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Synthesis of dihydrodehydrodiconiferyl alcohol and derivatives through intramolecular C–H insertion

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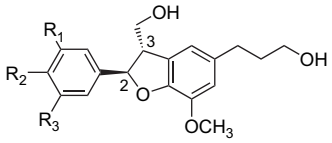
Abstract—The natural dihydrobenzofuran neolignan **1** and its derivative **3** have been prepared through intramolecular C–H insertion catalyzed by a Rh(II) chiral complex. Moderate diastereo and enantioselectivities were observed. The *cis* and *trans* diastereomers were separated and unambiguously identified. The absolute configurations of the major isomers were established through chiral HPLC analysis and study of the Cotton effects in their circular dichroism curves.

1. Introduction

Dihydrobenzofuran neolignans are a subtype of natural products of great interest regarding to their biological activities. Thus, they have been proved to have antioxidant,[1] antitumoral,[2] neuritogenic[3] and antimicrobial[4] activities, to be useful in the treatment of liver fibrosis,[5] and to be able to act as adenosine antagonist agents.[6] They possess a core skeleton of 2,3-dihydrobenzofuran with an aryl substituent on C-2 and a methyl, hydroxymethyl or methoxycarbonyl group on C-3. Most of them have been assigned a *trans* 2,3 relative stereochemistry, and some of which have been described as *cis* had to be reassigned.[7] The main synthetic approaches to these neolignans are biomimetic oxidative coupling of phenylpropenes,[8] pericyclic reactions[8] or intramolecular C–H coupling of aryl tosylhydrazones with Ru(II) salts.[9] We have reported the preparation of this kind of compounds through the reaction of benzoxasilepins with benzaldehydes in the presence of Lewis acids,[10] a modification of the Sakurai–Hosomi reaction.[11] Now we present a different way of synthesis based on the intramolecular C–H insertion of the products resulting from treatment of diazo compounds with Rh(II) salts.[12] Here we advance the synthesis of the natural bioactive neolignans dihydrodehydrodiconiferyl alcohol (**1**)[13], 3-*O*-demethyldihydrodehydrodiconiferyl alcohol (**2**)[14] and the synthetic derivative **3**, which incorporates a phenyl ring with three methoxy groups, a common pattern in this class of compounds.



1: R_1=H, R_2=OH, R_3=OMe
2: R_1=H, R_2=R_3=OH
3: R_1=R_2=R_3=OMe

2. Results and discussion

2.1. Strategy

Scheme 1 shows the retrosynthetic analysis for these compounds. After decomposition of the diazo compounds and C–H insertion, the dihydrobenzofurans would be formed. Simple transformations would lead to the desired products. Diazoesters can be prepared from the condensation products of appropriate aromatic precursors. This strategy allows the presence of different substitution patterns on the rings, which could afford, not only the desired structures, but other neolignans with this skeleton.

2.2. Synthetic approach

Eugenol was transformed into alcohol **4**,[10] and then the hydroxy group protected as pivaloate to give **5** (see Scheme 2). Claisen rearrangement by heating in *N*,*N*′-dimethylaniline yielded **6**. Its coupling with several benzyl iodides[15] in the presence of potassium carbonate in acetone allowed the isolation of the esters **7**, **8** and **9**. Ozonization of these compounds in DCM in the presence of NaOH, MeOH[16] and

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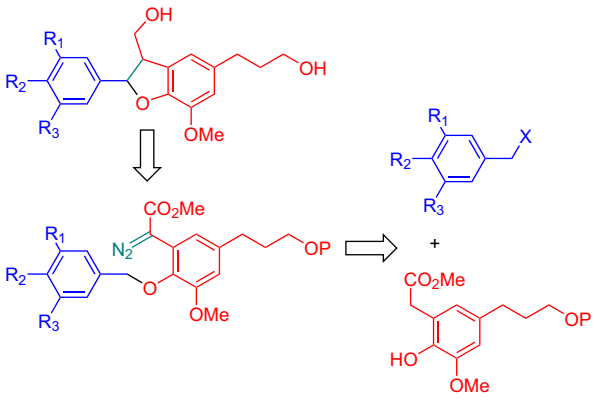
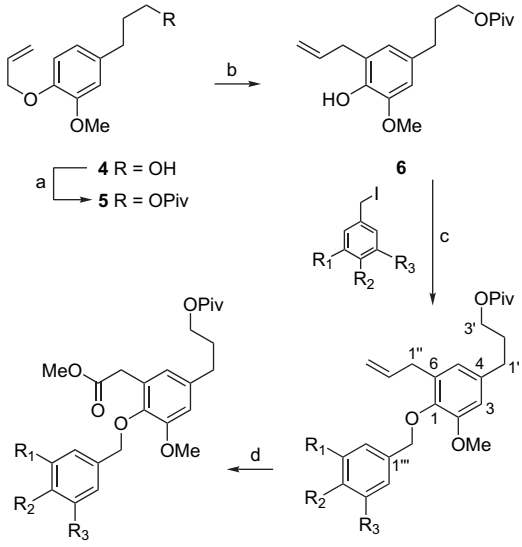


Scheme 1. Retrosynthetic analysis for preparation of compounds **1**–**3**.

pyridine resulted in the double bond degradation into the corresponding methyl esters,[17] thus allowing good isolated yields of **10**, **11** and **12**.

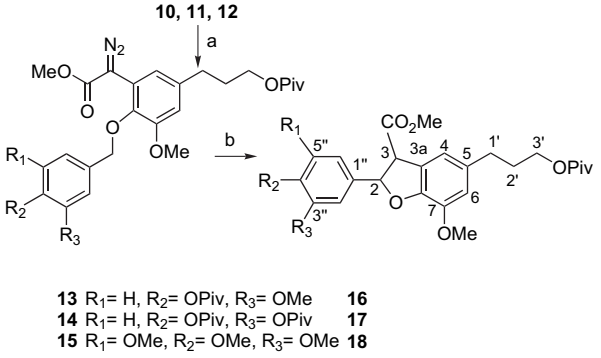


Scheme 2. *Reagents and conditions*: (a) pivaloyl chloride, DMAP, Py, Δ, 79%; (b) DMA, Δ, 91%; (c) K_2CO_3, acetone, Δ, 74, 61 and 82% to yield **7**, **8** and **9**, respectively and (d) O_3, NaOH, CH_2Cl_2, MeOH, Py, −78 °C; 90, 61 and 74% (**10**, **11** and **12**, respectively).

The presence of a benzylic methylene α to ester position in **10**, **11** and **12**, allowed the introduction of a diazo group by reaction of these compounds with azides in basic media. Several organic azides, different bases and reaction conditions were tested, and in all cases low yields were obtained. Alternative activation procedures also failed. The best results were obtained by direct treatment with *p*-ABSA (*p*-acetamidobenzenesulfonylazide) and DBU in CH_3CN (around 30% yield). In this way, diazo derivatives **13**, **14** and **15** were obtained. The low yields in our substrates when compared with those reported for model systems[12d] could be attributed to undesired reactions due to the presence of the oxygenated aliphatic side chains.

2.3. Stereoselectivity in the C–H insertion

The insertion step was performed using the rhodium chiral complex Rh_2[(*S*)-DOSP]$_4$ (tetrakis[(*S*)-(−)-*N*-(*p*-dodecylphenylsulfonyl)prolinato]dirhodium (II)) as catalyst,[18] which had previously been reported to give the best results on similar substrates.[12d,19] In order to get the reaction to proceed, strict anhydrous conditions were needed, as very small traces of water react with the intermediate carbenoids to yield α-hydroxy esters. In all three cases the insertion proceeds instantly with quantitative yields (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) *p*-ABSA, DBU, CH_3CN, from 0 °C to rt 27, 30 and 29% (**13**, **14** and **15**, respectively) and (b) Rh_2[(*S*)-DOSP]$_4$, toluene, 0 °C, quantitative.

