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Generating *cis*-aza-diaryl and triaryl ethers *via* organoBrønsted acid catalysed aza-Darzens chemistry

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As the Founder and Editor in Chief for Tetrahedron: Asymmetry we dedicate this paper to Professor Stephen Davies with thanks to his friendship, advice and outstanding service to organic chemistry.

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ABSTRACT

We report the efficient combination of S_NAr and organic Brønsted acid catalysis protocols for the construction of *cis*-aziridine-derived biaryl and triaryl ethers. Using aza-Darzens chemistry mono-*cis*-aziridine-biaryl and bis-(*cis*-aziridine)-triaryl ethers have been generated; these motifs have significant potential as easily synthesised, functionalised precursors of a glycopeptide backbone.

1. Introduction

Glycopeptides such as vancomycin [1] [**1**, (X = Cl, Fig. 1)] are frontline antibiotic therapies with an intriguing and conserved structural **C**-O-**D**-O-**E** 'backbone'. Appended with two 16-membered macrocycles it is equipped with **C**-O-**D** and **D**-O-**E** biaryl ethers 'stitched' together *via* a heptapeptide chain. Triaryl biether **C**-O-**D**-O-**E** motifs are critical components of these natural products affording them with point chiral and atropisomeric stereocenters, structure complexity and conformational rigidity. Thus, synthetic routes affording glycopeptides require, at the outset, innovative approaches to the construction of the triaryl **C**-O-**D**-O-**E** motif. An initial assessment of this group suggests it should be relatively straightforward to generate with pre-requisite functionality for subsequent transformations/incorporation into the natural product. But, upon closer analysis this key motif presents numerous synthesis challenges, which if its construction is incorporated at a late-stage in the natural product synthesis can be problematic. Interestingly, in all glycopeptide natural product syntheses to date late-stage aryl ether construction was undertaken (with varying degrees of success). For example, Terada and co-workers used toxic thallium(III) nitrate to mediate an oxidative aryl ether cyclization [3] (not shown) and, although **2** (Fig. 1) was generated in a 20% yield, it was afforded with an inseparable and unidentified by-product.

Pearson and co-workers exploited late-stage biaryl ether construction using cyclopentadienyl ruthenium (CpRu) complexes as photocleavable activators and S_NAr chemistry. Here, cesium carbonate mediated an efficient intramolecular S_NAr on **3** which, after mild CpRu cleavage (UV irradiation), afforded **4** in a good overall yield (Scheme 1) [4]. A number of strategies have been developed for assembling the 'halogen-free' Orienticin C [2] [**2** (X = H, Fig. 1) aglycone version] triaryl biether backbone. As similar as **1** is to **2** it

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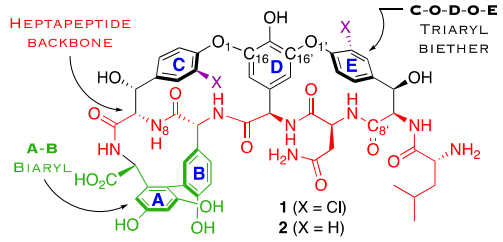
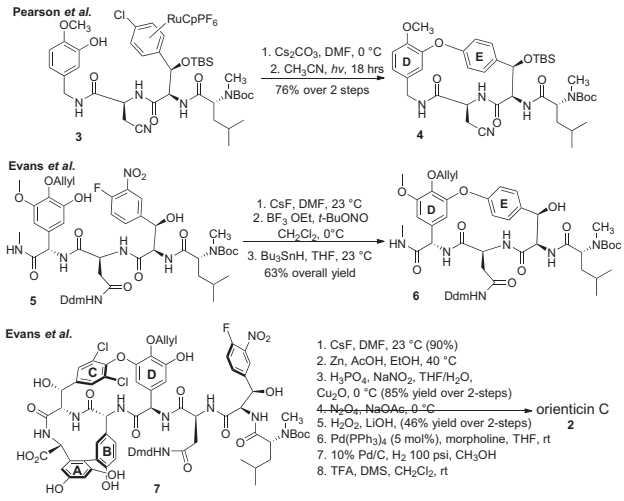


Fig. 1. Vancomycin aglycone **1** (X = Cl) and Orienticin C aglycone **2** (X = H).



Scheme 1. S_NAr synthesis of bi/triaryl macrocyclic ethers.

does exhibit one key difference which for our preliminary studies was important; it lacks chiral atropisomerism on the **C**- and **E**-aryl rings.

Previous syntheses of biaryl/triaryl ethers have exploited late-stage cesium fluoride/S_NAr chemistry. For example, Evans and co-workers transformed halogen-free tetrapeptide **5** into macrocycle **6** (Scheme 1); exploiting this late-stage macrocyclic chemistry on the more complex glycopeptide precursor **7** a similar cesium fluoride mediated S_NAr afforded, after successive manipulation (Scheme 1), Orienticin C (**2**, Fig. 1) [5].

Aziridines are highly versatile heterocycles used to generate sought-after azasugars, β-lactams, polymers, α- and β-amino acids, chiral auxiliaries and pyrrolidines [6]. They are also widely used key intermediates en route to structure and function diverse natural products. By way of example, Trost and co-workers [7] synthesised (+)-Agelastatin A **11** (Scheme 2) *via* *N*-tosyl *cis*-aziridine **10**; itself derived from pyrrole **8**, *N*-heterocyclic carbene **9** and PINTs. Jouillé and co-workers [8] developed a highly convergent route to Ustiloxin F (**15**) *via* cyclopeptide precursor **14** (90% yield) using a copper(I) acetate catalysed regio- and stereoselective ring-opening of *cis*-aziridine **13** with phenol **12**.

2. Overview

Organic Brønsted acid catalysis is, now, an indispensable 'tool' in the synthetic chemists' 'toolbox'. [9]. As part of an ongoing investigation developing simple, organic Brønsted acid catalysed routes to important heterocycles we required an organocatalytic approach to *cis*-aziridines equipped with biaryl or triaryl-ethers.

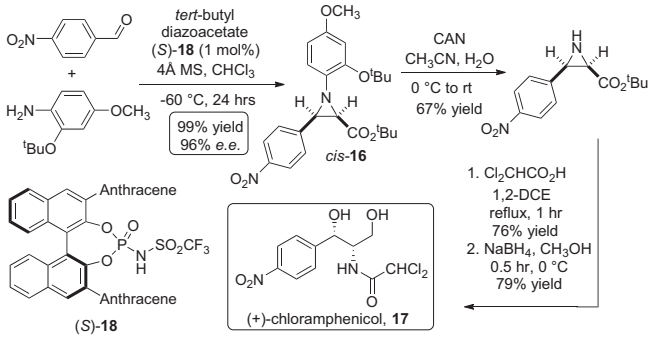
Our *rac*-aza-Darzens protocol uses an aldehyde, amine, alkyl diazoacetate and pyridinium triflate; a cheap, 'off the shelf' catalyst which readily affords structure and function diverse *N*-substituted *cis*-$C_{2,3}$-disubstituted *rac*-aziridines [10]. Similarly, using (*S*)-**18**, optically active [11] *cis*-aziridines are afforded in excellent yields and diastereoselectivites. We applied both protocols to a simple natural product synthesis; thus, *cis*-**16** was transformed into the antibiotic (+)-chloramphenicol (**17**, Scheme 3) in 3-steps and 41% overall yield.

Using our knowledge of organic Brønsted acid catalysed aza-Darzens chemistry we envisaged an 'early-stage' construction of *cis*-aziridine-derived biaryl and triaryl ethers. These, we imagine, would serve as convenient staging posts en route to advanced neoteric glycopeptide intermediates. In this study we outline:

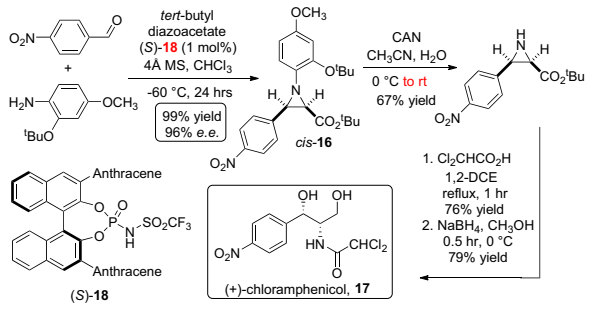
a) Synthetic routes to strategic, regioselectively and orthogonally functionalised **C**-O-**D** biaryl ether building blocks.
b) A synthetic route to an important regioselectively and orthogonally functionalised **C**-O-**D**-O-**E** triaryl ether building block.
c) Single aza-Darzens *cis*-aziridination of a regioselectively protected mono-aldehyde affording a biaryl *cis*-aziridine derived **C**-O-**D** motif.
d) aza-Darzens *cis*-aziridination of a *bis*-aldehyde-derived triaryl biether appended on the central aryl with an alkene or an ester, see for example (*cis*-aziridine-**C**)-O-**D**-(C═C)—O-(aldehyde-**E**) **19** (Q is a C═C, Scheme 4).
e) Asymmetric aminohydroxylation of a C═C appended to the **D** ring a component of the **C**-O-**D** motif and subsequent transformation of the α-amino alcohol into the prerequisite α-amino acid.

3. Results and discussion

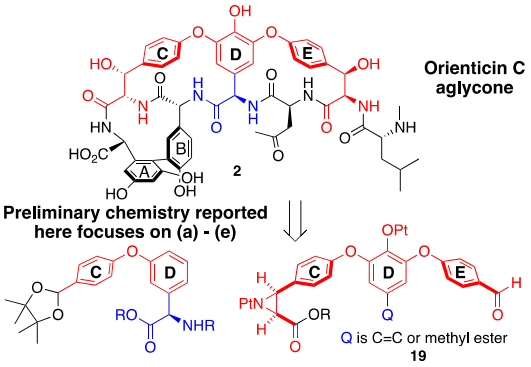
Generating the prerequisite *cis*-aziridine-derived **C**-O-**D**-O-**E** backbone (*cf.* **2**) necessitated a straightforward synthesis of *bis*-



Scheme 2. Use of *cis*-aziridines in natural product synthesis.



Scheme 3. Asymmetric aza-Darzens catalysed by (*S*)-**18**.



Scheme 4. Functionalised biaryl and triaryl ethers.

Table 1
Solvent, temperature and time optimization for the synthesis of biaryl ether **23** and triaryl biether **22**.

Entry	Solvent	Temp	Time	Yield **23**	Yield **22**
1[a]	DMF	25 °C	24 h	0%	0%
2[a]	DMF	70 °C	4 h	<20%	0%
3[a]	DMF	160 °C	4 h	<5%	0%
4[a]	DMA	70 °C	48 h	20%	0%
5[a]	DMA	160 °C	0.5 h	21%	0%
6[a]	DMSO	160 °C	2 h	<5%	0%
7[b]	DMSO	160 °C	2 h	32%	5%
8[c]	DMSO	160 °C	1 h	42%	<5%
9[d]	DMSO	160 °C	2 h	21%	56%

[a] 2.5eq^n K_2CO_3.
[b] 2eq^n Cs_2CO_3.
[c] 2.5eq^n Cs_2CO_3.
[d] 3.2 eq^n Cs_2CO_3.

