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Racemic Synthesis of Linderuca C from lignin derived starting materials

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Dedicated with best wishes to Dr Alan Aitken for over 40 years of high level synthetic organic chemistry

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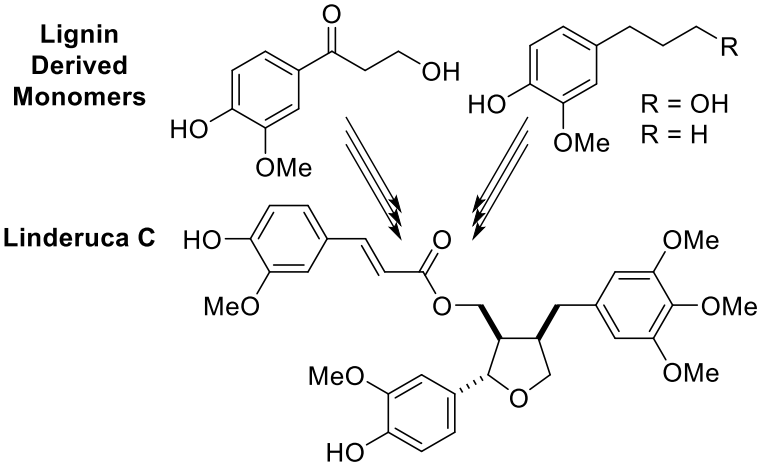
Abstract

The biopolymer lignin represents a sustainable source of mono-aromatic compounds and, consequently, an alternative to oil for accessing potential feedstock chemicals. Here we report the first synthesis of the natural product Linderuca C, a pharmacologically active compound belonging to the large family of lignans from three different lignin-derived compounds. These can be prepared either by oxidative or reductive depolymerisation of lignin. A key step investigated the use of a Ti-mediated cyclisation reaction.. The synthesised sample of Linderuca C was compared using NMR methods to the data reported in the literature, confirming the assigned structure.



Keywords: Linderuca C, lignin, sustainable synthesis, natural product, Ti-mediated cyclisation.

Introduction

The biopolymer lignin continues to be of interest as a source of aryl ring-containing compounds. The interest arises from a need to decrease the Chemical Industry's dependence on oil for the production of aromatic feedstock chemicals. This raison d'etre has driven the development of lignin depolymerisation methods and has resulted in the production of a wide range of monomers from lignin including, for example, structures **1**-**4** in pure form (Figure 1A).[1-9] A key difference between the lignin- and oil-derived monomers is the presence of aryl-methoxy substituents, an almost unavoidable consequence of the structure of the natural polymer, lignin. Methods do exist to remove these often unwanted substituents.[10-12] In addition, studies have focused on the preparation of natural products and other bioactive compounds that contain methoxy-substituted aryl rings. For example, we have reported the synthesis of the natural product Descuranolide A **5** (Figure 1B) and cyclic peptides starting from lignin-derived monomers **1** and **2**.[13] A range of other examples of this approach have also been published including Sels' approach to MeO-bisphenol A analogues.[14]

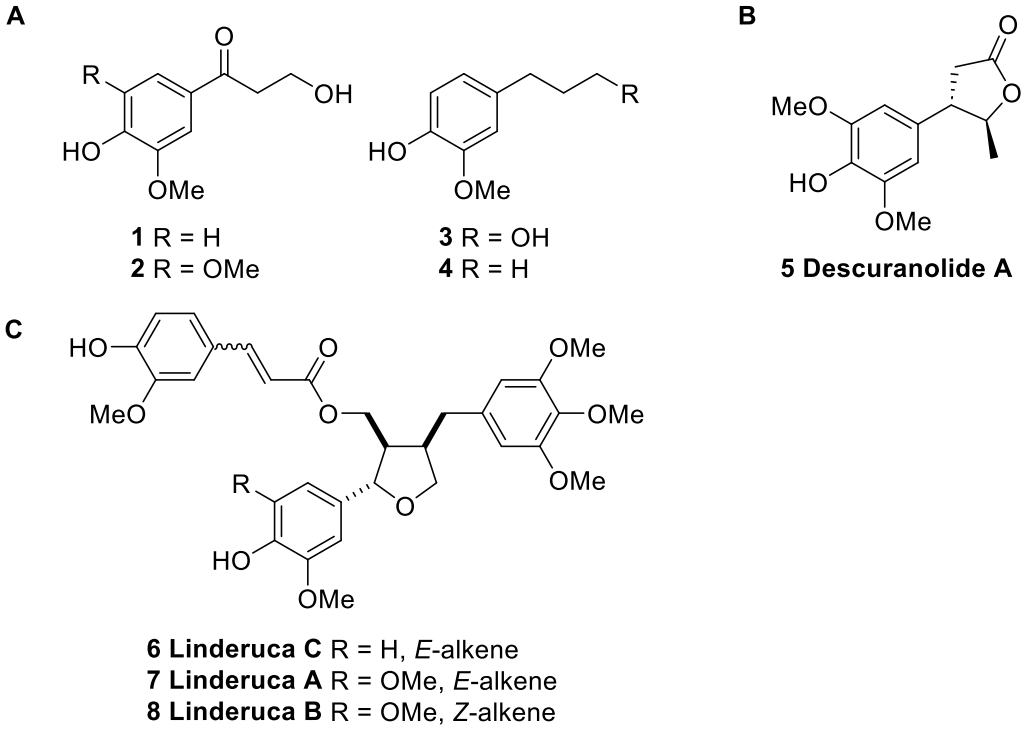


Figure 1. A) Monomers derivable in pure form from lignin through oxidative (**1**, **2**) or reductive (**3**, **4**) depolymerisation strategies. B) The natural product Descuranolide A **5** prepared from a lignin-derived monomer. C) The lignan natural products Linderuca A-C **6**-**8**.

