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DETERMINATION OF THE STEREOCHEMISTRY OF 1-SUBSTITUTED 3-ARYLTETRAHYDROISOQUINOLINES BY ^{1}H NMR SPECTROSCOPY

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Abstract — The *cis*-1,3-disubstituted tetrahydroisoquinolines 2 can be obtained in a highly diastereoselective fashion through Pictet-Spengler cyclization of the 1,2-bis(3,4-dimethoxyphenyl)-ethylamine with aliphatic and aromatic aldehydes under acidic conditions. However, the epimeric *trans*-1,3-disubstituted tetrahydroisoquinolines 3 are also isolated as minor products. The stereochemistry of the tetrahydroisoquinolines was unambiguously assigned on the basis of the ^{1}H NMR data, and are supported by difference NOE measurements.

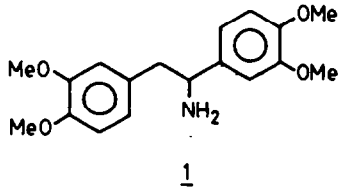
The regioselectivity of the Pictet-Spengler reaction[1] of phenethylamines with carbonyl compounds is well known,[2] but the stereochemistry involved has been less fully investigated. In the cases studied the stereoselectivity of the reaction appears to vary considerably. Whereas certain amines give predominantly one isomer, other substrates afford nearly equal amounts of the two possible isomers. For example, Bates reported that the cyclization of epinephrine[3] and norepinephrine[4] with acetaldehyde, under acidic conditions, afforded a 1:1 mixture of the epimeric *cis*- and *trans*-tetrahydro-4,6,7-isoquinolinetriols. In contrast, tetrahydroisoquinoline products of the condensations conducted under nearly neutral conditions were mixtures of the corresponding epimers of the 6,7- and 7,8-dihydroxy substituted derivatives, whose ratio depended on the pH. It has also been found[5] that the acid-catalyzed condensations of L-Dopa with acetaldehyde gave a 95:5 mixture of the *cis*- and *trans*-aminoacids, respectively.

Moreover, we have recently described[6,7] the phenolic cyclization of two 1,2-diarylethylamines with acetaldehyde. Although the 1-(3,4-dimethoxyphenyl)-2-(2-bromo-5-hydroxy-4-methoxyphenyl)ethylamine gave stereoselectively the *cis*-tetrahydroisoquinoline, the corresponding debrominated amine afforded a 2.5:1 mixture of the *cis*- and *trans*-3-aryltetrahydroisoquinoline derivatives.

On the other hand, since we had previously reported[8] the regioselective synthesis of 1-substituted 6,7-dialkoxy-3-aryltetrahydroisoquinolines by Pictet-Spengler condensation of the 1,2-bis(3,4-dimethoxyphenyl)ethylamine 1 with several aliphatic and aromatic aldehydes, it seemed worthwhile to reinvestigate the stereochemical course of these reactions. In this report, we describe the isolation and complete characterization of the diastereomeric 3-aryltetrahydroisoquinolines 2 and 3, which result from the above mentioned Pictet-Spengler cyclizations.

RESULTS AND DISCUSSION

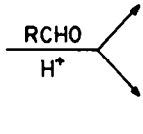
We undertook the Pictet-Spengler reaction of the 1,2-bis(3,4-dimethoxyphenyl)-ethylamine 1[9] with aliphatic (acetaldehyde and propionaldehyde) and aromatic (benzaldehyde and veratraldehyde) aldehydes, according to the previously described procedures.[8] Thus, we have found that the tetrahydroisoquinolines obtained as the major products were the corresponding *cis*-1,3-disubstituted derivatives 2a-d, as it can be deduced by ^{1}H NMR observations (see below).

