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Tetrahedron
Tetrahedron 62 (2006) 4979–4987

An effective method for the preparation of mono *N*-alkyl derivatives of 1,1′-bis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline)

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Received 30 June 2005; revised 8 February 2006; accepted 23 February 2006
Available online 31 March 2006

Abstract—The condensation of 1,1′-bis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) with alkyl, aralkyl and aryl aldehydes, but not ketones, in ethanol or chloroform provides useful cyclic aminal [8-substituted 5,6,10,11,15b,15c-hexahydro-2,3,13,14-tetramethoxy-8*H*-imidazo[5,1-*a*:4,3-*a*′]diisoquinoline] intermediates that when subsequently treated with sodium cyanoborohydride in ethanol, followed by the addition of 2 M hydrochloric acid, gave monosubstituted *N*-alkyl 1,1′-bis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) derivatives in very high yields. The rates of the initial condensation with four different aldehydes were measured, and the entire sequence was successfully applied in one example to a 'one-pot' process; this signals a versatile route to differentially *N*-substituted 1,1′-bis(1,2,3,4-tetrahydroisoquinoline) derivatives.

1. Introduction

Reductive alkylation[1–14] is a general method for the preparation of tertiary amines from secondary amines, and hydride reagents have been used for this purpose with particular success.[4,6] We envisaged that this method would provide a means of attaching substituents through the nitrogen atoms of *rac*-1,1′-bis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) **1** in an ongoing study of heterocyclic ligands by our group[15,16] and that of others.[17,18] However, it has been reported[19] that while the corresponding *meso* compound underwent two-fold reductive N,N′-dimethylation through treatment with formalin/sodium borohydride, the *racemic* compound **1** gave none of the expected product but a modest yield of an N-cyanomethylation product. As far as we can determine, this reaction has not been pursued. In our hands, two-fold reductive alkylation of *rac*-bisisoquinoline **1** with sodium cyanoborohydride, under neutral or acidic conditions, or with sodium (triacetoxy)borohydride, also proved impossible to achieve in one step. Instead, the heterocycle **1** condensed extremely efficiently under the reaction conditions with aldehydes, to yield the corresponding aminal derivatives **2**. Compounds **2** were stable to reduction under the reaction conditions. Further investigation revealed that the condensation reaction was general and proceeded with a range of aldehydes, but not ketones, under mild conditions that neither require acid catalysis nor the presence of the reducing agent (Scheme 1).

Apart from the example of reductive methylation, previous literature reactions between reduced bisisoquinolines like **1** and aldehydes have normally involved only the use of formaldehyde as partner.[20–22] Motivation for these studies has been as a structural tool because the products, through the equivalence or otherwise of the new aminal methylene protons, can be used to distinguish the original heterocycle from its *meso* diastereomer.

2. Results and discussion

2.1. Heterocycle with aldehyde/ketone condensation

In the current study, bis(tetrahydroisoquinoline) **1** was found to react completely with three, and in many cases fewer, equivalents of aliphatic, aromatic and heteroaromatic aldehydes in ethanol at room temperature within an hour. Treatment with butanone under similar conditions failed to yield any condensation product, although acetone was found to react in low yield under more forcing conditions.[23] The ability to use pi-excessive and pi-deficient carbocyclic and heterocyclic aldehydes is an illustration of the wide generality of the reaction. Workup was achieved simply by evaporation

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.02.082.
Keywords: 1,1′-Bis(1,2,3,4-tetrahydroisoquinoline); Reductive alkylation; Condensation; Ligands; Reaction rates.
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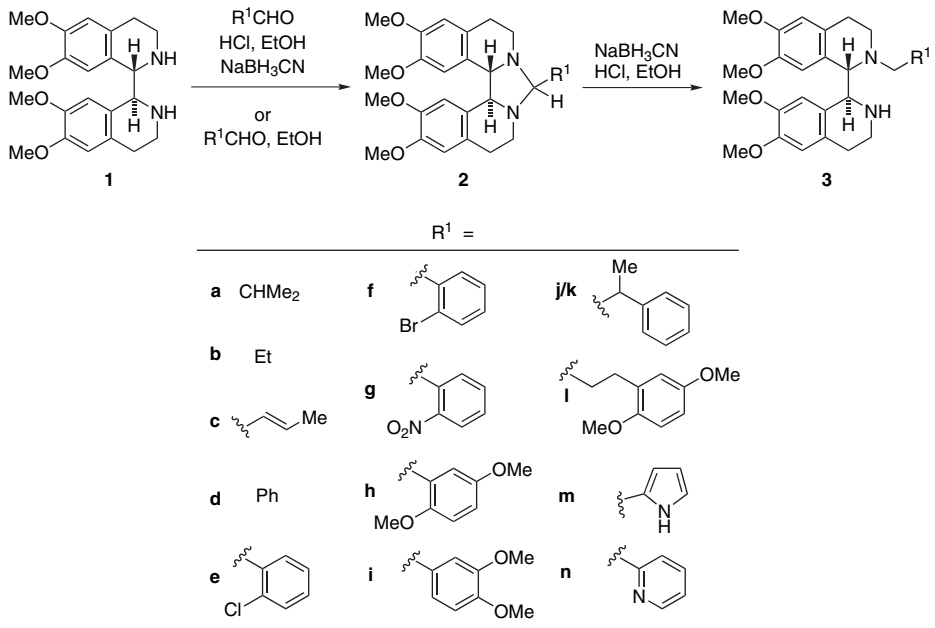
doi:10.1016/j.tet.2006.02.082



Scheme 1.

of solvent under reduced pressure (to remove any non-volatile unreacted aldehyde) and recrystallisation.

In the case of reaction with 2-phenylpropanal, leading to derivative **2j/k**, evaporation of solvent and analysis by ^{1}H NMR spectroscopy revealed formation of diastereomers, as shown by the appearance of duplicate sets of aromatic singlets for the H5, H5′, H8 and H8′ protons. Such detail was not important for the present study but was pursued for characterisation purposes. The product **2j/k** was recrystallised in order to attempt separation of the unequally distributed (62:38) diastereoisomers. The minor component **2j** crystallised in preference to the major isomer **2k**, and several recrystallisations gave a sample of the single diastereomer **2j** as a pure compound. It was not possible to determine the stereochemistry at the stereogenic centres in the bisisoquinoline portion of the molecule relative to the aldehyde-derived centre by spectroscopic methods and a sample could not be suitably crystallised for X-ray crystallography. Attempts to isolate a pure sample of the second diastereomer **2k** led only to production of more of the minor isomer **2j**. Eventually the crystallisation process gave very significant conversion of the material to what was originally the minor isomer **2j**. It was therefore concluded that the original mixture **2j/2k** resulted from a degree of kinetic control, so that the original major product **2k** was a kinetic rather than the thermodynamic product.

2.2. Rate comparisons

Qualitative differences were perceived in the rates of reactions with certain aldehydes. Attempts were made to compare rates of conversion at ice-bath temperatures in ethanol, but the results after evaporative workup were ambiguous. Attention then turned to deuteriochloroform as a solvent, so that progress in reactions could be monitored directly by ^{1}H NMR spectroscopy. Initially, the reaction of isobutyraldehyde with a slight sub-equimolar quantity of bis(tetrahydroisoquinoline) **1** in deuteriochloroform at 273 K was monitored in the probe of the NMR instrument using residual chloroform as an internal standard. The reaction was found to reach 86% conversion (percentage product over the sum of the bisisoquinoline **1** and product **2a**) within 48 min. A natural log plot of the aldehyde/bisisoquinoline **1** concentration ratio versus time subtended a straight line that revealed a rate of 8.809×10^{-5} mol/s with an R^2 factor of 0.98. Unfortunately other aldehydes of interest reacted too slowly at 273 K to yield useful data for comparisons. Reactions of isobutyraldehyde, 2-chlorobenzaldehyde, 2,5-dimethoxybenzaldehyde and 3,4-dimethoxybenzaldehyde, with slightly sub-equimolar quantities of bis(tetrahydroisoquinoline) **1**, were then carried out sequentially at 308 K. Conversions of 85% of the products **2a**, **2e**, **2h** and **2i** were attained after 6, 37, 108 and 260 min, respectively (Fig. 1). Further, calculation of rates, as above, yielded values of 38.56×10^{-5}, 7.259×10^{-5}, 0.2591×10^{-5} and 0.2452×10^{-5} mol/s, respectively, which translated into relative rates of 157: 29.6: 1.06: 1.00 (Table 1). It was concluded that the

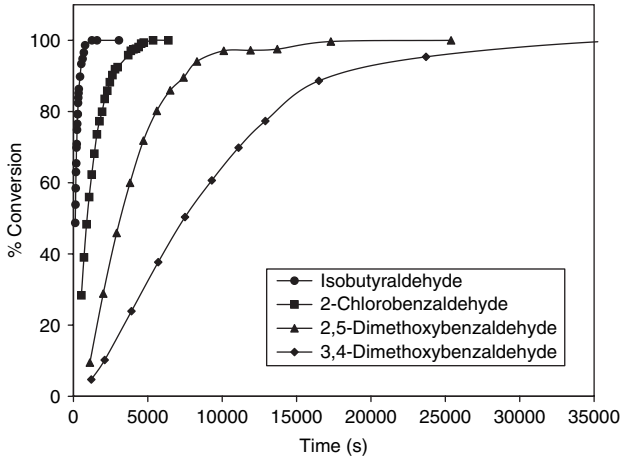
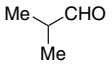
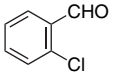
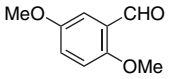
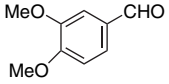


Figure 1. Plot of conversion versus time for reactions of 1,1′-bis(tetrahydroisoquinoline) **1** with isobutyraldehyde, 2-chlorobenzaldehyde, 2,5-dimethoxybenzaldehyde and 3,4-dimethoxybenzaldehyde.

