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The synthesis of carbon-linked bisbenzylisoquinolines via ruthenium-mediated olefin-metathesis

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ABSTRACT

Novel laudanosine dimers in which two laudanosine units are linked at C-2′ via a two and four-carbon linker have been prepared using ruthenium-mediated olefin-metathesis. In addition, a second four-carbon linker between the two isoquinoline *N*-atoms was also present leading to a novel macrocyclic ring system. Five of these compounds showed higher cytostatic activity on three cancer cell lines than thalicarpine.

1. Introduction

Over 200 bisbenzylisoquinoline (BBI) alkaloids are known, the majority of these have one or two ether linkages between the two benzylisoquinoline moieties.[1] These alkaloids show a range of interesting biological activities.[1] An example of these alkaloids is the related *Thalictrum* alkaloid, thalicarpine **1** (Fig. 1),[2] which comprises the benzylisoquinoline, *S*-laudanosine, connected via an ether linkage to an aporphine moiety. At the initial clinical trials, 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,[3–8] however, phase II clinical trials stopped after no antitumour effect was observed.[6,8] There is also a small group of alkaloids that have one of the linking ether bonds replaced by a biphenyl linkage.[9] For example, (+)-tiliarine **2** (Fig. 1) contains a biphenyl linkage and behaves as a selective in vitro inhibitor of human melanoma cell growth.[10]

Inspired by the structure and biological activity of these bisbenzylisoquinolines, we became interested in the synthesis of the novel laudanosine dimers of the type **3** (Fig. 1), in which two laudanosine units are linked at C-2′ through a two- to four-carbon linker. It is noted that none of the BBI alkaloids isolated has more than one direct C–C linkage, therefore in the example **4**, a second four-carbon linker between the two isoquinoline *N*-atoms was also synthesised leading to a novel macrocyclic ring system.

In this paper, we report the results of an examination of the ruthenium-mediated cross-metathesis (CM) reaction[11–21] as a method to synthesise novel mono-tethered BBI derivatives (compounds of the type **3**). Earlier we reported the synthesis of two BBI derivatives (**10** and **11**) having a two-carbon linker using the Heck–Mizoroki coupling reaction, however, the preparation of four-carbon-linked BBI compounds (for example) **4**, **17**, **19** and **20** would be much more difficult using this coupling methodology.[22] The ruthenium-catalysed ring-closing metathesis (RCM) reaction[11–21] for the synthesis of the conformationally restricted macrocyclic BBI derivative **4** is also described. Grubbs' first and second generation catalysts, **5** and **6**, respectively, were employed in this study (Fig. 2).

2. Discussion

2.1. Synthesis of C2′ carbon-linked BBI derivatives

Our approach to the target molecules **3** (alkene linker, m=n=1) was based on a cross-metathesis reaction of racemic *N*-trifluoroacetyl-2′-allylnorlaudanosine **7** (Scheme 1).[23] Racemic compounds were used in this study because of their ready availability in our laboratory. Utilising the ability of a type I olefin like compound **7** to homocouple rapidly,[11] the racemic 2′-allyllaudanosine derivative *rac*-**7** was treated with 10 mol % of the Grubbs' I catalyst **5** and the reaction mixture was heated at reflux in freshly distilled dichloromethane for 24 h under a nitrogen atmosphere. The homocoupled product **8** was readily obtained in 72% yield after purification by column chromatography. The ^{1}H NMR spectrum of **8** showed a broad overlapping signal for the olefinic and the H1 and H1′ protons at ca. δ 5.4. Because of the symmetry, the olefinic protons are equivalent, therefore it was not possible to measure the coupling constant or determine the (*E*)- or (*Z*)-olefin geometry for these compounds (Fig. 3).

^{1}H NMR analysis showed signals for two major isomers in a ratio of 55:45, which were assumed to be the *meso* and the racemic forms of **8**. These were indicated by the doubling up of

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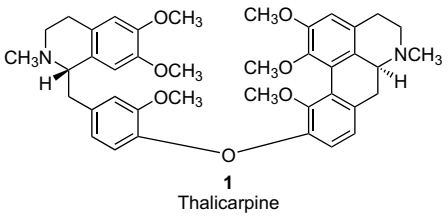
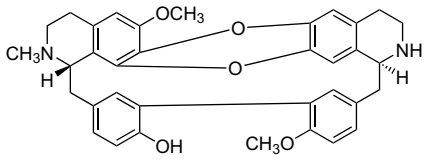
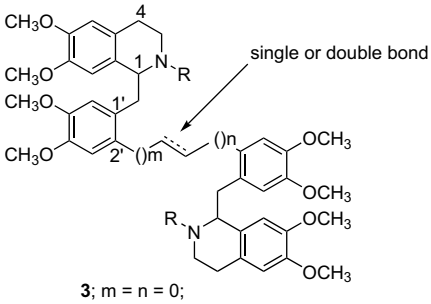
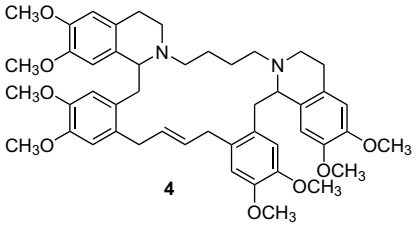


1
Thalicarpine



2
(+)-Tiliarine





4

Figure 1.

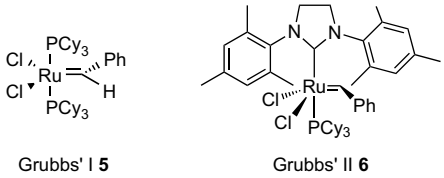
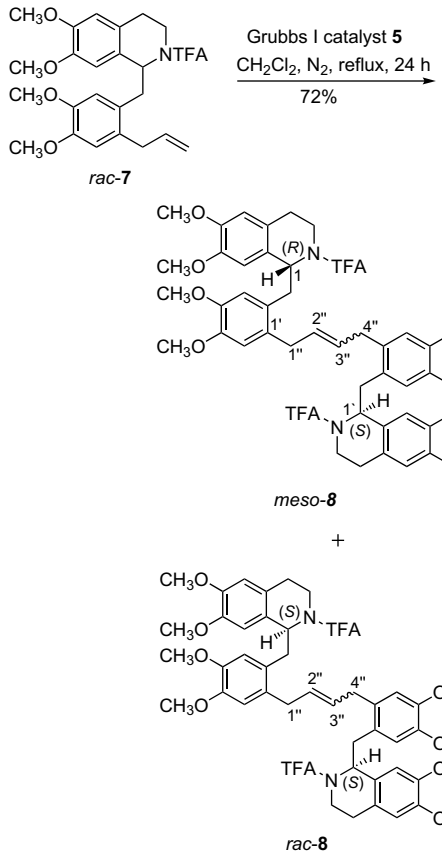


Figure 2. Grubbs' first and second generation catalysts.



Scheme 1. Cross-metathesis reaction of the 2′-allyllaudanosine derivative **7** [only the (*S*,*S*) enantiomer is shown for *rac*-**8**].

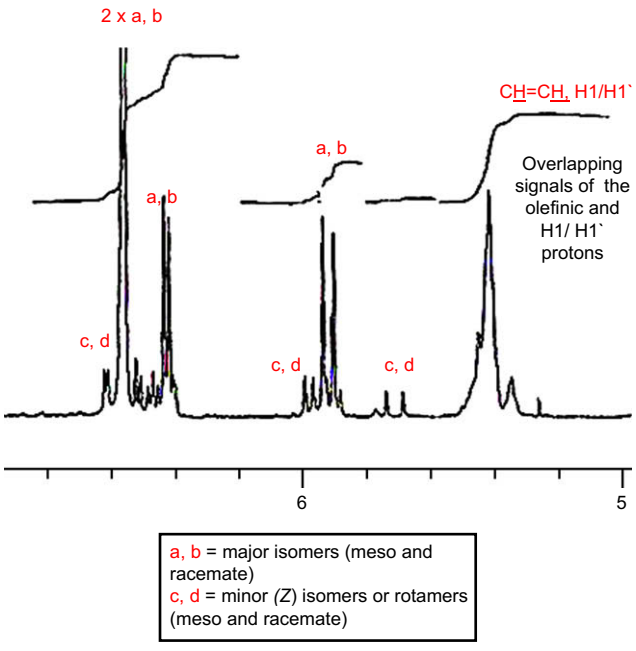
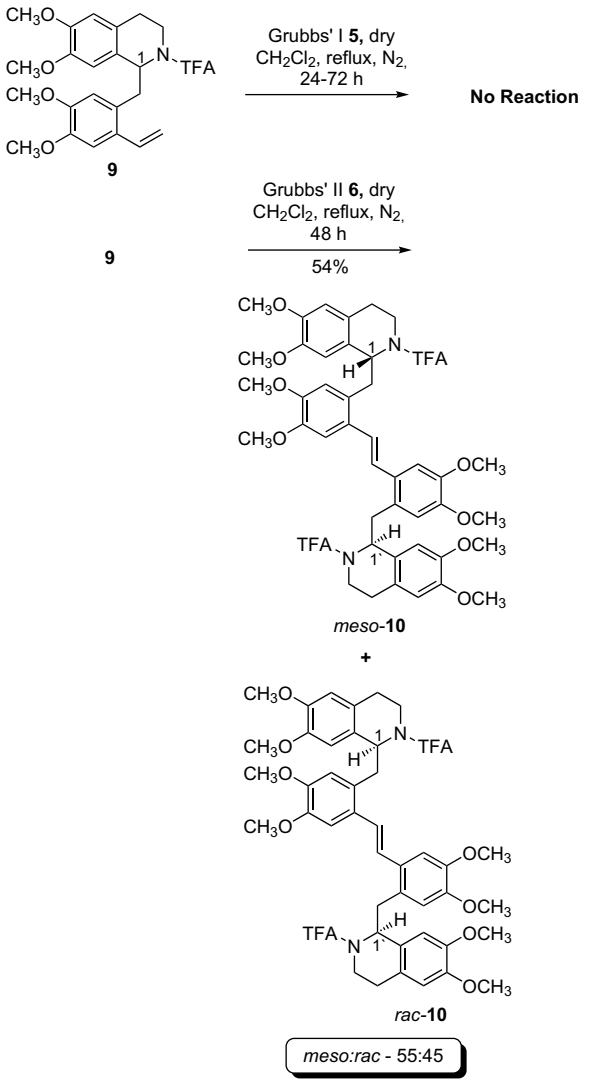


Figure 3. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the aromatic region of **8** showing pairs of aromatic signals.

the major aromatic proton signals a and b in the ^{1}H NMR spectrum (Fig. 3). Based on the previous studies on the CM reactions of type I olefins,[24] the (*E*)-olefin geometry was expected for these major isomers. A pair of minor signals (**c** and **d**) was also observed in the ^{1}H NMR spectrum of **8** representing either amide rotamers or a different alkene geometry (*Z*) to that of the major products. These signals comprised ca. 20% of the product mixture (Fig. 3).

