099 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.28–7.39 (5H, m, CH(9, 10 and 11)), 4.57 (2H, s, CH_2(7)), 3.71 (1H, ddd, *J* 6.5, 6.0, 4.5 Hz, CH(5)), 3.58 (1H, dd, *J* 9.5, 4.5 Hz, CH_2(6a)), 3.54 (1H, dd, *J* 9.5, 6.5 Hz, CH_2(6b)), 2.80 (1H, qd, *J* 7.0, 4.5 Hz, CH(4)), 2.39 (1H, d, *J* 6.0 Hz, OH(12)), 1.22 (3H, d, *J* 7.0, CH_3(13)), 0.15 (9H, s, CH_3(1)); δ_C (100 MHz, $CDCl_3$) 138.0, (C(8)), 128.5 (CH), 127.8 (CH), 127.8 (CH), 107.1 (C(3)), 87.3 (C(2)), 73.4 (CH_2(7)), 72.6 (CH(5)), 72.0 (CH_2(6)), 30.7 (CH(4)), 17.0 (CH_3(13)), 0.2 (CH_3(1)); *m*/*z* (ESI): 277 (MH^+); HRMS (ESI): MH^+ found 277.1625. $C_{16}H_{25}O_2Si$ requires 277.1618 (2.4 ppm error).

*4.2.8. (2R,3R)-1-(Benzyloxy)-3-methyl-4-pentyn-2-ol **39**.*



To a solution of alkyne **38** (3.60 g, 13.1 mmol, 1.0 equiv) in THF (170 mL) at 0 °C was added dropwise via syringe tetra-*n*-butylammonium fluoride [1.0 M in THF] (14.4 mL, 14.4 mmol, 1.1 equiv) solution and the resultant mixture stirred for 1 h at 0 °C. At this time the reaction was concentrated in vacuo and the crude purified by flash chromatography (SiO_2, 1:1 petrol/Et_2O) to afford the title compound, **39**, (2.30 g, 11.3 mmol, 86%) as a colourless oil. R_f (1:1 petrol/Et_2O) 0.44; $[\alpha]_D^{26}$ +20.5 (*c* 1.15, $CHCl_3$); ν_{max} 3428, 3294, 2873, 1454, 1367, 1207, 1099, 739, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.28–7.39 (5H, m, CH(8, 9 and 10)), 4.57 (2H, s, CH_2(6)), 3.74 (1H, dddd, *J* 7.0, 5.0, 4.5, 4.5 Hz, CH(4)), 3.59 (1H, dd, *J* 9.5, 4.5 Hz, CH_2(5a)), 3.55 (1H, dd, *J* 9.5, 7.0 Hz, CH_2(5b)), 2.75 (1H, qdd, *J* 7.5, 4.5, 2.5 Hz, CH(3)), 2.40 (1H, d, *J* 5.0 Hz, OH(11)), 2.13 (1H, d, *J* 2.5 Hz, CH(1)), 1.25 (3H, d, *J* 7.5 Hz, CH_3(12)); δ_C (100 MHz, $CDCl_3$) 137.7 (C(7)), 128.3 (CH), 127.6 (CH), 84.7 (C(2)), 73.3 (CH_2(6)), 72.3 (CH(4)), 72.0 (CH_2(5)), 70.6 (CH(1)), 29.2 (CH(3)), 16.9 (CH_3(12)); *m*/*z* (ESI): 205 (MH^+), 227 (MNa^+); HRMS (ESI): MNa^+ found 227.1044. $C_{13}H_{16}NaO_2Si$ requires 227.1043 (0.8 ppm error).

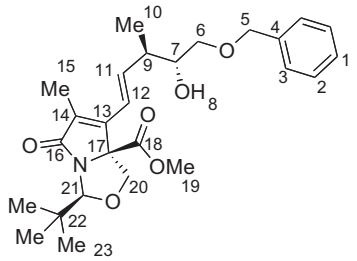
4.2.9. (2R,3R,4E)-1-(Benzyloxy)-3-methyl-5-(tri-n-butylstannyl)-4-penten-2-ol ***26****.*



To alkyne **39** (11.6 g, 56.8 mmol, 1.0 equiv) was added tri-*n*-butyltin hydride (26 mL, 96.5 mmol, 1.7 equiv) at rt. The neat reaction mixture was stirred and gently heated to 80 °C then AIBN (1.86 g, 11.4 mmol, 0.20 equiv) added portionwise. [Caution: upon initial addition of AIBN the internal temperature raises to 130 °C and vigorous nitrogen evolution is observed!] Once the reaction cooled to 80 °C the slow portionwise addition of AIBN is continued to maintain constant temperature. The reaction was then stirred at 80 °C for 50 min before being cooling to rt and directly purified by flash chromatography (SiO_2, 4:1 petrol/Et_2O) to afford the title compound, **26**, as a viscous colourless oil (18.8 g, 37.9 mmol, 67%) and an inseparable 10:1 *E*/*Z* mixture. Data given for (*E*)-**26**: R_f (4:1 petrol/Et_2O) 0.36; $[\alpha]_D^{21}$ +13.6 (*c* 1.96, $CHCl_3$); ν_{max} 3455, 3030, 2957, 2925, 2871, 1655, 1597, 1455, 1375, 1095, 999 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.28–7.38 (5H, m, CH(8, 9 and 10)), 5.85–6.07 (2H, m, CH(1 and 2)), 4.59 (2H, s, CH_2(6)), 3.66–3.69 (1H, m, CH(4)), 3.54 (1H, dd, *J* 9.5, 3.0 Hz, CH_2(5a)), 3.42 (1H, dd, *J* 9.5, 7.5 Hz, CH_2(5b)), 2.40 (1H, qdd, *J* 7.0, 6.5, 6.5 Hz, CH(3)), 2.23 (1H, d, *J* 3.0 Hz, OH(11), 1.44–1.52 (6H, m, CH_2(15)), 1.25–1.34 (6H, m, CH_2(14)), 1.03–1.06 (3H, d, *J* 7.0 Hz, CH_3(12)), 0.85–0.92 (15H, m, CH_2(13) and CH_3(16)); δ_C (100 MHz, $CDCl_3$) 150.3 (CH(1)), 138.2 (C(7)), 129.6 (CH(2)), 128.6 (CH), 127.8 (CH), 127.8 (CH), 73.5 (CH(4)), 73.5 (CH_2(6)), 72.6 (CH_2(5)), 44.7 (CH(3)), 29.2 (CH_2(15)), 27.4 (CH_2(14)), 16.3 (CH_3(12)), 13.9 (CH_3(16)), 9.6 (CH_2(13)); *m*/*z* (CI, NH_3): 497 MH^+(^{120}Sn), 13), 439 (100), 308 (46), 291 (41), 91 (62%). HRMS (CI, NH_3): MH ($^{116}Sn)^+$ found 493.2428. $C_{25}H_{45}O_2^{116}Sn$ requires 493.2437 (0.1 ppm error).

The ^1H and ^{13}C NMR spectra exhibited additional signals for (4*Z*)-**26**: δ_H (400 MHz, $CDCl_3$) 6.42 (1H, dd, *J* 12.5, 10.0 Hz, CH(2)), 4.56 (2H, m, CH_2(6)), 2.28 (1H, d, *J* 3.0 Hz, OH(11)), 2.08–2.15 (1H, m, CH(3)); δ_C (100 MHz, $CDCl_3$) 130.3 (CH(2)), 17.7 (CH_3(12)), 10.5 (CH_2(13)).

4.2.10. (3S,7aR)-Methyl 7-((3R,4R,1E)-5-(benzyloxy)-4-hydroxy-3-methylpent-1-enyl)-3-tert-butyl-6-methyl-5-oxo-1,3,5,7a-tetrahydropyrrolo[1,2-c]oxazole-7a-carboxylate ***24****.*

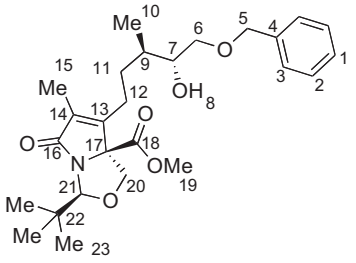


To a solution of triflate **25** (3.31 g, 8.20 mmol, 1.0 equiv) in degassed DMF (40 mL), was added 2-trifurylphosphine (153 mg, 0.66 mmol, 0.08 equiv) and bis-palladium tris-dibenzylidenacetone (150 mg, 0.16 mmol, 0.02 equiv). The solution was stirred at rt for 5 min changing colour from brown to orange. Stannane **26** (4.08 g, 8.2 mmol, 1.0 equiv) in degassed DMF (20 mL) was then added via cannula. The reaction mixture was heated at 50 °C for 15 h. Once the reaction was complete the solution was concentrated in vacuo, then water (50 mL) and CH_2Cl_2 (50 mL) added. The layers were separated and the aqueous extracted CH_2Cl_2 (3×50 mL), the combined organics were washed with brine (50 mL) dried ($MgSO_4$), filtered and concentrated in vacuo. The crude mixture was purified by careful flash chromatography (SiO_2, 3:2→1:1 petrol/EtOAc) to afford the title compound, (1*E*)-**24**, (3.28 g, 7.17 mmol, 87%) and isomer (1*Z*)-**24** (0.15 g, 0.33 mmol, 4%) as viscous yellow oils that solidified as yellow glasses upon standing.