Table 1. Reaction rates for the condensation of 1,1′-bis(tetrahydroisoquinoline) **1** with aldehydes as determined by ^{1}H NMR spectroscopy in $CDCl_3$ at 308 K

Aldehyde	Reaction rate ($\times 10^{-5}$ mol/s)	Relative rate
	38.56 (8.809)[a]	157
	7.259	29.6
	0.2591	1.06
	0.2452	1.00

[a] Reaction rate at 273 K.

condensation efficiency was directly related to the electrophilicity of the carbonyl partner, an observation that also explained the reluctance of ketones to participate within reasonable reaction times.

The reliability of the difference in rates between 2,5- and 3,4-dimethoxybenzaldehyde was tested through a competition reaction. An equimolar mixture of the two aldehydes was treated in deuteriochloroform with a slightly sub-equimolar (total 2 mol of aldehydes to 1 mol of bisisoquinoline) quantity of bis(tetrahydroisoquinoline) **1** at 308 K, and again the progress of the reaction monitored by ^{1}H NMR spectroscopy. On this occasion dimethylsulfone (DMS) was used as an internal standard. There was 53% conversion based on the amounts of new isoquinoline derivatives observed after 15 h, and the expected products, **2h** and **2i**, were formed in a ratio of 80:20, respectively. The latter selectivity was remarkable given the similarity of the aldehydes, and appeared from the linear trend in product formation for each of **2h** and **2i** not to arise through equilibration. The greater reactivity of the 2,5-dimethoxybenzaldehyde was attributed to the proximity of the 2-methoxy group to the aldehyde and its inductive effect on the carbonyl carbon. In continuation of the study, a competitive reaction at 273 K involving equimolar quantities of bis(tetrahydroisoquinoline) **1**, isobutyraldehyde and 2,5-dimethoxybenzaldehyde in deuteriochloroform gave 75% conversion to a 100:0 ratio of products **2a** and **2h**, respectively, within 48 min.

These results reinforced the qualitative differences in reactivity that had already been observed and were fully consistent with carbonyl electrophilicity as the major controlling factor. It is notable that there were sufficient differences in the rates to enable high selectivity to be achieved between reasonably similar aldehydes.

2.3. Reductive cleavage

In order to test the possible intermediacy of the condensation products **2** in the originally planned double reductive alkylation sequence, the isobutyraldehyde condensation product **2a** was subjected to treatment with excess sodium cyanoborohydride in ethanol in the presence of hydrochloric acid. The reaction failed when the reducing reagent was initially added to an acidified ethanol solution of the substrate **2a**. Treatment at room temperature or at reflux gave only the unreacted substrate **2a** in small but steadily decreasing amounts with time. Similarly, reduction using sodium (triacetoxy)-borohydride in dichloroethane, failed. Unfortunately, there was no distinct new product evident as a result of consumption of the substrate. In contrast, when 2 M aqueous hydrochloric acid was added slowly to a solution of the substrate **2a**, immediately after addition of sodium cyanoborohydride, complete conversion to a new product was observed to take place in the absence of side products within an hour at room temperature. Aqueous extractive workup afforded the anticipated *N*-isobutyryl product **3a** in virtually quantitative yield. Treatment of aminals **2h** and **2l** with sodium cyanoborohydride, and then hydrochloric acid, similarly afforded the mono-alkylated derivatives **3h** and **3l** in high yield, thereby suggesting that the process was general.

In retrospect, the demands of this late order of addition of acid would naturally preclude formation of the doubly alkylated product in a one-pot process, since one could not achieve the second aminal formation and the second cleavage until acid was added. However, it would leave open the possibility of a general 'one-pot' mono-alkylation procedure, from the parent bis(tetrahydroisoquinoline) **1**. Unsymmetrically *N*-alkylated derivatives of bis(tetrahydroisoquinoline) **1** should therefore be accessible by the relatively simple procedure of aldehyde condensation followed by reductive ring opening. This new method was demonstrated in one case, bis(tetrahydroisoquinoline) **1** to its *N*-isobutyl derivative in 86% yield, and future work will exploit this sequence in the synthesis of unsymmetrical ligands **4** for host–guest chemistry and catalysis.

2.4. Spectroscopic comparisons

The ^{1}H and ^{13}C NMR spectra of the condensation products **2** were useful from a structural standpoint. As expected, they showed clearly the unsymmetrical nature of the two isoquinoline ring systems through the appearance of separate signals for each of the chemically non-equivalent protons and carbons. More importantly, amongst all the resonances in the ^{1}H NMR spectra the signals for H15b/H15c and H1/H15 showed the most major differences in chemical shift in all derivatives, with those at H15b and H15 appearing at 0.7–0.8 and ca. 0.5 ppm, respectively, higher field than the signals for the corresponding protons from the second ring system (Fig. 2). Also notable, the signals for $H_\beta 5$ resonated at ca. 0.5 ppm higher field than the signals for their geminal partners, $H_\alpha 5$, in all cases, and those for $H_\alpha 10$ resonated at 0.4–0.5 ppm higher field than their geminal partners, $H_\beta 10$, but only in the cases where the group directly attached at C9 was aromatic, where R^1 was alkyl, aralkyl or alkenyl, the H10 signals were almost identical in chemical shift. The high field shift of the signals mentioned above was obviously related to the now unsymmetrical nature of the molecules and the concomitant presence of the aminal substituent that imparted asymmetry to the molecule; the extreme positions of these particular signals were more especially probably a reflection of pyramidalization through sp^3 hybridisation

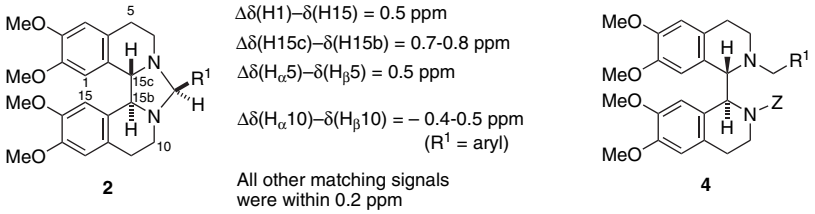


Figure 2.

at the nitrogens and comparatively fixed positions of the protons relative to the rest of the molecule due to rigidity in the imidazolidine rings. The major points of chemical shift difference in the ^{13}C NMR spectra were at C15b/C15c (3–6 ppm), C5/C11 (3–4 ppm) and C6/C10 (4–8 ppm). Consideration of these structural findings will assist in future ligand design since they reflect the more significant regions of the ligands and something of their conformational preferences in the ground state.

Molecular ions were not observed in the electron impact mass spectra of derivatives **2a**–**n**, but in all cases a large peak, often the base peak, was observed at 191 amu less than that expected for the molecular ion. This was consistent with fragmentation of the molecular ion through loss of one isoquinoline ring ($C_{11}H_{13}NO_2$) as a neutral species. The only exception to this behaviour was that of the nitrobenzaldehyde derivative **2g**, which gave a relatively minor fragment ion at M−191. Instead, the base peak had occurred at *m*/*z* 191. In the molecules derived from non-aromatic aldehydes there was also observed fragment ions through loss of the C-8 substituent, thus C_3H_7 and C_2H_5 from **2a** and **2b**, respectively.

3. Conclusion

In summary, a method has been developed that enables unsymmetrical, mono *N*-substituted 1,1′-bis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) derivatives to be prepared efficiently. The process involves a kinetically driven condensation reaction between the bis(tetrahydroisoquinoline) **1** and various aldehydic partners, which can be highly selective. The intermediates and products of the overall process show distinctive spectroscopic properties that are helpful in defining structural features for future ligand design.

4. Experimental

4.1. Condensation reactions of bis(tetrahydroisoquinoline) 1 with aldehydes

General procedure: Bis(tetrahydroisoquinoline) **1** (77 mg, 0.20 mmol) was dissolved in absolute EtOH (8 mL) and the solution stirred at ambient temperature as the aldehyde (0.60 mmol) was added dropwise or in solid portions. The mixture was then maintained at room temperature or warmed to reflux for the time specified, when TLC analysis indicated that the starting bisisoquinoline **1** had been consumed. Volatile material was removed by rotary evaporation and the residue was recrystallised.