The 2′-vinyllaudanosine derivative **9**[23] was subjected to the same CM conditions as in Scheme 1 using 10 mol % of Grubbs' I catalyst **5** over a period of 24–72 h. Under these conditions, no homocoupled product **10** was observed (Scheme 2). The result obtained was not surprising since the styrene **9** is hindered due to the closeness of the *ortho* isoquinoline moiety, which would be classified as a type II olefin, resulting in a slow homocoupling reaction rate with catalyst **5**.[11]

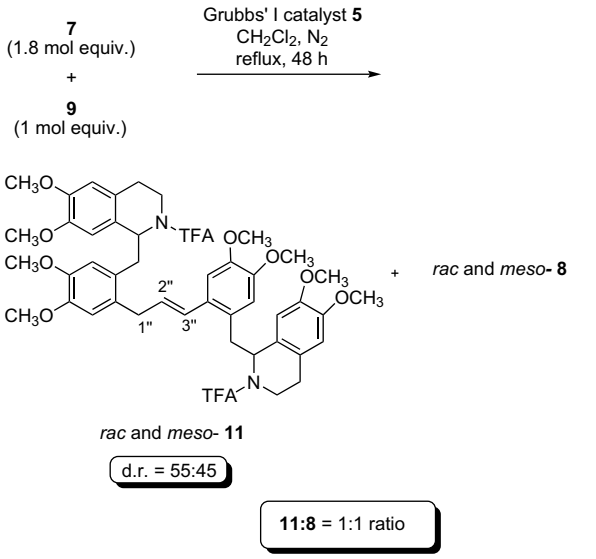
The literature indicated that Grubbs' II catalyst **6** would increase the reactivity of a non-bulky styrene to a level of a type I olefin,



Scheme 2. Cross-metathesis of the 2′-vinyllaudanosine derivative **9** [only (*S*,*S*)-**10** was shown for *rac*-**10**].

while a bulky styrene would still react as a type II olefin.[11] Therefore, Grubbs' II catalyst **6** was used in an attempt to increase the reactivity of the styrene **9** to the level of a type I olefin and allow for its rapid homocoupling reaction. In the event, a solution of the styrene **9** and Grubbs' II catalyst **6** (10 mol %) was heated at reflux for 48 h and the homocoupled product **10** was obtained in 54% yield. The product had the same NMR as that reported in the literature.[22] The starting styrene **9** was also recovered in 17% yield. The reaction yield might have been improved if a longer reaction time was permitted or if fresh catalyst was added after 48 h, however, these variations were not examined. The geometry of the double bond in **10** was anticipated to be 100% (*E*) although this could not be readily determined by NMR due to the symmetry of **10**. Chang and co-worker have reported 100% (*E*)-stilbenes being obtained from CM reactions of different styrene systems, which supported our proposed (*E*)-olefin geometry for **10**.[25]

The cross-metathesis reaction between the olefin **7** (1.8 mol equiv) and olefin **9** (1 mol equiv) was carried out in dichloromethane solution at reflux temperature (Scheme 3). The less reactive Grubbs' I catalyst **5** was chosen for this study since it was shown above that Grubbs' II catalyst **5** enhanced the reactivity of the styrene **9** to the type I level and this may have resulted in a non-selective CM reaction. After a 24 h period, TLC analysis indicated the formation of a small amount of a more polar compound consistent with the derivative **11**

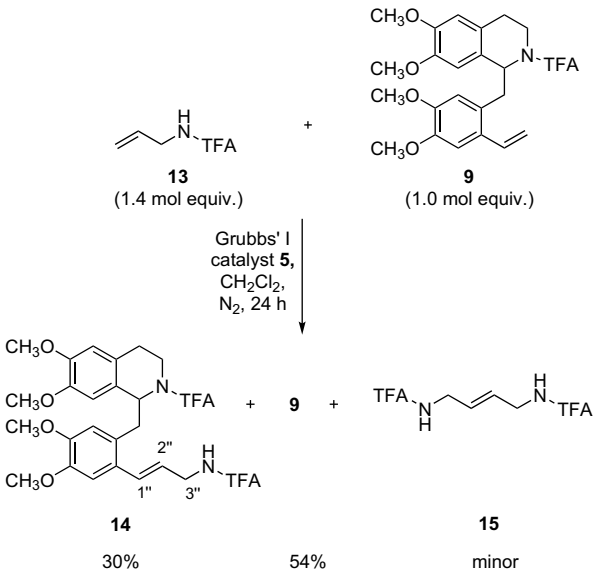


Scheme 3. CM between type I olefin **7** and type II olefin **9** [only (*S*,*S*)-**11** was shown for *rac*-**11**].

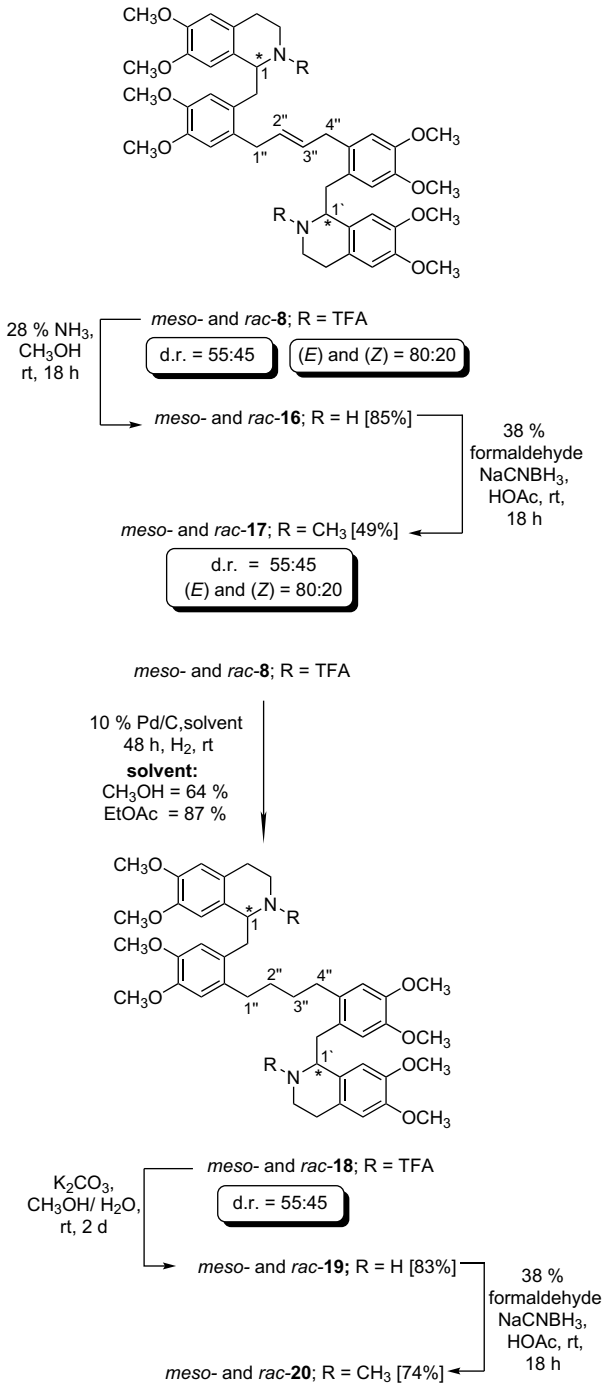
along with significant amounts of unreacted **7** and **9**. The reaction mixture was heated at reflux for an additional 24 h, however, the TLC analysis showed no significant change. The crude reaction mixture was purified by column chromatography to recover approximately 50% of a mixture of the starting materials **7** and **9**. A more polar fraction was obtained in approximately 15% yield. However, ^{1}H NMR analysis of this fraction indicated the presence of the desired CM product **11** (dr=55:45) and the homocoupled product **8** in a 1:1 ratio.

To investigate if steric factors were responsible for the low conversion rate in the formation of compound **11**, the CM reaction of the 2′-vinyllaudanosine derivative **9** with a less hindered alkene **13** was investigated.

The amide **13** was subjected to the CM reaction conditions with the 2′-vinyllaudanosine derivative **9** using Grubbs' I catalyst **5**. This reaction gave the corresponding CM product **14** in 30% yield along with the recovered styrene **9** in 54% yield. The reaction was repeated for an additional 48 h, however, no significant change was observed in conversion to the product **14**, rather there was more decomposition material obtained. ^{1}H NMR analysis of **14** showed the expected (*E*)-alkene signals at δ 6.76 (d, 1H, *J* 15.5 Hz, H1″) and 5.98



Scheme 4. The CM reaction between type II olefin **9** and type I olefin **13**.



Scheme 5. Synthesis of BBI derivatives **16**–**20**.

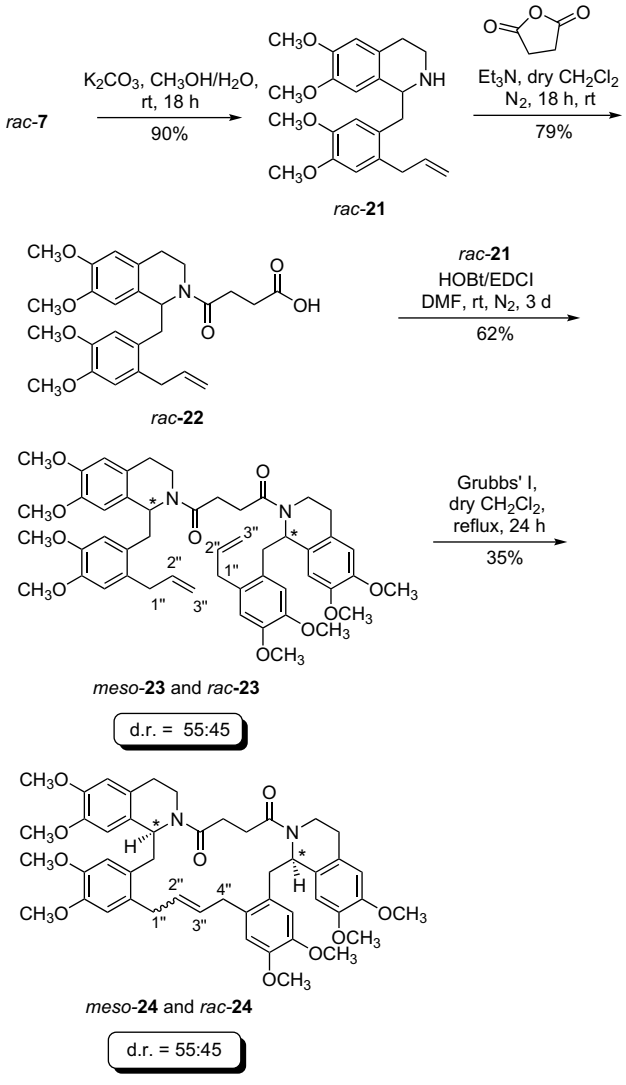
(dt, 1H, *J* 15.5, 5.5 Hz, H2″). The amide proton signal was also observed at δ 7.62 (br s, 1H, NH) confirming the structure of **14**. MS analysis of **14** also confirmed its molecular formula. In one of the minor column chromatography fractions, traces of the starting material **9** and the homocoupled product **15** were observed. From the above results, it was evident that poor yields of the desired cross-coupled products arose from the CM reactions of **9** with both hindered (**7**, Scheme 3) and unhindered (**13**, Scheme 4) allyl systems.

