ROYAL SOCIETY OF CHEMISTRY

Journal Name

ARTICLE

Synthesis of the Natural Product Descurainolide and Cyclic Peptides from Lignin-derived Aromatics

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Alternative sources of potential feedstock chemicals are of increasing importance as the availability of oil decreases. The biopolymer lignin is viewed as a source of useful mono-aromatic compounds as exemplified by the industrial scale production of vanillin from this biomass. Alternative lignin-derived aromatics are available in pure form but to date examples of the use of these types of compounds are rare. Here we address this issue by reporting the conversion of an aromatic keto-alcohol to the *anti-* and *syn-*isomers of Descurainolide A. The key step involves a rhodium-catalyzed allylic substitution reaction. Enantio-enriched allylic alcohols were generated *via* an isothiourea-catalyzed kinetic resolution enabling access to both the (2*R*,3*R*) and (2*S*,3*S*) enantiomers of *anti-*Descurainolide A. In addition we show that the lignin-derived keto-alcohols can be converted into unnatural amino acid derivatives of tyrosine. Finally, these amino acids were incorporated into cyclic peptide scaffolds through the use of both chemical and an enzyme-mediated macrocylisation.

Introduction

Lignin is the second most abundant naturally occurring polymer after cellulose.[1] At present, only 1-2% of industrially produced lignin is converted into commercial products with the rest being used as a low value fuel.[1] It is clear that applications of this renewable material remain underexplored.[2] The large number of aromatic units present in lignin has inspired methods to obtain substituted-phenolic building blocks.[3,4] Whilst considerable efforts have been channelled into lignin depolymerisation,[5] many of these processes lead to major separation challenges if pure aromatic building blocks are required.[6,7] An alternative approach investigates the processing of native lignins[8] through the use of highly selective catalytic transformations.[9] The advantage of this second approach is that it delivers pure monomers albeit with moderate lignin conversions. However, this approach will only be viable in an industrial context if the pure monomers are useful.[10,11] Recently we have shown that phenolic monomer **1** can be obtained *via* the selective oxidation of lignin's β-O-4 units at the benzylic alcohol and subsequent C-O bond cleavage (Scheme 1A).[11] Monomer **1** was obtained *in pure form* from birch lignin. Here, in the first part of the work, we report the use of the renewable keto-alcohol **1** as a starting point in natural product synthesis, specifically, a natural product that contains an electron-rich aromatic ring (from **1** via **2** to **3**, Scheme 1B). In a second novel application of renewable building block **1** and its analogue **4**, we also report the synthesis of the unnatural tyrosine derivatives **5** and **6**. This section of work culminates in the incorporation of **5** and **6** into cyclic peptides **7** and **8**.
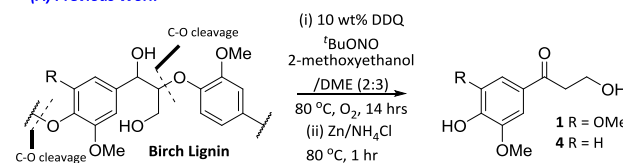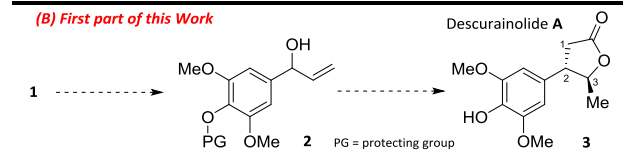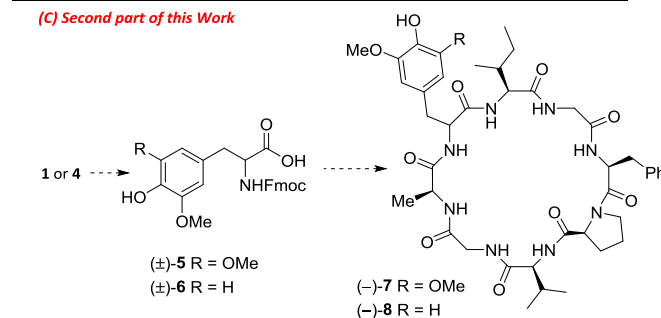

Scheme 1A: Key steps in the depolymerisation of lignin to give the aromatic monomer 1. **1B**: Planned application of **1** in the synthesis of a natural product **3** via **2**. **1C**: Planned application of **1** and **4** in the formation of an unnatural amino acids which are subsequently incorporated into cyclic peptide scaffolds.

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Electronic Supplementary Information (ESI) available: Detailed synthetic procedures and data for novel compounds. See DOI: 10.1039/x0xx00000x