4.1.1. Reaction with isobutyraldehyde. This reaction occurred at room temperature within 1 h to yield *5,6,10,11,15b,15c-hexahydro-8-(1-methylethyl)-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2a** as white needles (78 mg, 90%) mp 172–174 °C (EtOAc), R_f 0.52 (MeOH) (Found: C, 70.97; H, 7.75; N, 6.14. $C_{26}H_{34}N_2O_4$ requires: C, 71.21; H, 7.81; N, 6.39%). IR (KBr): 1607, 1515, 1464, 1348, 1272, 1247, 1225, 1129, 851, 779 cm^{-1}. UV (MeOH): 242, 288 nm. ^{1}H NMR ($CDCl_3$) δ: 1.13 (3H, d, *J* 6.7 Hz, 8-CH(CH_3)$_a$(CH$_3$)$_b$), 1.14 (3H, d, *J* 6.8 Hz, 8-CH(CH$_3$)$_a$(CH_3)$_b$), 2.08 (1H, m, 8-C*H*(CH$_3$)$_a$(CH$_3$)$_b$), 2.49 (1H, m, H$_\beta$5), 2.85 (1H, m, H$_\beta$6), 2.89 (2H, m, (H11)$_2$), 2.90 (1H, m, H$_\alpha$5), 2.98 (2H, m, (H10)$_2$), 3.09 (1H, m, H$_\alpha$6), 3.48 (1H, d, *J* 9.3 Hz, H15b), 3.52 (3H, s, 14-OMe), 3.64 (1H, d, *J* 7.3 Hz, H8), 3.69 (3H, s, 2-OMe), 3.84 (3H, s, 13-OMe), 3.88 (3H, s, 3-OMe), 4.21 (1H, d, *J* 9.3 Hz, H15c), 5.93 (1H, s, H15), 6.45 (1H, s, H1), 6.63 (1H, s, H12), 6.73 (1H, s, H4); ^{13}C NMR ($CDCl_3$) δ: 19.6 (8-CH(CH$_3$)$_a$(*C*H$_3$)$_b$), 20.2 (8-CH(*C*H$_3$)$_a$(CH$_3$)$_b$), 26.5 (C5), 29.9 (C11), 30.2 (8-*C*H(CH$_3$)$_a$(CH$_3$)$_b$), 40.9 (C10), 49.8 (C6), 55.5 (14-OMe), 55.6 (13-OMe), 55.8 (3-OMe), 55.9 (2-OMe), 65.3 (C15c), 67.8 (C15b), 88.3 (C8), 110.8 (C12), 111.05 (C15), 111.11 (C4), 113.3 (C1), 125.6 (C15a), 127.0 (C15d), 127.1 (C11a), 130.2 (C4a), 145.9 (C14), 146.3 (C2), 147.4 (C3), 147.5 (C13); Mass spectrum (EI): *m*/*z* 395 (M−43, 21%), 247 (87), 232 (100).

4.1.2. Reaction with propionaldehyde. This reaction occurred at room temperature within 50 min to yield *8-ethyl-5,6,10,11,15b,15c-hexahydro-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2b** as white needles (74 mg, 87%) mp 196–197 °C (EtOH), R_f 0.41 (MeOH) (Found: C, 70.51; H, 7.37; N, 6.40. $C_{25}H_{32}N_2O_4$ requires: C, 70.73; H, 7.60; N, 6.60%). IR (KBr): 1607, 1480, 1459, 1349, 1254, 1227, 1130, 850, 788 cm^{-1}. UV (MeOH): 242, 288 nm. ^{1}H NMR ($CDCl_3$) δ: 1.11 (3H, t, *J* 7.5 Hz, 8-CH$_2$CH_3), 1.83 (2H, dq, *J* 7.0, 7.5 Hz, 8-CH_2CH$_3$), 2.43 (1H, br d, *J* 14.7 Hz, H$_\beta$5), 2.82 (1H, m, H$_\alpha$11), 2.84 (1H, m, H$_\beta$6), 2.90 (1H, m, H$_\alpha$5), 2.98 (1H, m, H$_\alpha$10), 3.00 (1H, m, H$_\beta$11), 3.06 (1H, m, H$_\alpha$6), 3.10 (1H, m, H$_\beta$10), 3.50 (1H, d, *J* 9.0 Hz, H15b), 3.56 (3H, s, 14-OMe), 3.68 (3H, s, 2-OMe), 3.84 (3H, s, 13-OMe), 3.87 (3H, s, 3-OMe), 4.00 (1H, d, *J* 7.0 Hz, H8), 4.29 (1H, d, *J* 9.0 Hz, H15c), 5.97 (1H, s, H15), 6.37 (1H, s, H1), 6.64 (1H, s, H12), 6.72 (1H, s, H4); ^{13}C NMR ($CDCl_3$) δ: 10.2 (8-CH$_2$*C*H$_3$), 23.1 (8-*C*H$_2$CH$_3$), 25.3 (C5), 29.2 (C11), 38.9 (C10), 46.2 (C6), 55.7 (13-OMe), 55.7 (14-OMe), 55.8 (3-OMe), 55.9 (2-OMe), 64.7 (C15c), 69.7 (C15b), 83.5 (C8), 110.9 (C12), 111.5 (C4), 111.8 (C15), 112.9 (C1), 125.2 (C15a), 126.7 (C11a), 127.5 (C15d), 129.6 (C4a), 146.0 (C14), 146.39 (C2 or C3), 147.42 (C2 or C3), 147.9 (C13);

Mass spectrum (EI): *m/z* 395 (M−29, 4%), 247 (2), 233 (100), 218 (87).

4.1.3. Reaction with crotonaldehyde. This occurred at room temperature within 40 min to yield *5,6,10,11,15b,15c-hexahydro-8-(prop-1-enyl)-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2c** as white needles (80 mg, 92%) mp 201–202 °C (EtOH), R_f 0.59 (MeOH) (Found: C, 71.51; H, 7.68; N, 6.32. $C_{26}H_{32}N_2O_4$ requires: C, 71.54; H, 7.39; N, 6.42%). IR (KBr): 1610, 1518, 1453, 1349, 1257, 1227, 1131, 965, 854, 777 cm^{-1}. UV (MeOH): 242, 287 nm. ^1H NMR ($CDCl_3$) δ: 1.83 (3H, dd, *J* 6.4, 1.5 Hz, 8-CHCHCH_3), 2.45 (1H, br d, *J* 12.5 Hz, $H_\beta5$), 2.82 (1H, m, $H_\beta6$), 2.83 (1H, m, $H_\alpha11$), 2.87 (1H, m, $H_\alpha5$), 2.96 (1H, m, $H_\beta11$), 2.98 (1H, m, $H_\alpha6$), 3.09 (1H, m, $H_\alpha10$), 3.09 (1H, m, $H_\beta10$), 3.54 (1H, d, *J* 9.0 Hz, H15b), 3.63 (3H, s, 14-OMe), 3.73 (3H, s, 2-OMe), 3.86 (3H, s, 13-OMe), 3.89 (3H, s, 3-OMe), 4.32 (1H, d, *J* 9.0 Hz, H15c), 4.36 (1H, d, *J* 7.5 Hz, H8), 5.66 (1H, dd, *J* 15.5, 1.5 Hz, 8-C*H*CHCH$_3$), 5.98 (1H, dq, *J* 15.5, 6.4 Hz, 8-CHC*H*CH$_3$), 6.17 (1H, s, H15), 6.48 (1H, s, H1), 6.66 (1H, s, H12), 6.74 (1H, s, H4); ^{13}C NMR ($CDCl_3$) δ: 17.9 (8-CHCH*C*H$_3$), 25.5 (C5), 29.2 (C11), 41.1 (C10), 45.4 (C6), 55.7 (13-OMe), 55.8 (14-OMe), 55.9 (3-OMe), 56.0 (2-OMe), 64.1 (C15c), 69.4 (C15b), 83.8 (C8), 111.2 (C12), 111.57 (C15), 111.60 (C4), 112.7 (C1), 125.8 (C15a), 126.9 (C11a), 128.0 (C15d), 129.0 (8-*C*HCHCH$_3$), 129.9 (C4a), 132.2 (8-CH*C*HCH$_3$), 146.2 (C14), 146.5 (C2), 147.5 (C3), 147.9 (C13); Mass spectrum (EI): *m/z* 246 (M−190, 17%), 245 (100), 244 (60), 230 (46).

