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. 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 isoiothiourea-catalyzed kinetic resolution enabling access to both the (2R,3R) and (2S,3S) 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 macrocyclisation.

Introduction

Lignin is the second most abundant naturally occurring polymer after cellulose. At present, only 1-2% of industrially produced lignin is converted into commercial products with the rest being used as a low value fuel. It is clear that applications of this renewable material remain underexplored. The large number of aromatic units present in lignin has inspired methods to obtain substituted-phenolic building blocks. Whilst considerable efforts have been channelled into lignin depolymerisation, many of these processes lead to major separation challenges if pure aromatic building blocks are required. An alternative approach investigates the processing of native lignins through the use of highly selective catalytic transformations. 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. 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). 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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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 enanti-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 enanti-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 trialkoxyarylsubstituents have been reported.

![Scheme 2 Our Retrosynthetic Analysis of 3 from keto-alcohol 1.](image)

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).[^22] 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).[^23] 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 TBSCI, followed by 1,2-reduction of the enone using NaBH₄ with CeCl₃·7H₂O[^24] 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) TBSCI, DMAP, Imidazole, DCM, rt, 1 h, 89% (ii) PivCl, DMAP, Imidazole, DCM, 1 h, 87% (b) NaBH₄, CeCl₃·7H₂O, MeOH, 1 h, 95% for 2a, 93% for 2b (c) Methyl chloroformate, LiHMDS, THF, 1 h, -10 °C, 15% for 14a, 89% for 14b. See Scheme S1 for more detail.](image)
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). 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). 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 regiosomer (Schemes 4, S2 and Figure S1).

![Synthesis of anti-(±)-Descurainolide A](image)

**Scheme 4** Synthesis of anti-(±)-Descurainolide A: (a) NaH, Dimethyl malonate, RhCl(PPPh3)3 (5 mol%), P(OMe)3 (20 mol%), THF, 40 °C, 1 h, 87% (b) LiCl, H2O, DMSO, 140 °C, 16 h, 76% (c) 1L, 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.

Treatment of purified (±)-16 with LiCl in DMSO/H2O afforded y-olefinic ester (±)-17 in 76% yield and iodolactonisation using I2/MeCN at 0 °C furnished (±)-18 in an anti:syn ratio of 19:1 (Figure S2). 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).

![Synthesis of syn-(±)-Descurainolide A](image)

**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, BrN, 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 an 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 confirmed that the natural material had the proposed relative stereochemistry (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. 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. 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_Kin) 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 Pr3NET in toluene at -78 °C (Table 1, entries 1-4). Lower, but still synthetically useful, selectivity was obtained for alcohols 2e and 2f bearing O-tosyl and O-trifllyl 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 (2R,3S)-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< 22) are employed, and with high conservation of enantiomeric excess (ee). At 40 °C, we observed erosion of ee, from 99% (S)-14b to 83% of (R)-16. However, at 40 °C the α-π-σ
isomerisation between the two enantiomers of the π-allylrhodium(III) complex, which is reported to be slow, is slightly enhanced in this system. However, at ambient temperature, we obtained a high $ee$ (99%) for both (R)- and (S)- 16.

![Scheme 6](image-url) Preparative kinetic resolution of allylic alcohols (±)-2a-f

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$^a$Calculated by HPLC analysis. $^b$Determined by HPLC analysis. $^c$Calculated using the equations developed by Kagan. $^d$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-(2R,3R)-3 and anti-(2S,3S)-3 respectively (Schemes 7 and 54 and Table S3). Chiral HPLC analysis of anti-(2S,3S) and anti-(2R,3R)-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-(2R,3R)-3 (Figure S6) confirmed the allylic substitution reaction occurred with the precedent retention of configuration and the absolute configuration of anti-(2R,3R)-3.$^{15}$

Repeated attempts to obtain a sample of the natural product from the group that originally isolated it was 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). In summary of part 1, the renewable lignin-derived ketolcohol 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.

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).$^{17}$

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

![Scheme 7](image-url) Synthesis of anti-(2R,3S)- and anti-(2S,3S)-Descuranolide A (3): (a) Methyl chloroformate, LiHMDS, THF, 1 h, −10 °C; 95% for R-14b, 74% for $S$-14b (b) NaH, Dimethyl malonate, HCO$_2$(IPPh$_3$)$_2$ (5 mol%), PO($O$Me)$_2$ (20 mol%), THF, 22 °C, 16 h; 79% for R-16, 85% for $S$-16 (c) LiCl, H$_2$O, DMSO, 140 °C, 16 h; 47% for 17-R, 55% for 17-S (d) I$_2$, MeCN, 0 °C to rt, 48 h; 45% for anti-(2R,3S)-19, 48% for anti-(2S,3S)-19 (e) Pd/C, H$_2$, NaOAc, MeOH, rt, 16 h; 52% for anti-(2R,3R)-19, 59% for anti-(2S,3S)-19 (f) 2 M HCl/5,4-dioxane (1:1), 100 °C, 12 h; 42% for anti-(2S,3S)-3, 61% for anti-(2R,3S)-3.