(1*E*)-**24**: R_f (3:2 petrol/Et_2O) 0.20; $[\alpha]_D^{25}$ −74.8 (*c* 1.10, $CHCl_3$); ν_{max} 3464, 2960, 2927, 2870, 1746, 1712, 1650, 1455, 1359, 1278, 1228, 1119 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.28–7.39 (5H, m, CH(1, 2 and 3)), 6.30 (1H, d, *J* 16.5 Hz, CH(12)), 5.95 (1H, dd, *J* 16.5, 7.5 Hz, CH(11)), 4.89 (1H, d, *J* 8.5 Hz, CH_2(20a)), 4.65 (1H, s, CH(21)), 4.55 (2H, s, CH_2(5)), 3.64–3.73 (4H, m, CH(7) and CH_3(19)), 3.50 (1H, dd, *J* 9.5, 3.5 Hz, CH_2(6a)), 3.37 (1H, dd, *J* 9.5, 7.5 Hz, CH_2(6b)), 3.22 (1H, d, *J* 8.5 Hz, CH_2(20b)), 2.46 (1H, qdd, *J* 7.5, 6.5, 6.5 Hz, CH(9)), 2.28 (1H, br s, OH(8)), 1.89 (3H, s, CH_3(15)), 1.06 (3H, d, *J* 6.5 Hz, CH_3(10)), 0.92 (9H, s, CH_3(23)); δ_C (100 MHz, $CDCl_3$) 178.8 (C=O(16)), 170.6 (C=O(18)), 149.6 (C(13)), 140.9 (CH(11)), 137.8 (C(4)), 130.8 (C(14)), 128.6 (CH), 128.0 (CH), 127.9 (CH), 120.9 (CH(12)), 96.1 (CH(21)), 75.6 (C(17)), 73.6 (CH_2(5)), 73.5 (CH(7)), 72.4 (CH_2(6)), 70.3 (CH_2(20)), 53.0 (CH_3(19)), 40.7 (CH(9)), 35.3 (C(22)), 24.8 (CH_3(23)), 16.2 (CH_3(10)), 9.3 (CH_3(15)); *m*/*z* (ESI): 458 (MH^+), 480 (MNa^+); HRMS (ESI): MNa^+ found 480.2354. $C_{26}H_{35}NNaO_6$ requires 480.2357 (0.3 ppm error).

(1*Z*)-**24**: R_f (3:2 petrol/Et_2O) 0.19; $[\alpha]_D^{25}$ −112.5 (*c* 1.10, $CHCl_3$); ν_{max} 3464, 2960, 2927, 2870, 1746, 1712, 1650, 1455, 1359, 1278, 1228, 1119 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.28–7.39 (5H, m, CH(1,2 and 3)), 5.77 (1H, dd, *J* 11.5, 10.5 Hz, CH(11)), 5.65 (1H, dd, *J* 11.5, 1.0 Hz, CH(12)), 4.73 (1H, d, *J* 8.5 Hz, CH_2(20a)), 4.66 (1H, s, CH(21)), 4.54 (2H, s, CH_2(5)), 3.71 (3H, s, CH_3(19)), 3.60 (1H, m, CH(7)), 3.50 (1H, dd, *J* 9.5, 3.0 Hz, CH_2(6a)), 3.30 (1H, dd, *J* 9.5, 8.0 Hz, CH_2(6b)), 3.27 (1H, d, *J* 8.5 Hz, CH_2(20b)), 2.41 (1H, d, *J* 2.5 Hz, OH(8)), 2.29–2.39 (1H, m, CH(9)), 1.83 (3H, s, CH_3(15)), 0.94 (3H, d, *J* 6.5 Hz, CH_3(10)), 0.92 (9H, s, CH_3(23)); δ_C (100 MHz, $CDCl_3$) 178.8 (C=O(16)), 170.1 (C=O(18)), 149.7 (C(13)), 141.2 (CH(11)), 137.7 (C(4)), 132.1 (C(14)), 128.7 (CH), 128.1 (CH), 127.8 (CH), 118.9 (CH(12)), 96.9 (CH(21)), 77.5 (C(17)), 73.6 (CH_2(5)), 73.5 (CH(7)), 72.6 (CH_2(6)), 70.8 (CH_2(20)), 53.0 (CH_3(19)), 41.0 (CH(9)), 37.2 (C(22)), 24.9 (CH_3(23)), 16.8 (CH_3(10)), 10.9 (CH_3(15)); *m*/*z* (ESI): 458 (MH^+), 480 (MNa^+); HRMS (ESI): MNa^+ found 480.2352. $C_{26}H_{35}NNaO_6$ requires 480.2357 (0.5 ppm error).

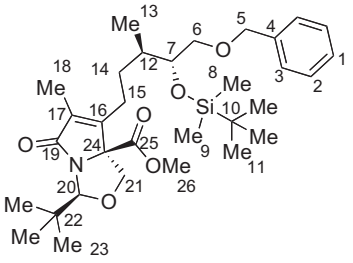
4.2.11. (3S,7aR)-Methyl 7-((3R,4R)-5-(benzyloxy)-4-hydroxy-3-methylpentyl)-3-tert-butyl-6-methyl-5-oxo-1,3,5,7a-tetrahydropyrrolo[1,2-c]oxazole-7a-carboxylate ***40****.*



To a solution of alkene (1*E*)-**24** (7.22 g, 15.8 mmol, 1.0 equiv) in DME (800 mL) was added *p*-tosylhydrazine (57.0 g, 306 mmol, 20 equiv) and the solution was heated to reflux. A solution of aqueous sodium acetate [1.0 M] (306 mL, 306 mmol, 20 equiv) was added dropwise over 1 h. The reaction mixture was heated at reflux overnight, then further tosylhydrazine (20 g, 107 mmol, 6.8 equiv) and aqueous sodium acetate [1.0 M] (100 mL, 100 mmol, 6.3 equiv) added in single portions. The mixture was heated for

a further 24 h then cooled to rt and concentrated in vacuo. To the crude mixture was added aqueous 3 M sodium hydroxide (300 mL) and CH_2Cl_2 (3×250 mL) and this was stirred for 30 min during, which time a white precipitate formed. The layers were separated and the aqueous extracted with CH_2Cl_2 (3×250 mL). The organics were filtered to remove the precipitated tosyl salts, dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting crude was purified by flash chromatography (SiO_2, 1:1 petrol/Et_2O) to afford the title compound, **40**, (6.45 g, 14.2 mmol, 89%) as a clear glass. R_f (2:1 petrol/EtOAc) 0.32; ν_{max} 3443, 2959, 2870, 1742, 1709, 1455, 1284, 1229, 1115 cm^{-1}; $[\alpha]_D^{21}$ −129.2 (*c* 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.28–7.37 (5H, m, CH(1, 2 and 3)), 4.79 (1H, d, *J* 8.5 Hz, CH_2(20a)), 4.63 (1H, s, CH(21)), 4.56 (1H, d, *J* 12.0 Hz, CH_2(5a)), 4.53 (1H, d, *J* 12.0 Hz, CH_2(5b)), 3.72 (3H, s, CH_3(19)), 3.56 (1H, dd, *J* 9.0, 3.0 Hz, CH_2(6a)), 3.48–3.54 (1H, m, CH(7)), 3.34 (1H, dd, *J* 9.0, 7.5 Hz, CH_2(6b)), 3.21 (1H, d, *J* 8.5 Hz, CH_2(20b)), 2.47 (1H, br s, OH(8)), 2.37 (1H, ddd, *J* 14.0, 9.5, 5.5 Hz, CH_2(12a)), 2.10 (1H, dddd, *J* 14.0, 6.5, 5.0, 1.0 Hz, CH_2(12b)), 1.79 (3H, d, *J* 1.0 Hz, CH_3(15)), 1.62 (1H, dddd, *J* 14.0, 9.5, 6.5, 3.5 Hz, CH_2(11a)), 1.47–1.54 (1H, m, CH (9)), 1.23–1.27 (1H, m, CH_2(11b)), 0.92 (9H, s, CH_3(23)), 0.87 (3H, d, *J* 7.0 Hz, CH_3(10)); δ_C (100 MHz, $CDCl_3$) 179.1 (C=O(16)), 170.4 (C=O(18)), 154.4 (C(13)), 137.8 (C(4)), 131.8 (C(14)), 128.6 (CH), 128.0 (CH), 127.9 (CH), 96.4 (CH(21)), 77.9 (C(17)), 73.9 (CH(7)), 73.6 (CH_2(5)), 72.6 (CH_2(6)), 71.0 (CH_2(20)), 53.0 (CH_3(19)), 35.8 (CH(9)), 35.3 (C(22)), 30.1 (CH_2(11)), 24.8 (CH_3(23)), 24.4 (CH_2(12)), 15.2 (CH_3(10)), 9.1 (CH_3(15)); *m*/*z* (ESI): 460 (MH^+), 482 (MNa^+); HRMS (ESI): MNa^+ found 482.2522. $C_{26}H_{37}NNaO_6$ requires 482.2513 (1.9 ppm error).

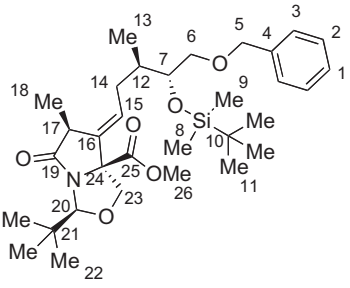
*4.2.12. (3S,7aR)-Methyl 7-((3R,4R)-5-(benzyloxy)-4-(tert-butyldimethylsilyloxy)-3-methylpentyl)-3-tert-butyl-6-methyl-5-oxo-1,3,5,7a-tetrahydropyrrolo[1,2-c]oxazole-7a-carboxylate **41**.*