4.1.4. Reaction with benzaldehyde. This reaction occurred at reflux within 16.5 h to yield *5,6,10,11,15b,15c-hexahydro-8-phenyl-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2d** as white needles (85 mg, 91%) mp 215–217 °C (EtOAc), R_f 0.76 (MeOH) (Found: C, 73.61; H, 6.84; N, 5.71. $C_{29}H_{32}N_2O_4$ requires: C, 73.71; H, 6.82; N, 5.93%). IR (KBr): 1606, 1515, 1461, 1346, 1255, 1224, 1126, 850, 786 cm^{-1}. UV (MeOH): 242, 288 nm. ^1H NMR ($CDCl_3$) δ: 2.44 (1H, br d, *J* 12.9 Hz, $H_\beta5$), 2.46 (1H, m, $H_\alpha10$), 2.72 (1H, m, $H_\alpha11$), 2.86 (1H, m, $H_\beta11$), 2.88 (1H, m, $H_\alpha6$), 2.88 (1H, m, $H_\beta6$), 2.88 (1H, m, $H_\beta10$), 3.00 (1H, m, $H_\alpha5$), 3.65 (3H, s, 14-OMe), 3.75 (3H, s, 2-OMe), 3.76 (1H, d, *J* 8.7 Hz, H15b), 3.84 (3H, s, 13-OMe), 3.91 (3H, s, 3-OMe), 4.51 (1H, d, *J* 8.7 Hz, H15c), 5.18 (1H, s, H8), 6.23 (1H, s, H15), 6.54 (1H, s, H1), 6.64 (1H, s, H12), 6.76 (1H, s, H4), 7.35 (1H, t, *J* 7.5 Hz, H4″), 7.41 (2H, dd, *J* 7.5, 6.4 Hz, H3″ and H5″), 7.67 (2H, d, *J* 6.4 Hz, H2″ and H6″); ^{13}C NMR ($CDCl_3$) δ: 25.5 (C4), 29.2 (C11), 41.1 (C10), 46.0 (C6), 55.7 (13-OMe), 55.8 (14-OMe), 55.8 (3-OMe), 56.0 (2-OMe), 64.4 (C15c), 70.5 (C15b), 84.8 (C8), 111.2 (C12), 111.59 (C15), 111.64 (C4), 112.7 (C1), 125.8 (C15a), 127.0 (C11a), 128.15 (C4″), 128.2 (C1″), 128.20 (C15d), 128.22 (C3″ and C5″), 129.1 (C2″ and C6″), 130.0 (C4a), 138.1, 146.2 (C14), 146.5 (C2), 147.5 (C3), 148.0 (C13); Mass spectrum (EI): *m/z* 282 (M−190, 16%), 281 (100), 266 (20), 177 (18).

4.1.5. Reaction with 2-chlorobenzaldehyde. This reaction occurred at reflux within 8.5 h to yield *8-(2-chlorophenyl)-5,6,10,11,15b,15c-hexahydro-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2e** as white needles (77 mg, 76%) mp 201–202 °C (EtOAc), R_f 0.78 (MeOH) (Found: C, 68.87; H, 6.09; N, 5.41. $C_{29}H_{31}N_2O_4Cl$ requires: C, 68.70; H, 6.16; N, 5.53%). IR (KBr): 1605, 1515, 1461, 1361, 1337, 1257, 1223, 1128, 1030, 808, 784, 776 cm^{-1}. UV (MeOH): 242, 288 nm. ^1H NMR ($CDCl_3$) δ: 2.38 (1H, m, $H_\alpha10$), 2.47 (1H, br d, *J* 15.1 Hz, $H_\beta5$), 2.70 (1H, m, $H_\alpha11$), 2.83 (1H, m, $H_\alpha6$), 2.83 (1H, m, $H_\beta6$), 2.87 (1H, m, $H_\beta10$), 2.88 (1H, m, $H_\beta11$), 3.02 (1H, ddd, *J* 15.1, 9.4, 6.0 Hz, $H_\alpha5$), 3.64 (3H, s, 14-OMe), 3.75 (3H, s, 2-OMe), 3.79 (1H, d, *J* 9.0 Hz, H15b), 3.84 (3H, s, 13-OMe), 3.91 (3H, s, 3-OMe), 4.49 (1H, d, *J* 9.0 Hz, H15c), 5.48 (1H, s, H8), 6.21 (1H, s, H15), 6.54 (1H, s, H1), 6.63 (1H, s, H12), 6.77 (1H, s, H4), 7.28 (1H, ddd, *J* 7.2, 7.1, 2.3 Hz, H4′), 7.32 (1H, ddd, *J* 7.2, 7.1, 1.9 Hz, H5′), 7.43 (1H, dd, *J* 7.2, 1.9 Hz, H3′), 7.98 (1H, dd, *J* 7.2, 2.3 Hz, H6′); ^{13}C NMR ($CDCl_3$) δ: 25.8 (C5), 29.3 (C11), 41.7 (C10), 46.1 (C6), 55.7 (13-OMe), 55.85 (14-OMe), 55.85 (3-OMe), 56.0 (2-OMe), 64.0 (C15c), 70.3 (C15b), 81.7 (C8), 111.1 (C12), 111.7 (C4), 111.7 (C15), 112.8 (C1), 125.9 (C15a), 126.5 (C5′), 127.1 (C11a), 128.0 (C15d), 129.2 (C4′), 129.5 (C3′), 130.0 (C4a), 130.9 (C6′), 135.4 (C1′), 135.8 (C2′), 146.2 (C14), 146.5 (C2), 147.5 (C3), 148.0 (C13); Mass spectrum (EI): *m/z* 317 (M−189, 32%), 315 (100), 300 (19), 280 (17), 177 (25).

4.1.6. Reaction with 2-bromobenzaldehyde. This was performed on exactly half the normal scale and occurred at reflux within 2.5 h. The crude product was chromatographed on alumina, eluting with a light petroleum–Et_2O–MeOH gradient to yield *8-(2-bromophenyl)-5,6,10,11,15b,15c-hexahydro-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2f** as white needles (40 mg, 72%) mp 207.5–209 °C (EtOAc), R_f 0.80 (EtOAc) (Found: C, 63.24; H, 5.87; N, 5.09. $C_{29}H_{31}N_2O_4Br$ requires: C, 63.16; H, 5.67; N, 5.08%). IR (KBr): 1517, 1463, 1340, 1314, 1259, 1232, 1126, 1019, 857, 787, 749 cm^{-1}. UV (MeOH): 214, 287 nm. ^1H NMR ($CDCl_3$) δ: 2.37 (1H, m, $H_\alpha10$), 2.48 (1H, br d, *J* 15.1 Hz, $H_\beta5$), 2.71 (1H, m, $H_\alpha11$), 2.77–2.93 (4H, m, $H_\alpha6$, $H_\beta6$, $H_\beta10$ and $H_\beta11$), 3.03 (1H, ddd, *J* 15.1, 8.7, 5.7 Hz, $H_\alpha5$), 3.64 (3H, s, 14-OMe), 3.76 (3H, s, 2-OMe), 3.78 (1H, d, *J* 9.0 Hz, H15b), 3.85 (3H, s, 13-OMe), 3.91 (3H, s, 3-OMe), 4.50 (1H, d, *J* 9.0 Hz, H15c), 5.40 (1H, s, H8), 6.23 (1H, s, H15), 6.56 (1H, s, H1), 6.63 (1H, s, H12), 6.77 (1H, s, H4), 7.20 (1H, ddd, *J* 7.9, 7.5, 1.5 Hz, H4′), 7.38 (1H, ddd, *J* 7.5, 7.5, 1.1 Hz, H5′), 7.62 (1H, dd, *J* 7.9, 1.1 Hz, H3′), 7.97 (1H, dd, *J* 7.5, 1.5 Hz, H6′); ^{13}C NMR ($CDCl_3$) δ: 25.9 (C5), 29.4 (C11), 41.7 (C10), 46.1 (C6), 55.7 (13-OMe), 55.9 (14-OMe), 55.9 (3-OMe), 56.0 (2-OMe), 64.1 (C15c), 70.2 (C15b), 83.8 (C8), 111.2 (C12), 111.6 (C15), 111.7 (C4), 112.8 (C1), 125.6 (C1′), 126.0 (C15a), 127.1 (C11a), 127.1 (C5′), 128.1 (C15d), 129.6 (C4′), 130.0 (C4a), 131.4 (C6′), 132.8 (C3′), 137.4 (C2′), 146.2 (C14), 146.5 (C2), 147.5 (C3), 148.0 (C13); Mass spectrum (EI): *m/z* 361 (M(^{81}Br)−191, 88%), 359 (100), 280 (43), 191 (41), 176 (43).