![Scheme 8](image-url) Reaction Conditions: (a) K$_2$CO$_3$, BnBr, DMF, rt, 3 h (b) 2,2-dimethoxypropane, pTSA.H$_2$O (catalytic), DCM: 91% for (±)-28 and 89% for (±)-29 over 2 steps (c) HCl/10% w/f, H$_2$, NaOAc, MeOH, rt, 12 h (d) Dns-Martin Periodinane, DCM, rt, 2 h (e) NaClO$_2$, NaH$_2$PO$_4$, 2-methyl-2-butene, $N$-Boc/H$_2$O, rt, 12 h (f) SO$_2$, DCM then EtOH; 78% for (±)-30 and 68% for 31 over 4 steps (g) pTSA.H$_2$O, 77% for (±)-32 and 69% for (±)-33.
careful separation, the major diastereoisomer (relative stereochemistry unassigned) of (±)-28 and (±)-29 respectively were subjected to debenzylation,\textsuperscript{37}\textsuperscript{a} Dess-Martin oxidation,\textsuperscript{37}\textsuperscript{b} Pinnick oxidation\textsuperscript{37}\textsuperscript{c} and esterification\textsuperscript{37}\textsuperscript{d} to furnish (±)-30 and (±)-31 in 78% and 68% over four steps. Subsequent removal of the acetal groups using pTSA.H\textsubscript{2}O provided diol-esters (±)-32 and (±)-33 in 77% and 69%, respectively.\textsuperscript{38}

Exposure of (±)-32 and (±)-33 to Et\textsubscript{3}SiH and BF\textsubscript{3}.OEt\textsubscript{2} in DCM at -78 °C for 2 h gave α-hydroxy esters (±)-34 and (±)-35 in moderate yields (Scheme 9).\textsuperscript{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\textsubscript{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\textsubscript{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.\textsuperscript{30}

![Scheme 9](image)

Scheme 9 (a) Et\textsubscript{3}SiH, BF\textsubscript{3}.OEt\textsubscript{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\textsubscript{3}, DMF, rt, 3 h, 88% for (±)-36 and 78% for (±)-37 (d) (i) Pd/C (10% wt), H\textsubscript{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\textsubscript{2}O (1:1) for 1 h at room temperature gave the amino acid (±)-41, which was recrystallized to provide suitable quality crystals.\textsuperscript{30} This analysis confirmed the assigned structure of (±)-41.

![Scheme 10](image)

Scheme 10 (a) Pd/C (10% wt), H\textsubscript{2}, EtOAc, 1 h; (b) LiOH, THF:H\textsubscript{2}O (1:1), rt, 1 h, 88% crude yield. The thermal ellipsoid plot for anti-(±)-41 is shown at 50% ellipsoid probability.\textsuperscript{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-chlorotriyl chloride resin was used to couple N-Fmoc protected amino acids (±)-5 and (±)-6 with seven other naturally occurring amino acids (Scheme 11).\textsuperscript{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](image)

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\textsubscript{2}O, 2% trisopropylsilane, 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% H₂O, 2% triisopropylsilane. Peptides 42 and 43 (as 1:1 mixtures of diastereoisomers) were isolated in 52% and 45% yield respectively. The chemical cyclisation 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. 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.

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 by comparison of the 1H-15N HSQC spectra with the spectrum of a related cyclic peptide (S)-44 prepared using enantiomeric pure (-)-(S)-Tyrosine (Y) (Figure 1). The 1H-15N 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 Y₁ 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 Y₂ in Figure 1A), whereas, the analogous signal in the assigned 2(R)-7 diastereomer was located 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 1H-15N HSQC analysis to that of (S)-44 (Tables S8-S11).

In the final part of this study, the enzyme-mediated cyclisation of linear peptide 42 was explored using the macrocyclase enzyme PtgGmac. 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. Based on the understanding of the mechanism of PtgGmac, 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 PtgGmac was not influenced by the stereochemistry at the unnatural amino acid stereogenic center in this system.

Conclusions

In conclusion, we have synthesized the (2R,3R)- and (2S,3S)-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 enantiotopic 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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28 In addition, an analog of (±)-2a in which the TBS-group was replaced by a benzyl group was prepared but found to be difficult to work with (Scheme 51).


30 CCDC 1505597 (anti-(±)-3), CCDC 1505596 ((S)-2a), CCDC 1505598 ((S)-14b), CCDC 1510492 (anti-(2R,3R)-3) and CCDC 1506889 ((±)-41) contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


33 For selected examples, see (a) T. Ohkuma, H. Ooka, T. Ikaruya, R. Noyori, J. Am. Chem. Soc. 1995, 117, 10417–10418 (b) J. C. Ruble,