However, the reaction always afforded *cis*/*trans* mixtures (Table 1); a 3:1 diastereoselectivity in favour of the *cis* isomer was observed with **16** and **17**, while **18** gave no diastereoselectivity. The observed enantioselectivities were also low (Table 1), and all the efforts to improve them were unsuccessful as the reaction did not proceed below 0 °C. It was highly surprising to see these poor stereoselectivities on the basis of the published results for the simple 2-phenyl-2,3-dihydrobenzofuran core skeleton.[12d] Fortunately, the diastereomers could be separated by column chromatography, and the mixture of enantiomers analyzed by HPLC (provided with a chiral column and a circular dichroism detector), which allowed us to assign their absolute configuration.

2D-NOESY spectra allowed us to differentiate between *cis* and *trans* isomers, although not in a definitive manner. H-2

Table 1. Stereoselectivity in the intramolecular C–H insertions[a]

	16 (R_1=OMe, R_2=OPiv, R_3=H)	**17** (R_1=R_2=OPiv, R_3=H)	**18** (R_1=R_2=R_3=OMe)
cis:*trans*	75:25	77:23	50:50
trans	ee=34%, t_{R1}=12.8 (−) major, t_{R2}=14.8 (+) minor	[b]	ee=6%, t_{R1}=14.3 (+) minor, t_{R2}=17.8 (−) major
cis	ee=29%, t_{R1}=15.5 (−) minor, t_{R2}=26.5 (+) major	ee=28%, t_{R1}=19.7 (−) minor, t_{R2}=22.5 (+) major	ee=20%, t_{R1}=24.3 (+) major, t_{R2}=27.5 (−) minor

[a] Retention times (t_R) in minutes. Signs in parenthesis are due to the Cotton effect observed for the circular dichroism spectrum.

[b] Reliable HPLC analysis could not be performed with the available sample of the minor *trans* isomer.

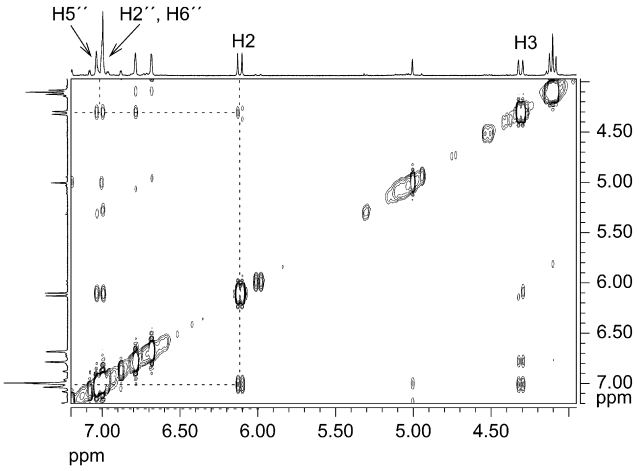


Figure 1. 2D-NOESY spectrum of **16**-*trans*.

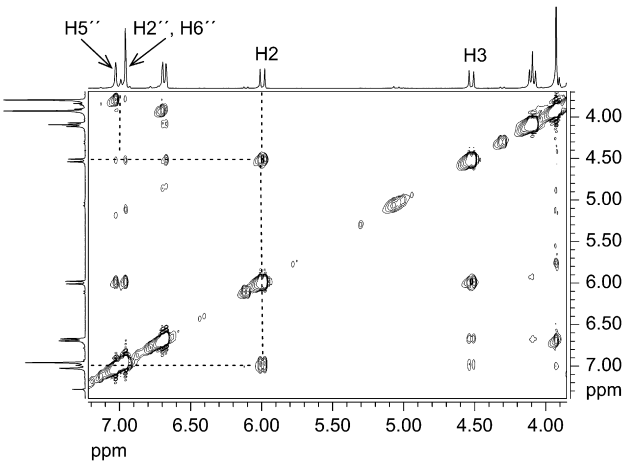


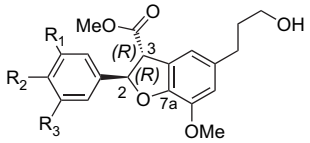
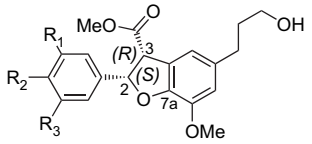
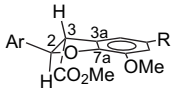
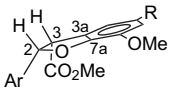
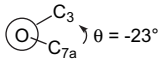
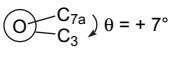
Figure 2. 2D-NOESY spectrum of **16**-*cis*.

and H-3 show cross peaks in both compounds, but much stronger in the *cis* compounds, as it can be observed for **16**-*cis* and **16**-*trans* (Figs. 1 and 2). It can also be observed that the coupling constants between H-2 and H-3 are very similar: 8.4 Hz for **16**-*cis* and 9.5 Hz for **16**-*trans*. Therefore, *J* values are not useful to distinguish *cis*/*trans* diastereomers. However, as we had previously observed for similar compounds,[10] there is a significant difference in chemical shifts between the methoxycarbonyl groups, appearing at 3.81 ppm in the *trans* isomer and at 3.27 ppm in the *cis* one; this effect is due to the fact that in the *cis* isomer this methyl is located in the shielding zone of the phenyl group on C-2. Similar results were obtained for **17**[20] and **18** (Table 1).

The analysis of the circular dichroism spectra allowed to establish the absolute configurations of the prepared *trans*-2-phenyl-2,3-dihydrobenzofurans, as their observed Cotton effect can be connected with the configuration through the well established rules given by Antus.[21] The five-membered ring in the dihydrobenzofuran should adopt an envelope conformation, with a characteristic torsion angle (C7a–O–C2–C3), in which the phenyl ring on C-2 is in an equatorial disposition. Therefore, it can establish a correlation between the sign of the band ^1L_b (α) in the dichroism spectrum, which appears around 280 nm, and the helicity (P or M) of the five-membered ring in the dihydrobenzofuran. The sign of the Cotton effect is highly influenced by the nature of the substituents on the aromatic rings, especially if there is a methoxy group on the position 7. As the products we prepared, **16** and **18**, have that methoxy group, the P helicity is connected with a positive Cotton effect, and M with a negative. Following these criteria, the absolute configurations of **16** and **18**-*trans* have been assigned (Table 2).

However, the application of the same rules to the *cis* diastereomers was somewhat obscured because the ^1L_b band is hardly perceptible. This phenomenon could be due to the fact that, in these compounds, the five-membered ring is almost in a planar conformation, and therefore there is no helicity. X-ray structures previously described by us[22] confirm

Table 2. Absolute configuration of the major enantiomer from the insertion reaction

	trans isomers	*cis* isomers
	 **16**-*trans*: R_1= H, R_2= OPiv, R_3= OMe **18**-*trans*: R_1= OMe, R_2= OMe, R_3= OMe	 **16**-*cis*: R_1= H, R_2= OPiv, R_3= OMe **17**-*cis*: R_1= H, R_2= OPiv, R_3= OPiv **18**-*cis*: R_1= OMe, R_2= OMe, R_3= OMe
Projection of the dihydrobenzofuran ring		
Newman projection through O–C2 bond[a]		
Helicity Cotton effect	*M* Negative (^1L_b band)	*P* Positive (^1L_a band)

[a] Calculated dihedral θ values (MOPAC, AM1).

this point. However, as the strong ^1L_a band (which appears around 250 nm) has the same sign as the ^1L_b band, it could be used to establish the absolute configuration[23] for the *cis* isomers (Table 2). As a result, we can propose that the absolute configuration for the major enantiomer of the *trans* compounds is (2*R*,3*R*), while for the *cis* is (2*S*,3*R*), in all the studied cases.