2.2. Synthesis of the tethered bisbenzylisoquinoline derivative 16–20

The *N*-TFA deprotection of **8** was carried out using 28% NH_3 in methanol at rt and afforded the corresponding amine **16** in good yield (85%). ^{1}H NMR analysis of **16** showed an 80:20 mixture of two isomers. Since the *N*-TFA groups had been removed, these isomers could not be rotamers. We therefore concluded that **16** was an 80:20 mixture of the (*E*)- and (*Z*)-isomer and that when the *N*-TFA group was removed, the *meso* and racemate forms have identical NMR spectra. The olefinic proton signals of **16**, which were obscured by the H1 and H1′ proton signals, were now clearly visible at δ 5.44 (br s, 2H, C*H*═C*H*) for the major (*E*)-isomer and δ 5.61 (br s, 2H, C*H*═C*H*) for the minor (*Z*)-isomer. Because of the signal overlap, the olefinic coupling constants could not be determined.

The amine **16** was subjected to reductive N-methylation to give the corresponding *N*-methylated compound **17** in moderate yield. The *N*-methylated products **17**, however, clearly showed the *meso* and racemic forms of (*E*)-**17** in a 55:45 ratio by ^{1}H NMR analysis. The characteristic *N*-methyl signals of **17** were observed in the ^{1}H NMR spectrum at δ 2.51 (s, 6H, 2×NC*H*$_3$) for the *meso* and the racemic forms. ^{1}H NMR analysis also showed 20% of a minor pair of isomers that were thought to be the *meso* and racemate forms of (*Z*)-**17** (Scheme 5).

The synthesis of the unsaturated BBI derivative **18** was carried out under hydrogenation conditions using palladium on activated carbon in methanol or ethyl acetate. Ethyl acetate proved to be the best solvent and afforded the desired product **18** in higher purity and in a yield of 87%. The ^{1}H NMR spectrum of **18** showed only four aromatic proton signals. This suggested that due to the more flexible and



Scheme 6. Synthesis of BBI derivative **24** via ring-closing metathesis.

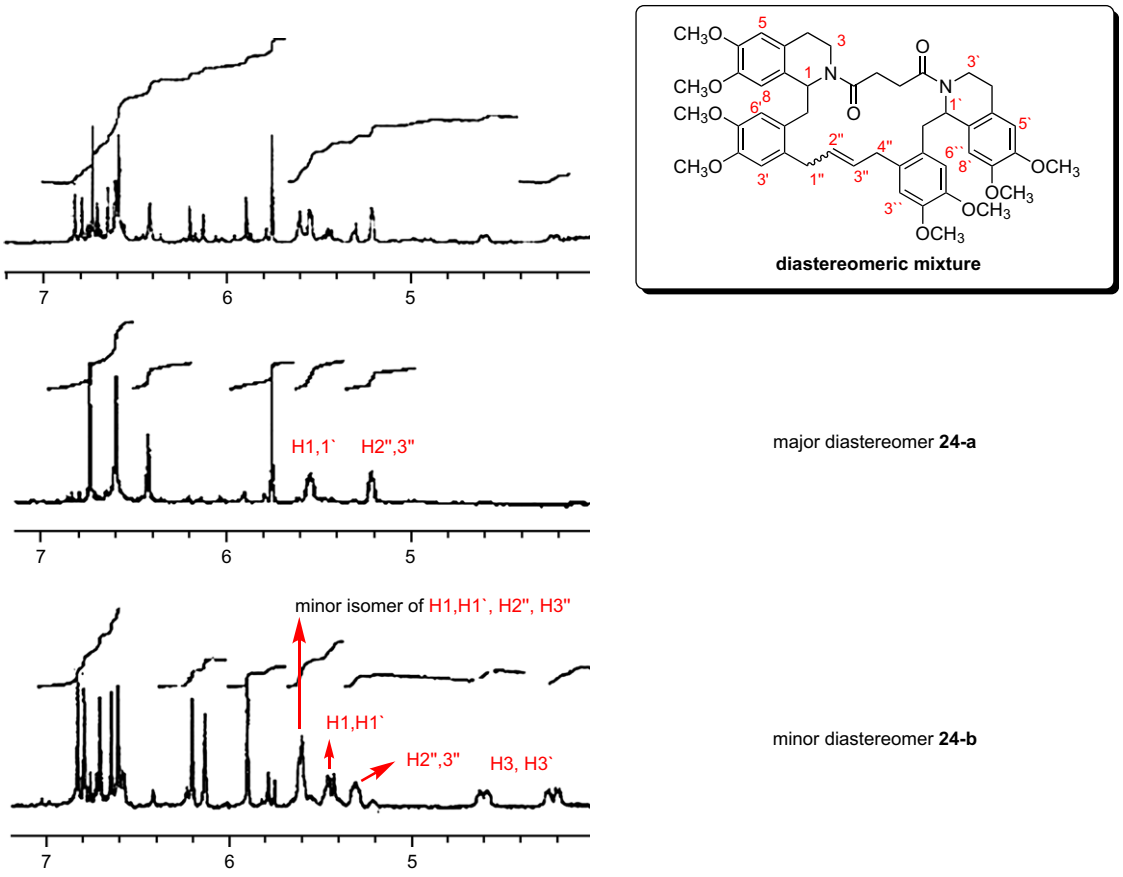


Figure 4. The ^{1}H NMR spectra (300 MHz, $CDCl_3$) of the aromatic region of the diastereomeric mixture of **24** (top), the major diastereomer **24-a** (middle) and minor diastereomer **24-b** (traces of the **24-a**) (bottom).

extended nature of the saturated tether, the ^{1}H NMR analysis was not able to distinguish between the *meso* and the racemate forms of **18**. A minor amide rotamer was also detected (ca. 5%) (Scheme 5).

The *N*-TFA deprotection of **18** was carried out using K_2CO_3 in aqueous methanol over 2 days at rt to afford **19** in good yield of 83%. As observed in the starting material **16**, the *meso* and racemic forms of **19** could not be distinguished as only four aromatic singlet resonances were observed in the ^{1}H NMR spectrum. The deprotected product **19** was subsequently N-methylated to afford the corresponding product **20** in 74% yield. Similar to **19**, the *meso* and racemate forms of **20** could not be distinguished in the ^{1}H NMR spectrum (Scheme 5).

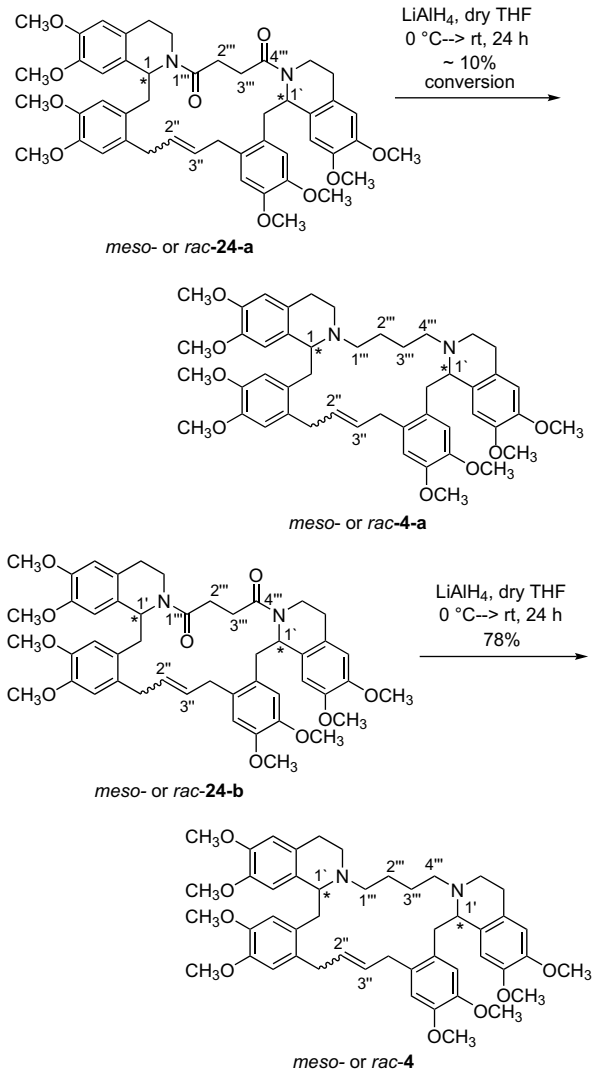
2.3. Synthesis of the macrocyclic BBI derivative 4

The racemic amine **21** was synthesised in high yield by base-catalysed *N*-TFA deprotection of *rac*-**7**. A subsequent nucleophilic ring-opening reaction of succinic anhydride with the amine **21** afforded the carboxylic acid **22** in 79% yield. The four-carbon tether between the isoquinoline nitrogens was formed by an amide coupling reaction between **21** and **22** (1:1 molar ratio) using EDCI/HOBT to afford the tethered amide **23** in 62% yield (Scheme 6). The reaction occurred slowly over 3 days, possibly due to the sterically hindered nature of the secondary amine component **21**.

^{1}H NMR analysis of **23** showed the presence of the *meso* and racemic forms of **23** in a ratio (not necessarily, respectively) of 55:45. In addition, the ^{1}H NMR analysis showed two amide rotamer forms of these isomers were also detected and accounted for 30% of the mixture. RCM of **23** was used to construct the tether between the C2′ positions of the benzyl groups by subjecting a solution of **23** in dry dichloromethane to Grubbs' I catalyst at reflux for 24 h. This reaction afforded the ring closed derivative **24** in 35% yield (Scheme 6). ^{1}H NMR analysis of **24** showed a mixture of diastereomers in a 55:45 ratio. The major and minor diastereomers of **24** were extremely difficult to completely separate by PTLC. The major diastereomer **24-a** could be obtained in ca. 95% purity by PTLC while **24-b** was more difficult to purify. The ^{1}H NMR spectra of these isomers are shown in Figure 4. The major diastereomer **24-a** appeared as one isomer in the ^{1}H NMR spectrum and showed only four aromatic singlet resonances. Interestingly, the minor diastereomer **24-b** showed ^{1}H NMR resonances for two isomers in a 55:45 ratio. These two isomers could arise from either amide rotamers, or from (*E*)- and (*Z*)-isomers. Further experiments indicated that these two isomers were rotamers (Scheme 7).

The heats of formations of the (*E*)-isomer and (*Z*)-isomer of *meso*-**24** and *rac*-**24** were calculated using Spartan Pro and the AM1 forcefield (Fig. 5). Based on these calculations, it was predicted that the (*Z*)-isomer of *rac*-**24** and *meso*-**24** had the larger (more negative) heat of formation and therefore were expected to be thermodynamically more stable than the corresponding (*E*)-isomers. Therefore it was speculated that **24-a** was (*Z*)-*rac*-**24** and **24-b** was (*Z*)-*meso*-**24**. However, due to the symmetry of **24**, it was not possible to exactly identify the (*Z*)- or (*E*)-geometry of these isomers based on ^{1}H NMR analysis.

