Synthesis of dihydrodehydrodiconiferyl alcohol: the revised structure of lawsonicin†

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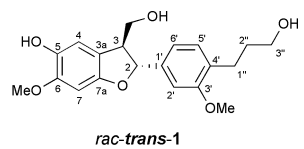
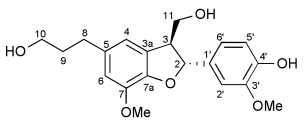
Structural revision of lawsonicin, a natural product of *Lawsonia alba*, is reported based upon comparison of its spectral data with that of the naturally occurring dihydrobenzo[*b*]furan neolignan (*rac*)-*trans*-dihydrodehydrodiconiferyl alcohol, which is found to be identical. A concise synthesis of dihydrodehydrodiconiferyl alcohol, *via* Rh_2[*S*-DOSP]$_4$-catalysed intramolecular C–H insertion, is described.

Introduction

Isolation and structural elucidation of lawsonicin (*rac*-***trans*-1**), a natural product of *Lawsonia alba*, was reported by one of us in 2003[1] (Fig. 1). Although the assignment of a core 2-aryl-(3′,4′-substituted)-2,3-*trans*-dihydrobenzo[*b*]furan is unambiguous, the 5,6-substitution pattern of the benzofuran ring was not conclusively established. Lawsonicin is of unknown biosynthesis;[2] however, its formula, $C_{20}H_{24}O_6$, implies that the molecule may derive from dimerisation of coniferyl alcohol ($C_{10}H_{12}O_3$) and belong to a class of known 2-aryl-2,3-dihydrobenzo[*b*]furan lignans.



rac-***trans*-1**



rac-***trans*-2**

Fig. 1 Structures of racemic 2,3-*trans* epimers of lawsonicin (**1**) and dihydrodehydrodiconiferyl alcohol (**2**).

Lignans constitute a large group of plant secondary metabolites whose biosynthesis involves the dimerisation of phenylpropenes.[3] Resonance stabilisation of a radical formed from a (phenylpropene) monolignol facilitates oxidative coupling of radical partners (or electrophilic attack of a single radical upon a second monolignol molecule),[4] to give structurally diverse products, of which 8-8′-linked lignans are the most common. The established biosynthesis of dehydrodiisoeugenols, *via* bimolecular coupling of phenoxy radicals derived from laccase-catalysed oxidation of 2-methoxy-4-*trans*-propenylphenol (isoeugenol),[5,6] is widely applied to 8-5′-linked lignan (neolignan) biosynthesis and can be delineated for dimerisation of coniferyl alcohol (**3**) (Fig. 2).[6,7]

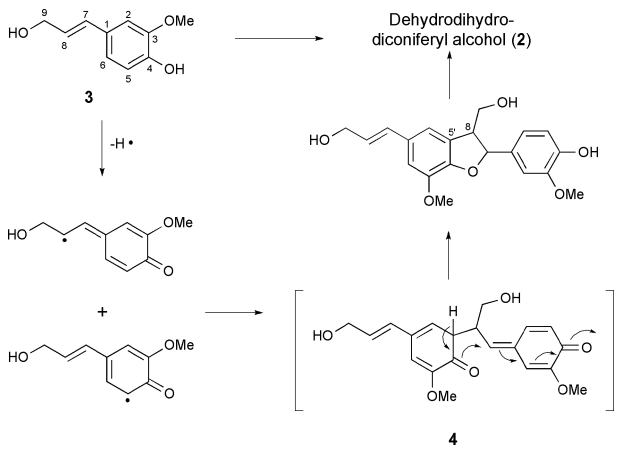


Fig. 2 Schematised biosynthesis of dihydrodehydrodiconiferyl alcohol *via* 8-5′ radical coupling.

8-5′-Dimerisation leads to an intermediate *p*-quinone methide, **4**,[8,9] intramolecular cyclisation of which installs the dihydrobenzo[*b*]furan core, prior to an enzymatic allylic alcohol reduction.[10] Dihydrodehydrodiconiferyl alcohol, **2**, is furnished in this overall oxidoreductive process. Added structural classes of lignan may be defined, featuring an 8-*O*4′, 8-3′, 8-2′ or 8-1′ linkage and potentially involving further post-dimerisation modifications. However, the ascribed connectivity of lawsonicin (*rac*-***trans*-1**) cannot be rationalised within these established pathways for monolignol dimerisation, and we herein propose structural revision of lawsonicin, to the known neolignan, dihydrodehydrodiconiferyl alcohol[11–14] (*rac*-***trans*-2**,[15] Fig. 1).

Results and discussion

A comparison of ^{1}H and ^{13}C NMR data for *rac*-***trans*-1** with that reported for *rac*-***trans*-2** was first made (Table 1). ^{1}H NMR data is similar for the two molecules, although small differences

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† Electronic supplementary information (ESI) available: ^{13}C NMR spectra for compounds **2**, **8**, **10–14**, **16–20** and the isolated natural product. See DOI: 10.1039/b918179b

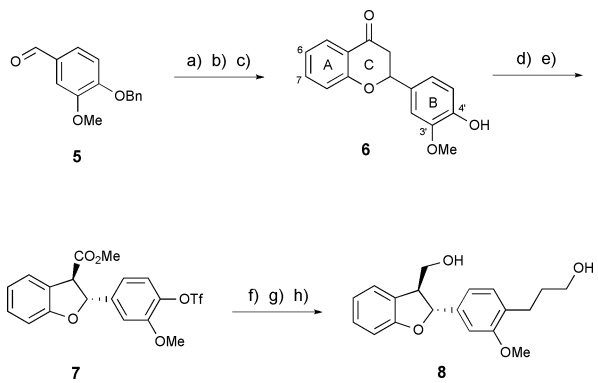
Table 1 Reported ^{1}H and ^{13}C NMR data ($CDCl_3$)[a] of lawsonicin (*rac-**trans**-***1***)[1] and dihydrodehydrodiconiferyl alcohol (*rac-**trans**-***2***)[17]

