# THE TOTAL SYNTHESIS OF THE PAVINE ALKALOID THALIMONINE

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*Abstract*- The synthesis of the pavine alkaloid (±)-thalimonine (**1**) by the acid-mediated cyclization of the corresponding 1,2-dihydroisoquinoline (**10**) is reported. The latter compound was synthesized by a multistep reaction from 4-methoxy-2,3-methylenedioxybenzaldehyde. The resolution of (±)-**1** to its (-)-enantiomer was performed.

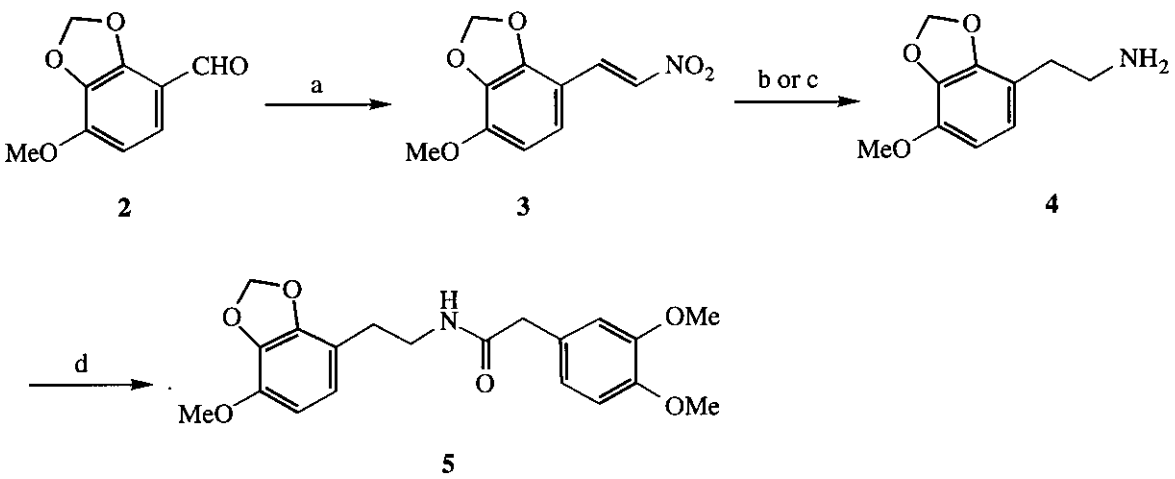
Pavines represent a relatively small subgroup of the isoquinoline alkaloids.[1] Various pharmacological activities have been attributed to the pavines but no pavinoid species yet been shown to be therapeutic agent,[1] although some investigations are underway.[2]

One member of this subgroup is (-)-thalimonine (**1**), which was recently isolated from *Thalictrum simplex* Leded by *Velcheva* et al.[3] One of the various synthetic routes to the pavine skeleton is the acid-mediated cyclization of corresponding 1,2-dihydroisoquinolines whose aromatic rings are substituted by electron-donating groups.[1,4] This synthetic route was applied to the synthesis of (±)–thalimonine where the required appropriately substituted 1-benzylisoquinoline was synthesized by a multistep reaction starting from 4-methoxy-2,3-methylenedioxybenzaldehyde (**2**). Compound (**2**) was prepared according to literature procedures.[5,6]

As shown in Scheme 1, the nitrostyrene (**3**) was obtained by the reaction of benzaldehyde (**2**) with $MeNO_2$. It was reduced to the amine (**4**) hydrochloride by catalytic hydrogenation in a MeOH and 1N HCl mixture over 10% Pd/C catalyst with a yield 67%. Because of the insolubility of **3** in solvents commonly used for catalytic hydrogenation, this method for the reduction of nitrostyrene (**3**) on a larger

scale could not be applied. Alternatively, the reduction could be done with $LiAlH_4$ in dry THF. Condensation of the amine (**4**) with 3,4-dimethoxyphenylacetyl chloride prepared from 3,4-dimethoxyphenylacetic acid, furnished the amide (**5**).