The major and minor diastereomers **24-a** and **24-b**, respectively, were individually subjected to carbonyl reduction reactions using $LiAlH_4$ (Scheme 7). After 24 h, only the diastereomer **24-b** had undergone carbonyl reduction and gave the corresponding bisamine **4-b** in 78% yield. The successful formation of compound **4-b** was evident from the replacement of the eight aromatic proton signals of **4-**



Scheme 7. Carbonyl reduction of the major diastereomer **24-a** and the minor diastereomer **24-b** by $LiAlH_4$.

b with four newly formed aromatic proton signals of **4-b** in the ^1H NMR spectrum (Fig. 6) due to the lack of amide rotamers resulting from the reduction of the carbonyl groups in **24-b**.

The major diastereomer **24-a**, however, showed only ca. 10% conversion to its bisamine after 24 h. The different rates of carbonyl reduction between the major diastereomer **24-a** and the minor diastereomer **24-b** could be explained using molecular models

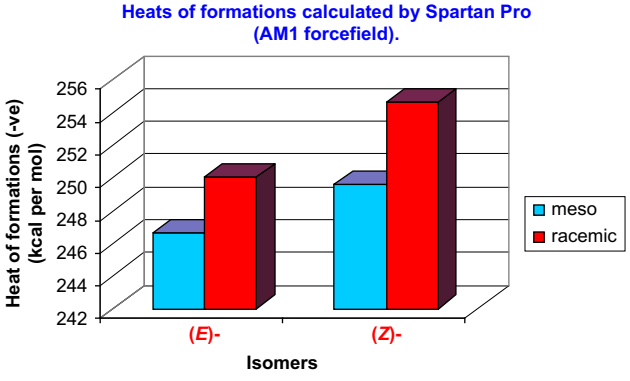


Figure 5. Heat of formation calculations for the ring closed derivative **24** (Spartan Pro, AM1 forcefield).

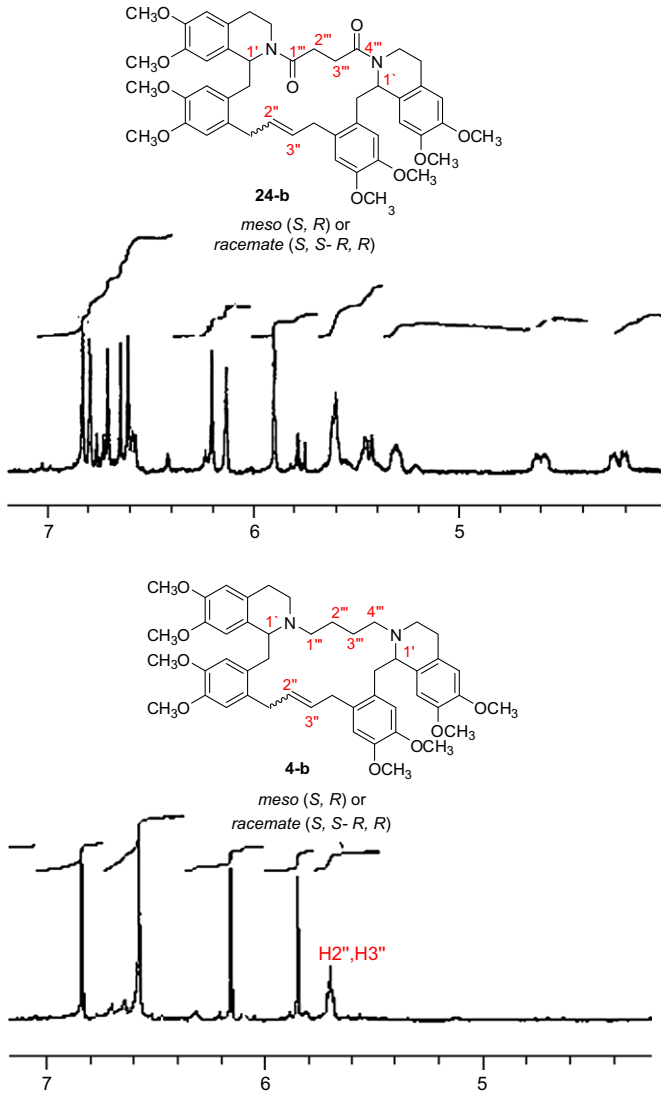


Figure 6. ^1H NMR spectrum (300 Hz, $CDCl_3$) of the aromatic regions of the minor diastereomer **24-b** (top) and its reduced form **4-b** (bottom).

generated by Spartan Pro. The (*Z*)-*rac*-**24** shown in Figure 7 has a more open conformation than (*Z*)-*meso*-**24**, which is more folded. Therefore carbonyl reduction could occur more rapidly in the case of (*Z*)-*rac*-**24** compared to (*Z*)-*meso*-**24**.

Cytostaticity studies against the cancer cell lines, H460 (human non-small cell lung), MCF-7 (human breast) and SF-268 (human CNS), were performed at the Peter MacCallum Cancer Institute, Melbourne using NCI protocols. Initially the % cell growth of cells incubated with 20 μM of the compounds, **4**, **11**, **16**, **19** and **20**, were examined. Thalicarpine **1** was tested at 25 μM. The results are presented in Table 1. Compound **16** (Table 1, entry 2) showed the highest cyctostatic activity on all three cell lines, and all compounds (Table 1, entries 2–6) showed stronger cytostatic activity than thalicarpine **1** (Table 1, entry 1). The IC_{50} of the most active compounds, **16**, **19** and **20**, were determined to be 7–26 μM (Table 1, entries 1–3) on the same three cell lines, which indicated they had moderate cytotoxicity.

In conclusion, five of the initially targeted compounds (**4** and **17**–**20**) were successfully synthesised using CM and RCM reactions. The attempted synthesis of the BBI derivatives **10** and **11** having a two-carbon linker using CM reactions proved less efficient than the Heck–Mizoroki coupling methodology described in our previous work.[22] However, the successfully prepared and novel four-

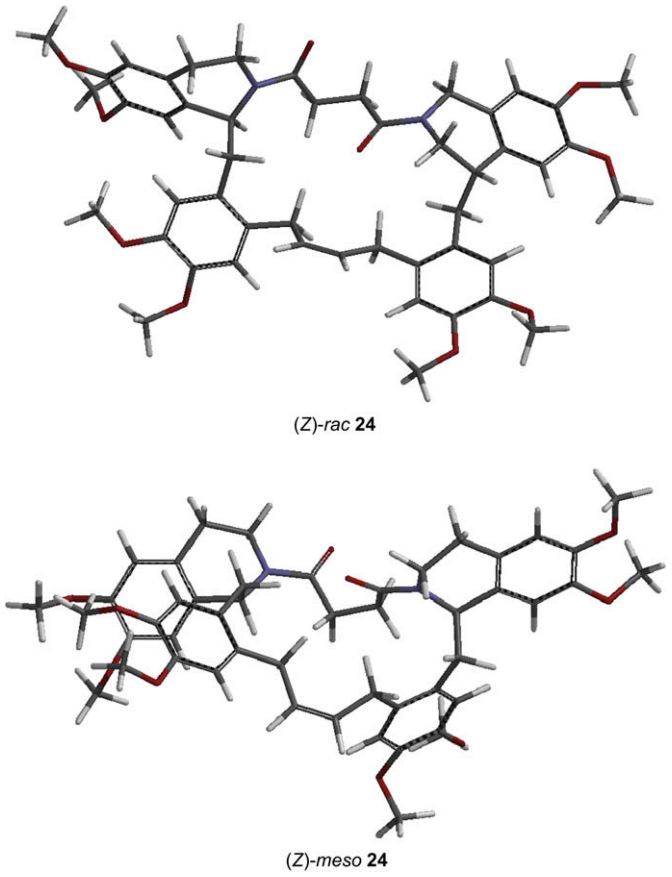


Figure 7. Spartan generated (AM1 forcefield) structures of (*Z*)-*rac*-**24** (top) and (*Z*)-*meso*-**24** (bottom) showing the more open conformation of (*Z*)-*rac*-**24** compared to the more folded one for (*Z*)-*meso*-**24**.

Table 1
Cytostatic studies on cancer cell lines

Entry	Compound	Percentage cell growth at 20 μM (IC_{50}, μM)		
		H460	MCF-7	SF-268
1	**1**	15[a]	63[a]	54[a]
2	*meso* and *rac*-**16**	0.3 (7)	2 (ND)[b]	1 (ND)[b]
3	*meso* and *rac*-**19**	5 (9)	26 (10)	24 (25)
4	*meso* and *rac*-**20**	3 (10)	21 (16)	5 (26)
5	*meso* or *rac*-**4**	3	25	57
6	*meso* and *rac*-**11**	15	66	34

[a] Percentage cell growth at 25 mM.
[b] Not determined.

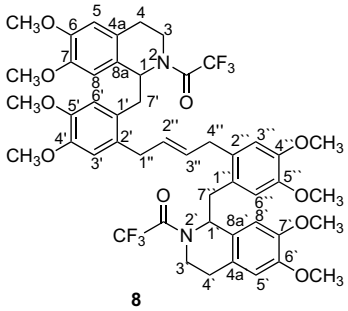
carbon-linked BBI compounds, **4**, **17**, **19** and **20**, would be much more difficult to prepare using our previously described coupling methodology.[22] This study therefore demonstrates the strengths and limitations of the CM and RCM reactions to prepare linked BBI derivatives. Compound **16** showed the highest cytostatic activity on three cancer cell lines, while compounds **4**, **11**, **19** and **20** all showed higher cytostatic activity than thalicarpine **1**.

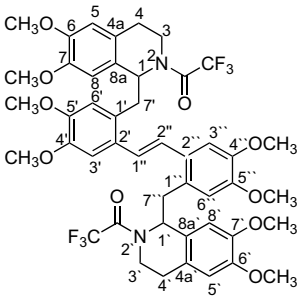
3. Experimental

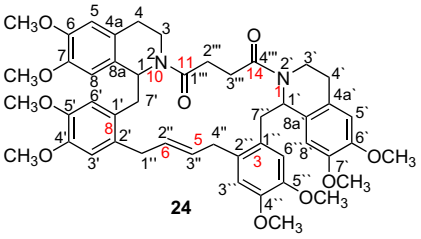
3.1. General

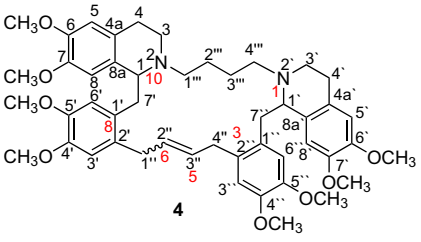
Petrol refers to the fraction of petroleum spirit with a boiling point of 40–60 °C. All ^{1}H NMR spectra were performed at 300 MHz and all ^{13}C NMR (DEPT) spectra at 75 MHz in $CDCl_3$ solution, unless otherwise noted. All spectra were referenced to $CDCl_3$ (^{1}H, δ 7.26 ppm and ^{13}C NMR, δ 77.00 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 compounds **8** and **10** as shown below. The numbering used for compounds **4** and **24** in the NMR analysis is shown below in black, systematic numbering is shown in red.









