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

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Keywords

synthesis, bis, benzylisoquinolines, their, cytostatic, activities, CMMB

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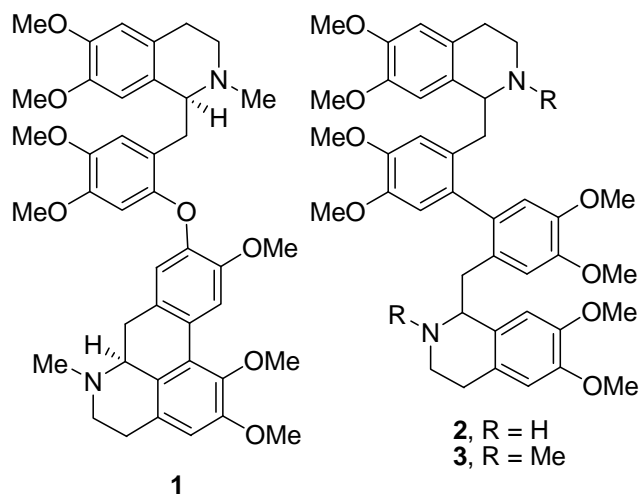
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Abstract: The novel laudanosine dimers in which two laudanosine units are linked *via* a C-2' biaryl bond have been prepared by a sequence that involves formation of the biaryl bond first and then formation of the isoquinoline rings. Two of these compounds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

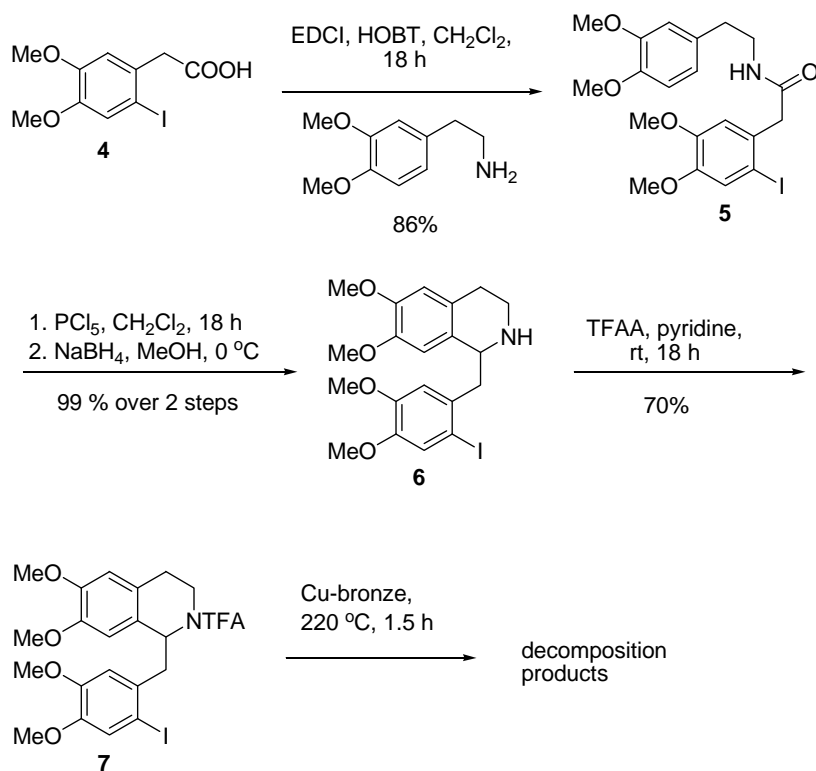
Over two hundred bisbenzylisoquinoline alkaloids are known, the majority of these have one or two ether linkages between the two benzylisoquinoline moieties.¹ However, a number of these alkaloids have one of the linking ether bonds replaced by a biphenyl linkage.² The bisbenzylisoquinoline alkaloids show a range of interesting biological activities.¹ The related *Thalictrum* alkaloid, thalicarpine **1**,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 trials 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 cytotoxicities 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.



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 desired bi-aryl coupled product. The key compound **7** was prepared as shown in Scheme 1 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 *et al.*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 lead to quantitative decomposition of the material and no recognisable products could be isolated.

