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The synthesis of 2′,2′-bis-benzylisoquinolines and their cytostatic activities

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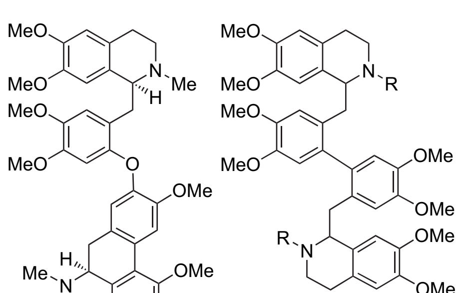
Abstract—The novel laudanosine dimers in which two laudanosine units are linked via a C-2′ biaryl bond have been prepared by a sequence that involves formation of the biaryl bond first and then formation of the isoquinoline rings. Two of these compounds showed higher cytostatic activity on three cancer cell lines than thalicarpine.

1. Introduction

Over 200 bis-benzylisoquinoline 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 bis-benzylisoquinoline alkaloids show a range of interesting biological activities.[1] The related *Thalictrum* alkaloid, thalicarpine **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 **2** and **3**, in which two laudanosine units are linked via a C-2′ biaryl bond, and an examination of their cytostatic activities on cancer cell lines. This paper describes the successful synthesis of *rac*- and *meso*-**2** and a single diastereomer of **3** and their cytostatic activities on three cancer cell lines.

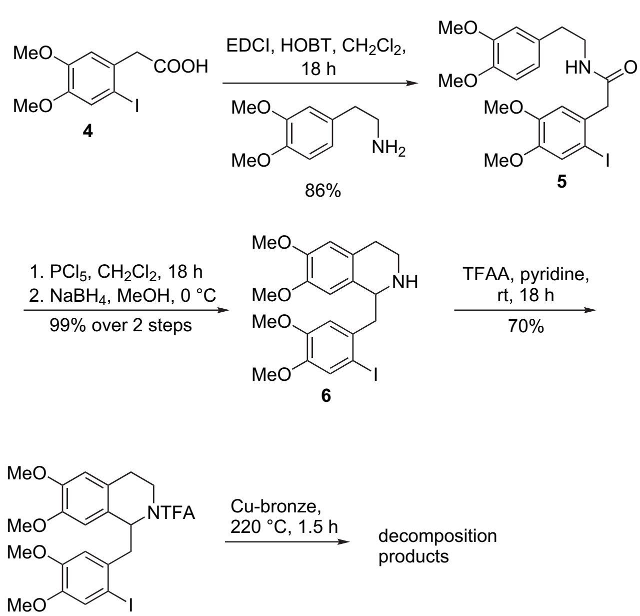


1

2, R = H
3, R = Me

2. Results and discussion

Our initial approach to the target molecules **2** and **3** is shown in Scheme 1 and was based on an Ullmann coupling reaction of *N*-trifluoroacetyl-2′-iodonorlaudanosine **7**, to deliver the



Scheme 1.

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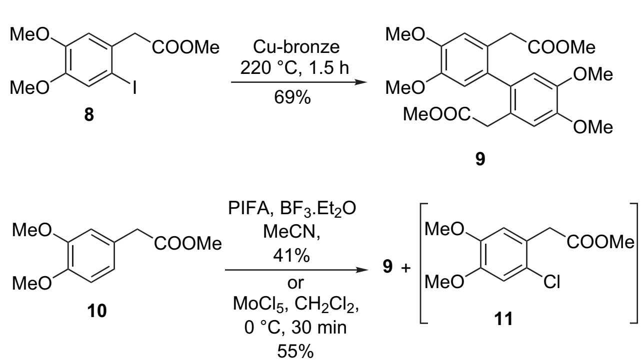
desired biaryl coupled product. The key compound **7** was prepared from the known compound, 2-iodo-4,5-dimethoxyphenylacetic acid **4**[10] as shown in Scheme 1, using standard procedures. The Bischler–Napieralski cyclisation of **5** was carried out efficiently using PCl_5 in CH_2Cl_2 according to the procedure of Ziolkowski and Czarnocki[11] Surprisingly the amide **5** has only been reported once and not in a readily accessible journal.[12] The iodides **6** and **7** are new compounds, while the corresponding 2′-bromo analogues of these compounds are known.[13] Heating compound **7**, or its corresponding 2′-bromo derivative, in the presence of copper-bronze at 220 °C under solvent free conditions for 1.5 h leads to quantitative decomposition of the material and no recognisable products could be isolated.