To a stirred solution of alcohol **40** (6.34 g, 13.8 mmol, 1.0 equiv) in CH_2Cl_2 (330 mL) cooled to −10 °C (ice/salt cooling bath) was added 2,6-lutidine (3.20 mL, 27.6 mmol, 2.0 equiv). The reaction mixture was stirred for 5 min then TBSOTf (4.75 mL, 20.7 mmol, 1.5 equiv) was added dropwise via syringe. After 40 min the solution was poured into a stirred solution of saturated aqueous ammonium chloride (400 mL) and diluted with CH_2Cl_2 (200 mL). The layers were separated, the aqueous extracted with CH_2Cl_2 (3×500 mL), the organics combined, washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude was purified by flash chromatography (SiO_2, 3:1 petrol/Et_2O) to afford the title compound, **41**, (7.86 g, 13.7 mmol, 99%) as a pale yellow glass. R_f (3:1 petrol/Et_2O) 0.23; ν_{max} 2957, 2859, 1744, 1713, 1461, 1254, 1228, 1115 cm^{-1}; $[\alpha]_D^{21}$ −46.7 (*c* 0.70, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.28–7.36 (5H, m, CH(1, 2, and 3)), 4.75 (1H, d, *J* 8.0 Hz, CH_2(21a)), 4.62 (1H, s, CH(20)), 4.50 (1H, d, *J* 12.0 Hz, CH_2(5a)), 4.46 (1H, d, *J* 12.0 Hz, CH_2(5b)), 3.72 (3H, s, CH_3(26)), 3.66–3.70 (1H, m, CH(7)), 3.39 (1H, dd, *J* 10.0, 5.5 Hz, CH_2(6a)), 3.36 (1H, d, *J* 10.0, 6.0 Hz, CH_2(6b)), 3.16 (1H, d, *J* 8.0 Hz, CH_2(21b)), 2.32 (1H, ddd, *J* 14.5, 11.0, 6.5 Hz, CH_2(15a)), 2.06 (1H, ddd, *J* 14.5, 12.0, 4.5 Hz, CH_2(15b)), 1.79 (3H, s, CH_3(18)), 1.61–1.68 (1H, m, CH(12)), 1.37–1.47 (1H, m, CH_2(14a)), 1.16–1.24 (1H, m, CH_2(14b)), 0.90–0.94 (12H, m, CH_3(13, 23)), 0.87 (9H, s, CH_3(11)), 0.03 (3H, s, CH_3(8)), 0.02 (3H, s, CH_3(9)); δ_C (100 MHz, $CDCl_3$) 179.2 (C=O(19)), 170.4 (C=O(25)), 154.7 (C(16)), 138.2 (C(4)), 131.5 (C(17)), 128.5 (CH), 127.8 (CH), 127.8 (CH), 96.3 (CH(20)), 77.8 (C(24)), 75.2 (CH(7)), 73.5 (CH_2(5)), 72.5 (CH_2(21)), 70.9 (CH_2(6)), 53.0 (CH_3(26)), 36.0 (CH(12)), 35.3 (C(22)), 28.4 (CH_2(14)), 26.0 (CH_3(11)), 25.2 (CH_2(15)), 24.9 (CH_3(23)), 18.3 (C(10)), 16.2 (CH_3(13)), 9.1 (CH_3(18)), −4.1 (CH_3(8)), −4.7 (CH_3(9)); *m*/*z* (CI, NH_3): 574 (MH^+, 100%); HRMS (CI, NH_3): MH^+ found 574.3561. $C_{32}H_{52}NO_6Si$ requires 574.3564 (0.6 ppm error).

*4.2.13. Deconjugation of enone **41** under basic conditions. Preparation of (3S,6S,7aR,E)-methyl 7-((3R,4R)-5-(benzyloxy)-4-(tert-butyldimethylsilyloxy)-3-methylpentylidene)-3-tert-butyl-6-methyl-5-oxohexahydropyrrolo[1,2-c]oxazole-7a-carboxylate α-**23**.* To a stirred solution of enone **41** (6.60 g, 11.5 mmol, 1.0 equiv) in THF (500 mL) at −78 °C was added dropwise via syringe KHMDS [0.5 M in toluene] (46 mL, 23.0 mmol, 2.0 equiv). The resultant bright yellow solution was stirred at −78 °C for 45 min then removed from the cool and rapidly poured into conical flask containing vigorously stirred water (1.75 L). Immediately after quenching, CH_2Cl_2 (500 mL) was added and the layers separated. The aqueous layer was further extracted with CH_2Cl_2 (3×500 mL), the combined organics washed with saturated brine (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford a pale yellow glass. ^1H NMR analysis of the crude reaction mixture identified a ~10:1:10 mixture of α-**23** and β-**23** with starting material **41**, respectively. Repeated purification by flash chromatography (SiO_2, 3:1 petrol/Et_2O) afforded α-**23** (3.30 g, 5.75 mmol, 50%, 92% BRSM), β-**23** (300 mg, 0.52 mmol, 5%, 8% BRSM) and recovered enone **41** (3.00 g, 5.23 mmol, 45%), respectively as viscous yellow oils that solidified on standing as yellow glasses.

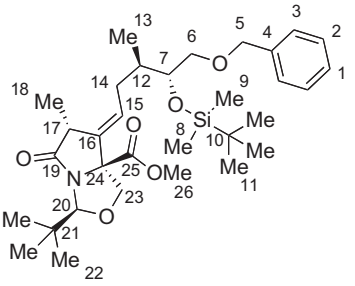
*4.2.14. (3S,6S,7aR,E)-Methyl 7-((3R,4R)-5-(benzyloxy)-4-(tert-butyldimethylsilyloxy)-3-methylpentylidene)-3-tert-butyl-6-methyl-5-oxohexahydropyrrolo[1,2-c]oxazole-7a-carboxylate α-**23**.*



R_f (3:1 petrol/Et_2O) 0.27; $[\alpha]_D^{19}$ −31.7 (*c* 0.81, $CHCl_3$); ν_{max} 2957, 2933, 2859, 1727, 1462, 1322, 1290, 1120 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25–7.34 (5H, m, CH(1,2 and 3)), 5.41–5.46 (1H, m, CH(15)), 4.87 (1H, s, CH(20)), 4.82 (1H, d, *J* 8.0 Hz, CH_2(23a)), 4.50 (1H, d, *J* 12.0 Hz, CH_2(5a)), 4.47 (1H, d, *J* 12.0 Hz, CH_2(5b)), 3.75 (3H, s, CH_3(26)), 3.65–3.70 (1H, m, CH(7)), 3.36–3.44 (2H, m, CH_2(6a, 6b)), 3.32 (1H, d, *J* 8.0 Hz, CH_2(23b)), 3.23 (1H, q, *J* 8.0 Hz, CH(17)), 2.17–2.22 (1H, m, CH(14a)), 1.72–1.84 (2H, m, CH(12, 14b)), 1.46 (3H, d, *J* 7.5 Hz, CH_3(18)), 0.88 (9H, s, CH_3(22)), 0.86 (9H, s, CH_3(11)), 0.81 (3H, d, *J* 6.5 Hz, CH_3(13)), 0.01 (6H, br s, CH_3(8,9)); δ_C (100 MHz, $CDCl_3$) 181.6 (C=O(19)), 171.7 (C=O(25)), 138.2 (C(16)), 137.4 (C(4)), 128.4 (CH), 127.7 (CH), 127.7 (CH), 127.1 (CH(15)), 97.4 (CH(20)), 75.4 (C(24)), 75.0 (CH(7)), 73.4 (CH_2(5)), 72.8 (CH_2(23)), 72.6 (CH_2(6)), 52.8 (CH_3(26)), 44.2 (CH(17)), 36.5 (CH(12)), 35.4 (C(21)), 30.0 (CH_2(14)), 25.9 (CH_3(22)), 24.9 (CH_3(11)), 18.2 (C(10)), 18.2 (CH_3(18)), 16.4 (CH_3(13)), −4.2 (CH_3(8)), −4.8 (CH_3(9)); *m*/*z* (ESI): 574 (MH^+), 596

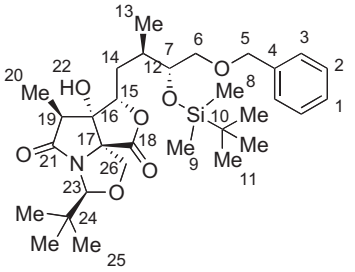
(MNa$^+$); HRMS (ESI): MNa$^+$ found 596.3394. $C_{32}H_{51}NNaO_6S$ requires 596.3378 (2.8 ppm error).

*4.2.15. (3S,6R,7aR,E)-Methyl 7-((3R,4R)-5-(benzyloxy)-4-(tert-butyldimethylsilyloxy)-3-methylpentylidene)-3-tert-butyl-6-methyl-5-oxohexahydropyrrolo[1,2-c]oxazole-7a-carboxylate β-**23**.*



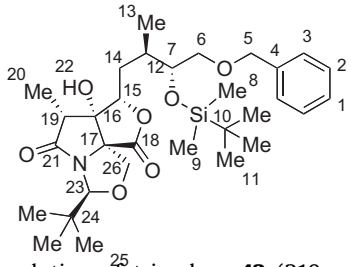
R_f (3:1 petrol/Et$_2$O) 0.30; $[\alpha]_D^{19}$ −11.5 (*c* 1.25, CHCl$_3$); ν_{max} 2957, 2930, 2858, 1728, 1456, 1325, 1288, 1120 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.26–7.34 (5H, m, CH(1, 2 and 3)), 5.47 (1H, ddd, *J* 7.5, 7.5, 2.5 Hz, CH(15)), 4.85 (1H, s, CH(20)), 4.82 (1H, d, *J* 8.5 Hz, CH$_2$(23a)), 4.52 (1H, d, *J* 12.0 Hz, CH$_2$(5a)), 4.46 (1H, d, *J* 12.0 Hz, CH$_2$(5b)), 3.71 (3H, s, CH$_3$(26)), 3.66–3.69 (1H, m, CH(7)), 3.48 (1H, qd, *J* 7.5, 2.5 Hz, CH(17)), 3.33–3.42 (2H, m, CH$_2$(6a, 6b)), 3.27 (1H, d, *J* 8.5 Hz, CH$_2$(23b)), 2.16–2.27 (1H, m, CH$_2$(14a)), 1.97–2.05 (1H, m, CH$_2$(14b)), 1.75–1.82 (1H, m, CH(12)), 1.35 (3H, d, *J* 7.5 Hz, CH$_3$(18)), 0.90 (9H, s, CH$_3$(22)), 0.85–0.88 (12H, m, CH$_3$(11, 13)), 0.03 (6H, br s, CH$_3$(8, 9)); δ_C (100 MHz, CDCl$_3$) 181.4 (C=O(19)), 172.0 (C=O(25)), 138.3 (C(16)), 136.6 (C(4)), 128.5 (CH), 127.8 (CH(15)), 127.8 (CH), 127.8 (CH), 98.5 (CH(20)), 75.0 (C(24)), 74.6 (CH(7)), 73.4 (CH$_2$(5)), 72.7 (CH$_2$(23)), 72.6 (CH$_2$(6)), 52.8 (CH$_3$(26)), 42.2 (CH(17)), 36.6 (CH(12)), 35.5 (C(21)), 30.1 (CH$_2$(14)), 26.0 (CH$_3$(22)), 24.9 (CH$_3$(11)), 18.3 (C(10)), 16.5 (CH$_3$(13)), 16.2 (CH$_3$(18)), −4.7 (CH$_3$(8)), −4.1 (CH$_3$(9)); *m*/*z* (ESI): 574 (MH$^+$), 596 (MNa$^+$); HRMS (ESI): MNa$^+$ found 596.3393. $C_{32}H_{51}NNaO_6Si$ requires 596.3378 (2.6 ppm error).