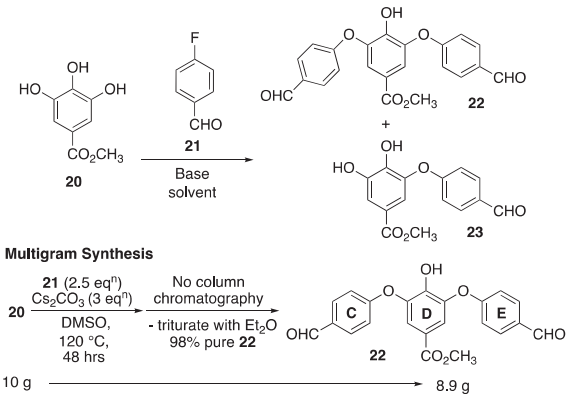
aldehyde-derived triaryl biether **22** (Scheme 5). We envisaged undertaking a double S_NAr between methyl gallate **20** and 4-fluorobenzaldehyde **21**. At room temperature using DMF and excess potassium carbonate (2.5 eq^n) no reaction was observed (Entry 1, Table 1). The same reaction at 70 °C (oil bath) afforded **23** but in a poor yield and only after 48 h (Entry 2). Disappointingly, attempts at increasing the yield by heating at 160 °C afforded 1-(4-dimethylamino)benzaldehyde (Entry 3). We presume this was generated *via* an S_NAr reaction between dimethylamine, a thermal decomposition product of DMF, and **21**. Negating this DMA and microwave irradiation (160 °C) afforded **23** in a 21% yield (Entry 5) in only 30 min (*cf.* 48 h, oil bath). Gratifyingly, substituting cesium carbonate for potassium carbonate in DMA increased the yield of **23**—32% and triaryl biether **22** was observed for the first time albeit in 5% yield (Entry 7). Finally, after reaction optimization using DMSO and 3.2 equivalents of **21** at 160 °C for 2 h, dialdehyde **22** was obtained in a 56% yield which in conjunction with mono-aldehyde (**23**) afforded a 77% overall yield (Entry 9).

The advantageous role of cesium carbonate was attributed to the "cesium effect" [12]. Dipolar aprotic DMSO, DMA and DMF are able to dissolve cesium salts affording homogeneous, dissociated free-ions or solvent-separated ion-pairs. Thus, with cesium carbonate a basic and 'naked' carbonate anion results which in conjunction with the solvated and highly polarized Cs^+ (1.67 Å) facilitates a considerably more efficient S_NAr process.

Although microwave irradiation offered a fast and efficient route to key building block **22** it was limited to 500 mg 'batch' syntheses. Demonstrating the robust nature of the small-scale microwave reaction it was adapted and developed into a protocol capable of generating multigram quantities. Thus, using DMSO at 120 °C (aluminium heating block), 2.5 equivalents of **21** and a 48-h reaction time **22** was afforded with minimal reduction in yield. With a large quantity of impure **22**/**23** (2:1) in hand we were keen to purify it avoiding the use of flash chromatography and large quantities of solvent; gratifyingly, careful trituration of the impure mixture with cold (0 °C) diethyl ether selectively dissolved the more *non-polar* **22** leaving the majority of the more *polar* catechol **23** behind. Evaporating the ether and repeating the process on semi-purified product afforded nearly 9 g of **22** with an estimated (^{1}H NMR) purity of 98% (Scheme 5).

It was important to establish that the S_NAr had afforded the desired 3,5-triaryl ether **22** (*cf.* **C**-O-**D**-O-**E** backbone of **1** and **2**) and not the 3,4-regioisomer (not shown). A mechanistic rational supporting 3,5-biaryl ether formation focused on the p*K*a differences of the hydroxyls and the increased stability of the more acidic 4-hydroxy phenol (p*K*a 8) which after deprotonation undergoes ester conjugation generating a quinone-like species (not shown).

In contrast, deprotonating the less acidic 3-hydroxyphenol (p*K*a 12) affords a more reactive and less stabilized phenoxide which efficiently reacts with **21** affording *meta*-aldehyde **23** and, subsequently, 3,5-*bis*-arylaldehyde **22**. Conclusive evidence for 3,5-dietherification was sought. Pale brown monoclinic crystals were grown from ether and analysed *via* X-ray diffraction. These confirmed **22** to be the symmetric 3,5-disubstituted triaryl biether. In depth analysis of **22** established it had a non-planar conformation; the **C** and **E** aryl rings tilted at ~70° to the central **D**-ring (Fig. 2, top right image). Curiously, this is comparable to the 80° 'tilt' identified in the crystal structure of the **C**-O-**D**-O-**E** part of



Scheme 5. S_NAr reaction between **22** and **21** affording aldehyde-derived triaryl biether **22** and biaryl ether **23**.

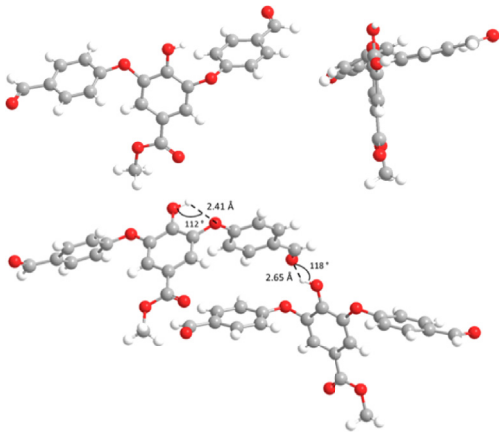


Fig. 2. X-ray crystal structure of **22**. Dashed lines outline intra and intermolecular hydrogen bonds. Numerical values outline bond lengths and dihedral bond angles.

vancomycin (**1**, Fig. 1) [13]. Further analysis afforded substantive evidence of an intermolecular 2.65 Å hydrogen bond between the 4-phenol hydroxyl on **D** (**22**) and a carbonyl lone-pair on a second molecule of **22** ring **E** with a 118° O–H···O dihedral angle (Fig. 2, lower image, right hand side). Moreover, an intramolecular O–H···O hydrogen bond (dihedral angle 112°) was identified in **22** that formed a 5-membered ring between the 4-hydroxyl on **D** and one of the lone pairs on the oxygen biaryl ether (Fig. 2, lower image, top-middle).

Microfluidic reaction conditions confer many benefits *e.g.* less reagent/solvent consumption, more controllable heat transfer, better mixing and improved safety profiles – the latter is especially important with reactive and or unstable species [14]. Incorporating a flow synthesis regime (Uniqsis FlowSyn [15]), a static mixer and a column packed with cesium carbonate we wanted to probe the μfluidic synthesis of **22** and **23** *via* the reaction of DMSO solutions of **20** and **21**. Interestingly, despite numerous and widespread applications of S_NAr chemistry its use in flow chemistry is, practically, non-existent and no *double* S_NAr reactions on a single substrate (*cf.* **20** → **22**, Scheme 4) have been reported. Using excess cesium carbonate, relative to methyl gallate, it should be possible to increase the reaction rate and efficiency of the S_NAr biaryl ether coupling. Pumping (1 mL/min) a 1.1 M DMSO solution of **20** and a 2.5 M solution of fluorobenzaldehyde through a heated glass column (150 °C, 6.6 × 100 mm, packed with Cs_2CO_3) improved the yield and rate of the S_NAr reaction. The desired **22** and **23** (1:1) were generated in an improved 81% yield. Following trituration with cold ether **23** was selectively removed; this allowed **23** to be resubmitted to an S_NAr with **21**. Using this protocol the overall yield of **22** was increased to 91%.

Incorporating the bi- and triaryl ethers into an organocatalytic Brønsted acid aza-Darzens reaction, our goal, ultimately, is to ring-open the *cis*-aziridines and generate aryl ether derived β-hydroxy-α-amino acids. Initiating this aspect of our work required an *O*-methyl, *O*-benzyl ether, or a 4-methoxybenzylidine acetal protected methyl gallate *e.g.* **25** (Scheme 6) [16] which we hoped to transform into 4-benzoxy-3,4-dihydroxybenzoate methyl ester (not shown). Transacetalisation of methyl gallate with **24** (4 Å MS, 0.5 mol% PTSA) in toluene at reflux afforded cyclic acetal **25** (Scheme 5). Disappointingly, attempts at mediating an S_NAr with **21** using the reagents, conditions, and solvents in Table 1 were, by and large, low yielding (Scheme 6, Path A). Changing tack an Ullman etherification using **25**, 4-bromobenzaldehyde (**27**), copper(II) oxide, potassium carbonate and pyridine (Scheme 6, Path B) was also unsuccessful; no reaction was observed and the starting materials were returned in good yield. Finally, **21** and **25** did react *via* an S_NAr at 75 °C in acetonitrile but the product (**26**) was afforded in a poor 20% yield (Scheme 6, Path C).

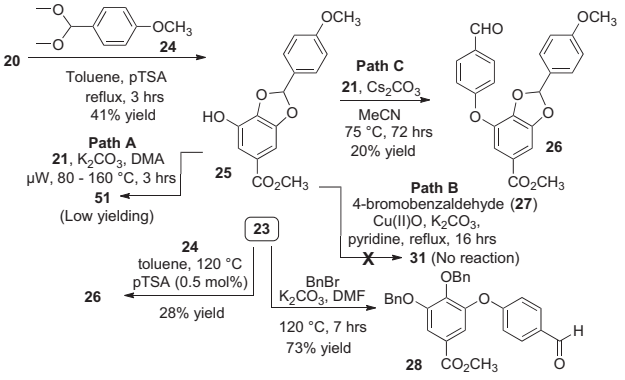
Negating this a switch from an 'acetal 1st - S_NAr 2nd route, that is **20** → **25** → **26** to a 'S_NAr 1st – acetal 2nd route *i.e.* **20** → **23** → **28** (Scheme 6) allowed biaryl catechol **23** to be transformed into diol-protected mono-aldehyde **28** in a slightly improved yield (Scheme 6). Generating *bis*-4,5-*O*-benzyl ether **28** was straightforward. Reacting **23** with benzyl bromide and potassium carbonate in DMF at 120 °C for 7 h afforded **28** in a 73% yield (Scheme 6); no evidence of any mono-*O*-benzylated (not shown) adducts were found.

With the successful synthesis of **28** in hand we wanted to generate a methyl ether on the 4-position of the '**D**-ring' of aza-Darzens precursor **29**. Reacting **23** with one equivalent each of lithium carbonate and iodomethane in DMF 4-methyl ether **29** was afforded in a 71% yield (Scheme 7). Confirming the regioselectivity of the etherification was important. Commercially available methyl 3,5-dihydroxy-4-methoxybenzoate reacted (S_NAr) with one equivalent of **21** and cesium carbonate. The ^1H and ^{13}C NMR spectra of this product matched those obtained from the **23** → **29** route (Scheme 7).

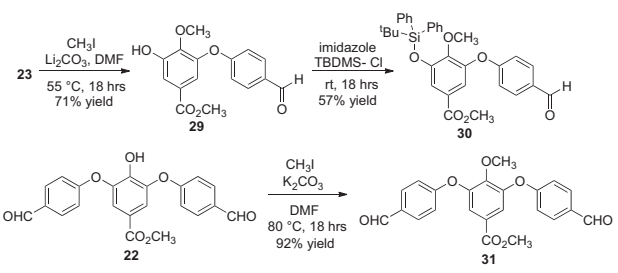
Finally, orthogonal *O*-protection of **29** employed *tert*-butyldiphenylsilyl chloride (1.1 eq^n) and imidazole (2.2 eq^n) in DMF, TBDPS ether **30** was obtained in an unoptimized 57% yield (Scheme 7). *O*-Methyl and *O*-benzyl triaryl biether **31** and **39** were generated in an excellent 92% (Scheme 7) and 87% yields respectively (Scheme 10).

With aldehyde **28** in hand our focus switched to its transformation into the corresponding *rac*-aziridine **32** (Scheme 8). Incorporating a one-pot, two-stage aziridination protocol the prerequisite imine was generated from 2-*tert*-butoxyaniline and, without further purification or isolation, it was activated with pyridinium triflate (10 mol%) and reacted with *tert*-butyl diazoacetate. After 12 h the reaction was judged complete, and the product was purified *via* flash column chromatography. Mono-*cis*-aziridine ($C_{2,3}J$ 6.7 Hz) **32** was afforded in a 64% yield (Scheme 8).