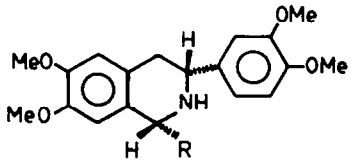


1

a: R=Me ; b: R=Et

c: R=Ph ; d: R=3,4(MeO)$_2$Ph

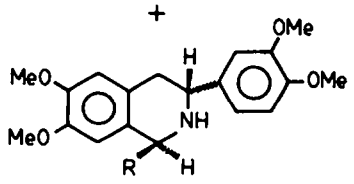




2

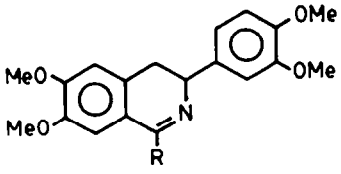
Major

+



3

Minor



4

c: R=Ph ; d: R=3,4(MeO)$_2$Ph

The mother liquors from the crystallization of the above tetrahydroisoquinolines 2 were subjected to flash column chromatography[10] and the corresponding epimeric *trans*-1,3-disubstituted tetrahydroisoquinolines 3a-d were isolated as the minor products. Besides, it was observed that the 1,3-diaryltetrahydroisoquinolines underwent air oxidation[11] during the usual work-up procedure to afford the corresponding 3,4-dihydroisoquinoline derivatives 4c and 4d in low yield.

The ^{1}H NMR spectroscopic data unequivocally confirmed the structures suggested for the tetrahydroisoquinolines 2 and 3, whose stereochemistry was deduced by measurements of the difference Nuclear Overhauser Effect (NOE)[12] and selective ^{1}H-^{1}H decoupling experiments. In all tetrahydroisoquinolines 2, the diastereotopic methylene protons H-4 and methine proton H-3 form a typical ABX system (J_{AX}= 3.5 and J_{BX}= 11.5 Hz), which is consistent with an axial position for H-3 and, therefore, an equatorial orientation for the 3-aryl group. However, the tetrahydroisoquinolines 3 show deceptively simple spectra and the H-4 and H-3 protons appear as an apparent A_2X system (J_{AX}= 7.0 Hz), which does not allow the determination of the orientation of H-3.

The difference in the distance of the H-1 and H-3 protons, which is the most distinctive feature differentiating the proposed configurations, is supported by the significant positive or no NOE between these protons of the tetrahydroisoquinolines 2 and 3 respectively. Thus, the observation of a NOE between H-3 and H-1 in the tetrahydroisoquinolines 2 suggests a *cis*-1,3-diaxial relationship between these protons (Table 1). Taking into account these facts, we may conclude that isoquinolines 2 present a preferential conformation for the heterocyclic ring of a

half-chair, with a *cis* configuration and with the substituents at C-1 and C-3 in pseudoequatorial and equatorial positions, respectively.

In contrast, in the isoquinoline series 3, H-1 is unaffected when H-3 is irradiated, and viceversa. On the other hand, the observation of an increase in intensity of the signal for the substituents at C-1 on irradiation of H-3 is consistent with axial and pseudoaxial positions for H-3 and R, respectively (Figure 1). The inverse experiment gives a similar result (Table 1). These results are in clear agreement with a *trans* configuration for the tetrahydroisoquinolines 3. In addition, the data of the NOE experiments have allowed us to assign unequivocally the resonances of the aliphatic and aromatic protons (Table 1).