*4.2.16. (3S,6S,6aS,7S,9aS)-7-[(2R,3R)-4-(Benzyloxy)-3-{[tert-butyl(dimethyl)silyl]oxy}-2-methylbutyl]-3-tert-butyl-6a-hydroxy-6-methyldihydrofuro[3′,4′:2,3]pyrrolo[1,2-c][1,3]oxazole-5,9(6H)-dione α-**42**.*



To a stirred solution of alkene α-**23** (2.66 g, 4.64 mmol, 1.0 equiv) in *tert*-BuOH (37 mL) and water (9 mL) at rt, was added OsO_4 (1.25 g, 4.87 mmol, 1.05 equiv) and *N*-methylmorpholine-*N*-oxide [NMO] (0.57 g, 4.87 mmol, 1.05 equiv). The flask was sealed, protected from the light with foil, and stirred at rt for 6 days, with the addition of an extra portion of NMO (0.57 g, 4.87 mmol, 1.05 equiv) every 24 h. The resultant black mixture was then quenched by the addition of a solution of saturated aqueous sodium sulfate (50 mL) and the mixture stirred for 12 h. The resultant slurry was filtered through Celite® and the filter pad rinsed with EtOAc (250 mL). Water (50 mL) was added, the layers separated and the aqueous further extracted with EtOAc (3×50 mL). The combined organics were dried (MgSO$_4$), filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (SiO$_2$, 1:1 petrol/Et$_2$O→Et$_2$O) to afford the title compound, α-**42**, as a colourless foam. R_f (1:1 petrol/Et$_2$O) 0.26; $[\alpha]_D^{20}$ −33.4 (*c* 1.00, CHCl$_3$); ν_{max} 3437, 2957, 2932, 2858, 1788, 1735, 1705, 1463, 1364, 1327, 1299, 1252, 1146, 1104, 1038 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.29–7.37 (5H, m, CH(1, 2 and 3)), 4.83 (1H, s, CH(23)), 4.48–4.51 (1H, m, CH(15)), 4.48 (2H, s, CH$_2$(5)), 4.21 (1H, d, *J* 9.0 Hz, CH$_2$(26a)), 3.79 (1H, d, *J* 9.0 Hz, CH$_2$(26b)), 3.73–3.78 (1H, m, CH(7)), 3.42–3.50 (2H, m, CH$_2$(6a, 6b)), 3.25 (1H, s, OH(22)), 2.56 (1H, q, *J* 7.5 Hz, CH(19)), 1.93–2.04 (2H, m, CH(12) and CH$_2$(14a)), 1.36–1.44 (1H, m, CH(14b)), 1.23 (3H, d, *J* 7.5 Hz, CH$_3$(20)), 1.04 (3H, d, *J* 6.5 Hz, CH$_3$(13)), 0.97 (9H, s, CH$_3$(25)), 0.88 (9H, s, CH$_3$(11)), 0.05 (3H, s, CH$_3$(8)), 0.03 (3H, s, CH$_3$(9)); δ_C (100 MHz, CDCl$_3$) 182.1 (C=O(21)), 173.0 (C=O(18)), 137.6 (C(4)), 128.6 (CH), 128.2 (CH), 128.1 (CH), 100.1 (CH(23)), 81.3 (C(16)), 80.9 (CH(15)), 74.2 (CH(7)), 73.8 (CH$_2$(5)), 72.8 (C(17)), 72.6 (CH$_2$(6)), 67.7 (CH$_2$(26)), 50.7 (CH(19)), 35.5 (C(24)), 33.7 (CH(12)), 31.8 (CH$_2$(14)), 26.0, 25.7, 18.2 (C(10)), 17.7 (CH$_3$(13)), 11.2 (CH$_3$(20)), −4.2 (CH$_3$(8)), −4.7 (CH$_3$(9)); *m*/*z* (CI, NH$_3$): 593 (MNH$_4^+$, 29), 576 (MH$^+$, 100), 518 (25), 91 (27%); HRMS (CI, NH$_3$): MH$^+$ found 576.3356. $C_{31}H_{50}NO_7Si$ requires 576.3357 (0.2 ppm error).

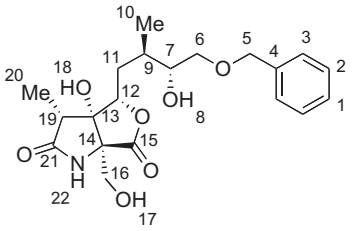
*4.2.17. (3S,6R,6aS,7S,9aS)-7-[(2R,3R)-4-(Benzyloxy)-3-{[tert-butyl(dimethyl)silyl]oxy}-2-methylbutyl]-3-tert-butyl-6a-hydroxy-6-methyldihydrofuro[3′,4′:2,3]pyrrolo[1,2-c][1,3]oxazole-5,9(6H)-dione β-**42**.*



To a stirred solution of tricycle α-**42** (210 mg, 0.365 mmol, 1.0 equiv) in CHCl$_3$ (7 mL) was added dropwise via microsyringe DBU (5 μL, 0.036 mmol, 0.10 equiv). The resultant solution was stirred for 24 h at rt and then concentrated onto silica and purified by flash chromatography (SiO$_2$, 1:1 petrol/Et$_2$O→Et$_2$O) to afford in order of elution, the title compound, β-**35**, as a colourless foam (159 mg, 0.276 mmol, 76% [84% BRSM]) and then recovered starting material, α-**42**, as a viscous, colourless oil (21 mg, 0.036 mmol, 10%). Data for β-**42**: R_f (1:2 petrol/Et$_2$O) 0.43; $[\alpha]_D^{20}$ −19.2 (*c* 2.96, CHCl$_3$); ν_{max} 3364, 2951, 2933, 1791, 1765, 1710, 1459, 1362, 1347, 1254, 1168, 1094, 1079, 1035 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.29–7.37 (5H, m, CH(1, 2 and 3)), 4.88 (1H, s, CH(23)), 4.49 (2H, s, CH$_2$(5)), 4.38 (1H, dd, *J* 8.5, 6.0 Hz, CH$_2$(15)), 4.14 (1H, d, *J* 9.0 Hz, CH$_2$(26a)), 3.96 (1H, d, *J* 9.0 Hz, CH$_2$(26b)), 3.82 (1H, s, OH(22)), 3.71–3.75 (1H, m, CH(7)), 3.44–3.54 (2H, m, CH$_2$(6a, 6b)), 2.86 (1H, q, *J* 7.5 Hz, CH(19)), 2.03 (1H, ddd, *J* 14.5, 8.5, 4.0 Hz, CH$_2$(14a)), 1.78–1.85 (1H, m, CH(12)), 1.33 (1H, ddd, *J* 14.5, 9.0, 6.0 Hz, CH$_2$(14b)), 0.97–1.03 (15H, m, CH$_3$(13, 20 and 25)), 0.87 (9H, s, CH$_3$(11)), 0.05 (3H, s, CH$_3$(8)), 0.01 (3H, s, CH$_3$(9)); δ_C (100 MHz, CDCl$_3$) 180.5 (C=O(21)), 173.1 (C=O(18)), 137.1 (C(4)), 128.6 (CH), 128.3 (CH), 128.3 (CH), 99.0 (CH(23)), 82.6 (C(16)), 81.5 (CH(7)), 74.0 (CH$_2$(5)), 73.6 (CH(7)), 72.8 (C(17)), 72.5 (CH$_2$(6)), 68.6 (CH$_2$(26)), 48.3 (CH(19)), 36.0 (C(24)), 32.4 (CH$_2$(12)), 32.2 (CH$_2$(14)), 25.9, 25.6, 18.1 (C(10)), 17.6 (CH$_3$(13)), 7.7 (CH$_3$(20)), −4.3 (CH$_3$(8)), −4.8 (CH$_3$(9)); *m*/*z* (CI, NH$_3$): 593 (MNH$_4^+$, 78), 576 (MH$^+$, 100), 518 (72), 91 (28%); HRMS (CI, NH$_3$): MH$^+$ found 576.3352. $C_{31}H_{50}NO_7Si$ requires 576.3357 (0.8 ppm error).

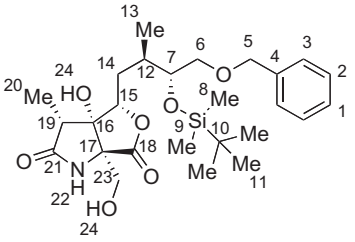
*4.2.18. (3R,3aS,4S,6aS)-4-[(2R,3R)-4-(Benzyloxy)-3-hydroxy-2-methylbutyl]-3a-hydroxy-6a-(hydroxymethyl)-3-methyldihydro-1H-furo[3,4-b]pyrrole-2,6(3H,4H)-dione **43**.*

Anhydrous HCl gas was bubbled through a vigorously stirred solution of tricycle β-**42** (516 mg, 0.896 mmol, 1.0 equiv) and 1,3-propanedithiol (99 μL, 0.986 mmol, 1.1 equiv) in 2,2,2-trifluoroethanol (10 mL) for 45 min at rt. Upon completion, the residual acid was purged with a stream of argon for 10 min. The



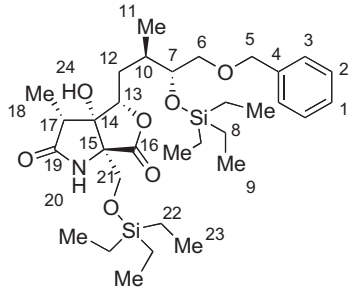
mixture was then concentrated in vacuo and purified by flash chromatography (SiO_2, 14:1 CH_2Cl_2/MeOH) to afford the title compound, **43**, as a colourless foam (231 mg, 0.673 mmol, 75%); recrystallisation from boiling $CHCl_3$ afforded colourless microcrystals. Mp 153–154 °C; R_f (14:1 CH_2Cl_2/MeOH) 0.34; $[\alpha]_D^{24.5}$ +4.9 (*c* 1.0, MeOH); ν_{max} 3382, 3030, 2941, 2870, 1769, 1691, 1453, 1429, 1366, 1318, 1235, 1204, 1152, 1099, 1066, 951, 736, 698 cm^{-1}; δ_H (400 MHz, 3:1 $CDCl_3/CD_3OD$) 7.11–7.19 (5H, m, CH(1, 2 and 3)), 4.36 (1H, d, *J* 11.9 Hz, CH_2(5a)), 4.32 (1H, d, *J* 11.9 Hz, CH_2(5b)), 4.23 (1H, dd, *J* 8.2, 4.9 Hz, 1H, CH(12)), 3.66 (1H, d, *J* 12.0 Hz, CH_2(16a)), 3.61 (1H, d, *J* 12.0 Hz, CH_2(16b)), 3.35–3.39 (2H, m, CH(7) and CH_2(6a)), 3.25 (1H, dd, *J* 10.6, 3.5 Hz, CH_2(6b)), 2.25 (1H, q, *J* 7.6 Hz, CH(19)), 1.90 (1H, ddd, *J* 14.5, 4.9, 4.9 Hz, CH_2(11a)), 1.56–1.63 (1H, m, CH(9)), 1.43 (1H, ddd, *J* 14.5, 8.2, 7.3 Hz, CH_2(11b)), 1.02 (3H, d, *J* 7.6 Hz, CH_3(20)), 0.77 (3H, d, *J* 6.8 Hz, CH_3(10)); δ_C (100 MHz, 3:1 $CDCl_3/CD_3OD$) 181.7 (C=O(21)), 176.9 (C=O(15)), 140.9 (C(4)), 131.5 (CH(2)), 131.0 (CH(1)), 131.0 (CH(3)), 90.5 (CH(12)), 84.9 (C(13)), 77.7 (CH(7)), 76.6 (CH_2(5)), 75.5 (CH_2(6)), 71.4 (C(14)), 63.9 (CH_2(16)), 51.6 (CH(19)), 36.6 (CH(9)), 34.7 (CH_2(11)), 20.1 (CH_3(10)), 13.7 (CH_3(20)); *m*/*z* (ESI): 394 (MH^+), 416 (MNa^+); HRMS (ESI): MH^+ found 394.1866. $C_{20}H_{28}NO_7$ requires 394.1860 (1.4 ppm error).