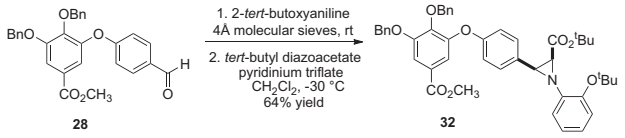
Future studies required an optically active α-amino acid be installed on the central **D**-aryl ring (**38**, Scheme 9). This, we envisaged, could be accomplished *via* a Sharpless asymmetric α-aminohydroxylation and, subsequent, alcohol oxidation. Initiating a model study, 3-(4,4',5,5')-tetramethyl-1,3-dioxolan-2-yl)phenol **33** was coupled to 3-bromobenzaldehyde *via* a procedure reported by Buchwald and co-workers that used 10 mol% copper(I) iodide and 20 mol% 1,10-phenanthroline in pyridine (120 °C); **34** was afforded in a 67% yield. Wittig chemistry transformed *meta*-aldehyde-derived biaryl ether **34** into styrene **35** (Scheme 9) in an excellent 95% yield, whilst its oxidation employed a mixture of benzyl carbamate, $(DHQ)_2PHAL$ (6 mol%), potassium osmate (4 mol%) and *tert*-butyl hypochlorite. The desired α-amino alcohol **36** was afforded with an excellent 96% *e.e.* (Phenomenex Lux cellulose-1). Subsequent oxidation of the 1° alcohol using TEMPO, sodium hypochlorite and 10 mol% sodium bromide generated carboxylic acid **37** in an 87% yield which, after esterification (CH_3I, K_2CO_3, DMF), was hydrogenated using 10% Pd/C affording 1° amine **38** in an 88%



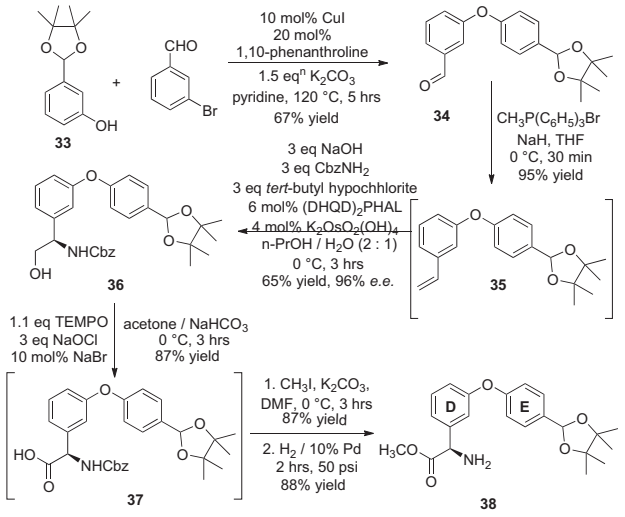
Scheme 6. Synthetic routes to biaryl-mono-aldehyde **26** and **28** from starting materials **23** and **25**.



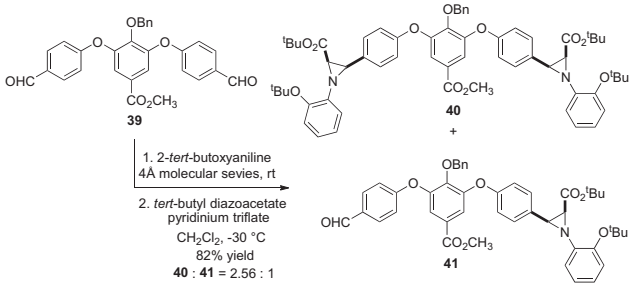
Scheme 7. Synthesis of orthogonally *O*-protected biaryl ether **30** from catechol **29** and *O*-methylation of triaryl ether **22** generating *bis*-aldehyde **31**.



Scheme 8. One-pot, two-step synthesis of *cis*-aza-biaryl ether **32** from *bis*-4,5-*O*-benzyl biaryl ether aldehyde **28**.



Scheme 9. Asymmetric synthesis of biaryl ether derived α-aryl α-amino carboxylate methyl ester **38**.



Scheme 10. One-pot, two-step synthesis of *bis*-*cis*-aziridine derived triaryl biether **40** and *mono*-*cis*-aziridine derived triaryl biether **41** from **39**.

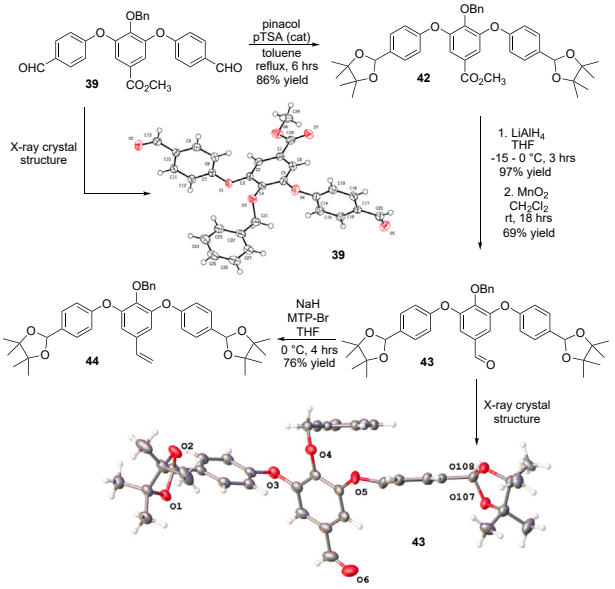
yield.

Confident the mono-aza-Darzens *cis*-aziridination was robust, we wanted to evaluate, for the first time, if a racemic double-aza-Darzens was viable using 2-*tert*-butoxyaniline, *tert*-butyl diazoacetate, *O*-benzyl *bis*-aldehyde **39**, pyridinium triflate (10 mol%) and the conditions outlined in Scheme 10. Gratifyingly, after work-up, ^{1}H NMR indicated the impure reaction mixture contained two *cis*-aziridines and a small amount of a tentatively assigned *trans*-aziridine (*J* 2.4 Hz, not isolated and not shown). Further analysis (^{1}H NMR) revealed the *cis*:*trans* diastereoselectivity to be > 99:1. Subsequent purification *via* flash chromatography afforded a combined 82% yield of *cis*-**40** and *cis*-**41** (both $C_{2,3}$ aziridines had *J* 6.7 Hz). Physicochemical analysis established the major product was double *cis*-aziridine **40** (59% yield, Scheme 10) whilst the minor was mono-*cis*-aziridine **41** (23% yield). We propose that *bis*-*cis*-aziridine **40** originates, presumably, from mono-*cis*-aziridine **41**. But, generating **40** with two *cis*-aziridines raised the question of their relative stereochemistry; that is, does it have meso- or C_2-symmetry?

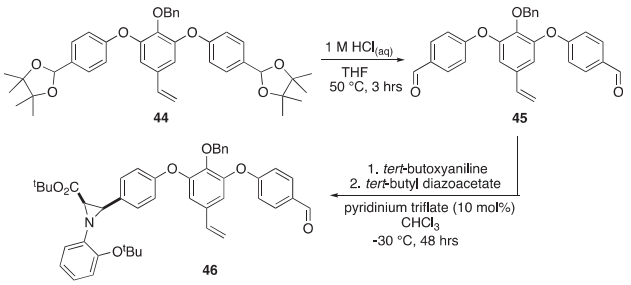
Although it is feasible the *cis*-aziridine in **41** impacts the diastereoselectivity of the second aza-Darzens reaction its influence, over 15 atoms, is likely to be minimal and certainly not predictable. Nevertheless we wanted to use X-ray diffraction to determine the relationship between the *cis*-aziridines in **40**. Disappointingly, all attempts at obtaining crystals suitable for X-ray diffraction failed, with either 'gummy' or amorphous solids formed. Thus, at the present time it is not possible to assign if *bis*-*cis*-aziridine **40** has meso- or C_2-symmetry. Additional studies are ongoing which aim to clarify this and will, in due course, be reported.

It was important to demonstrate the 'core' triaryl biether **D**-ring was, similar to biaryl aldehyde **34** (Scheme 9), suited to alkene synthesis and, presumably, thereafter amenable to asymmetric α-amino hydroxylation. Clearly, chemoselective reduction of the ester in **39** would likely fail, with the more reactive aldehydes being reduced in preference. Negating this acetal **42** was synthesised (86% yield) from **39** using Dean-Stark conditions, pinacol and 0.5 mol% of PTSA,[23] following this the ester was reduced with lithium aluminium hydride in an excellent 97% yield. Oxidation of the 1° alcohol using excess activated manganese (II) dioxide afforded aldehyde **43** in a 69% yield. A small monoclinic crystal of **43** was submitted to X-ray diffraction [18]; this confirmed the presence of both pinacols, the aldehyde and the benzyl ether. Aldehyde **43** underwent a Wittig reaction using two equivalents of sodium hydride and an equimolar amount of methyltriphenylphosphonium bromide affording vinyl-**44** (Scheme 11) in a 51% yield. The slightly lower yield and reaction rate (*cf*. **35**, Scheme 8) was attributed to the lower reaction temperature and equivalents of Wittig reagent used. Conducting the reaction at 0 °C, whilst increasing the equivalents of Wittig reagent from two to three afforded **44** in an improved 76% yield (Scheme 11).

In contrast to methyl acetals the sterically hindered pinacol acetals are more challenging to cleave; often requiring elevated temperature and stronger, aqueous acidic conditions. In order to be sure that the pinacol acetal was readily hydrolysed in the presence of other acid sensitive groups **44** was deemed a good substrate. Dissolving **44** in a 1:1 mixture of tetrahydrofuran and 1 M aqueous hydrochloric acid the reaction was monitored (TLC) every 2 h; after 6 h no change was observed. Increasing the temperature to 50 °C



Scheme 11. Transforming ester **42** into styrene **44** and the X-ray crystal structure of mono-aldehyde **43**.



Scheme 12. Synthesis of *rac*-mono-*cis*-aziridine derived alkene **46** from dialdehyde **45**.

and stirring for a further 3 h **44** was completely consumed. Subsequent flash column chromatography afforded **45** (Scheme 12) in a 90% yield. No alkene polymerization or aldehyde hydration was observed. Finally, mono-aziridination of **45** was accomplished using pyridinium triflate (10 mol%) and 2-*tert*-butoxyaniline (0.98 eq[n]), the desired mono-*cis*-aziridine **46** (*J* $C_{2,3}$ 6.7 Hz) was afforded in a 65% yield, which based on recovered **46**, increased to 87% yield.

4. Conclusion

In summary, we have demonstrated the facile application of single or double early stage S_NAr and aza-Darzens chemistry for the straightforward production of functionalised *cis*-aziridine-derived biaryl ethers and triaryl biethers – potential precursors to α- or β-amino acid derived backbone **C**-O-**D**-O-**E** scaffolds found in glycopeptide natural products. Using either conventional flask or flow-chemistry protocols the first example of a double S_NAr on a single substrate has been shown to be viable on a multigram scale. Furthermore, we have demonstrated the feasibility of incorporating aryl ether bond formation early on in the synthesis of the **C**-O-**D**-O-**E** component, and as natural product precursors and sought-after motifs, they can be adorned with readily manipulated functional groups, *e.g.* phenol, ester and aldehyde, without invoking a protecting/deprotecting group strategy. Finally, we show how a double aldehyde derived starting material can be transformed *via* an organoBrønsted acid catalysed aza-Darzens reaction into a mono- or *bis*-*cis*-aziridine-derived triaryl biether adorned with ester, aldehyde, alkene and *O*-benzyl ether functional groups.