An alternative and successful synthesis of **2** and **3** is shown in Scheme 3, which involved formation of the key biaryl bond early in the synthesis and then construction of the isoquinoline rings. To this end several methods to prepare the known biphenyl **9**[13–15] were examined (Scheme 2). Under traditional Ullmann coupling reaction conditions,[13] heating compound **8** in the presence of copper-bronze at 220 °C under solvent free conditions for 1.5 h gave the desired biphenyl **9** in 69% yield. When the corresponding bromo analogue of **8** was employed the yield of **9** was reduced to 45% due to the formation of the debromo-derivative **10**. Alternatively, the biphenyl **9** could be obtained by direct oxidative coupling of **10** using phenyliodotrifluoroacetate (PIFA)/$BF_3 \cdot Et_2O$ in MeCN[16] or molybdenum(V) chloride ($MoCl_5$)[17]/4Å molecular sieves (MS) in yields of 41 and 55%, respectively. The latter method also produced the ring chlorinated product **11**, which was the major product in the absence of an HCl scavenger. For example, treatment of **10** with $MoCl_5$ alone has **11** in 50% yield and the desired biphenyl **9** in <10% yield. Although the addition of inorganic bases ($NaHCO_3$, NaH_2PO_4 or Na_2CO_3) reduced the amount of **11** formed to 20–40% the yield of the desired biphenyl **9** was still relatively low (10–20%). We found that the addition of 4 Å MS to the reaction mixture worked the best and suppressed the formation of **11** to 10% yield.

The biphenyl **9** was then taken through to the bis-benzylisoquinoline **2** as shown in Scheme 3 using the chemistry described in Scheme 1. The ^{1}H NMR resonances attributed to the methylene protons α to the carbonyl group of the bis-amide **13** appeared as an ABq at δ 3.23 (J_{AB}=15.3 Hz). Presumably the presence of the adjacent biaryl axis made these methylene protons diastereotopic. The Bischler–Napieralski



Scheme 2.

cyclisation of the bis-amide **13** using PCl_5 in CH_2Cl_2 gave the resulting bis-1,2-dihydro-isoquinoline **14** that was immediately reduced with sodium borohydride to give **2** as a 2:1 mixture of diastereomers (*rac*-**2** and *meso*-**2**, not necessarily respectively) in 67% yield. The bis-imine **14** was extremely unstable and if the Bischler–Napieralski cyclisation reaction was left for more than 2 h at rt total decomposition occurred. An alternative cyclisation procedure using triflic anhydride in the presence of DMAP was not successful.[18] The instability of symmetrical di-imines is not a new phenomenon,[19] however, even attempting sequential Bischler–Napieralski cyclisation and reduction of each amide according to the method of Czarnocki[19] failed to yield the desired compound. Whilst only a limited number of cyclisation conditions were studied, the PCl_5 cyclisation conditions seemed to be the best for this application.

The two isomers of **2** were readily separated by column chromatography and had NMR and ESI-MS spectral data consistent with their proposed structures. The major diastereomer of **2** was converted to **3** by reductive N-methylation in excellent yield (Scheme 3).

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 25 μM of the compounds, thalicarpine **1**, **2** (major diastereomer), **2** (minor diastereomer) and **3**. The results are presented in Table 1. Compound **3** (Table 1, entry 4) showed the weakest cytostatic activity on all cell lines, while both the major and minor diastereomers of **2** (Table 1, entries 2 and 3) showed stronger cytostatic activity than thalicarpine (entry 1). The IC_{50} of the major isomer of **2** was determined to be >40 μM on the same three cell lines, which indicated it had only modest cytotoxicity.

