2009

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Publication Details

Batenburg-Nguyen, U. T., Ung, A. T. & Pyne, S. G. (2009). The synthesis of carbon linked bis-benzylisoquinolines using Mizoroki-Heck and Sonagashira coupling reactions. Tetrahedron, 65 (1), 318-327.

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Abstract

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Disciplines

Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

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The synthesis of carbon linked bis-benzylisoquinolines using Mizoroki-Heck and Sonagashira coupling reactions

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Abstract: Novel laudanosine dimers in which two laudanosine units are linked at C-2' *via* a two or three-carbon linker (alkane, alkene or alkyne) have been prepared using palladium-catalysed cross-coupling reactions (Mizoroki-Heck and Sonagashira reactions). In one example, a second three-carbon linker between the two isoquinoline N-atoms was also present leading to a novel macrocyclic ring system.

1. Introduction

Over two hundred bisbenzylisoquinoline alkaloids are known, the majority of these have one or two ether linkages between the two benzylisoquinoline moieties.[1] However, a number of these alkaloids have one of the linking ether bonds replaced by a biphenyl linkage.[2] The bisbenzylisoquinoline alkaloids show a range of interesting biological activities.[1] The related *Thalictrum* alkaloid, thalicarpine **1** (Figure 1),[3] comprises the benzylisoquinoline, *S*-laudanosine, connected *via* an ether linkage to an aporphine moiety. This molecule was found to have significant biological activity against the Walker 256 carcinoma and antiproliferative activity on a broad range of human and animal cell lines *in vitro* and *in vivo*.[4,5] Initial clinical trails on this compound appeared encouraging,[4-9] however phase II clinical trials stopped after no antitumour effect was observed.[7,9]

Inspired by the structure and biological activity of thalicarpine we became interested in the synthesis of the novel laudanosine dimers of the type **2** and **3** (Figure 1), in which two laudanosine units are linked at C-2' through a two or three-carbon linker (alkane, alkene or alkyne). In the example **3**, a second three-carbon linker between the two isoquinoline N-atoms was also present leading to a macrocyclic ring system. This paper describes the successful synthesis of the racemic and meso forms of these target compounds, and in one case the pure (*S*,*S*)-enantiomer.

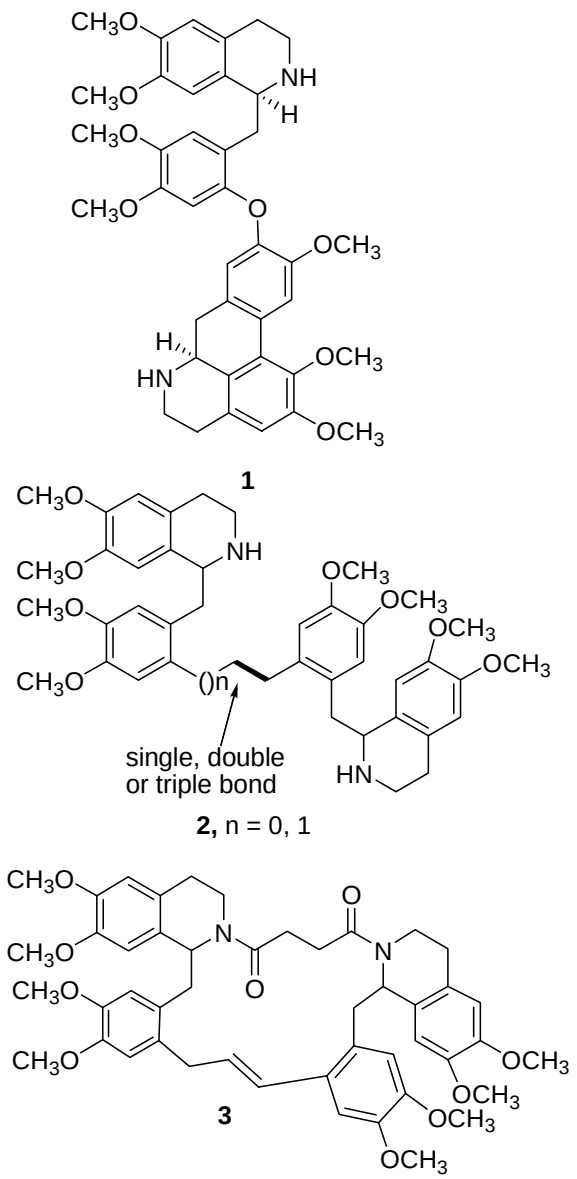
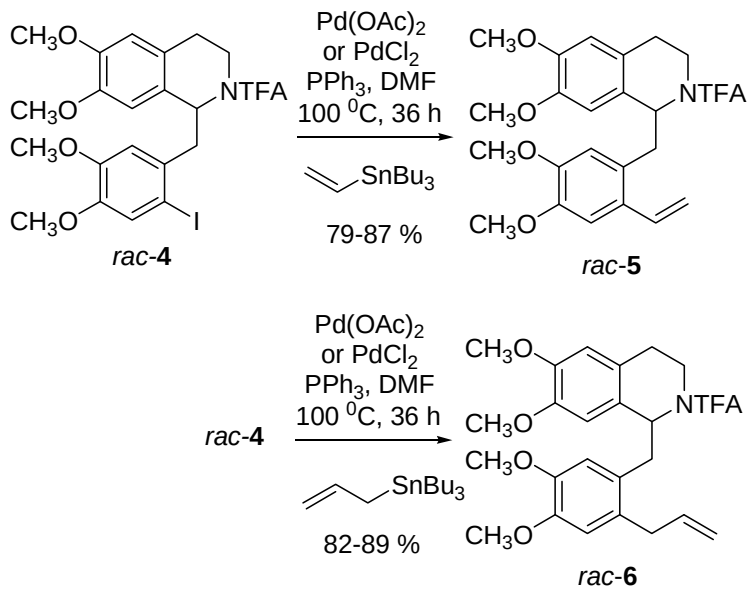


Figure 1

2. Discussion

Our approach to the target molecules **2** (alkene linker) was based on a Mizoroki-Heck coupling reaction of racemic *N*-trifluoroacetyl-2'-iodonorlaudanosine **4**[10] and the racemic alkenes *rac*-**5** and *rac*-**6**. The alkenes *rac*-**5** and *rac*-**6** were efficiently prepared from *rac*-**4** using Stille coupling reactions (Scheme 1). Palladium acetate gave slightly better yields of *rac*-**5** and *rac*-**6** (87% and 89%, respectively) than palladium chloride (79% and 82%, respectively).

Scheme 1



The Mizoroki-Heck coupling reaction of *rac*-**4** and *rac*-**5** using palladium acetate as the catalyst gave mixtures of the regioisomeric products *rac*-**7** and *rac*-**8** (Scheme 2). These were difficult to separate by column chromatography. These regioisomers were both isolated as mixtures of the racemic and meso forms (*ca* 55 : 45 to 60 : 40). The formation of regioisomers in Mizoroki-Heck reactions on related substrates is well documented and has been shown to be dependent upon the steric and electronic nature of the substrates and the nature of the ligand, solvent, base and catalyst.[11-20] The ratio of **7** and **8** formed in these reactions was also dependent upon the reaction solvent, the ligand, and the nature of the base (Table 1). The combination of *N*,*N*-dimethylglycine (DMG), sodium acetate and *N*-methylpyrrolidinone (NMP) at 130 ^{o}C for 18 h, resulted in the best yields (combined yield of 66%) and regioselectivities for **7** over **8** (80 : 20, respectively) (Table 1, Entry 3). These conditions represented a significant improvement over the more traditional Heck conditions shown in Table 1, Entry 1. The use of silver salts increased the regioselectivity (90 : 10), but decreased the yield of **7** and **8** significantly (Table 1, Entry 5). The regioisomers **7** and **8** could not be easily separated by column chromatography. On a preparative scale, using the conditions in Table 1, Entry 3, the major regioisomer **7** could be isolated pure (as a mixture of racemate and meso forms) by simply adding methanol to the reaction flask at the end of the reaction (Scheme 3). Pure *rac/meso*-**7** precipitated out as a white solid in 54% yield. A small amount of *meso*-**7** could be isolated by trituration of this white solid with dichloromethane in which *meso*-**7** was much more soluble than *rac*-**7**. This synthetic sequence

was repeated using (*S*)-**4**[21] and (*S*)-**5**[21] which allowed the unequivocal assignment of the (*S*,*S*)-, *rac*- and *meso*-forms of **7** (Figure 2). Column chromatography of the initial mother liquors from which *rac*-**7** precipitated then gave pure regioisomer **8** (as a mixture of racemate and meso forms) in 12% yield (Scheme 3).

Scheme 2

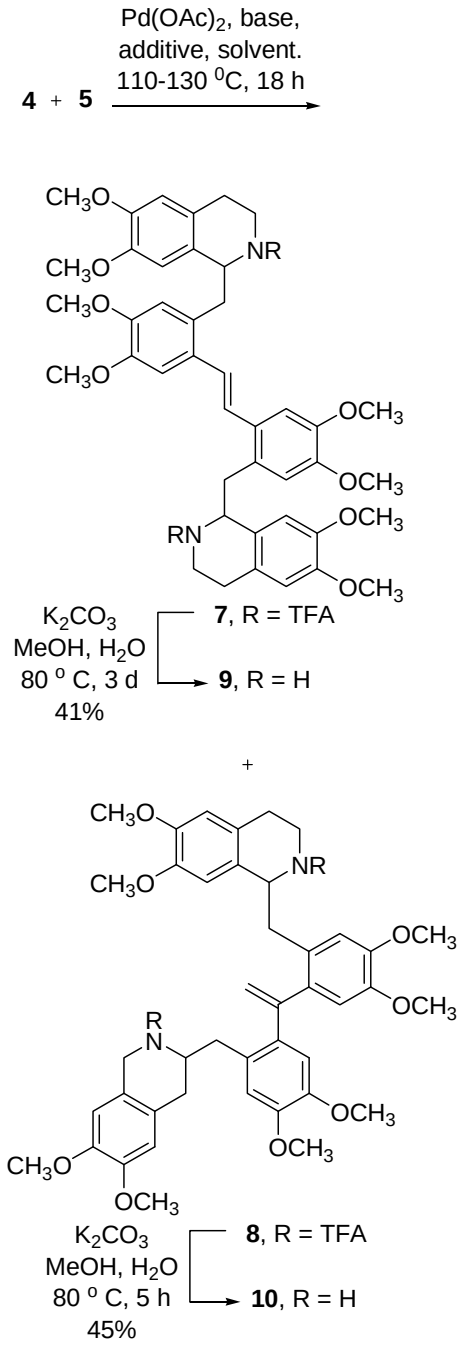


Table 1. Mizoroki-Heck coupling reactions of **4** and **5** with $Pd(OAc)_2$ at 130 ^oC.

Entry	Additive	Base	Solvent	**7** : **8**[b]	Yield (%) of **7** + **8**[c]
1	Ph_3P[a]	Et_3N	MeCN	50 : 50	29
2	Ph_3P	NaOAc	NMP	60 : 40	50
3	NMG	NaOAc	NMP	80 : 20	66
4	-	NaOAc	NMP	40 : 60	54
5	NMG	NaOAc/ Ag_3PO_4	NMP	90 : 10	24

[a]Reaction temperature 110 ^oC. [b]From ^1H NMR analysis.
[c]Combined yield of **7** and **8** after column chromatography.

Base hydrolysis of *rac/meso*-**7** and *rac/meso*-**8** then gave *rac/meso*-**9** and *rac/meso*-**10**, respectively (Scheme 2). A mixture of *rac/meso*-**10** could be separated by preparative TLC. The stereochemistry of the individual isomers (whether *rac* or *meso*) however, could not be determined.