4.1.7. Reaction with 2-nitrobenzaldehyde. This reaction occurred at reflux within 3.5 h to yield *5,6,10,11,15b,15c-hexahydro-8-(2-nitrophenyl)-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2g** as pale yellow needles (58 mg, 56%) mp 192–194 °C (EtOAc), R_f 0.61 (MeOH) (Found: C, 67.05; H, 6.27; N, 7.90. $C_{29}H_{31}N_3O_6$ requires: C, 67.30; H, 6.04; N, 8.12%). IR (KBr): 1608, 1517, 1463, 1350, 1258, 1226, 1131, 1018, 857, 786 cm^{-1}. UV

(MeOH): 242, 288 nm. ^{1}H NMR ($CDCl_3$) δ: 2.32 (1H, m, H_α10), 2.50 (1H, m, H_β5), 2.68 (1H, m, H_α11), 2.80 (1H, m, H_β10), 2.80 (1H, m, H_β11), 2.87 (1H, m, H_α6), 2.87 (1H, m, H_β6), 3.01 (1H, m, H_α5), 3.63 (3H, s, 14-OMe), 3.70 (1H, d, *J* 9.0 Hz, H15b), 3.75 (3H, s, 2-OMe), 3.83 (3H, s, 13-OMe), 3.91 (3H, s, 3-OMe), 4.45 (1H, d, *J* 9.0 Hz, H15c), 5.59 (1H, s, H8), 6.21 (1H, s, H15), 6.55 (1H, s, H1), 6.61 (1H, s, H12), 6.77 (1H, s, H4), 7.48 (1H, ddd, *J* 7.9, 7.5, 1.5 Hz, H4′), 7.63 (1H, ddd, *J* 7.9, 7.5, 1.1 Hz, H5′), 7.78 (1H, dd, *J* 7.9, 1.5 Hz, H6′), 8.15 (1H, dd, *J* 7.9, 1.1 Hz, H3′); ^{13}C NMR ($CDCl_3$) δ: 26.0 (C5), 29.3 (C11), 42.0 (C10), 46.4 (C6), 55.7 (13-OMe), 55.9 (14-OMe), 55.9 (3-OMe), 56.0 (2-OMe), 64.2 (C15c), 70.0 (C15b), 79.7 (C8), 111.2 (C12), 111.6 (C4), 111.3 (C15), 112.8 (C1), 123.5 (C6′), 125.8 (C15a), 127.1 (C11a), 127.7 (C15d), 128.8 (C4′ or C5′), 130.0 (C4a), 130.7 (C3′), 132.0 (C4′ or C5′), 132.4 (C1′), 146.2 (C14), 146.6 (C2), 147.6 (C3), 148.0 (C13), 151.2 (C2′); Mass spectrum (EI): *m*/*z* 326 (M−191, 12%), 192 (27), 191 (100), 176 (35).

4.1.8. Reaction with 2,5-dimethoxybenzaldehyde. This reaction, on 20 times larger scale, occurred at room temperature within 1 h to yield *8-(2,5-dimethoxyphenyl)-5,6,10,11,15b,15c-hexahydro-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2h** as colourless needles (1.56 g, 75%) mp 179–180 °C (EtOAc), R_f 0.59 (EtOAc) (Found: C, 69.93; H, 6.48; N, 5.07. $C_{31}H_{36}N_2O_6$ requires: C, 69.91; H, 6.81; N, 5.26%). IR (KBr): 3001, 2910, 2834, 1610, 1518, 1353, 1258, 1155, 1127, 1021, 856, 785, 712 cm^{-1}. UV (MeOH): 224, 291 nm. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.42 (1H, br d, *J* 14.9 Hz, H_β5), 2.46 (1H, m, H_α10), 2.70 (1H, m, H_α11), 2.86 (2H, m, H_α6 and H_β6), 2.90 (2H, m, H_β10 and H_β11), 3.01 (1H, ddd, *J* 14.9, 9.4, 5.6 Hz, H_α5), 3.63 (3H, s, 14-OMe), 3.74 (3H, s, 2-OMe), 3.78 (1H, d, *J* 9.1 Hz, H15b), 3.80 (3H, s, 5′-OMe), 3.84 (3H, s, 13-OMe), 3.84 (3H, s, 2′-OMe), 3.91 (3H, s, 3-OMe), 4.46 (1H, d, *J* 9.1 Hz, H15c), 5.53 (1H, s, H8), 6.15 (1H, s, H15), 6.51 (1H, s, H1), 6.61 (1H, s, H12), 6.75 (1H, s, H4), 6.86 (1H, dd, *J* 8.7, 2.3 Hz, H4′), 6.89 (1H, d, *J* 8.7 Hz, H3′), 7.55 (1H, d, *J* 2.3 Hz, H6′); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ: 25.7 (C5), 29.3 (C11), 41.6 (C10), 46.1 (C6), 55.6 (2-OMe), 55.7 (13-OMe), 55.78 (14-OMe), 55.85 (3-OMe), 56.0 (5′-OMe), 56.4 (2′-OMe), 63.9 (C15c), 70.6 (C15b), 78.7 (C8),111.0 (C12), 111.6 (C4), 111.7 (C15), 111.8 (C4′), 112.9 (C1), 113.6 (C3′), 115.9 (C6), 126.1 (C11a), 127.1 (C15a), 127.4 (C1′), 128.2 (C4a), 130.1 (C15d), 146.0 (C14), 146.4 (C2), 147.4 (C3), 147.8 (C13), 153.2 (C2′), 153.5 (C5′); Mass spectrum (EI): *m*/*z* 341 (M−191, 100%), 310 (22), 191 (58), 176 (70), 151 (28), 146 (32), 133 (25), 121 (37), 91 (39), 77 (41), 57 (26).

4.1.9. Reaction with 3,4-dimethoxybenzaldehyde. This reaction, on twice the scale and with only 2 equiv of aldehyde, occurred at room temperature within 1 h to yield *8-(3,4-dimethoxyphenyl)-5,6,10,11,15b,15c-hexahydro-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2i** as colourless prisms (0.141 g, 68%) mp 202.5–204 °C (EtOAc), R_f 0.56 (EtOAc) (Found: C, 69.79; H, 7.20; N, 5.05. $C_{31}H_{36}N_2O_6$ requires: C, 69.91; H, 6.81; N, 5.26%). IR (KBr): 2934, 2835, 1609, 1515, 1464, 1259, 1227, 1128, 1019, 857, 780 cm^{-1}. UV (MeOH): 231, 283 nm. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.45 (1H, m, H_β5), 2.48 (1H, m, H_α10), 2.75 (1H, m, H_α11), 2.85 (1H, m, H_α6), 2.87 (1H, m, H_β10), 2.87 (1H, m, H_β11), 2.90 (1H, m, H_β6), 3.01 (1H, m, H_α5), 3.64 (3H, s, 2-OMe), 3.75 (3H, s, 14-OMe), 3.78 (1H, obscured d, H15b), 3.86 (3H, s, 13-OMe), 3.91 (3H, s, 3-OMe), 3.92 (6H, s, 3′-OMe and 4′-OMe), 4.50 (1H, d, *J* 9.0 Hz, H15c), 5.18 (1H, s, H8), 6.20 (1H, s, H15), 6.52 (1H, s, H1), 6.64 (1H, s, H12), 6.77 (1H, s, H4), 6.93 (1H, d, *J* 8.3 Hz, H5′), 7.22 (1H, br s, H2′), 7.24 (obscured d, H6′); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ: 25.5 (C5), 29.2 (C11), 40.8 (C10), 46.0 (C6), 55.65 (13-OMe), 55.80 (3′-OMe or 4′-OMe), 55.82 (3′-OMe or 4′-OMe), 55.82 (2-OMe), 55.88 (3-OMe), 56.0 (14-OMe), 64.3 (C15c), 70.3 (C15b), 84.5 (C8), 110.6 (C5′), 111.0 (C12), 111.48 (C15), 111.53 (C4), 111.7 (C2′), 112.6 (C1), 121.1 (C6′), 125.6 (C15a), 126.9 (C11a), 128.0 (C15d), 129.9 (C4a), 130.4 (C1′), 146.1 (C14), 146.4 (C2), 147.4 (C3), 147.9 (C13), 148.8 (C3′ or C4′), 148.9 (C3′ or C4′); Mass spectrum (EI): *m*/*z* 531 ((M−H)$^+$, 0.5%), 395 (0.75), 341 (100), 326 (26), 191 (13), 176 (20), 151 (15), 77 (9).