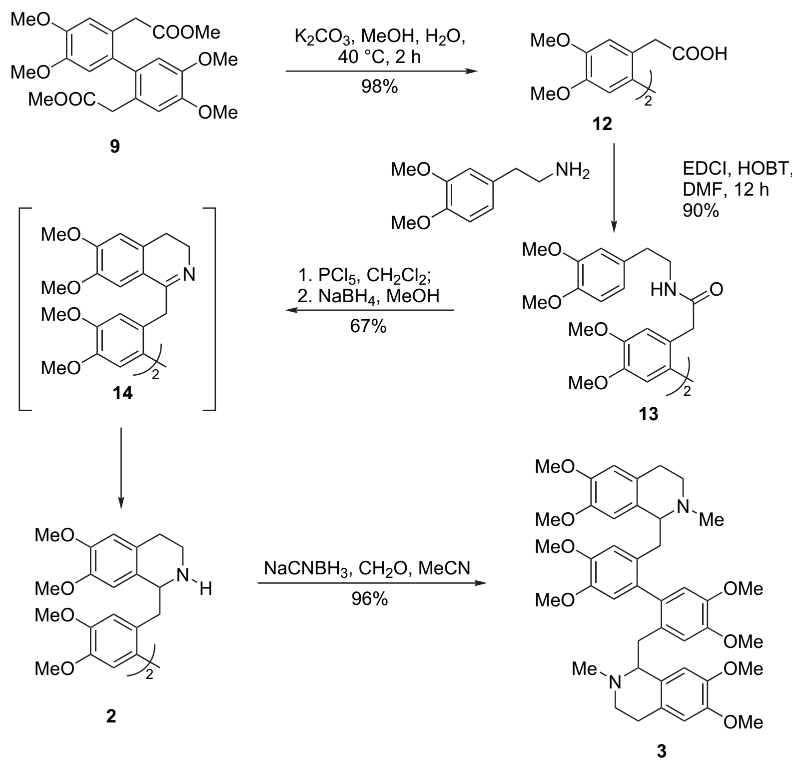
3. Conclusions

In conclusion, the novel laudanosine dimers **2** and **3**, in which two laudanosine units are linked via a C-2′ biaryl bond have been prepared by a sequence that involves formation of the biaryl bond first and then formation of the isoquinoline rings. The *rac*- and *meso*-forms of **2** were readily separated by column chromatography. Compound **3** showed the weakest cytostatic activity on three cancer cell lines, while both the major and minor diastereomers of **2** showed higher cytostatic activity than thalicarpine **1**.

4. Experimental

4.1. General

PS refers to the fraction of petroleum spirit with a boiling point of 40–60 °C. All ^{1}H NMR spectral analyses were performed at 300 MHz and all ^{13}C NMR (DEPT) spectral analyses 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



Scheme 3.

Table 1. Cytostatic studies on cancer cell lines

Entry	Compound	Percentage cell growth		
		H460	MCF-7	SF-268
1	**1**	15	63	54
2	**2** (Major)	0.8	16.4	40.9
3	**2** (Minor)	5.4	26.1	23.7
4	**3**	95	131	78

cases NOESY and TOCSY experiments. ^{13}C NMR assignments were based upon DEPT, gHSQC and gHMBC experiments. Compounds **4**,[10] **8**[20] and **10**[21] were prepared according to the literature.

4.1.1. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(2-iodo-4,5-dimethoxyphenyl)acetamide 5. Compound **4**[10] (1.11 g, 3.45 mmol), 2-[3,4-dimethoxyphenyl]ethylamine (1.45 mL, 8.62 mmol), HOBT (512 mg, 3.79 mmol) and EDCI (730 mg, 3.79 mmol) were dissolved in dry DMF (15 mL) under N_2 and the solution was stirred for 18 h at rt. The mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (2×20 mL). The extracts were combined, washed with H_2O (2×30 mL), dried ($MgSO_4$), filtered and evaporated. The title compound was isolated as a white solid (1.44 g, 86%) after purification by flash silica gel chromatography with CH_2Cl_2/EtOAc (3:1) as mobile phase. Mp 176–178 °C. ^{1}H NMR: δ 7.19 (s, 1H, Ar–*H*-3), 6.77 (s, 1H, Ar–*H*-6), 6.71 (d, 1H, *J*=8.1 Hz, Ar–*H*-5′), 6.64 (d, 1H, *J*=2.1 Hz, Ar–*H*-2′), 6.58 (dd, 1H, *J*=8.1, 2.1 Hz, Ar–*H*-6′), 5.41 (t, *J*=6.9 Hz, 1H, N*H*), 3.87 (s, 3H, OC*H*$_3$-4), 3.85 (s, 3H, OC*H*$_3$-4′), 3.84 (s, 3H, OC*H*$_3$-3′), 3.82 (s, 3H, OC*H*$_3$-5), 3.60 (s, 2H, Ar–C*H*$_2$), 3.47 (q, 2H, *J*=6.9 Hz, Ar–CH$_2$–C*H*$_2$–NH), 2.71 (t, 2H, *J*=6.9, Ar–C*H*$_2$–CH$_2$–NH). ^{13}C NMR: δ 169.6 (*C*=O), 149.6 (Ar–*C*–OCH$_3$-5), 149.0 (Ar–*C*–OCH$_3$-3′), 148.7 (Ar–*C*–OCH$_3$-4), 147.6 (Ar–*C*–OCH$_3$-4′), 130.9 (Ar–*C*-1), 130.5 (Ar–*C*-1′), 121.6 (Ar–*C*–H-3), 120.5 (Ar–*C*–H-6′), 113.0 (Ar–*C*–H-6), 111.7 (Ar–*C*–H-5′), 111.1 (Ar–*C*–H-2′), 88.8 (Ar–*C*-2), 56.1 (Ar–O*C*H$_3$), 55.9 (Ar–O*C*H$_3$), 55.84 (Ar–O*C*H$_3$), 55.81 (Ar–O*C*H$_3$), 48.1 (Ar–*C*H$_2$–CO), 40.6 (Ar–CH$_2$–*C*H$_2$–NH), 35.8 (Ar–*C*H$_2$–CH$_2$–NH). MS (EI$^+$): *m*/*z* 485 (M$^+$ 3%), 164 (100%); HRMS (EI$^+$): calcd for $C_{20}H_{24}INO_5$=485.0699 ($M^{\cdot+}$), found 485.0696.