	δ^{1}H/ppm		δ^{13}C/ppm[c]	
Position[b]	*rac-**trans**-***1***	*rac-**trans**-***2***	*rac-**trans**-***1***	*rac-**trans**-***2***
2	5.41 (1H, d, J = 7.0 Hz)	5.54 (1H, d, J = 7.6 Hz)	88.0	87.9
3	3.45 (1H, ddd, J = 8.0, 7.0, 5.0 Hz)	3.60 (1H, q, J = 7.6 Hz)	53.8	53.8
3a	—	—	127.9	127.7
4	6.56 (1H, s)	6.67 (1H, s)	116.1	116.0
5	—	—	133.1	133.0
6	6.60 (1H, s)	6.67 (1H, s)	112.8	112.4
7	—	—	144.2	144.2
7a	—	—	146.7	146.6
7-OMe	3.77 (3H, s)	3.88 (3H, s)	55.9	56.0
8	2.54 (2H, t, J = 7.5 Hz)	2.67 (2H, t, J = 7.3 Hz)	32.0	32.0
9	1.70 (2H, tt, J = 7.5, 6.5 Hz)	1.88 (2H, tt, J = 7.3, 6.6 Hz)	34.5	34.6
10	3.53 (2H, t, J = 6.5 Hz)	3.69 (2H, t, J = 6.6 Hz)	62.3	62.3
11	3.74 (2H, m)	3.90 (2H, d, J = 7.6 Hz)	64.0	63.9
1′	—	—	135.5	135.4
2′	6.85 (1H, d, J = 1.9 Hz)	6.94 (1H, d, J = 1.7 Hz)	108.9	108.8
3′	—	—	146.5	146.6
3′-OMe	3.75 (3H, s)	3.86 (3H, s)	56.0	56.0
4′	—	—	145.7	145.6
5′	6.72 (1H, d, J = 8.1 Hz)	6.87 (1H, d, J = 8.1 Hz)	114.5	114.3
6′	6.77 (1H, dd, J = 8.1, 1.9 Hz)	6.91 (1H, dd, J = 8.1, 1.7 Hz)	119.5	119.4

[a] Chemical shifts are referenced to residual solvent (δ^{1}H) or solvent (δ^{13}C) for *rac-**trans**-***1***, and to tetramethylsilane for *rac-**trans**-***2***. [b] Refers to the numbering of *rac-**trans**-***2*** (Fig. 1) and reported assignments for *rac-**trans**-***2***.[2] [c] Literature chemical shifts for both molecules were reported to 0.1 ppm. Correction of reported chemical shifts, C4 (–0.4 ppm), C10 (+0.8 ppm), C11 (+0.4 ppm) and 3′-OMe (+2.3 ppm) for *rac-**trans**-***1***,[1] is based upon the actual ^{13}C NMR spectrum of lawsonicin.

in reported chemical shift are difficult to attribute. Integral, multiplicity of resonance and coupling constants are largely consistent, and discrepancies appear only for assignment of the ^{1}H-11 multiplicity in a spectral region of substantial overlap, and also as disparate assignment of the ^{1}H-3 multiplicity. Importantly, $^{4}J_{H4\text{-}H6}$ coupling is not observed for *rac-**trans**-***2***, indicating that the *para*-relationship, inferred on this basis between aromatic protons of the benzofuran ring for *rac-**trans**-***1***, may be mistaken. ^{13}C NMR data is an excellent match for the two molecules and aromatic δCH values support the structural assignment of *rac-**trans**-***2***. Firstly, those of the benzofuran ring: δ^{13}CH-4 (116.0 ppm) is expected to be similar for either molecule; however, δ^{13}CH-7 (*rac-**trans**-***1***) is expected at higher field than δ^{13}CH-6 (*rac-**trans**-***2***), and the observed δ^{13}CH = 112.8 ppm is consistent with a δ^{13}CH-6 (*rac-**trans**-***2***) assignment.[16] Secondly, the 2-aryl substituent: δ^{13}CH-5′ (*rac-**trans**-***1***) is expected at lower field than δ^{13}CH-5′ (*rac-**trans**-***2***), *i.e.* δ^{13}CH-5′ > δ^{13}CH-2′/δ^{13}CH-6′ (*rac-**trans**-***1***) and the ^{13}C NMR data support the (2-aryl)-3′-methoxy-4′-hydroxy-substitution pattern of *rac-**trans**-***2***.

In order to model δ^{13}CH-5′, -2′ and -6′ of *rac-**trans**-***1***, we prepared derivative **8**, bearing the (2-aryl)-3′,4′-disubstitution pattern of lawsonicin, *via* a B-ring-substituted flavanone **6**. 3′-Methoxy-4′-hydroxyflavanone[18] (**6**) was prepared *via* Claisen–Schmidt condensation of vanillin benzyl ether (**5**) and 2′-hydroxy acetophenone,[19] followed by cyclisation of the resulting hydroxychalcone derivative and benzyl ether hydrogenolysis. Conversion of **6** to a triflic ester was straightforward and oxidative ring contraction[20] proceeded to give the expected *rac-trans*-dihydrobenzo[*b*]furan derivative **7** in moderate yield.[21] Low-yielding Heck coupling with methyl acrylate, catalytic hydrogenation and methyl ester reduction steps furnished **8** (Scheme 1).