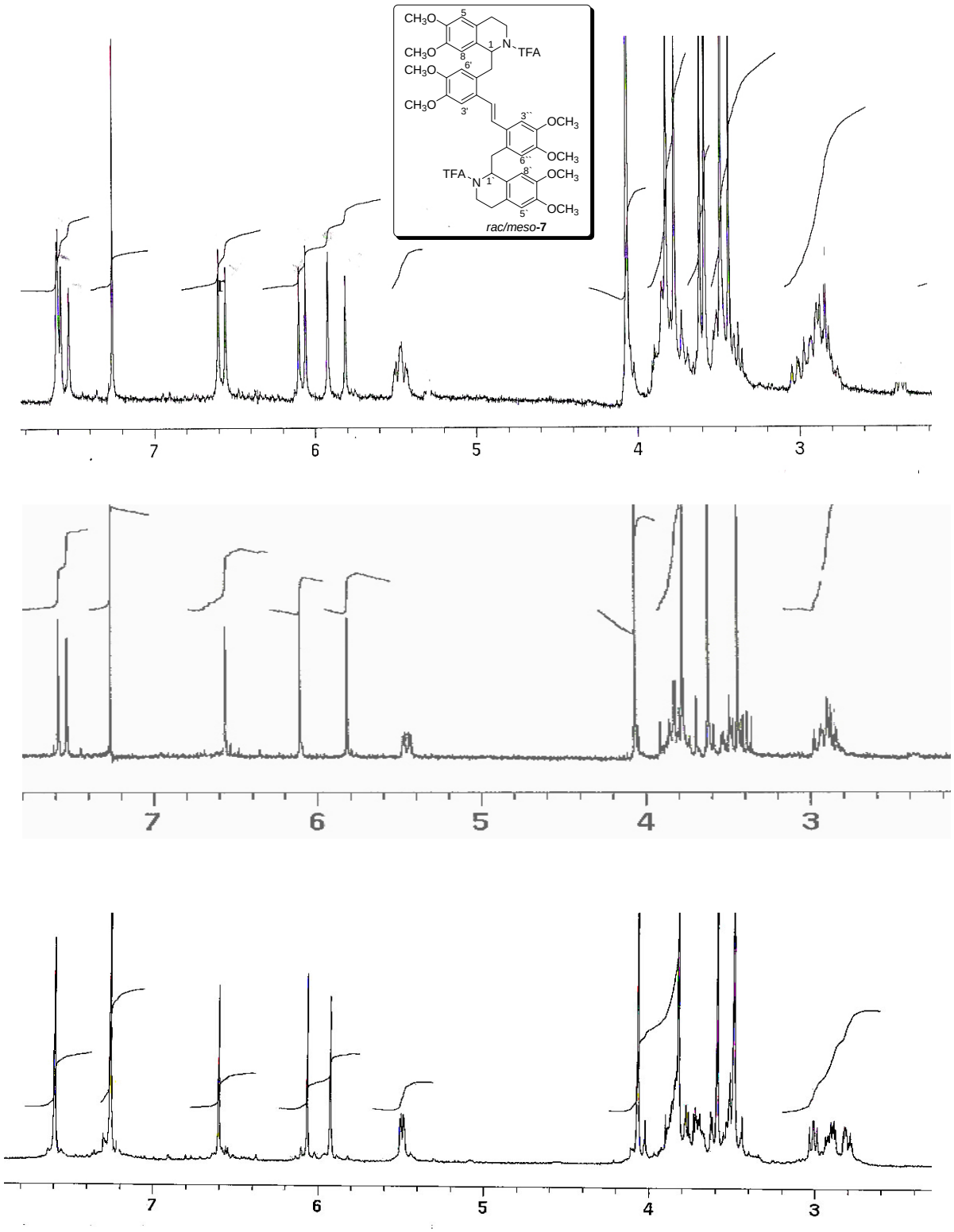
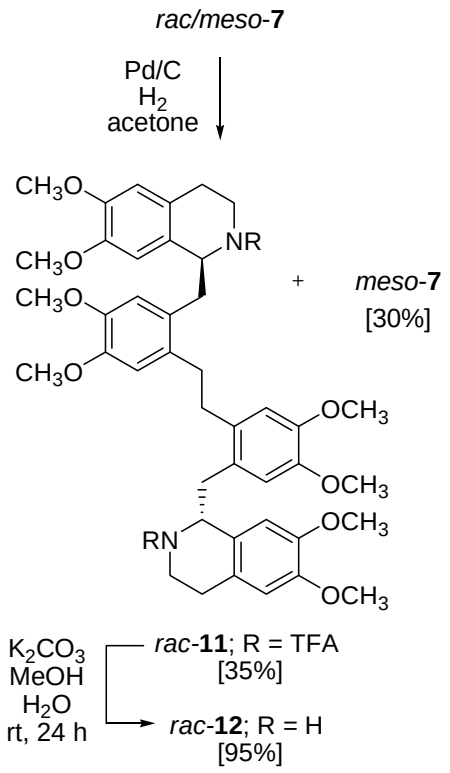


Figure 2. The ^{1}H NMR spectra (300 MHz, $CDCl_3$) of the mixture of *meso*-**7** and *rac*-**7** (top), (*S*,*S*)-**7** (middle) and *meso*-**7** (bottom).

Rac/meso-**7** was found to be insoluble in most solvents commonly employed for hydrogenation reactions (e.g. MeOH, EtOH, EtOAc) but was found to be partially soluble in acetone. Hydrogenation of *rac/meso*-**7** in acetone resulted in the selective hydrogenation of the more soluble *rac*-**7**. After filtration of the catalyst, addition of methanol to the solution resulted in the precipitation of pure *meso*-**7** in 30% yield while further purification of the mother liquors by column chromatography gave *rac*-**11** in 35% yield (Scheme 3). Base hydrolysis of *rac*-**11** then gave *rac*-**12** in 95% yield (Scheme 3).

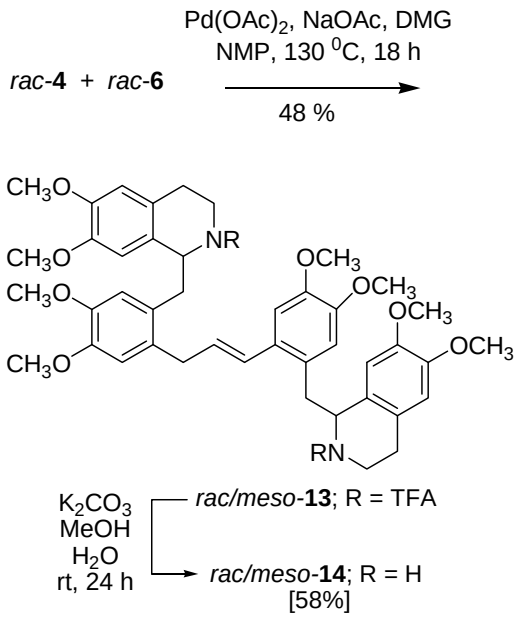
Scheme 3



[only the (*S*,*S*)-isomer shown)]

Under similar Mizoroki-Heck coupling reaction conditions to those described in Scheme 2, *rac*-**4** and *rac*-**6** underwent a Mizoroki-Heck coupling reaction to give **13** in 48% yield as *ca* 60 : 40 mixture of the racemic and meso forms (not necessarily respectively) (Scheme 4). This mixture was then converted to an inseparable mixture of *rac/meso*-**14** upon base hydrolysis (Scheme 4).

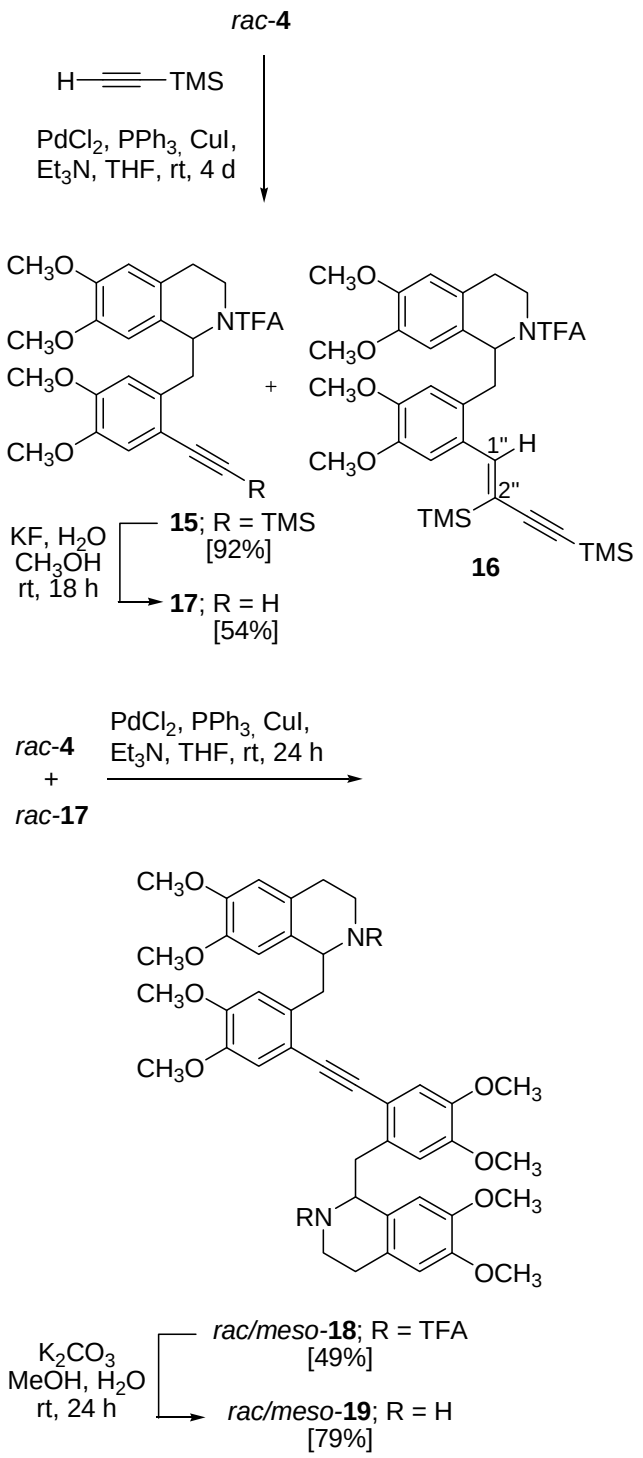
Scheme 4



A Sonagashira coupling reaction between *rac*-**4** and trimethylsilylacetylene (3 equiv) gave a mixture of the desired product *rac*-**15** (45%) and the undesired ene-yne *rac*-**16** (52%) (Scheme 5). The structure of the ene-yne *rac*-**16** was based upon the downfield ^{1}H NMR chemical shift of its alkene proton at δ 8.15 (s, 1H).[22-24] The alternative regioisomic product would be expected to have an alkene chemical shift at *ca* δ 7.0.[22-24] When 1.5 equiv of trimethylsilylacetylene was employed the yield of *rac*-**15** was 92% (Scheme 5). *Rac*-**15** was converted to the primary alkyne *rac*-**17** which underwent a Sonagashira coupling reaction with *rac*-**4** to give *rac/meso*-**18** in 49% yield. The ^{1}H and ^{13}C NMR spectra of this compound indicated a single stereoisomer had formed (no doubling up of resonances was observed). This suggested that either the *meso*- or the *rac*- form of **18** had failed to form in this reaction or that either *meso*- or *rac*-**18** was unstable to the reaction conditions and decomposed. A more likely explanation is that, because of the rigid alkyne tether, the two stereogenic centres in the isoquinoline ring are too remote to interact and thus the *rac* and *meso* forms of **18** have the same NMR chemical

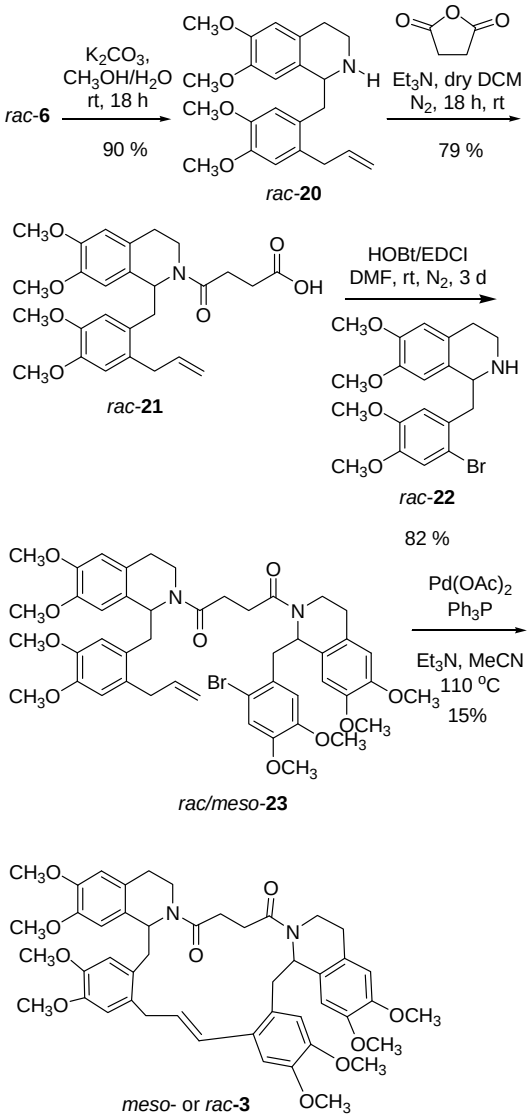
shifts. Base hydrolysis of *rac/meso*-**18** gave *rac/meso*-**19** in 79% yield. The NMR spectra of **19** also did not show the doubling up of resonances.

Scheme 5



Base hydrolysis of *rac*-**6** gave the secondary amine *rac*-**20** in 90% yield (Scheme 6) which was condensed with succinic anhydride to give the amido acid *rac*-**21** in 79% yield. An amide coupling reaction between the acid *rac*-**21** and the 2'-bromobenzylisoquinoline derivative *rac*-**22**[24] gave the bisamide **23** as a mixture of the racemic and meso forms (Scheme 6). Attempts to convert *rac/meso*-**23** to the target macrocyclic compound **3** using the Mizoroki-Heck reaction conditions developed in Schemes 2 and 4 were unsuccessful and resulted in a complex mixture of products. However, under the more traditional Heck reaction conditions ($Pd(OAc)_2$, Ph_3P, Et_3N) the desired compound **3** was obtained in 15% yield. NMR analysis of **3** indicated that a single isomer was obtained, with only one set of separate resonances observed for each different isoquinoline moiety. We made no attempts to determine whether this was the racemic or meso form of **3**. The NMR evidence suggested that either the *meso*- or the *rac*- form of **3** had failed to form in this reaction or that either *meso*- or *rac* forms of **23** or **3** were unstable to the reaction conditions and decomposed. ^{1}H NMR analysis of **3** clearly indicated that the (*E*)-isomer of **3** was obtained (δ 6.93 (d, 1H, *J* 15.3 Hz)).

Scheme 6



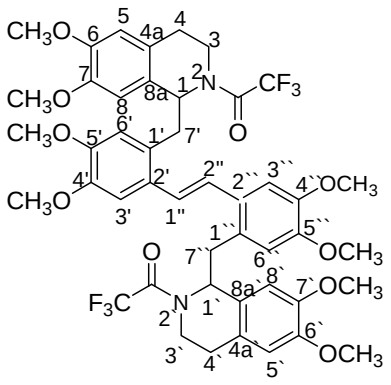
In summary, several novel laudanosine dimers in which two laudanosine units are linked at C-2' *via* a two or three-carbon linker (alkane, alkene or alkyne) have been prepared using palladium-catalysed cross-coupling reactions. In one example, a second three-carbon linker between the two isoquinoline N-atoms was also present leading to the novel macrocyclic ring system **3**. The biological activities of the N-deprotected bisisoquinoline compounds and the macrocyclic compound **3** will be reported in a separate publication.