2.4. Preparation of the target molecules

To conclude the synthesis, **16** and **18** (*cis* and *trans*) were treated with $LiAlH_4$, with excellent results, in order to reduce the methyl ester and to remove the pivaloyl protecting group in a single step. Strict anhydrous conditions had to be used to avoid epimerization of the *cis* isomers into the *trans*, and for the same reason, the *cis* isomers had to be reduced at low temperature. In this way we obtained **1**-*trans* and **1**-*cis* (81, 100% yield). Their spectroscopic data are in agreement with those described for the natural products (*trans*)[13] and its isomer.[10] The same conditions were used to prepare **3**-*trans* and **3**-*cis* (81, 80% yield, respectively). No loss of stereochemical integrity was observed under those conditions. Again NOE effects between H-2 and H-3 were observed in both diastereomers of **3**, although the comparison of chemical shifts of the signals in ^1H NMR due to H-2 proved to be a better tool to distinguish both diastereomers, 5.84 ppm (8.4 Hz) for *trans* and 5.57 ppm (7.4 Hz) for the *cis*.

3. Conclusion

Two dihydrobenzofuran neolignans have been prepared through a convergent strategy in which the key step is an intramolecular C–H insertion in the presence of a chiral rhodium catalyst. The process can be extended to the preparation of other natural products with different substitution patterns on the aromatic rings. Although the stereoselectivity of the reaction was moderate to low, both *cis* and *trans* isomers could be isolated and identified thoroughly using several NMR techniques. Additionally, the circular dichroism data allowed to establish the absolute configuration of all the chiral compounds.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 or Avance DRX 500 spectrometer. Chemical shifts are given in parts per million relative to TMS. Carbon substitution degrees were established by DEPT multipulse sequence, and ^{13}C NMR peak assignments were made with the aid of 2D NMR (HMBC, HMQC, COSY and NOESY). Infrared spectra were recorded in liquid film between NaCl plates on a FT-IR Mattson Genesis II spectrometer, and mass spectra were performed on a AutoSpec-Q VG-Analytical (Fisons) (HRMS) instrument, using the Fast Atom Bomb technique (FAB) with a 1% NaI doped matrix of thioglycerol or glycerol.

The reactions were monitored by TLC (unless other technique is specified), using Macherey Nagel Alugram Sil G/UV_{254} plates. UV light and 5% phosphomolibdic or sulfuric acid solutions in methanol were employed for revealing. SDS 60 A CC 35–70 μm silica was used for column chromatography. All solvents were purified and dried following standard procedures.[24] Enantiomeric excesses were calculated from chiral HPLC performed in a Jasco HPLC chromatograph equipped with a circular dichroism detector and a Daicel Chiracel OD-H 150×4.6 mm column and eluting with mixtures of hexane and isopropanol.

4.2. Synthesis of dihydrobenzofuran neolignans 1 and 3

4.2.1. Allyl 2-methoxy-4-(3-pivaloyloxypropyl)phenyl ether (5). A solution of **4** (0.535 g, 2.4 mmol) in anhyd CH_2Cl_2 (2.4 mL) was added to a mixture of dimethylaminopyridine (30 mg, 0.24 mmol) and pyridine (0.6 mL, 7.2 mmol) under an argon atmosphere. Pivaloyl chloride (0.3 mL, 2.4 mmol) was added and the solution was refluxed for 14 h. The reaction crude mixture was washed with 5% HCl (3×40 mL) and brine (40 mL), dried over anhyd $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography yielding **5** (0.594 g, 1.9 mmol, 79%). Colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.82 (1H, d, J=7.9 Hz, H6); 6.72 (1H, d, J=2.1 Hz, H3); 6.70 (1H, dd, J=7.9 Hz, J=2.1 Hz, H5); 6.09 (1H, ddt, J=17.3 Hz, J=10.8 Hz, J=5.4 Hz, H2″); 5.40 (1H, ddd, J=17.3 Hz, J=3.0 Hz, J=1.5 Hz, H3″); 5.28 (1H, ddd, J=10.4 Hz, J=3.0 Hz, J=1.5 Hz, H3″); 4.60 (2H, dt, J=5.4 Hz, J=1.5 Hz, H1″); 4.09 (2H, t, J=6.5 Hz, H3′); 3.88 (3H, s, OMe); 2.65 (2H, t, J=7.6 Hz, H1′); 1.95 (2H, m, H2′); 1.23 (9H, s, OCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.50 (C, CO); 149.34 (C, C2); 146.23 (C, C1); 134.25 (C, C4); 133.514 (CH, C2″); 120.13 (CH, C5); 117.75 (CH_2, C3″); 113.62 (CH, C6); 112.10 (CH, C3); 69.98 (CH_2, C1″); 63.48 (CH_2, C3′); 55.84 (CH_3, OMe); 38.72 (C, OCO*C*(CH_3)$_3$); 31.67 (CH_2, C1′); 30.35 (CH_2, C2′); 27.18 (CH_3, OCOC(*C*H_3)$_3$). IR (film) ν_{max}: 2959, 2936, 2871, 1726, 1514, 1463, 1283, 1263, 1230, 1159, 1034, 997, 926, 804 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{18}H_{26}O_4Na$): 329.1723, found: 329.1725 $[M+Na]^+$.

4.2.2. 2-Methoxy-4-(3-pivaloyloxypropyl)-6-(2-propenyl)phenol (6). A solution of **5** (9.792 g, 32 mmol) in *N*,*N*′-dimethylaniline (82 mL, 640 mmol) was refluxed under an inert atmosphere for 24 h. The reaction crude mixture was diluted with CH_2Cl_2 (80 mL), washed with 5% HCl (9×50 mL) and brine (100 mL), dried over anhyd $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography yielding **6** (8.743 g, 29 mmol, 91%). Yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.58 (2H, s, H3, H5); 6.02 (ddt, 1H, J=16.6 Hz, J=10.0 Hz, J=6.6 Hz, H2″); 5.58 (1H, s, OH); 5.10 (1H, ddd, J=17.1 Hz, J=3.4 Hz, J=1.4 Hz, H3″); 5.06 (1H, ddd, J=10.4 Hz, J=3.4 Hz, J=1.4 Hz, H3″); 4.09 (2H, t, J=6.5 Hz, H3′); 3.89 (3H, s, OMe); 3.40 (2H, dt, J=6.5 Hz, J=1.4 Hz, H1″); 2.62 (2H, t, J=7.7 Hz, H1′); 1.94 (2H, m, H2′); 1.24 (9H, s, OCOC(*C*H_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, CO); 146.20 (C, C2); 141.48 (C, C1); 136.64 (CH, C2″); 132.29 (C, C4); 125.52 (C, C6); 121.83 (CH, C5); 115.35 (CH_2, C3″); 108.82 (CH, C3); 63.53 (CH_2, C3′); 55.95 (CH_3, OMe); 38.73 (C, OCO*C*(CH_3)$_3$); 33.82 (CH_2, C1″); 31.81 (CH_2, C1′); 30.52 (CH_2, C2′); 27.18

(CH_3, $OCOC(CH_3)_3$). IR (film) ν_{max}: 3453, 2971, 2936, 2871, 1724, 1604, 1499, 1462, 1435, 1286, 1156, 1075, 909 cm^{-1}. HRFABMS (*m/z*): calcd ($C_{18}H_{26}O_4Na$): 323.1723, found: 329.1728 $[M+Na]^+$.

4.3. General procedure for the reaction between 6 and several benzyl iodides

K_2CO_3 (1.5 equiv) was added to a solution of **6** (1.0 equiv) and benzyl iodide (1.0–1.5 equiv) in acetone (7 mL) under an inert atmosphere. The mixture was refluxed until the reaction was completed (TLC monitoring). The reaction crude mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3×30 mL). The organic extracts dried over anhyd $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography.