4.1.2. (*R*,*S*)-1-[(2-Iodo-4,5-dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 6. PCl_5 (107 mg, 0.51 mmol) was added to a stirred solution of **5** (100 mg, 0.21 mmol) in dry CH_2Cl_2 (5 mL) and the resulting mixture stirred for 18 h at rt under an N_2 atmosphere. The solution was diluted with CH_2Cl_2 (10 mL), washed with satd aqueous $NaHCO_3$ (2×20 mL), dried over $MgSO_4$, filtered and evaporated. The resulting imine was dissolved in dry ice-cold MeOH (5 mL) and sodium borohydride (46 mg, 1.21 mmol) was added. The ice bath was removed and the mixture stirred at rt for 1 h. The solvent was evaporated under reduced pressure and the residue dissolved in CH_2Cl_2 (10 mL). The solution was washed with satd aqueous Na_2CO_3 solution (2×10 mL), dried (K_2CO_3), filtered and evaporated to yield the free amine as a white film (95 mg, 99%) that did not require further purification. ^{1}H NMR: δ 7.20 (s, 1H, Ar–*H*-3′), 6.72 (s, 1H, Ar–*H*-6′), 6.71 (s, 1H, Ar–*H*-5), 6.53 (s, 1H, Ar–*H*-8), 4.14 (dd, 1H, *J*=9.6, 4.2 Hz, Ar–*H*-1), 3.79 (s, 6H, OC*H*$_3$-6, 7), 3.77 (s, 3H, OC*H*$_3$-5′), 3.76 (s, 3H, OC*H*$_3$-4′), 3.19 (dd, 1H, *J*=14.1, 4.2 Hz, Ar–C*H*$_a$–CH–), 2.91–2.84 (m, 3H, Ar–CH$_2$–C*H*$_2$–NH, Ar–C*H*$_b$–CH–), 2.70 (d, 2H, *J*=12.9, 6.3, Ar–C*H*$_2$–CH$_2$–NH). ^{13}C NMR: δ 149.4 (Ar–*C*–OCH$_3$-5′), 148.5 (Ar–*C*–OCH_3-4′), 147.8 (Ar–*C*–OCH_3-7), 147.3 (Ar–*C*–OCH_3-6), 134.1 (Ar–*C*-8a), 129.9 (Ar–*C*-4a), 127.2 (Ar–*C*-1′), 122.0 (Ar–*C*–H-6′), 114.0 (Ar–*C*–H-3′), 111.9 (Ar–*C*–H-5), 109.9 (Ar–*C*–H-8), 89.0 (Ar–*C*-2′), 56.4 (Ar–OCH_3-6), 56.2 (Ar–OCH_3-7), 56.1 (Ar–OCH_3-5′), 56.0 (Ar–OCH_3-4′), 55.5 (*C*-1), 47.0 (Ar–*C*H–NH), 40.7 (Ar–CH_2–CO, Ar–CH_2–CH_2–NH), 29.4 (Ar–CH_2–CH_2–NH). MS (EI^+): *m/z* 469 (M^+ 6%), 340 (100%); HRMS (CI^+): calcd for $C_{20}H_{25}INO_4$=470.0828 (M+H^+), found 470.0825.