4.1. Experimental section

Air and water-sensitive reactions were carried out under a nitrogen atmosphere and anhydrous conditions with magnetic stirring unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates (0.2 mm), with visualization by UV light and/or potassium permanganate stain followed by heating. Flash column chromatography was performed using Davisil silica gel 60 (40–63 μm). ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer 500 (500 MHz), an Oxford Gemini 400 spectrometer (400 MHz) or an Oxford Gemini 300 spectrometer (300 MHz). Chemical shifts are reported in δ (ppm) and referenced to residual solvent signals (^1H NMR: $CDCl_3$ at 7.26 ppm, CD_3CN at 1.94 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, CD_3CN at 1.32, 118.26 ppm). Signal multiplicities are described as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad. FT-IR spectra were recorded on a Perkin Elmer Spectrum 100 spectrometer as thin films on sodium chloride plates and are reported in wavenumbers (cm^{-1}). Optical rotations were measured using a Perkin Elmer 241 polarimeter with a 1 mL cell (path length 1 dm) and are reported as follows: $[\alpha]_D^{T/°C}$ concentration (c = g/100 mL, solvent). MALDI-TOF mass spectra were recorded on a Shimadzu Axima-CFR spectrometer. High resolution mass spectrometry (HRMS) was carried out by the EPSRC National Mass Spectrometry Facility (Swansea, UK). Melting points of crystalline solids were recorded using a Stuart Scientific SMP1 apparatus (solvent of crystallization in brackets) and are uncorrected. Percentage yield refers to the isolated yield of analytically pure material unless otherwise stated. Dichloromethane was distilled from calcium hydride before use. Chloroform and *d*-chloroform were filtered through basic alumina and stored over 4 Å molecular sieves. Tetrahydrofuran was distilled from sodium/benzophenone prior to use. All other solvents and reagents were purchased from commercial sources (Sigma-Aldrich, Alfa Aesar, Fluorochem and Fisher Scientific) and used as received.

4.1.1. Methyl 3,5-bis(4-formylphenoxy)-4-hydroxybenzoate (**22**)

4.1.1.1. ***Synthesis A****: microwave irradiation.* To a 15 mL microwave vial under a nitrogen atmosphere was added methyl 3,4,5-trihydroxybenzoate **20** (500 mg, 2.72 mmol, 1 equiv.), cesium carbonate (2.41 g, 7.40 mmol, 2.7 equiv.) and a magnetic stirrer bar. Dimethyl sulfoxide (7 mL) was added, and the resulting mixture stirred vigorously for 10 min at room temperature before the addition of 4-fluorobenzaldehyde **21** (0.93 mL, 8.69 mmol, 3.2 equiv.) *via* a 2.5 mL syringe. The vial was sealed with a PTFE-lined aluminium crimp cap and the dark red suspension heated at 160 °C in a Biotage microwave reactor for 3 h, after which the reaction mixture was allowed to cool to room temperature and poured into a 250 mL separating funnel containing 1 M aqueous hydrochloric acid (50 mL). The aqueous mixture was extracted with ethyl acetate (2 × 50 mL) and the combined organic extracts were washed with distilled water (3 × 50 mL) and then brine (50 mL). The solution was dried over magnesium sulfate, filtered, and the solvent removed *in vacuo* to afford a dark brown residue. Purification *via* flash column chromatography on silica gel (eluent: dichloromethane/ethyl acetate 9:1; $R_f = 0.30$) afforded a pale-yellow solid (600 mg, 1.53 mmol, 56% yield) whose physicochemical characteristics were consistent with those of title compound **22**.

M.p. 161–162 °C; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.95 (s, 2H, -C*H*O), 7.92 (d, *J* 8.8 Hz, 4H, Ar-*H*), 7.65 (s, 2H, Ar-*H*), 7.17 (d, 4H, *J* 8.8 Hz, Ar-*H*), 6.50 (s, 1H, -O*H*), 3.84 (s, 3H, -CO_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.9 (-*C*HO), 165.3 (-CO_2CH_3), 161.7, 144.6, 143.0, 133.0, 132.2, 122.8, 119.0, 117.4, 52. (-CO_2CH_3); FT-IR (ATR): υ (cm^{-1}) = 3079 (O–H), 2846 (C–H), 1692 (*ester* C=O), 1669 (*aldehyde* C=O), 1578, 1502, 1423, 1341, 1194; MS (MALDI-TOF): *m/z* 414.82 $[M+Na]^+$; HRMS (APCI) exact mass calculated for $C_{22}H_{17}O_7$ requires *m/z* 393.0969, found *m/z* 393.0965 $[M+H]^+$.

4.1.2. Methyl 3-(4-formylphenoxy)-4,5-dihydroxybenzoate (**23**)

A by-product was isolated during the column chromatography ($R_f = 0.60$; dichloromethane/methanol 2%); this was identified as methyl 3-(4-formylphenoxy)-4,5-dihydroxybenzoate **23** (165 mg, 0.57 mmol, 21% yield).

M.p. 191–193 °C (chloroform); ^1H NMR (300 MHz, CD_3OD) δ 9.77 (s, 1H, -C*H*O), 7.86 (d, *J* 9.0 Hz, 2H, Ar-*H*), 7.36 (s, 1H, Ar-*H*), 7.19 (s, 1H, Ar-*H*), 7.02 (d, *J* 9.0 Hz, 2H, Ar-*H*), 3.79 (s, 3H, -CO_2CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ = 191.3, 166.6, 163.3, 146.8, 142.9, 141.8, 133.6, 131.3, 120.8, 116.2, 114.6, 113.2, 51.1; FT-IR (thin film): υ (cm^{-1}) = 3217 (O–H), 1686 (C=O), 1593, 1504, 1439, 1319, 1224, 1156; MS (MALDI-TOF) *m/z* 311.12 $[M+Na]^+$; HRMS (NESI) exact mass calculated for $C_{15}H_{11}O_6$ requires *m/z* 287.0561, found *m/z* 287.0566 $[M-H]^-$.

*4.1.3. Methyl 3,5-bis(4-formylphenoxy)-4-hydroxybenzoate (**22**)*

*4.1.3.1. **Synthesis B**: conventional heating.* To a 500 mL two-necked round-bottom flask was added methyl 3,4,5-trihydroxybenzoate **20** (9.93 g, 53.9 mmol, 1 equiv.) and a magnetic stirrer bar. The white solid was dissolved in dimethyl sulfoxide (160 mL) under a nitrogen atmosphere. Cesium carbonate (52.7 g, 162 mmol, 3 equiv.) was added in one portion and the resulting mixture stirred at room temperature for 15 min before the addition of 4-fluorobenzaldehyde **21** (14.4 mL, 135 mmol, 2.5 equiv.) *via* a 25 mL syringe. The flask was fitted with a reflux condenser and the reaction mixture heated at 120 °C for 48 h using an aluminium heating block mounted on a hotplate magnetic stirrer. When no further conversion from **20** to **22** was observed by thin layer chromatography (eluent: dichloromethane/ethyl acetate 9:1), the reaction mixture was cooled to 0 °C, quenched with 1 M aqueous hydrochloric acid (200 mL) and poured into a 2 L separating funnel. The aqueous mixture was extracted with ethyl acetate (2 × 200 mL) and the combined organic extracts were washed with distilled water (3 × 300 mL) and then brine (250 mL). The solution was dried over magnesium sulfate, filtered, and the solvent removed *in vacuo* to afford a dark brown solid. Trituration with diethyl ether (0 °C) afforded a cream solid (8.89 g, 22.7 mmol, 42% yield) whose physicochemical properties were consistent with those of the title compound (**22**) described previously.

*4.1.4. Methyl 3,5-bis(4-formylphenoxy)-4-hydroxybenzoate (**22**)*

*4.1.4.1. **Synthesis C**: flow reactor.* A Uniqsis Flow Syn reactor was fitted with a 6.6 × 100 mm glass column packed with cesium carbonate (5 g). The column was pre-heated to 150 °C. A solution of methyl 3,4,5-trihydroxybenzoate **20** (200 mg, 1.09 mmol, 1 equiv.) in dimethyl sulfoxide (2 mL), solution A, and a solution of 4-fluorobenzaldehyde **26** (0.4 mL, 2.78 mmol, 2.5 equiv.) in dimethyl sulfoxide (2 mL), solution B, were pumped simultaneously through the glass column, each with a flow rate of 1 mL/min. The dark red solution was collected in a 250 mL separating funnel containing 1 M hydrochloric acid (50 mL) at room temperature. The aqueous mixture was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with distilled water (3 × 50 mL) and then brine (50 mL). The organic solution was dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification *via* flash column chromatography on silica gel (eluent: dichloromethane/ethyl acetate 9:1) afforded **22** as a pale-yellow solid (141 mg, 0.36 mmol, 33% yield) and **23** as a light brown solid (91 mg, 0.32 mmol, 29% yield). The physicochemical properties of these compounds matched the data obtained from the microwave-promoted synthesis outlined above.

*4.1.5. Methyl 3-(4-formylphenoxy)-4,5-dihydroxybenzoate (**22**)*

To a 15 mL microwave vial was added methyl 3,4,5-trihydroxybenzoate **20** (1 g, 5.43 mmol, 1 equiv.), cesium carbonate (3.89 g, 11.9 mmol, 2.2 equiv.) and a magnetic stirrer bar. The vial was purged with nitrogen, sealed with a PTFE-lined aluminium crimp cap and dimethyl sulfoxide (10 mL) was added *via* a 20 mL syringe. The resulting reaction mixture was stirred vigorously for 10 min at room temperature before the addition of 4-fluorobenzaldehyde **21** (0.7 mL, 6.53 mmol, 1.2 equiv.) *via* a 2 mL syringe. The dark red suspension was heated to 120 °C in a Biotage microwave reactor for 90 min. The reaction mixture was allowed to cool to room temperature and poured into a 250 mL separating funnel containing 1 M aqueous hydrochloric acid (50 mL). The aqueous mixture was extracted with ethyl acetate (2 × 50 mL) and the combined organic extracts were washed with distilled water (2 × 100 mL) and then brine (100 mL). The resulting solution was dried over magnesium sulfate, filtered, and the solvent removed *in vacuo* to afford a dark brown residue. Purification *via* flash column chromatography on silica gel (eluent: dichloromethane/ethyl acetate 9:1) afforded a yellow solid (603 mg, 2.09 mmol, 39% yield) whose physicochemical properties matched those of the title compound (**22**). By-product **23** was isolated in a 7% yield (149 mg, 0.38 mmol); the physicochemical properties were as outlined previously.

*4.1.6. Methyl 7-hydroxy-2-(4-methoxyphenyl)benzo[d][1,3]dioxole-5-carboxylate (**25**)[17]*

A flame-dried 250 mL two-necked round-bottom flask fitted with a Soxhlet apparatus containing 4 Å molecular sieves was charged with a solution of *p*-anisaldehyde dimethyl acetal **24** (2.18 g, 12.0 mmol, 1.25 equiv.) in anhydrous toluene (100 mL) and a magnetic stirrer bar. Methyl gallate **20** (1.77 g, 9.60 mmol, 1 equiv.) and *para*-toluenesulfonic acid (8 mg, 0.046 mmol, 0.5 mol%) were added, and the solution heated at reflux for 3 h. After cooling to room temperature, the majority of the solvent was removed *in vacuo*. The residue was redissolved in dichloromethane (50 mL) and washed with saturated aqueous sodium carbonate solution (50 mL). The addition of hexane (50 mL) resulted in the precipitation of a pale-yellow solid, which was filtered and recrystallised from dichloromethane/hexane (1:1) to afford a cream solid whose physicochemical properties matched those previously reported for **25** (1.20 g, 3.97 mmol, 41% yield).

M.p. 130–132 °C (dichloromethane/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* 8.8 Hz, 2H, Ar-*H*), 7.27 (d, *J* 1.5 Hz, 1H, Ar-*H*), 7.11 (d, *J* 1.5 Hz, 1H, Ar-*H*), 6.93 (s, 1H, -C*H*-), 6.89 (d, *J* 8.8 Hz, 2H, Ar-*H*), 5.00 (s, 1H, -O*H*), 3.81 (s, 3H, -OCH_3), 3.77 (s, 3H, -OCH_3); FT-IR (thin film): υ (cm^{-1}) = 3347 (O–H), 2920 (C–H), 2850 (C–H), 1696 (C=O), 1637, 1617, 1516, 1449, 1375, 1257, 1081; MS (MALDI-TOF) *m/z* 325.08 $[M+Na]^+$.