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Descurainolide A (**3**) is a natural product isolated from the seeds of the plant *Descurainia Sophia*.[12] It contains a five-membered lactone ring and a 2,6-dimethoxy-phenol ring analogous to that in **1**.[12] The absolute stereochemistry of **3** is currently not assigned.[12] Whilst no biological activity has been directly associated with **3** to date, extracts from the seeds of the *D. Sophia* plant have been used to treat coughs, asthma and oedema.[12] Uses as a cardiotonic or in cancer therapy have also been proposed.[12] The synthesis of highly enantio-enriched samples of both enantiomers of **3** was viewed as important as it should: i) showcase the use of the renewable monomer **1**; ii) provide both enantiomers of **3** for biological assessment and iii) enable the assignment of the absolute configuration of the natural product. We envisaged that the construction of the lactone ring in **9**, a potential precursor of **3**, could be achieved by diastereoselective iodolactonisation[13] of a suitably protected γ-olefinic ester **10**. Compound **10** could be obtained by hydrolysis of one of the esters in **11** followed by decarboxylation of the resulting carboxylic acid (Scheme 2). Compound **11** is the expected product of a transition metal-catalyzed allylic substitution reaction between dimethyl malonate and allylic carbonate **12**.[14] This reaction would enable the selective formation of the C1-C2 bond, delivering the required branched allylic system.[15] Although, our initial study was aimed at racemic **3**, this reaction is known to proceed with retention of stereochemistry at the allylic center. This should enable access to either enantiomer of **3**, provided highly enantio-enriched forms of **12** are available (*vide infra*). The allylic carbonate **12** could be obtained from **2** (Scheme 1B), which in turn could be prepared from our lignin-derived monomer **1**. Previously, we have shown that **13** can be obtained in one step from **1**.[12] Whilst electron-rich substituents in aromatics of the general structure **2** are tolerated in the rhodium-catalyzed reaction,[16] to the best of our knowledge no examples of the use of trialkoxyaryl-substituents have been reported.
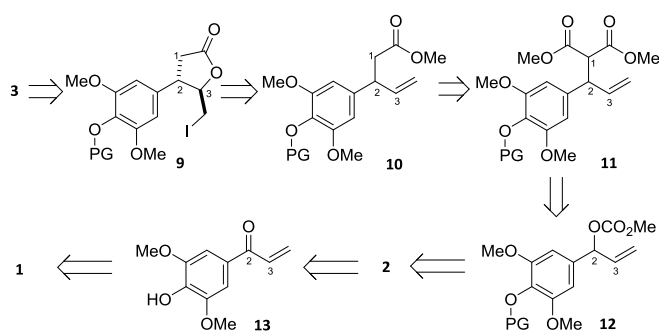
Scheme 2 Our Retrosynthetic Analysis of **3** from keto-alcohol **1**.

In contrast to the relatively small natural product **3**, cyclic peptides are, arguably, most suitable for targeting large sites.[17] Extended binding pockets or surfaces, for example protein-protein interactions,[18] are often considered "undruggable" by small molecules. Natural cyclic peptides, such as cyclosporin A

(an immunosuppressant drug), possess drug-like cell permeability and oral bioavailability that apparently defy the physicochemical requirements for bioavailability predicted by Lipinski's Rule of Five.[19] More recently, synthetic cyclic peptides have been used to investigate the relationship between macrocycle structure and cell permeability.[20]

Whilst some naturally occurring cyclic peptides contain modified amino acids (for example the patellamides[21] in which serine and threonine residues are processed to oxazoline and thiazoline/thiazole rings), synthetic chemistry has enabled a number of unnatural amino acids to be built into cyclic peptides. Through the production of the tyrosine analogues **5** and **6** from our keto-alcohols **1** and **4**, cyclic peptides containing these unnatural amino acids were prepared. Tyrosine analogues of this type are alternatively synthesized by employing tyrosine phenol lyases (TPL).[22a] In addition, unnatural amino acid analogues of Tyr, such as those containing aromatic methoxy groups are important to help investigate the role of Tyr in different enzymes (*e. g.* cytochrome c oxidase).[22b] The ability to separate diastereomeric cyclic peptides was also required here and enabled a detailed NMR study. Overall, through the use of two different applications, the utility of the lignin-derived keto-alcohols **1** and **4** was demonstrated.

Results and Discussion

Part 1: Application of 1 to Natural Product Synthesis

Initially, it was decided to use silyl-protection for the phenol in **13**. Treatment of **13** with TBSCl, followed by 1,2-reduction of the enone using NaBH$_4$ with CeCl$_3$.7H$_2$O[23] afforded allylic alcohol (±)-**2a**. To install the C1-C2 bond (**11**, Scheme 2), allylic carbonate (±)-**14a** was prepared by treating (±)-**2a** with LiHMDS and then methyl chloroformate. The choice of the allylic carbonate over allylic acetate was based on the observation that oxidative insertion, the first step of the transition metal catalyzed allylic substitution, is faster for allylic carbonates than for allylic acetates.[24] Also, the influence of leaving groups on the regioselectivity of the reaction (branched *versus* linear) has previously been studied.[25]
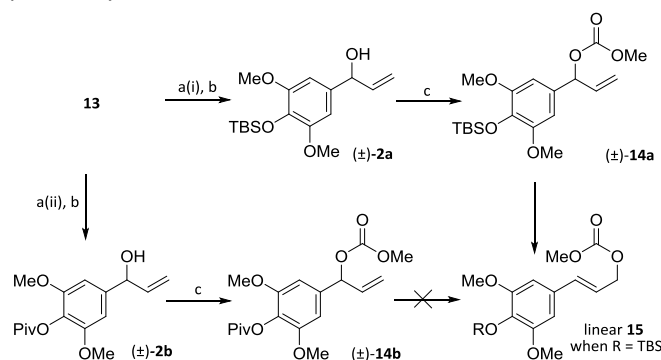

Scheme 3 Synthesis of Allylic Carbonates **14a** and **14b:** (a) (i) TBSCl, DMAP, Imidazole, DCM, rt, 1 h, 90% (ii) PivCl, DMAP, Imidazole, DCM, 1 h, 87% (b) NaBH$_4$, CeCl$_3$.9H$_2$O, MeOH, 1 h, 95% for **2a**, 91% for **2b** (c) Methyl chloroformate, LiHMDS, THF, 1 h, -10 °C, 15% for **14a**, 89% for **14b**. See Scheme S1 for more detail.