3. Experimental

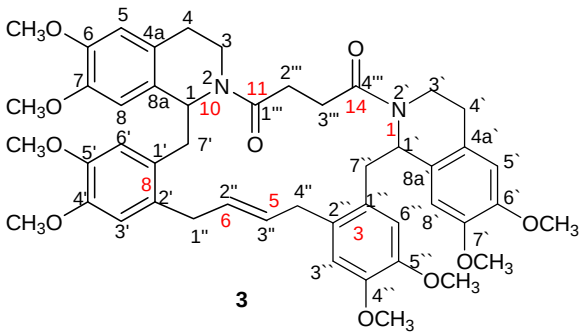
3.1 General procedures

Petrol refers to the fraction of petroleum spirit with a boiling point of 40-60 °C. All ^{1}H NMR spectra were performed at 300 MHz and all ^{13}C NMR (DEPT) spectra at 75 MHz in $CDCl_3$ solution, unless otherwise noted. All spectra were referenced to $CDCl_3$ (^{1}H δ 7.26 ppm and ^{13}C NMR δ 77.00 ppm). ^{1}H NMR assignments were achieved with the aid of gCOSY, and in some cases NOESY and TOCSY experiments. ^{13}C NMR assignments were based upon DEPT, gHSQC and gHMBC experiments. All compounds were homogeneous by TLC analysis and judged to be of >95% purity based upon ^{1}H NMR analysis.

Compound numbering of isoquinoline derivatives is based on that of compound **7** as shown below. The numbering used for **3** in the NMR analysis in shown below in black, systematic numbering is shown in red.



7



3

3.2 General method for Stille coupling reactions.

To a thick walled tube (sealed tube) containing a solution of the 2'-iodolaudanosine **4**, $PdCl_2$ and PPh_3 in dry DMF under N_2 was added allyltributylstannane or tributylvinylstannane. The tube was sealed under a N_2 atmosphere and the mixture was stirred and heated at 110 ^{0}C for 36 h. The solution was cooled, diluted with CH_2Cl_2 and washed with H_2O (4 x) and then brine. The CH_2Cl_2 layer was evaporated and the residue was redissolved in CH_3CN and extracted with hexane. The CH_3CN layer was evaporated and the residue was purified by column chromatography (EtOAc: petrol (1 : 1)) (unless indicated otherwise) to afford the pure products.

3.2.1 (*RS*) 1-(2'-Ethenyl-4',5'-dimethoxyphenyl)methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (5).

The 2'-iodolaudanosine derivative **4** (492 mg, 0.870 mmol), $Pd(OAc)_2$ (16 mg, 0.071 mmol), PPh_3 (43 mg, 0.174 mmol) and tributylvinylstannane (333 mg, 1.04 mmol, 0.29 mL) in dry DMF (10 mL) under N_2 was treated as described above using the general Stille coupling reaction conditions to afford a residue which was purified by column chromatography to afford **5** (352 mg, 87 %) as a yellow solid. The yellow solid was recrystallized from EtOAc : petrol (1 : 1) and was a 95 : 5 mixture of rotamers. R_f 0.48 (EtOAc: petrol (1 : 1)). M.p. 132-134 ^{0}C. ^{1}H NMR of the major rotamer (500 MHz): δ 6.97 (s, 1H, H3'), 6.81 (dd, 1H, *J* 17.0, 11.0 Hz, H1''), 6.56 (s, 1H, H8), 6.39 (s, 1H, H5), 6.08 (s, 1H, H6'), 5.50 (t, 1H, *J* 7.0 Hz, H1), 5.46 (d, 1H, *J* 17.0 Hz, H2''(*E*)), 5.13 (d, 1H, *J* 11.0 Hz, H2''(*Z*)), 3.87 (dt, 1H, *J* 9.0, 4.0 Hz, H3), 3.87 (s, 3H, OC$\underline{H_3}$-4'), 3.82 (s, 3H, OC$\underline{H_3}$-6), 3.70 (s, 3H, OC$\underline{H_3}$-7), 3.63-3.61 (m, 1H, H3), 3.57 (s, 3H, OC$\underline{H_3}$-5'), 3.16 (d, 2H, *J* 7.0 Hz, H7'), 2.92-2.83 (m, 1H, H4), 2.71 (m, 1H, H4). ^{1}H NMR of the minor rotamer (in part): δ 6.57 (s, 1H, H8), 6.41 (s, 1H, H5), 5.84 (s, 1H, H6'), 3.84 (s,

3H, OC$\underline{H}_3$-4'), 3.84 (s, 3H, OC$\underline{H}_3$-6), 3.78 (s, 3H, OC$\underline{H}_3$-7), 3.51 (s, 3H, OC$\underline{H}_3$-5'). ^{13}C NMR of the major rotamer (125 MHz): (signals for $\underline{C}OCF_3$ and $CO\underline{C}F_3$ were not observed) δ 148.8 (C4'), 148.5 (C6), 148.3 (C7), 147.6 (C5'), 133.9 (CH-1''), 130.4 (C2'), 127.3 (C4a), 126.4 (C8a), 125.4 (C1'), 114.5 (CH_2-2''), 114.1 (CH-3'), 111.2 (CH-5), 111.0 (CH-8), 108.5 (CH-6'), 56.2 (O$\underline{C}H_3$-4'), 56.2 (O$\underline{C}H_3$-6), 56.1 (O$\underline{C}H_3$-7), 56.0 (O$\underline{C}H_3$-5'), 55.6 (CH-1), 41.0 (CH_2-3), 38.2 (CH_2-7'), 28.7 (CH_2-4). MS (ESI$^+$) *m/z* 466.1 (MH$^+$, 50 %). HRMS (EI$^+$): calcd for $C_{24}H_{26}NO_5F_3$, 465.1763 (M$^+$). Found 465.1762.

3.2.2 (*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1-(4',5'-dimethoxy-2'-(2''-propenyl)-phenyl)methyl-6,7-dimethoxyisoquinoline (6).

The 2'-iodolaudanosine derivative **4** (711 mg, 1.26 mmol), $Pd(OAc)_2$ (23 mg, 0.102 mmol), PPh_3 (61 mg, 0.232 mmol), allyltributylstannane (499 mg, 1.51 mmol, 0.46 mL) and dry DMF (5 mL) under N_2 was treated as described above using the general Stille coupling reaction conditions to afford an oil which was purified by column chromatography to give 68 (536 mg, 89 %) as a white solid. Compound **6** was recrystallized from diethyl ether and was a 95 : 5 mixture of rotamers. R_f 0.63 (EtOAc : petrol (1 : 1)). M.p. 140-144 ^{0}C. ^{1}H NMR of the major rotamer: δ 6.62 (s, 1H, H3'), 6.58 (s, 1H, H5), 6.53 (s, 1H, H6'), 6.00 (s, 1H, H8), 5.91-5.78 (m, 1H, H2''), 5.49 (dd, *J* 8.1, 6.0 Hz, 1H, H1), 5.02 (dd, 1H, *J* 10.2, 0.9 Hz, H3''(*Z*)), 4.94 (dd, 1H, *J* 17.2, 0.9 Hz, H3''(*E*)), 3.85 (s, 3H, OC$\underline{H}_3$-4'), 3.84 (s, 3H, OC$\underline{H}_3$-6), 3.98-3.92 (m, 1H, H3), 3.76 (s, 3H, OC$\underline{H}_3$-7), 3.74-3.64 (m, 1H, H3), 3.56 (s, 3H, OC$\underline{H}_3$-5'), 3.12 (dd, 2H, *J* 4.8, 1.5 Hz, H1''), 3.04 (d, 1H, *J* 6.0 Hz, H7'), 3.03 (d, 1H, *J* 8.1 Hz, H7'), 2.96-2.88 (m, 1H, H4), 2.83-2.75 (m, 1H, H4). ^{1}H NMR of the minor rotamer (in part): δ 6.55 (s, 1H, H8), 3.80 (s, 3H, OC$\underline{H}_3$-6), 3.49 (s, 3H, OC$\underline{H}_3$-5'). ^{13}C NMR of the major rotamer: (signals for $\underline{C}OCF_3$ and $CO\underline{C}F_3$ were not observed), δ 148.4 (C4'), 148.1 (C6), 147.4 (C7), 147.4 (C5'), 137.5 (CH-2''), 131.2 (C2'), 127.4 (C4a), 126.6 (C8a), 125.1 (C1'), 115.9 (CH_2-3''), 114.2 (CH-3'), 113.1 (CH-5), 111.2 (CH-8), 110.9 (CH-6'), 56.2 (O$\underline{C}H_3$-4'), 56.1 (O$\underline{C}H_3$-6), 55.8 (O$\underline{C}H_3$-7, O$\underline{C}H_3$-5'), 55.6 (CH-1), 40.8

(CH_2-3), 39.1 (CH_2-1''), 36.7 (CH_2-7'), 28.7 (CH_2-4). ^{13}C NMR of the minor rotamer (in part): δ 114.9 (CH-3'), 113.8 (CH-5), 111.5 (CH-8), 111.4 (CH-6'), 27.4 (CH_2-4). MS (CI^+): *m/z* 480 (MH^+, 100 %). HRMS (CI^+): calcd for $C_{25}H_{29}NO_5F_3$, 480.1998 (MH^+). Found 480.2000.

3.3 General method for Mizoroki-Heck coupling reactions.

A mixture of palladium acetate, *N*,*N*-dimethylglycine (DMG), sodium acetate and both coupling partners were placed in a thick walled tube (sealed tube) under N_2. Dry *N*-methylpyrolidinone (NMP) was added and the reaction mixture was bubbled with argon prior to sealing the tube. The reaction mixture was heated at 130 ^0C for 18 h. The reaction mixture was cooled and then diluted with CH_2Cl_2 and the solution was washed with H_2O (3 x), brine and dried ($MgSO_4$). The solution was evaporated to give a dark oil that was purified by column chromatography (EtOAc : petrol (1 : 1)) (unless otherwise stated) to give the desired product.

3.3.1 (1*RS*, 1`*RS*) and (*R*, *S*) (*E*) 2',2``-(1'',2''-Ethenediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (7)** and **(1*RS*, 1`*RS*) (*E*) 2',2``-(1'',1''-Ethenediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (8).

The 2'-iodolaudanosine derivative **4** (203 mg, 0.354 mmol), the 2'-vinyllaudanosine derivative **5** (166 mg, 0.354 mmol), $Pd(OAc)_2$ (8 mg, 0.035 mmol), DMG (73 mg, 0.708 mmol), NaOAc (56 mg, 0.708 mmol) and dry NMP (5 mL) under N_2 were treated as described above in the general Mizoroki-Heck coupling reaction procedure to give a crude mixture. To the mixture was added methanol (5 mL) and the product **7** precipitated out as a white solid (164 mg, 54 %). The regioisomer **8** remained in the solution and was purified by column chromatography (CH_2Cl_2 : EtOAc : petrol (3 : 2 : 3)) to give **8** (36 mg, 12 %) as a yellow oil. Compound **7** was a 55 : 45 mixture of diastereomers. Compound **8** was a 60

: 40 mixture of diastereomers. A minor rotamer (~ 5 %) was also observed in the ^{1}H NMR spectra of both **7** and **8**.

Compounds **7** and **8** were also prepared according to the conditions outlined in Table 1 under, essentially, the same conditions using the quantities of catalyst, base and additives shown in the Table.

A small amount of (*S*,*S*)-**7** (13 mg, 15 %) was obtained under the same Mizoroki-Heck coupling reaction conditions using a mixture of (*S*)-**5** (60 mg, 0.105 mmol) and (*S*)-**4** (80 mg, 0.171 mmol), $Pd(OAc)_2$ (3 mg, 0.013 mmol), DMG (27 mg, 0.258 mmol), NaOAc (21 mg, 0.258 mmol) and NMP (2 mL). A mixture of (*S*)-**5** and (*S*)-**4** (67 mg) was also recovered. Compound (*S*,*S*)-**8** was also observed in the reaction, however, not in significant quantity or purity to characterize.