*4.1.7. Methyl 7-(4-formylphenoxy)-2-(4-methoxyphenyl)benzo[d][1,3]dioxole-5-carboxylate (**26**)*

A 15 mL microwave vial containing 4 Å molecular sieves was flame-dried and allowed to cool to room temperature under a flow of nitrogen. Methyl 3-(4-formylphenoxy)-4,5-dihydroxybenzoate **23** (100 mg, 0.347 mmol, 1 equiv.), anhydrous toluene (7 mL), *para*-anisaldehyde dimethyl acetal **24** (66 mg, 0.364 mmol, 1.05 equiv.), and *para*-toluenesulfonic acid (0.35 mg, 0.0018 mmol, 0.5 mol%) were added. The vial was sealed with a PTFE-lined aluminium crimp cap and the stirred suspension was heated at 110 °C for 6 h. After cooling to room temperature, sodium carbonate (0.4 mg, 0.0038 mmol, 1.09 mol%) was added and the mixture stirred at room temperature for 1 h before being filtered to remove the molecular sieves. The solvent was removed *in vacuo*, and purification *via* flash column chromatography on silica gel (eluent: dichloromethane 100%; R_f = 0.30) afforded a pale-yellow solid whose physicochemical properties were consistent with those of the title compound **26** (20 mg, 0.049 mmol, 28% yield).

M.p. 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H, -C*H*O), 7.82 (d, *J* 8.7 Hz, 2H, Ar-*H*), 7.46–7.39 (m, 4H, Ar-*H*), 7.07–7.02 (m, 3H, Ar-*H*), 6.90 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 3.85 (s, 3H, -CO_2CH_3), 3.80 (s, 3H, -OCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.8 (-*C*HO), 165.8 (-*C*O_2CH_3), 161.8, 161.5, 150.0, 142.7, 136.4, 132.0, 131.7, 128.0, 126.9, 124.9, 118.3, 116.9, 114.1, 112.65, 106.8, 55.4 (-OCH_3), 52.4 (-CO_2CH_3); FT-IR (thin film): υ (cm^{-1}) = 3076 (C–H), 3011 (C–H), 2949 (C–H), 2843 (C–H), 2733 (C–H), 1717 (*ester* C=O), 1696 (*aldehyde* C=O), 1614, 1600, 1518, 1500, 1442, 1367, 1301, 1253, 1222, 1178, 1157, 1020, 1006; MS (MALDI-TOF) *m/z* 405.25 $[M-H]^-$; HRMS (HNESP) exact mass calculated for $C_{23}H_{19}O_7$ requires *m/z* 407.1125, found *m/z* 407.1128 $[M+H]^+$.

4.1.8. Methyl 3,4-bis(benzyloxy)-5-(4-formylphenoxy)benzoate (**28**)

To a 250 mL round-bottom flask containing methyl 3-(4-formylphenoxy)-4,5-dihydroxybenzoate **23** (333 mg, 1.16 mmol, 1 equiv.) under a nitrogen atmosphere was added *N*,*N*-dimethylformamide (35 mL) and a magnetic stirrer bar. Potassium carbonate (481 mg, 3.48 mmol, 3 equiv.) was added to the stirred orange solution in one portion, following by the addition of benzyl bromide (0.41 mL, 3.48 mmol, 3 equiv.) *via* a 1 mL syringe. The resulting suspension was heated to 120 °C for 7 h. After cooling to room temperature, distilled water (30 mL) was added, followed by 1 M aqueous hydrochloric acid (40 mL). The mixture was extracted with ethyl acetate (2 × 50 mL) and the combined organic layers were washed with distilled water (2 × 100 mL) and then brine (100 mL) before being dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification *via* flash column chromatography on silica gel (eluent: petroleum ether/diethyl ether 7:3; $R_f = 0.20$) afforded a cream solid whose physicochemical properties were consistent with those of the title compound **28** (398 mg, 0.85 mmol, 73% yield).

M.p. 88–90 °C (hexane/dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H, -C*H*O), 7.74 (d, *J* 8.6 Hz, 2H, Ar-*H*), 7.55 (s, 1H, Ar-*H*), 7.40–7.29 (m, 6H, Ar-*H*), 7.19–7.08 (m, 5H, Ar-*H*), 6.96 (d, *J* 8.6 Hz, 2H, Ar-*H*), 5.12 (s, 2H, -CH_2Ph), 5.00 (s, 2H, -CH_2Ph), 3.81 (s, 3H, -CO_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.7, 166.0, 162.9, 153.2, 147.7, 144.7, 136.6, 136.0, 131.9, 131.3, 128.7, 128.3, 128.2, 128.15, 127.7, 125.9, 116.7, 116.7, 112.1, 75.2, 71.4, 52.4; FT-IR (thin film): υ (cm^{-1}) = 3064 (O–H), 3033, 2952, 2736 (C–H), 1724 (C=O), 1697, 1584, 1503, 1427, 1341, 1220, 1157, 1076; MS (MALDI-TOF) *m/z* 491.05 $[M+Na]^+$, 507.00 $[M+K]^+$; HRMS (HNESP) exact mass calculated for $C_{29}H_{25}O_6$ requires *m/z* 469.1646, found *m/z* 469.1642 $[M+H]^+$.

4.1.9. Methyl 3-(4-formylphenoxy)-5-hydroxy-4-methoxybenzoate (**29**)

To a 15 mL microwave vial containing methyl 3-(4-formylphenoxy)-4,5-dihydroxybenzoate **23** (603 mg, 2.09 mmol, 1 equiv.) and a magnetic stirrer bar under a nitrogen atmosphere was added *N*,*N*-dimethylformamide (10 mL). To the stirred orange solution was added lithium carbonate (155 mg, 2.09 mmol, 1 equiv.) in one portion, followed by the addition of iodomethane (0.13 mL, 2.09 mmol, 1 equiv.) dropwise *via* a 1 mL syringe. The vial was sealed with a PTFE-lined aluminium crimp cap and heated to 55 °C for 18 h using a sand bath. After cooling to room temperature, the mixture was poured into a 250 mL separating funnel containing distilled water (20 mL), to which 1 M aqueous hydrochloric acid (50 mL) was added. The mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with distilled water (3 × 100 mL) and subsequently brine (100 mL). The organic solution was dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification *via* flash column chromatography on silica gel (eluent: dichloromethane/diethyl ether 5%; $R_f = 0.31$) afforded an orange oil whose physicochemical properties were consistent with those of the title compound **29** (449 mg, 1.49 mmol, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H, -C*H*O), 7.81 (d, *J* 8.8 Hz, 2H, Ar-*H*), 7.47 (d, 1H, Ar-*H*), 7.25 (d, 1H, Ar-*H*), 6.99 (d, *J* 8.8 Hz, 2H, Ar-*H*), 5.95 (s, 1H), 5.23 (s, 1H, -O*H*), 3.88 (s, 3H, -OCH_3), 3.80 (s, 3H, -OCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.6, 166.1, 162.4, 148.6, 147.95, 132.1, 131.8, 126.1, 120.7, 116.8, 61.3, 52.5; FT-IR (thin film): υ (cm^{-1}) = 3384 (O–H), 2955, 2843 (C–H), 1709 (C=O), 1582, 1503, 1436, 1354, 1227, 1156; MS (MALDI-TOF) *m/z* 325.03 $[M+Na]^+$; HRMS (NESI) exact mass calculated for $C_{16}H_{15}O_6$ $[M+H]^+$ requires *m/z* 303.0863, found *m/z* 303.0866.

4.1.10. Methyl 3-((tert-butyldiphenylsilyl)oxy)-5-(4-formylphenoxy)-4-methoxybenzoate (**30**)

To a 5 mL round-bottom flask containing methyl 3-(4-formylphenoxy)-5-hydroxy-4-methoxybenzoate **29** (100 mg, 0.33 mmol, 1 equiv.) and a magnetic stirrer bar under a nitrogen atmosphere was added *N*,*N*-dimethylformamide (2 mL). To the stirred orange solution was added imidazole (50 mg, 0.73 mmol, 2.2 equiv.) in one portion, followed by the addition of *tert*-butyldiphenylchlorosilane (95 μL, 0.36 mmol, 1.1 equiv.) *via* a 250 μL syringe. The pale-yellow solution was stirred at room temperature for 18 h before being poured into a 50 mL separating funnel containing 5% aqueous sodium bicarbonate solution (10 mL) and the organics extracted with hexane (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification *via* flash column chromatography on silica gel (eluent: petroleum ether/diethyl ether 1:1; $R_f = 0.56$) afforded a colourless oil whose physicochemical properties were consistent with those of the title compound **30** (102 mg, 0.19 mmol, 57% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H, -C*H*O), 7.72–7.64 (m 6H, Ar-*H*), 7.39–7.18 (m, 8H, Ar-*H*), 6.75 (d, *J* 8.6 Hz, 2H, Ar-*H*), 3.66 (s, 3H, -CO_2CH_3), 3.56 (s, 3H, -OCH_3), 1.06 (s, 9H, -C(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.8, 165.7, 162.9, 149.8, 147.6, 147.2, 135.5, 132.3, 132.0, 131.2, 130.1, 127.8, 125.4, 119.5, 117.2, 116.4, 60.8, 52.2, 26.6, 19.7; FT-IR (thin film): υ (cm^{-1}) = 3074 (C–H), 2956 (C–H), 2859 (C–H), 1726 (C=O), 1700 (C=O), 1603, 1582, 1506, 1430, 1345, 1227, 1155, 1109, 1071, 999; MS (MALDI-TOF) *m/z* 579.28 $[M+K]^+$; HRMS (NESI) exact mass calculated for $C_{32}H_{33}O_6Si$ requires *m/z* 541.2041, found *m/z* 541.2038 $[M+H]^+$.

4.1.11. Methyl 3,5-bis(4-formylphenoxy)-4-methoxybenzoate (**31**)

To a 15 mL microwave vial was added methyl 3,5-*bis*(4-formylphenoxy)-4-hydroxybenzoate **22** (500 mg, 1.27 mmol, 1 equiv.), potassium carbonate (352 mg, 2.55 mmol, 2 equiv.) and a magnetic stirrer bar. *N*,*N*′-Dimethylformamide (6 mL) was added and the vial sealed with a PTFE-lined aluminium crimp cap. The suspension was stirred at room temperature for 15 min. Iodomethane (111 μL, 1.78 mmol, 1.4 equiv.) was added *via* a 250 μL syringe, and the mixture heated at 80 °C for 24 h. After cooling to room temperature, the suspension was poured into a 250 mL separating funnel containing ethyl acetate (50 mL) and 1 M aqueous hydrochloric acid (50 mL). The aqueous layer was re-extracted with ethyl acetate (50 mL) and the combined organic layers were washed with distilled water (2 × 100 mL) and subsequently brine (100 mL) before being dried over magnesium sulfate and filtered. The solvent was removed *in vacuo* to afford a yellow oil whose physicochemical characteristics were consistent with those of the title compound (**31**, 478 mg, 1.18 mmol, 92%) was used as is.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 2H, -C*H*O), 7.81 (d, *J* 8.7 Hz, 4H, Ar-*H*), 7.62 (s, 2H, Ar-*H*), 7.01 (d, *J* 8.7 Hz, 4H, Ar-*H*), 3.81 (s, 3H, -OCH_3), 3.72 (s, 3H, -OCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) 190.6, 165.1, 162.4, 148.7, 148.1, 132.1, 131.8, 126.1, 120.7, 117.0, 61.3 (-OCH_3), 52.5; FT-IR (thin film): υ (cm^{-1}) = 2955 (C–H), 2836 (C–H), 2738 (C–H), 1727 (*ester* C=O), 1697 (*aldehyde* C=O), 1602, 1579, 1503, 1421, 1335, 1223, 1156; MS (MALDI-TOF) *m/z* 429.2 $[M+Na]^+$, 445.21 $[M+K]^+$; HRMS (NESP) exact mass calculated for $C_{23}H_{19}O_7$ requires *m/z* 407.1125, found *m/z* 407.1125 $[M+H]^+$.