3.2. (1*RS*,1′*RS*) and (*R*,*S*) (*E* and *Z*) 2′,2″-(1″,4″-But-2″-enediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4′,5′-dimethoxyphenyl)methyl]isoquinoline (8)

A mixture of the 2′-allyllaudanosine derivative **7**[22] (400 mg, 0.854 mmol) and Grubbs' I catalyst **5** (70 mg, 0.085 mmol) was

dissolved in dry CH_2Cl_2 (2 mL) under a N_2 atmosphere and the solution was heated at reflux for 24 h. The solvent was evaporated and the crude product was purified by column chromatography (EtOAc/petrol (1:1)) to afford pure **8** (284 mg, 72%) as a mixture of (*E*)- and (*Z*)-isomer (80:20) in both *meso* and racemate forms (55:45). R_f 0.19 (EtOAc/petrol (1:1)). ^{1}H NMR of the major (*E*)-diastereomer: δ 6.58 (s, 4H, H3′, H3″, H5, H5′), 6.46 (s, 2H, H8, H8′), 5.95 (s, 2H, H6′, H6″), 5.46–5.40 (m, 4H, H1, H1′and C*H*=C*H*), 3.87 (dt, 2H, *J* 9.0, 3.6 Hz, H3, H3′), 3.83 (s, 6H, OC*H*$_3$-4′, OC*H*$_3$-4″), 3.78 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.71 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-7′), 3.66–3.58 (m, 2H, H3, H3′), 3.49 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″), 3.10–3.06 (m, 4H, H1″, H4″), 3.04–2.94 (m, 4H, H7′, H7″), 2.89–2.83 (m, 2H, H4, H4′), 2.76–2.67 (m, 2H, H4, H4′). ^{1}H NMR of the minor (*E*)-diastereomer (in part): 6.44 (s, 4H, H8, H8′), 5.93 (s, 4H, H6′, H6″), 3.47 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″). ^{1}H NMR of the major (*Z*)-isomer (in part): δ 6.01 (s, 4H, H8, H8′), 5.98 (s, 4H, H6′, H6″), 3.73 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-7′), 3.44 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″). ^{13}C NMR of the major (*E*)-diastereomer: δ 156.0 (q, *J* 35.6 Hz, *C*OCF$_3$), 148.4 (C4′, C4″), 147.4 (C6, C6′), 146.2 (C7, C7′), 142.2 (C5′, C5″), 131.8 (C2′, C2″), 130.4 (*C*H=CH), 127.3 (C4a, C4a′), 126.5 (C8a, C8a′), 125.1 (C1′, C1″), 116.8 (q, *J* 286.3 Hz, CO*C*F$_3$), 114.3 (CH-6′, CH-6″), 113.1 (CH-8, CH-8′), 111.1 (CH-3′, CH-3″), 111.9 (CH-5, CH-5′), 56.1 (6×OCH$_3$), 55.8 (OCH$_3$-5′, OCH$_3$-5″), 55.5 (CH-1, CH-1′), 40.8 (CH$_2$-1″, CH$_2$-4″), 38.2 (CH$_2$-7′, CH$_2$-7″), 35.5 (CH$_2$-3, CH$_2$-3′), 28.7 (CH$_2$-4, CH$_2$-4′). ^{13}C NMR of the minor (*E*)-diastereomer (in part): δ 27.4 (CH$_2$-4, CH$_2$-4′). MS (ESI$^+$): *m*/*z* 931 (MH$^+$, 10 %), 953.2 (M+Na$^+$, 15 %). HRMS (ESI$^+$): calcd for $C_{48}H_{53}N_2O_{10}F_6$ 931.3604 (MH$^+$), found 931.3592.

3.3. (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 (10)

A mixture of the 2′-vinyllaudanosine derivative **9**[22] (113 mg, 0.243 mmol) and Grubbs' II catalyst **6** (31 mg, 0.036 mmol) was dissolved in dry CH_2Cl_2 (2 mL) under a N_2 atmosphere and the solution was heated at reflux for 48 h. The solvent was evaporated and the crude product was purified by column chromatography (EtOAc/petrol (1:1)) to afford pure **10** (55 mg, 54%). Compound **10** was isolated as a 55:45 mixture of *meso*-**10** and *rac*-**10**. The starting material **9** (19 mg, 17%) was also recovered. The spectral data of **10** obtained from this reaction were identical to that reported from previous work.[22]

3.4. (1*RS*,1′*RS*) and (1*RS*,1′*SR*) (*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 (66) and (*RS*) (*E*) 1-(2′-cinnamyl-4′,5′-dimethoxyphenyl)methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (11)

To a mixture of the 2′-vinyllaudanosine derivative **9**[22] (63 mg, 0.134 mmol), the 2′-allyllaudanosine[22] derivative **7** (114 mg, 0.244 mmol) and Grubbs' I catalyst **5** (11 mg, 0.013 mmol) was added dry CH_2Cl_2 (2 mL) under a N_2 atmosphere and the solution was heated at reflux for 48 h. The solvent was evaporated and the crude product was purified by column chromatography (EtOAc/petrol (1:1)) to give a mixture (18 mg) of the desired product **11** and the homocoupled product **8**, which has the same R_f and could not be separated. The starting materials **9** (16 mg, 26%) and **7** (26 mg, 27%) were also recovered. The NMR of the mixture consisting of compounds **11** and **18** (1:1 ratio) corresponded to the NMR of each individual compound, **11** and **8**, that had been previously synthesised.[22]

3.5. (*RS*) (*E*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4′,5′-dimethoxy-2′-(3″-trifluoroacetyl-1″-propenyl)phenyl]methylisoquinoline (14)

To a mixture of the 2′-vinyllaudanosine derivative **9**[22] (88 mg, 0.189 mmol), *N*-TFA allylamine **13**[26] (40 mg, 0.261 mmol) and Grubbs' I catalyst **5** (15 mg, 0.019 mmol) was added dry CH_2Cl_2 (2 mL) under a N_2 atmosphere and the solution was heated at reflux for 48 h. The solvent was evaporated and the crude product was purified by column chromatography (EtOAc/petrol (1:1)) to give the desired product **14** (34 mg, 30%) as a yellow oil. The starting material **9** (48 mg, 54%) was also recovered. R_f 0.38 (EtOAc/petrol (1:1)). ^{1}H NMR: δ 7.62 (br s, 1H, NH), 6.94 (s, 1H, H3′), 6.76 (d, 1H, *J* 15.5 Hz, H1″), 6.60 (s, 1H, H5), 6.26 (s, 1H, H6′), 5.98 (dt, 1H, *J* 15.5, 5.5 Hz, H2″), 5.69 (s, 1H, H8), 5.35 (dd, 1H, *J* 10.0, 3.5 Hz, H1), 4.19 (dt, 1H, *J* 15.5, 5.5 Hz, H3″), 4.09 (dt, 1H, *J* 15.5, 5.5 Hz, H3″), 3.95–3.91 (m, 1H, H3), 3.87 (s, 3H, OC*H*$_3$-5′), 3.82 (s, 3H, OC*H*$_3$-7), 3.73–3.68 (m, 1H, H3), 3.66 (s, 3H, OC*H*$_3$-4′), 3.44 (s, 3H, OC*H*$_3$-6), 3.23 (dd, 1H, *J* 13.0, 3.5 Hz, H7′), 2.94–2.92 (m, 1H, H4), 2.91 (dd, 1H, *J* 13.0, 10.0 Hz, H7′), 2.83–2.78 (m, 1H, H4). ^{13}C NMR: δ 157.4 (q, *J* 36.6 Hz, *C*OCF$_3$), 156.1 (q, *J* 36.7 Hz, *C*OCF$_3$), 148.4 (C4′, C5′), 148.2 (C7), 146.9 (C6), 129.6 (CH-1″), 128.7 (C1′), 127.0 (C2′), 125.9 (C4a), 124.5 (C8a), 123.9 (CH-2″), 118.3 (q, *J* 286.1 Hz, CO*C*F$_3$), 116.5 (q, *J* 286.0 Hz, CO*C*F$_3$), 114.8 (CH-6′), 111.3 (CH-8), 111.0 (CH-5), 109.1 (CH-3′), 56.0 (OCH$_3$-5′, OCH$_3$-7), 55.9 (OCH$_3$-4′), 55.5 (OCH$_3$-6), 55.3 (CH-1), 41.3 (CH$_2$-3″), 40.9 (CH-3), 39.6 (CH$_2$-7′), 28.4 (CH$_2$-4). MS (EI$^+$): *m*/*z* 590 (M$^+$, 30%). HRMS (ESI$^+$): calcd for $C_{27}H_{29}N_2O_6F_6$ 591.1930 (MH$^+$), found 591.1959.

3.6. (1*RS*,1′*RS*) and (*R*,*S*) (*E* and *Z*) 2′,2″-(1″,4″-But-2″-enediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4′,5′-dimethoxyphenyl)methyl]isoquinoline (16)

To a solution of the *N*-TFA protected amine **8** (243 mg, 0.262 mmol) in CH$_3$OH (2 mL) was added dropwise 28% aqueous NH$_3$ (2 mL). The reaction mixture was stirred at rt for 18 h. The solvent was evaporated and the residue was purified by column chromatography (CH$_3$OH/EtOAc (1:4)) to give **16** (189 mg, 85% yield) as a yellow solid. Compound **16** was obtained as an 80:20 mixture of (*E*)- and (*Z*)-isomer, respectively. R_f 0.13 (CH$_3$OH/EtOAc (1:4)), mp 158–160 °C. ^{1}H NMR of (*E*)-**16**: δ 6.68 (s, 2H, H3′, H3″), 6.65 (s, 2H, H5, H5′), 6.57 (s, 2H, H8, H8′), 6.46 (s, 2H, H6′, H6″), 5.44 (br s, 2H, C*H*=C*H*), 4.06 (br s, 2H, *J* 9.0, 4.8 Hz, H1, H1′), 3.84 (s, 6H, OC*H*$_3$-4′, OC*H*$_3$-4″), 3.81 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.79 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-7′), 3.71 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″), 3.31 (d, 4H, *J* 3.3 Hz, H1″, H4″), 3.21–3.18 (m, 2H, H3, H3′), 3.15 (dd, 2H, *J* 12.9, 6.0 Hz, H7′, H7″), 2.90–2.81 (m, 4H, H7′, H7″, H3, H3′), 2.72 (dt, 4H, *J* 9.2, 6.2 Hz, H4, H4′). ^{1}H NMR of (*Z*)-**16** (in part): δ 6.71 (s, 2H, H3′, H3″), 6.64 (s, 2H, H5, H5′), 6.47 (s, 2H, H6′, H6″), 5.61 (br s, 2H, C*H*=C*H*), 4.15–4.06 (m, 1H, H1). ^{13}C NMR of (*E*)-**16**: δ 147.7 (C4′, C4″, C6, C6′), 146.7 (C7, C7′), 147.1 (C5′, C5″), 131.4 (C2′, C2″), 130.7 (C4a, C4a′), 130.1 (*C*H=CH), 129.3 (C8a, C8a′), 127.6 (C1′, C1″), 114.0 (CH-6′, CH-6″), 113.4 (CH-8, CH-8′), 112.1 (CH-3′, CH-3″), 101.8 (CH-5, CH-5′), 56.6 (CH-1, CH-1′), 56.2 (OCH$_3$-4′, OCH$_3$-4″), 56.1 (OCH$_3$-6, OCH$_3$-6′, OCH$_3$-7, OCH$_3$-7′), 56.2 (OCH$_3$-5′, OCH$_3$-5″), 41.0 (CH$_2$-3, CH$_2$-3′), 39.5 (CH$_2$-7′, CH$_2$-7″), 35.8 (CH$_2$-1″, CH$_2$-4″), 29.7 (CH$_2$-4, CH$_2$-4′). MS (ESI$^+$): *m*/*z* 739 (MH$^+$, 10%). HRMS (ESI$^+$): calcd for $C_{44}H_{55}N_2O_8$ 739.3958 (MH$^+$), found 739.3950.