7: R_f 0.31 (CH_2Cl_2 : EtOAc : petrol (3 : 2 : 3)). (*S*,*S*)-**7:** $[\alpha]_D^{25}$ + 29 (0.84, $CHCl_3$). M.p. (*meso*-**7** and *rac*-**7**) 226-228 ^{0}C. ^{1}H NMR of the major diastereomer, *meso*-**7:** δ 7.58 (s, 4H, C<u>H</u>=C<u>H</u>, H3', H3``), 6.58 (s, 2H, H5, H5`), 6.05 (s, 2H, H6', H6``), 5.91 (s, 2H, H8, H8`), 5.47 (dd, 2H, *J* 9.5, 5.4 Hz, H1, H1`), 4.05 (s, 6H, OC<u>H$_3$</u>-5', OC<u>H$_3$</u>-5``), 3.85 (dd, 2H, *J* 8.1, 3.9 Hz, H3, H3`), 3.81 (s, 6H, OC<u>H$_3$</u>-4', OC<u>H$_3$</u>-4``), 3.71-3.65 (m, 2H, H3, H3`), 3.57 (s, 6H, OC<u>H$_3$</u>-6, OC<u>H$_3$</u>-6`), 3.53 (t, 2H, *J* 13.2, 5.4 Hz, H7', H7``), 3.47 (s, 6H, OC<u>H$_3$</u>-7, OC<u>H$_3$</u>-7`), 2.99 (dd, 2H, *J* 13.2, 9.5 Hz, H7', H7``), 2.92-2.86 (m, 2H, H4, H4`), 2.81-2.76 (m, 2H, H4, H4`). ^{1}H NMR of the minor rotamer of *meso*-**7** (in part): δ 7.45 (s, 2H, H3', H3``), 7.53 (s, 2H, C<u>H</u>=C<u>H</u>), 5.79 (s, 2H, H8, H8`), 6.48 (s, 2H, H5, H5`). 3.76 (s, 6H, OC<u>H$_3$</u>-5', OC<u>H$_3$</u>-5``), 3.71 (s, 6H, OC<u>H$_3$</u>-4', OC<u>H$_3$</u>-4``), 3.60 (s, 6H, OC<u>H$_3$</u>-6, OC<u>H$_3$</u>-6`), 3.42 (s, 6H, OC<u>H$_3$</u>-7, OC<u>H$_3$</u>-7`). $^{13}$C NMR of the major diastereomer, *meso*-**7**: δ 156.1 (q, *J* 35.5 Hz, <u>C</u>OCF$_3$), 148.9 (C5', C5``), 148.3 (C4', C4``), 148.2 (C6, C6`), 147.1 (C7, C7`), 130.0 (C1', C1``), 127.1 (C2', C2``), 126.1 (C4a, C4a`), 125.5 (C8a, C8a`), 125.0 (<u>C</u>H=<u>C</u>H), 115.2 (CH-6', CH-6``), 113.5 (q, *J* 270.1 Hz, CO<u>C</u>F$_3$), 111.9 (CH-8, CH-8`), 111.1 (CH-5, CH-5`), 108.5 (CH-3', CH-3``), 56.1 (O<u>C</u>H$_3$-4', O<u>C</u>H$_3$-4``, O<u>C</u>H$_3$-6, O<u>C</u>H$_3$-6`, O<u>C</u>H$_3$-7, O<u>C</u>H$_3$-7`), 55.8 (O<u>C</u>H$_3$-5', O<u>C</u>H$_3$-5``), 55.5 (CH-1, CH-1`), 41.4 ($CH_2$-3, CH-3`), 38.9 ($CH_2$-7', $CH_2$-7``), 28.6 (CH_2-4, CH_2-4`). ^{1}H NMR of the minor diastereomer,

rac-**7:** δ 7.56 (s, 2H, C<u>H</u>=C<u>H</u>), 7.51 (s, 2H, H3', H3``), 6.54 (s, 2H, H5, H5`), 6.09 (s, 2H, H6', H6``), 5.80 (s, 2H, H8, H8`), 5.43 (dd, 2H, *J* 10.5, 3.3 Hz, H1, H1`), 3.99 (s, 6H, OC<u>H</u>$_3$-5', OC<u>H</u>$_3$-5``), 3.80 (m, 2H, H3, H3`), 3.76 (s, 6H, OC<u>H</u>$_3$-4', OC<u>H</u>$_3$-4``), 3.60 (s, OC<u>H</u>$_3$-6, OC<u>H</u>$_3$-6`), 3.49 (m, 2H, H3', H3`), 3.42 (s, OC<u>H</u>$_3$-7, OC<u>H</u>$_3$-7`), 3.38 (m, 2H, H7', H7``), 2.93 (dd, 2H, *J* 13.2, 10.5 Hz, H7', H7``), 2.91 (m, 2H, H4, H4`), 2.86 (m, 2H, H4, H4`). ^{13}C NMR of the minor diastereomer, *rac*-**7:** δ 156.1 (q, *J* 35.5 Hz, <u>C</u>OCF$_3$), 148.9 (C5', C5``), 148.3 (C4', C4``), 148.2 (C6, C6`), 147.1 (C7, C7`), 130.0 (C1', C1``), 127.1 (C2', C2``), 126.1 (C4a, C4a`), 125.5 (C8a, C8a`), 125.0 (<u>C</u>H=<u>C</u>H), 115.2 (CH-6', CH-6``), 113.5 (q, *J* 270.1 Hz, CO<u>C</u>F$_3$), 111.9 (CH-8, CH-8`), 111.1 (CH-5, CH-5`), 108.5 (CH-3', CH-3``), 56.1 (O<u>C</u>H$_3$-4', O<u>C</u>H$_3$-4``, O<u>C</u>H$_3$-6, O<u>C</u>H$_3$-6`, O<u>C</u>H$_3$-7, O<u>C</u>H$_3$-7`), 55.8 (O<u>C</u>H$_3$-5', O<u>C</u>H$_3$-5``), 55.5 (CH-1, CH-1`), 41.4 (CH$_2$-3, CH-3`), 38.9 (CH$_2$-7', CH$_2$-7``), 28.6 (CH$_2$-4, CH$_2$-4`). MS (ESI$^+$): *m/z* 925.1 (M+Na$^+$, 100 %). HRMS (ESI$^+$): calculated for $C_{46}H_{49}N_2O_{10}F_6$, 903.3291 (MH$^+$). Found 903.3251.

8: R$_f$ 0.25 (CH$_2$Cl$_2$: EtOAc : petrol (3 : 2 : 3)). ^{1}H NMR of the major diastereomer, *rac*-**8:** δ 6.61 (s, 2H, H3', H3``), 6.52 (s, 4H, H5, H5`, H6', H6``), 5.94 (s, 2H, H8, H8`), 5.39 (t, 2H, *J* 7.5 Hz, H1, H1`), 4.95 (s, 2H, C=C<u>H</u>$_2$), 3.84 (s, 6H, OC<u>H</u>$_3$-5', OC<u>H</u>$_3$-5``), 3.82 (s, 6H, OC<u>H</u>$_3$-4', OC<u>H</u>$_3$-4``), 3.74 (s, 6H, OC<u>H</u>$_3$-6, OC<u>H</u>$_3$-6`), 3.76-3.70 (m, 2H, H3, H3`), 3.56 (s, 6H, OC<u>H</u>$_3$-7, OC<u>H</u>$_3$-7`), 3.33-3.10 (m 2H, H3, H3`), 2.95-2.76 (m, 4H, H7', H7``, H4, H4`), 2.70-2.53 (m, 4H, H7', H7``, H4, H4`). ^{1}H NMR of the minor diastereomer, *meso*-**8** (in part): δ 6.65 (s, 2H, H3', H3``), 6.56 (s, 2H, H5, H5`), 5.92 (s, 2H, H8, H8`), 5.49 (s, 2H, H1, H1`), 4.78 (s, 2H, C=C<u>H</u>$_2$), 3.79 (s, 6H, OC<u>H</u>$_3$-5', OC<u>H</u>$_3$-5``), 3.78 (s, 6H, OC<u>H</u>$_3$-4', OC<u>H</u>$_3$-4``), 3.76 (s, 6H, OC<u>H</u>$_3$-6, OC<u>H</u>$_3$-6`), 3.51 (s, 6H, OC<u>H</u>$_3$-7, OC<u>H</u>$_3$-7`). $^{13}$C NMR of the major diastereomer, *rac*-**8:** δ 155.9 (q, *J* 35.0 Hz, <u>C</u>OCF$_3$), 148.6 (C4', C4``), 148.5 (C6, C6`), 147.9 (C5', C5``), 147.8 (C7, C7`), 135.7 (<u>C</u>=CH$_2$), 127.4 (C1', C1``, C2', C2``), 126.9 (C4a, C4a`), 125.0 (C8a, C8a`), 120.8 (C=<u>C</u>H$_2$), 114.1 (CH-3', CH-3``), 113.8 (CH-5, CH-5`), 112.5 (q, *J* 224.8 Hz, CO<u>C</u>F$_3$), 111.2 (CH-6, CH-6`), 110.4 (CH-8, CH-8`), 56.2 (O<u>C</u>H$_3$-4', O<u>C</u>H$_3$-4``), 56.2 (O<u>C</u>H$_3$-6,

O<u>C</u>H_3-6`), 56.1 (O<u>C</u>H_3-5', O<u>C</u>H_3-5``), 55.7 (O<u>C</u>$H_3$-7, O<u>C</u>$H_3$-7`), 55.4 (CH-1, CH-1`), 41.4 ($CH_2$-3, $CH_2$-3`), 38.1 ($CH_2$-7', $CH_2$-7``), 28.8 (CH_2-4, CH_2-4`). ^{13}C NMR of the minor diastereomer, *meso*-**8** (in part): δ 135.8 (<u>C</u>=CH_2), 127.3 (C1', C1``, C2', C2``), 124.8 (C8a, C8a`), 120.5 (C=<u>C</u>H_2), 38.0 (CH_2-7', CH_2-7``). MS (ESI$^+$): *m/z* 925.0 (M+Na$^+$, 20 %). HRMS (ESI$^+$): calculated for $C_{46}H_{49}N_2O_{10}F_6$, 903.3291 (MH$^+$). Found 903.3315.

3.3.2 (1*RS*, 1`*RS*) and (*R*, *S*) (*E*) 2',2``-(1'',3''-Prop-2''-enediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (13).

The 2'-iodolaudanosine derivative **4** (255 mg, 0.462 mmol), the 2'-allyllaudanosine derivative **6** (232 mg, 0.462 mmol), $Pd(OAc)_2$ (12 mg, 0.046 mmol), DMG (95 mg, 0.927 mmol), NaOAc (73 mg, 0.927 mmol) and dry NMP (5 mL) were treated as described above using the general Heck coupling reaction procedure to give a dark oil. The oil was purified by column chromatography to give the desired product **13** (199 mg, 48 %) as a yellow solid. Product **13** was a 60 : 40 mixture of diastereomers and a minor rotamer (~ 5 %) was also observed in the ^{1}H NMR spectrum. R_f 0.19 (EtOAc : petrol (1 : 1)). M.p. 102-104 ^{0}C. ^{1}H NMR of the major diastereomer: δ 6.86 (s, 1H, H3``) 6.68 (s, 1H, H3'), 6.56 (s, 1H, H5), 6.53 (s, 1H, H5``), 6.48 (s, 1H, H6'), 6.42 (d, 1H, *J* 14.1 Hz, H3''), 6.37 (s, 1H, H6``), 5.97 (s, 2H, H8, H8`), 5.97-5.92 (m, 1H, H2''), 5.47 (dd, 2H, *J* 8.7, 5.7 Hz, H1, H1`), 3.91-3.83 (m, 2H, H3, H3`), 3.79 (s, 12H, OC<u>H</u>$_3$-6, OC<u>H</u>$_3$-6`, OC<u>H</u>$_3$-4', OC<u>H</u>$_3$-4``), 3.55-3.50 (m, 2H, H3, H3`), 3.70 (s, 6H, OC<u>H</u>$_3$-7, OC<u>H</u>$_3$-7`), 3.48 (s, 6H, OC<u>H</u>$_3$-5', OC<u>H</u>$_3$-5``), 3.32-3.18 (m, 2H, H1''), 3.12-2.99 (m, 4H, H7', H7``), 2.87-2.77 (m, 2H, H4, H4`), 2.73-2.65 (m, 2H, H4, H4`). ^{1}H NMR of the minor diastereomer (in part): δ 6.85 (s, 1H, H3``), 6.67 (s, 1H, H3'), 6.56 (s, 1H, H5), 6.53 (s, 1H, H5``), 6.47 (s, 1H, H6'), 6.42 (d, 1H, *J* 14.1 Hz, H3''), 6.36 (s, 1H, H6``), 6.00 (s, 1H, H8), 5.92 (s, 1H, H8`), 5.43 (dd, 2H, *J* 8.7, 5.7 Hz, H1, H1`), 3.74 (s, 12H, OC<u>H</u>$_3$-6, OC<u>H</u>$_3$-6`, OC<u>H</u>$_3$-4', OC<u>H</u>$_3$-4``), 3.66 (s, 6H, OC<u>H</u>$_3$-7, OC<u>H</u>$_3$-7`), 3.46 (s, 6H, OC<u>H</u>$_3$-5', OC<u>H</u>$_3$-5``). $^{13}$C NMR of the major diastereomer: δ 155.9 (q, *J* 36.1 Hz, <u>C</u>O$CF_3$), 148.2 (C6, C6`), 148.1 (C4', C4``), 147.3 (C5', C5``), 147.1 (C7, C7`), 131.5 (C1``),

129.8 (C1'), 129.5 (CH-3''), 127.5 (CH-2''), 127.1 (C2``), 126.5 (C2'), 126.2 (C4a`), 126.0 (C4a), 125.1 (C8a`), 125.0 (C8a), 114.1 (q, *J* 286.5 Hz, CO<u>C</u>$F_3$), 114.0 (CH-6'), 133.8 (CH-6``), 113.0 (CH-3'), 110.9 (CH-5, CH-5`), 110.6 (CH-8, CH-8`), 108.5 (CH-3``), 55.8 (8 x $OCH_3$), 55.3 (CH-1, CH-1`), 40.6 ($CH_2$-3, $CH_2$-3`), 38.0 ($CH_2$-7', $CH_2$-7``), 36.0 (CH_2-1''), 28.4 (CH_2-4, CH_2-4`). $^{13}$C NMR of the minor diastereomer (in part): δ 148.1 (C6, C6`), 147.9 (C4', C4``), 147.1 (C5', C5``), 147.0 (C7, C7`), 131.5 (C1``), 129.8 (C1'), 129.7 (CH-3''), 127.6 (CH-2''), 127.2 (C2``), 126.5 (C2'), 126.3 (C4a`), 126.0 (C4a), 125.1 (C8a`), 125.0 (C8a), 114.0 (CH-6'), 133.7 (CH-6``), 113.1 (CH-3'), 110.8 (CH-5, CH-5`), 110.7 (CH-8, CH-8`), 108.4 (CH-3``), 40.6 (CH_2-3, CH_2-3`), 37.9 (CH_2-7', CH_2-7``), 36.1 (CH_2-1''), 28.5 (CH_2-4, CH_2-4`). MS (ESI^+) *m/z* 916.72 (MH^+, 10 %), *m/z* 954.74 ($M+K^+$, 100 %). HRMS (ESI^+) calcd for $C_{47}H_{51}N_2O_{10}F_6$, 917.3448 (MH^+). Found 917.3451.

3.4 General method for hydrogenation reactions.

3.4.1 (1*RS*, 1`*RS*) and (*R*,*S*) 2',2``-(1'',2''-Ethanediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (11).