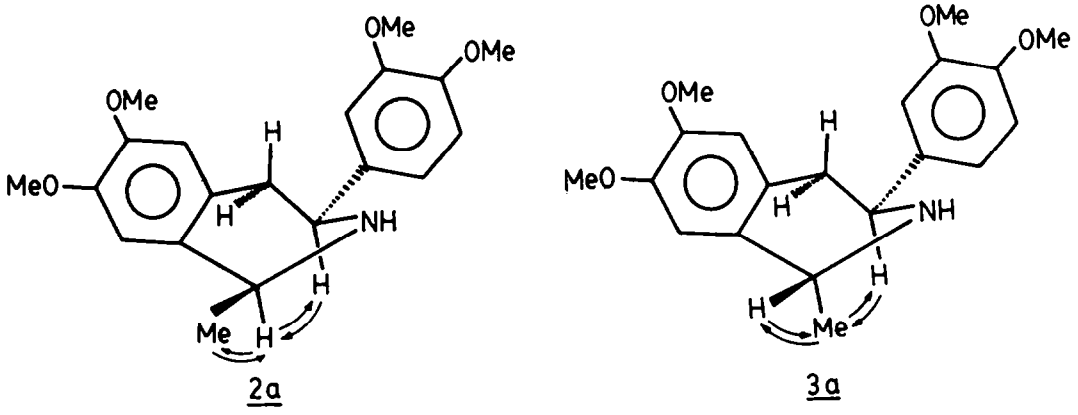


Figure 1

In conclusion, our results indicate that the Pictet-Spengler cyclization is highly diastereoselective for the synthesis of 1-substituted 6,7-dialkoxy-3-aryltetrahydroisoquinolines. In fact, the *cis*-1,3-disubstituted diastereomers 2 were always obtained as the major products, though accompanied by lesser quantities of the corresponding *trans* epimers 3 (Table 2). Since the less sterically hindered isomer is always the major product, the reaction seems to be a thermodynamically controlled process.

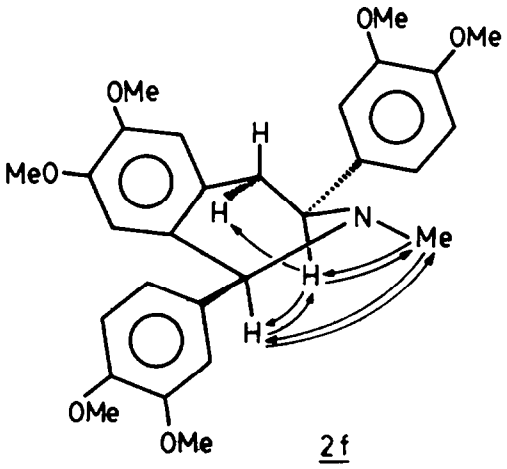


Figure 2

In order to complete our investigations on the stereochemistry of 3-aryltetrahydroisoquinolines, we have also studied the corresponding *N*-methyl derivatives,[8] obtained from the *cis*-1,3-disubstituted diastereomers 2c and 2d by *N*-alkylation with formaldehyde-formic acid. It was observed that the *N*-alkylation took place with retention of configuration and good yields. NOE experiments established the equatorial character of the *N*-methyl substituent. As an example, the observed NOE for 2f are shown in Figure 2.

Table 1. Selected 250 MHz ^{1}H NMR Data[a] and Results of Difference NOE Experiments[b] on the 3-Aryltetrahydroisoquinolines 2 and 3

Compound	Irradiated proton δ (ppm), J (Hz)		Observed NOE
2a	CH_3	1.51 (d,J=6.5)	H-1, H-8
	H-3	3.98 (dd,J=3.6, 11.9)	H-1, H-2', H-6', $H\text{-}4_e$
	H-1	4.26 (q,J=6.5)	CH_3, H-3, H-8
3a	CH_3	1.53 (d,J=6.7)	H-1, H-8, H-3
	H-3	4.22 (t,J=7.1)	H-4, H-2', H-6', CH_3
	H-1	4.30 (q,J=6.7)	CH_3, H-8
	H-4	2.88 (d,J=7.1)	H-3, H-5, H-2', H-6'
2b	H-1	4.14 (broad d)	CH_2-CH_3, H-3, H-8
	H-3	3.95 (dd,J=3.5, 10.0)	H-1, $H\text{-}4_e$, H-2', H-5', H-6'
3b	H-1	3.96[c]	CH_2-CH_3, H-8
	H-3	4.18 (dd,J=3.1, 7.0)	H-4, H-2', H-6', CH_2CH_3
2c	H-1	5.21 (s)	H-3, H-8, H-2", H-6"
	H-3	4.14 (dd,J=3.5, 11.5)	H-1, $H\text{-}4_e$, H-2', H-6'
	$H\text{-}4_e$	2.89 (dd,J=3.5, 15.5)	H-3, $H\text{-}4_a$, H-5
	$H\text{-}4_a$	3.11 (dd,J=11.5, 15.5)	$H\text{-}4_e$, H-5, H-8
3c	H-1	5.31 (s)	H-8, H-2", H-6"
	H-3	4.01 (t,J=7.3)	H-4, H-2', H-6', H-2", H-6"
2d	H-1	5.16 (s)	H-3, H-8, H-2", H-6"
	H-3	4.14 (dd,J=3.5, 11.1)	H-1, $H\text{-}4_e$, H-2', H-6"
	$H\text{-}4_a$	3.10 (dd,J=11.1, 15.6)	H-3, $H\text{-}4_e$, H-5
3d	H-1	5.24 (s)	H-8, H-2", H-6"
	H-3	4.03 (t,J=7.3)	H-4, H-2", H-6"