It was found that allylic carbonate (±)-**14a** was unstable on storage and purification on silica giving numerous compounds, one of which was the linear isomer **15** (Scheme 3).[26,27] It was therefore decided to use an electron-withdrawing substituent on the phenolic oxygen which led to the preparation of the stable pivolate-protected (±)-**14b** from **13**, via alcohol (±)-**2b**, (Scheme 3).[28] The exposure of (±)-**14b** to rhodium-catalyzed allylic substitution with dimethyl malonate (5 mol% of RhCl(PPh₃)₃ and 20 mol% of P(OMe)₃ in THF at 40 °C provided (±)-**16** in high yield (87%) as a single regioisomer (Schemes 4, S2 and Figure S1).[29]
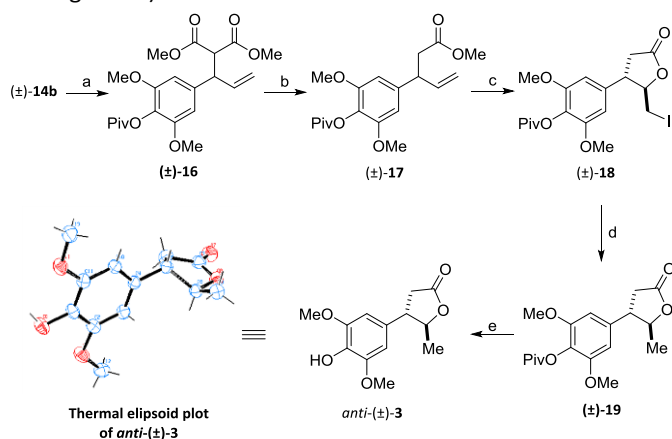
Scheme 4 Synthesis of *anti*-(±)-Descurainolide A: (a) NaH, Dimethyl malonate, RhCl(PPh₃)₃ (5 mol%), P(OMe)₃ (20 mol%), THF, 40 °C, 1 h, 87% (b) LiCl, H₂O, DMSO, 140 °C, 16 h, 76% (c) I₂, MeCN, 0 °C to rt, 46 h, 70% combined yield (d) Pd/C, H₂, NaOAc, MeOH, rt, 16 h, 86% (e) 2 M HCl/1,4-dioxane (1:1), 100 °C, 12 h, 70%. The thermal ellipsoid plot for *anti*-(±)-**3** is also shown at 50% ellipsoid probability.[30]

Treatment of purified (±)-**16** with LiCl in DMSO/H₂O afforded γ-olefinic ester (±)-**17** in 76% yield[31] and iodolactonisation using I₂/MeCN at 0 °C furnished (±)-**18** in a *anti:syn* ratio of 19:1 (Figure S2).[32] After careful separation, dehalogenation of *anti*-(±)-**18**, using Pd/H₂ and NaOAc in MeOH provided *anti*-(±)-**19** in 86% yield and removal of the Piv-group with 2M HCl/ 1,4-dioxane gave *anti*-(±)-Descurainolide A (**3**) in a 62% yield. X-ray crystallographic analysis of *anti*-(±)-**3** confirmed the bond connectivity and relative stereochemistry (Scheme 4).[30]
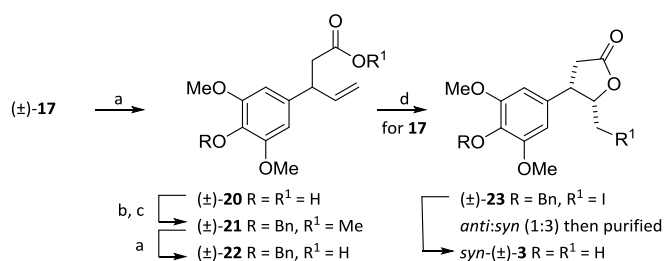
Scheme 5 Synthesis of *syn*-(±)-Descurainolide A: (a) 4 M NaOH, THF/MeOH (1:1), 100 °C, 92% for (±)-**15** and 90% for (±)-**17** (b) NaH, MeI, DMF, rt, 1 h, 95% (c) NaH, BnBr, DMF, rt, 1 h, 83% (d) I₂, NaHCO₃ (aq), DCM, rt, 12 h, 85% combined yield (e) Pd/C, H₂, NaOAc, MeOH, rt, 16 h, 62% *syn*-(±)-**3**.

Attempts to tune the iodolactonisation reaction of (±)-**17** to enable the preparation of sufficient amounts of *syn*-(±)-**18** en route to *syn*-(±)-**3** proved unsuccessful (Table S1). However, conversion of Piv-protected ester (±)-**17** via (±)-**20** and (±)-**21** to benzyl protected acid (±)-**22,** and subsequent iodolactonisation using I₂ and aqueous NaHCO₃ provided (±)-**23** in a *anti:syn* ratio of 1:3 (Figure S3) and 85% combined yield (Schemes 5 and S3). After careful separation, hydrogenolysis of *syn*-(±)-**23** over palladium on carbon gave *syn*-(±)-**3** in 62% yield. Detailed comparison of the NMR data associated with our samples of *anti*-(±)-**3** and *syn*-(±)-**3** with that reported for the isolated Descurainolide A[12] confirmed that the natural material had the proposed relative stereochemistry[12] (Table S2).