To a solution of alkene **7** (73 mg, 0.083 mmol) in acetone (80 mL) was added 10 % Pd/C (10 mg) in a round bottom flask sealed with a suba seal. The flask was purged with nitrogen and then a hydrogen filled balloon was secured on top of the flask, allowing the hydrogen to circulate inside the flask. The reaction mixture was stirred at RT for 3 d under a H_2 atmosphere. Nitrogen was then bubbled into the solution for 2 min and CH_2Cl_2 (1 mL) was added until the solution became completely homogenous. Pd/C was filtered and the solvent was evaporated to give a crude mixture of *meso*-**7** and *rac*-**11**. The crude mixture was dissolved in CH_2Cl_2 (1 mL) and methanol (4 mL) was added slowly resulting in the precipitation of *meso*-**7.** The pure *meso*-**7** (22 mg, 30 %) was filtered as a white solid. The filtrate was evaporated and then purification by column chromatography (CH_2Cl_2 : EtOAc : petrol (3 : 2 : 3)) gave pure *rac*-**11** (26 mg, 35 %) a yellow oil.

11: R_f 0.39 (CH_2Cl_2 : EtOAc : petrol (3 : 2 : 3)). ^{1}H NMR: δ 6.62 (s, 2H, H3', H3``), 6.57 (s, 2H, H5, H5`), 6.30 (s, 2H, H6', H6``), 5.90 (s, 2H, H8, H8`), 5.40 (dd, 2H, *J* 8.4, 5.1 Hz, H1, H1`), 3.93-3.85 (m, 2H, H3, H3`), 3.82 (s, 6H, OC$\underline{H_3}$-4', OC$\underline{H_3}$-4``), 3.79 (s, 2H, OC$\underline{H_3}$-5', OC$\underline{H_3}$-5``), 3.66 (s, 2H, OC$\underline{H_3}$-6, OC$\underline{H_3}$-6`), 3.64-3.55 (m, 2H, H3, H3`), 3.48 (s, 6H, OC$\underline{H_3}$-7, OC$\underline{H_3}$-7`), 2.94 (dd, 2H, *J* 13.5, 5.1 Hz, H7', H7``), 2.82 (s, 4H, H1'', H2''), 2.81 (dd, 2H, *J* 13.5, 8.4 Hz, H7', H7``), 2.78-2.62 (m, 4H, H4, H4`). ^{13}C NMR: (signals for $\underline{C}OCF_3$ and $CO\underline{C}F_3$ were not observed), δ 148.1 (C4', C4``), 147.8 (C6, C6`), 147.0 (C5', C5``), 146.8 (C7, C7`), 132.7 (C2', C2``), 126.8 (C1', C1``), 126.1 (C4a, C4a`), 124.9 (C8a, C8a`), 114.2 (CH-6', CH-6``), 112.9 (CH-3', CH-3``), 110.9 (CH-5, CH-5`), 110.8 (CH-8, CH-8`), 55.8 (8 x O$\underline{C}H_3$), 55.5 (C1, C1`), 40.7 ($CH_2$-3, $CH_2$-3`), 38.0 (CH_2-7', CH_2-7``), 33.5 (CH_2-1'', CH_2-2''), 29.0 (CH_2-4, CH_2-4`). MS (ESI$^+$): *m/z* 905.1 (MH$^+$, 20 %). HRMS (ESI$^+$): calcd for $C_{46}H_{51}N_2O_{10}F_6$, 905.3448 (MH$^+$). Found 905.3411.

3.5 General method for Sonagashira coupling Reactions.

3.5.1 (*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxy-2'-(trimethylsilylethynyl)phenyl)methylisoquinoline (15).

Compound **4** (300 mg, 0.530 mmol), $PdCl_2$ (5 mg, 0.027 mmol), PPh_3 (14 mg, 0.053 mmol) and CuI (10 mg, 0.053 mmol) were added to a dry flask under a N_2 atmosphere. Dry THF (45 mL) was added followed by the addition of Et_3N (80 mg, 0.795 mmol, 0.11 mL). The solution was stirred for 5 min before trimethylsilylacetylene (78 mg, 0.795 mmol, 0.11 mL) was added. The reaction was stirred at rt for 4 d. The solvent was evaporated and the crude mixture was purified by column chromatography (CH_2Cl_2 : EtOAc : petrol (3 : 1 : 3)) to give **15** (266 mg, 92 %) as a brown solid. Compound **15** was a 95 : 5 mixture of rotamers. R_f 0.77 (CH_2Cl_2 : EtOAc : petrol (3 : 1: 3)). M.p. 114-118 ^{0}C. ^{1}H NMR of the major rotamer: δ 6.85 (s, 1H, H3'), 6.65 (s, 1H, H6'), 6.56 (s, 1H, H5), 6.33 (s, 1H, H8), 5.66 (t, 1H, *J* 7.2, 6.9 Hz, H1), 3.93 (dt, 1H, *J* 12.0, 4.5 Hz, H3), 3.82 (s, 6H, OC$\underline{H_3}$-4' and OC$\underline{H_3}$-5'), 3.78 (s, 3H, OC$\underline{H_3}$-6), 3.69 (s, 3H, OC$\underline{H_3}$-7), 3.63 (dt, 1H, *J* 11.7, 4.5 Hz, H3), 3.42 (dd, 1H, *J* 13.5, 6.9 Hz,

H7'), 3.13 (dd, 1H, *J* 13.5, 7.2 Hz, H7'), 2.95-2.85 (m, 1H, H4), 2.74-2.66 (m, 1H, H4), 0.16 (s, 9H, $Si(C\underline{H}_3)_3$). ^{13}C NMR of the major rotamer: δ 155.4 (q, *J* 34.3 Hz, $\underline{C}OCF_3$), 149.4 (C4'), 148.3 (C5'), 147.6 (C6), 147.5 (C7), 132.5 (C2'), 126.8 (C1'), 124.9 (C4a), 115.7 (C8a), 114.6 (CH-3'), 114.5 (q, *J* 204.9 Hz, $CO\underline{C}F_3$), 112.3 (CH-6'), 111.1 (CH-5), 110.4 (CH-8), 103.7 ($Ar\underline{C}{\equiv}CSi(CH_3)_3$), 95.9 ($\underline{C}Si(CH_3)_3$), 56.0 ($O\underline{C}H_3$-4'), 55.9 ($O\underline{C}H_3$-5', $O\underline{C}H_3$-6 and $O\underline{C}H_3$-7), 54.7 (CH-1), 40.3 (CH_2-3), 39.5 (CH_2-7'), 28.7 (CH_2-4), 0.1 ($Si(\underline{C}H_3)_3$). ^{13}C NMR of the minor rotamer (in part): δ 40.7 (CH_2-3), 37.9 (CH_2-7'), 27.3 (CH_2-4). MS (CI^+): *m/z* 536 (MH^+, 10 %). HRMS (EI^+): calcd for $C_{27}H_{32}NO_5F_3Si$, 535.2002 (M^+). Found 535.1984.

3.5.2 (*R,S*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxy-2'-(2''-trimethylsilyl-2''-(trimethylsilylethynyl)ethenyl)phenyl)methylisoquinoline (16).

Compound **4** (300 mg, 0.530 mmol), $PdCl_2$ (4.5 mg, 0.027 mmol), PPh_3 (13.6 mg, 0.053 mmol) and CuI (10 mg, 0.053 mmol) were added to a dry flask under a N_2 atmosphere. Dry THF (45 mL) was added to the mixture followed by the addition of Et_3N (161 mg, 1.59 mmol, 0.11 mL). The solution was stirred for 5 min before trimethylsilylacetylene (158 mg, 1.59 mmol, 0.22 mL) was added. The reaction was stirred at rt for 4 d. The solvent was evaporated and the crude mixture was purified by column chromatography (CH_2Cl_2 : EtOAc : petrol (3 : 1 : 3)) to give **16** (175 mg, 52 %) as a brown oil, and **15** (130 mg, 45 %) as a brown solid.

16: R_f 0.74 (CH_2Cl_2 : EtOAc : petrol (3 : 1: 1)). ^1H NMR: δ 8.15 (s, 1H, H1''), 6.66 (s, 1H, H3'), 6.56 (s, 2H, H6', H5), 5.97 (s, 1H, H8), 5.45 (dd, 1H, *J* 8.4, 5.4 Hz, H1), 3.88 (s, 3H, $OC\underline{H}_3$-4'), 3.84-3.80 (m, 1H, H3), 3.82 (s, 3H, $OC\underline{H}_3$-5'), 3.77 (s, 3H, $OC\underline{H}_3$-6), 3.70-3.59 (m, 1H, H3), 3.52 (s, 3H, $OC\underline{H}_3$-7), 3.18 (dd, 1H, *J* 13.5, 8.4 Hz, H7'), 3.12 (dd, 1H, *J* 13.5, 5.4 Hz, H7'), 2.95-2.85 (m, 1H, H4), 2.78-2.70 (m, 1H, H4), 0.16 (s, 9H, $Si(C\underline{H}_3)_3$), 0.13 (s, 9H, $Si(C\underline{H}_3)_3$). ^{13}C NMR: (signals for $\underline{C}OCF_3$ and $CO\underline{C}F_3$ were not observed), δ 149.1 (C4'), 148.5 (C5', C6), 147.5 (C7), 141.3 (CH-1''), 129.9 (C2'), 128.7 (C1'), 126.1 (C4a), 125.1 (C8a), 123.2 (C2''), 113.6 (CH-3'), 111.4 (CH-6'), 111.1 (CH-5, CH-

8), 110.7 (C≡CSi(CH_3)$_3$), 106.4 (C≡CSi(CH_3)$_3$), 56.0 (4 x OCH_3, CH-1), 41.1 (CH_2-3), 37.9 (CH_2-7'), 28.6 (CH_2-4), 0.35 (Si(CH_3)$_3$), 0.10 (Si(CH_3)$_3$). MS (ESI^+): *m/z* 634 (MH^+, 100 %). HRMS (ESI^+): calcd for $C_{24}H_{24}NO_5F_3$, 634.2653 (MH^+). Found 634.2610.

3.5.3 (*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxy-2'-ethynylphenyl)methylisoquinoline (17).

A mixture of **15** (130 mg, 0.240 mmol) in CH_3OH (2 mL) and H_2O (0.5 mL) was added KF (150 mg, 2.59 mmol). The suspension was stirred at rt for 18 h. The solvent was evaporated and the residue was redissolved in EtOAc. The reaction mixture was washed with 0.1 M HCl then brine and dried ($MgSO_4$). The solvent was evaporated to give an oil which was purified by column chromatography (CH_2Cl_2 : EtOAc : petrol (3 :1: 4)) to give **17** (60 mg, 54 % yield) as a brown oil. Compound **17** was a 95 : 5 mixture of rotamers. R_f 0.38 (CH_2Cl_2 : EtOAc : petrol (3 : 1 : 4)). ^{1}H NMR of the major rotamer: δ 6.95 (s, 1H, H3'), 6.59 (s, 1H, H6'), 6.56 (s, 1H, H5), 6.55 (s, 1H, H8), 5.76 (dd, *J* 7.8, 5.7 Hz, H1), 3.98 (dd, 1H, *J* 13.5, 4.8 Hz, H3), 3.86 (s, 6H, OC$\underline{H_3}$-4' and OC$\underline{H_3}$-5'), 3.75 (s, 6H, OC$\underline{H_3}$-6 and OC$\underline{H_3}$-7), 3.68-3.58 (m, 1H, H3), 3.47 (dd, 1H, *J* 13.8, 5.7, H7'), 3.17 (dd, 1H, *J* 13.8, 7.8 Hz, H7'), 3.16 (s, 1H, ArC≡C$\underline{H}$), 2.96-2.87 (m, 1H, H4), 2.73-2.65 (m, 1H, H4). ^{1}H NMR of the minor rotamer (in part): δ 6.97 (s, 1H, H3'), 6.61 (s, 1H, H6'), 6.43 (s, 1H, H5), 6.36 (s,1H, H8). ^{13}C NMR of the major rotamer: δ 155.8 (q, *J* 34.3 Hz, $\underline{C}OCF_3$), 149.7 (C4'), 148.4 (C5'), 147.9 (C6), 147.8 (C7), 133.2 (C2'), 127.1 (C1'), 125.3 (C4a), 115.0 (CH-3'), 114.5 (C8a), 114.0 (q, *J* 225.1 Hz, CO$\underline{C}F_3$), 112.7 (CH-6'), 111.2 (CH-5), 110.4 (CH-8), 82.6 (Ar$\underline{C}$≡CH), 79.6 (ArC≡$\underline{C}$H), 56.1 (3 x O$\underline{C}H_3$), 56.0 (O$\underline{C}H_3$-7), 54.8 (CH-1), 40.4 (CH_2-3), 39.8 (CH_2-7'), 28.9 (CH_2-4). MS (CI^+): *m/z* 464.1 (MH^+, 100 %). HRMS (EI^+): calcd for $C_{24}H_{24}NO_5F_3$, 463.1607 (M^+). Found 463.1606.

3.5.4 (1*RS*, 1`*RS*) and (*R*,*S*) 2',2``-(1'',2''-Ethynediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (18).