[a] s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet. Subscript *a* or *e* indicates an axial or equatorial hydrogen where this can be distinguished by the splitting pattern.

[b] Performed as described in Experimental.

[c] Signal overlapped with the MeO signals.

EXPERIMENTAL

Microanalyses were carried out by the "Colegio Universitario de Álava" (Spain). Melting points were determined on either Electrothermal 1A 6304 or Büchi apparatus and are uncorrected. For thin-layer chromatography Merck Kieselgel GF 254 plates (0.2 mm thick) were used. Visualization was accomplished by UV light or by spraying with Dragendorff's reagent.[13] The flash column chromatography[10] was carried out on Merck Kieselgel 60 (0.040-0.063 nm, 230-400 mesh). IR spectra were recorded in KBr on a Perkin-Elmer 1430 spectrophotometer. The 250 MHz ^{1}H NMR spectra were performed on a Bruker WM-250 spectrometer at ambient temperature. ^{1}H-{^{1}H} NOE experiments were carried out in the difference mode[12] by irradiation of all the lines of a multiplet.[14] Chemical shifts are expressed in δ values relative to internal TMS and coupling constants in Hz.

The Pictet-Spengler condensation of the 1,2-bis(3,4-dimethoxyphenyl)ethylamine 1 with acetaldehyde, propionaldehyde, benzaldehyde, and veratraldehyde under acidic conditions, following the literature procedures,[8] afforded as the major products the corresponding *cis*-1,3-disubstituted tetrahydroisoquinolines 2 (Table 2):

cis-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline 2a. IR (KBr) ν_{max} cm^{-1}: 3320 (NH). ^{1}H NMR ($CDCl_3$) δ ppm: 1.51 (3H, d, J= 6.5, Me), 1.80 (1H, broad s, NH, exchangeable with D_2O), 2.83 (1H, dd, J_{AX}= 3.6 and J_{AB}= 15.6,

H-4_e), 2.97 (1H, dd, J_{BX}= 11.9 and J_{AB}= 15.6, H-4_a), 3.85 (3H, s, MeO), 3.88 (3H, s, MeO), 3.89 (3H, s, MeO), 3.91 (3H, s, MeO), 3.98 (1H, dd, J_{AX}= 3.6 and J_{BX}= 11.9, H-3), 4.26 (1H, q, J= 6.5, H-1), 6.58 (1H, s, H-5), 6.73 (1H, s, H-8), 6.86 (1H, d, J_{ortho}= 8.2, H-5'), 6.98 (1H, dd, J_{ortho}= 8.2 and J_{meta}= 1.9, H-6'), 7.03 (1H, d, J_{meta}= 1.9, H-2').