In an attempt to determine the absolute configuration of natural *anti*-**3**, access to both enantiomers of a protected lignin-derived allylic alcohol **2** was required. In this regard, acylative kinetic resolution is an attractive strategy as it would allow access to both enantiomers from the readily available racemate.[33] The Smith group has reported that the isothiourea HyperBTM **24** is an effective catalyst for the kinetic resolution of challenging aryl-alkenyl alcohols in which the catalyst must differentiate between two sp²-hybridized substituents during the selectivity-determining acylation step.[34] Moreover, this methodology is particularly effective for alcohols bearing electron-rich aryl rings, such as those derived from monomers of lignin.

To assess the applicability of this method for the preparation of enantiomerically enriched *anti*-**3**, the selectivity (S=k_{fast}/k_{slow}) for the kinetic resolution of a range of protected allylic alcohols **2a-f** was investigated (Table 1). Both tri- and disubstituted allylic alcohols **2a-d** bearing either *O*-silyl or *O*-pivaloyl protecting groups underwent highly selective kinetic resolution (S = 29-64) using isobutyric anhydride (0.6 eq) and HyperBTM **24** (1 mol%) in the presence of *i*Pr₂NEt in toluene at -78 °C (Table 1, entries 1-4).[34] Lower, but still synthetically useful, selectivity was obtained for alcohols **2e** and **2f** bearing *O*-tosyl and *O*-triflyl groups, respectively (Table 1, entries 5 and 6).

As the kinetic resolution of alcohol (±)-**2b** gave the highest selectivity, this process was performed on a preparative scale (3.4 mmol, 1.0 g). In this case, leaving the kinetic resolution to reach 57% conversion allowed (*S*)-**2b** to be isolated as a single enantiomer in 37% yield (Scheme 6), with the recovered isobutyrate ester (*R*)-**25b** (47% yield, 75% *ee*) readily hydrolysed with 1M KOH to give (*R*)-**2b** (75% *ee*). The enantiopurity of (*R*)-**2b** was further enhanced through a second kinetic resolution using enantiomeric (2*R*,3*S*)-HyperBTM (ent-**24**) to acylate selectively the remaining minor enantiomer, requiring only 20% conversion to obtain (*R*)-**2b** in 92% *ee*. Overall, highly enantiomerically enriched (*S*)- and (*R*)-**2b** could be obtained from (±)-**2b** in a combined 72% yield, demonstrating the powerful nature of acylative kinetic resolution.

With (*R*)-**2b** and (*S*)-**2b** in hand, the synthesis of both enantiomers of *anti*-**3** was achieved (Schemes 7 and S4). Conversion of (*S*)-**2b** into (*S*)-**14b** enabled the absolute configuration of (*S*)-**14b** to be confirmed by X-ray analysis (Figure S5). The subsequent Rh(I)-catalysed allylic substitution reaction was expected to proceed with retention of stereochemistry (double inversion) when soft nucleophiles (pK$_a$ < 22) are employed,[15] and with high conservation of enantiomeric excess (*cee*).[35] At 40 °C, we observed erosion of *ee*, from 99% (*S*)-**14b** to 83% of (*R*)-**16**. Perhaps at 40 °C the σ-π-σ

isomerisation between the two enantiomers of the π-allylrhodium(III) complex, which is reported to be slow,[15c] is slightly enhanced in this system. However, at ambient temperature, we obtained a high *cee* (~99%) for both (*R*)- and (*S*)-**16**.
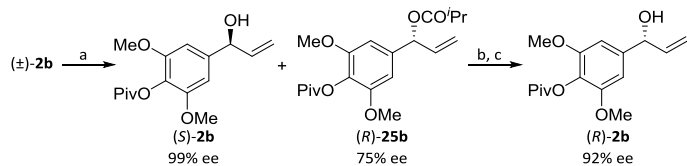
Scheme 6 Preparative kinetic resolution of (±)-**2b**: (a) (2*S*,3*R*)-HyperBTM **24** (1 mol%), (*iPrCO*)₂O (0.6 eq), *i*Pr₂NEt (0.5 eq), PhMe, −78 °C, 37% for (*S*)-**2b** and 47% for (*R*)-**25b**; (b) 1M KOH, MeOH/H₂O, rt, quant.; (c) (2*R*,3*S*)-HyperBTM (*ent*-**24**) (1 mol%), (*iPrCO*)₂O (0.15 eq), *i*Pr₂NEt (0.2 eq), PhMe, −78 °C, 75% for (*R*)-**2b**.

**Table 1** Kinetic resolution of allylic alcohols (±)-**2a**-**f**
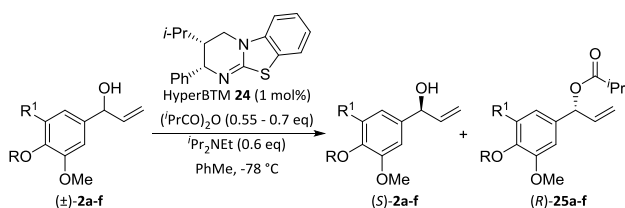
entry	R	R¹	conv. (%)^a	2 ee (%)^b (yield, %)	25 ee (%)^b (yield, %)	S^c
1	TBS	MeO	**2a** 56	99^d (44)	78 (50)	43
2	Piv	MeO	**2b** 57	99 (30)	75 (52)	64
3	TBS	H	**2c** 52	89 (39)	81 (43)	29
4	Piv	H	**2d** 53	97 (38)	85 (47)	49
5^e	Ts	MeO	**2e** 56	93 (36)	72 (41)	20
6	Tf	MeO	**2f** 44	55 (48)	71 (35)	10

^{a}Calculated by HPLC analysis. ^{b}Determined by HPLC analysis. ^{c}Calculated using the equations developed by Kagan.[36] ^{d}Proof of the absolute configuration of (*S*)-**2a** came from X-ray crystallographic analysis (Figure S4). ^{e}Reaction performed in THF.