4.1.12. tert-Butyl 3-(4-(2,3-bis(benzyloxy)-5-(methoxycarbonyl) phenoxy)phenyl)-1-(2-(tert-butoxy)phenyl)-cis-aziridine-2-carboxylate (**32**)

To a flame-dried 5 mL microwave vial containing crushed 4 Å molecular sieves under a nitrogen atmosphere was added a solution of methyl 3,4-*bis*(benzyloxy)-5-(4-formylphenoxy)benzoate

28 (100 mg, 0.21 mmol, 1 equiv.) and 2-*tert*-butoxyaniline (33 mg, 0.20 mmol, 0.95 equiv.) in anhydrous dichloromethane (2 mL). The mixture was stirred slowly at room temperature for 18 h. After the addition of pyridinium triflate (5 mg, 0.02 mmol, 10 mol%), the vial was sealed with a PTFE-lined aluminium crimp cap and cooled to 0 °C. *Tert*-butyl diazoacetate (30 μL, 0.21 mmol, 1 equiv.) was added dropwise *via* a 100 μL syringe. The solution was stirred at 0 °C for 18 h before being filtered through a short plug of silica and eluted with diethyl ether (3 × 5 mL). The organic solvent was removed *in vacuo* to afford a dark yellow residue. Purification *via* flash column chromatography on silica gel (eluent: petroleum ether/diethyl ether/dichloromethane 8:1:1; $R_f = 0.20$), afforded a white solid whose physicochemical properties were consistent with those of the title compound **32** (89 mg, 0.12 mmol, 64% yield).

M.p. 39–41 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.15 (m, 14H, Ar-*H*), 6.94–6.82 (m, 6H, Ar-*H*), 5.10 (s, 2H, -C*H*$_2$Ph), 5.06 (s, 2H, -C*H*$_2$Ph), 3.76 (s, 3H, -OC*H*$_3$), 3.38 (d, *J* 6.7 Hz, 1H, *aziridine* C–*H*), 2.96 (d, *J* 6.7 Hz, 1H, *aziridine* C–*H*), 1.31 (s, 9H, -C(C*H*$_3$)$_3$), 1.16 (s, 9H, -C(C*H*$_3$)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 166.2, 156.6, 153.0, 150.1, 148.0, 146.55, 144.1, 137.1, 136.4, 130.2, 129.45, 128.6, 128.5, 128.2, 128.15, 128.0, 127.7, 125.4, 123.14, 123.11, 123.0, 120.1, 117.4, 114.8, 110.6, 81.3, 80.3, 75.2, 71.3, 53.4, 52.2, 47.4, 47.0, 28.7, 27.9; FT-IR (thin film): υ (cm^{-1}) 3070, 3035, 2976, 2880, 1716 (C=O), 1585, 1490, 1424, 1367, 1338, 1210, 1164, 1077; HRMS (NESI) exact mass calculated for $C_{45}H_{48}O_8N$ requires *m/z* 730.3374, found *m/z* 730.3376 $[M+H]^+$.

4.1.13. 3-(3-(4,4,5,5-Tetramethyl-1,3-dioxolan-2-yl)phenoxy) benzaldehyde (**34**)

A 20 mL microwave vial was charged with 3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenol **33** (1 g, 4.5 mmol), 3-bromobenzaldehyde (0.5 mL, 4.5 mmol), potassium carbonate (0.9 g, 6.75 mmol), 1,10-phenanthroline (162 mg, 0.90 mmol) and copper(I) iodide (86.0 mg, 0.45 mmol). Anhydrous pyridine (15 mL) was added *via* syringe. The vial was heated at 190 °C under microwave irradiation for 5 h after which it was allowed to cool to room temperature and diluted by addition of DCM (100 mL) in a 250 mL separating funnel. The solution was washed with aqueous saturated copper sulfate (100 mL), aqueous 1 M hydrochloric acid (100 mL), saturated brine (40 mL), and dried with magnesium sulfate. Filtering off the drying agent and removing the solvent afforded an oil that was purified *via* flash chromatography on silica gel (5% ethyl acetate in 40–60 petroleum ether. The product, a pale-yellow oil (67% yield), was analysed and confirmed to be the title compound (**34**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H, CHO), 7.60 (d, *J* 7.7 Hz, 1H, Ar-*H*), 7.51–7.46 (m, 2H, Ar-*H*), 7.37 (t, *J* 7.7 Hz, 1H, Ar-*H*), 7.31–7.26 (m, 2H, Ar-*H*), 7.21–7.18 (m, 1H, ArH), 6.99 (dd, *J* 7.7 and 2.1 Hz, 1H, ArH), 5.95 (s, 1H), 1.31 (s, 3H, CH_3), 1.25 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.6, 158.3, 156.2, 142.4, 138.1, 130.4, 130.0, 124.6, 124.5, 122.2, 119.5, 118.6, 117.2, 99.3, 83.0, 24.2, 22.2; FT-IR (thin film): υ (cm^{-1}) 2979, 1703, 1584, 1481; MS (MALDI) 365.2 $[M + K]^+$; HRMS (HNESP) exact mass calculated for $C_{20}H_{22}O_4$ requires *m/z* 327.1598 found *m/z* 327.1595 $[M+H]^+$.

4.1.14. (4,4,5,5-Tetramethyl)-2-(3-vinylphenoxy)phenyl)-1,3-dioxolane (**35**)

To a 50 mL flame dried round bottom flask, equipped with a magnetic stirrer bar, under nitrogen was added methyltriphenylphosphonium bromide (2.2 g, 6.13 mmol) in anhydrous tetrahydrofuran (30 mL) and the flask cooled to 0 °C. Sodium hydride (60% w/w in mineral oil [235 mg, 6.13 mmol]) was added and the mixture stirred at 0 °C for 10 min 3-(3(4,4,5,5-Tetramethyl-1,3-dioxolan-2-yl)phenoxy)benzaldehyde **34** (1 g, 3.06 mmol) was added and the mixture stirred at 0 °C for an additional 30 min. Diluting the reaction with ethyl acetate (100 mL), the solution was transferred to a 250 mL separating funnel, washed with saturated brine (100 mL), dried with magnesium sulfate, filtered and the solvent removed under reduced pressure. After solvent removal the largely pure material was passed through a plug of silica gel and eluted quickly with 20% diethyl ether in 40–60 petroleum ether. The pale-yellow oil (95% yield) was carried on to the synthesis of **35**.

4.1.15. Benzyl (R)-2-hydroxy-1-(3-(3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenoxy)phenyl)ethylcarbamate (**36**)

To a 25 mL round bottom flask, equipped with a magnetic stirrer bar, under nitrogen was added benzyl carbamate (489 mg, 3.24 mmol) and sodium hydroxide (129 mg, 3.24 mmol). 1-Propanol (4 mL) water (5 mL) was added *via* syringe and the mixture cooled to 0 °C. *Tert*-butyl hypochlorite (0.37 mL, 3.24 mmol) was added and the mixture stirred at 0 °C for 10 min. A solution of $(DHQD)_2PHAL$ (50.4 mg, 0.06 mmol) in 1-propanol (4 mL) was added, followed by 4,4,5,5-tetramethyl-2-(3-)3-vinylphenoxy)phenyl)-1,3-dioxolane **35** (350 mg, 1.08 mmol) in 1-propanol (4 mL). Adding potassium osmate dihydrate (15.9 mg, 0.04 mmol) the reaction was stirred for 3 h changing from deep green to yellow. Quenching it with saturated aqueous sodium sulfite (30 mL), it was diluted with ethyl acetate (50 mL) and transferred to a 250 mL separating funnel. The organic layer was separated, washed with saturated brine (40 mL), dried with magnesium sulfate, filtered and the solvent removed *in vacuo*. The product was purified *via* flash chromatography on silica agel (30% ethyl acetate in 40–60 petroleum ether) affording an oil in a 65% yield. A sample was submitted to chiral HPLC analysis [cellulose 1 *iso*-hexane/iso-propanol: 85/15 1 mL/min, 8.85 min (1st peak), 17.31 min (2nd peak, 96% *e.e.*)]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13–6.87 (m, 11H, Ar-*H*), 6.69 (s, 1H, Ar-*H*), 5.88 (s, 1H, Ar-*H*), 5.12 (s, 1H), 5.00 (s, 1H), 4.91 (s, 1H), 4.60 (s, 1H), 3.45 (m, 1H), 3.15 (m, 1H), 1.25 (s, 6H, 2 x CH_3), 1.21 (s, 6H, 2 x CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 157.2, 150.5, 141.5, 137.9, 136.9, 136.3, 134.4, 128.6, 128.5, 128.2, 128.17, 128.15, 128.0, 127.9, 117.5, 113.8, 99.6, 82.7, 75.3 72.9, 67.0, 48.4, 24.5, 22.25; $[\alpha]_D^{25}$ -15.1 (c 1.0 $CHCl_3$); FT-IR (thin film): υ (cm^{-1}) 3406, 3333, 2977, 1704 (C=O), 1584, MS (MALDI) 514.4 $[M + Na]^+$; HRMS (HNESP) exact mass calculated for $C_{29}H_{33}NO_6NH_4$ requires *m/z* 509.2646, found *m/z* 509.2655 $[M + NH_4]^+$.

4.1.16. Methyl (R)-2-(benzyloxycarbonylamino)-2-(3-(3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenoxy)phenyl)acetate (**38**)

To a 25 mL round bottom flask, equipped with a magnetic stirrer bar, under nitrogen was added benzyl (*R*)-2-hydroxy-1-(3-(3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenoxy)phenyl)ethylcarbamate **36** (0.3 g, 0.61 mmol). Acetone (10 mL) and aqueous sodium bicarbonate solution (5 mL) were added and the mixture cooled to 0 °C. To this was added sequentially sodium bromide (8 mg, 0.07 mmol) and TEMPO (105 mg, 0.67 mmol). Sodium hypochlorite (11% chlorine) (1.03 mL, 1.83 mmol) was added dropwise *via* syringe over a period of 10 min, while the mixture was vigorously stirred and maintained at 0 °C. After 3 h, acetone was removed under reduced pressure, the residue diluted with water (10 mL), transferred into a 50 mL separating funnel and washed with ether (2 × 20 mL). The aqueous phase was acidified to pH 4 and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with saturated brine (10 mL), dried, filtered and the solvent removed *in vacuo* to yield a colourless oil (87% yield). Without purification the oil was added to a 50 mL round bottom flask equipped with a stirrer bar, potassium carbonate (109 mg, 0.8 mmol) and anhydrous DMF (3 mL). Iodomethane was added *via* syringe and the reaction stirred for 2 h at ambient temperature. The reaction was diluted with ethyl acetate (50 mL), transferred to a

separating funnel and washed with water (50 mL) and saturated brine (30 mL). Drying the organics, the solvent was removed under reduced pressure and the crude material was isolated in a 92% yield and used directly in the synthesis of amine **37**.

4.1.17. Methyl (R)-2-amino-2(3-(3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenoxy)phenyl)acetate (**38**)

To a 25 mL round bottom flask, equipped with a stirrer bar, was added under nitrogen **37** (200 mg, 0.39 mmol) and 10% palladium on carbon (41 mg, 0.04 mmol). Ethyl acetate was added (5 mL) and the flask sealed with a suba-seal. A balloon of hydrogen was attached, and the reaction stirred vigorously for 2 h at ambient temperature. After which it was filtered through a short plug of silica gel eluting with ethyl acetate (10 mL). The solvent was removed under reduced pressure affording a colourless oil in an 88% yield. Subsequent physicochemical analysis confirmed this to be the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.21 (M, 3H, Ar-H), 7.19–6.83 (m, 5H, Ar-*H*), 5.87 (s, 1H), 4.51 (s, 1H), 3.63 (s, 3H), 1.85 (br s, 2H, N*H*$_2$), 1.23 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 157.8, 141.0, 129.0, 128.7.0, 120.5, 120.4, 118.1, 117.1, 116.4, 116.0, 98.4, 81.8, 57.4, 51.4, 23.25, 21.15; FT-IR (thin film): υ (cm^{-1}) 3389 (NH_2), 2978 (C–H), 1740 (*ester and aldehyde* C=O), 1585, 1484, 1253, 1157, 1063; MS (MALDI-TOF) *m/z* 424.3 $[M+K]^+$; HRMS (HNESP) exact mass calculated for $C_{22}H_{28}O_5N$ requires *m/z* 386.1962, found *m/z* 386.1964 $[M+H]^+$.