To a mixture of 2'-iodolaudanosine **4** (144 mg, 0.255 mmol), **17** (118 mg, 0.255 mmol), $PdCl_2$ (2 mg, 0.0127 mmol), PPh_3 (7 mg, 0.026 mmol) and CuI (5 mg, 0.026 mmol) under a N_2 atmosphere was added distilled THF (10 mL). Et_3N (39 mg, 0.383 mmol, 0.051 mL) was subsequently added and the mixture was stirred at rt for 24 h. The solvent was evaporated and the residue was purified by column chromatography (CH_2Cl_2 : CH_3OH : petrol (3 :1 : 4)) to give **18** (113 mg, 49 %) as a white solid. Compound **18** was a 95 : 5 mixture of rotamers. R_f 0.26 (CH_2Cl_2 : CH_3OH : petrol (3 : 1: 4)). M.p. 168-172 ^{0}C. ^{1}H NMR of the major rotamer: δ 7.17 (s, 2H, H3', H3``), 6.63 (s, 2H, H6', H6``), 6.58 (s, 2H, H5, H5`), 6.51 (s, 2H, H8, H8`), 5.69 (dd, 2H, *J* 8.0, 6.0 Hz, H1, H1`), 4.02 (bd, 2H, *J* 13.5 Hz, H3, H3`), 3.84 (s, 6H, OC$\underline{H_3}$-4', OC$\underline{H_3}$-4``), 3.82 (s, 2H, OC$\underline{H_3}$-5', OC$\underline{H_3}$-5``), 3.76 (s, 2H, OC$\underline{H_3}$-6, OC$\underline{H_3}$-6`), 3.73 (s, 6H, OC$\underline{H_3}$-7, OC$\underline{H_3}$-7`), 3.72-3.66 (m, 2H, H3, H3`), 3.26 (dd, 2H, *J* 14.1, 6.0 Hz, H7', H7``), 3.13 (dd, 2H, *J* 14.1, 8.0 Hz, H7', H7``), 2.99-2.89 (m, 2H, H4, H4`), δ 2.81-2.73 (m, 2H, H4, H4`). ^{1}H NMR of the minor rotamer (in part): δ 6.66 (s, 2H, H6', H6``), 6.59 (s, 2H, H5, H5`), 6.50 (s, 2H, H8, H8`), 5.05 (s, 2H, H1, H1`). $^{13}$C NMR of the major rotamer: δ 155.5 (q, *J* 38.4 Hz, $\underline{C}OCF_3$), 150.3 (C4', C4``), 148.5 (C5', C5``), 148.1 (C6, C6`), 147.9 (C7, C7`), 134.5 (C2', C2``), 127.1 (C1', C1``), 125.2 (C4a, C4a`), 118.6 (q, *J* 254.2 Hz, $CO\underline{C}F_3$), 115.0 (CH-3', CH-3``), 114.1 (C8a, C8a`), 112.6 (CH-6', CH-6``), 111.3 (CH-5, CH-5`), 110.2 (CH-8, CH-8`), 81.1 (Ar$\underline{C}\equiv\underline{C}$Ar), 56.2 (O$\underline{C}H_3$-4', O$\underline{C}H_3$-4``, O$\underline{C}H_3$-5', O$\underline{C}H_3$-5``), 56.1 (O$\underline{C}H_3$-6, O$\underline{C}H_3$-6`, O$\underline{C}H_3$-7, O$\underline{C}H_3$-7`), 55.0 (CH-1, CH-1`), 40.2 ($CH_2$-3, $CH_2$-3`), 40.1 ($CH_2$-7', $CH_2$-7``), 29.0 (CH_2-4, CH_2-4`). MS (ESI$^+$): *m/z* 901.3 (MH^+, 50 %). HRMS (ESI$^+$): calcd for $C_{46}H_{47}N_2O_{10}F_6$, 901.3135 (MH^+). Found 901.3066.

3.6 General method for N-TFA deprotection.

To a solution of the *N*-TFA protected amine in a mixture of CH_3OH and H_2O was added solid K_2CO_3. The reaction mixture was stirred at rt for 18 h. The CH_3OH was evaporated and the residue was dissolved in EtOAc. The solution was washed with H_2O (3 x) and then brine and evaporated to give a

yellow oil. The oil was purified by column chromatography (CH_3OH : EtOAc: NH_3 (4 : 6 : 0.1)) (unless stated otherwise) to give the free amine.

3.6.1 (1*RS* and 1`*RS*) and (*R,S*) 2',2``-(1'',2''-Eth-(*E*)-enediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (9).

The *N*-TFA protected stilbene **7** (108 mg, 0.123 mmol), CH_3OH (5 mL), H_2O (0.6 mL) and K_2CO_3 (89 mg, 0.641 mmol) were treated as described above using the general *N*-TFA deprotection reaction procedure except that the mixture was heated at 80 ^{0}C for 3 d to give a yellow oil. The oil was purified by column chromatography to give **9** (36 mg, 41 %) as a yellow oil. Product **9** was a 55 : 45 mixture of *meso*-**9** and *rac*-**9**. R_f 0.07 (CH_3OH : EtOAc (4 : 6)). ^{1}H NMR of *meso*-**9:** δ 7.07 (s, 2H, C<u>H</u>=C<u>H</u>), 6.72 (s, 2H, H3', H3``), 6.64 (s, 2H, H6', H6``), 6.57 (s, 2H, H5, H5`), 6.55 (s, 2H, H8, H8`), 4.17 (dd, 2H, *J* 9.0, 4.5 Hz, H1, H1`), 3.87 (s, 6H, OC<u>H</u>$_3$-4', OC<u>H</u>$_3$-4``), 3.84 (s, 6H, OC<u>H</u>$_3$-5', OC<u>H</u>$_3$-5``), 3.83 (s, 6H, OC<u>H</u>$_3$-6, OC<u>H</u>$_3$-6`), 3.71 (s, 6H, OC<u>H</u>$_3$-7, OC<u>H</u>$_3$-7`), 3.31 (dd, 2H, *J* 13.8, 4.5 Hz, H7', H7``), 3.20 (dt, 2H, *J* 12.0, 4.6 Hz, H3, H3`), 2.98 (dd, 2H, *J* 13.8, 9.0 Hz, H7', H7``), 2.89 (dt, 2H, *J* 12.0, 5.4 Hz, H3, H3`), 2.72 (t, 4H, *J* 5.4 Hz, H4, H4`). ^{1}H NMR of *rac*-**9** (in part): δ 7.16 (s, 2H, C<u>H</u>=C<u>H</u>), 6.74 (s, 2H, H3', H3``), 6.71 (s, 2H, H6`, H6``), 6.59 (s, 2H, H5, H5`), 6.57 (s, 2H, H8, H8`), 4.14 (dd, 2H, *J* 11.1, 3.9 Hz, H1, H1`), 3.90 (s, 6H, OC<u>H</u>$_3$-4', OC<u>H</u>$_3$-4``), 3.86 (s, 6H, OC<u>H</u>$_3$-5', OC<u>H</u>$_3$-5``), 3.71 (s, 6H, OC<u>H</u>$_3$-6, OC<u>H</u>$_3$-6`), 3.50 (s, 6H, OC<u>H</u>$_3$-7, OC<u>H</u>$_3$-7`). ^{13}C NMR of *meso*-**9**: δ 148.9 (C5', C5``), 148.3 (C4', C4``), 147.8 (C6, C6`), 147.2 (C7, C7`), 130.7 (C1', C1``), 130.1 (C2', C2``), 130.0 (C4a, C4a`), 127.6 (C8a, C8a`), 126.8 (<u>C</u>H=<u>C</u>H), 113.9 (CH-6', CH-6``), 112.1 (CH-3', CH-3``), 110.0 (CH-5, CH-5`), 109.4 (CH-8, CH-8`), 57.0 (CH-1, CH-1`), 56.3 (O<u>C</u>H$_3$-5', O<u>C</u>H$_3$-5``), 56.2 (O<u>C</u>H$_3$-4', O<u>C</u>H$_3$-4``, O<u>C</u>H$_3$-6, O<u>C</u>H$_3$-6`), 56.1 (O<u>C</u>H$_3$-7, O<u>C</u>H$_3$-7`), 40.9 (CH_2-3, CH_2-3`), 40.1 (CH_2-7', CH_2-7``), 29.8 ($CH_2$-4, $CH_2$-4`). $^{13}$C NMR of *rac*-**9** (in part): δ 148.3 (C4', C4``), 147.4 (C7, C7`), 130.8 (C1', C1``), 130.3 (C2', C2``), 129.2 (C4a, C4a`), 128.3 (<u>C</u>H=<u>C</u>H), 113.5 (CH-6', CH-6``), 109.9 (CH-5, CH-5`),

56.6 (CH-1, CH-1`), 55.9 (O<u>C</u>$H_3$-7, O<u>C</u>$H_3$-7`), 41.1 (CH_2-3, O<u>C</u>H_3-3'), 40.0 (CH_2-7', CH_2-7``), 28.6 (CH_2-4, CH_2-4`). MS (ESI^+): *m/z* 710.92 (MH^+, 20 %). HRMS (ESI^+): calcd for $C_{42}H_{51}N_2O_8$, 711.3645 (MH^+). Found 711.3662.

3.6.2 (1*RS*, *1`RS*) and (*R*,*S*) 2',2``-(1,1-Ethenediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (10).

Compound **8** (38 mg, 0.044 mmol), CH_3OH (3 mL), H_2O (0.6 mL) and K_2CO_3 (30 mg, 0.218 mmol) were treated as described above using the general *N*-TFA deprotection reaction procedure except that the reaction mixture was heated at 80 ^{0}C for 5 h to give an oil. The oil was purified by column chromatography (CH_3OH : EtOAc (4 : 6)) to give **10** (14 mg, 45 %) as a yellow oil. Product **10** was obtained as a diastereomeric mixture which was separated by PTLC (CH_2Cl_2 : EtOAc : CH_3OH : NH_3 (10 : 5 : 1: 0.1)) into the major diastereomer (11 mg) and minor diastereomer (3 mg). R_f (major diastereomer): 0.30 (DCM : EtOAc : CH_3OH : NH_3 (10 : 5 : 1: 0.1)). R_f (minor diastereomer): 0.24 (DCM : EtOAc : CH_3OH : NH_3 (10 : 5 : 1: 0.1)). ^{1}H NMR of the major diastereomer: δ 7.01 (s, 2H, H3', H3``), 6.72 (s, 2H, H6', H6``), 6.53 (s, 2H, H5, H5`), 5.99 (s, 2H, H8, H8`), 4.10 (dd, 2H, *J* 10.2, 4.5 Hz, H1, H1`), 3.86 (s, 6H, OC<u>H</u>$_3$-4', OC<u>H</u>$_3$-4``), 3.82 (s, 6H, OC<u>H</u>$_3$-5', OC<u>H</u>$_3$-5``), 3.77 (s, 6H, OC<u>H</u>$_3$-6, OC<u>H</u>$_3$-6`), 3.65 (s, 6H, OC<u>H</u>$_3$-7, OC<u>H</u>$_3$-7`), 3.06 (dt, 2H, *J* 11.8, 5.1 Hz, H3, H3`), 2.92 (dd, 2H, *J* 13.8, 4.5 Hz, H7', H7``), 2.80 (ddd, 2H, *J* 11.8, 6.6, 4.8 Hz, H3, H3`), 2.73-7.65 (m, 4H, H4, H4`), 2.40 (dd, 2H, *J* 13.8, 10.2 Hz, H7', H7``). ^{1}H NMR of the minor diastereomer: δ 6.96 (s, 2H, H3', H3``), 6.66 (s, 2H, H6', H6``), 6.53 (s, 2H, H5, H5`), 6.06 (s, 2H, H8, H8`), 4.06 (dd, 2H, *J* 8.4, 6.6 Hz, H1, H1`), 3.80 (s, 18H, OC<u>H</u>$_3$-4', OC<u>H</u>$_3$-4``, OC<u>H</u>$_3$-5', OC<u>H</u>$_3$-5``, OC<u>H</u>$_3$-6, OC<u>H</u>$_3$-6`), 3.62 (s, 6H, OC<u>H</u>$_3$-7, OC<u>H</u>$_3$-7`), 3.10 (dt, 2H, *J* 12.0, 5.7 Hz, H3, H3`), 2.90 (dd, 2H, *J* 13.8, 6.0 Hz, H7', H7``), 2.84 (dd, 2H, *J* 11.7, 5.4 Hz, H3, H3`), 2.68 (t, 4H, *J* 5.7 Hz, H4, H4`), 2.53 (dd, 2H, *J* 13.8, 8.4 Hz, H7', H7``). ^{13}C NMR of the major diastereomer: δ 150.9 (C4', C4``), 148.5 (C5', C5``), 147.5 (C6, C6`), 147.2 (C7, C7`), 133.6 (C2', C2`` and <u>C</u>=$CH_2$), 130.8 (C1', C1``), 129.2 (C4a, C4a`), 129.2 (C8a,

C8a`), 120.2 (ArC=$\underline{C}H_2$), 115.2 (CH-3', CH-3``), 114.6 (CH-6', CH-6``), 111.9 (CH-5, CH-5`), 108.7 (CH-8, CH-8`), 56.2 (O$\underline{C}H_3$-4', O$\underline{C}H_3$-4``), 56.0 (O$\underline{C}H_3$-5', O$\underline{C}H_3$-5``, O$\underline{C}H_3$-6, O$\underline{C}H_3$-6`), 55.6 (O$\underline{C}H_3$-7, O$\underline{C}H_3$-7`), 54.9 (CH-1, CH-1`), 41.4 ($CH_2$-3, CH-3`), 40.4 (CH_2-7', CH_2-7``), 29.7 ($CH_2$-4, $CH_2$-4`). $^{13}$C NMR of the minor diastereomer: δ 150.7 (C4', C4``), 148.6 (C5', C5``), 147.6 (C6, C6`), 147.0 (C7, C7`), 134.6 (C2', C2`` and $\underline{C}$=CH_2), 131.0 (C1', C1``), 129.4 (C4a, C4a`), 127.1 (C8a, C8a`), 119.9 (C=$\underline{C}H_2$), 114.7 (CH-3', CH-3``), 114.3 (CH-6', CH-6``), 112.0 (CH-5, CH-5`), 109.7 (CH-8, CH-8`), 56.2 (O$\underline{C}H_3$-4', O$\underline{C}H_3$-4``, O$\underline{C}H_3$-5' O$\underline{C}H_3$-5``), 56.0 (O$\underline{C}H_3$-6, O$\underline{C}H_3$-6`), 55.9 (O$\underline{C}H_3$-7, O$\underline{C}H_3$-7`), 55.4 (CH-1, CH-1`), 41.0 ($CH_2$-3, CH-3`), 40.5 ($CH_2$-7', $CH_2$-7``), 29.6 (CH_2-4, CH_2-4`). MS (ESI$^+$): *m/z* 711.2 (MH$^+$, 100 %), 733.2 (M+Na$^+$, 80 %). HRMS (ESI$^+$): calcd for $C_{42}H_{51}N_2O_8$, 711.3645 (MH$^+$). Found 711.3660.