4.1.3. (*R*,*S*)-1-[(2-Iodo-4,5-dimethoxyoxophenyl)methyl]-2-trifluoroacetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 7. Compound **6** (95 mg, 0.20 mmol) was dissolved in dry pyridine (2 mL) and trifluoroacetic anhydride (1.5 mL) was added. The solution was stirred for 18 h at rt. The mixture was diluted and stirred with 1 M HCl solution (10 mL) for 30 min, then extracted with CH_2Cl_2 (2×20 mL). The extracts were washed with satd aqueous $NaHCO_3$ solution (2×20 mL), dried ($MgSO_4$), filtered and evaporated. Purification by flash silica gel chromatography with EtOAc/PS (1:1) as mobile phase yielded the title compound as an orange film (81 mg, 70%). ^{1}H NMR: δ 7.19 (s, 1H, Ar–*H*-3′), 6.65 (s, 1H, Ar–*H*-6′), 6.60 (s, 1H, Ar–*H*-5), 6.52 (s, 1H, Ar–*H*-8), 5.71 (dd, 1H, *J*=8.1, 6.3 Hz, *H*-1), 4.05–4.01 (m, 1H, Ar–CH_2–CH_a–$NCOCF_3$), 3.86 (s, 3H, OCH_3-6), 3.84 (s, 3H, OCH_3-7), 3.78 (s, 3H, OCH_3-5′), 3.74 (s, 3H, OCH_3-4′), 3.70 (d, 1H, *J*=5.7 Hz, Ar–CH_2–CH_b–$NCOCF_3$), 3.26 (dd, 1H, *J*=14.0, 6.3 Hz, Ar–CH_a–CH), 3.25 (dd, 1H, *J*=14.0, 8.1 Hz, Ar–CH_b-CH), 3.02–2.91 (m, 1H, Ar–CH_a–CH_2–$NCOCF_3$), 2.79 (dt, 1H, *J*=15.9, 3.9 Hz, Ar–CH_b–CH_2–$NCOCF_3$). ^{13}C NMR: δ (*C*=O not observed) 149.4 (Ar–*C*–OCH_3-6), 148.7 (Ar–*C*–OCH_3-5′), 148.5 (Ar–*C*–OCH_3-7), 147.9 (Ar–*C*–OCH_3-4′), 132.3 (Ar–*C*-1′), 126.6 (Ar–*C*-4a), 125.1 (Ar–*C*-8a), 121.7 (Ar–*C*–H-3′), 116.8 (q, *J*=284.1 Hz, $NCOCF_3$), 113.1 (Ar–*C*–H-6′), 111.2 (Ar–*C*–H-5), 110.4 (Ar–*C*–H-8), 89.8 (Ar–*C*-2′), 56.3 (Ar–OCH_3-6), 56.2 (Ar–OCH_3-7), 56.1 (Ar–OCH_3-5′), 56.0 (Ar–OCH_3-4′), 54.5 (Ar–*C*H–$NCOCF_3$), 45.6 (Ar–CH_2–CH_2–$NCOCF_3$), 40.4 (Ar–CH_2–CH), 28.9 (Ar–CH_2–CH_2–$NCOCF_3$). MS (EI^+): *m/z* 565 (M^+ 4%), 288 (100%); HRMS (EI^+): calcd for $C_{22}H_{23}IF_3NO_5$=565.0573 ($M^{\cdot+}$), found 565.0576.

4.1.4. Dimethyl 2,2′-(4,4′,5,5′-tetramethoxybiphenyl-2,2′-diyl)diacetate 9. *Method 1*. To a solution of **10**[21] (129 mg, 0.62 mmol) and PIFA (250 mg, 0.58 mmol) in dry MeCN (10 mL) at 0 °C under N_2 was added $BF_3\cdot Et_2O$ (150 µL). After 10 min the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2×20 mL). The extracts were combined, washed with satd aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered and evaporated. Purification by flash silica gel chromatography using EtOAc/PS (3:7) as the eluent yielded the title compound as clear crystals (53 mg, 41%).

Method 2. The title compound was also prepared in 55% yield (clear crystals, 110 mg) by stirring **10**[21] (200 mg, 0.95 mmol) in dry CH_2Cl_2 (20 mL) with powdered molecular sieves (4 Å, 500 mg) for 30 min and cooling the mixture to 0 °C. $MoCl_5$ (570 mg, 2.11 mmol) was added to the reaction mixture and stirring was continued at 0 °C for 2 h after which the mixture was diluted with water (15 mL) and extracted with DCM (2×20 mL). The extracts were combined, washed with satd aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered and evaporated. Purification by flash silica gel chromatography using EtOAc/PS (3:7) as the eluent yielded the title compound.

Method 3. The title compound was also prepared in 69% yield (clear crystals, 172 mg) by heating **8**[20] (200 mg, 0.60 mmol) with freshly activated copper-bronze[22] (200 mg) in a Wheaton vial at 220 °C for 1.5 h. The heat was removed and the mixture suspended in EtOAc (50 mL), filtered and the solvent evaporated. The title compound was purified by flash silica gel chromatography using EtOAc/PS (3:7) as the eluent.