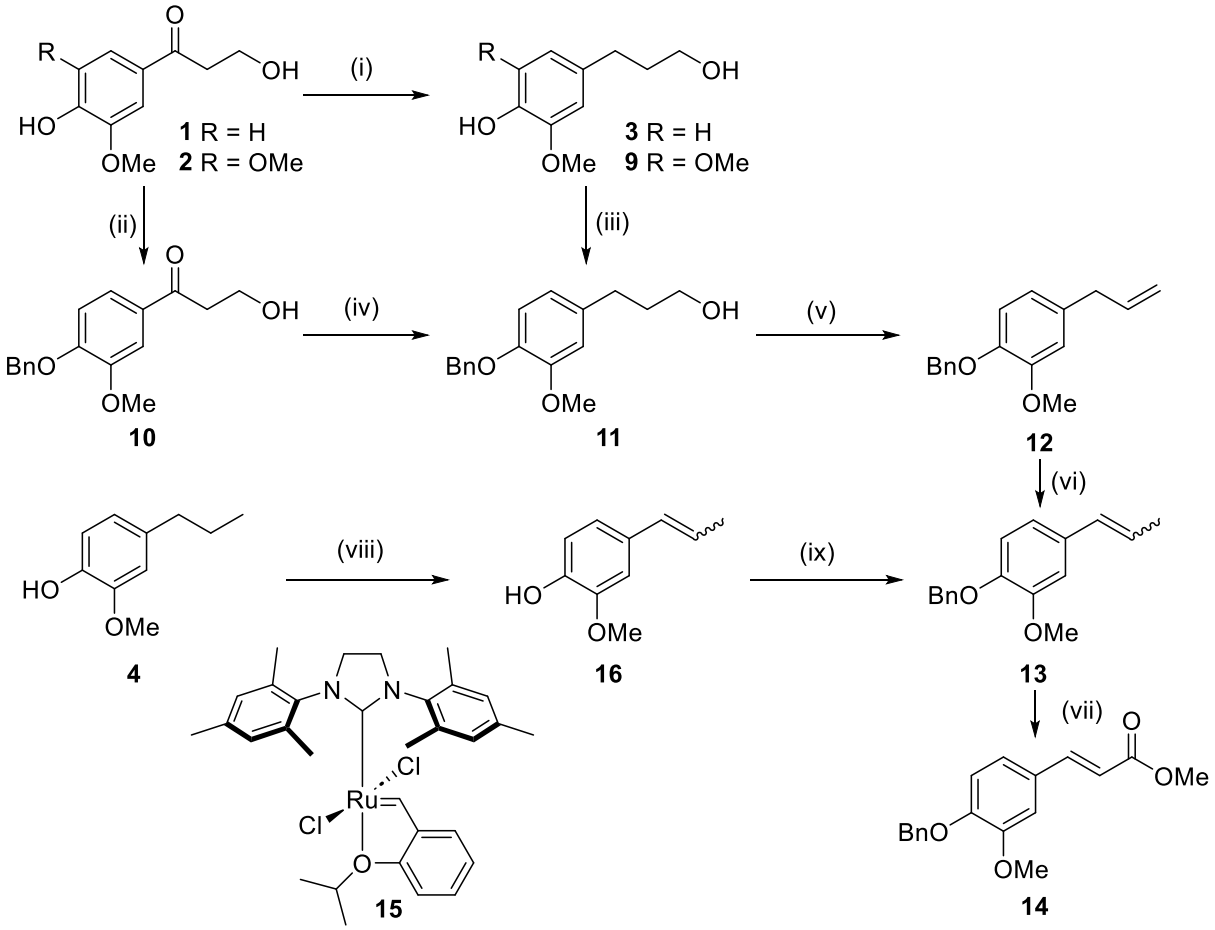
The natural product target of this study, Linderuca C **6**, is a member of the large family of natural products known as the lignans.[15] In more detail, three lignans, called Linderuca A-C (**6**-**8**, Figure 1C) belonging to the 2-aryl-4-benzyltetrahydrofuran class of lignans, were isolated from the twigs of the Chinese spicebush *Lindera glauca* in 2014.[16] The three structures differ either in the alkene stereochemistry or the number of aryl-methoxy substituents in one of the 3 aromatic rings. Natural products **6**-**8** showed significant anti-proliferative effects on various human tumour cell lines (lung: A549, ovary: SK-OV-3, skin: SK-MEL-2 and colon: HCT-15), as well as the

ability to inhibit nitric oxide production in lipopolysaccharide-stimulated BV-2 cells (modified microglial murine cells).[16] To the best of our knowledge, Linderuca C **6** has not been synthesised previously and so we became interested in methods for its preparation. A key component of our strategy was to start from lignin-derived aryl-containing monomers, partly due to the presence of the aryl-methoxy groups within the structure of **6**.

Whilst several approaches to the 2-aryl-4-benzyltetrahydrofuran class of lignans have been reported previously,[17-22] we decided to explore the use of a precedented Ti-mediated cyclisation reaction.[23] Here, we describe the adventures we have had on this journey to a racemic sample of the natural product **6**. This report was also inspired by the long term commitment to high level synthetic organic chemistry demonstrated over more than 40 years by our excellent colleague at St Andrews, Alan Aitken.[24-30]

Results and Discussion

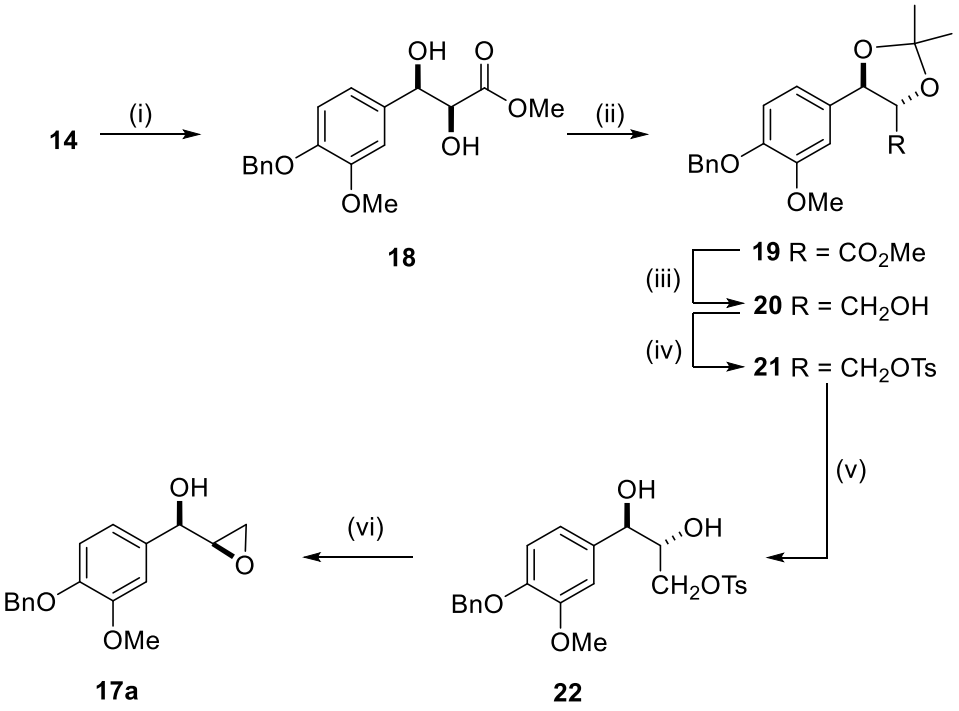
Three different lignin-derived aryl ring-containing compounds **1**, **3** and **4** were selected as starting materials. These sustainable compounds differ in that a lignin oxidation (followed by cleavage) method was used to prepare **1**,[7-9] whereas reductive depolymerisation using exhaustive hydrogenation of either lignin or wood itself led to **3** and **4** (and in some cases **9**, Scheme 1).[4-6]



Scheme 1. Synthesis of **14** from lignin-derived monomers **1**, **3** and **4**. (i) for **2** to **9** only, $NaBH_3CN$, $BF_3{\cdot}OEt_2$, r.t., 12 h, 82%. See ref. 9 (ii) 2.0 eq. BnBr, 2.0 eq. K_2CO_3, acetone, reflux, 20 h, 99%. (iii) 1.1 eq. BnBr, 2.0 eq. K_2CO_3, acetone, reflux, 97%. (iv) 6 eq. $BF_3.OEt_2$, 4.8 eq. sodium cyanoborohydride, THF, r.t., 12 h, 50 °C, 6 h, 64%. (v)

1.5 eq. 2-nitrophenyl selenocyanate, 1.5 eq. tributyl phosphine, THF, r.t., 1 h, 54%. (vi) 10 mol% $MgCl_2.6H_2O$, 5 mol% $RuH_2(CO)(PPh_3)_3$, EtOH, 80 °C, 1 h, 95% (*E*/*Z* 95:5). (vii) 4 eq. methyl acrylate, 1 mol% Hoveyda-Grubbs catalyst **15**, DCE, 70 °C, 16 h, 73%. (viii) 1.25 eq. DDQ, AcOH, 1,4-dioxane, r.t., 16 h, 29% *E*/*Z* 95:5) (ix) 1.1 eq. BnBr, 2.2 eq. K_2CO_3, acetone, reflux, 12 h, 99% (*E*/*Z* 95:5).