Scheme 1 Synthesis of a (2-aryl)-3′,4′-disubstituted analogue of lawsonicin. *Reagents and conditions*: (a) 2′-hydroxyacetophenone, dioxane, 50% w/v KOH (aq.), EtOH, △ (75%); (b) NaOAc, MeOH, △ (70%); (c) H_2 (1 atm), 10% Pd/C, CH_2Cl_2–MeOH, rt (100%); (d) Tf_2O, Et_3N, CH_2Cl_2, –78 °C→rt (67%); (e) $HClO_4$, trimethyl orthoformate, $Tl(NO_3)_2{\cdot}3H_2O$, rt (46%); (f) $PdCl_2$, PPh_3, methyl acrylate, Et_3N, DMF, 110 °C (30%); (g) H_2 (1 atm), 10% Pd/C, CH_2Cl_2–MeOH, rt (100%); (h) $LiAlH_4$, Et_2O, rt (94%).

The ^{13}C NMR spectrum of model compound **8** ($CDCl_3$, 400 MHz) correlates poorly with that of lawsonicin; ^{13}C-1′, ^{13}C-3′ and ^{13}CH-5′ appear substantially downfield of the corresponding nuclei in lawsonicin, whilst ^{13}C-4′ is upfield (Table 2).

Observed differences, $\Delta\delta$ (ppm), are as expected for the comparison of a 3′-methoxy-4′-(3-hydroxypropyl)-aryl substituent with the 3′-methoxy-4′-hydroxy aryl group of dihydrodehydrodiconiferyl alcohol. However, due to small inconsistencies in the ^{13}C NMR data reported elsewhere for *rac-**trans**-***2***,[12,22] we wished to finally

Table 2 ^{13}C NMR data[a] of (2-aryl)-3′,4′-disubstituted analogue, **8**

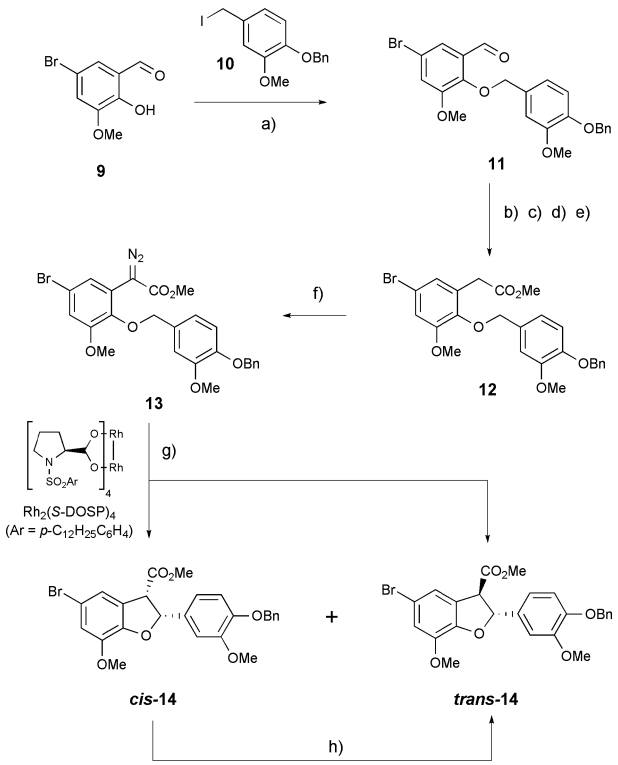
Position	δ^{13}C/ppm (**8**)	$\Delta\delta$ (**8** *vs. rac-**trans**-***1**)
1′	141.04	+5.54
2′	107.95	–0.95
3′	157.86	+11.36
4′	130.14	–15.56
5′	130.50	+16.0
6′	118.21	–1.0

[a] Chemical shifts are referenced to solvent signal ($CDCl_3$).

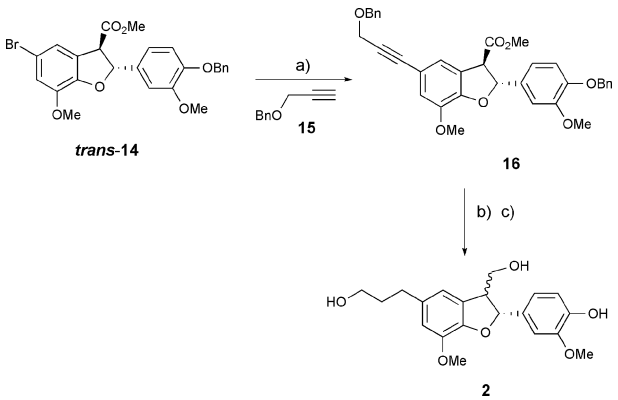
verify the structural revision of lawsonicin by comparison of authentic samples.

Although the oxidative rearrangement of a simple flavanone had proved successful (Scheme 1), attempted rearrangement of various 6,7-disubstituted flavanones failed to yield a functionalised 2,3-dihydrobenzo[*b*]furan core precursor to the reported structure of lawsonicin, and so we wished to avoid the potentially difficult cyclisation of an A-ring-substituted flavanone for preparation of *rac-trans*-dihydrodehydrodiconiferyl alcohol (*rac-**trans***-**2**). Therefore, a synthetic approach to *rac-**trans***-**2** involving intramolecular C–H insertion of an α-diazoester, as the key step for formation of the dihydrobenzo[*b*]furan ring, was adopted. The presence of a (pivaloate) protected 5-(3-hydroxypropyl) side chain was detrimental to the yield in preparation of a closely related α-diazo methyl ester,[23] and we chose, therefore, to prepare a 5-bromo-2,3-dihydrobenzo[*b*]furan, ***trans***-**14**, in order to later introduce the 3-hydroxypropyl side chain under Pd^0 catalysis.