Using the previously established protocols (*R*)- and (*S*)-**16** were converted to *anti*-(2*R*,3*R*)-**3** and *anti*-(2*S*,3*S*)-**3** respectively (Schemes 7 and S4 and Table S3). Chiral HPLC analysis of *anti*-(2*S*,3*S*) and *anti*-(2*R*,3*R*)-**3** and analysis of the two compounds by circular dichroism (Figure S7) demonstrated that the two samples of **3** were highly optically enriched enantiomers of each other. X-ray crystallographic analysis of *anti*-(2*R*,3*R*)-**3** (Figure S6) confirmed the allylic substitution reaction occurred with the precedented retention of configuration and the absolute configuration of *anti*-(2*R*,3*R*)-**3**.[15]

Repeated attempts to obtain a sample of the natural product from the group that originally isolated it were unsuccessful. This hindered our attempts to assign the absolute configuration of native Descuranolide A (**3**), due to the small values for the optical rotation of **3** that we observed and that are reported in the literature (Table

S3).[12] In summary of part 1, the renewable lignin-derived keto-alcohol **1** was converted to both of the potential diastereomers of the natural product **3** enabling confirmation of the relative stereochemistry. Assignment of the absolute configuration will require reisolation of the natural material due to the low optical rotation of **3**.
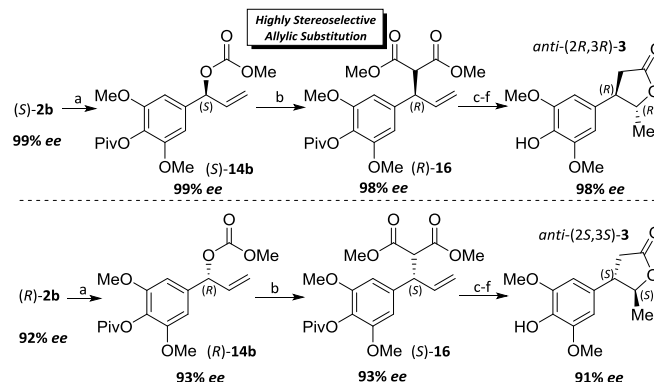
Scheme 7 Synthesis of *anti*-(2*R*,3*R*)- and *anti*-(2*S*,3*S*)-Descurainolide A (**3**): (a) Methyl chloroformate, LiHMDS, THF, 1 h, -10 °C; 95% for *R*-**14b**, 74% for *S*-**14b** (b) NaH, Dimethyl malonate, RhCl(PPh₃)₃ (5 mol%), P(OMe)₃ (20 mol%), THF, 22 °C, 16 h; 79% for *S*-**16**, 85% for *R*-**16** (c) LiCl, H₂O, DMSO, 140 °C, 16 h; 47% for *R*-**17**, 55% for *S*-**17** (d) I₂, MeCN, 0 °C to rt, 48 h; 45% for *anti*-(2*R*,3*S*)-**18**, 48% for *anti*-(2*S*,3*R*)-**18** (e) Pd/C, H₂, NaOAc, MeOH, rt, 16 h; 52% for *anti*-(2*R*,3*R*)-**19**, 59% for *anti*-(2*S*,3*S*)-**19** (f) 2 M HCl/1,4-dioxane (1:1), 100 °C, 12 h; 42% for *anti*-(2*S*,3*S*)-**3**, 61% for *anti*-(2*R*,3*R*)-**3**.

Part 2: Application of 1 and 4 to Cyclic Peptide Synthesis

Having demonstrated that renewable aromatic monomer **1** could be used as a starting point in natural product synthesis, we turned to our second application in the synthesis of unnatural amino and cyclic peptides. Both building blocks **1** and **4** (Scheme 1) were converted to their corresponding triols (±)-**26** and (±)-**27** in three synthetic steps (Schemes S5 and S7).[37]
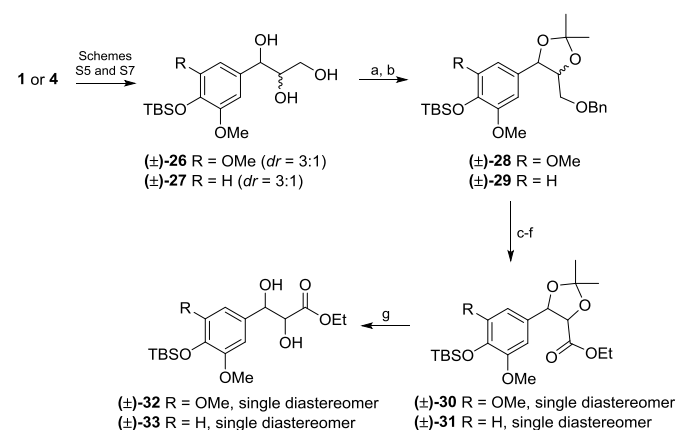

Scheme 8 ^{a}Reaction Conditions: (a) K₂CO₃, BnBr, DMF, rt, 3 h (b) 2,2-dimethoxypropane, *p*TSA.H₂O (catalytic), DCM; 91% for (±)-**28** and 89% for (±)-**29** over 2-steps (c) Pd/C (10% wt), H₂ gas, NaOAc, MeOH, rt, 12 h (d) Dess-Martin Periodinnane, DCM, rt, 2 h (e) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*BuOH/H₂O, rt, 12 h (f) SOCl₂, DCM then EtOH; 78% for (±)-**30** and 68% for (±)-**31** over 4-steps (g) *p*TSA.H₂O, 77% for (±)-**32** and 69% for (±)-**33**.