The synthetic route to Linderuca C **6** starting from **1** first involved benzylation of the phenolic oxygen to give **10**. Conversion of **10** to **11** was then achieved using an analogous approach to that previously applied to the conversion of **2** to **9** (Scheme 1).[9] Compound **11** could also be intercepted by the direct benzylation of **3**. Subsequent dehydration of **11** to give **12** and double bond isomerisation, according to the protocol of Koh *et al*,[31] gave **13** - the required substrate for an olefin metathesis reaction. The conversion of **13** to the methyl ester of benzyl ferulic acid **14** proceeded smoothly in the presence of the Hoveyda–Grubbs II metathesis catalyst **15**,[32] as previously reported by Fogg *et al*.[33] An alternative route from **4** proceeded via its conversion under unoptimized oxidative conditions to **16**. Phenolic oxygen benzylation in **16** produced **13**, intercepting the route from **1** and **3** (Scheme 1).

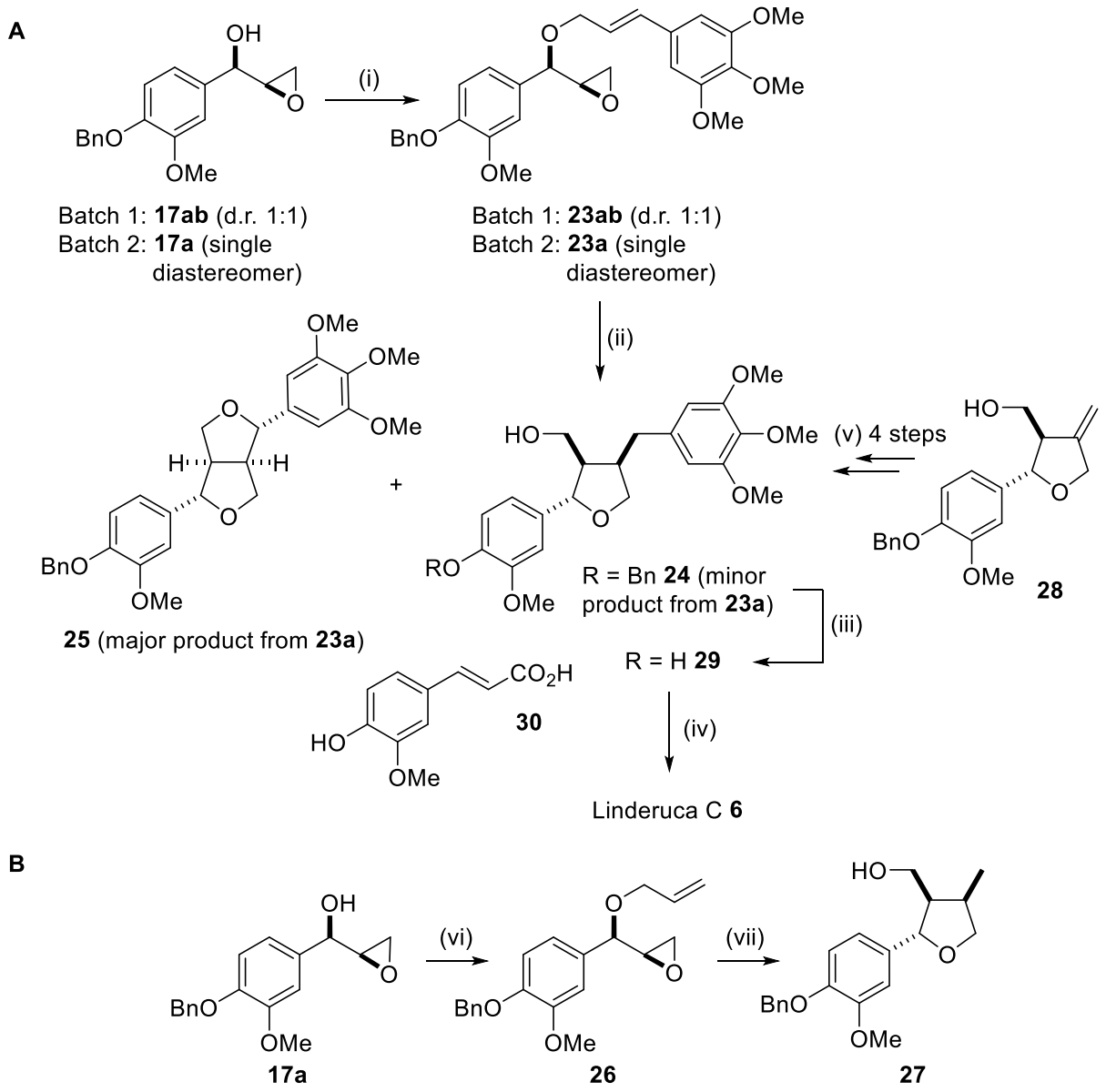


Scheme 2. Synthesis of epoxide **17a** from **14**. (i) 0.75 eq. citric acid, 1.1 eq. NMO, 0.1 mol% OsO_4 in ^tBuOH (2.5 wt%), MeCN : acetone : H_2O (3 : 3 : 1), r.t., 16 h, 94%. (ii) 0.1 eq. CSA, 2 eq. 2,2-dimethoxypropane, toluene, 70 °C, 99%. (iii) 1.1 eq. $LiAlH_4$, THF, -78 °C – r.t., 1 h. (iv) 1.5 eq. TsCl, 1.5 eq. Et_3N, 0.1 eq. DMAP, DCM, r.t., 16 h, 98% (over 2 steps). (v) 6 : 1 MeCN : 3 M $HCl_{(aq)}$, r.t., 16 h, 99%. (vi) 2.0 eq. K_2CO_3, MeOH, r.t., 30 min, 93%.

Having demonstrated that **14** was readily available from a range of lignin-derived aromatic starting materials, studies next focused on the conversion of **14** initially to a diastereomeric mixture of epoxides **17ab** (Scheme 3). The details of this reaction sequence are provided in the Supplementary Material and this diastereomeric mixture of **17ab** is referred to as Batch1 in the following discussion. Alternatively, inspired by the reports of Hou *et al.*[34] and Lalwani and Sudalai,[35] α,β-unsaturated ester **14** was converted to a sample of the single diastereomer **17a** (Scheme 2). This involved Upjohn dihydroxylation of **14** with 0.75 eq. of citric acid as an

additive which gave **18** in excellent yield.[36,37] Subsequent protection of the diol functionality in **18** as the corresponding ketal in **19**, followed by ester reduction to generate **20** was preferred over direct reduction of **18** as this avoided the challenging purification of a triol. Subsequent tosylation of **20** led to **21**, and then ketal deprotection to give **22** enabled facile formation of the desired epoxide **17a**. Comparison of the analytical data collected for **17a** (referred to as Batch 2 in the subsequent discussion) with that in the literature[23,38] confirmed the assigned relative stereochemistry of **17a**.