4.1.18. Methyl 4-(benzyloxy)-3,5-bis(4-formylphenoxy)benzoate (**39**)

A 250 mL round-bottom flask was charged with a solution of **22** (3.01 g, 7.65 mmol, 1 equiv.) in *N*,*N*-dimethylformamide (50 mL) under a nitrogen atmosphere. Potassium carbonate (712 mg, 11.5 mmol, 1.5 equiv.) was added in one portion, followed by the addition of benzyl bromide (0.91 mL, 7.65 mmol, 1 equiv.) *via* a 2 mL syringe. The mixture was stirred at room temperature for 18 h before being transferred to a 250 mL separating funnel containing 1 M aqueous hydrochloric acid (100 mL). The organics were extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with water (3 × 100 mL) and subsequently brine (100 mL). The organic layer was dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification *via* flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 30%; R_f 0.38) afforded a pale-yellow solid whose physicochemical characteristics were consistent with those of the title compound **39** (3.21 g, 6.64 mmol, 87% yield).

M.p. 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 2H, -C*H*O), 7.79 (d, *J* 8.8 Hz, 4H, Ar-*H*), 7.59 (s, 2H, Ar-*H*), 7.15–7.07 (m, 3H, Ar-*H*), 6.97–6.94 (m, 6H, Ar-*H*), 4.98 (s, 2H, -C*H*$_2$Ph), 3.80 (s, 3H, -OC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 165.1, 162.2, 148.5, 147.0, 135.75, 132.03, 131.8, 128.4, 128.3, 128.1, 126.4, 120.3, 116.9, 75.6, 52.5; FT-IR (thin film): υ (cm^{-1}) 3069 (C–H), 2956 (C–H), 2835 (C–H), 2745 (C–H), 1724 (d) (*ester and aldehyde* C=O), 1602, 1503, 1422, 1337, 1229, 1157; MS (MALDI-TOF) *m/z* 505.0 $[M+Na]^+$, 520.96 $[M+K]^+$; HRMS (NESP) exact mass calculated for $C_{29}H_{22}O_7Na$ requires *m/z* 505.1258, found *m/z* 505.1250 $[M+Na]^+$.

4.1.19. rac, cis-Di-tert-butyl 3,3'-(((2-(benzyloxy)-5-(methoxycarbonyl)-1,3-phenylene)bis(oxy))bis(4,1-phenylene)) bis(1-(2-(tert-butoxy)phenyl)aziridine-2-carboxylate) (**40**)

A 5 mL microwave vial containing 4 Å molecular sieves was flame-dried and cooled under a flow of nitrogen. A solution of methyl 4-(benzyloxy)-3,5-*bis*(4-formylphenoxy)benzoate **39** (100 mg, 0.21 mmol, 1 equiv.) and 2-*tert*-butoxyaniline (67 mg, 0.40 mmol, 1.95 equiv.) in dry chloroform (1.5 mL) was added, along with a magnetic stirrer bar. The vial was sealed with a PTFE-lined aluminium crimp cap and the reaction mixture was stirred slowly at room temperature for 18 h. Pyridinium triflate (5 mg, 0.021 mmol, 10 mol%) was added, and the vial was resealed before being cooled to −30 °C in a chiller bath. *Tert*-butyl diazoacetate (32 μL, 0.23 mmol, 2.2 equiv.) was added *via* a 100 μL syringe and the mixture was stirred at −30 °C for 16 h. After warming to room temperature, the solution was filtered through a short plug of silica, eluting with diethyl ether (3 × 5 mL). The solvent was removed *in vacuo*, and purification *via* flash column chromatography on silica gel (eluent: petroleum ether/diethyl ether/dichloromethane 7:2:1; R_f = 0.26) afforded a white solid whose physicochemical properties were consistent with those of the title compound **40** (224 mg, 0.22 mmol, 59% yield).

M.p. 78–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* 8.6 Hz, 4H, Ar-*H*), 7.34 (s, 2H, Ar-*H*), 7.33–7.24 (m, 4H, Ar-*H*), 7.05–6.87 (m, 13H, Ar-*H*), 5.11 (s, 2H, -C*H*$_2$Ph), 3.71 (s, 3H, -CO_2C*H*$_3$), 3.40 (d, *J* 6.7 Hz, 2H, *aziridine* C–*H*), 2.99 (d, *J* 6.7 Hz, 2H, *aziridine* C–*H*), 1.33 (s, 18H, -C(C*H*$_3$)$_3$), 1.17 (s, 18H, -C(C*H*$_3$)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 165.65, 156.2, 150.7, 148.0, 146.5, 145.4, 136.7, 132.0, 130.6, 129.6, 128.5, 128.3, 128.27, 128.2, 125.6, 123.2, 123.15, 123.0, 120.95, 117.7, 117.6, 116.8, 116.4, 81.4, 80.4, 75.35, 52.2, 47.4, 47.0, 28.7, 27.9; FT-IR (thin film): υ (cm^{-1}) 2979 (C–H), 1721 (C=O), 1582, 1494, 1423, 1368, 1334, 1260, 1216, 1161, 1043, 978, 846; MS (MALDI-TOF) *m/z* 1005.25 $[M]^+$; HRMS (NESP) exact mass calculated for $C_{61}H_{72}N_3O_{11}$ requires *m/z* 1022.5161, found *m/z* 1022.5169 $[M + NH_4]^+$.

4.1.20. rac, cis-tert-Butyl 3-(4-(2-(benzyloxy)-3-(4-formylphenoxy)-5-(methoxycarbonyl)phenoxy)phenyl)-1-(2-(tert-butoxy)phenyl)aziridine-2-carboxylate (**41**)

A by-product was isolated during the flash column chromatography (R_f = 0.23); this was identified as *rac*, *cis*-*tert*-butyl 3-(4-(2-(benzyloxy)-3-(4-formylphenoxy)-5-(methoxycarbonyl)phenoxy)phenyl)-1-(2-(*tert*-butoxy)phenyl)aziridine-2-carboxylate **41** (64 mg, 0.087 mmol, 23% yield; R_f = 0.23).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H, -C*H*O), 7.77 (d, *J* 8.8 Hz, 2H, Ar-*H*), 7.49–6.89 (m, 17H, Ar-*H*), 5.04 (s, 2H, -C*H*$_2$Ph), 3.76 (s, 3H, -CO_2C*H*$_3$), 3.42 (d, *J* 6.7 Hz, 1H, *aziridine* C–*H*), 3.00 (d, *J* 6.7 Hz, 1H, *aziridine* C–*H*), 1.50 (s, 9H, -C(C*H*$_3$)$_3$), 1.17 (s, 9H, -C(C*H*$_3$)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.8, 167.0, 165.4, 162.6, 155.9, 151.0, 148.2, 148.0, 146.4, 146.2, 136.2, 132.0, 131.6, 131.5, 131.0, 129.7, 128.3, 128.29, 126.0, 123.1, 123.08, 120.9, 118.7, 118.0, 117.7, 116.8, 81.4, 80.4, 75.4, 52.4, 47.4, 46.9, 28.7, 27.9; FT-IR (thin film): υ (cm^{-1}) 3063 (C–H), 2978 (C–H), 1724 (*ester* C=O), 1699 (*aldehyde* C=O), 1580, 1504, 1491, 1452, 1422, 1392, 1368, 1333, 1306, 1223, 1157, 1040, 1005; MS (MALDI-TOF) *m/z* 782.1 $[M+K]^+$; HRMS (HNESP) exact mass calculated for $C_{45}H_{46}NO_9$ requires *m/z* 744.3167, found *m/z* 744.3165 $[M+H]^+$.

4.1.21. Methyl 4-(benzyloxy)-3,5-bis(4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenoxy)benzoate (**42**)

A 100 mL two-neck round-bottom flask was charged with a solution of methyl 4-(benzyloxy)-3,5-*bis*(4-formylphenoxy)benzoate **39** (1.0 g, 2.55 mmol, 1 equiv.) in dry toluene (40 mL). The flask was fitted with a Dean-Stark apparatus and reflux condenser under a nitrogen atmosphere. Pinacol (692 mg, 5.86 mmol, 2.3 equiv.) and *para*-toluenesulfonic acid (20 mg, 0.11 mmol, 5 mol%) were added, and the solution heated at reflux for 6 h. After cooling to room temperature, triethylamine (0.1 mL, 0.72 mmol, 0.3 equiv.) was added *via* a 1 mL syringe and the solution stirred for a further 30 min before the solvent was removed *in vacuo*. Purification *via* flash column chromatography on silica gel (eluent: petroleum ether/diethyl ether 1:1; R_f = 0.58) afforded a white solid whose physicochemical properties were consistent with those of the title compound **42** (1.50 g, 2.19 mmol, 86% yield).

M.p. 132–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* 8.7 Hz,

4H, Ar-*H*), 7.41 (s, 2H, Ar-*H*), 7.24–7.12 (m, 5H, Ar-*H*), 6.88 (d, *J* 8.7 Hz, 4H, Ar-*H*), 5.90 (s, 2H, -C*H*- *pin.*), 5.04 (s, 2H, -CH_2Ph), 3.73 (s, 3H, -CO_2CH_3), 1.26 (s, 12H, -C(CH_3)$_2$-), 1.22 (s, 12H, -C(CH_3)$_2$-); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 157.3, 150.3, 145.9, 136.5, 134.8, 128.5, 128.3, 128.15, 128.1, 125.7, 117.7, 117.4, 99.6, 82.7, 75.3, 52.3, 24.5, 22.3; FT-IR (thin film): υ (cm^{-1}) 2980 (C–H), 2932 (C–H), 2877 (C–H), 1727 (C=O), 1614, 1583, 1504, 1453, 1425, 1391, 1380, 1373, 1332, 1222, 1157, 1075, 1040, 1006; MS (MALDI-TOF) *m/z* 681.7; HRMS (HNESP) exact mass calculated for $C_{41}H_{50}O_9N$ requires *m/z* 700.3480, found *m/z* 700.3496 $[M + NH_4]^+$.

4.1.22. (4-(Benzyloxy)-3,5-bis(4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenoxy)phenyl) aldehyde (**43**)

4.1.22.1. Part 1. To a flame-dried 250 mL round-bottom flask was added lithium aluminium hydride (118 mg, 3.11 mmol, 2.5 equiv.) and dry tetrahydrofuran (40 mL) under a nitrogen atmosphere. The mixture was cooled to −15 °C using an salt ice bath before a solution of methyl 4-(benzyloxy)-3,5-*bis*(4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenoxy)benzoate **42** (2.62 g, 4.56 mmol, 1 equiv.) in tetrahydrofuran (15 mL) was added dropwise *via* a 20 mL syringe. The mixture was allowed to warm to 0 °C and stirred for 2 h. On complete disappearance of the starting material by thin layer chromatography (petroleum ether/diethyl ether 1:1), ethyl acetate (50 mL) and 1 M aqueous sodium hydroxide (50 mL) were added simultaneously in small portions while maintaining the temperature at 0 °C. The reaction mixture was transferred to a 500 mL separating funnel and the aqueous phase extracted with ethyl acetate (2 × 75 mL). The combined organic phases were washed with brine (150 mL), dried over magnesium sulfate, filtered, and the solvent removed *in vacuo* affording a colourless oil whose physicochemical properties were consistent with those of the title compound (2.42 g, 4.42 mmol, 97% yield); no further purification was required.