4.3.1. (3-Methoxy-4-pivaloyloxybenzyl) [2-methoxy-4-(3-pivaloyloxypropyl)-6-(2-propenyl)phenyl] ether (7). Starting from 4-methoxy-3-pivaloyloxybenzyl iodide (1.5 g, 4.3 mmol) and 0.88 g (2.9 mmol) of **6**, and following the general procedure during 6 h, **7** was obtained as a colourless oil (74%). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.14 (1H, br s, H2‴); 7.00 (2H, br s, H5‴, H6‴); 6.65 (1H, d, *J*=1.9 Hz, H3); 6.61 (1H, d, *J*=1.9 Hz, H5); 5.94 (1H, ddt, *J*=17.5 Hz, *J*=9.7 Hz, *J*=6.4 Hz, H2″); 5.04 (2H, m, H3″); 4.97 (2H, s, $ArCH_2O$); 4.10 (2H, t, *J*=6.5 Hz, H3′); 3.88 (3H, s, CH_3O–C2); 3.84 (3H, s, CH_3O–C3‴); 3.37 (2H, dt, *J*=6.5 Hz, *J*=1.5 Hz, H1″); 2.66 (2H, t, *J*=7.7 Hz, H1′); 1.97 (2H, m, H2′); 1.40 (9H, s, $ArOCOC(CH_3)_3$); 1.25 (9H, s, $ROCOC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.49 (C, RO*C*O); 176.64 (C, ArO*C*O); 152.56 (C, C2); 151.08 (C, C3‴); 143.89 (C, C1); 139.70 (C, C4‴); 137.20 (CH, C2″); 137.10 (C, C4); 136.74 (C, C1‴); 133.84 (C, C6); 122.34 (CH, C5‴); 121.74 (CH, C5); 119.97 (CH, C6‴); 115.58 (CH_2, C3″); 112.08 (CH, C2‴); 110.65 (CH, C3); 74.27 (CH_2, $ArCH_2O$); 63.53 (CH_2, C3′); 55.88 (CH_3, OCH_3); 55.75 (CH_3, OCH_3); 39.03 (C, $ArOCOC(CH_3)_3$); 38.75 (C, $ROCOC(CH_3)_3$); 34.24 (CH_2, C1″); 32.01 (CH_2, C1′); 30.28 (CH_2, C2′); 27.22 (CH_3, $OCOC(CH_3)_3$). IR (film) ν_{max}: 2970, 2934, 2870, 1753, 1725, 1588, 1509, 1480, 1462, 1282, 1154, 1117, 1034 cm^{-1}. HRFABMS (*m/z*): calcd ($C_{31}H_{42}O_7Na$): 549.2823, found: 549.2818 $[M+Na]^+$.

4.3.2. [2-Methoxy-4-(3-pivaloyloxypropyl)-6-(2-propenyl)phenyl] (3,4-dipivaloyloxybenzyl) ether (8). Starting from 3,4-dipivaloyloxybenzyl iodide (1.43 g, 3.4 mmol) and 1.04 g (3.4 mmol) of **6**, and following the general procedure for 15 h, **8** was obtained as a colourless oil (65%). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.32 (1H, dd, *J*=8.3 Hz, *J*=2.0 Hz, H6‴); 7.27 (1H, d, *J*=2.0 Hz, H2‴); 7.13 (1H, d, *J*=8.3 Hz, H5‴); 6.64 (1H, d, *J*=2.0 Hz, H3); 6.61 (1H, d, *J*=2.0 Hz, H5); 5.94 (1H, ddt, *J*=17.7 Hz, *J*=9.4 Hz, *J*=6.5 Hz, H2″); 5.03 (2H, m, H3″); 4.96 (2H, s, $ArCH_2O$); 4.10 (2H, t, *J*=6.5 Hz, H3′); 3.86 (3H, s, OCH_3); 3.37 (2H, dt, *J*=6.5 Hz, *J*=1.4 Hz, H1″); 2.65 (2H, t, *J*=7.7 Hz, H1′); 1.97 (2H, m, H2′); 1.37 (18H, s, $ArOCOC(CH_3)_3$); 1.24 (9H, s, $ROCOC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.50 (C, RO*C*O); 175.85 (C, ArO*C*O); 175.76 (C, ArO*C*O); 152.51 (C, C2); 143.83 (C, C1); 142.38 (C, C3‴)*; 141.96 (C, C4‴)*; 137.19 (CH, C2″); 137.16 (C, C4); 136.73 (C, C1‴); 133.77 (C, C6); 125.36 (CH, C6‴); 123.07 (CH, C5‴); 122.58 (CH, C2‴); 121.74 (CH, C5); 115.58 (CH_2, C3″); 110.63 (CH, C3); 73.46 (CH_2, $ArCH_2O$); 63.53 (CH_2, C3′); 55.68 (CH_3, OCH_3); 39.09 (C, $ArOCOC(CH_3)_3$); 38.73 (C, $ROCOC(CH_3)_3$); 34.18 (CH_2, C1″); 31.99 (CH_2, C1′); 30.26 (CH_2, C2′); 27.20 (CH_3, $OCOC(CH_3)_3$). * Assignments may be interchanged. IR (film) ν_{max}: 2964, 2926, 2900, 2862, 1750, 1716, 1578, 1472, 1272, 1248, 1144, 1107 cm^{-1}. HRFABMS (*m/z*): calcd ($C_{35}H_{48}O_8Na$): 619.3241, found: 619.3239 $[M+Na]^+$.

4.3.3. [2-Methoxy-4-(3-pivaloyloxypropyl)-6-(2-propenyl)phenyl] (3,4,5-trimethoxybenzyl) ether (9). Starting from 3,4,5-trimethoxybenzyl iodide (1.04 g, 3.3 mmol) and 1.0 g (3.3 mmol) of **6**, and following the general procedure for 15 h, **9** was obtained as a colourless oil (82%). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.72 (2H, s, H2‴, H6‴); 6.65 (1H, d, *J*=1.9 Hz, H3); 6.61 (1H, d, *J*=1.9 Hz, H5); 5.94 (1H, ddt, *J*=17.5 Hz, *J*=9.5 Hz, *J*=6.5 Hz, H2″); 5.04 (2H, m, H3″); 4.91 (2H, s, $ArCH_2O$); 4.10 (2H, t, *J*=6.5 Hz, H3′); 3.89 (9H, s, CH_3O); 3.87 (3H, s, CH_3O–$C_{4‴}$); 3.38 (2H, dt, *J*=6.5 Hz, *J*=1.5 Hz, H1″); 2.66 (2H, t, *J*=7.7 Hz, H1′); 1.96 (2H, m, H2′); 1.24 (9H, s, $OCOC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.48 (C, RO*C*O); 153.13 (C, C3‴, C5‴)*; 152.6 (C, C2)*; 143.93 (C, C1); 137.52 (C, C4‴); 137.24 (CH, C2″); 137.12 (C, C4); 133.81 (C, C1‴); 133.72 (C, C6); 121.73 (CH, C5); 115.56 (CH_2, C3″); 110.66 (CH, C3); 104.93 (CH, C2‴, C6‴); 74.77 (CH_2, $ArCH_2O$); 63.50 (CH_2, C3′); 60.81 (CH_3, $C_{4‴}$–OCH_3); 56.04 (CH_3, $C_{3‴}$–OCH_3 y $C_{5‴}$–OCH_3)#; 55.75 (CH_3, C_2–OCH_3)#; 38.74 (C, $ROCOC(CH_3)_3$); 34.21 (CH_2, C1″); 31.99 (CH_2, C1′); 30.28 (CH_2, C2′); 27.21 (CH_3, $ROCOC(CH_3)_3$). * and # Assignments may be interchanged. IR (film) ν_{max}: 2957, 2936, 2835, 1721, 1587, 1457, 1420, 1282, 1234, 1152, 1125, 1004 cm^{-1}. HRFABMS (*m/z*): calcd ($C_{28}H_{38}O_7Na$): 509.2510, found: 509.2509 $[M+Na]^+$.

4.4. General procedure for ozonolysis of 7, 8 and 9

A solution of NaOH (5 equiv) in MeOH (5 mL) was added to a solution of allyl derivatives in CH_2Cl_2 (25 mL) and the mixture cooled to −80 °C. A stream of O_3 was bubbled through the stirred solution (20 min, TLC monitoring). The reaction crude mixture was diluted with water (30 mL) and 5% HCl (10 mL), and then extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with 5% HCl (2×10 mL) and brine (2×10 mL), dried over anhyd $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography.