The primary alcohols in (±)-**26** and (±)-**27** were selectively protected as benzyl ethers, and the remaining diols were protected as acetals to give (±)-**28** and (±)-**29** (Scheme 8). After

careful separation, the major diastereoisomer (relative stereochemistry unassigned) of (±)-**28** and (±)-**29** respectively were subjected to debenzylation,[37a] Dess-Martin oxidation, [37b] Pinnick oxidation[37c] and esterification[37d] to furnish (±)-**30** and (±)-**31** in 78% and 68% over four steps. Subsequent removal of the acetal groups using pTSA.H_2O provided diol-esters (±)-**32** and (±)-**33** in 77% and 69%, respectively.[38]

Exposure of (±)-**32** and (±)-**33** to Et_3SiH and $BF_3.OEt_2$ in DCM at **-78 °C** for 2 h gave α-hydroxy esters (±)-**34** and (±)-**35** in moderate yields (Scheme 9).[39] This benzylic deoxygenation protocol was found to be very substrate dependent and this was the main factor that defined the route taken from **1** and **4** to **5** and **6** respectively. After conversion of the remaining alcohol in (±)-**34** and (±)-**35** to the corresponding tosylate using LiHMDS and TsCl, subsequent reaction with NaN_3 in DMF gave azido-esters (±)-**36** and (±)-**37** in 88% and 78% yields respectively. The reduction of the azide group was accomplished using Pd/C (10 wt%) in ethyl acetate under an atmosphere of H_2 gas. The treatment of the resulting crude amines with FmocCl then gave N-Fmoc protected amino esters (±)-**38** and (±)-**39** in 93% and 98% yields respectively. Hydrolysis of the ester and deprotection of the TBS-silyl ether occurred when (±)-**38** and (±)-**39** were refluxed in 2 M HCl:1,4-dioxane (1:1) for 12 h, furnishing N-Fmoc protected amino acids (±)-**5** in 72% yield and (±)-**6** in 76% yield.[40]
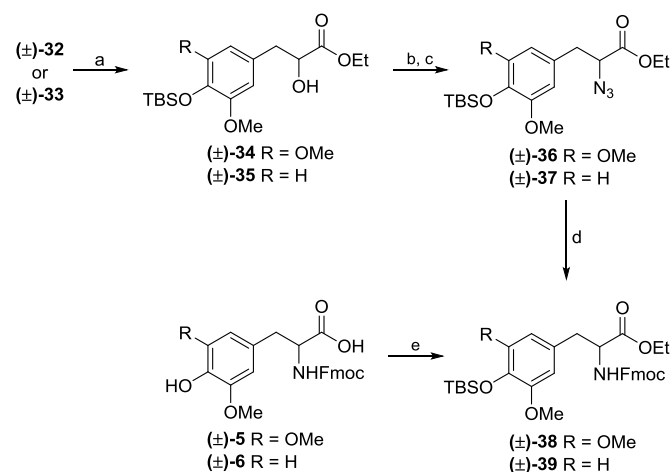

Scheme 9 (a) Et_3SiH, $BF_3.OEt_2$, DCM, -78 °C, 2 h, 56% for (±)-**34** and 66% for (±)-**35** (b) LiHMDS, TsCl, THF, rt, 1 h, 75% and 60% (c) NaN_3, DMF, rt, 3 h, 88% for (±)-**36** and 78% for (±)-**37** (d) (i) Pd/C (10% *wt*), H_2, EtOAc, 1 h (ii) FmocCl, THF, 1 h, 93% for (±)-**38** and 98% for (±)-**39** (e) 2 M HCl:1,4-dioxane (1:1), 100 °C, 12 h, 72% for (±)-**5** and 76% for (±)-**6**.

At this stage, the application of the S- and G- functionalized lignin phenolic monomers **1** and **4** in the synthesis of N-Fmoc protected unnatural amino acids has been demonstrated. In addition, the treatment of the crude amino-ester (±)-**40** (Scheme 10) with LiOH in THF:H_2O (1:1) for 1 h at room temperature gave the amino acid (±)-**41**, which was recrystallized to provide suitable quality crystals.[30] This analysis confirmed the assigned structure of (±)-**41**.
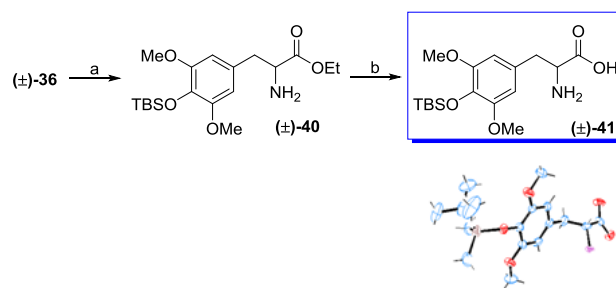
Scheme 10 (a) Pd/C (10% *wt*), H_2, EtOAc, 1 h; (b) LiOH, THF:H_2O (1:1), rt, 1 h, 88% crude yield. The thermal ellipsoid plot for *anti*-(±)-**41** is shown at 50% ellipsoid probability.[25]