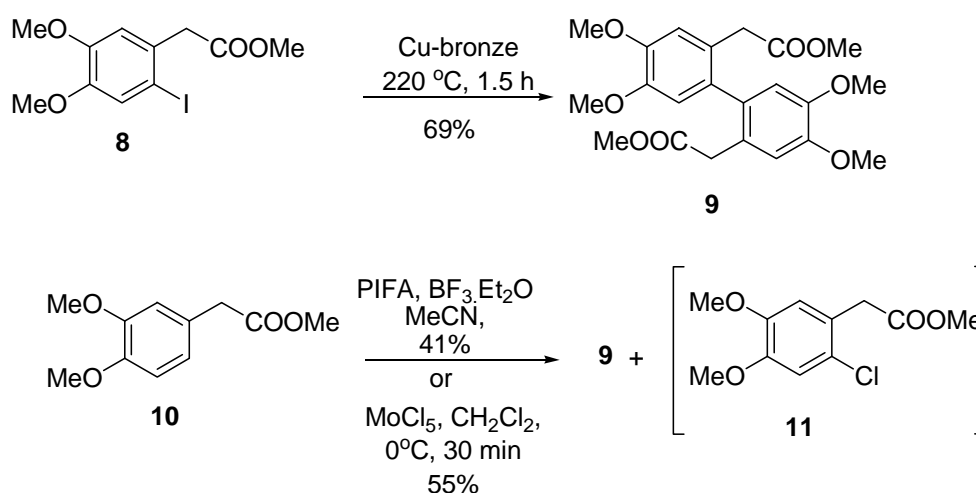
Scheme 1



An alternative and successful synthesis of **2** and **3** is shown in Scheme 3, this synthesis 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)/BF₃·Et₂O in MeCN¹⁶ or molybdenum (V) chloride (MoCl₅)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 a HCl scavenger. For example, treatment of **10** with MoCl₅ alone have **11** in 50% yield and the desired biphenyl **9** in <10 % yield. Although the addition of inorganic bases (NaHCO₃, NaH₂PO₄ or Na₂CO₃) 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 4Å MS to the reaction mixture worked the best and suppressed the formation of **11** to 10% yield.