cis-3-(3,4-dimethoxyphenyl)-1-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 2b. IR (KBr) ν_{max} cm^{-1}: 3340 (NH). ^1H NMR ($CDCl_3$) δ ppm: 1.01 (3H, t, J= 7.4, CH_3-CH_2), 1.75 (2H, m, CH_3-CH_2), 2.06 (1H, broad s, NH, exchangeable with D_2O), 2.78 (1H, dd, J_{AX}= 3.5 and J_{AB}= 15.4, H-4_e), 2.93 (1H, dd, J_{BX}= 10.0 and J_{AB}= 15.4, H-4_a), 3.85 (3H, s, MeO), 3.87 (3H, s, MeO), 3.89 (3H, s, MeO), 3.91 (3H, s, MeO), 3.95 (1H, dd, J_{AX}= 3.5 and J_{BX}= 10.0, H-3), 4.14 (1H, broad d, H-1), 6.58 (1H, s, H-5), 6.74 (1H, s, H-8), 6.86 (1H, d, J_{ortho}= 8.1, H-5'), 6.99 (1H, dd, J_{ortho}= 8.1 and J_{meta}= 1.8, H-6'), 7.04 (1H, d, J_{meta}= 1.8, H-2').

cis-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline 2c. IR (KBr) : no bands in the 3100-3500 cm^{-1} region. ^1H NMR ($CDCl_3$) δ ppm: 1.8 (1H, broad s, NH, exchangeable with D_2O, 2.89 (1H, dd, J_{AX}= 3.5 and J_{AB}= 15.5, H-4_e), 3.11 (1H, dd, J_{BX}= 11.5 and J_{AB}= 15.5, H-4_a), 3.61 (3H, s, MeO), 3.86 (3H, s, MeO), 3.87 (3H, s, MeO), 3.89 (3H, s, MeO), 4.14 (1H, dd, J_{AX}= 3.5 and J_{BX} = 11.5, H-3), 5.21 (1H, s, H-1), 6.21 (1H, s, H-8), 6.61 (1H, s, H-5), 6.83 (1H, d, J_{ortho}= 8.1, H-5'), 7.00 (1H, dd, J_{ortho}= 8.1 and J_{meta}= 1.9, H-6'), 7.05 (1H, d, J_{meta}= 1.9, H-2'), 7.35 (5H, m,Ph).

cis-1,3-bis(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 2d. IR (KBr): no bands in the 3100-3500 cm^{-1} region. ^1H NMR ($CDCl_3$) δ ppm: 2.02 (1H, broad s, NH, exchangeable with D_2O), 2.89 (1H, dd, J_{AX}= 3.5 and J_{AB}= 15.6 H-4_e), 3.10 (1H, dd, J_{BX}= 11.1 and J_{AB}= 15.6, H-4_a), 3.64 (3H, s, MeO), 3.85 (3H, s, MeO), 3.86 (3H, s, MeO), 3.88 (3H, s, MeO), 3.90 (6H, s, 2 x MeO), 4.14 (1H, dd, J_{AX}= 3.5 and J_{BX}= 11.1, H-3), 5.16 (1H, s, H-1), 6.26 (1H, s, H-8), 6.62 (1H, s, H-5), 6.85 (2H, d, J_{ortho}= 8.0, H-5' and H-5"), 7.00 (4H, m, H-2', H-6', H-2", and H-6").

The mother liquors from the crystallization of the above tetrahydroisoquinolines 2 were evaporated to dryness and the residues were flash column chromatographed to yield the corresponding *trans*-1,3-disubstituted tetrahydroisoquinolines 3:

trans-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline 3a. IR (KBr) ν_{max} cm^{-1}: 3340 (NH). ^1H NMR ($CDCl_3$) δ ppm: 1.53 (3H, d, J= 6.7, Me), 1.88 (1H, broad s, NH, exchangeable with D_2O), 2.88 (2H, d, J= 7.1, H-4_e and H-4_a), 3.85 (3H, s, MeO), 3.87 (3H, s, MeO), 3.89 (3H, s, MeO), 3.90 (3H, s, MeO), 4.22 (1H, t, J= 7.1, H-3), 4.30 (1H, q, J= 6.7, H-1), 6.58 (1H, s, H-5), 6.61 (1H, s, H-8), 6.85 (1H, d, J_{ortho}= 8.2, H-5'), 6.96 (1H, dd, J_{ortho}= 8.2 and J_{meta}= 1.9, H-6'),7.02 (1H, d, J_{meta}= 1.9, H-2').