3.6.3 (1*RS*, *1`RS*) and (*R*,*S*) 2',2``-(1'',2''-Ethanediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (12).

Compound *rac*-**11** (4 mg, 0.003 mmol), CH_3OH (1 mL), H_2O (0.5 mL) and K_2CO_3 (12 mg, 0.085 mmol) was treated as described above using the general *N*-TFA deprotection reaction procedure to afford *rac*-**12** (3 mg, 95 % yield) as a yellow oil without the need for further purification. R_f 0.14 (DCM : EOAc : CH_3OH : NH_3 (10 : 5 : 1 : 0.1)). ^{1}H NMR: δ 6.67 (s, 2H, H3', H3``), 6.57 (s, 2H, H5, H5`), 6.55 (s, 2H, H6', H6``), 6.43 (s, 2H, H8, H8`), 4.05 (dd, 2H, *J* 9.3, 5.1 Hz, H1, H1`), 3.82 (s, 6H, OC$\underline{H_3}$-4', OC$\underline{H_3}$-4``), 3.80 (s, 6H, OC$\underline{H_3}$-5', OC$\underline{H_3}$-5``), 3.75 (s, 6H, OC$\underline{H_3}$-6, OC$\underline{H_3}$-6`), 3.67 (s, 6H, OC$\underline{H_3}$-7, OC$\underline{H_3}$-7`), 3.14 (dd, 2H, *J* 12.3, 6.3 Hz, H3, H3`), 3.06 (dd, 2H, *J* 13.8, 5.1 Hz, H7', H7``), 2.84 (dd, 2H, *J* 12.3, 6.6 Hz, H3, H3`), 2.82 (s, 4H, H1'', H2''), 2.75 (dd, 2H, *J* 13.8, 9.3 Hz, H7', H7``), 2.66 (m, 4H, H4, H4`). ^{13}C NMR: δ 147.5 (C5', C5``), 147.4 (C4', C4``), 147.2 (C6, C6`), 146.8 (C7, C7`), 132.5 (C1', C1``), 132.0 (C2', C2``), 131.9 (C4a, C4a`), 127.0 (C8a, C8a`), 113.4 (CH-6', CH-6``), 112.9 (CH-3', CH-3``), 111.7 (CH-5, CH-5`), 109.6 (CH-8, CH-8`), 56.4 (CH-1, CH-1`), 55.8

(8 x O<u>C</u>H_3), 40.7 (CH_2-3, CH_2-3`), 38.9 (CH_2-7', CH_2-7``), 34.1 (CH_2-1'', CH_2-2''), 29.3 (CH_2-4, CH_2-4`). MS (ESI^+): *m/z* 713.3 (MH^+, 100 %). HRMS (ESI^+): calcd for $C_{42}H_{53}N_2O_8$, 713.3802 (MH^+). Found 713.3781.

3.6.4 (1*RS*, *1`RS*) and (1*RS*, 1`*SR*) 2',2``-(1'',3''-Prop-2(*E*)-enediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'dimethoxyphenyl)methyl]isoquinoline (14).

Compound **13** (152 mg, 0.170 mmol), CH_3OH (8 mL), H_2O (2 mL) and K_2CO_3 (118 mg, 0.850 mmol) was treated as described above using the general *N*-TFA deprotection procedure to give an oil. The oil was purified by column chromatography to give **60** (72 mg, 58 %) as a yellow oil. Product **14** was a 60 : 40 mixture of diastereomers. R_f 0.1 (CH_3OH : EtOAc : NH_3 (1 : 4 : 0.1)). ^1H NMR of the major diastereomer: δ 6.96 (s, 1H, H3``), 6.73 (s, 2H, H3', H5``), 6.64 (d, 1H, *J* 15.0 Hz, H3''), 6.63 (s, 1H, H5`), 6.58 (s, 2H, H6', H6``), 6.49 (s, 1H, H8`), 6.48 (s, 1H, H8), 6.10 (m, 1H, H2''), 4.11 (dd, 1H, *J* 8.4, 5.4 Hz, H1`), 4.03 (m, 1H, H1), 3.82 (s, 24H, 8 x OC<u>H</u>$_3$), 3.51 (d, 2H, *J* 6.3 Hz, H1''), 3.17 (dd, 2H, *J* 13.2, 5.4 Hz, H7', H7`), 3.12 (dd, 2H, *J* 12.0, 6.9 Hz, H3, H3`), 2.87 (dd, 2H, *J* 13.2, 8.4 Hz, H7', H7``), 2.81 (dd, 2H, *J* 12.0, 5.1 Hz, H3, H3`), 2.70 (m, 4H, H4, H4`). $^1H$ NMR of the minor diastereomer (in part): δ 6.72 (s, 2H, H3', H5``), 6.62 (s, 1H, H5`), 6.53 (s, 2H, H6', H6``), 6.46 (s, 1H, H8`), 6.42 (s, 1H, H8), 6.07 (m, 1H, H2''), 4.14 (m, 1H, H1`), 4.05 (m, 1H, H1), 3.70 (s, 24H, 8 x OC<u>H</u>$_3$). $^{13}C$ NMR of the major diastereomer: δ 148.3 (C6, C6`), 148.0 (C4', C4``), 147.8 (C5', C5``), 147.1 (C7, C7`), 131.1 (C1'), 131.0 (C1``), 129.8 (CH-3''), 129.5 (C2', C2``), 128.9 (C4a, C4a`), 128.3 (C8a, C8a`), 127.5 (CH-2''), 114.0 (CH-3'), 113.5 (CH-3``), 112.1 (CH-6', CH-6``, CH-5, CH-5'), 109.8 (CH-8), 109.3 (CH-8'), 56.2 (8 x $OCH_3$, CH-1), 41.2 ($CH_2$-3, $CH_2$-3`), 39.4 ($CH_2$-7', $CH_2$-7``), 36.6 (CH_2-1''), 29.6 (CH_2-4, CH_2-4`). ^{13}C NMR of the minor diastereomer (in part): δ 131.0 (C1``), 129.7 (CH-3''), 129.5 (C2', C2``), 128.5 (C8a, C8a`), 127.4 (CH-2''), 113.9 (CH-3'), 36.7 ($CH_2$-1''), 29.7 ($CH_2$-4, $CH_2$-4`). MS (ESI^+): *m/z* 724.88 (MH^+, 100 %). HRMS (ESI^+): calcd for $C_{43}H_{53}N_2O_8$, 725.3802 (MH^+). Found 725.3783.

3.6.5 (1*RS*, *1`RS*) and (*R*,*S*) 2',2``-(1'',2''-Ethynediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (19).

Compound **18** (56 mg, 0.062 mmol), CH_3OH (20 mL), H_2O (2 mL) and K_2CO_3 (44 mg, 0.311 mmol) were treated as described above using the general *N*-TFA deprotection reaction procedure to afford an oil. The oil was purified by column chromatography (CH_3OH : EtOAc (1 : 5)) to give **19** (34 mg, 79 % yield) as a brown solid. R_f 0.06 (EtOAc). M.p. 208-210 ^{0}C. ^{1}H NMR: δ 7.20 (s, 2H, H3', H3``), 7.00 (s, 2H, H6', H6``), 6.59 (s, 2H, H5, H5`), 6.35 (s, 2H, H8, H8`), 4.73 (t, 2H, *J* 7.5 Hz, H1, H1`), 3.84 (s, 6H, OC$\underline{H_3}$-4', OC$\underline{H_3}$-4``), 3.82 (s, 6H, OC$\underline{H_3}$-5', OC$\underline{H_3}$-5``), 3.81 (s, 6H, OC$\underline{H_3}$-6, OC$\underline{H_3}$-6`), 3.65 (s, 6H, OC$\underline{H_3}$-7, OC$\underline{H_3}$-7`), 3.51 (td, 2H, *J* 12.0, 4.5 Hz, H3, H3`), 3.36 (d, 4H, *J* 7.5 Hz, H7', H7``), 3.25-3.18 (m, 2H, H4, H4`), 3.13 (td, 2H, *J* 12.0, 4.5 Hz, H3, H3`), 3.00-2.92 (m, 2H, H4, H4`). $^{13}$C NMR: δ 149.9 (C4', C4``), 149.5 (C5', C5``), 149.3 (C6, C6`), 148.0 (C7, C7`), 131.1 (C2', C2``), 124.9 (C1', C1``, C4a, C4a`), 124.3 (C8a, C8a`), 122.0 (CH-3', CH-3``), 115.0 (CH-6', CH-6``), 110.9 (CH-5, CH-5`), 110.2 (CH-8, CH-8`), 89.9 (Ar$\underline{C}$≡$\underline{C}$Ar), 57.2 (O$\underline{C}H_3$-4', O$\underline{C}H_3$-4``, O$\underline{C}H_3$-5', O$\underline{C}H_3$-5``), 56.5 (O$\underline{C}H_3$-6, O$\underline{C}H_3$-6`, O$\underline{C}H_3$-7, O$\underline{C}H_3$-7`), 55.3 (CH-1, CH-1`), 45.7 ($CH_2$-3, $CH_2$-3`), 40.2 ($CH_2$-7', $CH_2$-7``), 26.3 (CH_2-4, CH_2-4`). MS (ESI^+): *m/z* 709.1 (MH^+, 5 %). HRMS (ESI^+): calcd for $C_{42}H_{49}N_2O_8$, 709.3489 (MH^+). Found 709.3474.

3.7 Synthesis of macrocycle 3 (Scheme 6).

3.7.1 (*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxy-2'-(2''-propenyl)-phenyl)methylisoquinoline (20).

N-TFA protected amine **6** (70 mg, 0.146 mmol), K_2CO_3 (100 mg, 0.730 mmol), CH_3OH (7 mL) and H_2O (1 mL) were treated as described above using the general *N*-TFA deprotection procedure to give a yellow oil. The oil was purified by column chromatography (CH_3OH : EtOAc (1 : 5)) to afford the amine **20** (50 mg, 90 %) as a yellow oil. R_f 0.21 (CH_3OH : EtOAc (1 : 5)). ^{1}H NMR: δ 6.73 (s, 2H, H3'), 6.71 (s, 1H, H6'), 6.58 (s, 1H, H5), 6.44 (s, 1H, H8), 5.98-3.85 (m, 1H, H2''), 5.06 (dd, 1H, *J*

9.6, 1.8 Hz, H3''(*Z*)), 5.01 (dd, 1H, *J* 17.1, 1.8 Hz, H3''(*E*)), 4.17 (dd, 1H, *J* 8.7, 5.7 Hz, H1), 3.85 (s, 6H, OC$\underline{H}_3$-4', OC$\underline{H}_3$-5'), 3.82 (s, 3H, OC$\underline{H}_3$-6), 3.73 (s, 3H, OC$\underline{H}_3$-7), 3.32 (d, 2H, *J* 6.0 Hz, H1''), 3.27 (dd, 1H, *J* 12.0, 6.3 Hz, H3), 3.22 (dd, 1H, *J* 13.8, 5.7 Hz, H7'), 2.97 (dd, 1H, *J* 12.0, 5.7 Hz, H3), 2.89 (dd, 1H, *J* 13.8, 8.7 Hz, H7'), 2.77-2.69 (m, 2H, H4). ^{13}C NMR: δ 147.9 (C4', C5'), 147.5 (C6), 147.2 (C7), 137.6 (CH-2''), 130.8 (C2'), 129.9 (C1'), 129.0 (C4a), 127.0 (C8a), 115.9 (CH_2-3''), 114.0 (CH-3'), 113.4 (CH-6'), 112.0 (CH-5), 109.8 (CH-8), 56.4 (O$\underline{C}H_3$-4'), 56.3 (O$\underline{C}H_3$-5'), 56.2 (O$\underline{C}H_3$-6), 56.1 (O$\underline{C}H_3$-7, CH-1), 40.8 (CH_2-1''), 38.2 (CH_2-7'), 37.0 (CH_2-3), 29.2 (CH_2-4). MS (CI^+): *m/z* 384 (MH^+, 60 %). HRMS (CI^+): calcd for $C_{23}H_{30}NO_4$, 384.2175 (MH^+). Found 384.2178.

3.7.2 (*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1(4',5'-dimethoxy-2'-(2''-propenyl)-phenyl)methylisoquinoline 2-(4-oxo)butanoic acid (21).