Mp 142–144 °C (lit.[20] mp 145 °C). ^{1}H NMR: δ 6.84 (s, 2H, Ar–*H*-6), 6.72 (s, 2H, Ar–*H*-3), 3.92 (s, 6H, OCH_3-5), 3.83 (s, 6H, OCH_3-4), 3.60 (s, 6H, CO_2CH_3), 3.35 (ABq, 4H, *J*=16.5 Ar–CH_2). ^{13}C NMR: δ 172.4 (*C*=O), 148.1 (Ar–*C*–OCH_3-4), 147.4 (Ar–*C*–OCH_3-5), 132.8 (Ar–*C*-1), 124.6 (Ar–*C*-2), 113.2 (Ar–*C*–H-3), 112.5 (Ar–*C*–H-6), 55.8 (Ar–OCH_3), 55.7 (Ar–OCH_3), 51.8 (CO_2CH_3), 37.9 (Ar–CH_2). MS (CI^+): *m/z* 419 (M+H, 100%); HRMS (EI^+): calcd for $C_{22}H_{26}O_8$=418.1627 ($M^{\cdot+}$), found 418.1615.

4.1.5. 2,2′-(4,4′,5,5′-Tetramethoxybiphenyl-2,2′-diyl)-diacetic acid 12. Compound **9** (150 mg, 0.36 mmol) was dissolved in methanol (2 mL) and added to a 40 °C stirred solution of K_2CO_3 (99 mg, 0.72 mmol) in H_2O (2 mL). After 2 h the reaction was removed from the heat and the methanol evaporated. The aqueous residue was acidified with 10% aqueous HCl solution to pH 1, extracted with CH_2Cl_2 (2×20 mL), dried ($MgSO_4$), filtered and evaporated to dryness to yield the title compound as a white solid (137 mg, 98%). No further purification was required. Mp 228–230 °C (lit.[20] 228–230 °C). ^{1}H NMR: δ 9.72 (br s, 1H, COO*H*), 6.77 (s, 1H, Ar–*H*-3), 6.60 (s, 1H, Ar–*H*-6), 3.89 (s, 3H, OCH_3-5), 3.82 (s, 3H, OCH_3-4), 3.45 (ABq, 2H, *J*=17.7 Ar–CH_2–CO). ^{13}C NMR: δ 179.1 (*C*=O), 148.3 (Ar–*C*–OCH_3-4), 147.7 (Ar–*C*–OCH_3-5), 132.9 (Ar–*C*-1), 124.5 (Ar–*C*-2), 113.1 (Ar–*C*–H-6), 112.8 (Ar–*C*–H-3), 55.9 (Ar–OCH_3), 55.8 (Ar–OCH_3), 37.3 (Ar–CH_2–COOH). MS (ESI−): *m/z* 389 (M^-, 37%), 114 (100%); HRMS (ESI−): calcd for $C_{20}H_{21}O_8$=389.1236 (M^-), found 389.1218.

4.1.6. *N*,*N*′-Di-[2-(3,4-dimethoxyphenyl)ethyl]-2,2′-(4,4′,5,5′-tetramethoxybiphenyl-2,2′-diyl)diacetamide 13. The diacid **12** (130 mg, 0.33), 2-[3,4-dimethoxyphenyl]-ethylamine (0.28 mL, 1.65 mmol), HOBT (99 mg, 0.73 mmol) and EDCI (128 mg, 0.66 mmol) were dissolved in dry DMF (6 mL) under N_2 and the solution was stirred for 18 h at rt. The mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (2×20 mL). The extracts were combined, washed with H_2O (2×30 mL), dried ($MgSO_4$), filtered and evaporated. The title compound was isolated as a white solid (214 g, 90%) after purification by flash silica gel chromatography with CH_2Cl_2/EtOAc (3:1) as mobile phase. Mp 162–164 °C. ^{1}H NMR: δ 6.81 (s, 1H, Ar–*H*-3′), 6.72 (d, 1H, *J*=8.1 Hz, Ar–*H*-5), 6.63 (d, 1H, *J*=2.1 Hz, Ar–*H*-2), 6.58 (s, 1H, Ar–*H*-6′), 6.55 (dd, *J*=8.1, 2.1 Hz, Ar–*H*-6), 5.78 (t, 1H, *J*=5.4 Hz, N*H*), 3.87 (s, 3H, OCH_3-4′), 3.85 (s, 3H, OCH_3-4), 3.81 (s, 3H, OCH_3-3), 3.80 (s, 3H, OCH_3-5′), 3.35 (dt, 2H, *J*=6.9, 5.4 Hz, Ar–CH_2–CH_2–