trans-3-(3,4-dimethoxyphenyl)-1-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 3b. IR (KBr) ν_{max} cm^{-1}: 3350 (NH). ^1H NMR ($CDCl_3$) δ ppm: 1.11 (3H, t, J= 7.4, CH_3-CH_2), 1.89 (3H, m, NH and CH_3-CH_2), 2.92 (2H, m, H-4_e and H-4_a), 3.90 (3H, s, MeO), 3.91 (3H, s, MeO), 3.94 (3H, s, MeO), 3.96 (4H, m, MeO and H-1), 4.18 (1H, t, J= 7.0, H-3), 6.62 (1H, s, H-5), 6.67 (1H, s, H-8), 6.90 (1H, d, J_{ortho}= 8.2, H-5'), 7.01 (1H, dd, J_{ortho}= 8.2 and J_{meta}= 1.8, H-6'), 7.10 (1H, d,J_{meta}= 1.8, H-2').

trans-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline 3c. IR (KBr) ν_{max} cm^{-1}: 3320 (NH). ^1H NMR ($CDCl_3$) δ ppm: 1.82 (1H, broad s, NH, exchangeable with D_2O), 2.96 (2H, d, J= 7.3, H-4_e and H-4_a), 3.73 (3H, s, MeO), 3.85 (3H, s, MeO), 3.86 (3H, s, MeO), 3.89 (3H, s, MeO), 4.01 (1H, t, J= 7.3, H-3), 5.31 (1H, s, H-1), 6.45 (1H, s, H-8), 6.66 (1H, s, H-5), 6.77 (1H, d, J_{ortho}= 8.2, H-5'), 6.80 (1H, dd, J_{ortho}= 8.2 and J_{meta}= 1.7, H-6'), 6.94 (1H, d, J_{meta}= 1.7, H-2'), 7.23 (5H, m,Ph).

trans-1,3-bis(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 3d. IR (KBr) ν_{max} cm^{-1}: 3330 (NH). ^1H NMR ($CDCl_3$) δ ppm: 1.89 (1H, broad s, NH, exchangeable with D_2O), 2.96 (2H, d, J= 7.3, H-4_e and H-4_a), 3.75 (3H, s, MeO), 3.83 (3H, s, MeO), 3.85 (3H, s, MeO), 3.86 (3H, s, MeO), 3.87 (3H, s, MeO), 3.89 (3H, s, MeO), 4.03 (1H, t, J= 7.3, H-3), 5.24 (1H, s, H-1), 6.46 (1H, s, H-8), 6.62 (1H, dd, J_{ortho}= 8.2 and J_{meta}= 2.0, H-6"), 6.66 (1H, s, H-5), 6.78 (4H, m, H-5', H-6', H-2", and H-5"), 6.94 (1H, d, J_{meta}= 1.6, H-2').

In the flash column chromatographic separation of the mother liquors from the 1,3-diaryltetrahydroisoquinolines 2c and 2d, the corresponding dihydroisoquinoline derivatives 4c and 4d were also isolated:

3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline 4c. R_f= 0.5 (chloroform/ethyl acetate, 7:3), yield: 2%, M.P 124-126°C (methanol). (Found: C, 74.38; H, 6.19; N, 3.45. $C_{25}H_{25}NO_4$ requires: C, 74.44; H, 6.20; N, 3.47%) (Lit.[15] M.P. (hydroiodide) 215-217°C).

1,3-bis(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline 4d. R_f= 0.4 (chloroform/ethyl acetate, 7:3), yield: 2%, M.P. 188-190°C (methanol). (Found: C, 69.91; H, 6.23; N, 3.00. $C_{27}H_{29}NO_6$ requires: C, 69.97; H, 6.26; N, 3.02%). (Lit.[15] M.P. (hydroiodide) 235-237°C).