3.7. (1*RS*,1′*RS*) and (*R*,*S*) (*E* and *Z*) 2′,2″-(1″,4″-But-2″-enediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4′,5′-dimethoxyphenyl)methyl-2-methyl]isoquinoline (17)

To a solution of the amine **16** (37 mg, 0.501 mmol) in CH$_3$CN (1 mL) was added 38% formaldehyde (2 mL). NaCNBH$_3$ (18 mg, 0.260 mmol) was subsequently added and the reaction mixture was stirred at rt for 20 min. The pH was then adjusted to 6–7 using glacial acetic acid and the reaction mixture was stirred at rt for 18 h. The solvent was evaporated and the residue was dissolved in EtOAc. The solution was washed with satd K$_2$CO$_3$ (2×), then dried (MgSO$_4$) and concentrated in vacuo to give an oil, which was purified by column chromatography (CH$_2$Cl$_2$/EtOAc/CH$_3$OH/NH$_3$ (10:5:1:0.1)) to afford **17** (19 mg, 49% yield) as a yellow oil. Compound **17** was an 80:20 mixture of (*E*)- and (*Z*)-isomer, respectively, for both *meso*-**17** and *rac*-

17 (dr=55:45). R_f 0.39 (DCM/EtOAc/CH_3OH/NH_3 (10:5:1:0.1)). ^1H NMR of (*E*)-**17**, major diastereomer: δ 6.54 (s, 2H, H3′, H3″), 6.53 (s, 2H, H5, H5′), 6.50 (s, 2H, H8, H8′), 5.68 (s, 2H, H6′, H6″), 5.71 (br s, 2H, C*H*═C*H*), 3.80 (s, 6H, OC*H*$_3$-4′, OC*H*$_3$-4″), 3.76 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.74 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-7′), 3.62 (dd, 2H, *J* 8.4, 4.2 Hz, H1, H1′), 3.39 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″), 3.24–3.14 (m, 2H, H3, H3′), 3.07 (dd, 2H, *J* 13.5, 4.2 Hz, H7′, H7″), 2.91 (t, 4H, *J* 4.5 Hz, H1″, H4″), 2.87 (dd, 2H, *J* 13.5, 8.4 Hz, H7′, H7″), 2.85–2.76 (m, 4H, H3, H3′, H4, H4′), 2.65–2.54 (m, 2H, H4, H4′), 2.51 (s, 6H, 2×NC*H*$_3$). ^1H NMR of (*E*)-**17**, minor diastereomer (in part): δ 6.49 (s, 2H, H8, H8′), 5.67 (s, 2H, H6′, H6″), 3.41 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″). ^1H NMR of (*Z*)-**17** (in part): δ 6.57 (s, 2H, H3′, H3″), 6.56 (s, 2H, H5, H5′), 5.71 (s, 2H, H6′, H6″). ^{13}C NMR of (*E*)-**17**, major diastereomer: δ 148.5 (C4′, C4″), 148.0 (C6, C6′), 147.5 (C7, C7′), 146.7 (C5′, C5″), 132.0 (C2′, C2″), 130.3 (*C*H═*C*H), 130.1 (C4a, C4a′), 128.5 (C8a, C8a′), 125.9 (C1′, C1″), 114.6 (CH-6′, CH-6″), 113.1 (CH-8, CH-8′), 111.5 (CH-3′, CH-3″), 111.4 (CH-5, CH-5′), 64.5 (CH-1, CH-1′), 56.3 (O*C*H$_3$-4′, OCH$_3$-4″), 56.2 (OCH$_3$-6, OCH$_3$-6′), 56.1 (O*C*H$_3$-7, OCH$_3$-7′), 55.6 (OCH$_3$-5′, OCH$_3$-5″), 45.1 (CH_2-3, CH_2-3′), 41.0 (2×N*C*H$_3$), 37.2 (CH_2-7′, CH_2-7″), 35.6 (CH_2-1″, CH_2-4″), 23.4 (CH_2-4, CH_2-4′). ^{13}C NMR of (*E*)-**17**, minor diastereomer (in part): δ 64.7 (CH-1, CH-1′), 40.7 (2×N*C*H$_3$), 35.6 (CH_2-1″, CH_2-4″), 22.9 (CH_2-4, CH_2-4′). MS (ESI$^+$): *m*/*z* 767.5 (MH$^+$, 10%). HRMS (ESI$^+$): calcd for $C_{46}H_{59}N_2O_8$ 767.4271 (MH$^+$), found 767.4234.

3.8. (1*RS*,1′*RS*) and (*R*,*S*) 2′,2″-(1″,4″-Butanediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4′,5′-dimethoxyphenyl)methyl]isoquinoline (18)

To a solution of the alkene **8** (284 mg, 0.308 mmol) in EtOAc (5 mL) was added 10% Pd/C (21 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 48 h under a H_2 atmosphere. Nitrogen was then bubbled into the solution for 2 min before the Pd/C was filtered. The filtrate was concentrated in vacuo to give pure **18** (248 mg, 87%) as a yellow oil. R_f 0.85 (EtOAc/petrol (1:1)). ^1H NMR: δ 6.62 (s, 2H, H3′, H3″), 6.58 (s, 2H, H5, H5′), 6.45 (s, 2H, H8, H8′), 6.00 (s, 2H, H6′, H6″), 5.45 (dd, 2H, *J* 8.1, 5.7 Hz, H1, H1′), 3.89 (dt, 2H, *J* 12.0, 5.0 Hz, H3, H3′), 3.83 (s, 12H, OC*H*$_3$-4′, OC*H*$_3$-4″, OC*H*$_3$-7, OC*H*$_3$-7′), 3.68 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.65–3.61 (m, 2H, H3, H3′), 3.50 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″), 3.08–3.03 (m, 2H, H4′, H4″), 2.98–2.88 (m, 4H, H7′, H7″), 2.77–2.71 (m, 2H, H4, H4′), 2.42–2.38 (m, 4H, H1″, H4″), 1.51–1.47 (m, 4H, H2″, H3″). ^{13}C NMR: δ 155.1 (q, *J* 35.5 Hz, *C*OCF$_3$), 148.4 (C4′, C4″), 148.0 (C6, C6′), 147.3 (C7, C7′), 147.0 (C5′, C5″), 134.0 (C2′, C2″), 126.8 (C4a, C4a′), 126.5 (C8a, C8a′), 125.2 (C1′, C1″), 114.3 (CH-6′, CH-6″), 113.8 (q, *J* 286.9 Hz, CO*C*F$_3$), 112.6 (CH-8, CH-8′), 111.1 (CH-3′, CH-3″), 111.0 (CH-5, CH-5′), 56.1 (OCH$_3$-4′, OCH$_3$-4″, OCH$_3$-6, OCH$_3$-6′), 56.0 (OCH$_3$-7, OCH$_3$-7′), 55.8 (OCH$_3$-5′, OCH$_3$-5″), 55.6 (CH-1, CH-1′), 40.8 (CH_2-3, CH_2-3′), 32.2 (CH_2-7′, CH_2-7″), 38.2 (CH_2-4, CH_2-4′), 31.7 (CH_2-1″, CH_2-4″), 28.7 (CH_2-2″, CH_2-3″). MS (ESI$^+$): *m*/*z* 933.3 (MH$^+$, 70%). HRMS (ESI$^+$): calcd for $C_{48}H_{55}N_2O_{10}F_6$ 933.3761 (MH$^+$), found 933.3800.

3.9. (1*RS*,1′*RS*) and (*R*,*S*) 2′,2″-(1″,4″-Butyldiyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4′,5′-dimethoxyphenyl)methyl]isoquinoline] (19)

To a solution of the *N*-TFA protected amine **18** (247 mg, 0.267 mmol) in a mixture of CH_3OH (20 mL) and H_2O (2 mL) was added K_2CO_3 (184 mg, 1.34 mmol). The resulting solution was stirred at rt for 2 days. CH_3OH was evaporated and the residue was dissolved in EtOAc. The solution was washed with H_2O (3×), brine and then dried ($MgSO_4$). The EtOAc was evaporated and the residue was purified by column chromatography (CH_3OH/EtOAc/NH_3 (1:5:0.1)) to afford the amine **19** (164 mg, 83%) as a yellow solid. R_f 0.09 (CH_3OH/EtOAc/NH_3 (1:5:0.1)), mp 130–134 °C. ^1H NMR: δ 6.64 (s, 4H, H3′, H3″, H6′, H6″), 6.56 (s, 2H, H5, H5′), 6.46 (s, 2H, H8, H8′), 4.10 (dd, 2H, *J* 4.4, 2.4 Hz, H1, H1′), 3.82 (s, 12H, OC*H*$_3$-4′, OC*H*$_3$-4″, OC*H*$_3$-5′, OC*H*$_3$-5″), 3.78 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.70 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-7′), 3.21–3.07 (m, 4H, H3, H3′ and H7′, H7″), 2.92–2.76 (m, 4H, H3, H3′ and H7′, H7″), 2.71–2.69 (m, 4H, H4, H4′), 2.60–2.56 (m, 4H, H1″, H4″), 2.32 (br s, 2H, 2×N*H*), 1.61–1.59 (m, 4H, H2″, H3″). ^{13}C NMR: δ 147.8 (C4′, C4″), 147.7 (C5′, C5″), 147.2 (C6, C6′), 147.1 (C7, C7′), 133.7 (C2′, C2″), 133.7 (C1′, C1″), 128.7 (C4a, C4a′), 127.4 (C8a, C8a′), 114.0 (CH-3′, CH-3″), 112.9 (CH-6′, CH-6″), 112.0 (CH-5, CH-5′), 110.0 (CH-8, CH-8′), 56.7 (CH-1, CH-1′), 56.2 (OCH$_3$-4′, OCH$_3$-4″, OCH$_3$-5′, OCH$_3$-5″), 56.1 (OCH$_3$-6, OCH$_3$-6′, OCH$_3$-7, OCH$_3$-7′), 40.9 (CH_2-3, CH_2-3′), 39.2 (CH_2-7′, CH_2-7″), 32.8 (CH_2-4, CH_2-4′), 32.0 (CH_2-1″, CH_2-4″), 29.9 (CH_2-2″, CH_2-3″). MS (ESI$^+$): *m*/*z* 741.5 (MH$^+$, 30 %). HRMS (ESI$^+$): calcd for $C_{44}H_{57}N_2O_8$ 741.4150 (MH$^+$), found 741.4121.