Scheme 2

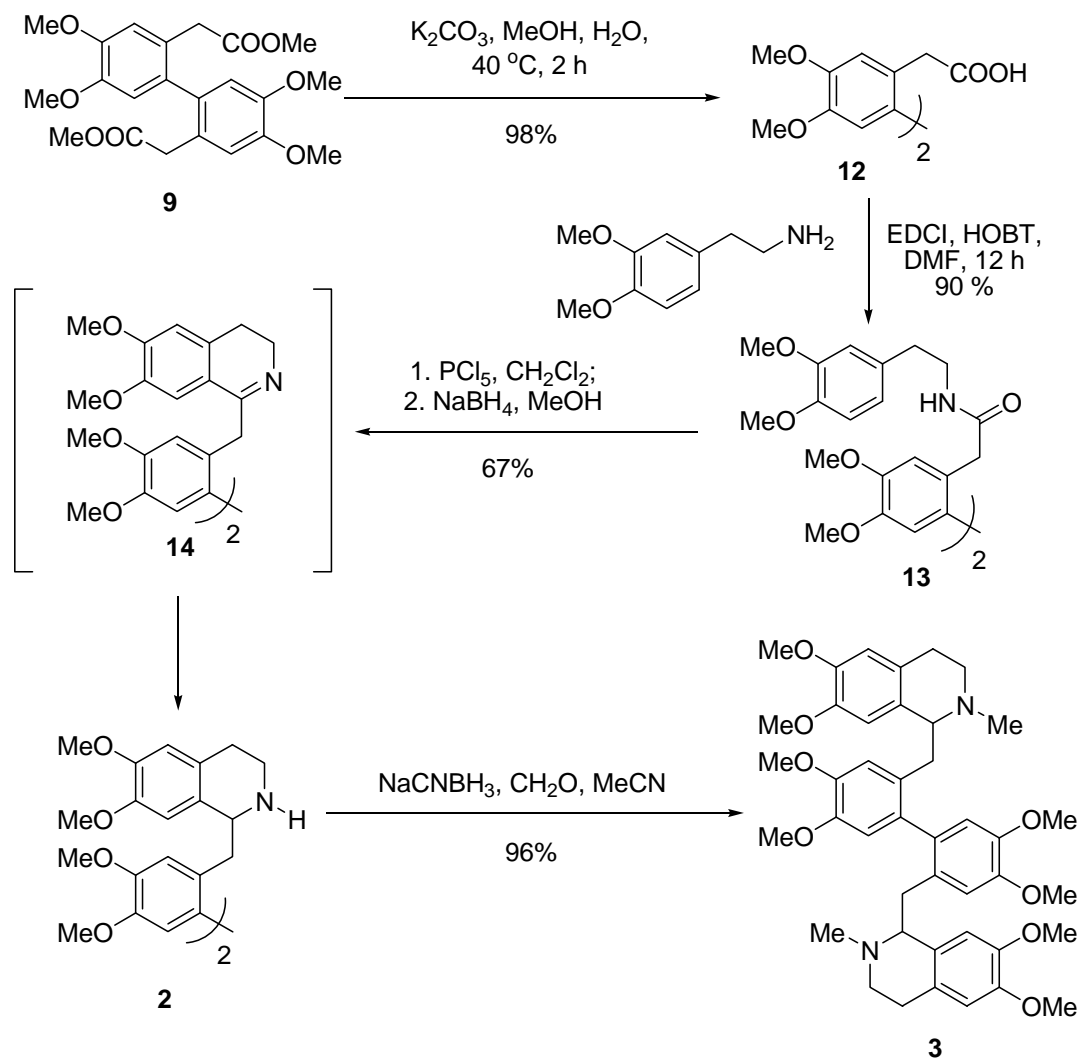


The biphenyl **9** was then taken through to the bis-benzylisoquinoline **2** as shown in Scheme 3 using the chemistry described in Scheme 1. The ¹H NMR resonances attributed to the methylene protons α to the carbonyl group of the bis-amide **13** appeared as an ABq at δ 3.23 (*J*_{AB} = 15.3 Hz). Presumably the presence of the adjacent biaryl axis made these methylene protons diastereotopic. The Bischler-Napieralski cyclisation of the the bis-amide **13** using PCl₅ in CH₂Cl₂ 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 longer than 2 h at rt total decomposition occurred. An alternative cyclization 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 Czarnocki¹⁹ failed to yield the desired compound. Whilst only a limited number of cyclization conditions were studied, the PCl_5 cyclization 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).

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 μ M of the compounds, thalicipine **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 IC₅₀ 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.

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

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 3 cancer cell lines, while both the major and minor diastereomers of **2** showed higher cytostatic activity than thalicarpine **1**.

EXPERIMENTAL

PS refers to the fraction of petroleum spirit with a boiling point of 40-60 °C. All ¹H NMR spectra were performed at 300 MHz and all ¹³C NMR (DEPT) spectra at 75 MHz in CDCl₃ solution, unless otherwise noted. All spectra were referenced to CDCl₃ (¹H δ 7.26 ppm and ¹³C NMR δ 77.00 ppm). ¹H NMR assignments were achieved with the aid of gCOSY, and in some cases NOESY and TOCSY experiments. ¹³C NMR assignments

were based upon DEPT, gHSQC and gHMBC experiments. Compounds **4**,¹⁰ **8**²⁰ and **10**²¹ were prepared according to the literature.

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 N₂ and the solution was stirred for 18 h at rt. The mixture was diluted with H₂O (30 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The extracts were combined, washed with H₂O (2 x 30 mL), dried (MgSO₄), filtered and evaporated. The title compound was isolated as a white solid (1.44 g, 86 %) after purification by flash silica gel chromatography with CH₂Cl₂:EtOAc (3:1) as mobile phase. M.P. 176-178 °C. ¹H 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, NH), 3.87 (s, 3H, OCH₃-4), 3.85 (s, 3H, OCH₃-4'), 3.84 (s, 3H, OCH₃-3'), 3.82 (s, 3H, OCH₃-5), 3.60 (s, 2H, Ar-CH₂), 3.47 (q, 2H, *J* = 6.9 Hz, Ar-CH₂-CH₂-NH), 2.71 (t, 2H, *J* = 6.9, Ar-CH₂-CH₂-NH). ¹³C NMR: δ 169.6 (C=O), 149.6 (Ar-C-OCH₃-5), 149.0 (Ar-C-OCH₃-3'), 148.7 (Ar-C-OCH₃-4), 147.6 (Ar-C-OCH₃-4'), 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-OCH₃), 55.9 (Ar-OCH₃), 55.84 (Ar-OCH₃), 55.81 (Ar-OCH₃), 48.1 (Ar-CH₂-CO), 40.6 (Ar-CH₂-CH₂-NH), 35.8 (Ar-CH₂-CH₂-NH). MS (EI⁺): *m/z* 485 (M⁺ 3 %), 164 (100 %), HRMS (EI⁺) Calcd for C₂₀H₂₄INO₅ = 485.0699 (M⁺), found 485.0696.