*4.2.19. (3R,3aS,4S,6aS)-4-((2R,3R)-4-(Benzyloxy)-3-(tert-butyldimethylsilyloxy)-2-methylbutyl)-3a-hydroxy-6a-(hydroxymethyl)-3-methyldihydro-1H-furo[3,4-b]pyrrole-2,6(3H,6aH)-dione **44**.*



To a stirred solution of triol **43** (31 mg, 79.0 μmol, 1.0 equiv) and 2,6-lutidine (37 μL, 316 μmol, 4.0 equiv) in DMF (2 mL) cooled to −10 °C (ice/salt cooling bath) was added dropwise via syringe TBSOTf (54 μL, 237 μmol, 3.0 equiv). The reaction was stirred for 2 h at −10 °C and then quenched by the addition of saturated aqueous NH_4Cl (2 mL). Following warming to rt, the mixture was diluted with water (50 mL) and extracted with Et_2O (5×10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 19:1 CH_2Cl_2/MeOH) to afford the title compound, **44**, as a colourless, viscous oil (22 mg, 43.0 μmol, 55%). R_f (19:1 CH_2Cl_2/MeOH) 0.19; $[\alpha]_D^{24.5}$ +18.4 (*c* 0.47, $CHCl_3$); ν_{max} 3394, 2954, 2930, 2883, 2856, 1769, 1696, 1457, 1362, 1252, 1071, 1038, 1007, 835, 776, 734, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29–7.36 (5H, m, CH(1, 2 and 3)), 6.92 (1H, s, NH(22)), 4.50 (2H, s, CH_2(5)), 4.37 (1H, dd, *J* 9.2, 5.2 Hz, CH(15)), 4.21 (1H, s, OH(25)), 3.80–3.88 (2H, m, CH_2(23a, 23b)), 3.73 (1H, ddd, *J* 7.3, 5.6, 2.7 Hz, CH(7)), 3.53 (1H, dd, *J* 9.8, 7.3 Hz, CH_2(6a)), 3.46 (1H, dd, *J* 9.8, 5.6 Hz, CH_2(6b)), 2.37 (1H, q, *J* 7.7 Hz, CH(19)), 2.09 (1H, dd, *J* 11.9, 9.2 Hz, CH_2(14a)), 1.56–1.66 (2H, m, CH(12) and CH_2(14b)), 1.01 (3H, d, *J* 6.5 Hz, CH_3(13)), 0.99 (3H, d, *J* 7.7 Hz, CH_3(20)), 0.86 (9H, s, CH_3(11)), 0.03 (3H, s, CH_3(8)), 0.01 (3H, s, CH_3(9)); δ_C (100 MHz, $CDCl_3$) 177.5 (C=O(21)), 173.1 (C=O(18)), 136.9 (C(4)), 128.5 (CH), 128.4 (CH), 128.3 (CH(1)), 86.4 (CH(15)), 81.8 (C(16)), 73.9 (CH_2(5)), 73.8 (CH(7)), 71.7 (CH_2(6)), 68.3 (C(17)), 62.2 (CH_2(23)), 46.2 (CH(19)), 31.3 (CH(12)), 28.7 (CH_2(14)), 25.7 (CH_3(11)), 18.0 (C(10)), 17.2 (CH_3(13)), 10.9 (CH_3(20)), −4.3 (CH_3(8)), −4.9 (CH_3(9)); *m*/*z* (ESI): 508 (MH^+), 530 (MNa^+); HRMS (ESI): MH^+ found 508.2725. $C_{26}H_{42}NO_7Si_2$ requires 508.2725 (0.1 ppm error).

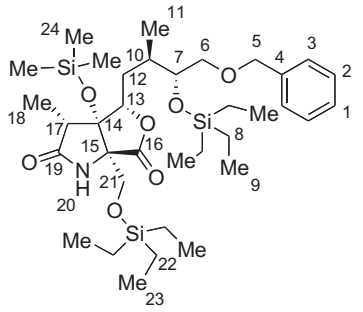
*4.2.20. (3R,3aS,4S,6aS)-4-{(2R,3R)-4-(Benzyloxy)-2-methyl-3-[triethylsilyloxy]butyl}-3a-hydroxy-3-methyl-6a{triethylsilyloxymethyl} dihydro-1H-furo[3,4-b]pyrrole-2,6(3H,4H)-dione **45**.*



To a stirred solution of triol **43** (228 mg, 0.58 mmol, 1.0 equiv) and 2,6-lutidine (470 μL, 4.06 mmol, 7.0 equiv) in DMF (17 mL) cooled to −10 °C (ice/salt cooling bath) was added TESOTf (790 μL, 3.48 mmol, 6.0 equiv) dropwise via syringe. The reaction was stirred for 2 h at −10 °C and then quenched by the addition of saturated aqueous NH_4Cl (20 mL). Following warming to rt, the mixture was diluted with water (150 mL) and extracted with Et_2O (4×50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 30:1→9:1 CH_2Cl_2/Me_2CO) to afford the title compound, **45**, as a colourless, viscous oil (326 mg, 0.52 mmol, 90%). R_f (19:1 CH_2Cl_2/Me_2CO) 0.30; $[\alpha]_D^{24}$ +10.7 (*c* 1.05, $CHCl_3$); ν_{max} 3422, 3263, 2956, 2912, 2878, 1778, 1710, 1457, 1413, 1378, 1238, 1090, 1009, 986, 911, 734, 698, 673 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.28–7.36 (5H, m, CH(1, 2 and 3)), 5.90 (1H, s, NH(20)), 4.49 (2H, s, CH_2(5)), 4.35 (1H, dd, *J* 7.7, 6.4 Hz, CH(13)), 4.04 (1H, s, OH(24)), 4.02 (1H, d, *J* 10.7 Hz, CH_2(21a)), 3.84 (1H, d, *J* 10.7 Hz, CH_2(21b)), 3.74 (1H, ddd, *J* 6.3, 5.8, 3.1 Hz, CH(7)), 3.49 (1H, dd, *J* 9.7, 6.3 Hz, CH_2(6a)), 3.41 (1H, dd, *J* 9.7, 5.8 Hz, CH_2(6b)), 2.40 (1H, q, *J* 7.6 Hz, CH(17)), 2.07 (1H, ddd, *J* 14.4, 6.4, 4.2 Hz, CH_2(12a)), 1.80–1.85 (1H, m, CH(10)), 1.59 (1H, ddd, *J* 14.4, 8.8, 7.7 Hz, CH_2(12b)), 1.19 (3H, d, *J* 7.6 Hz, CH_3(18)), 1.01 (3H, d, *J* 6.9 Hz, CH_3(11)), 0.95 (9H, t, *J* 8.0 Hz, CH_3), 0.93 (9H, t, *J* 8.0 Hz, CH_3), 0.64 (6H, q, *J* 8.0 Hz, CH_2), 0.58 (6H, q, *J* 8.0 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 177.9 (C=O(19)), 173.1 (C=O(16)), 138.1 (C(4)), 128.6 (CH), 128.1 (CH), 128.0 (CH(1)), 87.5 (CH(13)), 81.5 (C(14)), 74.5 (CH(7)), 73.4 (CH_2(5)), 72.2 (CH_2(6)), 67.6 (C(15)), 62.3 (CH_2(21)), 45.8 (CH(17)), 33.2 (CH(10)), 29.8 (CH_2(12)), 16.5 (CH_3(11)), 10.6 (CH_3(18)), 6.5 (CH_3), 6.1 (CH_3), 4.6 (CH_2), 3.6 (CH_2); *m*/*z* (ESI): 622 (MH^+), 644 (MNa^+); HRMS (ESI): MH^+ found 622.3599. $C_{32}H_{55}NO_7Si_2$ requires 622.390 (1.4 ppm error).