3.10. (1*RS*,1′*RS*) and (*R*,*S*) 2′,2″-(1″,4″-Butyldiyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4′,5′-dimethoxyphenyl)methyl-2-methyl]isoquinoline (20)

The amine **19** (73 mg, 0.099 mmol) was treated as described above in the synthesis of **18** using CH_3CN (2 mL), 38% formaldehyde (4 mL) and $NaCNBH_3$ (36 mg, 0.514 mmol) to give an oil, which was purified by column chromatography (CH_2Cl_2/EtOAc/CH_3OH/NH_3 (10:5:1:0.1)) to give **20** (56 mg, 74%) as a yellow oil. R_f 0.37 (CH_2Cl_2/EtOAc/CH_3OH/NH_3 (10:5:1:0.1)). ^1H NMR: δ 6.58 (s, 2H, H3′, H3″), 6.55 (s, 2H, H5, H5′), 6.52 (s, 2H, H8, H8′), 5.74 (s, 2H, H6, H6′), 3.82 (s, 6H, OC*H*$_3$-4′, OC*H*$_3$-4″), 3.81 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.76 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-7′), 3.66 (dd, 2H, *J* 9.3, 4.5 Hz, H1, H1′), 3.43 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″), 3.23 (ddd, 2H, *J* 13.2, 8.1, 3.6 Hz, H3, H3′), 3.10 (dd, 2H, *J* 13.5, 4.5 Hz, H7′, H7″), 2.94–2.87 (m, 2H, H3, H3′), 2.83–2.78 (m, 2H, H4, H4′), 2.72 (dd, 2H, *J* 13.5, 9.3 Hz, H7′, H7″), 2.64–2.56 (m, 2H, H4, H4′), 2.54 (s, 6H, 2×NC*H*$_3$), 2.26–2.24 (m, 4H, H1″, H4″), 1.48–1.40 (m, 4H, H2″, H3″). ^{13}C NMR: δ 147.9 (C4′, C4″), 147.6 (C6, C6′), 147.0 (C7, C7′), 146.4 (C5′, C5″), 133.9 (C2′, C2″), 128.7 (C4a, C4a′), 127.5 (C8a, C8a′), 124.9 (C1′, C1″), 114.4 (CH-3′, CH-3″), 112.8 (CH-5, CH-5′), 111.6 (CH-8, CH-8′), 111.4 (CH-6′, CH-6″), 64.6 (CH-1, CH-1′), 56.2 (OCH$_3$-4′, OCH$_3$-4″ and OCH$_3$-6, OCH$_3$-6′), 56.0 (OCH$_3$-7, OCH$_3$-7′), 55.6 (OCH$_3$-5′, OCH$_3$-5″), 31.6 (CH_2-1″, CH_2-4″), 24.7 (CH_2-2″, CH_2-3″). MS (ESI$^+$): *m*/*z* 769.4 (MH$^+$, 30%). HRMS (ESI$^+$): calcd for $C_{46}H_{61}N_2O_8$ 769.4428 (MH$^+$), found 769.4396.

3.11. (*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(4′,5′-dimethoxy-2′-(2″-propenyl)-phenyl) methylisoquinoline (21)

N-TFA protected amine **7** (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 **21** (50 mg, 90%) as a yellow oil. R_f 0.21 (CH_3OH/EtOAc (1:5)). ^1H NMR: δ 6.73 (s, 1H, H3′), 6.71 (s, 1H, H6′), 6.58 (s, 1H, H5), 6.44 (s, 1H, H8), 5.98–5.85 (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*H*$_3$-4′, OC*H*$_3$-5′), 3.82 (s, 3H, OC*H*$_3$-6), 3.73 (s, 3H, OC*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 (OCH$_3$-4′), 56.3 (OCH$_3$-5′), 56.2 (OCH$_3$-6), 56.1 (OCH$_3$-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.

3.12. (*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1(4′,5′-dimethoxy-2′-(2″-propenyl)-phenyl) methylisoquinoline 2-(4-oxo)butanoic acid (22)

To a solution of the amine **21** (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 solution was concentrated and the residue was redissolved in EtOAc. The solution was washed with 1 M $KHSO_4$ (2×) and then brine. The solution was dried ($MgSO_4$) and concentrated, and the crude mixture was purified by column chromatography (CH_3OH/EtOAc (1:5)) to give **22** (334 mg, 79%) as a white solid. The product **22** was a 70:30 mixture of rotamers by ^1H NMR analysis. R_f 0.71 (CH_3OH/EtOAc (1:5)), mp 138–140 °C. ^1H 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), 5.76 (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*H*$_3$-5′), 3.83 (s, 3H, OC*H*$_3$-6), 3.75 (s, 3H, OC*H*$_3$-7), 3.70–3.65 (m, 2H, H3), 3.50 (s, 3H, OC*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), 2.79–2.73 (m, 4H, H2‴, H3‴). ^1H 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*)), 4.88–4.84 (m, 1H, H1), 4.73 (ddd, 1H, *J* 8.4, 5.7, 2.4 Hz, H3), 3.87 (s, 3H, OC*H*$_3$-5′), 3.81 (s, 3H, OC*H*$_3$-7), 3.79 (s, 3H, OC*H*$_3$-4′), 3.32 (d, 2H, *J* 6.3 Hz, H1″), 3.27–3.17 (m, 1H, H4), 3.12–3.08 (m, 1H, H7′), 2.91–2.89 (m, 1H, H4), 2.87–2.85 (m, 1H, H7′), 1.90–1.84 (m, 4H, H2‴, H3‴). ^{13}C NMR of the major rotamer: δ 175.5 (*C*OOH), 169.8 (N*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*C*H$_3$-4′, O*C*H$_3$-5′), 54.9 (O*C*H$_3$-6), 54.6 (O*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 (*C*OOH), 170.2 (N*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.

3.13. (1*RS*,1′*RS*) and (*R*,*S*) 2,2′-(1‴,4‴-Dioxo-1‴,4‴-butanediyl)-2′,2″-(1″,4″-prop-2-enediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4′,5′-dimethoxy-phenyl)methyl]isoquinoline (23)

To a mixture of the acid **22** (64 mg, 0.131 mmol), amine **21** (50 mg, 0.131 mmol), HOBT (20 mg, 0.144 mmol) and EDCI (25 mg, 0.131 mmol) was added dry DMF (3 mL) under a N_2 atmosphere. The mixture was stirred at rt for 3 days. EtOAc was added and the solution was washed with H_2O (3×), then dried ($MgSO_4$) and concentrated to give a solid, which was purified by column chromatography (CH_3OH/EtOAc (1:5)) to give **23** (69 mg, 62%) as a white solid. Compound **23** was a 55:45 mixture of diastereomers. A minor rotamer of **23** (30%) was also observed. R_f 0.88 (CH_3OH/EtOAc (1:5)), mp 142–144 °C. ^1H NMR of the major diastereomer: δ 6.56 (s, 6H, H3′, H3″, H5, H5′, H6′, H6″), 5.89 (s, 2H, H8, H8′), 5.79–5.68 (m, 2H, 2×H2″), 5.50 (dd, 2H, *J* 8.7, 4.2 Hz, H1, H1′), 5.08–4.80 (m, 4H, 2×H3″), 3.81 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″), 3.82–3.78 (m, 2H, H3, H3′), 3.79 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-7′), 3.72 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.66–3.54 (m, 2H, H3, H3′), 3.46 (s, 6H, OC*H*$_3$-4′, OC*H*$_3$-4″), 3.00 (d, 4H, *J* 5.7 Hz, 2×H1″), 3.01–2.95 (m, 2H, H7′, H7″), 2.90–2.84 (m, 2H, H7′, H7″), 2.83–2.79 (m, 4H, H4, H4′), 2.77 (br s, 4H, H2‴, H3‴). ^1H NMR of the minor diastereomer (in part): δ 6.59 (s, 2H, H3′, H3″), 6.57 (s, 2H, H5, H5′), 6.53 (s, 2H, H6′, H6″), 5.88 (s, 2H, H8, H8′), 5.84–5.80 (m, 2H, 2×H2″), 5.48 (dd, 2H, *J* 8.7, 4.2 Hz, H1, H1′), 5.04–4.98 (m, 4H, H3, H3), 3.71 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-7′), 3.45 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.46 (s, 6H, OC*H*$_3$-4′, OC*H*$_3$-4″), 3.11–3.07 (m, 2H, H7′, H7″), 3.02 (d, 4H, *J* 5.7 Hz, 2×H1″). ^1H NMR minor rotamer of *both* diastereomers (in part), note: * indicates the minor diastereomer: δ 6.64 (s, 2H, H3′, H3″), 6.50 (s, 2H, H5, H5′), 6.47 (s, 2H, H5*, H5′*), 6.36 (s, 2H, H6′, H6″), 6.34 (s, 2H, H6′*, H6″*), 5.93 (s, 2H, H8, H8′), 5.84 (s, 2H, H8*, H8′*), 5.40 (dd, 2H, *J* 9.9, 5.1 Hz, H1, H1′), 5.39 (dd, 2H, *J* 9.9, 5.1 Hz, H1*, H1′*), 4.72–4.68 (m, 2H, 2×H3″), 4.60–4.55 (m, 2H, 2×H3″*). ^{13}C NMR of the major diastereomer: δ 171.1 (*C*O), 148.0 (C5′, C5″), 147.7 (C7, C7′, C6, C6′), 147.3 (C4′, C4″), 137.2 (2×CH-2″), 131.2 (C8a, C8a′), 128.7 (C4a, C4a′), 128.4 (C1′, C1″), 126.1 (C2′, C2″), 115.7 (2×CH_2-3″), 114.0 (CH-3′, CH-3″), 112.5 (CH-6′, CH-6″), 111.0 (CH-8, CH-8′), 110.8 (CH-5, CH5′), 55.8 (8×O*C*H$_3$), 54.5 (CH-1, CH-1′), 41.1 (CH_2-3, CH_2-3′), 38.1 (CH_2-7′, CH_2-7″), 36.3 (2×CH_2-1″), 28.9 (CH_2-4, CH_2-4′), 28.4 (CH_2-2‴, CH_2-3‴). ^{13}C NMR of the minor diastereomer (in part): δ 171.1 (*C*O), 148.3 (C5′, C5″), 147.7 (C7, C7′, C6, C6′), 146.7 (C4′, C4″), 137.1 (2×CH-2″), 132.0 (C8a, C8a′), 115.3 (2×CH_2-3″), 57.2 (CH-1, CH-1′), 41.1 (CH_2-3, CH_2-3′), 38.7 (CH_2-7′, CH_2-7″), 36.9 (2×CH_2-1″), 29.0 (CH_2-4, CH_2-4′), 27.9 (CH_2-2‴, CH_2-3‴). MS (ESI^+): *m*/*z* 849.5 (MH^+, 20%). HRMS (ESI^+): calcd for $C_{50}H_{61}N_2O_{10}$ 849.4326 (MH^+), found 849.4376.