4.1.10. Reaction with 2-phenylpropanal. The reaction with 2-phenylpropanal on twice the scale occurred at room temperature within 0.5 h to yield a 62:38 diastereomeric mixture of products (218 mg, 84%) mp 145–151 °C. Fractional crystallisation using EtOAc afforded the minor diastereomer *(8R*,15bR*,15cS*,1′R*)-5,6,10,11,15b,15c-hexahydro-8-(1-phenylethyl)-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2j** as colourless prisms mp 184–186 °C (EtOAc), R_f 0.65 (EtOAc) (Found: C, 74.27; H, 7.50; N, 5.41. $C_{31}H_{36}N_2O_4$ requires: C, 74.37; H, 7.25; N, 5.60%). IR (KBr): 2921, 1609, 1514, 1463, 1353, 1275, 1254, 1228, 1130, 1019, 854, 780, 699 cm^{-1}. UV (MeOH): 211, 286 nm. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 1.53 (3H, d, *J* 6.9 Hz, $(H2')_3$), 2.13 (1H, ddd, *J* 13.6, 3.2, 3.2 Hz, H_α10), 2.17 (1H, d, *J* 15.2 Hz, H_β11), 2.29 (1H, ddd, *J* 12.2, 11.9 Hz, H_β10), 2.72 (1H, ddd, *J* 11.8, 3.2, 3.2 Hz, H_α11), 2.89 (1H, ddd, *J* 16.1, 4.0, 3.9 Hz, H_β5), 2.98 (1H, ddd, *J* 16.1, 9.7, 5.7 Hz, H_α5), 3.12 (2H, m, H_α6 and H_β6), 3.19 (1H, m, H1′), 3.45 (1H, d, *J* 9.0 Hz, H15b), 3.55 (3H, s, 2-OMe), 3.68 (3H, s, 14-OMe), 3.86 (6H, s, 3-OMe and 13-OMe), 4.12 (1H, m, H8), 4.28 (1H, d, *J* 9.0 Hz, H15c), 5.93 (1H, s, H1), 6.37 (1H, s, H15), 6.64 (1H, s, H12), 6.66 (1H, s, H4), 7.25 (1H, t, *J* 7.3 Hz, H4″), 7.34 (2H, dd, *J* 7.5, 7.3 Hz, H3″ and H5″), 7.41 (2H, d, *J* 7.5 Hz, H2″ and H6″); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.1 (C2′), 20.1 (C11), 30.0 (C5), 40.8 (C6), 42.5 (C1′), 48.4 (C10), 56.1 (2-OMe), 56.2 (3-OMe), 56.3 (13-OMe), 56.4 (14-OMe), 66.0 (C15c), 69.2 (C15b), 88.0 (C8), 111.3 (C4), 111.7 (C12), 112.0 (C1), 113.5 (C15), 125.9 (C15d), 127.0 (C4″), 127.8 (C4a), 128.0 (C11a), 128.7 (C1″), 128.9 (C2″, C3″, C5″, C6″), 130.9 (C15a), 146.4 (C2), 146.7 (C14), 147.8 (C13), 148.2 (C3); Mass spectrum (EI): *m*/*z* 499 ((M−H)$^+$, 0.5%), 393 (42), 309 (53), 294 (27), 191 (100), 176 (25), 105 (22).

The initially major isomer could not be obtained pure but was identified as *(8R*,15bR*,15cS*,1′S*)-5,6,10,11,15b,15c-hexahydro-8-(1-phenylethyl)-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2k** through analysis of the ^{1}H and ^{13}C NMR data of a highly enriched sample, colourless prisms, mp 184–185 °C (dec), R_f 0.75 (EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (3H, d, *J* 6.8 Hz, $(H2')_3$), 2.39 (1H, br d, *J* 15.1 Hz, H_β5), 2.46 (1H, m, H_α6), 2.58 (1H, m, H_β6), 2.67 (1H, m, H_β11), 2.69 (1H, m, H_α10), 2.77 (1H, m,

H_α5), 2.97 (1H, m, H_α11), 3.15 (1H, m, H_β10), 3.22 (1H, m, H1′), 3.43 (1H, d, *J* 9.0 Hz, H15b), 3.57 (3H, s, 14-OMe), 3.78 (3H, s, 2-OMe), 3.83 (3H, s, 13-OMe), 3.86 (1H, br s, H8), 3.87 (3H, s, 3-OMe), 4.20 (1H, d, *J* 9.0 Hz, H15c), 6.30 (1H, s, H15), 6.62 (1H, s, H12), 6.68 (1H, s, H4), 6.73 (1H, s, H1), 7.21 (1H, t, *J* 7.2 Hz, H4″), 7.32 (2H, dd, *J* 7.5, 7.2 Hz, H3″ and H5″), 7.37 (2H, d, *J* 7.5 Hz, H2″ and H6″); ^{13}C NMR ($CDCl_3$, 75.6 MHz) *δ*: 16.2 (C2′), 27.6 (C5), 30.4 (C11), 42.1 (C1′), 43.3 (C10), 50.6 (C6), 55.80 (12-OMe), 55.83 (13-OMe), 55.93 (3-OMe), 56.1 (2-OMe), 65.4 (C15c), 66.4 (C15b), 88.1 (C8), 110.5 (C15), 111.38 (C4), 111.43 (C12), 114.1 (C1), 126.1 (C4″), 127.1 (C15d), 128.0 (C15a), 128.1 (C3″, C5″), 128.3 (C2″, C6″), 128.5 (C11a), 131.0 (C4a), 144.7 (C1″), 146.3 (C14), 146.6 (C2), 147.6 (C13), 148.0 (C3).

4.1.11. Reaction with 3-(2,5-dimethoxyphenyl)propanal. This reaction was performed on four times the scale with only 1.5 mol equiv of aldehyde, at room temperature within 1 h to yield *8-[2-ethyl(2,5-dimethoxyphenyl)]-5,6,10,11,15b,15c-hexahydro-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2l** as white rosettes (0.292 g, 58%) mp 181–183.5 °C (EtOAc), R_f 0.37 (EtOAc) (Found: C, 70.63; H, 7.10; N, 4.89. $C_{33}H_{40}N_2O_6$ requires: C, 70.69; H, 7.19; N, 5.00%). IR (KBr): 2927, 2830, 2360, 1609, 1504, 1464, 1228, 1126, 1050, 855 cm^{-1}. UV (MeOH): 240, 278 nm. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 2.09 (1H, m, H1′), 2.48 (1H, br d, *J* 13.6 Hz, H_β5), 2.72 (1H, m, H_a2), 2.86 (1H, m, H_β11), 2.86 (1H, m, H_β6), 2.91 (1H, m, H_α5), 2.92 (1H, m, H_b2), 3.05 (1H, m, H_α10), 3.07 (1H, m, H_α11), 3.08 (1H, m, H_α6), 3.33 (1H, m, H_β10), 3.55 (1H, d, *J* 9.0 Hz, H15b), 3.60 (3H, s, 13-OMe), 3.71 (3H, s, 3-OMe), 3.78 (3H, s, 2″-OMe), 3.82 (3H, s, 5″-OMe), 3.87 (3H, s, 14-OMe), 3.90 (3H, s, 2-OMe), 4.16 (1H, dd, *J* 9.0, 4.1 Hz, H8), 4.32 (1H, d, *J* 9.0 Hz, H15c), 6.04 (1H, s, H15), 6.41 (1H, s, H1), 6.68 (1H, s, H12), 6.72 (1H, dd, *J* 8.7, 3.0 Hz, H4″), 6.74 (1H, s, H4), 6.80 (1H, d, *J* 8.7 Hz, H3″), 6.83 (1H, d, *J* 3.0 Hz, H6″); ^{13}C NMR ($CDCl_3$, 75.6 MHz) *δ*: 25.4 (C5), 27.1 (C2′), 29.3 (C11), 30.3 (C1′), 39.1 (C10), 46.2 (C6), 55.6 (2-OMe), 55.7 (13-OMe), 55.7 (5″-OMe), 55.8 (2-OMe), 55.8 (5″-OMe), 55.9 (3-OMe), 64.7 (C15c), 69.8 (C15b), 82.1 (C8), 110.9 (C12), 111.0 (C4″), 111.2 (C3″), 111.5 (C4), 111.9 (C15), 112.9 (C1), 116.1 (C6″), 125.4 (C11a), 126.8 (C15a), 127.7 (C4a), 129.7 (C15d), 131.8 (C1″), 146.1 (C13), 146.4 (C3), 147.4 (C2), 148.0 (C14), 151.7 (C5″), 153.5 (C2″); Mass spectrum (EI): *m/z* 559 (M−1$^+$, 0.8%), 409 (1), 395 (7), 369 (15), 338 (6), 219 (10), 218 (100), 202 (8), 191 (12).

4.1.12. Reaction with pyrrole-2-carboxaldehyde. This reaction occurred at reflux within 13 h to yield *5,6,10,11,15b,15c-hexahydro-8-(pyrrol-2-yl)-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2m** as a microcrystalline white solid (80 mg, 87%) mp 234–236 °C (EtOAc), R_f 0.75 (MeOH) (Found: C, 70.33; H, 6.67; N, 9.07. $C_{27}H_{31}N_3O_4$ requires: C, 70.26; H, 6.77; N, 9.10%). IR (KBr): 1605, 1514, 1455, 1345, 1262, 1226, 1123, 1017, 855, 716 cm^{-1}. UV (MeOH): 241, 283 nm. ^{1}H NMR ($CDCl_3$) *δ*: 2.45 (1H, m, H_β5), 2.48 (1H, m, H_α10), 2.73 (1H, m, H_α11), 2.83 (1H, m, H_β6), 2.88 (1H, m, H_β11), 2.89 (1H, m, H_β10), 2.95 (1H, m, H_α5), 2.96 (1H, m, H_α6), 3.63 (3H, s, 14-OMe), 3.69 (1H, d, *J* 9.0 Hz, H15b), 3.75 (3H, s, 2-OMe), 3.85 (3H, s, 13-OMe), 3.90 (3H, s, 3-OMe), 4.42 (1H, d, *J* 9.0 Hz, H15c), 5.22 (1H, s, H8), 6.19 (1H, s, H15), 6.25 (1H, m, H4′), 6.36 (1H, br s, H3′), 6.51 (1H, s, H1), 6.64 (1H, s, H12), 6.75 (1H, s, H4), 6.77 (1H, br s, H5′), 9.09 (1H, br s, NH); ^{13}C NMR ($CDCl_3$) *δ*: 25.5 (C5), 29.2 (C11), 41.3 (C10), 46.2 (C6), 55.7 (13-OMe), 55.8 (3-OMe), 55.9 (14-OMe), 56.0 (2-OMe), 63.8 (C15c), 69.9 (C15b), 79.0 (C8), 108.6 (C3′ or C4′), 108.7 (C3′ or C4′), 111.2 (C12), 111.5 (C15), 111.7 (C4), 112.7 (C1), 117.0 (C5′), 125.5 (C15a), 127.0 (C11a), 127.7 (C15d), 128.3 (C2′), 129.9 (C4a), 146.2 (C14), 146.6 (C2), 147.6 (C3), 148.0 (C13); Mass spectrum (EI): *m/z* 271 (M−190, 15%), 270 (100), 255 (21), 191 (12), 176 (18).