R_f = 0.21 (eluent: petroleum ether/diethyl ether 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* 8.6 Hz, 4H, Ar-*H*), 7.22–7.15 (m, 5H, Ar-*H*), 6.97 (d, *J* 8.6 Hz, 4H, Ar-*H*), 6.73 (s, 2H, Ar-*H*), 5.97 (s, 2H, -C*H*-*pin.*), 5.01 (s, 2H, -CH_2Ph), 4.48 (s, 2H, -CH_2OH), 1.33 (s, 12H, -C(CH_3)$_2$-), 1.29 (s, 12H, -C(CH_3)$_2$-); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 150.8, 141.1, 137.2, 137.0, 134.5, 128.6, 128.3, 128.1, 128.1, 117.9, 114.4, 99.8, 82.8, 75.4, 64.5, 24.6, 22.3; FT-IR (thin film): υ (cm^{-1}) 3458 (O–H), 2984 (C–H), 2932 (C–H), 2877 (C–H), 1610, 1586, 1507, 1435, 1370, 1322, 1219, 1154, 1075, 1034, 989; MS (MALDI-TOF) *m/z* 693.12 $[M+K]^+$; HRMS (HNESP) exact mass calculated for $C_{40}H_{50}O_8N$ requires *m/z* 672.3530, found *m/z* 672.3531 $[M + NH_4]^+$.

4.1.22.2. Part 2. A 250 mL round-bottom flask was charged with a solution of 4-(benzyloxy)-3,5-bis(4-(dimethoxymethyl)phenoxy) benzyl alcohol (447 mg, 0.68 mmol, 1 equiv.) in anhydrous dichloromethane (50 mL) under a nitrogen atmosphere. Activated manganese dioxide (1.19 g, 13.7 mmol, 20 equiv.) was added in small portions and the mixture stirred at room temperature for 18 h. On confirmation of the complete disappearance of starting material by thin layer chromatography (eluent: petroleum ether/ethyl acetate 20%), the mixture was filtered through celite and the solvent removed *in vacuo*. Purification *via* flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 20%; R_f = 0.38) afforded a white solid whose physicochemical characteristics were consistent with those of the title compound **43** (307 mg, 0.47 mmol, 69% yield).

M.p. 118–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1H, -C*H*O), 7.43 (d, *J* 8.6 Hz, 4H, Ar-*H*), 7.19–7.13 (m, 7H, Ar-*H*), 6.92 (d, *J* 8.6 Hz, 4H, Ar-*H*), 5.91 (s, 2H), 5.12 (s, 2H), 1.27 (s, 12H, -C(CH_3)$_2$-), 1.23 (s, 12H, -C(CH_3)$_2$-); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.7, 156.9, 151.3, 146.8, 136.4, 135.4, 132.0, 128.5, 128.3, 128.27, 128.22, 118.1, 118.05, 116.45, 116.4, 99.5, 82.8, 75.3, 24.5, 22.3; FT-IR (thin film): υ (cm^{-1}) 2977 (C–H), 2936 (C–H), 2864 (C–H), 1696 (C=O), 1614, 1579, 1507, 1435, 1377, 1325, 1222, 1150, 1119, 1075, 1044; MS (MALDI-TOF) *m/z* 691.44 $[M+K]^+$; HRMS (HNESP) exact mass calculated for $C_{40}H_{48}O_8N$ requires *m/z* 670.3374, found *m/z* 670.3390 $[M + NH_4]^+$.

4.1.23. 4,4'-((2-(Benzyloxy)-5-vinyl-1,3-phenylene)bis(oxy)) bis((dimethoxymethyl)benzene) (**44**)

A 250 mL round-bottom flask under a nitrogen atmosphere was charged with methyl triphenylphosphonium bromide (1.09 g, 3.06 mmol, 4 equiv.) and tetrahydrofuran (40 mL). The suspension was stirred while being cooled to 0 °C in an ice bath before the addition of sodium hydride (60% in mineral oil, 122 mg, 3.06 mmol, 4 equiv.). After 1 h, a solution of 4-(benzyloxy)-3,5-*bis*(4-(dimethoxymethyl)phenoxy)benzaldehyde **43** (500 mg, 0.77 mmol, 1 equiv.) in tetrahydrofuran (10 mL) was added dropwise to the flask *via* a 20 mL syringe, and the resulting mixture stirred at 0 °C for a further 3 h or until complete disappearance of the starting material by thin layer chromatography (eluent: petroleum ether/ethyl acetate 20%). Diethyl ether (75 mL) was added, and the mixture transferred to a 500 mL separating funnel containing cold distilled water (100 mL). The aqueous phase was extracted with diethyl ether (2 × 100 mL) and the combined organic layers washed with brine (150 mL) before being dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification *via* flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 20%; R_f = 0.53) afforded a white solid whose physicochemical properties were consistent with those of the title compound **44** (379 mg, 0.58 mmol, 76% yield).

M.p. 116–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* 8.6 Hz, 4H, Ar-*H*), 7.14–7.07 (m, 5H, Ar-*H*), 6.90 (d, *J* = 8.6 Hz, 4H, Ar-*H*), 6.74 (s, 2H, Ar-*H*), 6.40 (dd, *J* 17.5, 11.0 Hz, 1H, -C*H*=CH_2), 5.90 (s, 2H, -C*H*- *pin.*), 5.45 (dd, *J* 17.5, 0.4 Hz, 1H, -CH=CH_2), 5.08 (d, *J* = 11.0 Hz, 1H, -CH=CH_2), 4.93 (s, 2H, -CH_2Ph), 1.27 (s, 12H, -CH(CH_3)$_2$-), 1.22 (s, 12H, -CH(CH_3)$_2$-); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 150.4, 141.7, 136.9, 135.3, 134.3, 133.8, 128.5, 128.2, 128.0, 127.95, 117.5, 114.4, 114.2, 99.7, 82.7, 75.3, 24.5, 22.3; FT-IR (thin film): υ (cm^{-1}) 2983 (C–H), 2928 (C–H), 2855 (C–H), 1610, 1569, 1503, 1428, 1410, 1390, 1321, 1228, 1155, 1076, 1031, 990; MS (MALDI-TOF) *m/z* 689.69 $[M+K]^+$; HRMS (HNESP) exact mass calculated for $C_{41}H_{50}O_7N$ requires *m/z* 668.3582, found *m/z* 668.3581 $[M + NH_4]^+$.

4.1.24. 4,4'-(2-(Benzyloxy)-5-vinyl-1,3-phenylene)bis(oxy) dibenzaldehyde (**44**)

A 5 mL microwave vial was charged with a colourless solution of 4,4'-((2-(benzyloxy)-5-vinyl-1,3-phenylene)*bis*(oxy))*bis*((dimethoxymethyl)benzene) **43** (50 mg, 0.08 mmol, 1 equiv.) in tetrahydrofuran (1 mL). 1 M aqueous hydrochloric acid (1 mL) was added, and the solution was heated at 50 °C with stirring for 3 h. On complete disappearance of the starting material by thin layer chromatography (eluent: petroleum ether/ethyl acetate 20%), the organic solvent was removed *in vacuo* and the residue extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification *via* flash column chromatography on silica gel (eluent: petroleum ether/diethyl ether 50%; R_f = 0.31) afforded a white solid whose physicochemical characteristics were consistent with those of the title compound **44** (31 mg, 0.069 mmol, 90% yield).

M.p. 101–103 °C; ^{1}H NMR (400 MHz, CDC_3) δ 9.92 (s, 2H, -C*H*O), 7.82 (d, *J* 8.6 Hz, 4H, Ar-*H*), 7.16–6.94 (m, 11H, Ar-*H*), 6.59 (dd, *J* 17.5, 11.0 Hz, 1H, -C*H*=CH_2), 5.65 (d, *J* 17.5 Hz, 1H, -CH=CH_2), 5.29 (d, *J* 11.0 Hz, 1H, -CH=CH_2), 4.92 (s, 2H, -CH_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 162.7, 148.75, 142.8, 136.1, 134.7, 132.0, 131.5, 128.2, 128.16, 117.0, 116.7, 115.4, 75.6; FT-IR (thin film): υ (cm^{-1}) 3070,

3033, 2834, 2741, 1696 (C=O), 1600, 1585, 1569, 1501, 1454, 1430, 1408, 1321, 1225, 1154, 1104, 1057, 1026; MS (MALDI-TOF) *m/z* 473.32 $[M+Na]^+$; HRMS (HNESP) exact mass calculated for $C_{29}H_{26}O_5N$ requires *m/z* 468.1805, found *m/z* 468.1802 $[M + NH_4]^+$.

*4.1.25. tert-Butyl 3-(4-(2-(benzyloxy)-3-(4-formylphenoxy)-5-vinylphenoxy)phenyl)-1-(2-tert-butoxyphenyl)aziridine-2-carboxylate (**46**)*

A 5 mL microwave vial containing crushed 4 Å molecular sieves was flame-dried and cooled under nitrogen. The vial was charged with 4,4'-((2-(benzyloxy)-5-vinyl-1,3-phenylene)*bis*(oxy))dibenzaldehyde **45** (100 mg, 0.22 mmol, 1 equiv.) and a solution of 2-*tert*-butoxyaniline (36 mg, 0.22 mmol, 0.98 equiv.) in chloroform (1 mL). The mixture was stirred at room temperature for 16 h. Pyridinium triflate (5 mg, 0.02 mmol, 10 mol%) was added, and the vial sealed with a PTFE-lined aluminium crimp cap. *Tert*-butyl diazoacetate (31 μL, 0.22 mmol, 1 equiv.) was added dropwise *via* syringe. The mixture was stirred at room temperature for a further 16 h and filtered through a short plug of silica gel, eluting with diethyl ether (3 × 5 mL). The solvent was removed *in vacuo* to afford a brown oil. Purification *via* flash column chromatography on silica gel (eluent: petroleum ether/diethyl ether/dichloromethane (8:1:1); R_f 0.20) afforded a pale red liquid whose physicochemical properties were consistent with those of the title compound **46** (46 mg, 0.025 mmol, 49%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H -C*H*O), 7.81 (d, *J* 8.7 Hz, 2H, Ar-*H*), 7.54 (d, *J* 8.7 Hz, 2H, Ar-*H*), 7.26–6.83 (m, 15H, Ar-*H*), 6.49 (dd, *J* 10.9, 17.5 Hz, 1H, -C*H*=CH_2), 5.58 (d, *J* 17.5 Hz, 1H, -CH=C*H*$_2$), 5.22 (d, *J* 10.9 Hz, 1H, -CH=C*H*$_2$), 5.00 (s, 2H, -C*H*$_2$Ph), 3.48 (d, *J* 6.7 Hz, 1H, *aziridine* -C*H*-), 3.05 (d, *J* 6.7 Hz, 1H, *aziridine* -C*H*-), 1.38 (s, 9H, -C(C*H*$_3$)$_3$), 1.23 (s, 9H, -C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 167.2, 163.2, 156.5, 151.4, 148.6, 148.1, 146.6, 142.0, 136.8, 135.3, 134.4, 132.15, 131.4, 130.7, 129.7, 128.5, 128.4, 128.3, 123.3(2), 123.2, 121.1, 117.8, 116.7, 115.3, 115.0, 114.9, 81.5, 80.5, 75.65, 47.55, 47.2, 28.9, 28.1; FT-IR (thin film): υ (cm^{-1}) 3065, 3033, 2976, 2930, 2733, 2250, 1744 (*ester* C=O), 1696 (*aldehyde* C=O), 1596, 1584, 1568, 1490, 1452, 1428, 1407, 1392, 1367, 1319, 1225, 1155, 1111, 1028; HRMS (HNESP) exact mass calculated for $C_{45}H_{46}NO_7$ requires *m/z* 712.3269, found *m/z* 712.3265 $[M+H]^+$.

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Appendix A. Supplementary data

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[18] Crystallographic Data (Excluding Structure Factors) for the Structures in This Paper Have Been Deposited with the Cambridge Crystallographic Data Centre as Supplementary Information Witht the Following Numbers CCDC 1895463 (**22**), CCDC 1895459 (**39**) and CCDC 1895499 (**43**). Copies of the Data Can Be Obtained, Free of Charge, on Application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).