3.14. (1*RS*,1′*RS*) and (*R*,*S*) 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)-tetradeca-5-phene (24)

A solution of **23** (44 mg, 0.056 mmol) and Grubbs' I catalyst **5** (5 mg, 0.006 mmol) in dry CH_2Cl_2 (25 mL) was heated at reflux for 24 h under a N_2 atmosphere. The solvent was evaporated and the crude oil was purified by column chromatography (CH_3OH/EtOAc (2:8)) to give **24** (16 mg, 35 %) as a clear oil. Compound **24** was a 55:45 mixture of diastereomers, which were separated by PTLC (CH_3OH/EtOAc (2:8)).

*Compound **24-a***. R_f 0.69 (CH_3OH/EtOAc (2:8)). ^1H NMR: δ 6.71 (s, 2H, H3′, H3″), 6.57 (s, 2H, H5, H5′), 6.40 (s, 2H, H6′, H6″), 5.73 (s, 2H, H8, H8′), 5.53 (dd, 2H, *J* 6.0, 2.4 Hz, H1, H1′), 5.19 (t, 2H, *J* 4.8 Hz, H2″, H3″), 3.84 (s, 12H, OC*H*$_3$-5′, OC*H*$_3$-5″, OC*H*$_3$-7, OC*H*$_3$-7′), 3.87–3.77 (m, 2H, H3, H3′), 3.73 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.64–3.57 (m, 4H, H1″, H4″), 3.49 (dd, 2H, *J* 12.6, 5.4 Hz, H3, H3′), 3.37 (s, 6H, OC*H*$_3$-4′, OC*H*$_3$-4″), 3.36–3.32 (m, 2H, H2‴, H3‴), 3.30 (dd, 2H, *J* 13.3, 6.0 Hz, H7′, H7″), 2.99 (dd, 2H, *J* 13.3, 2.4 Hz, H7′, H7″), 2.67–2.57 (m, 2H, H4, H4′), 2.37–2.32 (m, 2H, H4, H4′), 2.18 (dt, 2H, *J* 14.1, 4.8 Hz, H2‴, H3‴). ^{13}C NMR: δ 171.5 (*C*O), 147.8 (C5′, C5″), 147.4 (C7, C7′), 147.3 (C6, C6′), 145.9 (C4′, C4″), 133.3 (C8a, C8a′), 129.4 (CH-2″, CH-3″), 128.3 (C4a, C4a′), 127.6 (C1′, C1″), 127.3 (C2′, C2″), 114.4 (CH-8, CH-8′), 112.9 (CH-3′, CH-3″), 111.3 (CH-6′, CH-6″), 110.8 (CH-5, CH5′), 56.0 (O*C*H$_3$-5′, O*C*H$_3$-5″, O*C*H$_3$-7, O*C*H$_3$-7′), 55.8 (O*C*H$_3$-6, O*C*H$_3$-6′), 55.3 (O*C*H$_3$-4′, O*C*H$_3$-4″), 55.0 (CH-1, CH-1′), 41.7 (CH_2-3, CH_2-3′), 37.9 (CH_2-7′, CH_2-7″), 31.5 (CH_2-1″, CH_2-4″), 28.3 (CH_2-2‴, CH_2-3‴), 28.1 (CH_2-4, CH_2-4′).

*Compound **24-b***. R_f: 0.66 (CH_3OH/EtOAc (2:8)). ^1H NMR of the major rotamer: δ 6.81 (s, 2H, H3′, H3″), 6.69 (s, 2H, H5, H5′), 6.59 (s, 2H, H6′, H6″), 5.88 (s, 2H, H8, H8′), 5.43 (dd, 2H, *J* 9.0, 3.6 Hz, H1, H1′), 5.29 (t, 2H, *J* 8.4 Hz, H2″, H3″), 4.22–4.17 (m, 2H, H3, H3′), 3.85 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″), 3.83 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-7′), 3.80–3.76 (m, 2H, H3, H3′), 3.60 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.59 (s, 6H, OC*H*$_3$-4′, OC*H*$_3$-4″), 3.59–3.51 (m, 2H, H1″, H4″), 3.12–3.04 (m, 2H, H1″, H4″), 2.94–2.86 (m, 4H, H7′, H7″), 2.75–2.65 (m, 2H, H4, H4′), 2.52–2.47 (m, 2H, H4, H4′), 2.35–2.26 (m, 4H, H2‴, H3‴). ^1H NMR of the minor rotamer (in part): δ 6.77 (s, 2H, H3′, H3″), 6.63 (s, 2H, H5, H5′), 6.18 (s, 2H, H6′, H6″), 6.11 (s, 2H, H8, H8′), 5.60–5.58 (m, 4H, H1, H1′, H2″, H3″), 4.60–4.57 (m, 2H, H3, H3′), 4.22–4.17 (m, 2H, H3, H3′), 3.90 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″), 3.87 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-7′), 3.78 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.48 (s, 6H, OC*H*$_3$-4′, OC*H*$_3$-4), 2.80–2.76 (m, 4H,

H7′, H7″), 2.64–2.62 (m, 2H, H4, H4′), 2.39–2.62 (m, 2H, H4, H4′). ^{13}C NMR of the major rotamer: δ 171.7 (*C*O), 148.5 (C5′, C5″), 146.8 (C7, C7′), 147.0 (C6, C6′), 147.8 (C4′, C4″), 132.2 (C8a, C8a′), 128.6 (CH-2″, CH-3″), 128.3 (C4a, C4a′), 128.1 (C1′, C1″), 128.0 (C2′, C2″), 115.5 (CH-8, CH-8′), 112.2 (CH-3′, CH-3″), 110.6 (CH-6′, CH-6″), 110.0 (CH-5, CH5′), 56.0 (O*C*H$_3$-5′, O*C*H$_3$-5″, O*C*H$_3$-7, O*C*H$_3$-7′), 55.8 (O*C*H$_3$-6, O*C*H$_3$-6′), 55.3 (O*C*H$_3$-4′, O*C*H$_3$-4″), 54.8 (CH-1, CH-1′), 41.5 (CH$_2$-3, CH$_2$-3′), 39.7 (CH$_2$-7′, CH$_2$-7″), 31.8 (CH$_2$-1″, CH$_2$-4″), 29.8 (CH$_2$-2‴, CH$_2$-3‴), 27.0 (CH$_2$-4, CH$_2$-4′). ^{13}C NMR of the minor rotamer (in part): δ 132.4 (C8a, C8a′), 128.7 (CH-2″, CH-3″), 128.2 (C4a, C4a′), 111.8 (CH-3′, CH-3″), 36.1 (CH$_2$-3, CH$_2$-3′), 35.0 (CH$_2$-7′, CH$_2$-7″), 26.2 (CH$_2$-4, CH$_2$-4′). MS (ESI$^+$): *m*/*z* 821.5 (MH$^+$, 20%). HRMS (ESI$^+$): calcd for $C_{46}H_{57}N_2O_{10}$ 821.4013 (MH$^+$), found 821.4033.

3.15. (1*RS*,1′*RS*) and (*R*,*S*) (*Z*) or (*E*) 1,10-(1,2)-Di-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolina)-3,8-(1,2)-di-(3,4-dimethoxy)benzenacyclotetradeca-5-phene (4-b)

To a slurry of $LiAlH_4$ (13 mg, 0.348 mmol) in THF (1 mL) at 0 °C under a N_2 atmosphere was added a solution of the amide **24-b** (24 mg, 0.029 mmol) in dry THF (1 mL). The resulting mixture was brought to rt and was stirred for 24 h. The solution was treated subsequently with H_2O (0.14 mL), 1 M NaOH (0.14 mL) and H_2O (0.46 mL). The mixture was left to stir for 1 h. The solids were filtered and washed with EtOAc. The solution was dried ($MgSO_4$) and then concentrated in vacuo to give **4-b** (18 mg, 78%) as a white oil of >95% purity from NMR and TLC analysis. R_f 0.06 (CH_3OH/EtOAc (2:8)). ^{1}H NMR: δ 6.82 (s, 2H, H3′, H3″), 6.56 (s, 2H, H5, H5′), 6.13 (s, 2H, H6′, H6″), 5.83 (s, 2H, H8, H8′), 5.68 (t, 2H, *J* 4.2 Hz, H2″, H3″), 3.85 (s, 6H, OC*H*$_3$-5′, OC*H*$_3$-5″), 3.82 (s, 6H, OC*H*$_3$-7, OC*H*$_3$-7′), 3.71–3.66 (m, 6H, H1″, H4″ and H1, H1′), 3.60 (s, 6H, OC*H*$_3$-6, OC*H*$_3$-6′), 3.51 (s, 6H, OC*H*$_3$-4′, OC*H*$_3$-4″), 3.30–3.24 (m, 4H, H3, H3′, H7′, H7″), 2.84 (dd, 2H, *J* 10.8, 4.2 Hz, H3, H3′), 2.75 (dd, 2H, *J* 13.2, 9.0 Hz, H7′, H7″), 2.60–2.56 (m, 4H, H1‴, H4‴), 2.46–2.38 (m, 4H, H4, H4′), 1.58–1.54 (m, 4H, H2‴, H3‴). ^{13}C NMR: δ 147.5 (C5′, C5″), 147.3 (C7, C7′), 146.3 (C6, C6′), 145.2 (C4′, C4″), 131.4 (C1′, C1″), 130.1 (C2′, C2″, CH-2″, CH-3″), 129.0 (C4a, C4a′), 126.1 (C8a, C8a′), 115.46 (CH-6′, CH-6″), 112.5 (CH-3′, CH-3″), 112.0 (CH-8, CH-8′), 111.4 (CH-5, CH-5′), 62.1 (CH-1, CH-1′), 56.1 (OCH$_3$-5′, OCH$_3$-5″), 55.8 (OCH$_3$-7, OCH$_3$-7′, OCH$_3$-6, OCH$_3$-6′), 55.5 (OCH$_3$-4′, OCH$_3$-4″), 52.7 (CH$_2$-1‴, CH$_2$-4‴), 43.1 (CH$_2$-3, CH$_2$-3′), 40.8 (CH$_2$-7′, CH$_2$-7″), 30.6 (CH$_2$-1″, CH$_2$-4″), 25.4 (CH$_2$-2‴, CH$_2$-3‴), 23.7 (CH$_2$-4, CH$_2$-4′). MS (ESI$^+$): *m*/*z* 793.5 (MH$^+$, 100%). HRMS (ESI$^+$): calcd for $C_{48}H_{61}N_2O_8$ 793.4428 (MH$^+$), found 793.4393.

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