4.1.13. Reaction with pyridine-2-carboxaldehyde. This reaction occurred at reflux within 2 h to yield *5,6,10,11,15b,15c-hexahydro-8-(pyridin-2-yl)-2,3,13,14-tetramethoxy-8H-imidazo[5,1-a:4,3-a′]diisoquinoline* **2n** as tan needles (48 mg, 50%) mp 200–201 °C (acetone), R_f 0.58 (MeOH) (Found: C, 70.95; H, 6.47; N, 8.76. $C_{28}H_{31}N_3O_4$ requires: C, 71.02; H, 6.60; N, 8.87%). IR (KBr): 1607, 1513, 1460, 1336, 1255, 1224, 1126, 1017, 849, 788, 759 cm^{-1}. UV (MeOH): 242, 288 nm. ^{1}H NMR ($CDCl_3$) *δ*: 2.39 (1H, ddd, *J* 10.5, 5.3, 4.3 Hz, H_α10), 2.47 (1H, br d, *J* 14.7 Hz, H_β5), 2.73 (1H, ddd, *J* 15.8, 4.5, 3.8 Hz, H_α11), 2.83 (1H, m, H_β6), 2.84 (1H, m, H_β11), 2.92 (1H, m, H_α6), 2.93 (1H, m, H_β10), 3.00 (1H, m, H_α5), 3.65 (3H, s, 14-OMe), 3.74 (1H, d, *J* 9.0 Hz, H15b), 3.76 (3H, s, 2-OMe), 3.84 (3H, s, 13-OMe), 3.90 (3H, s, 3-OMe), 4.53 (1H, d, *J* 9.0 Hz, H15c), 5.13 (1H, s, H8), 6.29 (1H, s, H15), 6.59 (1H, m, H1), 6.62 (1H, s, H12), 6.76 (1H, s, H4), 7.26 (1H, ddd, *J* 7.5, 4.1, 1.1 Hz, H5′), 7.75 (1H, ddd, *J* 7.5, 7.5, 1.9 Hz, H4′), 7.82 (1H, d, *J* 7.5 Hz, H3′), 8.67 (1H, d, *J* 4.1 Hz, H6′); ^{13}C NMR ($CDCl_3$) *δ*: 25.8 (C5), 29.3 (C11), 41.9 (C10), 46.3 (C6), 55.8 (3-OMe), 55.7 (13-OMe), 55.9 (14-OMe), 56.1 (2-OMe), 64.7 (C15c), 70.1 (C15b), 86.1 (C8), 111.2 (C12), 111.3 (C15), 111.7 (C4), 112.9 (C1), 123.0 (C5′), 123.1 (C3′), 126.1 (C15a), 127.1 (C11a), 128.0 (C15d), 130.3 (C4a), 136.5 (C4′), 146.2 (C14), 146.6 (C2), 147.6 (C3), 147.9 (C13), 149.3 (C6′), 159.0 (C2′); Mass spectrum (EI): *m/z* 395 (M−78, 6%), 283 (18), 282 (100), 281 (68), 190 (20), 176 (12), 93 (18).

4.2. Kinetic studies of the condensation reactions of bis(tetrahydroisoquinoline) 1 with aldehydes

General procedure: A solution of aldehyde (0.0521 mmol) in $CDCl_3$ (0.2 mL) was added to an ice-cooled solution of bis(tetrahydroisoquinoline) **1** (20 mg, 0.0521 mmol) in $CDCl_3$ (0.5 mL) in a 5 mm diameter NMR tube. The NMR tube was immediately capped, shaken vigorously and inserted into the temperature-conditioned NMR probe. The composition of the mixture was analysed by ^{1}H NMR spectroscopy at regular intervals, and the integration of relevant signals and thus percentage composition or component abundance relative to residual chloroform as an internal standard was measured and calculated.

Relative reaction rates were initially assessed in a preliminary study and then measured under precisely defined conditions. For the fastest reaction, that with isobutyraldehyde, each datum point was collected using spectra acquired with one scan, an acquisition time of 2.6 s and a recycle

delay of 10 s. For the remaining slower reactions, each datum point was extracted from an experiment that was acquired using 16 scans with an acquisition time of 4.6 s and a recycle delay of 6 s.

Reaction at 273 K with:

(a) isobutyraldehyde gave unreacted bis(tetrahydroisoquinoline) **1** (δ 4.51, H1, H1′) and imidazolidine **2a** (δ 6.00, H15; 6.49, H1) in the integral ratio of 1.24:1.00 (85% conversion).
(b) 2-chlorobenzaldehyde gave unreacted bis(tetrahydroisoquinoline) **1** (δ 6.60, H5, H5′) and imidazolidine **2e** (δ 6.20, H15; 6.53, H1) in the integral ratio of 1.00:0.02 (2% conversion).
(c) 2,5-dimethoxybenzaldehyde gave unreacted bis(tetrahydroisoquinoline) **1** (δ 6.79, H8, H8′) but no imidazolidine **2h** (δ 6.15, H15; 6.51, H1) leaving the integral ratio of 1.00:0.00 (0% conversion).

4.3. Reductive cleavage of imidazolidines 2a, 2h and 2l

General procedure: Aqueous HCl (10 mL of 2 M/g solution of imidazolidine) was added dropwise to a suspension of imidazolidine and $NaBH_3CN$ (3 mol equiv) in absolute EtOH (100 mL/g of imidazolidine) at room temperature. The mixture immediately became clear and the solution was measured to have pH 1. The resultant mixture was stirred at ambient temperature for 1 h, then satd aq $NaHCO_3$ (20 mL/g of imidazolidine) was added dropwise followed by H_2O. The mixture was extracted with EtOAc, the extracts were dried over Na_2SO_4 and the solution was evaporated to dryness. Chromatography of the residue on alumina, eluting with a gradient of light petroleum, EtOAc and MeOH, afforded the major product.

4.3.1. Reductive cleavage of imidazolidine (2a). Imidazolidine **2a** (0.150 g, 0.342 mmol) afforded *2-isobutyl-6,6′,7,7′-tetramethoxy-1,1′-bis(1,2,3,4-tetrahydroisoquinoline)* **3a** as colourless needles (0.144 g, 95%) mp 130–131 °C (EtOAc), R_f 0.44 (EtOAc/Al_2O_3) (Found: C, 70.98; H, 8.33; N, 6.03. $C_{26}H_{36}N_2O_4$ requires: C, 70.88; H, 8.24; N, 6.36%). IR (KBr): 2954, 2835, 1608, 1518, 1466, 1360, 1262, 1226, 1116, 1032, 866, 776 cm^{-1}. UV (MeOH): 215, 285 nm. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.90 (3H, d, J 6.8 Hz, 2″-(CH_3)$_a$(CH_3)$_b$), 0.92 (3H, d, J 6.8 Hz, 2″-(CH_3)$_a$(CH_3)$_b$), 1.79 (1H, m, H2″), 2.21 (1H, dd, J 12.4, 7.5 Hz, H$_a$1″), 2.37 (1H, dd, J 12.4, 6.8 Hz, H$_b$1″), 2.56 (1H, m, H$_\beta$4), 2.73 (1H, ddd, J 15.8, 4.9, 4.5 Hz, H$_\alpha$4′), 2.83 (1H, m, H$_\beta$3), 2.88 (1H, m, H$_\alpha$4), 2.91 (1H, m, H$_\beta$4′), 3.02 (1H, ddd, J 12.0, 5.6, 4.5 Hz, H$_\alpha$3′), 3.27 (1H, ddd, J 12.0, 9.0, 4.9 Hz, H$_\beta$3′), 3.43 (1H, m, H$_\alpha$3), 3.45 (3H, s, 7-OMe), 3.47 (3H, s, 7′-OMe), 3.58 (1H, d, J 8.6 Hz, H1), 3.83 (3H, s, 6-OMe), 3.83 (3H, s, 6′-OMe), 3.95 (1H, d, J 8.6 Hz, H1′), 5.77 (1H, s, H8), 5.79 (1H, s, H8′), 6.58 (1H, s, H5), 6.59 (1H, s, H5′); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ: 20.3 (2″-(CH_3)$_a$(CH_3)$_b$), 20.9 (2″-(CH_3)$_a$(CH_3)$_b$), 23.1 (C4), 26.7 (C2″), 29.0 (C4′), 39.1 (C3′), 43.4 (C3), 55.2 (7-OMe), 55.3 (7′-OMe), 55.8 (6-OMe, 6′-OMe), 59.0 (C1′), 62.4 (C1″), 65.0 (C1), 111.2 (C5), 111.3 (C5′), 113.9 (C8), 114.3 (C8′), 126.4 (C8a), 126.9 (C8a′), 127.0 (C4a), 127.6 (C4a′), 145.4 (C7), 145.5 (C7′), 147.5 (C6), 147.6 (C6′); Mass spectrum (EI): m/z 441 (M^+, 0.1%), 365 (0.3), 249 (13), 248 (100), 206 (27), 191 (19), 176 (24), 41 (28).