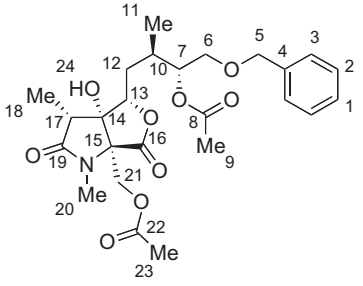
*4.2.21. (3R,3aS,4S,6aS)-4-{(2R,3R)-4-Benzyloxy-2-methyl-3-[triethylsilyloxy]butyl}-3-methyl-6a-{[triethylsilyloxy]methyl}-3a-[trimethylsilyloxy]dihydro-1H-furo[3,4-b]pyrrole-2,6(3H,4H)-dione **46**.*

To a solution of alcohol **45** (259 mg, 0.416 mmol, 1.0 equiv) and 2,6-lutidine (1.45 mL, 12.5 mmol, 30.0 equiv) in CH_2Cl_2 (13 mL), cooled to 0 °C was added dropwise via syringe TMSOTf (1.89 mL, 10.4 mmol, 25.0 equiv). The cool bath was then removed and the reaction was stirred for 20 h at rt. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL) and then extracted with CH_2Cl_2 (3×30 mL). The combined organic extract was dried ($MgSO_4$), filtered and concentrated in vacuo to afford an oily yellow residue. Flash chromatography (SiO_2, 39:1 CH_2Cl_2/Me_2CO) afforded a ~3:1 mixture of the title compound, **46**, and putative



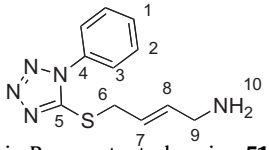
metathesised silyl compound **47** (246 mg, ~0.349 mmol, ~84%). This mixture was carried through without further purification although an analytical sample of **46** was obtained by preparative TLC (SiO_2, 1:2 petrol/Et_2O). R_f (39:1 CH_2Cl_2/Me_2CO) 0.33; $[\alpha]_D^{24}$ −3.9 (*c* 1.04, $CHCl_3$); ν_{max} 3179, 3104, 2955, 2912, 2877, 1772, 1718, 1684, 1456, 1378, 1279, 1234, 1179, 1087, 1032, 1005, 973, 840, 802, 736 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29–7.36 (5H, m, CH(1, 2 and 3)), 5.65 (1H, s, NH(20)), 4.50 (1H, d, *J* 12.0 Hz, CH_2(5a)), 4.43 (1H, d, *J* 12.0 Hz, CH_2(5b)), 4.27 (1H, dd, *J* 10.6, 2.0 Hz, CH(13)), 3.85 (1H, dd, *J* 11.4 Hz, CH_2(21a)), 3.77 (1H, d, *J* 11.4 Hz, CH_2(21b)), 3.74–3.79 (1H, m, CH(7)), 3.41 (1H, dd, *J* 9.5, 6.3 Hz, CH_2(6a)), 3.36 (1H, dd, *J* 9.5, 5.5 Hz, CH_2(6b)), 2.30 (1H, q, *J* 7.6 Hz, CH(17)), 1.90–1.96 (1H, m, CH(10)), 1.86 (1H, ddd, *J* 14.8, 5.3, 2.0 Hz, CH_2(12a)), 1.48 (1H, ddd, *J* 14.8, 10.6, 7.5 Hz, CH_2(12b)), 1.19 (3H, d, *J* 7.6 Hz, CH_3(18)), 1.03 (3H, d, *J* 6.8 Hz, CH_3(11)), 0.94 (9H, t, *J* 7.9 Hz, CH_3), 0.92 (9H, t, *J* 7.9 Hz, CH_3), 0.63 (6H, q, *J* 7.9 Hz, CH_2), 0.56 (6H, q, *J* 7.9 Hz, CH_2), 0.16 (9H, s, CH_3(24)); δ_C (100 MHz, $CDCl_3$) 176.8, (C=O(19)), 172.9 (C=O(16)), 137.9 (C(4)), 128.4 (CH), 127.8 (CH), 127.7 (CH(1)), 87.1 (CH(13)), 86.8 (C(14)), 74.4 (CH(7)), 73.4 (CH_2(5)), 72.5 (CH_2(6)), 68.4 (C(15)), 60.4 (CH_2(21)), 45.0 (CH(17)), 35.0 (CH(10)), 30.5 (CH_2(12)), 17.7 (CH_3(11)), 11.4 (CH_3(18)), 6.9 (CH_3), 6.7 (CH_3), 5.0 (CH_2), 4.3 (CH_2), 2.6 (CH_3(24)); *m*/*z* (ESI): 694 (MH^+), 716 (MNa^+); HRMS (ESI): MH^+ found 694.3989. $C_{35}H_{64}NO_7Si_3$ requires 694.3985 (0.5 ppm error).

*4.2.22. ((3R,3aS,4S,6aS)-4-((2R,3R)-4-(Benzyloxy)-3-(ethanoyloxy)-2-methylbutyl)-3a-hydroxy-1,3-dimethyl-2,6-dioxohexahydro-1H-furo[3,4-b]pyrrol-6a-yl)methyl ethanoate **50**.*



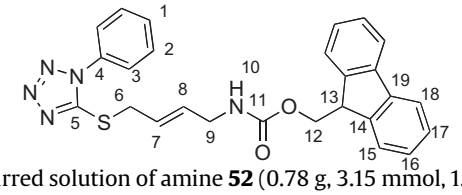
To a solution of the ~3:1 mixture of **46**/**47** (246 mg, ~0.349 mmol, 1.0 equiv) in THF (16 mL) cooled to −78 °C was added dropwise via microsyringe *n*-butyllithium [1.53 M in hexanes] (285 μL, 0.436 mmol, 1.25 equiv). The reaction was stirred for 30 min at −78 °C and then methyl iodide (220 μL, 3.49 mmol, 10.0 equiv) added via syringe. The reaction was stirred for a further 1 h at −78 °C and then the cool bath was removed and the reaction warmed to rt and stirred for an additional 45 min. Quenched by the addition of saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude methylated lactam mixture, **48**, as the same (inseparable) 3:1 mixture. The crude lactam was dissolved in 2,2,2-trifluoroethanol (10 mL) and anhydrous HCl gas was bubbled through the stirred solution for 45 min at rt. Upon completion, the residual acid was purged with a stream of argon for 10 min and the mixture was then concentrated in vacuo to afford the crude triol **49**. This material was dissolved in a mixture of acetic anhydride (2.5 mL) and pyridine (2.5 mL) and stirred for 16 h at rt. The reaction was quenched by the addition of 10% aqueous HCl (50 mL) and then extracted with CH_2Cl_2 (4×30 mL). The combined organic were washed with saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous brine (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the crude residue by flash chromatography (SiO_2, 9:1 CH_2Cl_2/Me_2CO) afforded the title compound, **50**, as a colourless film (119 mg, 0.242 mmol, 69% over the three-steps). R_f (9:1 CH_2Cl_2/Et_2O) 0.36; $[\alpha]_D^{23.5}$ +26.3 (*c* 1.01, $CHCl_3$); ν_{max} 3368, 2933, 1772, 1739, 1703, 1674, 1640, 1580, 1544, 1459, 1424, 1378, 1231, 1106, 1039, 955, 735 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29–7.36 (5H, m, CH(1, 2 and 3)), 4.95 (1H, ddd, *J* 7.0, 5.7, 4.1 Hz, CH(7)), 4.65 (1H, d, *J* 12.7 Hz, CH_2(21a)), 4.53 (2H, s, CH_2(5)), 4.33 (1H, dd, *J* 9.0, 5.7 Hz, CH(13)), 4.24 (1H, d, *J* 12.7 Hz, CH(21b)), 3.66 (1H, dd, *J* 10.2, 5.7 Hz, CH_2(6a)), 3.58 (1H, dd, *J* 10.2, 7.1 Hz, CH_2(6b)), 3.58 (1H, s, OH(24)), 2.84 (3H, s, CH_3(20)), 2.38 (1H, q, *J* 7.7 Hz, CH_3(17)), 2.05–2.12 (1H, m, CH_2(12a)), 2.07 (3H, s, CH_3), 2.06 (3H, s, CH_3), 1.82–1.89 (1H, m, CH(10)), 1.68 (1H, ddd, *J* 14.2, 10.0, 5.7 Hz, CH_2(12b)), 1.03 (3H, d, *J* 7.7 Hz, CH_3(18)), 1.02 (3H, d, *J* 6.4 Hz, CH_3(11)); δ_C (100 MHz, $CDCl_3$) 174.8 (C(19)), 170.6 (C), 169.9 (C), 169.8 (C(16)), 136.6 (C(4)), 128.5 (CH), 128.4 (CH), 128.3 (CH(1)), 85.9 (CH(13)), 79.8 (C(14)), 74.9 (CH(7)), 74.0 (CH_2(5)), 71.5 (C(15)), 67.9 (CH_2(6)), 57.5 (CH_2(21)), 45.1 (CH(17)), 29.3 (CH(10)), 29.3 (CH_2(12)), 26.1 (CH_3(20)), 21.0 (CH_3), 20.8 (CH_3), 16.7 (CH_3(11)), 10.6 (CH_3(18)); *m*/*z* (ESI): 492 (MH^+), 514 (MNa^+); HRMS (ESI): MNa^+ found 514.2049. $C_{25}H_{33}NNaO_9$ requires 514.2048 (0.3 ppm error).

*4.2.23. (E)-4-(1-Phenyl-1H-tetrazol-5-ylthio) but-2-en-1-amine **52**.*



To a solution of bis-Boc-protected amine **51** (1.00 g, 2.23 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL), was added trifluoroacetic acid (1.70 mL, 22.3 mmol, 10.0 equiv) at rt. After 12 h at rt, the mixture was poured into a separating funnel, washed with cold (0 °C) saturated aqueous $NaHCO_3$ (2×50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting crude product was purified by flash chromatography (SiO_2, 9:1 CH_2Cl_2/MeOH) to afford the allylic amine **52** (0.46 g, 1.86 mmol, 83%) as a viscous, yellow oil. R_f (9:1 CH_2Cl_2/MeOH) 0.15; ν_{max} 3422, 2914, 1500, 1438, 1205, 1138, 843, 801, 762, 724, 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.51–7.55 (5H, m, CH(1,2 and 3)), 6.70 (2H, d, *J* 7.5 Hz, CH_2(9)), 5.94 (1H, dt, *J* 14.5, 5.5 Hz, CH(7)), 5.77 (1H, dt, *J* 14.5, 7.5 Hz, CH(8)), 3.29 (2H, d, *J* 5.5 Hz, CH_2(6)), 2.18 (2H, br s, NH(10)); δ_C (100 MHz, $CDCl_3$) 154.3 (C(5)), 137.4 (CH(1)), 134.2 (C(4)), 130.6 (CH(8)), 130.3 (CH(2)), 124.3 (CH(3)), 123.7 (CH(7)), 43.7 (CH_2(9)), 35.1 (CH_2(6)); *m*/*z* (ESI): 248 (MH^+); HRMS (ESI): MH^+ found 248.1134. $C_{11}H_{14}N_5S$ requires 248.0964 (3.6 ppm error).