Subsequent conversion of the epoxide **17** (Batches 1 and 2, Scheme 3A) to the cyclisation precursor **23** (Batches 1 and 2 respectively) was achieved in moderate yields (see Supplementary Material for procedure and analytical data). An alternative route to **23a** as a single diastereomer was also developed (see Supplementary Material for more details). Reaction of the diastereomeric mixture **23ab** (Batch 1) using the methodology of Roy *et al.*[23] did enable the preparation of **24**, although **24** was always formed in low yields. On one occasion when using the pure diastereomer **23a**, it was possible to isolate the major compound from this reaction. This major compound was not assigned structure **24** but instead structure **25**. This most likely resulted from cyclisation of the initially formed THF ring-containing organotitanium species.[23,39] The stereochemistry of **25** was assigned by comparing the signals present in its ^{1}H NMR analysis to those reported in the literature for the analogous compounds Magnolin and Epimagnolin.[40]



Scheme 3. Synthesis of Linderuca C **6** from epoxide **17**. (i) 5.0 eq. NaH, 1.5 eq. (*E*)-5-(3-bromoprop-1-en-1-yl)-1,2,3-trimethoxybenzene, THF, 0 °C – r.t., 1.5 h, 52%. See supplementary material for discussion. (ii) 2.5 eq. $TiCp_2Cl_2$, 10 eq. Zn dust, THF, r.t., 2 h, 32%. (iii) H_2, 10 wt.% Pd/C, MeOH, r.t., 1 h, 95%. (iv) 1.2 eq. **30**, 1.1 eq. DIAD, 1.1 eq. PPh_3, THF, r.t., 48 h, 39%. (v) Scheme S3. [17] (vi) 1.1 eq. allyl bromide, 3.0 eq. NaH, THF, 0 °C – r.t., 1.5 h, 87%. (vii) 2.3 eq. $TiCp_2Cl_2$, 10 eq. Zn dust, THF, r.t., 2 h, 54%.

In contrast, cyclisation of **26** gave **27** in 54% yield under analogous conditions (Scheme 3B, see supplementary material for details). The presence of the trimethoxy-substituted aryl ring adjacent to the radical centre clearly plays an important role in the final outcome of the cyclisation of **23**. Assignment of the relative stereochemistry of **27** was confirmed using nOe experiments (Figure S2). Comparison of the ^{1}H NMR analysis of **24** with that of **27** supported the view that the relative stereochemistry of these two compounds was the same and therefore as required for the synthesis of the proposed structure of Linderuca C **6** (Table S1). In all the Ti-mediated cyclisations carried out to date, a small quantity of a stereoisomer of the THF ring-containing system was also observed. The stereochemistry of this minor product is currently unassigned.

At this stage, concerns about the supply of **24** available by this route were raised. It was therefore decided to supplement the available material via **28** inspired by a recently reported method (see supplementary material for details).[17] With sufficient amounts of **24** now available, the synthesis of Linderuca C was completed in 2 steps involving initial benzyl deprotection to give **29** followed by selective esterification using **30**. Careful purification enabled comparison of the NMR data collected for the authentic sample of Linderuca C **6** with that reported in the literature (Tables S2/S3). These comparisons showed good alignment of the chemical shifts and *J* couplings.

Conclusions

To the best of our knowledge, this report describes the first total synthesis of Linderuca C **6**, an example of the 2-aryl-4-benzyltetrahydrofuran class of lignans. Careful comparison using detailed NMR analysis of the synthesised sample of **6** with the data reported in the literature confirmed the assigned structure. The early phase of the synthesis focused on the conversion of three different lignin derivable starting compounds (**1**, **3** and **4**) to the methyl ester of benzyl ferulic acid **14**. Subsequent conversion of **14** to a suitably substituted epoxide enabled the use of a Ti-mediated cyclisation reaction. Whilst this reaction did deliver the required THF-containing product, this was not the major product. Novel insight was gained into this interesting reaction through comparison of the natural product system with a simplified model substrate.

Experimental Section

General. Compounds **10**,[41] **11**,[42] **12**,[43] **13**,[44] **14**,[45] **16**,[46] **18**,[47] **20**,[34] **22**,[38] and **28**.[23] were already described in the literature (see Supplementary Material for the synthetic procedures used here and relevant analytical data).

***Rel*-((2*S*,3*R*,4*R*)-2-(4-hydroxy-3-methoxyphenyl)-4-(3,4,5-trimethoxybenzyl)tetrahydrofuran-3-yl)methyl (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylate, Linderuca C (6).** A flame-dried flask was charged with **29** (53.0 mg, 0.132 mmol, 1.00 eq.), ferulic acid **30** (31.0 mg, 0.159 mmol, 1.20 eq.) and THF (0.3 cm^3) under a nitrogen atmosphere and the solution was cooled to 0˚C, before addition of PPh_3 (38.0 mg, 0.145 mmol, 1.10 eq.) and DIAD (0.03 cm^3, 0.145 mmol, 1.10 eq.). The resulting mixture was warmed to room temperature and stirred for 48 hours. The reaction was then quenched using saturated $NaHCO_{3(aq)}$ (5 cm^3) and the aqueous phase was extracted using EtOAc (3 x 5 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification on silica gel (0-50% EtOAc in pet ether) gave a single fraction of sufficient purity for characterisation of **6** (29.8 mg, 0.0513 mmol, 39%). IR (oil, ATR-FTIR, ν_{max}, cm^{-1}): 3399, 2922, 1701, 1632, 1510, 1423, 1263, 1155, 1030. ^{1}H NMR (700 MHz, CD_3OD): δ_H 2.61 (dd, *J* = 13.4, 10.4 Hz, 1H, H_a-13), 2.66 – 2.71 (m, 1H, H-11), 2.84 – 2.90 (m, 1H, H-10), 2.92 (dd, *J* = 13.4, 5.4 Hz, 1H, H_b-13), 3.72 (s, 3H, H-19), 3.76 (dd, *J* = 8.6, 5.6 Hz, 1H, H_a-9), 3.81 (s, 6H, H-17), 3.82 (s, 3H, H-3), 3.90 (s, 3H, H-29), 4.08 (dd, *J* = 8.5, 6.3 Hz, 1H, H_b-9), 4.27 (dd, *J* = 11.2, 7.7 Hz, 1H, H_a-12), 4.50 (dd, *J* = 11.2, 6.6 Hz, 1H, H_b-12), 4.80 (d, *J* = 7.5 Hz, 1H, H-8), 6.23 (d, *J* = 15.9 Hz, 1H, H-21), 6.55 (s, 2H, H-15), 6.78 (d, *J* = 8.1 Hz, 1H, H-7), 6.80 (d, *J* = 8.2 Hz, 1H, H-25), 6.83 (dd, *J* = 8.1, 2.0 Hz, 1H, H-6), 6.94 (d, *J* = 1.9 Hz, 1H, H-4), 7.01 (dd, *J* = 8.2, 2.0 Hz, 1H, H-24), 7.11 (d, *J* = 1.9 Hz, 1H, H-28), 7.39 (d, *J* = 15.9 Hz, 1H, H-22). ^{13}C NMR (176 MHz, MeOD): δ_C 35.0 (C-13), 44.0 (C-10), 50.5 (C-11), 56.4 (C-3), 56.5 (C-29), 56.6 (C-17), 61.1 (C-19), 63.9 (C-12), 73.7 (C-9), 85.2 (C-8), 107.0 (C-15), 111.0 (C-4), 111.6 (C-28), 115.2 (C-21), 116.1 (C-7), 116.5 (C-25), 120.3 (C-6), 124.2 (C-24), 127.6 (C-23), 134.9 (C-5), 137.4 (C-18), 138.0 (C-14), 147.0 (C-22),

147.3 (C-1), 149.0 (C-2), 149.4 (C-27), 150.7 (C-26), 154.5 (C-16), 168.9 (C-20). Found, *m/z*: 603.2186 $[M+Na]^+$. $C_{32}H_{36}O_{10}Na$. Calculated, *m/z*: 603.2201.