NH), 3.23 (ABq, 2H, *J*=15.3 Ar–CH_2–CO), 2.66 (t, 2H, *J*=6.9, Ar–CH_2–CH_2–NH). ^{13}C NMR: δ 171.1 (*C*=O), 148.9 (Ar–*C*–OCH_3-5′), 148.5 (2×Ar–*C*-OCH_3-4,4′), 147.6 (Ar–*C*–OCH_3-5), 132.6 (Ar–*C*-2′), 131.0 (Ar–*C*-1), 125.7 (Ar–*C*-1′), 120.5 (Ar–*C*–H-6), 113.2 (Ar–*C*–H-6′), 112.4 (Ar–*C*–H-3′), 111.6 (Ar–*C*–H-2), 111.1 (Ar–*C*–H-5), 56.0 (Ar–OCH_3), 55.9 (Ar–OCH_3), 55.8 (Ar–OCH_3), 55.7 (Ar–OCH_3), 40.8 (Ar–CH_2–CH_2–NH), 40.6 (Ar–CH_2–CO), 34.9 (Ar–CH_2–CH_2–NH). MS (ES$^+$): *m*/*z* 717 (M+H, 30%), 288 (100%); HRMS (ESI$^+$): calcd for $C_{40}H_{49}N_2O_{10}$=717.3387 (MH$^+$), found 717.3402.

4.1.7. (1*RS*,1‴*RS*) and (1*R*,1‴*S*)-2,2′-[Di-{(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl}]-4,4′,5,5′-biphenyl 2. PCl_5 (87 mg, 0.42 mmol) was added to a stirred solution of compound **13** (50 mg, 0.07 mmol) in dry CH_2Cl_2 (2 mL) and the resulting mixture stirred for 2 h at rt under an N_2 atmosphere. The solution was diluted with CH_2Cl_2 (10 mL), washed with satd aqueous $NaHCO_3$ (2×20 mL), dried ($MgSO_4$), filtered and evaporated. The resulting imine was dissolved in dry ice-cold MeOH (5 mL) and sodium borohydride (8 mg, 0.2 mmol) was added. The ice bath was removed and the mixture stirred at rt for 1 h. The solvent was evaporated under reduced pressure and the residue dissolved in CH_2Cl_2 (10 mL). The solution was washed with satd aqueous Na_2CO_3 solution (2×10 mL), dried (K_2CO_3), filtered and evaporated. The crude mixture was separated by column chromatography using CH_2Cl_2/EtOH/MeOH/NH_3 (10:5:1:0.1) as the eluent to yield pure samples of the major isomer as a white solid (20 mg, 42%, R_f 0.2) and the minor isomer as a white solid (12 mg, 25%, R_f 0.4); reflecting a combined yield of 67% for both diastereomers.

Major isomer. ^{1}H NMR (the individual methoxy signals could not be assigned unequivocally): δ 6.94 (s, 1H, Ar–*H*-3′), 6.46 (s, 1H, Ar–*H*-6′), 6.26 (s, 1H, Ar–*H*-5), 6.05 (s, 1H, Ar–*H*-8), 4.06–3.93 (m, 1H, *H*-1), 3.83 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.26–3.16 (m, 2H, Ar–CH_2–CH), 3.11–2.96 (m, 2H, Ar–CH_2–CH_2–NH), 2.91–2.70 (m, 2H, Ar-CH_2-CH_2-NH). ^{13}C NMR: δ 148.7 (Ar–*C*–OCH_3-5′), 148.1 (Ar–*C*–OCH_3-4′), 147.9 (Ar–*C*–OCH_3-7), 147.4 (Ar–*C*–OCH_3-6), 135.4 (Ar–*C*-1′), 134.3 (Ar–*C*-2′), 133.0 (Ar–*C*-4a), 123.9 (Ar–*C*-8a), 113.9 (Ar–*C*–H-3′), 112.6 (Ar–*C*–H-6′), 111.1 (Ar–*C*–H-8), 110.7 (Ar–*C*–H-5), 56.0 (Ar–OCH_3), 55.8 (Ar–OCH_3), 55.7 (Ar–OCH_3), 55.5 (Ar–OCH_3), 51.9 (*C*-1), 40.1 (Ar–CH_2–CH), 37.4 (Ar–CH_2–CH_2–NH), 25.0 (Ar–CH_2–CH_2–NH). MS: *m*/*z* (ES$^+$) 685 (M+H, 100%); HRMS (ES$^+$): calcd for $C_{40}H_{49}N_2O_8$=684.3489, found 684.3480.