To a solution of the amine **20** (332 mg, 0.867 mmol) in dry CH_2Cl_2 (8 mL) was added triethylamine (0.14 mL), followed by succinic anhydride (174 mg, 1.73 mmol) under a N_2 atmosphere. The reaction mixture was stirred at RT for 18 h. The organic layer was evaporated and the residue was redissolved in EtOAc. The solution was washed with 1M $KHSO_4$ (2 x), then brine. The solution was dried ($MgSO_4$) and evaporated and the crude mixture was purified by column chromatography (CH_3OH : EtOAc (1 : 5)) to give **21** (334 mg, 79 %) as a white solid. Product **21** was a 70 : 30 mixture of rotamers by ^{1}H NMR analysis. R_f 0.71 (CH_3OH : EtOAc (1 : 5)). M.p. 138-140 ^{0}C. ^{1}H NMR of the major rotamer: δ 6.63 (s, 1H, H5), 6.59 (s, 1H, H3'), 6.56 (s, 1H, H6'), 5.93 (s, 1H, H8), 5.83-5.70 (m, 1H, H2''), 5.51 (dd, 1H, *J* 9.0, 5.1 Hz, H1), 4.95 (dd, 2H, *J* 10.2, 1.8 Hz, H3''(*Z*)), 5.01 (dd, 1H, *J* 17.1, 1.8 Hz, H3''(*E*)), 3.85 (s, 3H, OC$\underline{H}_3$-5'), 3.83 (s, 3H, OC$\underline{H}_3$-6), 3.75 (s, 3H, OC$\underline{H}_3$-7), 3.70-3.65 (m, 2H, H3), 3.50 (s, 3H, OC$\underline{H}_3$-4'), 3.11 (dd, 1H, *J* 12.5, 5.1 Hz, H4), 3.02 (dd, 1H, *J* 13.5, 5.1 Hz, H7'), 3.00 (d, 2H, *J* 6.3 Hz, H1''), 2.89 (dd, 1H, *J* 13.5, 9.0 Hz, H7'), 2.82 (dd, 1H, *J* 12.5, 6.3 Hz, H4), 2.79-2.74 (m, 4H, H2''', H3'''). ^{1}H NMR of the minor rotamer (in part): δ 6.69 (s, 1H, H3'), 6.63 (s, 1H, H6'), 6.49 (s, 1H, H5), 6.44 (s, 1H, H8), 5.99-5.88 (m, 1H, H2''), 5.11 (d, 1H, *J* 10.2, 1.8 Hz, H3''(*Z*)), 5.00 (d,

1H, *J* 15.0, 1.8 Hz, H3''(*E*)), 4.86-4.84 (m, 1H, H1), 4.73 (ddd, 1H, *J* 8.4, 5.7, 2.4 Hz, H3), 3.87 (s, 3H, OC$\underline{H}_3$-5'), 3.81 (s, 3H, OC$\underline{H}_3$-7), 3.79 (s, 3H, OC$\underline{H}_3$-4'), 3.32 (d, 2H, *J* 6.3 Hz, H1''), 3.23-3.18 (m, 1H, H4), 3.12-3.08 (m, 1H, H7'), 2.92-2.89 (m, 1H, H4), 2.87-2.84 (m, 1H, H7'), 1.93-1.84 (m, 4H, H2''', H3'''). ^{13}C NMR of the major rotamer: δ 175.5 ($\underline{C}$OOH), 169.8 (N$\underline{C}$O), 146.9 (C5'), 146.5 (C4'), 146.1 (C6), 145.9 (C7), 136.4 (CH-2''), 130.0 (C1'), 127.2 (C2'), 126.7 (C4a), 124.6 (C8a), 114.4 (CH_2-3''), 113.1 (CH-6'), 111.6 (CH-3'), 110.1 (CH-5), 109.8 (CH-8), 54.9 (O$\underline{C}H_3$-4', O$\underline{C}H_3$-5'), 54.9 (O$\underline{C}H_3$-6), 54.6 (O$\underline{C}H_3$-7), 53.0 (CH-1), 40.5 (CH_2-3), 37.0 (CH_2-7'), 35.3 (CH_2-1'', CH_2- 4), 27.7 (CH_2-2'''), 27.2 (CH_2-3'''). ^{13}C NMR of the minor rotamer (in part): δ 175.3 ($\underline{C}$OOH), 170.2 (N$\underline{C}$O), 147.3 (C5'), 147.2 (C3'), 146.6 (C6), 146.4 (C7), 136.1 (CH-2''), 129.3 (C1'), 126.8 (C2'), 126.4 (C4a), 125.5 (C8a), 115.0 (CH_2-3''), 113.0 (CH-6'), 112.3 (CH-3'), 110.5 (CH-5), 108.9 (CH-8), 56.7 (CH-1), 37.8 (CH_2-7'), 36.0 (CH_2-1''), 35.0 (CH_2-3), 26.9 (CH_2-2'''), 26.2 (CH_2-3'''). MS (ESI$^+$): *m/z* 484 (MH$^+$, 70 %). HRMS (ESI$^+$): calcd for $C_{27}H_{34}NO_7$, 484.2335 (MH$^+$). Found 484.2329.

3.7.3 (1*RS*, 1`*RS*) and (*R*,*S*) 2'- (2''-Propenyl)-2``-bromo-2,2'-(1''',4'''-dioxo-1''',4'''-butanediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl] isoquinoline (23).

To a suspension of the amine **22** (148 mg, 0.349 mmol), the acid **21** (142 mg, 0.290 mmol), HOBT (44 mg, 0.319 mmol) and EDCI (61 mg, 0.319 mmol) was added dry DMF (6 mL) under a N_2 atmosphere. The reaction was stirred at RT for 3 d. The crude mixture was diluted with CH_2Cl_2 and washed with H_2O (4 x) and then brine. The CH_2Cl_2 was evaporated to give an oil which was purified by column chromatography (CH_3OH : EtOAc (1 : 5)) to give **23** (212 mg, 82 %) as a yellow solid. Product **23** was obtained as a 60 : 40 mixture of diastereomers which were each a 70 : 30 mixture of rotamers. R_f 0.74 (CH_3OH : EtOAc (1 : 5)). M.p. 145-148 ^{0}C. ^{1}H NMR of the major diastereomer: δ 6.96 (s, 1H, H3``), 6.57 (s, 5H, H3', H5, H5`, H6', H8`), 6.34 (s, 1H, H6``), 5.89 (s, 1H, H8), 5.72-5.67 (m, 1H, H2''), 5.47 (dd, 1H, *J* 9.0, 4.8 Hz, H1`), 5.18 (dd, 1H, *J* 9.0, 4.8 Hz, H1), 4.96-4.86 (m, 2H, H3''), 3.84 (s, 18H, 6 x $OCH_3$), 3.84-3.76 (m, 4H, H3, H3`), 3.72 (s, 6H, OCH_3-4', OCH_3-4``), 3.27-3.20 (m, 1H,

H4`), 3.09-3.05 (m, 1H, H4), 3.03-2.98 (m, 2H, H1''), 2.82-2.76 (m, 4H, H7', H7``), 2.68-2.60 (m, 6H, H4`, H4, H2''', H3'''). $^{1}$H NMR of the minor diastereomer (in part): δ 7.03 (s, 1H, H3``), 6.59 (s, 5H, H3', H5, H5`, H6', H8`), 6.20 (s, 1H, H6``), 5.84 (s, 1H, H8), 5.66-5.60 (m, 1H, H2''), 5.42 (dd, 1H, *J* 9.9, 4.2 Hz, H1`), 5.13 (dd, 1H, *J* 9.9, 4.2 Hz, H1), 5.05-5.02 (m, 2H, H3''), 2.30-2.26 (m, 4H, H2''', H3'''). ^{1}H NMR of the minor rotamer of both diasteromers (in part), (note-*- represents the rotamer of the minor diastereomer): δ 7.02 (s, 1H, H3``), 6.95 (s, 1H, H3``*), 6.54 (s, 5H, H3', H5, H5`, H6', H8`), 6.52 (s, 5H, H3', H5, H5`, H6', H8`*), 5.88 (s, 1H, H8), 5.86 (s, 1H, H8*), 4.76-4.68 (m, 2H, H3, H3`), 2.58-2.54 (m, 2H, H3'''), 2.32-2.28 (m, 2H, H2'''). ^{13}C NMR of the major diastereomer: δ 171.1 (2 x N<u>C</u>O), 148.3 (C5', C5``, C4', C4``), 148.1 (C6, C6`), 147.5 (C7, C7`), 137.7 (CH-2''), 132.3 (C1', C1``), 132.2 (C2', C2``), 128.8 (C4a, C4a`), 128.6 (C8a, C8a`), 115.7 (CH-6', CH6``), 115.3 ($CH_2$-3''), 111.6 (CH-3', CH-3``), 111.1 (CH-5, CH-5`), 110.8 (CH-8, CH-8`), 56.1 (8 x O<u>C</u>H_3), 53.5 (CH-1, CH-1``), 42.6 ($CH_2$-3`), 41.0 ($CH_2$-7``), 38.4 (CH_2-3), 36.6 (CH_2-7'), 36.0 (CH_2-1''), 29.1 (CH_2-3''', CH_2-2'''), 28.7 (CH_2-4`), 28.1 ($CH_2$-4). $^{13}$C NMR of the minor diastereomer (in part): δ 131.2 (C1', C1`), 129.8 (C2', C2`), 128.3 (C4a, C4a`), 126.8 (C8a, C8a`), 111.3 (CH-3', CH-3``), 111.0 (CH-5, CH5`), 110.3 (CH-8, CH8`), 35.7 (CH_2-1''). MS (ESI$^+$): *m/z* 886.79 (MH$^+$, 10 %). HRMS (ESI$^+$): calcd for $C_{47}H_{56}N_2O_{10}Br$, 887.3118 (MH$^+$). Found 887.3137.

3.7.4 (1*RS*, 1`*RS*) and (*R*,*S*) (*E*) 1,10-(1,2)-Di-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolina)-3,8-(1,2)-di-(3,4-dimethoxy)benzenacyclo-(11,14-dioxo)-propadeca-4-phene (3).

To a mixture of **23** (71 mg, 0.080 mmol), $Pd(OAc)_2$ (2 mg, 0.008 mmol) and PPh_3 (4 mg, 0.016 mmol) in a thick walled tube was added dry CH_3CN (2 mL) under a N_2 atmosphere. Triethylamine (25 mg, 0.240 mmol, 0.04 mL) was added and the reaction was bubbled with argon for 5 min prior to sealing the tube. The solution mixture was stirred and heated at 110 ^{0}C for 24 h. The solution was diluted with CH_2Cl_2, washed with H_2O, and then brine. The CH_2Cl_2 layer was evaporated to give an oil which was purified by column chromatography (CH_3OH : EtOAc (1 : 9)) to give **3** (12 mg, 15 %) as a yellow oil.

R_f 0.61 (CH_3OH : EtOAc (1 : 9)). ^{1}H NMR: δ 6.93 (d, 1H, *J* 15.3 Hz, H3''), 6.86 (s, 1H, H5`), 6.81 (s, 1H, H5), 6.64 (s, 1H, H3``), 6.59 (s, 1H, H3'), 6.49 (s, 1H, H6``), 6.02 (s, 1H, H6'), 5.95-5.88 (m, 1H, H2''), 5.90 (s, 1H, H8`), 5.88 (s, 1H, H8), 5.66 (dd, 1H, *J* 9.0, 3.0 Hz, H1`), 5.55 (dd, 1H, *J* 9.0, 3.0 Hz, H1), 4.40 (dd, 1H, *J* 13.5, 9.6 Hz, H3`), 4.00-3.85 (m, 1H, H3), 3.88 (s, 3H, OCH_3-5``), 3.85 (s, 6H, OC$\underline{H}_3$-5', OC$\underline{H}_3$-7), 3.83 (s, 3H, OC$\underline{H}_3$-7`), 3.73 (s, 3H, OC$\underline{H}_3$-6), 3.57 (s, 3H, OC$\underline{H}_3$-6`), 3.49 (s, 6H, OC$\underline{H}_3$-4', OC$\underline{H}_3$-4``), 3.70-3.64 (m, 1H, H3), 3.45-3.40 (m, 1H, H3`), 3.41-3.36 (m, 2H, H3'''), 3.34 (d, 2H, *J* 7.5 Hz, H1''), 3.23-3.18 (m, 2H, H7``, H7``), 3.04 (dd, 1H, *J* 13.2, 3.0 Hz, H7'), 2.99 (d, 1H, *J* 13.2, 9.0 Hz, H7'), 2.84-2.67 (m, 2H, H4, H4'), 2.43-2.38 (m, 1H, H2'''), 2.26-2.22 (m, 1H, H2'''). ^{13}C NMR: δ 172.1 ($\underline{C}$O), 171.2 ($\underline{C}$O), 147.9 (C6`), 147.7 (C6), 147.5 (C4', C4``), 147.3 (C5``), 147.0 (C5'), 146.6 (C7`), 146.2 (C7), 132.1 (CH-3''), 132.4 (C1``), 130.1 (C1'), 129.1 (C2``), 128.8 (C2'), 128.7 (CH-2''), 128.1 (C4a`), 126.0 (C4a), 126.5 (C8a, C8a`), 115.7 (CH-6``), 113.7 (CH-6'), 113.1 (CH-3``), 111.9 (CH-3'), 111.1 (CH-5`), 110.9 (CH-5), 110.8 (CH-8`), 109.5 (CH-8), 51.7 (8 x OCH_3), 54.8 (CH-1`), 54.3 (CH-1), 41.7 ($CH_2$-3`), 41.1 (CH_2-3), 40.2 (CH_2-7``), 39.0 (CH_2-7'), 36.6 (CH_2-1''), 29.7 (CH_2-3'''), 28.6 (CH_2-2'''), 28.3 (CH_2-4`), 28.0 (CH_2-4). MS (ESI$^+$): *m/z* 807.09 (MH^+, 5 %), *m/z* 844.86 ($M+K^+$, 20 %). HRMS (ESI$^+$): calcd for $C_{47}H_{55}N_2O_{10}$, 807.3857 (MH^+). Found 807.3842.

Acknowledgments:

We thank Johnson and Johnson Research Pty. Limited, Sydney and the University of Wollongong for supporting this research and Dr. Wayne Gerlach for encouragement and support.

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21. These compounds were a gift from the Johnson and Johnson Research Lab at the University of Wollongong. They were prepared using the literature procedure[10] and the procedure in Scheme 1 starting from (*S*)-**4** that was obtained from (*S*)-norlaudanosine.

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GRAPHICAL ABSTRACT

The synthesis of carbon linked bis-benzylisoquinolines using Mizoroki-Heck and Sonagashira coupling reactions

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