***Rel*-(*R*)-(4-(benzyloxy)-3-methoxyphenyl(*R*)-oxiran-2-yl)methanol (17a).** A flask was charged with **19** (3.78 g, 7.60 mmol) and a 6 : 1 mixture of MeCN : 3 M $HCl_{(aq)}$ (152 cm^3, 0.05 M solution), and the reaction was stirred at room temperature overnight. The reaction was quenched by addition of $NaHCO_{3(aq)}$ (150 cm^3). Solvents were removed under reduced pressure, and the aqueous phase was extracted using EtOAc (3 x 100 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*, to give *Rel*-(2*R*,3*R*)-3-(4-(benzyloxy)-3-methoxyphenyl)-2,3-dihydroxypropyl 4-methylbenzenesulfonate (**22**) (3.46 g, 7.59 mmol, >99%), which was used without purification. Analytical data were consistent with that previously published (see Supplementary Material).[38] To a solution of **22** (3.48 g, 7.60 mmol, 1.00 eq) in MeOH (38 cm^3) was added K_2CO_3 (2.10 g, 15.2 mmol, 2.0 eq), and the resultant suspension was stirred at room temperature for 30 minutes. The reaction was diluted with Et_2O (5 cm^3), filtered under vacuum and concentrated under reduced pressure. Purification on silica gel (0-40% EtOAc in pet. ether) afforded **17a** (2.02 g, 7.07 mmol, 93%) as a colourless, amorphous solid. Analytical data were consistent with those previously reported[23,38] but ^{1}H NMR spectrum reported here provides additional detail compared to the existing literature reports.[23,38] ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.28 (d, *J* = 5.0 Hz, 1H, –OH), 2.81 (dd, *J* = 4.9, 2.7 Hz, 1H, H_b-15), 2.85 (dd, *J* = 4.9, 4.0 Hz, 1H, H_a-15), 3.22 (ddd, *J* = 5.3, 4.0, 2.7 Hz, 1H, H-14), 3.92 (s, 3H, H-8), 4.42 (dd, *J* = 5.1, 5.1 Hz, 1H, H-13), 5.16 (s, 2H, H-5), 6.82 – 6.89 (m, 2H, H-11, H-12), 7.01 (d, *J* = 1.4 Hz, 1H, H-9), 7.27 – 7.33 (m, 1H, H-1), 7.34 – 7.39 (m, 2H, H-2), 7.41 – 7.46 (m, 2H, H-3). Compound **17a** was also prepared as a diastereomeric mixture with compound **17b** (see Supporting Material).

***Rel*-methyl (4*S*,5*R*)-5-(4-(benzyloxy)-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxolane-4-carbox-ylate (19).** A flask was charged with **18** (4.22 g, 12.7 mmol, 1.00 eq), CSA (295 mg, 1.27 mmol, 10.0 mol%) and toluene (50 cm^3, 0.25 M solution). To this suspension was added 2,2-dimethoxypropane (3.10 cm^3, 25.4 mmol, 2.00 eq), and the reaction was heated until **18** had fully dissolved (approximately 70˚C). At this stage, the solution was cooled to room temperature and quenched with saturated $NaHCO_{3(aq)}$ (50 cm^3). The layers were partitioned and the aqueous phase extracted with EtOAc (3 x 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification on silica gel (0-20% EtOAc in hexane) afforded **19** (4.67 g, 12.6 mmol, >99%) as an oil. IR (oil, ATR-FTIR, ν_{max}, cm^{-1}): 2890, 1755, 1514. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.55 (s, 3H, 1 x acetal Me), 1.60 (s, 3H, 1 x acetal Me), 3.78 (s, 3H, H-19), 3.91 (s, 3H, H-8), 4.35 (d, *J* = 7.6 Hz, 1H, H-13), 5.10 (d, *J* = 7.6 Hz, 1H, H-14), 5.16 (s, 2H, H-5), 6.87 (d, *J* = 8.3 Hz, 1H, H-12), 6.90 (dd, *J* = 6.6, 1.9 Hz, 1H, H-11), 6.98 (d, J = 1.9 Hz, 1H, H-9), 7.27 – 7.32 (m, 1H, H-1), 7.34 – 7.39 (m, 2H, H-2), 7.41 – 7.45 (m, 2H, H-3). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 25.9 (1 x acetal CH_3), 27.1 (1 x acetal CH_3), 52.6 (C-19), 56.1 (C-8), 71.1 (C-5), 80.7 (C-14), 81.2 (C-13), 110.1 (C-9), 111.6 (C-15), 113.9 (C-12), 119.2 (C-11), 127.4 (C-3), 128.0 (C-1), 128.7 (C-2), 130.5 (C-10), 137.1 (C-4), 148.5 (C-6), 149.9 (C-7), 171.0 (C-18). Found, *m/z*: 395.1464 $[M+Na]^+$. $C_{21}H_{24}O_6Na$. Calculated, *m/z*: 395.1471.

***Rel*-((4*R*,5*R*)-5-(4-(benzyloxy)-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methyl-benzenesulfonate (21).** A solution of ester **19** (4.67 g, 12.6 mmol, 1.00 eq) in dry THF (126 cm^3, 0.1 M solution) was cooled to -78˚C, before dropwise addition of $LiAlH_4$ (2.4 M solution in THF, 5.80 cm^3, 13.8 mmol, 1.10 eq) over 15 minutes. The reaction was then warmed to room temperature and stirred for 1 hour, before cooling to 0˚C and quenching by slow, careful addition of EtOAc (175 cm^3) and then water (15 cm^3). The reaction was filtered and the filtrate was concentrated under reduced pressure to give know compound *Rel*-((4*R*,5*R*)-5-(4-(benzyloxy)-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**20**)[34] (4.32 g, 12.6 mmol), which was