Benzyl iodide **10** was prepared in 77% yield from 4-hydroxy-3-methoxybenzyl alcohol. Coupling of **10** with 5-bromo-2-hydroxy-3-methoxybenzaldehyde (**9**) was carried out, followed by Wittig olefination, enol ether hydrolysis, oxidation and methylation with diazomethane, yielding methyl ester **12**. Diazo transfer, using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and DBU,[24] enabled conversion of **12** to **13** in good yield. Catalysis of the intramolecular C–H insertion of **13** was effected upon treatment with Rh_2[*S*-DOSP]$_4$,[25,26] and a 1.3 : 1 (*trans* : *cis*) ratio of separable 2,3-dihydroxybenzo[*b*]furan isomers, **14**, resulted, also in good yield. Pleasingly, epimerisation of ***cis***-**14** to its thermodynamically more stable ***trans***-**14** isomer proceeded smoothly upon treatment with sodium methoxide, following Hashimoto's conditions[27] (Scheme 2). Sonogashira coupling between ***trans***-**14** and prop-2-ynyloxymethyl benzene[28] (**15**) took place to give **16** in good yield.[29] Corresponding alkyne reduction and benzyl ether hydrogenolysis was then carried out, and required careful control of conditions in order to avoid dihydrobenzofuran ring-opening. Finally, methyl ester reduction using $LiAlH_4$ resulted in partial C3-epimerisation[30] and dihydrodehydrodiconiferyl alcohol **2** was obtained as a 10 : 3 (2,3-*trans* : 2,3-*cis*) diastereomeric product mixture, which we were unable to separate using HPLC (Scheme 3). Nonetheless, direct comparison of ^{1}H and ^{13}C NMR, and EIMS data for the product mixture, **2**, with that of lawsonicin, indicated the major isomer *rac-**trans***-**2** to be identical to lawsonicin.



Scheme 2 Synthesis of an aryl bromide functionalised precursor to dihydrodehydrodiconiferyl alcohol. *Reagents and conditions*: (a) KH, 18-crown-6, THF, 60 °C, 1.5 h (98%); (b) ^{n}BuLi, (methoxymethyl) triphenylphosphonium chloride, THF, –78 °C→rt, 5 h (70%); (c) $Hg(OAc)_2$, MeCN–H_2O, rt, 1 h (67%); (d) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4{\cdot}2H_2O$, ^{t}BuOH–H_2O, 0 °C→rt then rt, 14 h (86%); (e) CH_2N_2, Et_2O–THF, –78 °C→rt (95%); (f) *p*-ABSA, DBU, MeCN, 0 °C→rt then rt, 24 h (90%); (g) Rh_2[*S*-DOSP]$_4$ (1.3 mol%), toluene, 0 °C, 2 h (95%); (h) NaOMe, MeOH, –60 °C, 26 h (96%).



Scheme 3 Synthesis of dihydrodehydrodiconiferyl alcohol. *Reagents and conditions*: (a) $Pd(PPh_3)_4$ (13 mol%), CuI (0.53 equiv.), Et_3N, 90 °C, 6 h (73%); (b) H_2 (1 atm), 10% Pd/C, MeOH, rt, 3 h; then formic acid, 20 min (97%); (c) $LiAlH_4$, THF, –15 °C→0 °C, 3 h (100%).

Conclusions

An efficient synthesis of dihydrodehydrodiconiferyl alcohol **2**, in twelve linear steps and 16% yield, has been completed, although attenuated by partial C3-epimerisation in the final step. Valuable advantages of the described route are high-yielding diazo transfer and C–H insertion, for formation of the 2,3-dihydrobenzo[*b*]furan core, and a late-stage Pd^0-catalysed functionalisation, which permits the synthesis of analogues with varying C5-substitution. Of most importance, the major 2,3-*trans*-epimer of **2** has identical spectral data to the 2,3-dihydrobenzo[*b*]furan natural product,

lawsonicin, whose earlier reported structure is revised to 2,3-*trans*-dihydrodehydrodiconiferyl alcohol (*rac*-***trans*-2**). The identity of (*rac*-***trans*-2**) as a constituent of *Lawsonia alba* is confirmed.

Experimental

General techniques

Reagents and solvents were obtained from commercial suppliers and, if necessary, dried and distilled before use. THF was freshly distilled from sodium benzophenone ketal under argon. Toluene was distilled from sodium under argon. Dichloromethane, acetonitrile and triethylamine were freshly distilled from CaH_2. *N*,*N*-Dimethylformamide and hexamethyldisilazane were distilled from CaH_2 and stored over 4 Å molecular sieves. Reactions requiring a dry atmosphere were conducted in oven dried glassware under argon. Petrol refers to the fraction boiling between 40 and 60 °C. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 or 400 MHz spectrometers. ^{1}H chemical shifts are reported as values in ppm referenced to residual solvent. The following abbreviations are used to denote multiplicity and may be compounded: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, sext = sextet. Coupling constants, *J*, are measured in Hertz (Hz). ^{13}C spectra were proton decoupled and referenced to solvent. Signals are reported as s, d, t, q, depending on the number of directly attached protons (0, 1, 2 and 3, respectively), this being determined by DEPT experiments. Infra-red spectra were recorded either as neat solids or as oils on a Bio-Rad Golden Gate ATR FT–IR spectrometer fitted with an ATR accessory. Absorptions are given in wavenumbers (cm^{-1}) and the following abbreviations used to denote peak intensities: s = strong, m = medium, w = weak and/or br (broad). Low resolution mass spectra were recorded on a Micromass platform single quadrupole mass spectrometer in methanol or acetonitrile. Accurate mass spectra were recorded on a double focusing mass spectrometer.