When required, the isolated aldehydes were oxidized as follows. A solution of $NaClO_2$ (6 mmol) and $Na_2HPO_4 \cdot H_2O$ (6 mmol) in water (7 mL) was added dropwise to a solution of the aldehyde (2 mmol) and 2-methyl-2-butene (4 mL) in ^tBuOH (20 mL). After 18 h the mixture was diluted with H_2O (60 mL) and extracted with Et_2O (3×60 mL). The combined organic extracts were washed with 1 M aq NaOH (2×10 mL), brine (2×10 mL) and dried over anhyd $MgSO_4$. The filtrate was cooled to 0 °C and treated with a saturated solution of CH_2N_2 in Et_2O (4 mL). The solution was concentrated in vacuo and the residue was purified by flash chromatography.

4.4.1. [2-Methoxy-6-(methoxycarbonylmethyl)-4-(3-pivaloyloxypropyl)phenyl] (3-methoxy-4-pivaloyloxybenzyl) ether (10). Starting from 0.52 g (2 mmol) of **7** and following the general procedure, **10** was obtained as a colourless oil (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.12 (1H, br s, H2‴); 6.98 (2H, br s, H5‴, H6‴); 6.71 (1H, d, J=1.8 Hz, H3); 6.65 (1H, d, J=1.8 Hz, H5); 4.99 (2H, s, ArCH_2O); 4.10 (2H, t, J=6.4 Hz, H3′); 3.88 (3H, s, C_2–OCH_3); 3.84 (3H, s, $C_{3‴}$–OCH_3); 3.62 (3H, s, COOCH_3); 3.59 (2H, s, H1″); 2.66 (2H, t, J=7.7 Hz, H1′); 1.97 (2H, m, H2′); 1.39 (9H, s, ArOCOC(CH_3)$_3$); 1.24 (9H, s, ROCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, RO*C*OC(CH$_3$)$_3$); 176.64 (C, ArO*C*OC(CH$_3$)$_3$); 172.12 (C, *C*OOMe); 152.45 (C, C2); 151.07 (C, C3‴); 144.23 (C, C1); 139.72 (C, C4‴); 137.14 (C, C4); 136.54 (C, C1‴); 128.25 (C, C6); 122.37 (CH, C5); 122.31 (CH, C5‴); 119.10 (CH, C6‴); 112.12 (CH, C3); 111.86 (CH, C2‴); 74.10 (CH$_2$, Ar*C*H$_2$O); 63.52 (CH$_2$, C3′); 55.87 (CH$_3$, O*C*H$_3$); 55.74 (CH$_3$, O*C*H$_3$); 51.86 (CH$_3$, COO*C*H$_3$); 39.01 (C, ArOCO*C*(CH$_3$)$_3$); 38.74 (C, ROCO*C*(CH$_3$)$_3$); 35.74 (CH$_2$, C1″); 31.93 (CH$_2$, C1′); 30.19 (CH$_2$, C2′); 27.18 (CH$_3$, ArOCOC(*C*H$_3$)$_3$, ROCOC(*C*H$_3$)$_3$). IR (film) ν_{max}: 2968, 2935, 2870, 1752, 1725, 1509, 1478, 1462, 1282, 1154, 1118, 1033, 888 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{31}H_{42}O_9Na$): 581.2721, found: 581.2724 [M+Na]$^+$.

4.4.2. [2-Methoxy-6-(methoxycarbonylmethyl)-4-(3-pivaloyloxypropyl)phenyl] (3,4-dipivaloyloxybenzyl) ether (11). Starting from 1.83 g (3.1 mmol) of **8** and following the general procedure, **11** was obtained as a colourless oil (61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.30 (1H, dd, J=8.3 Hz, J=2.0 Hz, H6‴); 7.25 (1H, d, J=1.9 Hz, H2‴); 7.12 (1H, d, J=8.3 Hz, H5‴); 6.69 (1H, d, J=1.9 Hz, H3); 6.65 (1H, d, J=1.9 Hz, H5); 4.99 (2H, s, ArCH_2O); 4.10 (2H, t, J=6.4 Hz, H3′); 3.85 (3H, s, OCH_3); 3.62 (3H, s, COOCH_3); 3.60 (2H, s, H1″); 2.65 (2H, t, J=7.7 Hz, H1′); 1.96 (2H, m, H2′); 1.36 (9H, s, ArOCOC(CH_3)$_3$); 1.36 (9H, s, ArOCOC(CH_3)$_3$); 1.23 (9H, s, ROCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.46 (C, RO*C*O); 175.82 (C, ArO*C*O); 175.73 (C, ArO*C*O); 172.14 (C, *C*OOMe); 152.41 (C, C2); 144.15 (C, C1); 142.37 (C, C4‴); 141.98 (C, C3‴); 137.21 (C, C4); 136.59 (C, C1‴); 128.20 (C, C6); 125.42 (CH, C6‴); 123.07 (CH, C5‴); 122.62 (CH, C2‴); 122.34 (CH, C5); 111.84 (CH, C3); 73.27 (CH$_2$, Ar*C*H$_2$O); 63.52 (CH$_2$, C3′); 55.68 (CH$_3$, O*C*H$_3$); 51.88 (CH$_3$, COO*C*H$_3$); 39.09 (C, ArOCO*C*(CH$_3$)$_3$); 39.07 (C, ArOCO*C*(CH$_3$)$_3$); 38.74 (C, ROCO*C*(CH$_3$)$_3$); 35.73 (CH$_2$, C1″); 31.93 (CH$_2$, C1′); 30.20 (CH$_2$, C2′); 27.21 (CH$_3$, ArOCOC(*C*H$_3$)$_3$, ROCOC(*C*H$_3$)$_3$). IR (film) ν_{max}: 2971, 2873, 1758, 1726, 1590, 1480, 1278, 1258, 1156, 1026, 1116 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{35}H_{48}O_{10}Na$): 651.3140, found: 651.3139 [M+Na]$^+$.

4.4.3. [2-Methoxy-6-(methoxycarbonylmethyl)-4-(3-pivaloyloxypropyl)phenyl] (3,4,5-trimethoxybenzyl) ether (12). Starting from 0.89 g (1.8 mmol) of **9** and following the general procedure, **12** was obtained as a colourless oil (74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.71 (2H, s, H2‴, H6‴); 6.70 (1H, d, J=2.4 Hz, H3); 6.66 (1H, d, J=2.4 Hz, H5); 4.94 (2H, s, ArCH_2O); 4.10 (2H, t, J=6.4 Hz, H3′); 3.89 (9H, s, OCH_3); 3.86 (3H, s, C_2–OCH_3); 3.64 (3H, s, COOCH_3); 3.62 (2H, s, H1″); 2.66 (2H, t, J=7.6 Hz, H1′); 1.97 (2H, m, H2′); 1.23 (9H, s, OCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.54 (C, RO*C*O); 172.12 (C, *C*OOCH$_3$); 153.10 (C, C3‴, C5‴); 152.46 (C, C2); 144.25 (C, C1); 137.45 (C, C4‴); 137.19 (C, C4); 133.52 (C, C1‴); 128.22 (C, C6); 122.36 (CH, C5); 111.82 (CH, C3); 104.93 (CH, C2‴, C6‴); 74.64 (CH$_2$, Ar*C*H$_2$O); 63.51 (CH$_2$, C3′); 60.81 (CH$_3$, C_2–O*C*H$_3$); 56.03 (CH$_3$, O*C*H$_3$); 55.75 (CH$_3$, O*C*H$_3$); 51.89 (CH$_3$, COO*C*H$_3$); 38.74 (C, OCO*C*(CH$_3$)$_3$); 35.72 (CH$_2$, C1″); 31.92 (CH$_2$, C1′); 30.18 (CH$_2$, C2′); 27.19 (CH$_3$, OCOC(*C*H$_3$)$_3$). IR (film) ν_{max}: 2957, 2839, 1723, 1589, 1460, 1154, 1125, 1006 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{28}H_{38}O_9Na$): 541.2408, found: 541.2408 [M+Na]$^+$.