The linear peptides **42** and **43** (amino acid sequence: AXIGFPVG where X = (±)-**5** or (±)-**6** after removal of the Fmoc group respectively) were synthesised using a solid-phase peptide synthesis (SPPS) strategy. A preloaded Gly-2-chlorotrityl chloride resin was used to couple N-Fmoc protected amino acids (±)-**5** and (±)-**6** with seven other naturally occurring amino acids (Scheme 11).[41,42,43] After washing and swelling of the resin, suitably protected valine (V), proline (P), phenylalanine (F), glycine (G) and isoleucine (I) were successively double coupled using a 4-fold excess of amino acid for 20 mins at 75 °C making use of (i) DIC (0.5 M in DMF), Oxyma (1 M in DMF) and (ii) HBTU (0.5 M in DMF), DIEA (2 M in DMF) coupling reagent protocols. Prior to adding the next amino acid, the peptide-bound resin was Fmoc-deprotected with a solution of 20% piperidine in DMF for 10 min.
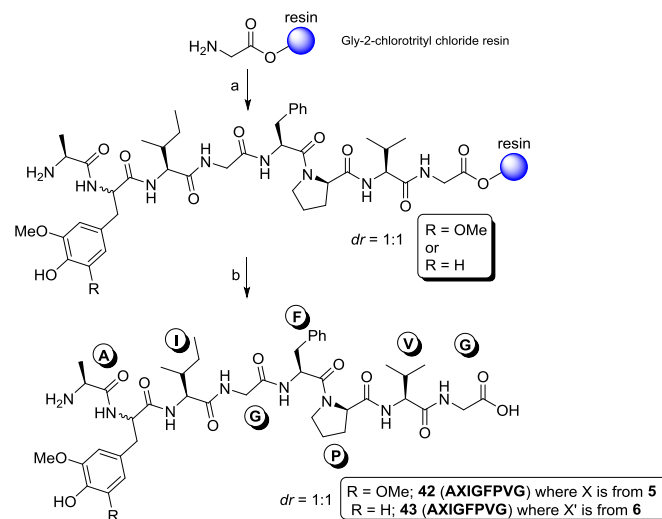
Scheme 11 Synthesis of cyclic peptide precursors **42** and **43**. (a) suitably protected natural amino acid or (±)-**5** or (±)-**6**, DIC (0.5 M in DMF), Oxyma (1 M in DMF) and/or HBTU (0.5 M in DMF), DIEA (2 M in DMF); (b) (i) 20% HFIP in DCM, 30 min and (ii) 94% trifluoroacetic acid, 4% H_2O, 2% triisopropylsilane, 2 hrs.

The unnatural amino acid (±)-**5** or (±)-**6** was then single coupled for 30 minutes, followed by Fmoc removal and double coupling of the terminal alanine residue. The final Fmoc-deprotection was carried out with a solution of 50% piperidine in DMF for 3 minutes and the resin was washed extensively. The

linear peptide was cleaved from the resin using a solution of 20% HFIP (hexafluoro isopropanol) in DCM followed by 94% trifluoroacetic acid, 4% H_2O, 2% triisopropylsilane. Peptides **42** and **43** (as 1:1 mixtures of diastereoisomers) were isolated in 52% and 45% yield respectively. The chemical cyclisation[43] of the linear peptides **42** (*dr* 1:1, X derived from (±)-**5**) and **43** (*dr* 1:1, X derived from (±)-**6**) was achieved using PyBOP and DIEA to give cyclic peptides **7** and **8** respectively, both as 1:1 mixture of diastereoisomers (Scheme 12). The use of HATU as the coupling reagent led to formation of the cycle that had also been modified by the coupling reagent, presumably through reaction of the unprotected phenolic OH.[44] No major differences in the rate of cyclisation of the diastereomeric linear peptides was observed. The two diastereoisomers of **7** and **8** were separated by semi-preparative RP-HPLC.
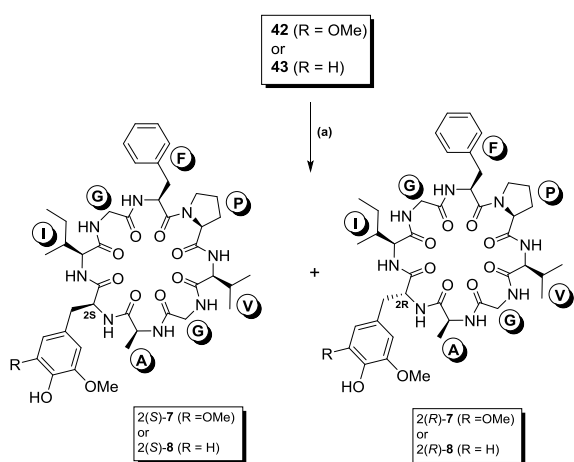
Scheme 12 Synthesis of cyclic peptides 2(*S*)-**7**, 2(*R*)-**7**, 2(*S*)-**8** and 2(*R*)-**8** (a) (i) PyBOP, DIEA, DMF (ii) RP-HPLC purification enabled separation of diastereomers.