Synthetic procedures

1-(Benzyloxy)-4-(iodomethyl)-2-methoxybenzene (10). To a stirred solution of 4-benzyloxy-3-methoxybenzyl alcohol[31] (2.33 g, 9.54 mmol) in THF (50 mL) at 0 °C was added I_2 (2.68 g, 10.56 mmol), imidazole (0.85 g, 12.49 mmol) and PPh_3 (2.82 g, 10.75 mmol). The mixture was stirred for 50 min at 0 °C before addition of a solution of $Na_2S_2O_3{\cdot}5H_2O$ (1.90 g) in H_2O (15 mL) followed by Et_2O (50 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (2 × 50 mL). The combined organic extracts were then washed with $Na_2S_2O_3$ (15 mL of an 11% w/v aqueous solution) dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2 eluted with petrol/EtOAc, 20 : 1) gave the title compound **10** as white needles (2.70 g, 80%). m.p. 82–83 °C. IR (solid): 2877 (w), 1587 (m), 1513 (m, br), 1257 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.29 (5H, m), 6.90 (1H, d, J = 2.0 Hz), 6.89 (1H, dd, J = 2.0, 8.1 Hz), 6.76 (1H, d, J = 8.1 Hz), 5.13 (2H, s), 4.45 (2H, s), 3.88 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.83 (s), 148.17 (s), 137.09 (s), 132.31 (s), 128.76 (d), 128.08 (d), 127.40 (d), 121.19 (d), 113.93 (d), 112.60 (d), 71.15 (t), 56.19 (q), 7.12 (t) ppm. MS (ES+): m/z (%) = 377 (100%) $[M+Na]^+$.

2-{[4-(Benzyloxy)-3-methoxybenzyl]oxy}-5-bromo-3-methoxybenzaldehyde (11). To a suspension of KH (0.57 g, 14.12 mmol) in THF (30 mL) was added a solution of 5-bromo-2-hydroxy-3-methoxybenzaldehyde (**9**) (1.64 g, 7.09 mmol) in THF (10 mL) at 0 °C. The mixture was stirred for 5 min before addition of a solution of benzyl iodide **10** (3.00 g, 8.47 mmol) and 18-crown-6 (1.04 g, 3.93 mmol) in THF (20 mL). The mixture was stirred at 60 °C for 1.5 h before addition of H_2O (20 mL) followed by EtOAc (50 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2 eluted with petrol/EtOAc, 12 : 1) gave the title compound **11** as a white solid (3.17 g, 98%). m.p. 126 °C. IR (solid): 2938 (w), 1684 (m), 1475 (m, br), 736 (m, br) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.09 (1H, s), 7.48 (1H, d, J = 2.1 Hz), 7.42-7.25 (5H, m), 7.23 (1H, d, J = 2.1 Hz), 6.89 (1H, d, J = 1.3 Hz), 6.81 (1H, t, J = 8.0 Hz), 6.77 (1H, dd, J = 8.0, 1.3 Hz), 5.13 (2H, s), 5.07 (2H, s), 3.92 (3H, s), 3.85 (3H, s) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 188.89 (d), 154.09 (s), 150.28 (s), 149.94 (s), 148.81 (s), 137.07 (s), 131.40 (s), 129.10 (s), 128.73 (d), 128.06 (d), 127.44 (d), 121.89 (d), 121.72 (d), 120.95 (d), 117.23 (s), 113.98 (d), 112.75 (d), 76.63 (t), 71.18 (t), 56.57 (q), 56.22 (q) ppm. MS (ES+): m/z (%) = 479 (98%) $[M+Na]^+$. HRMS (ES^+): m/z $[M+Na]^+$ calcd for $C_{23}H_{21}BrNaO_5$: 479.0470; found 479.0469.

(*E*)-2-{[4-(Benzyloxy)-3-methoxybenzyl]oxy}-5-bromo-1-methoxy-3-(2-methoxyvinyl)benzene (17). To a stirred suspension of (methoxymethyl) triphenylphosphonium chloride (3.37 g, 9.84 mmol) in THF (30 mL) was added ^{n}BuLi (4.5 mL of a 1.5M solution in hexane, 6.75 mmol). The mixture was stirred at room temperature for 30 min before cooling to −78 °C. A solution of aldehyde **11** (1.50 g, 3.28 mmol) in THF (15 mL) was added and the mixture stirred for 5 h, warming to room temperature during this time. The mixture was then concentrated *in vacuo*. Purification by column chromatography (SiO_2 eluted with petrol/EtOAc, 15 : 1) gave the title compound **17** as a white solid (1.11 g, 70%). m.p. 87 °C. IR (solid): 2935 (w), 2832 (w), 1638 (m), 1585 (w), 1513 (m), 1463 (s), 1265 (s, br), 736 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (2H, d, J = 7.4 Hz), 7.35 (2H, t, J = 7.4 Hz), 7.29 (1H, t, J = 7.4 Hz), 7.28 (1H, m), 7.03 (1H, d, J = 13.0 Hz), 7.01 (1H, s), 6.86-6.82 (3H, m), 5.87 (1H, d, J = 13.0 Hz), 5.16 (2H, s), 4.84 (2H, s), 3.89 (3H, s), 3.83 (3H, s), 3.55 (3H, s) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 153.90 (s), 150.74 (d), 149.81 (s), 148.28 (s), 143.60 (s), 137.29 (s), 132.81 (s), 130.84 (s), 128.71 (d), 128.00 (d), 127.41 (d), 121.21 (d), 120.11 (d), 116.87 (s), 113.99 (d), 113.03 (d), 112.66 (d), 99.40 (d), 75.02 (t), 71.23 (t), 56.62 (q), 56.21 (q), 56.16 (q) ppm. MS (ES+): m/z (%) = 507 (93%) $[M+Na]^+$. HRMS (ES^+): m/z $[M+Na]^+$ calcd for $C_{25}H_{25}BrNaO_5$: 507.0783; found 507.0778.