4.5. General procedure for the diazo transfer to 10, 11 and 12

DBU was added to a solution of the diazo derivatives and *p*-ABSA in CH_3CN (5 mL, freshly distilled) at 0 °C under an argon atmosphere. The mixture was allowed to reach room temperature and stirred for 18–24 h (TLC monitoring). The reaction crude mixture was diluted with CH_2Cl_2 (30 mL), washed with NH_4Cl aq saturated solution (3×10 mL) and brine (10 mL), dried over anhyd $MgSO_4$, concentrated in vacuo, and the residue was purified by flash chromatography.

4.5.1. [6-(Diazo(methoxycarbonyl)methyl)-2-methoxy-4-(3-pivaloyloxypropyl)phenyl] (3-methoxy-4-pivaloyloxybenzyl) ether (13). Compound **10** (0.555 g, 1 mmol), *p*-ABSA (1.486 g, 6 mmol) and DBU (1.2 mL) were reacted as described previously to yield **13** (0.159 g, 0.27 mmol, 27%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.04 (1H, d, J=1.7 Hz, H2″); 7.01 (1H, d, J=1.9 Hz, H5); 6.96 (1H, d, J=8.0 Hz, H5″); 6.89 (1H, dd, J=8.0 Hz, J=1.8 Hz, H6″); 6.69 (1H, d, J=1.9 Hz, H3); 4.95 (2H, s, ArCH_2O); 4.10 (2H, t, J=6.5 Hz, H3′); 3.89 (3H, s, C_2–OCH_3); 3.81 (3H, s, $C_{3″}$–OCH_3); 3.79 (3H, s, COOCH_3); 2.68 (2H, t, J=7.7 Hz, H1′); 1.98 (2H, m, H2′); 1.38 (9H, s, ArOCOC(CH_3)$_3$); 1.23 (9H, s, ROCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.46 (C, RO*C*O); 176.49 (C, ArO*C*O); 166.10 (C, *C*OOCH$_3$); 152.42 (C, C2); 151.06 (C, C3″); 142.08 (C, C1); 140.04 (C, C1″); 137.71 (C, C4); 135.41 (C, C4″); 122.34 (CH, C5″); 121.12 (CH, C5); 120.52 (CH, C6″); 120.06 (C, C6); 112.38 (CH, C2″); 111.71 (CH, C3); 74.92 (CH$_2$, Ar*C*H$_2$O); 74.71 (C, *C*N$_2$); 63.45 (CH$_2$, C3′); 55.86 (CH$_3$, C_2–O*C*H$_3$); 55.76 (CH$_3$, $C_{3″}$–O*C*H$_3$); 51.81 (CH$_3$, COO*C*H$_3$); 38.99 (C, *C*(CH$_3$)$_3$); 38.72 (C, *C*(CH$_3$)$_3$); 32.12 (CH$_2$, C1′); 30.18 (CH$_2$, C2′); 27.17 (CH$_3$, C(*C*H$_3$)$_3$). IR (film) ν_{max}: 2967, 2934, 2870, 2102, 1751, 1725, 1605, 1499, 1479, 1461, 1282, 1154, 1113, 1034 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{31}H_{40}N_2O_9Na$): 607.2626, found: 607.2631 [M+Na]$^+$.

4.5.2. [6-(Diazo(methoxycarbonyl)methyl)-2-methoxy-4-(3-pivaloyloxypropyl)phenyl] (3,4-dipivaloyloxybenzyl) ether (14). Compound **11** (0.497 g, 0.79 mmol), *p*-ABSA (1.1646 g, 4.7 mmol) and DBU (2.4 mL) were reacted as described previously to yield **14** (0.162 g, 0.25 mmol, 30%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.25 (1H, dd, J=7.8 Hz, J=2.1 Hz, H6″); 7.23 (1H, br s, H2″); 7.12 (1H, d, J=7.8 Hz, H5″); 7.04 (1H, d, J=1.6 Hz, H5); 6.68 (1H, d, J=1.7 Hz, H3); 4.96 (2H, s, ArCH_2O); 4.10 (2H, t, J=6.1 Hz, H3′); 3.85 (3H, s, OCH_3); 3.82 (3H, s,

COOCH_3); 2.68 (2H, t, J=7.7 Hz, H1′); 1.98 (2H, m, H2′); 1.36 (18H, s, ArOCOC(CH_3)$_3$); 1.23 (9H, s, ROCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, RO*C*O); 175.75 (C, ArO*C*O); 175.70 (C, ArO*C*O); 166.20 (C, *C*OOCH$_3$); 152.39 (C, C2); 142.38 (C, C3″)*; 142.21 (C, C4″)*; 142.08 (C, C1); 137.80 (C, C4); 135.57 (C, C1″); 125.74 (CH, C6″); 123.12 (CH, C2″); 122.93 (CH, C5″); 121.01 (CH, C5); 119.83 (C, C6); 111.68 (CH, C3); 73.90 (CH$_2$, Ar*C*H$_2$O); 71.09 (C, *C*N$_2$); 63.50 (CH$_2$, C3′); 55.81 (CH$_3$, OCH_3); 51.92 (CH$_3$, COO*C*H$_3$); 39.10 (C, ArOCO*C*(CH$_3$)$_3$); 38.75 (C, ROCO*C*(CH$_3$)$_3$); 32.16 (CH$_2$, C1′); 30.20 (CH$_2$, C2′); 27.20 (CH$_3$, OCOC(*C*H$_3$)$_3$). * Assignments may be interchanged. IR (film) ν_{max}: 2971, 2872, 2105, 1758, 1725, 1590, 1480, 1279, 1154, 1116 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{35}H_{46}N_2O_{10}Na$): 677.3045, found: 677.3041 [M+Na]$^+$.

4.5.3. 2-[Diazo(methoxycarbonyl)methyl)-6-methoxy-4-(3-pivaloyloxypropyl)phenyl] (3,4,5-trimethoxybenzyl) ether (15). Compound **13** (0.443 g, 1 mmol), *p*-ABSA (1.337 g, 5.4 mmol) and DBU (1.1 mL) were reacted as described previously to yield **15** (0.144 g, 0.26 mmol, 29%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.99 (1H, d, J=1.8 Hz, H5); 6.69 (1H, d, J=1.9 Hz, H3); 6.60 (2H, s, H2″, H6″); 4.90 (2H, s, ArCH_2O); 4.09 (2H, t, J=6.5 Hz, H3′); 3.90 (3H, s, C$_2$–OCH_3); 3.84 (9H, s, OCH_3); 3.78 (3H, s, COOCH_3); 2.67 (2H, t, J=7.7 Hz, H1′); 1.96 (2H, m, H2′); 1.22 (9H, s, ROCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.47 (C, RO*C*O); 166.08 (C, *C*OOCH$_3$); 153.02 (C, C3″, C4″); 152.39 (C, C2); 142.08 (C, C1); 137.70 (C, C4); 132.32 (C, C1″); 121.12 (CH, C5); 120.10 (C, C6); 111.65 (CH, C3); 105.37 (CH, C2″, C6″); 75.48 (CH$_2$, Ar*C*H$_2$O); 60.15 (C, *C*N$_2$); 63.41 (CH$_2$, C3′); 60.77 (CH$_3$, C$_{4''}$–OCH_3); 55.95 (CH$_3$, C$_2$–OCH_3)*; 55.86 (CH$_3$, C$_{3''}$–OCH_3)*; 51.85 (CH$_3$, COO*C*H$_3$); 38.71 (C, OCO*C*(CH$_3$)$_3$); 32.10 (CH$_2$, C1′); 30.19 (CH$_2$, C2'); 27.16 (CH$_3$, OCOC(*C*H$_3$)$_3$). * Assignments may be interchanged. IR (film) ν_{max}: 2955, 2840, 2099, 1723, 1590, 1492, 1459, 1426, 1279, 1234, 1154, 1126, 1006, 735 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{28}H_{36}N_2O_9Na$): 567.2313, found: 567.2316 [M+Na]$^+$.

4.6. General procedure for the C–H insertion of 13, 14 and 15

A Schlenk flask with 4 Å molecular sieves was purged with argon. A solution of the diazocompound in freshly distilled (sodium) toluene (2 mL) was introduced and the mixture cooled to 0 °C. A solution of tetrakis[(*S*)-(−)-*N*-(*p*-dodecylphenylsulfonyl)prolinato]dirhodium (0.01 equiv) in anhydrous toluene (1 mL) was cannulated into the flask. Nitrogen bubbled immediately and the yellow colour disappeared instantly. The mixture was concentrated in vacuo and the residue purified by flash chromatography.