used without purification. Analytical data for **20** were consistent with that previously reported (see Supplementary Material).[34] Into a flask was added **20** (4.32 g, 12.6 mmol, 1.00 eq), Et_3N (2.60 cm^3, 18.9 mmol, 1.50 eq), DMAP (153 mg, 1.26 mmol, 10.0 mol%), tosyl chloride (3.59 g, 18.9 mmol, 1.50 eq) and DCM (126 cm^3, 0.1 M solution). The reaction was stirred at room temperature overnight then quenched by addition of a saturated $NH_4Cl_{(aq)}$ solution (150 cm^3). The layers were partitioned and the aqueous layer was extracted using DCM (2 x 100 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification on silica gel (0-15% EtOAc in hexane) afforded **21** (6.15 g, 12.3 mmol, 98%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.43 (s, 3H, 1 x acetal Me), 1.51 (s, 3H, 1 x acetal Me), 2.44 (s, 3H, H-23), 3.84 – 3.91 (m, 4H, H-8, H-14), 4.12 (dd, *J* = 11.0, 4.1 Hz, 1H, H_b-18), 4.19 (dd, *J* = 11.0, 3.3 Hz, 1H, H_a-18), 4.79 (d, *J* = 8.5 Hz, 1H, H-13), 5.16 (s, 2H, H-5), 6.77 (dd, *J* = 8.4, 1.8 Hz, 1H, H-11), 6.83 (d, *J* = 8.3 Hz, 1H, H-12), 6.91 (d, *J* = 2.0 Hz, 1H, H-9), 7.28 – 7.33 (m, 3H, H-1, H-21), 7.34 – 7.39 (m, 2H, H-2), 7.41 – 7.45 (m, 2H, H-3), 7.74 – 7.77 (m, 2H, H-20). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 21.8 (C-23), 26.8 (1 x acetal CH_3), 27.2 (1 x acetal CH_3), 56.1 (C-8), 67.5 (C-18), 71.1 (C-5), 79.0 (C-13), 80.5 (C-14), 109.9 (C-15), 110.1 (C-9), 114.1 (C-12), 119.1 (C-11), 127.4 (C-3), 128.0 (C-21), 128.1 (C-20), 128.7 (C-1), 129.8 (C-2), 130.0 (C-19), 132.8 (C-10), 137.1 (C-4), 145.2 (C-22), 148.5 (C-6), 150.0 (C-7). Found, *m/z*: 521.1600 $[M+Na]^+$. $c_{27}H_{30}O_7SNa$. Calculated, *m/z*: 521.1610.

***Rel*-(*R*)-2-((*R*)-(4-(benzyloxy)-3-methoxyphenyl)(((*E*)-3-(3,4,5-trimethoxyphenyl)allyl)oxy)methyl)oxirane-(23a) and its diastereomer *Rel*-(*R*)-2-((*S*)-(4-(benzyloxy)-3-methoxyphenyl)(((*E*)-3-(3,4,5-trimethoxyphenyl)allyl)oxy)methyl)oxirane (23b).** A flame-dried flask containing the diastereomeric mixture **17ab** (*d.r.* 1 : 1, 0.49 g, 1.71 mmol, 1.00 eq.) in dry THF (10 cm^3, 0.17 M solution) under a nitrogen atmosphere was cooled to 0˚C, and to it was added NaH (60% dispersion, 0.21 g, 8.75 mmol, 5.00 eq.). The resultant suspension was stirred at 0˚C for 40 minutes. To this mixture was added the (*E*)-5-(3-bromoprop-1-en-1-yl)-1,2,3-trimethoxybenzene[48] (0.80 g, 2.60 mmol, 1.50 eq.) as a 0.26 M solution in dry THF. The reaction was then warmed to room temperature, and stirred for 1 hour. The reaction was quenched by addition of ice (5 g), water (50 cm^3). The aqueous phase was extracted using EtOAc (3 x 50 mL), the combined organic extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Purification on silica gel (0-60% EtOAc in hexane) afforded **23ab** (*d.r.* 1 : 1, 1.40 g, 2.84 mmol, 52%) as a yellow, amorphous solid. IR (oil, ATR-FTIR, ν_{max}, cm^{-1}): 2935, 1734, 1581, 1506, 1236, 1122. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.61 (dd, *J* = 4.8, 2.7 Hz, 1H, H-15_a in **23a**), 2.76 (dd, *J* = 4.9, 4.2 Hz, 1H, H-15_b in **23a**), 2.78 (dd, *J* = 5.4, 2.7 Hz, 1H, H-15_a in **23b**), 2.81 (dd, *J* = 5.3, 3.9 Hz, 1H, H-15_b in **23b**), 3.18 (ddd, *J* = 3.9, 2.7 Hz, 1H, H-14 in **23b**), 3.24 (ddd, *J* = 6.8, 4.1, 2.7 Hz, 1H, H-14 in **23a**), 3.84 (s, 6H, H-24 in **23a** & **23b**), 3.86 (s, 12H, H-22 in **23a** & **23b**), 3.91 (s, 3H, H-8 in **23b**), 3.91 (s, 3H, H-8 in **23a**), 4.01 – 4.07 (m, 3H, H-16_a in **23b**, H-13 in **23a** & **23b**), 4.13 (ddd, *J* = 12.7, 6.4, 1.5 Hz, 1H, H-16_a in **23a**), 4.14 (ddd, *J* = 12.6, 5.8, 1.5 Hz, 1H, H-16_b in **23b**), 4.20 (ddd, *J* = 12.6, 5.9, 1.6 Hz, 1H, H-16_b in **23a**), 5.16 (s, 4H, 5 in **23a** & **23b**), 6.17 (dt, *J* = 15.9, 6.2 Hz, 1H, H-17 in **23b**), 6.22 (dt, *J* = 15.8, 6.1 Hz, 1H, H-17 in **23a**), 6.46 (dt, *J* = 15.6, 1.2 Hz, 1H, H-18 in **23b**), 6.50 (dt, *J* = 16.0, 1.2 Hz, 1H, H-18 in **23a**), 6.58 (s, 2H, H-20 in **23b**), 6.60 (s, 2H, H-20 in **23a**), 6.78 – 6.85 (m, 2H, H-11 in **23a** & **23b**), 6.87 (td, *J* = 9.1, 8.6, 1.9 Hz, 3H, H-12 in **23a** & **23b**), 6.95 (dd, *J* = 6.1, 1.9 Hz, 2H, H-9 in **23a** & **23b**), 7.28 – 7.34 (m, 2H, H-1 in **23a** & **23b**), 7.34 – 7.40 (m, 4H, H-2 in **23a** & **23b**), 7.42 – 7.48 (m, 4H, H-3 in **23a** & **23b**). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 44.6 (C-15 in **23a**), 45.3 (C-15 in **23b**), 54.6 (C-14 in **23b**), 55.5 (C-14 in **23a**), 56.2 (C-22 in **23a** & **23b**), 56.2 (C-8 in **23a** & **23b**), 61.1 (C-24 in **23a** & **23b**), 69.5 (C-16 in **23a**), 69.6 (C-16 in **23b**), 71.1 (C-5 in **23a** & **23b**), 79.7 (C-13 in **23b**), 82.6 (C-13 in **23a**), 103.6 (C-20 in **23a** & **23b**), 110.5 (C-9 in **23a**), 110.8 (C-9 in **23b**), 113.7 (C-12 in **23b**), 113.8 (C-12 in **23a**), 119.7 (C-11 in **23a**), 120.1 (C-11 in **23b**), 125.5 (C-17 in **23a** & **23b**), 127.4 (C-3 in **23a** & **23b**), 128.0 (C-1 in **23b**), 128.0 (C-1 in **23a**), 128.7 (C-2 in **23a** & **23b**), 131.3 (C-10 in **23a** & **23b**), 132.5 (C-19 in **23b**), 132.5 (C-19 in **23a**), 132.6 (C-18 in **23b**), 132.7 (C-18 in **23a**), 137.2 (C-4 in **23a**), 137.2 (C-4 in **23b**), 138.0 (C-23 in **23a**), 138.0 (C-23 in **23b**),

148.4 (C-6 in **23a** & **23b**), 149.9 (C-7 in **23b**), 150.0 (C-7 in **23a**), 153.4 (C-21 in **23a** & **23b**). Found, *m/z*: 493.2221 $[M+H]^+$. $C_{29}H_{33}O_7$. Calculated, *m/z*: 493.2221.