(R,S)*-1-[(2-Iodo-4,5-dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **6*

PCl₅ (107 mg, 0.51 mmol) was added to a stirred solution of **5** (100 mg, 0.21 mmol) in dry CH₂Cl₂ (5 mL) and the resulting mixture stirred for 18 h at rt under a N₂ atmosphere. The solution was diluted with CH₂Cl₂ (10 mL), washed with sat. aqueous NaHCO₃ (2 x 20 mL), dried over MgSO₄, 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 CH₂Cl₂ (10 mL). The solution was washed with saturated aqueous Na₂CO₃ solution (2 x 10 mL), dried (K₂CO₃), filtered and evaporated to yield the free amine as a white film (95 mg, 99 %) that did not require further purification. ¹H 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, OCH₃-6, 7), 3.77 (s, 3H, OCH₃-5'), 3.76 (s, 3H, OCH₃-4'), 3.19 (dd, 1H, *J* = 14.1, 4.2 Hz, Ar-CH_a-CH-), 2.91-2.84 (m, 3H, Ar-CH₂-CH₂-NH, Ar-CH_b-CH-), 2.70 (d, 2H, *J* = 12.9, 6.3, Ar-CH₂-CH₂-NH). ¹³C NMR: δ 149.4 (Ar-C-OCH₃-5'), 148.5 (Ar-C-OCH₃-4'), 147.8 (Ar-C-OCH₃-7), 147.3 (Ar-C-OCH₃-6), 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-OCH₃-6), 56.2 (Ar-OCH₃-7), 56.1 (Ar-OCH₃-5'), 56.0 (Ar-OCH₃-4'), 55.5 (C-1), 47.0 (Ar-CH-NH), 40.7 (Ar-CH₂-CO, Ar-CH₂-CH₂-NH), 29.4 (Ar-CH₂-CH₂-NH). MS (EI⁺): *m/z* 469 (M⁺ 6 %), 340 (100 %), HRMS (CI⁺) calcd for C₂₀H₂₅INO₄ = 470.0828 (M+H⁺), found 470.0825.

(*R,S*)-1-[(2-Iodo-4,5-dimethoxyoxyphenyl)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 1M HCl solution (10 mL) for 30 min, then extracted with CH₂Cl₂ (2 x 20 mL). The extracts were washed with sat. aqueous NaHCO₃ solution (2 x 20 mL), dried (MgSO₄), 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 %). ¹H 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-CH₂-CH_a-NCOCF₃), 3.86 (s, 3H, OCH₃-6), 3.84 (s, 3H, OCH₃-7), 3.78 (s, 3H, OCH₃-5'), 3.74 (s, 3H, OCH₃-4'), 3.70 (d, 1H, *J* = 5.7 Hz, Ar-CH₂-CH_b-NCOCF₃), 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-CH₂-NCOCF₃), 2.79 (dt, 1H, *J* = 15.9, 3.9 Hz, Ar-CH_b-CH₂-NCOCF₃). ¹³C NMR: δ (C=O not observed) 149.4 (Ar-C-OCH₃-6), 148.7 (Ar-C-OCH₃-

5'), 148.5 (Ar-C-OCH₃-7), 147.9 (Ar-C-OCH₃-4'), 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, NCOCF₃), 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-OCH₃-6), 56.2 (Ar-OCH₃-7), 56.1 (Ar-OCH₃-5'), 56.0 (Ar-OCH₃-4'), 54.5 (Ar-CH-NCOCF₃), 45.6 (Ar-CH₂-CH₂-NCOCF₃), 40.4 (Ar-CH₂-CH), 28.9 (Ar-CH₂-CH₂-NCOCF₃). MS (EI+): m/z 565 (M^+ 4 %), 288 (100 %), HRMS (EI+) Calcd for C₂₂H₂₃IF₃NO₅ = 565.0573 (M^+), found 565.0576.

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 N₂ was added BF₃·Et₂O (150 μL). After 10 min the mixture was diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The extracts were combined, washed with sat. aqueous NaHCO₃ (20 mL), dried (MgSO₄), 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 CH₂Cl₂ (20 mL) with powdered molecular sieves (4 Å, 500 mg) for 30 min and cooling the mixture to 0 °C. MoCl₅ (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 x 20 mL). The extracts were combined, washed with sat. aqueous NaHCO₃ (20 mL), dried (MgSO₄), 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-bronze²² (200mg) 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.