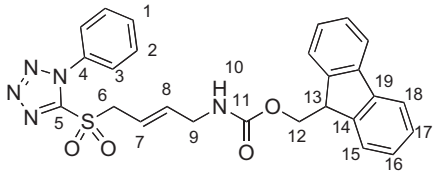
*4.2.24. (9H-Fluoren-9-yl)methyl (E)-4-(1-phenyl-1H-tetrazol-5-ylthio) but-2-enylcarbamate **53**.*



To a stirred solution of amine **52** (0.78 g, 3.15 mmol, 1.0 equiv) in THF/H_2O (2:1, 90 mL) at rt were added sequentially in single portions Fmoc-Cl (1.14 g, 4.4 mmol, 1.4 equiv) followed by $NaHCO_3$

(0.61 g, 7.24 mmol, 2.3 equiv). After stirring for 1 h, the reaction mixture was diluted with Et_2O (100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (9:1 petrol/EtOAc) to afford compound **53** (1.29 g, 2.74 mmol, 87%) as a viscous, clear oil. R_f (7:3 petrol/EtOAc) 0.41; ν_{max} 2924, 1712, 1502, 1243, 908, 732, 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.56–7.76 (9H, m, CH(1, 2, 3, 15 and 16)), 7.39 (2H, t, *J* 7.5 Hz, CH(18)), 7.31 (2H, dt, *J* 7.5, 1.0 Hz, CH(17)), 5.70–5.93 (2H, m, CH(7, 8)), 4.84 (1H, t, *J* 5.5 Hz, NH(10)), 4.41 (2H, d, *J* 7.0 Hz, CH_2(12)), 4.20 (1H, t, *J* 7.0 Hz CH(13)), 4.01 (2H, d, *J* 6.5 Hz, CH_2(6)), 3.79 (2H, t, *J* 5.0 Hz, CH_2(9)); δ_C (100 MHz, $CDCl_3$) 156.6 (C=O(11)), 154.1 (C(5)), 144.1 (C(14)), 141.4 (C(19)), 133.6 (C(4)), 132.6 (CH(1)), 130.3 (CH(2)), 129.9 (CH(7)), 127.8 (CH(17)), 127.2 (CH(16)), 125.1 (CH(15)), 124.9 (CH(3)), 123.9 (CH(18)), 120.2 (CH(8)), 66.5 (CH_2(12)), 46.9 (CH(13)), 41.8 (CH_2(9)), 34.3 (CH_2(6)); *m*/*z* (ESI): 470 (MH^+); HRMS (ESI): MH^+ found 470.1572; $C_{26}H_{24}N_5O_2S$ requires 470.1645 (0.1 ppm error).

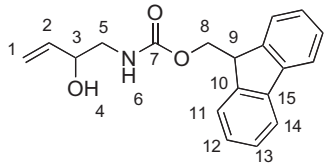
*4.2.25. (9H-Fluoren-9-yl)methyl (E)-4-(1-phenyl-1H-tetrazol-5-ylsulfonyl)but-2-enylcarbamate **22**.*



To a vigorously stirred rt solution of sulfide **53** (1.10 g, 2.34 mmol, 1.0 equiv) and $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (0.87 g, 0.70 mmol, 0.70 equiv) in EtOH (10 mL) was added dropwise H_2O_2 solution [34% w/v in water] (15 mL, 70.3 mmol, 30.0 equiv). The resultant solution was stirred for 7 h at room temperature before being quenched by the careful addition of saturated aqueous $Na_2S_2O_3$ (30 mL). The reaction mixture was then diluted with EtOAc (100 mL) and water (100 mL), extracted with further EtOAc (3×30 mL) before being dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (1:1 petrol/EtOAc) to afford the title compound, sulfone **22**, as a colourless solid (630 mg, 1.26 mmol, 54%). Mp 141–143 °C; R_f (7:3 petrol/EtOAc) 0.21; ν_{max} 1714, 1503, 1344, 1245, 1149 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.84–7.47 (9H, m, CH(1, 2, 3, 15 and 16)), 7.40 (2H, t, *J* 7.5 Hz, CH(18)), 7.32 (2H, dt, *J* 7.5, 1.0 Hz, CH(17)), 6.10–5.92 (1H, m, CH(8)), 5.74–5.59 (1H, m, CH(7)), 4.84 (1H, s, NH(10)), 4.46–4.39 (4H, m, CH_2(6, 12)), 4.21 (1H, t, *J* 6.5 Hz, CH(13)), 3.84 (2H, t, *J* 4.5 Hz, CH_2(9)); δ_C (100 MHz, $CDCl_3$) 156.1 (C=O(11)), 153.0 (C(5)), 143.7, 141.3 (CH(7)), 140.0, 132.9, 131.5, 129.7, 127.7, 127.0, 125.1, 124.9, 120.0, 114.7 (CH(8)), 66.8 (CH_2(12)), 59.0 (CH_2(6)), 47.2 (CH(13)), 42.2 (CH_2(9)); *m*/*z* (ESI): 502 (MH^+), 519 (MNH_4^+); HRMS (ESI): MH^+ found 502.1540. $C_{26}H_{24}N_5O_4S$ requires 502.1444 (0.6 ppm error).

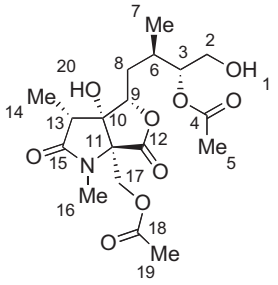
If the reactions were conducted at higher dilution or with fewer equivalents of hydrogen peroxide then the predominant product obtained was alcohol **55**.

*4.2.26. (±)-(9H-Fluoren-9-yl)methyl 2-hydroxybut-3-enylcarbamate **55**.*



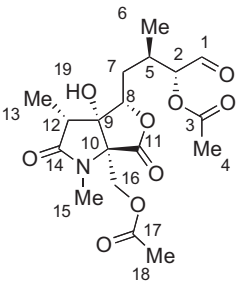
Mp 82–84 °C; R_f (7:3 petrol/EtOAc) 0.19; ν_{max} 3450, 2922, 1714, 1500, 1344, 1248, 1149, 760 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* 7.5 Hz, CH(14)), 7.59 (2H, d, *J* 7.5 Hz, CH(11)), 7.40 (2H, t, *J* 7.5 Hz, CH(13)), 7.31 (2H, dt, *J* 7.5, 1.0 Hz, CH(12)), 5.84 (1H, ddd, *J* 17.0, 10.5, 5.5 Hz, CH(2)), 5.33 (1H, d, *J* 17.0 Hz, CH_2(1a)), 5.20 (1H, d, *J* 10.5 Hz, CH_2(1b)), 4.48–4.41 (3H, m, CH_2(8), NH(6)), 4.25–4.17 (2H, m, CH(3, 9)), 3.42 (1H, ddd, *J* 13.5, 5.5, 3.5 Hz, CH_2(5a)), 3.15 (1H, ddd, *J* 13.5, 7.0, 5.5 Hz, CH_2(5b)), 2.77 (1H, s, OH(4)); δ_C (100 MHz, $CDCl_3$) 157.8 (C=O(7)), 144.5 (C(10)), 141.9 (CH(15)), 138.3 (CH(2)), 128.3 (CH(13)), 127.6 (CH(12)), 125.6 (CH(11)), 120.5 (CH(14)), 117.1 (CH_2(1)), 72.4 (CH(3)), 66.1 (CH_2(8)), 47.4 (CH(9)), 46.6 (CH_2(5)); *m*/*z* (ESI): 310 (MH^+); HRMS (ESI): MH^+ found 310.1428. $C_{19}H_{20}NO_3$ requires 310.1438 (3.1 ppm error).

*4.2.27. ((3R,3aS,4S,6aS)-4-((2R,3R)-3-(Ethanoyloxy)-4-hydroxy-2-methylbutyl)-3a-hydroxy-1,3-dimethyl-2,6-dioxohexahydro-1H-furo[3,4-b]pyrrol-6a-yl)methyl ethanoate **56**.*



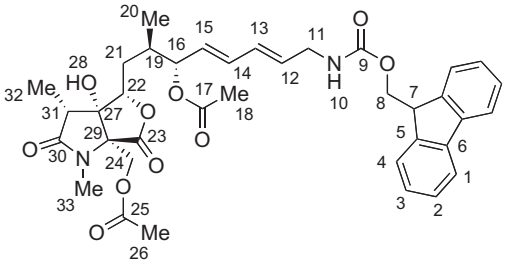
Benzyl ether **50** (82 mg, 0.167 mmol, 1.0 equiv) was dissolved in MeOH (6 mL) and then $Pd(OH)_2$/C [20% w/w] (12 mg, 17 μmol, 0.10 equiv) added. The reaction flask was connected to a three-way tap connected to vacuum and a hydrogen balloon and purged under five vacuum/hydrogen cycles. The reaction was then stirred for 1 h under an atmosphere of hydrogen. The catalyst was removed by filtration through a small pad of Celite®, which was rinsed with MeOH (3×10 mL). The filtrate was then concentrated in vacuo to afford the title compound, **56**, as a colourless foam (67 mg, 0.167 mmol, quantitative). R_f (19:1 CH_2Cl_2/MeOH) 0.19; $[\alpha]_D^{24.5}$ +33.2 (*c* 1.095, $CHCl_3$); ν_{max} 3403, 2945, 1770, 1736, 1679, 1458, 1430, 1386, 1232, 1041, 1018, 957 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.84 (1H, ddd, *J* 6.1, 6.0, 4.4 Hz, CH(3)), 4.70 (1H, d, *J* 12.8 Hz, CH_2(17a)), 4.35 (1H, dd, *J* 8.1, 6.2 Hz, CH(9)), 4.25 (1H, d, *J* 12.8 Hz, CH_2(17b)), 3.84 (1H, ddd, *J* 11.7, 6.1, 5.5 Hz, CH_2(2a)), 3.71 (1H, s, OH(20)), 3.70 (1H, ddd, *J* 11.7, 6.0, 5.5 Hz, CH_2(2b)), 2.86 (3H, s, CH_3(16)), 2.48 (1H, q, *J* 7.6 Hz, CH(13)), 2.22 (1H, dd, *J* 5.5, 5.5 Hz, OH(1)), 2.08–2.13 (1H, m, CH_2(8a)), 2.09 (3H, s, CH_3), 2.08 (3H, s, CH_3), 1.91–1.98 (1H, m, CH(6)), 1.69 (1H, ddd, *J* 14.4, 9.5, 6.2 Hz, CH_2(8b)), 1.25 (3H, d, *J* 7.6 Hz, CH_3(14)), 1.06 (3H, d, *J* 6.9 Hz, CH_3(7)); δ_C (100 MHz, $CDCl_3$) 174.9 (C=O(15)), 171.3 (C=O(4)), 170.1 (C=O(12)), 169.8 (C=O(18)), 86.2 (CH(9)), 80.0 (C(10)), 77.3 (CH(3)), 71.5 (C(11)), 61.4 (CH_2(2)), 57.6 (CH_2(17)), 45.0 (CH(13)), 29.7 (CH_3), 29.6 (CH_3), 26.2 (CH_3(16)), 21.0 (CH(6)), 20.8 (CH_2(8)), 16.7 (CH_3(7)), 10.9 (CH_3(14)); *m*/*z* (ESI): 402 (MH^+), 424 (MNa^+); HRMS (ESI): MNa^+ found 424.1581. $C_{18}H_{27}NNaO_9$ requires 424.1578 (0.8 ppm error).