4.6.1. 7-Methoxy-3-(methoxycarbonyl)-2-(3-methoxy-4-pivaloyloxy)phenyl-5-(3-pivaloyloxy-propyl)-2,3-dihydrobenzo[*b*]furan (16). Starting from **13** (0.12 g, 0.21 mmol) and following the general procedure, **16** was obtained (0.10 g, 0.19 mmol, 90%) as a *cis*:*trans* mixture (3:1), which could be separated by flash chromatography. Enantiomeric excesses were determined by chiral HPLC, being 34% for **16**-*trans* and 29% for **16**-*cis*.

16*-*trans. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.04 (1H, br s, H5″); 7.00 (2H, br s, H2″, H6″); 6.79 (1H, d, J=1.0 Hz, H4); 6.69 (1H, d, J=1.0 Hz, H6); 6.12 (1H, d, J=8.4 Hz, H2); 4.31 (1H, d, J=8.3 Hz, H3); 4.10 (2H, t, J=6.4 Hz, H3′); 3.91 (3H, s, C$_7$–OCH_3); 3.85 (3H, s, COOCH_3); 3.81 (3H, s, C$_{3''}$–OCH_3); 2.67 (2H, t, J=6.9 Hz, H1′); 1.96 (2H, m, H2′); 1.37 (9H, s, OCOC(CH_3)$_3$); 1.24 (9H, s, OCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, RO*C*O); 176.61 (C, ArO*C*O); 171.09 (C, *C*OOCH$_3$); 151.32 (C, C3″); 146.02 (C, C7a); 144.22 (C, C7); 140.15 (C, C4″); 138.68 (C, C1″); 135.08 (C, C5); 124.86 (C, C3a); 122.80 (CH, C2″)*; 118.25 (CH, C6″)*; 116.54 (CH, C4); 112.96 (CH, C6); 110.14 (CH, C5″); 86.21 (CH, C2); 63.44 (CH$_2$, C3′); 56.16 (CH, C3); 56.12 (CH$_3$, C$_7$–OCH_3)$^{\#}$; 55.98 (CH$_3$, C$_{3''}$–OCH_3)$^{\#}$; 52.69 (CH$_3$, COO*C*H$_3$); 39.04 (C, OCO*C*(CH$_3$)$_3$); 38.76 (C, OCO*C*(CH$_3$)$_3$); 31.97 (CH$_2$, C1′); 30.59 (CH$_2$, C2′); 27.21 (CH$_3$, OCOC(*C*H$_3$)$_3$); 27.17 (CH$_3$, OCOC(*C*H$_3$)$_3$). * and $^{\#}$ Assignments may be interchanged. IR (film) ν_{max}: 2966, 2935, 2870, 1750, 1725, 1606, 1499, 1460, 1281, 1201, 1154, 1112, 1032, 731 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{31}H_{40}O_9Na$): 579.2565, found: 579.2560 [M+Na]$^+$.

16*-*cis. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.03 (1H, br s, H5″)*; 6.96 (2H, br s, H2″, H6″)*; 6.70 (1H, d, J=1.6 Hz, H4); 6.68 (1H, d, J=1.6 Hz, H6); 6.00 (1H, d, J=9.7 Hz, H2); 4.52 (1H, d, J=9.7 Hz, H3); 4.09 (2H, t, J=6.4 Hz, H3′); 3.93 (3H, s, C$_7$–OCH_3); 3.80 (6H, s, C$_{3''}$–OCH_3); 3.27 (3H, s, COOCH_3); 2.67 (2H, t, J=7.7 Hz, H1′); 1.96 (2H, m, H2′); 1.37 (9H, s, OCOC(CH_3)$_3$); 1.24 (9H, s, OCOC(CH_3)$_3$). * Assignments may be interchanged. ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, RO*C*O); 176.59 (C, ArO*C*O); 170.43 (C, *C*OOCH$_3$); 151.00 (C, C3″); 147.10 (C, C7a); 144.31 (C, C7); 140.11 (C, C4″); 135.32 (C, C5); 125.80 (C, C3a); 122.23 (CH, C2″)*; 118.68 (CH, C6″)*; 117.19 (CH, C6); 112.96 (CH, C4); 110.53 (CH, C5″); 86.20 (CH, C2); 63.49 (CH$_2$, C3′); 56.03 (CH$_3$, C$_7$–OCH_3, C$_{3''}$–OCH_3); 54.55 (CH, C3); 51.93 (CH$_3$, COO*C*H$_3$); 39.02 (C, OCO*C*(CH$_3$)$_3$); 38.75 (C, OCO*C*(CH$_3$)$_3$); 31.97 (CH$_2$, C1′); 30.54 (CH$_2$, C2′); 27.21 (CH$_3$, OCOC(*C*H$_3$)$_3$); 27.17 (CH$_3$, OCOC(*C*H$_3$)$_3$). * Assignments may be interchanged. IR (film) ν_{max}: 2966, 2935, 2870, 1750, 1725, 1605, 1500, 1478, 1461, 1281, 1153, 1111, 1032, 731 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{31}H_{40}O_9Na$): 579.2565, found: 579.2561 [M$^+$Na]$^+$.

4.6.2. 7-Methoxy-3-(methoxycarbonyl)-2-(3,4-dipivaloyloxy)phenyl-5-(3-pivaloyloxypropyl)-2,3-dihydrobenzo[*b*]furan (17). Starting from **14** (0.042 g, 0.06 mmol) and following the general procedure, **17** was obtained (17 mg, 0.03 mmol, 50%) as a *cis*:*trans* mixture (77:23). The enantiomeric excess of **17**-*cis* was determined by chiral HPLC as 28%.

4.6.3. 7-Methoxy-3-(methoxycarbonyl)-5-(3-pivaloyloxypropyl)-2-(3,4,5-trimethoxy)phenyl-2,3-dihydrobenzo[*b*]furan (18). Starting from **15** (0.17 g, 0.31 mmol) and following the general procedure, **18** was obtained (0.16 g, 0.31 mmol, 99.8%) as a *cis*:*trans* mixture (1:1), which could be separated by flash chromatography. Enantiomeric excesses were determined by chiral HPLC, being 6.0% for **18**-*trans* and 20% for **18**-*cis*.

18*-*trans. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.79 (1H, d, J=1.0 Hz, H4); 6.69 (1H, d, J=1.0 Hz, H6); 6.66 (2H, s, H2″, H6″); 6.05 (1H, d, J=8.6 Hz, H2); 4.33 (1H, d, J=8.6 Hz, H3); 4.10 (2H, t, J=6.5 Hz, H3′); 3.91 (3H, s, C_7–OCH_3); 3.86 (6H, s, $C_{3''}$–OCH_3, $C_{5''}$–OCH_3); 3.85 (3H, s, $C_{4''}$–OCH_3); 3.84 (3H, s, COOCH_3); 2.67 (2H, t, J=6.8 Hz, H1′); 1.96 (2H, m, H2′); 1.24 (9H, s, OCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, ROCO); 171.14 (C, COOCH$_3$); 153.38 (C, C3″, C5″); 146.02 (C, C7a); 144.25 (C, C7); 137.94 (C, C4″); 135.60 (C, C1″); 135.02 (C, C5); 124.89 (C, C3a); 116.48 (CH, C4); 112.94 (CH, C6); 103.11 (CH, C2″); 86.69 (CH, C2); 63.39 (CH$_2$, C3′); 60.78 (CH$_3$, $C_{4''}$–OCH$_3$); 56.14 (CH$_3$, $C_{3''}$–OCH$_3$); 56.09 (CH$_3$, C_7–OCH$_3$)*; 56.08 (CH, C3)*; 52.68 (CH$_3$, COOCH$_3$); 38.73 (C, OCOC(CH$_3$)$_3$); 31.93 (CH$_2$, C1′); 30.54 (CH$_2$, C2′); 27.18 (CH$_3$, OCOC(CH$_3$)$_3$). * Assignments may be interchanged. IR (film) ν_{max}: 2955, 2837, 1722, 1587, 1458, 1282, 1153, 1123, 1005 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{28}H_{36}O_9Na$): 539.2252, found: 539.2248 [M+Na]$^+$.