Interestingly, detailed 1D and 2D NMR analysis of the cyclic peptides showed that each diastereoisomer of **7** and **8** consisted of two main conformers in varying ratios (Figures 1, S14, S23, S30 and S36). The absolute stereochemistry of the two diastereomers of **7** were assigned based by comparison of the ^{1}H-^{15}N HSQC spectra with the spectrum of a related cyclic peptide (*S*)-**44** prepared using enantiomeric pure L-(*S*)-Tyrosine (Y) (Figure 1). The ^{1}H-^{15}N HSQC analysis of (S)-**44** (Figure 1C) was very similar to that of one of the two diastereomers (Figure 1A) and very different from the analysis of the second diastereomer (Figure 1B), For example, the signal corresponding to the NH of the tyrosine residue in 2(*S*)-**44** (8.01/111.7 ppm, labeled as Y_b in Figure 1C) was similar in chemical shift to the signal for the analogous NH for the unnatural amino acid residue derived from (±)-**5** in what was assigned as the 2(*S*)-**7** diastereomer (8.02/111.8 ppm, labeled as X_b in Figure 1A), whereas, the analogous signal in the assigned 2(*R*)-**7** diastereomer was found at 8.07/124.7 ppm (Figure 1B). An analogous situation was observed for the two separated diastereomers of cyclic peptide **8** enabling one of them to be assigned as the 2(*S*)-**8**

diastereomer due to similarity of its ^{1}H-^{15}N HSQC analysis to that of (S)-**44** (Tables S8-S11).
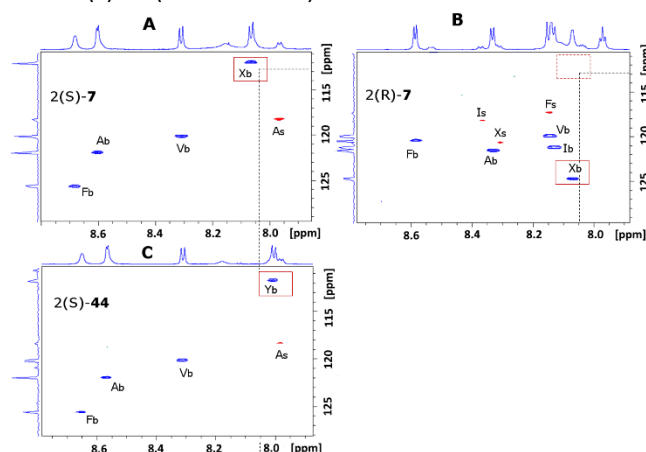

Figure 1: Assignment of the stereochemistry of the two diastereomers of cyclic peptide **7** by comparison with the ^{1}H-^{15}N HSQC analysis of 2(*S*)-**44**.

In the final part of this study, the enzyme-mediated cyclisation of linear peptide **42** was explored using the macrocyclase enzyme P*at*G$_{mac}$.[45] Previous reports have shown the effectiveness of this enzyme for the cyclization of a wide range of linear peptides that contain natural and unnatural amino acids.[46] Based on the understanding of the mechanism of P*at*G$_{mac}$,[45] the precursor linear peptide must have a C-terminal amino acid motif (AYD) that is recognised by the enzyme. Therefore, modified linear peptide **45** (VGAXIGFPAYD where X was derived from (±)-**5** was prepared and converted to the diastereomeric cyclic peptides 2(*S*)-**7** and 2(*R*)-**7**. The two diastereomers were formed in an approximately 1:1 (Scheme 13, Figures S21 and S22), implying that the rate of macrocyclisation by P*at*G$_{mac}$ was not influenced by the stereochemistry at the unnatural amino acid stereogenic center in this system.
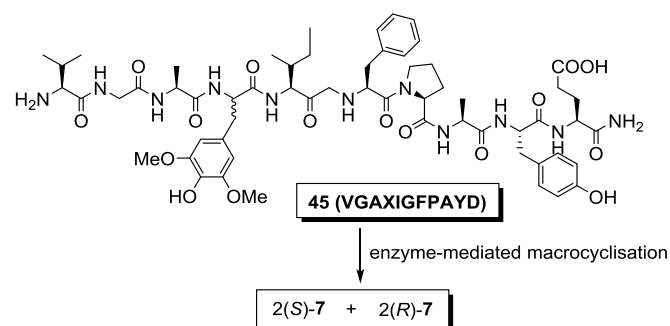
Scheme 13 (a) P*at*G$_{mac}$ enzyme, 20 mM bicine buffer, 500 mM NaCl, and 5% DMSO solution, pH = 8.1 and incubated at 37 °C (without shaking). No difference in the rates of formation of the two diastereomeric cyclic peptides was observed (Figure S21).

Conclusions

In conclusion, we have synthesized the (2*R*,3*R*)- and (2*S*,3*S*)-enantiomers of *anti*-Descurainolide A **3** from a lignin-derived, keto-alcohol **1**. The allylic alcohol (±)-**2b** was converted into highly enantio-enriched samples of both enantiomers using the

organocatalyst HyperBTM **24**. The rhodium catalyzed allylic substitution reaction proceeded with high conservation of enantiomeric excess and enabled the key C-C bond formation step. In addition, we have converted the lignin-derived phenolic monomers **1** and **4** into N-Fmoc protected unnatural amino acids **5** and **6**, respectively. These unnatural amino acids were incorporated into cyclic peptides **7** and **8**. Overall this work has showcased the applicability of these phenolic monomers in differing areas of synthetic organic chemistry.

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