Table 2. Synthesis and Characterization of the Diastereomeric 3-Aryltetrahydroisoquinolines 2 and 3

Compound	Yield (%)	Ratio 2:3	M.P.(°C)[a]	R_f	Formula	Calcd.(Found) (%) C	H	N
2a	75.0	8:1	131-132	0.2[b]	$C_{20}H_{25}NO_4$	(70.41) 69.97	(7.16) 7.29	(4.02) 4.08
3a	9.5		125-126	0.1[b]		(70.32)	(7.12)	(4.04)
2b	65.0	9:1	118-120	0.7[b]	$C_{21}H_{27}NO_4$	(70.03) 70.59	(7.28) 7.56	(3.84) 3.92
3b	7.0		123-124	0.3[b]		(69.98)	(7.34)	(3.87)
2c	81.0	30:1	74-75	0.7[c]	$C_{25}H_{27}NO_4$	(74.08) 74.07	(6.63) 6.67	(3.47) 3.46
3c	2.8		180-182	0.5[c]		(73.92)	(6.65)	(3.46)
2d	74.0	37:1	117-118	0.6[c]	$C_{27}H_{31}NO_6$	(70.02) 69.68	(6.79) 6.67	(3.00) 3.01
3d	2.0		140-142	0.4[c]		(70.01)	(6.83)	(3.03)
2e	68.0	-	138-139	0.7[d]	$C_{26}H_{29}NO_4$	74.76 (73.97)	6.92 (6.88)	3.34 (3.37)
2f	70.0	-	134-135	0.6[d]	$C_{28}H_{33}NO_6$	70.15 (70.03)	6.89 (6.89)	2.92 (2.91)

[a] Crystallization from methanol
[b] Eluent: chloroform/ethyl acetate (5:5)
[c] Eluent: Chloroform/ethyl acetate (7:3)
[d] Eluent: Dichloromethane/ethyl acetate (9.5:0.5)

The *N*-methylated 3-aryltetrahydroisoquinolines 2e and 2f were prepared[8] according to the Eschweiler-Clarke method, starting from the corresponding tetrahydroisoquinolines 2c and 2d (Table 2):

cis-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline 2e. ^{1}H NMR ($CDCl_3$) δ ppm: 1.94 (3H, s, MeN), 2.81 (1H, dd, J_{AX}= 3.1 and J_{AB} = 15.2, H-4$_e$), 3.26 (1H, dd, J_{BX}= 10.8 and J_{AB}= 15.2, H-4$_a$), 3.50 (1H, dd, J_{AX} = 3.1 and J_{BX}= 10.8, H-3), 3.58 (3H, s, MeO), 3.82 (3H, s, MeO), 3.89 (3H, s, MeO), 3.91 (3H, s, MeO), 4.35 (1H, s, H-1), 6.15 (1H, s, H-8), 6.53 (1H, s, H-5), 6.84 (1H, d, J_{ortho}= 8.1, H-5'), 6.96 (1H, dd, J_{ortho}= 8.1 and J_{meta}= 1.8, H-6'),7.00 (1H, d, J_{meta}= 1.8, H-2'), 7.19 (5H, m,Ph).

cis-1,3-bis(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 2f. ^{1}H NMR ($CDCl_3$) δ ppm: 1.95 (3H, s, MeN), 2.82 (1H, dd, J_{AX}= 3.0 and J_{AB}= 15.1, H-4$_e$), 3.27 (1H, dd, J_{BX}= 11.1 and J_{AB}= 15.1, H-4$_a$), 3.50 (1H, dd, J_{AX}= 3.0 and J_{BX}= 11.1, H-3), 3.62 (3H, s, MeO), 3.83 (3H, s, MeO), 3.86 (3H, s, MeO), 3.88 (3H, s, MeO), 3.89 (3H, s, MeO), 3.91 (3H, s, MeO), 4.28 (1H, s, H-1), 6.21 (1H, s, H-8), 6.54 (1H, s, H-5), 6.84 (2H, m, H-5' and H-5"), 6.94 (1H, dd, J_{ortho}= 7.6 and J_{meta}= 1.8, H-6"), 6.96 (1H, dd, J_{ortho}= 8.1 and J_{meta}= 1.9, H-6'), 6.99 (1H, d, J_{meta}= 1.8, H-2"), 7.01(1H, d, J_{meta}=1.9, H-2').

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