18*-*cis. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.70 (1H, d, J=1.3 Hz, H6); 6.68 (1H, d, J=1.3 Hz, H4); 6.64 (2H, s, H2″, H6″); 5.94 (1H, d, J=9.6 Hz, H2); 4.51 (1H, d, J=9.6 Hz, H3); 4.10 (2H, t, J=6.5 Hz, H3′); 3.93 (3H, s, C_7–OCH_3); 3.86 (6H, s, $C_{3''}$–OCH_3, $C_{5''}$–OCH_3); 3.84 (3H, s, $C_{4''}$–OCH_3); 3.31 (3H, s, COOCH_3); 2.67 (2H, t, J=7.7 Hz, H1′); 1.96 (2H, m, H2′); 1.24 (9H, s, OCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, ROCO); 170.48 (C, COOCH$_3$); 152.93 (C, C3″, C5″); 147.06 (C, C7a); 144.34 (C, C7); 137.74 (C, C4″); 135.30 (C, C5); 132.26 (C, C1″); 125.91 (C, C3a); 117.12 (CH, C4); 112.94 (CH, C6); 103.54 (CH, C2″, C6″); 86.63 (CH, C2); 63.46 (CH$_2$, C3′); 60.82 (CH$_3$, $C_{4''}$–OCH$_3$); 56.13 (CH$_3$, $C_{3''}$–OCH_3, $C_{5''}$–OCH$_3$); 55.98 (CH$_3$, C_7–OCH$_3$); 54.43 (CH, C3); 51.85 (CH$_3$, COOCH$_3$); 38.74 (C, OCOC(CH$_3$)$_3$); 31.95 (CH$_2$, C1′); 30.52 (CH$_2$, C2′); 27.19 (CH$_3$, OCOC(CH$_3$)$_3$). IR (film) ν_{max}: 2955, 2837, 1722, 1588, 1459, 1233, 1153, 1124, 1005 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{28}H_{36}O_9Na$): 539.2252, found: 539.2250 [M+Na]$^+$.

4.7. General procedure for the reduction and deprotection of 16 and 18 (*cis* and *trans*)

A solution of esters in THF (1.5 mL) was added dropwise to a cooled suspension (−20 °C for *cis* isomers and 0 °C for *trans*) of $LiAlH_4$ (20 equiv) in THF (1.5 mL). The mixture was stirred for 1 h and quenched by dropwise addition of water at the same temperature until the bubbling stopped. Then 5% aq HCl (20 mL) was added and the mixture was allowed to reach room temperature and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with brine (40 mL), dried over anhyd $MgSO_4$, concentrated in vacuo, and the residue purified by flash chromatography.

4.7.1. *trans*-Dihydrodehydrodiconiferyl alcohol (1-*trans*). Starting from 23 mg (0.04 mmol) of **16**-*trans*, and following the general procedure, **1**-*trans*[13] was obtained as a colourless oil (12 mg, 0.033 mmol, 81%).

4.7.2. *cis*-Dihydrodehydrodiconiferyl alcohol (1-*cis*). Starting from 35 mg (0.06 mmol) of **16**-*cis*, and following the general procedure, **1**-*cis*[10] was obtained as a colourless oil (21 g, 0.06 mmol, 100%).

4.7.3. *trans*-3-(Hydroxymethyl)-5-(3-hydroxypropyl)-7-methoxy-2-(3,4,5-trimethoxyphenyl)-2,3-dihydrobenzo-[*b*]furan (3-*trans*). Starting from 72 mg (0.14 mmol) of **18**-*trans*, and following the general procedure, **3**-*trans* was obtained as a colourless oil (46 mg, 0.11 mmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.69 (2H, br s, H4, H6); 6.66 (2H, s, H2″); 5.57 (1H, d, J=7.4 Hz, H2); 4.00 (1H, dd, J=10.9 Hz, J=6.0 Hz, CH_2OH); 3.93 (1H, dd, J=11.0 Hz, J=4.7 Hz, CH_2OH); 3.90 (3H, s, C_7–OCH_3); 3.85 (6H, s, $C_{3''}$–OCH_3, $C_{5''}$–OCH_3); 3.84 (3H, s, $C_{4''}$–OCH_3); 3.70 (2H, t, J=6.3 Hz, H3′); 3.63 (1H, m, H3); 2.68 (2H, t, J=7.7 Hz, H1′); 1.90 (2H, m, H2′). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 153.31 (C, C3″, C5″); 146.46 (C, C7a); 144.18 (C, C7); 137.67 (C, C4″); 136.85 (C, C1″); 135.53 (C, C5); 127.50 (C, C3a); 115.90 (CH, C4)*; 112.45 (CH, C6)*; 103.10 (CH, C2″, C6″); 87.80 (CH, C2); 63.84 (CH$_2$, CH$_2$OH); 62.24 (CH$_2$, C3′); 60.81 (CH$_3$, $C_{4''}$–OCH$_3$); 56.13 (CH$_3$, $C_{3''}$–OCH$_3$, $C_{5''}$–OCH$_3$); 55.99 (CH$_3$, C_7–OCH$_3$); 53.84 (CH, C3); 34.58 (CH$_2$, C2′); 31.98 (CH$_2$, C1′). * Assignments may be interchanged. IR (film) ν_{max}: 3379, 2934, 2876, 2837, 1592, 1494, 1458, 1420, 1324, 1123, 909, 729 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{22}H_{30}O_8Na$): 445.1833, found: 445.1830 [M+Na]$^+$.

4.7.4. *cis*-3-(Hydroxymethyl)-5-(3-hydroxypropyl)-7-methoxy-2-(3,4,5-trimethoxyphenyl)-2,3-dihydrobenzo[*b*]-furan (3-*cis*). Starting from 24 mg (0.05 mmol) of **18**-*cis*, and following the general procedure, **3**-*cis* was obtained as a colourless oil (15 mg, 0.04 mmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.77 (1H, d, J=1.3 Hz, H4); 6.72 (1H, d, J=1.3 Hz, H6); 6.71 (2H, s, H2″); 5.85 (1H, d, J=8.4 Hz, H2); 3.94 (3H, s, C_7–OCH_3); 3.91 (1H, dd, J=8.7 Hz, J=5.0 Hz, CH_2OH); 3.87 (1H, dd, J=8.7 Hz, J=6.7 Hz, CH_2OH); 3.89 (6H, s, $C_{3''}$–OCH_3, $C_{5''}$–OCH_3); 3.88 (3H, s, $C_{4''}$–OCH_3); 3.73 (2H, t, J=6.3 Hz, H3′); 3.69 (1H, m, H3); 2.71 (2H, t, J=7.7 Hz, H1′); 1.92 (2H, m, H2′). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 153.40 (C, C3″, C5″); 145.95 (C, C7a); 144.21 (C, C7); 135.73 (C, C5, C4″); 132.23 (C, C1″); 129.20 (C, C3a); 116.88 (CH, C4); 112.45 (CH, C6); 103.14 (CH, C2″, C6″); 87.07 (CH, C2); 63.00 (CH$_2$, CH$_2$OH); 62.27 (CH$_2$, C3′); 60.90 (CH$_3$, $C_{4''}$–OCH$_3$); 56.16 (CH$_3$, $C_{3''}$–OCH$_3$, $C_{5''}$–OCH$_3$); 55.99 (CH$_3$, C_7–OCH$_3$); 49.50 (CH, C3); 34.60 (CH$_2$, C2′); 31.99 (CH$_2$, C1′). IR (film) ν_{max}: 3379, 2936, 2835, 2998, 1591, 1494, 1459, 1421, 1123, 1324, 1233, 1208 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{22}H_{30}O_8Na$): 445.1833, found: 445.1834 [M+Na]$^+$.

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