Minor isomer. ^{1}H NMR: δ 6.83 (s, 1H, Ar–*H*-3′), 6.42 (s, 1H, Ar–*H*-6′), 6.09 (s, 1H, Ar–*H*-5), 5.79 (s, 1H, Ar–*H*-8), 3.97–3.87 (m, 1H, *H*-1), 3.80 (s, 3H, OCH_3-4′), 3.73 (s, 3H, OCH_3-5′), 3.72 (s, 3H, OCH_3-7), 3.65 (s, 3H, OCH_3-6), 3.10–2.82 (m, 2H, Ar–CH_2–CH), 2.74–2.67 (m, 2H, Ar–CH_2–CH_2–NH), 2.65–2.58 (m, 2H, Ar–CH_2–CH_2–NH). ^{13}C NMR: δ 148.1 (Ar–*C*–OCH_3-5′), 147.2 (Ar–*C*–OCH_3-4′), 147.1 (Ar–*C*–OCH_3-7), 146.9 (Ar–*C*–OCH_3-6), 133.4 (Ar–*C*-1′), 133.2 (Ar–*C*-2′), 129.4 (Ar–*C*-4a), 126.5 (Ar–*C*-8a), 113.6 (Ar–*C*–H-3′), 112.9 (Ar–*C*–H-6′), 111.4 (Ar–*C*–H-8), 109.3 (Ar–*C*–H-5), 56.1 (*C*-1), 55.9 (Ar–OCH_3), 55.8 (Ar–OCH_3), 55.7 (Ar–OCH_3), 55.6 (Ar–OCH_3), 39.3 (Ar–CH_2–CH), 39.2 (Ar–CH_2–CH_2–NH), 29.5 (Ar–CH_2–CH_2–NH). MS: *m*/*z* (ESI$^+$) 685 (M+H, 100%); HRMS (ESI$^+$): calcd for $C_{40}H_{49}N_2O_8$=685.3489, found 685.3480.

4.1.8. (1*RS*,1′*RS*),(1*R*,1′*S*),*PM*-2,2′-[Di-{(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolin-1-yl)methyl}]-4,4′,5,5′-biphenyl 3. The major isomer of **2** (8.6 mg) was dissolved in dry MeCN (0.5 mL) to which sodium cyanoborohydride (15 mg), 28% formaldehyde solution (0.2 mL) and acetic acid (two drops) were added and the solution was stirred for 3 h. The reaction was diluted with CH_2Cl_2 (10 mL), washed with satd aqueous $NaHCO_3$ solution (2×10 mL), dried over anhydrous K_2CO_3, filtered and evaporated. Purification by silica gel chromatography using CH_2Cl_2/EtOAc/MeOH/NH_3 (10:5:1:trace) as the eluent afforded the title compound as an opaque film (9 mg, 96%). ^{1}H NMR: δ 6.81 (s, 1H, Ar–*H*-3′), 6.38 (s, 1H, Ar–*H*-6′), 6.07 (s, 1H, Ar–*H*-5), 5.60 (s, 1H, Ar–*H*-8), 3.79 (s, 3H, OCH_3-4′), 3.70 (s, 3H, OCH_3-5′), 3.61 (s, 3H, OCH_3-7), 3.51 (s, 3H, OCH_3-6), 3.38 (s, 1H, *H*-1), 2.97–2.80 (m, 2H, Ar–CH_2–CH), 2.77–2.63 (m, 2H, Ar–CH_2–CH_2–NCH_3), 2.57–2.30 (m, 2H, Ar–CH_2–CH_2–NCH_3), 2.27 (s, 3H, NCH_3). ^{13}C NMR: δ 148.0 (Ar–*C*–OCH_3-5′), 147.5 (Ar–*C*–OCH_3-4′), 147.1 (Ar–*C*–OCH_3-7′), 146.6 (Ar–*C*–OCH_3-6′), 133.7 (Ar–*C*-1′), 130.0 (Ar–*C*-2), 126.0 (Ar–*C*-4a), 125.4 (Ar–*C*-8a), 113.4 (Ar–*C*–H-6′), 113.1 (Ar–*C*–H-3′), 111.2 (Ar–*C*–H-5), 110.7 (Ar–*C*–H-8), 64.1 (*C*-1), 56.2 (Ar–OCH_3), 56.1 (Ar–OCH_3), 56.0 (Ar–OCH_3), 55.8 (Ar–OCH_3), 45.7 (Ar–CH_2–CH), 42.9 (NCH_3), 37.6 (Ar–CH_2–CH_2–NCH_3), 24.2 (Ar–CH_2–CH_2–NCH_3). MS: *m*/*z* (ESI$^+$) 713 (MH$^+$, 100%); HRMS (ESI$^+$): calcd for $C_{42}H_{53}N_2O_8$=713.3802, found 713.3812.

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