***Rel*-((2*S*,3*R*,4*R*)-2-(4-(benzyloxy)-3-methoxyphenyl)-4-(3,4,5-trimethoxybenzyl)tetrahydro-furan-3-yl)methanol (24).** A flame-dried Schlenk flask was charged with $TiCp_2Cl_2$ (36.8 mg, 0.149 mmol, 2.50 eq.) and to this was added dry, degassed THF (11.8 cm^3) under a nitrogen atmosphere, followed by freshly activated[23,49,50] Zn dust (38.7 mg, 0.595 mmol, 10.0 eq). The resultant suspension was stirred for 1 hour at room temperature. Stirring was stopped to allow excess Zn dust to settle to the bottom of the flask. The supernatant was then added *via* cannula to a solution of **23ab** (29.3 mg, 0.0595 mmol, 1.00 eq, *d.r.* 1:1) in dry degassed THF (0.6 mL) and the reaction mixture was stirred at room temperature for 1 hour. The mixture was quenched using 10% aqueous H_2SO_4 (10 mL) and diluted with EtOAc (50 mL). The reaction was partitioned and the organic layer washed with H_2O (1 x 25 mL) followed by $NaHCO_{3(aq)}$ (1 x 25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **24** (9.4 mg, 0.0190 mmol, 32%) as a yellow oil. IR (oil, ATR-FTIR, ν_{max}, cm^{-1}): 2899, 1585, 1508, 1458, 1419, 1126, 995. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.39 – 2.48 (m, 1H, H-15), 2.55 (dd, *J* = 13.5, 10.9 Hz, 1H, H_a-18), 2.70 – 2.79 (m, 1H, H-16), 2.94 (dd, *J* = 13.5, 4.9 Hz, 1H, H_b-18), 3.75 – 3.95 (m, 15H, H-8, H_a-14, H-17, H-22, H-24), 4.06 (dd, *J* = 8.6, 6.5 Hz, 1H, H_b-14), 4.79 (d, *J* = 6.7 Hz, 1H, H-13), 5.15 (s, 2H, H-5), 6.40 (s, 2H, H-20), 6.79 (dd, *J* = 8.3, 2.0 Hz, 1H, H-11), 6.84 (d, *J* = 8.2 Hz, 1H, H-12), 6.91 (d, *J* = 2.0 Hz, 1H, H-9), 7.27 – 7.32 (m, 1H, H-1), 7.33 – 7.38 (m, 2H, H-2), 7.41 – 7.45 (m, 2H, H-3). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 34.2 (C-18), 42.5 (C-16), 52.7 (C-15), 56.2 (C-24), 56.3 (C-22), 61.0 (C-8), 61.1 (C-17), 71.2 (C-5), 73.0 (C-14), 82.8 (C-13), 105.7 (C-20), 109.6 (C-9), 114.0 (C-12), 118.1 (C-11), 127.4 (C-3), 128.0 (C-1), 128.7 (C-2), 135.5 (C-19), 136.0 (C-10), 136.3 (C-23), 137.3 (C-4), 147.7 (C-6), 149.9 (C-7), 153.4 (C-21). Found, *m/z*: 517.2200 $[M+Na]^+$. $C_{29}H_{34}O_7Na$. Calculated, *m/z*: 517.2203. Minor signals in the ^{1}H NMR spectrum likely belong to an isomer, with as yet unassigned stereochemistry, based on a previous literature report on a related system.[23] See Supplementary Material for alternative synthesis of **24** via **28** (Scheme 3).

Rel-(1*S*,3a*R*,4*S*,6a*R*)-1-(4-(benzyloxy)-3-methoxyphenyl)-4-(3,4,5 trimethoxyphenyl)tetrahydro -1H,3H-furo[3,4-c]furan (25). IR (oil, ATR-FTIR, ν_{max}, cm^{-1}): 2930, 1263, 1125. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.05 – 3.14 (m, 2H, H-15, H-18), 3.84 (s, 3H, H-8), 3.87 (s, 6H, H-22), 3.88 – 3.93 (m, 5H, H-24, H_a-14, H_a-17), 4.24-4.31 (m, 2H, H_b-14, H_b-17), 4.72-4.77 (m, 2H, H-13, H-16), 5.15 (s, 2H, H-5), 6.57 (s, 2H, H-20), 6.80 (dd, *J* = 8.4, 2.0 Hz, 1H, H-11), 6.85 (d, *J* = 8.3 Hz, 1H, H-12), 6.93 (d, *J* = 2.0 Hz, 1H, H-9), 7.27 – 7.32 (m, 1H, H-1), 7.33 – 7.38 (m, 2H, H-2), 7.41 – 7.45 (m, 2H, H-3). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 54.2 (C-15 or C-18), 54.6 (C-15 or C-18), 56.2 (C-24), 56.3 (C-22), 61.0 (C-8), 71.2 (C-5), 71.9 (C-14 or C-17), 72.1 (C-14 or C-17), 85.8 (C-13 or C-16), 86.2 (C-13 or C-16), 102.9 (C-20), 109.9 (C-9), 114.0 (C-12), 118.3 (C-11), 127.4 (C-3), 128.0 (C-1), 128.7 (C-2), 134.1 (C-10), 136.9 (C-4), 137.2 (C-19), 137.5 (C-23), 147.9 (C-6), 150.0 (C-7), 153.6 (C-21). Found, *m/z*: 515.2029 $[M+Na]^+$. $C_{29}H_{32}O_7Na$. Calculated, *m/z*: 515.2046.

***Rel*-(*R*)-2-((*R*)-(allyloxy)(4-(benzyloxy)-3-methoxyphenyl)methyl)oxirane (26).** A flame-dried flask containing **17a** (925 mg, 3.23 mmol, 1.00 eq.) in dry THF (32 mL) under a nitrogen atmosphere was cooled to 0˚C, and to it was added NaH (60% dispersion, 388 mg, 9.70 mmol, 3.00 eq.). The resultant suspension was stirred at 0˚C for 30 minutes. To this mixture was added freshly distilled allyl bromide (0.300 mL, 3.56 mmol, 1.10 eq.). The reaction was then warmed to room temperature, and stirred for 1 hour. The reaction was quenched by addition of $NH_4Cl_{(aq)}$ (25 mL) and the layers were partitioned. The aqueous layer was extracted using EtOAc (3 x 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification on silica gel (0-40% EtOAc in hexane) gave **26** (919 mg, 2.81 mmol, 87%) as a colourless oil. IR (oil, ATR-FTIR,