2-{2-[4-(Benzyloxy)-3-methoxybenzyloxy]-5-bromo-3-methoxyphenyl}acetaldehyde (18). To a stirred solution of enol ether **17** (202 mg, 0.42 mmol) in MeCN (20 mL) at 0 °C, was added H_2O (2 mL) and $Hg(OAc)_2$ (407 mg, 1.28 mmol). The mixture was stirred at room temperature for 1 h before addition of a solution of KI (0.67 g, 4.04 mmol)) in H_2O (20 mL). The resulting white precipitate was collected by filtration. Purification by column chromatography (SiO_2 eluted with petrol/EtOAc, 15 : 1) gave the title compound **18** as a white solid (133 mg, 67%). m.p. 125 °C. IR

(solid): 2938 (w), 2727 (w), 1721 (m), 1591 (m), 1514 (m), 1265 (s), 1206 (m), 849(w, br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.53$ (1H, t, $J = 1.8$ Hz), 7.43-7.33 (2H, m), 7.28 (1H, t, $J = 7.5$ Hz), 7.27–7.20 (2H, m) 6.95 (1H, d, $J = 2.5$ Hz), 6.85 (1H, d, $J = 1.5$ Hz), 6.80 (1H, d, $J = 2.1$ Hz), 6.76 (1H, d, $J = 8.1$ Hz), 6.73 (1H, dd, $J = 8.1$, 1.5 Hz), 5.15 (2H, s), 4.90 (2H, s), 3.89 (2×3H, s), 3.46 (2H, d, $J = 1.8$ Hz) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 198.97$ (d), 153.68 (s), 149.87 (s), 148.44 (s), 145.53 (s), 137.21 (s), 130.29 (s), 128.81 (s), 128.72 (d), 128.03 (d), 127.44 (d), 125.69 (d), 121.29 (d), 116.66 (s), 115.61 (d), 114.00 (d), 112.64 (d), 74.89 (t), 71.22 (t), 56.28 (q), 56.21 (q), 45.18 (t) ppm. MS (ES+): m/z (%) = 493 (87%) $[M+Na]^+$. HRMS (ES^+): m/z $[M+Na]^+$ calcd for $C_{24}H_{23}BrNaO_5$: 493.0627; found 493.0621.

2-{2-[4-(Benzyloxy)-3-methoxybenzyloxy]-5-bromo-3-methoxyphenyl}acetic acid (19). To a stirred suspension of aldehyde **18** (588 mg, 1.24 mmol) and 2-methyl-2-butene (4 mL of a 2M solution in THF, 8.0 mmol) in ^{t}BuOH (45 mL) was added a solution of $NaClO_2$ (283 mg, 2.5 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (2 mL of a 1.56M aqueous solution) dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 14 h before addition of EtOAc (30 mL) and brine (15 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2×30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2 eluted with 2% MeOH in CH_2Cl_2) gave the title compound as a white solid (527 mg, 86%). m.p. 133–134 °C. IR (solid): 2939 (m, br), 1709 (s), 1592 (m), 1514 (s), 736 (w, br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.42$-7.39 (2H, m), 7.25 (2H, t, $J = 7.6$ Hz), 7.31 (1H, d, $J = 7.3$ Hz), 6.99–6.96 (2H, m), 6.94 (1H, d, $J = 2.0$ Hz), 6.81-6.79 (2H, m), 5.13 (2H, s), 4.92 (2H, s), 3.85 (2×3H, s), 3.48 (2H, s) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 176.57$ (s), 153.51 (s), 149.81 (s), 148.34 (s), 145.37 (s), 137.25 (s), 130.46 (s), 129.74 (s), 128.71 (d), 128.01 (d), 127.48 (d), 125.61 (d), 121.24 (d), 116.41 (s), 115.56 (d), 113.97 (d), 112.56 (d), 74.93 (t), 71.19 (t), 56.24 (q), 56.13 (q), 35.50 (t) ppm. MS (ES–): m/z (%) = 485 (78%) $[M-H]^-$. HRMS (ES^+): m/z $[M+Na]^+$ calcd for $C_{24}H_{23}BrNaO_6$: 509.0576; found 509.0543.

2-{2-[4-(Benzyloxy)-3-methoxybenzyloxy]-5-bromo-3-methoxyphenyl}acetate (12). To a stirred solution of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (0.69 g 3.22 mmol) in Et_2O (20 mL) at 0 °C, was added KOH in EtOH (10 mL of a 4% w/v solution) in a flask fitted with reflux condenser. The mixture was warmed to 40 °C and a yellow solution of CH_2N_2 in Et_2O collected, cooling the receiver vessel at −78 °C. This fresh solution of CH_2N_2 in Et_2O was added to a stirred solution of carboxylic acid **19** in THF (10 mL) at −78 °C, *via* cannula until a yellow colour persisted. The mixture was then warmed to room temperature and stirred for 30 min before addition of Et_2O/AcOH (40 mL of a 9 : 1 mixture) dropwise. Concentration *in vacuo* gave a yellow residue. Purification by column chromatography (SiO_2 eluted with EtOAc/petrol, 1 : 8→1 : 4) gave the title compound **12** as a white solid (184 mg, 95%). m.p. 98 °C. IR (solid): 2948 (w), 1734 (m), 1591 (m), 697 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.42$-7.40 (2H, m), 7.35 (2H, t, $J = 7.5$ Hz), 7.30 (1H, d, $J = 7.0$ Hz), 6.96–6.95 (2H, m), 7.00-6.94 (3H, m), 5.15 (2H, s), 4.90 (2H, s), 3.90 (3H, s), 3.86 (3H, s), 3.60 (3H, s), 3.50 (2H, s) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 172.08$ (s), 153.97 (s), 150.24 (s), 148.66 (s), 145.91 (s), 137.71 (s), 131.13 (s), 130.84 (s), 129.12 (d), 128.42 (d), 127.85 (d), 126.00 (d), 121.46 (d) 116.77 (s), 115.74 (d), 114.39 (d), 112.87 (d), 75.21 (t), 71.64 (t), 56.65 (q), 56.58 (q), 52.61 (q), 36.00 (t) ppm. MS (ES+): m/z (%) = 523 (73%) $[M+Na]^+$. HRMS (ES^+): m/z $[M+Na]^+$ calcd for $C_{25}H_{25}BrNaO_6$: 523.0732; found 523.0729.