4.3.2. Reductive cleavage of imidazolidine (2h). Imidazolidine **2h** (0.100 g, 0.188 mmol) afforded *2-(2,5-dimethoxybenzyl)-6,6′,7,7′-tetramethoxy-1,1′-bis(1,2,3,4-tetrahydroisoquinoline)* **3h** as colourless needles (0.96 g, 96%) mp 133.5–135 °C (EtOAc), R_f 0.38 (EtOAc/Al_2O_3) (Found: C, 69.73; H, 7.46; N, 4.93. $C_{31}H_{38}N_2O_6$ requires: C, 69.64; H, 7.16; N, 5.24%). IR (KBr): 2934, 2832, 2361, 1610, 1516, 1464, 1262, 1232, 1112, 1023, 862 cm^{-1}. UV (MeOH): 221, 289 nm. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.49 (1H, m, H$_\beta$4′), 2.61 (1H, m, H$_\alpha$4), 2.85 (3H, m, H$_\alpha$3′, H$_\beta$3′ and H$_\alpha$4′), 2.95 (1H, m, H$_\beta$3), 2.97 (1H, m, H$_\beta$4), 3.43 (3H, s, 7′-OMe), 3.45 (3H, s, 7-OMe), 3.46 (1H, m, H$_\alpha$3), 3.57 (1H, d, J 9.1 Hz, H1), 3.66 (1H, d, J 12.3 Hz, H$_a$1″), 3.73 (1H, d, J 12.3 Hz, H$_b$1″), 3.74 (3H, s, 2‴-OMe), 3.77 (3H, s, 5‴-OMe), 3.80 (3H, s, 6′-OMe), 3.85 (3H, s, 6-OMe), 4.09 (1H, d, J 9.1 Hz, H1′), 5.67 (1H, s, H8), 5.76 (1H, s, H8′), 6.54 (1H, s, H5′), 6.63 (1H, s, H5), 6.79 (1H, m, H6‴), 6.80 (1H, m, H3‴), 6.82 (1H, m, H4‴); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ: 23.0 (C4), 27.6 (C4′), 38.1 (C3′), 43.1 (C3), 52.7 (C1″), 55.2 (7′-OMe), 55.3 (7-OMe), 55.6 (2‴-OMe), 55.8 (6′-OMe, 5‴-OMe), 55.9 (6-OMe), 57.6 (C1′), 62.5 (C1), 111.1 (C5′), 111.3 (C5), 111.6 (C4‴), 112.7 (C3‴), 113.9 (C8′), 114.2 (C8), 117.4 (C6‴), 124.7 (C8a), 124.9 (C8a′), 126.7 (C4a′), 127.0 (C4a), 128.0 (C1‴), 145.6 (C7), 145.7 (C7′), 147.8 (C6′), 147.9 (C6), 152.3 (C2‴), 153.3 (C5‴); Mass spectrum (EI): m/z 535 (M^+, 0.3%), 343 (17), 342 (91), 192 (52), 176 (27), 164 (33), 151 (100), 121 (60), 91 (25), 77 (25).

4.3.3. Reductive cleavage of imidazolidine (2l). Imidazolidine **2l** (0.200 g, 0.357 mmol) afforded *2-[3-(2,5-dimethoxybenzyl)propyl]-6,6′,7,7′-tetramethoxy-1,1′-bis(1,2,3,4-tetrahydroisoquinoline)* **3l** as colourless needles (0.157 g, 78%) mp 83.5–85.5 °C (EtOAc), R_f 0.40 (EtOAc/Al_2O_3) (Found: C, 68.55; H, 7.56; N, 4.45. $C_{33}H_{42}N_2O_6\cdot$EtOAc requires: C, 68.28; H, 7.74; N, 4.30%). IR (KBr): 2934, 2831, 2324, 1610, 1515, 1464, 1261, 1223, 1115, 1026, 861 cm^{-1}. UV (MeOH): 216, 287 nm. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.79 (2H, tt, J 7.5, 7.1 Hz, H2″), 2.56 (1H, m, H$_\beta$4), 2.58 (2H, m, H1″), 2.61 (2H, m, H3″), 2.74 (1H, m, H$_\alpha$4′), 2.86 (1H, m, H$_\beta$4′), 2.88 (1H, m, H$_\beta$3), 2.88 (1H, m, H$_\alpha$4), 3.01 (1H, ddd, J 12.2, 6.7, 5.3 Hz, H$_\alpha$3′), 3.29 (1H, ddd, J 12.2, 8.7, 4.9 Hz, H$_\beta$3′), 3.46 (1H, m, H$_\alpha$3), 3.46 (3H, s, 7′-OMe), 3.48 (3H, s, 7-OMe), 3.66 (1H, d, J 8.3 Hz, H1), 3.75 (3H, s, 5‴-OMe), 3.77 (3H, s, 2‴-OMe), 3.83 (6H, s, 6-OMe and 6′-OMe), 3.99 (1H, d, J 8.3 Hz, H1′), 5.78 (1H, s, H8), 5.80 (1H, s, H8′), 6.59 (1H, s, H5), 6.60 (1H, s, H5′), 6.68 (1H, dd, J 8.3, 3.0 Hz, H4‴), 6.70 (1H, d, J 3.0 Hz, H6‴), 6.76 (1H, d, J 8.3 Hz, H3‴); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ: 23.3 (C4), 27.9 (C3″), 28.2 (C2″), 28.7 (C4′), 39.1 (C3′), 43.6 (C3), 53.2 (C1″), 55.3 (7′-OMe), 55.4 (7-OMe), 55.6 (5‴-OMe), 55.82 (6′-OMe), 55.84 (2‴-OMe), 55.9 (6-OMe), 58.8 (C1′), 63.8 (C1), 110.7 (C4‴), 111.2 (C5), 111.3 (C5′, C3‴), 113.6 (C8′), 114.1 (C8), 116.2 (C6‴), 125.8 (C8a), 126.4 (C8a′), 126.9 (C4a′), 127.4 (C4a), 131.7 (C1‴), 145.6 (C7), 145.7 (C7′), 147.7 (C6, C6′), 151.7 (C5‴), 153.4 (C2‴); Mass spectrum (EI): m/z 563 (M^+, 0.25%), 371 (21), 370 (100), 206 (26), 192 (61), 176 (28), 121 (20), 91 (22), 77 (26), 43 (45).

4.4. 'One-pot' mono-alkylation of bis(tetrahydroisoquinoline) 1 with isobutyraldehyde

A solution of bis(tetrahydroisoquinoline) **1** (0.200 g, 0.521 mmol) and isobutyraldehyde (0.113 g, 1.562 mmol) in EtOH (20 mL) was stirred under argon at room temperature for 1 h. $NaBH_3CN$ (0.098 g, 1.562 mmol) and 2 M HCl (2.0 mL) were added sequentially, whereupon the white suspension immediately became clear. The resultant mixture was stirred at room temperature for 1 h, then satd aq $NaHCO_3$ (5 mL) was added dropwise followed by H_2O and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (5×20 mL). The combined organic extracts were dried over Na_2SO_4 and the solution evaporated to dryness, to afford a white crystalline solid. Analysis of the crude material by ^1H NMR spectroscopy indicated 100% conversion to the mono-alkylated product. Flash chromatography on Al_2O_3, eluting with EtOAc, afforded *2-isobutyl-6,6′,7,7′-tetramethoxy-1,1′-bis(1,2,3,4-tetrahydroisoquinoline)* **3a** as a white crystalline solid (0.197 g, 86%), which was identical by ^1H NMR spectroscopy to the earlier product.

Acknowledgements

The authors are indebted to the China Scholarship Council for the award of a Chinese Government Scholarship to B.D. and the Australian Research Council for an Australian Postgraduate Award to M.W.J. and UNSW Summer Vacation Scholarship to B.C. Financial support from the Australian Research Council is also gratefully acknowledged.

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