ν_{max}, cm^{-1}): 2924, 1512, 1260; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.59 (dd, *J* = 4.9, 2.7 Hz, 1H, H_b-15), 2.74 (dd, *J* = 4.5, 4.5 Hz, 1H, H_a-15), 3.20 (ddd, *J* = 6.7, 4.2, 2.7 Hz, 1H, H-14), 3.91 (s, 3H, H-8), 3.94 – 4.09 (m, 3H, H-13, H-16), 5.13 – 5.22 (m, 3H, H-5, H_b-18), 5.28 (dd, *J* = 17.3, 1.8 Hz, 1H, H_a-18), 5.93 (ddt, *J* = 16.4, 10.9, 5.6 Hz, 1H, H-17), 6.78 (dd, *J* = 8.2, 2.0 Hz, 1H, H-11), 6.86 (d, *J* = 8.1 Hz, 1H, H-12), 6.94 (d, *J* = 1.9 Hz, 1H, H-9), 7.28 – 7.33 (m, 1H, H-1), 7.35 – 7.40 (m, 2H, H-2), 7.42 – 7.46 (m, 2H, H-3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 44.6 (C-15), 55.5 (C-14), 56.2 (C-8), 69.9 (C-16), 71.1 (C-5), 82.4 (C-13), 110.4 (C-9), 113.8 (C-12), 117.4 (C-18), 119.7 (C-11), 127.4 (C-3), 128.0 (C-1), 128.7 (C-2), 131.3 (C-10), 134.6 (C-17), 137.2 (C-4), 148.3 (C-6), 150.0 (C-7). Found, *m/z*: 349.1411 $[M+Na]^+$. $C_{20}H_{22}O_4Na$. Calculated, *m/z*: 349.1416.

***Rel*-((2*S*,3*R*,4*R*)-2-(4-(benzyloxy)-3-methoxyphenyl)-4-methyltetrahydrofuran-3-yl)methanol (27).** A flame-dried Schlenk flask was charged with $TiCp_2Cl_2$ (712 mg, 2.86 mmol, 2.30 eq.) and to this was added dry, degassed THF (24.8 mL) under a nitrogen atmosphere, followed by freshly activated[23,49,50] Zn dust (811 mg, 12.4 mmol, 10.0 eq). The resultant suspension was stirred for 1 hour at room temperature. Stirring was stopped to allow excess Zn dust to settle to the bottom of the flask. The supernatant was then added *via* cannula to a solution of **26** (405 mg, 1.24 mmol, 1.00 eq.) in dry degassed THF (12.4 mL) and the reaction mixture was stirred at room temperature for 1 hour. The mixture was quenched using 10% aqueous H_2SO_4 (10 mL) and diluted with EtOAc (50 mL). The reaction was partitioned and the organic layer washed with H_2O (1 x 25 mL) followed by $NaHCO_{3(aq)}$ (1 x 25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification on silica gel (0-50% EtOAc in pet ether) gave **27** (220 mg, 0.67 mmol, 54%) as a colourless oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ_H 1.09 (d, *J* = 7.1 Hz, 3H, H-18), 2.29 – 2.31 (m, 1H, H-15), 2.52 – 2.62 (m, 1H, H-16), 3.62 (dd, *J* = 8.4, 5.6 Hz, 1H, H_b-14), 3.69 (ddd, *J* = 10.6, 6.3, 4.4 Hz, 1H, H_a-17), 3.82 (ddd, *J* = 10.7, 7.3, 4.9 Hz, 1H, H_b-17), 3.90 (s, 3H, H-8), 4.24 (dd, *J* = 8.4, 6.6 Hz, 1H, H_a-14), 4.66 (d, *J* = 7.3 Hz, 1H, H-13), 5.14 (s, 2H, H-5), 6.79 (dd, *J* = 8.2, 2.0 Hz, 1H, H-11), 6.83 (d, *J* = 8.1 Hz, 1H, H-12), 6.91 (d, *J* = 2.0 Hz, 1H, H-9), 7.27 – 7.31 (m, 1H, H-1), 7.36-7.38 (m, 2H, H-2), 7.40 – 7.46 (m, 2H, H-3). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 13.1 (C-18), 35.2 (C-16), 53.0 (C-15), 56.1 (C-8), 61.1 (C-14), 71.2 (C-5), 75.6 (C-17), 82.6 (C-13), 109.7 (C-9), 114.0 (C-11), 118.3 (C-12), 127.4 (C-3), 127.9 (C-1), 128.7 (C-2), 136.1 (C-10), 137.4 (C-4), 147.7 (C-6), 149.9 (C-7). Found, *m/z*: 351.1557 $[M+Na]^+$. $C_{20}H_{24}O_4Na$. Calculated, *m/z*: 351.1573. Minor signals in the ^{1}H NMR spectrum likely belong to an isomer, with as yet unassigned stereochemistry, based on a previous literature report on a related system.[23]

***Rel*-4-((2*S*,3*R*,4*R*)-3-(hydroxymethyl)-4-(3,4,5-trimethoxybenzyl)tetrahydrofuran-2-yl)-2-methoxyphenol (29).** A flask was charged with **24** (68 mg, 0.139 mmol, 1.00 eq.), Pd/C (7.00 mg, 10.0 wt%) and MeOH (1.4 cm^3), and the solution was degassed using N_2. The gas inlet was removed, and the flask was placed under negative pressure, then backfilled with H_2. The reaction was stirred vigorously to create a vortex for 1 hour, after which the H_2 inlet was removed and the reaction mixture filtered through celite. The solution was evaporated under reduced pressure. Purification on silica gel (0- 70% EtOAc in pet ether) afforded **29** (53.0 mg, 0.132 mmol, 95%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.40-2.47 (m, 1H, H-10), 2.55 (dd, *J* = 13.4, 11.0 Hz, 1H, H_b-13), 2.71-2.80 (m, 1H, H-11), 2.95 (dd, *J* = 13.5, 4.8 Hz, 1H, H_a-13), 3.75 – 3.86 (m, 11H, H-3 or H-19, H_b-9, H_b-12, H-17), 3.88 – 3.95 (m, 4H, H-3 or H-19, H_a-12), 4.06 (dd, *J* = 8.6, 6.5 Hz, 1H, H_a-9), 4.78 (d, *J* = 6.8 Hz, 1H, H-8), 5.59 (s, 1H, CH_2-O<u>H</u>), 6.41 (s, 2H, H-15), 6.81 (dd, *J* = 8.0, 1.9 Hz, 1H, H-6), 6.85 – 6.90 (m, 2H, H-4, H-7). ^{13}C NMR (126 MHz, $CDCl_3$): δ_c 34.2 (C-13), 42.5 (C-10), 52.8 (C-11), 56.1 (C-3), 56.3 (C-17), 61.0 (C-12), 61.0 (C-19), 73.0 (C-9), 82.9 (C-8), 105.7 (C-15), 108.4 (C-4), 114.3 (C-7), 118.9 (C-6), 134.8 (C-5), 136.3 (C-18), 136.4 (C-14), 145.2 (C-1), 146.8 (C-2), 153.4 (C-16). Found, *m/z*: 427.1729 $[M+Na]^+$. $C_{22}H_{28}O_7Na$. Calculated, *m/z*: 427.1733.

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Supplementary Material

Numbering system used for NMR assignments in Experimental Section of manuscript. Synthesis procedure for diastereomeric mixture **17ab**. Analytical data for known compounds prepared during this work. Synthesis procedures and analytical data for **23a** from **17a**. nOe studies on **27**. ^{1}H NMR assignment comparison between relevant protons of **24** and **27** in $CDCl_3$. Alternative Synthesis of **24** via **28** inspired by a literature route. NMR comparisons of synthesised Linderuca C (**6**) with literature report. NMR Spectra for Novel and Key Compounds.

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