α-Diazoester 13. To a stirred solution of carboxylic ester **12** (55 mg, 0.11 mmol) and 4-acetamidobenzenesulfonyl azide (76 mg, 0.316 mmol) in MeCN (6 mL) at 0 °C, was added DBU (0.12 mL, 0.874 mmol). The mixture was warmed to room temperature and stirred for 24 h before concentration *in vacuo*. Purification by column chromatography (SiO_2 eluted with EtOAc/petrol, 1 : 8) gave the title compound **13** as a yellow oil (52 mg, 90%). IR (film): 2951 (w), 1701 (m), 1268 (m, br), 740 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$-7.27 (6H, m), 6.94-6.93 (2H, m), 6.81 (1H, d, $J = 8.0$ Hz), 6.74 (1H, d (fine splitting), $J = 8.0$ Hz), 5.13 (2H, s), 4.87 (2H, s), 3.87 (3H, s), 3.86 (3H, s), 3.75 (3H, s) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 165.78$ (s), 153.40 (s), 149.75 (s), 148.58 (s), 142.88 (s), 137.24 (s), 129.52 (s), 128.73 (d), 128.02 (d), 127.43 (d), 123.91 (d), 122.47 (s), 121.57 (d), 117.15 (s), 114.67 (d), 113.72 (d), 112.47 (d), 75.69 (t), 71.16 (t), 56.35 (q), 56.04 (q), 52.21 (q) ppm. MS (ES+): m/z (%) = 549 (93%) $[M+Na]^+$. HRMS (ES^+): m/z $[M+Na]^+$ calcd for $C_{25}H_{23}BrN_2NaO_6$: 549.0637; found 549.0632.

Methyl-2-(4-(benzyloxy)-3-methoxyphenyl)-5-bromo-7-methoxy-[(2,3-*cis*)- and (2,3-*trans*)-]dihydro benzofuran-3-carboxylate (*rac-cis*-14 and *rac-trans*-14). To a stirred solution of α-diazoester **13** (52 mg, 0.099 mmol) in toluene (2 mL) was added a solution of tetrakis[(*S*)-(−)-*N*-(*p*-dodecylphenylsulfonyl)prolinato] dirhodium(II) (2.5 mg, 1.3 mol%) in toluene (1 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h before warming to room temperature and concentration *in vacuo*. Purification by column chromatography (SiO_2 eluted with EtOAc/hexane, 1 : 8) gave the title compound, a colourless oil, as a 1.3 : 1 (2,3-*trans* : 2,3-*cis*) ratio of isomers, which were separated by column chromatography (SiO_2 eluted with hexane/EtOAc, 10 : 1), (47 mg, 95%). To effect epimerisation of *rac-cis*-**14**; to a solution of *rac-cis*-**14** (23 mg, 0.046 mmol) in THF (1 mL) was added NaOMe (0.2 mL of a 1.11 M solution in MeOH, 0.22 mmol) at −60 °C. The mixture was stirred at −60 °C for 26 h before dropwise addition of 0.2 mL of sodium phosphate buffer (1 M, pH 7). The mixture was then warmed to room temperature and EtOAc (10 mL) was added. The organic phase was separated and the aqueous phase extracted with EtOAc (2×10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 eluted with EtOAc/petrol, 1 : 4) gave *rac-trans*-**14** as a white solid (22 mg, 96%). *rac-cis*-**14**: m.p. 102–104 °C. IR (solid): 2947 (w), 1736 (m), 1616 (w), 1261 (m, br), 1202 (m, br), 733 (m, br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$ (2H, d $J = 7.5$ Hz), 7.33 (2H, t, $J = 7.5$ Hz), 7.28 (1H, m), 6.96 (2H, m), 6.89 (1H, m), 6.82 (2H, m), 5.93 (1H, d, $J = 9.8$ Hz), 5.13 (2H, s), 4.50 (1H, d, $J = 9.8$ Hz), 3.89 (3H, s), 3.84 (3H, s), 3.22 (3H, s) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 170.05$ (s), 149.66 (s), 148.44 (s), 148.32 (s), 145.34 (s), 137.12 (s), 129.43 (s), 128.69 (d), 128.04 (d), 127.48 (d), 120.85 (d), 119.20 (d), 116.18 (d), 113.87 (d), 113.20 (s), 110.29 (d), 87.01 (d), 71.13 (t), 56.47 (q), 56.27 (q), 54.29 (d), 52.13 (q) ppm. MS (ES+): m/z (%) = 521 (99%) $[M+Na]^+$. HRMS (ES^+): m/z $[M+Na]^+$

calcd for $C_{25}H_{23}BrNaO_6$: 521.0576; found 521.0573. *rac-trans*-**14**: m.p. 70 °C (EtOH). IR (solid): 2953 (w), 1738 (m), 1261 (m, br), 733 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (2H, d, J = 7.5 Hz), 7.36 (2H, t, J = 7.5 Hz), 7.29 (1H, m), 7.09 (1H s), 6.95 (1H, s), 6.92 (1H, s), 6.87 (1H, broad d, J = 8.5 Hz), 6.83 (1H, d, J = 8.5 Hz), 6.05 (1H, d, J = 8.3 Hz), 5.14 (2H, s), 4.30 (1H, d, J = 8.3 Hz), 3.86 (2 × 3H, s), 3.81 (3H, s) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 170.75 (s), 150.09 (s), 148.65 (s), 147.32 (s), 145.27 (s), 137.13 (s), 132.73 (s), 128.72 (d), 128.03 (d), 127.38 (d), 126.54 (s), 120.12 (d), 118.83 (d), 116.13 (d), 114.16 (d), 112.83 (s), 110.00 (d), 87.02 (d), 71.18 (t), 56.49 (q), 56.29 (q), 55.78 (d), 53.04 (q) ppm. MS (ES+): m/z (%) = 521 (99%) $[M+Na]^+$. HRMS (ES^+): m/z $[M+Na]^+$ calcd for $C_{25}H_{23}BrNaO_6$: 521.0576; found 521.0557.