**Scheme 1**



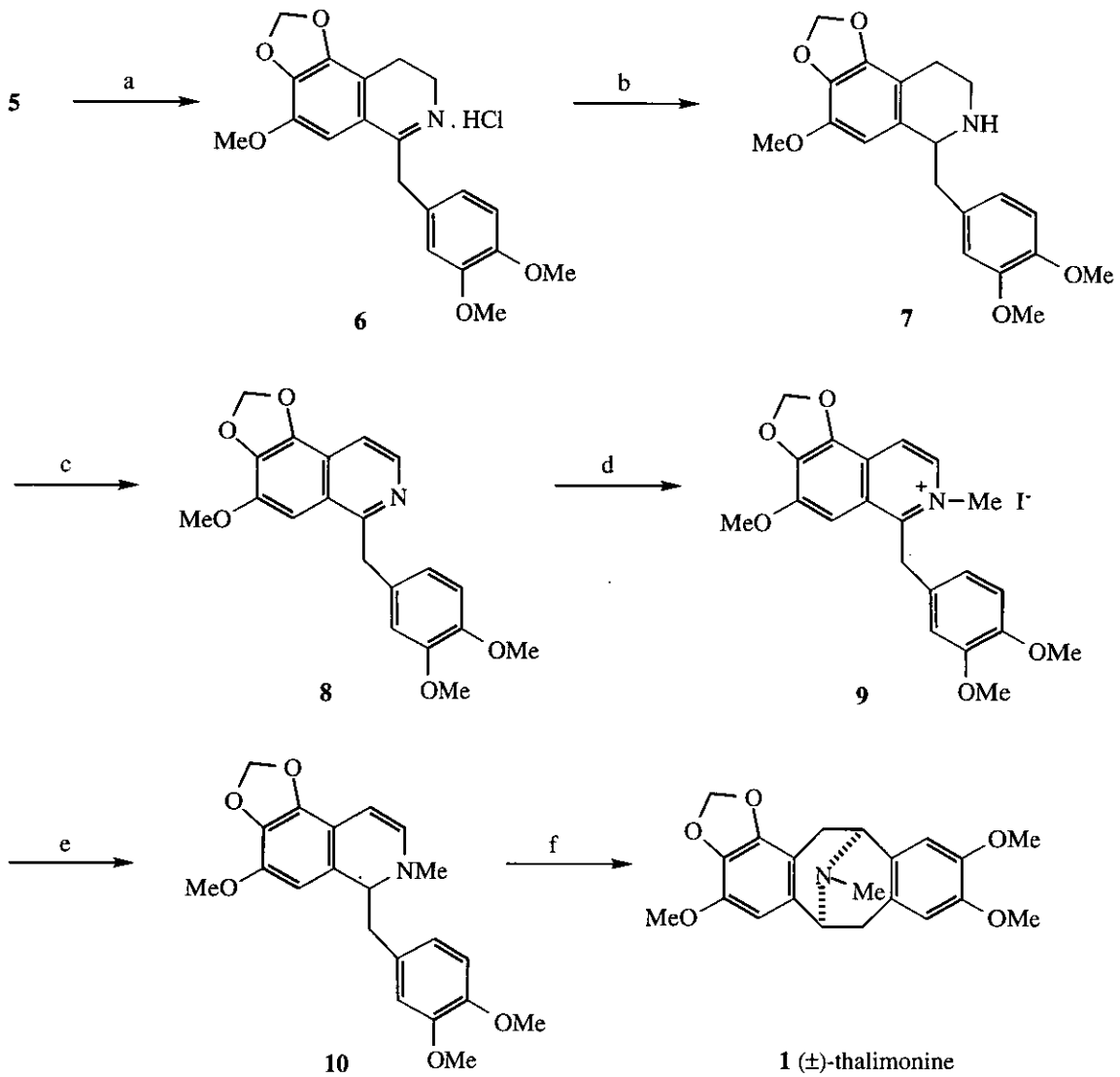

a) $MeNO_2$, $AcONH_4$ / AcOH, 100°C. b) $H_2$, 10% Pd/C in MeOH, aq. 1N HCl, rt. c) $LiAlH_4$ / THF, 80°C. d) 3,4-Dimethoxyphenylacetyl chloride, 10% aq. NaOH / $Et_2O$.

This amide was converted to the 3,4-dihydroisoquinoline hydrochloride (**6**) by a *Bischler-Napieralski* reaction with a yield of greater than 80% (*Scheme 2*). The reduction of **6** with $NaBH_4$ yielded the corresponding tetrahydroisoquinoline (**7**). Aromatization of **7** (reflux in toluene with 10% Pd/C) gave the isoquinoline (**8**). After the quaternization with MeI, the next step was the reduction of the 1,2-double bond in the methoiodide (**9**). When isoquinolinium salts are reduced with $NaBH_4$ under the usual aqueous-alcoholic solvent conditions, 1,2,3,4-tetrahydroisoquinolines are produced.[7] A nonprotic solvent, such as pyridine is required in order to form 1,2-dihydroisoquinolines.[7] Because of its unpleasant properties, attempts were made to avoid pyridine by replacing it with a different solvent like THF. However these attempts failed because of the insolubility of methoiodide salt (**9**). Therefore, the reduction of the methoiodide salt (**9**) to 1,2-dihydroisoquinoline (**10**) was made with $NaBH_4$ in pyridine using a procedure similiar to that reported by Chen.[4] The yield was 71 % after crystallization.

Beside the other spectral data, evidence of the reduction of the 1,2-double bond was supplied by its $^1H$-NMR spectrum. The α-hydrogens of the 1-benzyl group of **10**, observed as two separated dd with expected *J* values, and a signal integrated for 1H at δ 4.20 proved the existence of a proton at C-1 of the

isoquinoline nucleus. In addition, the chemical shifts and coupling constants of the ethylenic protons of C-3 and C-4 were in good agreement with the expected values.