*4.2.28. ((3R,3aS,4S,6aS)-4-((2R,3R)-3-(Ethanoyloxy)-2-methyl-4-oxobutyl)-3a-hydroxy-1,3-dimethyl-2,6-dioxohexahydro-1H-furo[3,4-b]pyrrol-6a-yl)methyl ethanoate **21**.*



To a stirred suspension of alcohol **56** (90 mg, 225 μmol, 1.0 equiv) in CH_2Cl_2 (5.5 mL) cooled to 0 °C was added in a single portion DMP (317 mg, 747 μmol, 3.3 equiv) before the cooling bath was removed. After stirring for 45 min at rt, the reaction was diluted with Et_2O (25 mL) and then quenched with a 1:1 solution of saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ (25 mL) and the mixture was stirred until homogeneous (15 min). The layers were separated and then the residual aqueous further extracted with Et_2O (3×25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was rapidly purified by flash chromatography (SiO_2, 3:1 CH_2Cl_2/Me_2CO) to afford the title compound, **21**, an unstable colourless foam that decomposes at rt (45.5 mg, 113 μmol, 51%). R_f (3:1 CH_2Cl_2/Me_2CO) 0.39; $[\alpha]_D^{18.5}$ +35.0 (*c* 0.40, $CHCl_3$); ν_{max} 3399, 2919, 2851, 1771, 1746, 1678, 1459, 1432, 1375, 1228, 1149, 1041, 1019 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.56 (1H, s, CH(1)), 4.97 (1H, d, *J* 3.9 Hz, CH(2)), 4.72 (1H, d, *J* 13.0 Hz, CH_2(16a)), 4.31 (1H, dd, *J* 7.4, 6.2 Hz, CH(8)), 4.24 (1H, d, *J* 13.0 Hz, CH_2(16b)), 2.96 (1H, s, OH(19)), 2.86 (3H, s, CH_3(15)), 2.50 (1H, q, *J* 7.6 Hz, CH(12)), 2.25–2.33 (1H, m, CH(5)), 2.21 (3H, s, CH_3), 2.10 (3H, s, CH_3), 1.81–1.89 (2H, m, CH_2(7a, 7b)), 1.26 (3H, d, *J* 7.6 Hz, CH_3(13)), 1.14 (3H, d, *J* 7.0 Hz, CH_3(6)); δ_C (100 MHz, $CDCl_3$) 199.5 (C=O(1)), 174.4 (C=O(14)), 170.6 (C=O), 170.3 (C=O(11)), 169.6 (C=O), 85.9 (CH(8)), 80.9 (CH(2)), 80.3 (C(9)), 71.4 (C(10)), 57.9 (CH_2(16)), 44.4 (CH(12)), 31.0 (CH(5)), 30.0 (CH_2(7)), 26.2 (CH_3(15)), 21.0 (CH_3), 20.6 (CH_3), 16.9 (CH_3(6)), 11.0 (CH_3(13)); *m*/*z* (ESI): 400 (MH^+), 422 (MNa^+); HRMS (ESI): MH^+ found 400.1596. $C_{18}H_{26}NO_9$ requires 400.1602 (0.8 ppm error).

*4.2.29. [(3R,3aS,4S,6aS)-4-[(2R,3R,4E,6E)-3-Acetoxy-8-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-2-methylocta-4,6-dien-1-yl]-3a-hydroxy-1,3-dimethyl-2,6-dioxotetrahydro-1H-furo[3,4-b]pyrrol-6a(6H)-yl]methyl acetate **15**.*



To a solution of sulfone **22** (55 mg, 109 μmol, 1.0 equiv) in THF (3.5 mL) cooled to −78 °C was added a solution of NaHMDS [1.0 M in THF] (109 μL, 109 μmol, 1.0 equiv) and the resultant pale green solution stirred for 15 min at −78 °C. A pre-prepared solution of aldehyde **21** (43.5 mg, 109 μmol, 1.0 equiv) in THF (2 mL) was added dropwise via cannula. The resultant solution was stirred for 1 h at −78 °C before being quenched by the addition of saturated aqueous brine (6 mL) and warmed to rt. The reaction was then diluted with further brine (10 mL) and extracted with Et_2O (5×20 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated in vacuo to afford a ~4.5:1 mixture of (4*E*,6*E*):(4*Z*,6*E*) isomers by ^1H NMR analysis. The crude residue was purified by flash chromatography (SiO_2, 19:1→9:1 CH_2Cl_2/Me_2CO) to afford, in order of elution, (4*Z*,6*E*)-**15** as a colourless foam (10.3 mg, 15.3 μmol, 14%) and the title compound, (4*E*,6*E*)-**15**, as a colourless foam (46.5 mg, 68.9 μmol, 63%).

(4*Z*, 6*E*)-**15**: R_f (9:1 CH_2Cl_2/Me_2CO) 0.36; δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* 7.6 Hz), 7.62 (2H, d, *J* 7.6 Hz), 7.39 (2H, dd, *J* 7.6, 7.6 Hz), 7.29 (2H, dd, *J* 7.6, 7.6 Hz), 6.55 (1H, dd, *J* 14.5, 11.7 Hz), 6.21 (1H, dd, *J* 10.5, 10.0 Hz), 5.90 (1H, br dd, *J* 6.0, 6.0 Hz), 5.80 (1H, ddd, *J* 14.5, 7.8, 5.0 Hz), 5.67 (1H, dd, *J* 10.0, 4.6 Hz), 5.35 (1H, dd, *J* 11.7, 10.5 Hz), 4.73 (1H, d, *J* 12.9 Hz), 4.39–4.34 (2H, m), 4.19–4.24 (2H, m), 4.20 (1H, d, *J* 12.9 Hz), 3.88–3.96 (1H, m), 3.68–3.76 (1H, m), 3.57 (1H, br s), 2.87 (3H, s), 2.38 (1H, q, *J* 7.6 Hz), 2.00–2.09 (2H, m), 2.03 (3H, s), 1.99 (3H, s), 1.62–1.68 (1H, m), 1.21 (3H, d, *J* 7.6 Hz), 1.04 (3H, d, *J* 6.9 Hz). This compound proved unstable in solution, undergoing isomerisation to (4*E*,6*E*)-**15**. This prevented the collection of any further characterisation data.

(4*E*,6*E*)-**15**: R_f (9:1 CH_2Cl_2/Me_2CO) 0.26; $[\alpha]_D^{24}$ +2.0 (*c* 1.0, CH_2Cl_2), lit. $[\alpha]_D^{23}$ +3.6 (*c* 1.0, CH_2Cl_2); ν_{max} 3398, 2941, 1771, 1728, 1694, 1525, 1450, 1429, 1383, 1232, 1145, 1107, 1041, 1018, 994, 759, 737 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.76 (2H, d, *J* 7.6 Hz, CH(1)), 7.60 (2H, d, *J* 7.60 Hz, CH(4)), 7.40 (2H, ddd, *J* 7.6, 7.6, 1.1 Hz, CH(2)), 7.30 (2H, ddd, *J* 7.6, 7.6, 1.1 Hz, CH(3)), 6.21 (1H, dd, *J* 14.9, 10.9 Hz, CH(14)), 6.13 (1H, dd, *J* 14.3, 10.9 Hz, CH(13)), 5.72 (1H, dt, J 14.5, 6.0 Hz, CH(12)), 5.56 (1H, dd, *J* 15.0, 7.0 Hz, CH(15)), 5.27 (1H, br t, *J* 5.5 Hz, NH(10)), 5.19 (1H, t, J 5.5 Hz, CH(16)), 4.69 (1H, d, *J* 12.9 Hz, CH_2(24a)), 4.37–4.41 (2H, m, CH(8)), 4.30 (1H, dd, *J* 8.8, 4.3 Hz, CH(22)), 4.24 (1H, d, *J* 12.9 Hz, CH_2(24b)), 4.19–4.22 (1H, m, CH(7)), 3.76–3.91 (2H, m, CH_2(11a, 11b)), 3.32 (1H, s, OH(28)), 2.86 (3H, s, CH_3(33)), 2.41 (1H, q, *J* 7.5 Hz, CH(31)), 2.07 (3H, s, CH_3), 2.05 (3H, s, CH_3), 1.85–1.98 (2H, m, CH_2(21a) and CH(19)), 1.61 (1H, ddd, *J* 15.1, 8.8, 6.8 Hz, CH_2(21b)), 1.24 (3H, d, *J* 7.7 Hz, CH_3(32)), 1.00 (3H, d, *J* 6.8 Hz, CH_3(20)); δ_C (125 MHz, $CDCl_3$) 174.6 (C=O(30)), 170.3 (C=O), 170.2 (C=O), 169.8 (C=O), 156.4 (C(9)), 143.9 (C(5)), 141.3 (C(6)), 132.8 (CH(14)), 131.3 (CH(12)), 130.5 (CH(13)), 128.7 (CH(15)), 127.7 (CH(2)), 127.0 (CH(3)), 125.1 (CH(4)), 120.0 (CH(1)), 86.8 (CH(22)), 80.2 (C(27)), 77.5 (CH(16)), 71.4 (C(29)), 66.8 (CH_2(8)), 57.8 (CH_2(24)), 47.3 (CH(7)), 44.3 (CH(31)), 42.6 (CH_2(11)), 34.0 (CH(19)), 30.6 (CH_2(21)), 26.2 (CH_3(33)), 21.2 (CH_3), 20.9 (CH_3), 16.7 (CH_3(20)), 11.0 (CH_3(32)); *m*/*z* (ESI): 675 (MH^+), 697 (MNa^+); HRMS (ESI): MH^+ found 675.2912. $C_{37}H_{43}N_2O_{10}$ requires 675.2915 (0.4 ppm error).

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