***rac*-Methyl-2-(4-(benzyloxy)-3-methoxyphenyl)-5-(3-(benzyloxy)prop-1-ynyl)-7-methoxy-(2,3-*trans*)-dihydrobenzofuran-3-carboxylate (16).** A solution of aryl bromide *rac-trans*-**14** (40 mg, 0.08 mmol), $Pd(PPh_3)_4$ (12 mg, 13 mol%), CuI (8 mg, 53 mol%) and prop-2-ynyloxymethyl benzene (**15**) (58 mg, 0.40 mmol) in Et_3N (2.5 mL) was stirred at 90 °C for 6 h and then filtered. Concentration of the filtrate *in vacuo* gave a brown residue, which was purified by column chromatography (EtOAc/hexane, 1 : 9) to give the title compound **16** as a light yellow oil (33 mg, 73%). IR (film): 2951 (w), 1739 (m), 1597 (m), 1225 (s), 741 (m, br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.27 (10H, m), 7.11 (1H, s), 6.95 (1H, s), 6.93 (1H, d, J = 1.6 Hz), 6.88 (1H, dd, J = 8.0, 1.6 Hz) 6.84 (1H, d, J = 8.3 Hz), 6.08 (1H, d, J = 8.4 Hz), 5.14 (2H, s), 4.67 (2H, s), 4.39 (2H, s), 4.31 (1H, d, J = 8.4 Hz), 3.87 (3H, s), 3.86 (3H, s), 3.81 (3H, s) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 170.92 (s), 150.09 (s), 148.65 (s), 144.36 (s), 137.71 (s), 137.15 (s), 132.81 (s), 128.73 (d), 128.64 (d), 128.28 (d), 128.06 (d), 128.05 (d), 127.39 (d), 125.31 (s), 121.33 (d), 118.88 (d), 116.35 (d), 115.78 (s), 114.17 (d), 110.04 (d), 87.17 (d), 86.66 (s), 83.62 (s), 71.94 (t), 71.20 (t), 58.20 (t), 56.30 (2 × q), 55.70 (d), 53.01 (q) ppm. MS (ES+): m/z (%) = 587 (100%) $[M+Na]^+$. HRMS (ES^+): m/z $[M+Na]^+$ calcd for $C_{35}H_{32}NaO_7$: 587.2046; found 587.2050.

***rac*-Methyl-(2,3-*trans*)-5-(3-hydroxypropyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (20).** A solution of benzyl ether **16** (9 mg, ~0.016 mmol) in MeOH (5 mL) was treated with 10% Pd/C (14 mg, 0.13 mmol) and stirred under H_2 (1 atm) for 3 h before filtration and concentration of the filtrate *in vacuo*. The resulting residue was taken into MeOH (5 mL), and fresh 10% Pd/C (14 mg, 0.13 mmol) and formic acid (0.1 mL of a 99% solution) was added. The mixture was then stirred for a further 20 min under H_2 (1 atm) before filtration and concentration of the filtrate *in vacuo*. Purification by column chromatography (SiO_2 eluted with hexane/EtOAc, 1 : 2) gave the title compound **20** as a colourless oil (6 mg, 97%). IR (film): 2926 (w), 1734 (m, br), 755 (w, br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.88–6.84 (2H, m), 6.81 (1H, d, J = 8.0 Hz), 6.78 (1H, s), 6.68 (1H, s), 6.02 (1H, d, J = 8.5 Hz), 5.60 (1H, s)), 4.30 (1H, d, J = 8.5 Hz), 3.88 (3H, s), 3.87 (3H, s), 3.80 (3H, s), 3.71 (2H, t, J = 6.5 Hz), 2.69 (2H, m), 1.91 (2H, tt, J = 7.5, 6.5 Hz) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 171.49 (s), 146.84 (s), 146.28 (s), 146.06 (s), 144.46 (s), 135.75 (s), 132.21 (s), 125.32 (s), 119.68 (d), 116.72 (d), 114.60 (d), 113.22 (d), 109.01 (d), 86.98 (d), 62.50 (t), 56.35 (2 × q), 56.23 (d), 52.83 (q), 34.83 (t), 32.21 (t) ppm. MS (ES+): m/z (%) = 411 (100%) $[M+Na]^+$. HRMS (ES^+): m/z $[M+Na]^+$ calcd for $C_{21}H_{24}NaO_7$: 411.1420; found 411.1425.

Dihydrodehydrodiconiferyl alcohol (2). To a suspension of $LiAlH_4$ (17 mg, 0.448 mmol) in THF (2 mL) at −15 °C was added a solution of methyl ester **20** (3 mg, 0.0077 mmol) in THF (1 mL) dropwise. The mixture was stirred for 3 h, warming from −15 °C to 0 °C during this time. Et_2O (5 mL) and EtOAc (10 mL) were then added and the resulting suspension was warmed to room temperature and stirred for 15 min. H_2O (5 mL) and EtOAc (10 mL) were added and the organic phase separated. The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic phases washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2 eluted with hexane/EtOAc, 1 : 2) gave the title compound **2**, a colourless oil, as a 10 : 3 (2,3-*trans* : [17] 2,3-*cis*[32]) diastereomeric product mixture (3 mg, *ca.* 100%).

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