M.P. 142-144 °C (lit.²⁰ M.P. 145 °C). ¹H NMR: δ 6.84 (s, 2H, Ar-H-6), 6.72 (s, 2H, Ar-H-3), 3.92 (s, 6H, OCH₃-5), 3.83 (s, 6H, OCH₃-4), 3.60 (s, 6H, CO₂CH₃), 3.35 (ABq, 4H,

$J = 16.5$ Ar-CH₂). ¹³C NMR: δ 172.4 (C=O), 148.1 (Ar-C-OCH₃-4), 147.4 (Ar-C-OCH₃-5), 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-OCH₃), 55.7 (Ar-OCH₃), 51.8 (CO₂CH₃), 37.9 (Ar-CH₂). MS (CI⁺): m/z 419 (M+H, 100 %), HRMS (EI⁺): Calcd for C₂₂H₂₆O₈ = 418.1627 (M⁺), found 418.1615.

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 K₂CO₃ (99 mg, 0.72 mmol) in H₂O (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 CH₂Cl₂ (2 x 20 mL), dried (MgSO₄), filtered and evaporated to dryness to yield the title compound as a white solid (137 mg, 98 %). No further purification was required. M.P. 228-230 °C, lit.²⁰ 228-230 °C. ¹H NMR: δ 9.72 (bs, 1H, COOH), 6.77 (s, 1H, Ar-H-3), 6.60 (s, 1H, Ar-H-6), 3.89 (s, 3H, OCH₃-5), 3.82 (s, 3H, OCH₃-4), 3.45 (ABq, 2H, $J = 17.7$ Ar-CH₂-CO).

¹³C NMR: δ 179.1 (C=O), 148.3 (Ar-C-OCH₃-4), 147.7 (Ar-C-OCH₃-5), 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-OCH₃), 55.8 (Ar-OCH₃), 37.3 (Ar-CH₂-COOH). MS (ESI⁻): m/z 389 (M⁻, 37 %), 114 (100 %), HRMS (ESI⁻): calcd for C₂₀H₂₁O₈ = 389.1236 (M⁻), found 389.1218.

***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 N₂ and the solution was stirred for 18 h at RT. The mixture was diluted with H₂O (30 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The extracts were combined, washed with H₂O (2 x 30 mL), dried (MgSO₄), filtered and evaporated. The title compound was isolated as a white solid (214 g, 90 %) after purification by flash silica gel chromatography with CH₂Cl₂:EtOAc (3:1) as mobile phase. M.P. 162-164 °C. ¹H 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, NH), 3.87 (s, 3H, OCH₃-4'), 3.85 (s, 3H, OCH₃-4), 3.81 (s, 3H, OCH₃-3), 3.80 (s, 3H, OCH₃-5'), 3.35 (dt, 2H, $J = 6.9, 5.4$ Hz, Ar-CH₂-CH₂-NH), 3.23 (ABq, 2H, $J = 15.3$ Ar-CH₂-CO), 2.66 (t, 2H, $J = 6.9$, Ar-CH₂-CH₂-NH). ¹³C NMR: δ 171.1 (C=O), 148.9 (Ar-C-OCH₃-5'), 148.5 (2x Ar-C-OCH₃-4, 4'), 147.6 (Ar-C-OCH₃-5), 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-OCH₃), 55.9 (Ar-OCH₃), 55.8 (Ar-OCH₃), 55.7 (Ar-OCH₃), 40.8 (Ar-CH₂-CH₂-NH), 40.6 (Ar-CH₂-CO), 34.9 (Ar-CH₂-CH₂-NH). MS (ES+): m/z 717 (M+H, 30 %), 288 (100 %), HRMS (ESI+): calcd for C₄₀H₄₉N₂O₁₀ = 717.3387 (MH⁺), found 717.3402.

(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

PCl₅ (87 mg, 0.42 mmol) was added to a stirred solution of compound **13** (50 mg, 0.07 mmol) in dry CH₂Cl₂ (2 mL) and the resulting mixture stirred for 2 h at rt under a N₂ atmosphere. The solution was diluted with CH₂Cl₂ (10 mL), washed with sat. aqueous NaHCO₃ (2 x 20 mL), dried (MgSO₄), 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 CH₂Cl₂ (10 mL). The solution was washed with saturated aqueous Na₂CO₃ solution (2 x 10 mL), dried (K₂CO₃), filtered and evaporated. The crude mixture was separated by column chromatography using CH₂Cl₂/EtOH/MeOH/NH₃ (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: ^1H 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, OCH₃), 3.75 (s, 3H, OCH₃), 3.58 (s, 3H, OCH₃), 3.52 (s, 3H, OCH₃), 3.26-3.16 (m, 2H, Ar-CH₂-CH), 3.11-2.96 (m, 2H, Ar-CH₂-CH₂-NH), 2.91-2.70 (m, 2H, Ar-CH₂-CH₂-NH). ^{13}C NMR: δ 148.7 (Ar-C-OCH₃-5'), 148.1 (Ar-C-OCH₃-4'), 147.9 (Ar-C-OCH₃-7), 147.4 (Ar-C-OCH₃-6), 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-OCH₃), 55.8 (Ar-OCH₃), 55.7 (Ar-OCH₃), 55.5 (Ar-OCH₃), 51.9 (C-1), 40.1 (Ar-CH₂-CH), 37.4 (Ar-CH₂-CH₂-NH), 25.0 (Ar-CH₂-CH₂-NH). MS: m/z (ES⁺) 685 (M+H, 100 %), HRMS (ES⁺): Calcd for C₄₀H₄₉N₂O₈ = 684.3489, found 684.3480.

Minor isomer: ^1H 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, OCH₃-4'), 3.73 (s, 3H, OCH₃-5'), 3.72 (s, 3H, OCH₃-7), 3.65 (s, 3H, OCH₃-6), 3.10-2.82 (m, 2H, Ar-CH₂-CH), 2.74-2.67 (m, 2H, Ar-CH₂-CH₂-NH), 2.65-2.58 (m, 2H, Ar-CH₂-CH₂-NH). ^{13}C NMR: δ 148.1 (Ar-C-OCH₃-5'), 147.2 (Ar-C-OCH₃-4'), 147.1 (Ar-C-OCH₃-7), 146.9 (Ar-C-OCH₃-6), 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-OCH₃), 55.8 (Ar-OCH₃), 55.7 (Ar-OCH₃), 55.6 (Ar-OCH₃), 39.3 (Ar-CH₂-CH), 39.2 (Ar-CH₂-CH₂-NH), 29.5 (Ar-CH₂-CH₂-NH). MS: m/z (ESI⁺) 685 (M+H, 100 %), HRMS (ESI⁺): Calcd for C₄₀H₄₉N₂O₈ = 685.3489, found 685.3480.

(1RS,1'RS),(1R,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 (2 drops) were added and the solution was stirred for 3 h. The reaction was diluted with CH₂Cl₂ (10 mL), washed with saturated aqueous NaHCO₃ solution (2 x 10 mL), dried over anhydrous K₂CO₃, filtered and evaporated. Purification by silica gel chromatography using CH₂Cl₂:EtOAc:MeOH:NH₃ (10:5:1:trace) as the eluent afforded

the title compound as an opaque film (9 mg, 96 %). ^1H 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, OCH₃-4'), 3.70 (s, 3H, OCH₃-5'), 3.61 (s, 3H, OCH₃-7), 3.51 (s, 3H, OCH₃-6), 3.38 (s, 1H, H-1), 2.97-2.80 (m, 2H, Ar-CH₂-CH), 2.77-2.63 (m, 2H, Ar-CH₂-CH₂-NCH₃), 2.57-2.30 (m, 2H, Ar-CH₂-CH₂-NCH₃), 2.27 (s, 3H, NCH₃). ^{13}C NMR: δ 148.0 (Ar-C-OCH₃-5'), 147.5 (Ar-C-OCH₃-4'), 147.1 (Ar-C-OCH₃-7'), 146.6 (Ar-C-OCH₃-6'), 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-OCH₃), 56.1 (Ar-OCH₃), 56.0 (Ar-OCH₃), 55.8 (Ar-OCH₃), 45.7 (Ar-CH₂-CH), 42.9 (NCH₃), 37.6 (Ar-CH₂-CH₂-NCH₃), 24.2 (Ar-CH₂-CH₂-NCH₃). MS: m/z (ESI+) 713 (MH⁺, 100 %), HRMS (ESI+): Calcd for C₄₂H₅₃N₂O₈ = 713.3802, found 713.3812.

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GRAPHICAL ABSTRACT

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

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