**Scheme 2**




a) $POCl_3$ / MeCN, 100°C. b) $NaBH_4$ / MeOH, 0-5°C. c) 10% Pd / C in toluene, 125-130°C. d) MeI / DMF, 150°C. e) $NaBH_4$ / pyridine, rt. f) $H_3PO_4$ / HCOOH, 100-105°C.

The final step in the synthesis of **1** was the cyclization of the 1,2-dihydroisoquinoline (**10**) to its isomer thalimonine by using a mixture of HCOOH and $H_3PO_4$. Thalimonine was purified by flash

chromatography and was obtained as a foam. Proof of the cyclization was provided by the $^1$H-NMR spectrum. The change of the aromatic substitution pattern as well as of the couplings of the aliphatic protons is in good agreement with the cyclized structure. The racemic thalimonine has the same characteristic spectral features as those reported for the natural (-)-isomer.[3] Attempts to crystallize (±)-thalimonine failed, although many solvents and solvent mixtures were tried. Therefore we tried to solve this problem by preparing a salt. Unfortunately, the $^1$H-NMR spectrum revealed that the crystalline hydrochloride salt of (±)-thalimonine is a 1:1 mixture of two diastereomers, which were formed due to blocked *N*-inversion of the lone pair of electrons. This phenomenon is similiar to that known for *N*-oxides of isoquinolines.[8] The resolution of (±)-thalimonine to pure (-)-enantiomer ($[\alpha]_D$= -119° (c= 0.26, MeOH)) was done by crystallization (1xMeOH) as (+)-O,O'-dibenzoyl-D-tartrate.[3]

## EXPERIMENTAL

*General.* TLC was carried out on precoated silica gel 60 $HF_{254}$ plates (*Merck*). Silica gel 60 (230-400 mesh, ASTM, *Merck*) was used for column chromatography.

**4-Methoxy-2,3-methylenedioxy-α-nitrostyrene (3).**[6] 4-Methoxy-2,3-methylenedioxybenzaldehyde[5,6] (**2**) (4.49 g; 24.9 mmol), $MeNO_2$ (3.3 mL; 61 mmol), $AcONH_4$ (1.94 g) in AcOH (20 mL) were heated at 100°C for 3 h under argon. After cooling, the reaction mixture was poured into cold $H_2O$ (150 mL). The crystalline precipitate was filtered, washed with $H_2O$ and dried to give fine yellow crystals: 4.65 g (83%); mp 156.2-159.8°C (MeOH) (lit., [6] 155°C (decomp)); IR (KBr): 1640*s*, 1620*s*, 1595, 1515*s*, 1500*s*, 1450*s*, 1445*s*, 1335*s*, 1290*s*, 1270*s*, 1205, 1175, 1110*s*; $^1$H-NMR ($CDCl_3$): 7.87 (*d*, *J* = 13.5, 1H), 7.76 (*d*, *J* = 13.5, 1H), 6.92 (*d*, *J* =8.7, 1H), 6.60 (*d*, *J* =8.7, 1H), 6.12 (*s*, 2H), 3.96 (*s*, 3H); $^{13}$C-NMR ($CDCl_3$): 148.4 (*s*), 146.8 (*s*), 137.3 (*s*), 135.6 (*d*), 134.0 (*d*), 125.7 (*d*), 108.3 (*d*), 107.2 (*s*), 102.4 (*t*), 56.6 (*q*); CIMS ($NH_3$): 241 (100, $[M+NH_4]^+$), 224 (6, $[M+1]^+$), 223 (6, $M^{+\cdot}$).

**2-(4-Methoxy-2,3-methylenedioxyphenyl)ethylamine (4). Catalytic reduction:** Nitrostyrene (**3**) (0.5 g; 2.24 mmol) was dissolved in MeOH (150 mL). To this solution aq. 1N HCl (11 mL, 5 equiv.) and Pd/C (10%, 0.1 g) were added. This was continuously shaken overnight under a $H_2$ atmosphere (50 psi). After filtration over Celite®, the solution was evaporated to dryness to yield a brownish yellow solid. Treating this solid with $CH_2Cl_2$ gave a colorless precipitate which was filtered and dried to give the hydrochloride of **4** (0.35 g, 67%); mp 215.8-216.3°C (MeOH-$Et_2O$); IR (KBr): 3400 (br), 3130 (br), 3050*s*, 1645, 1505,

1450, 1405*s*, 1290, 1275, 1170, 1140, 1090, 1050; $^1$H-NMR ($CD_3OD$): 6.62 (*d*, *J* = 8.6, 1H), 6.49 (*d*, *J* = 8.6, 1H), 5.88 (*s*, 2H), 3.78 (*s*, 3H), 3.08 (*t*, *J* =7.4, 2H), 2.82 (*t*, *J* = 7.4, 2H); $^{13}$C-NMR (DMSO-$d_6$): 146.9 (*s*), 142.9 (*s*), 134.9 (*s*), 122.9 (*d*), 108.2 (*d*), 101.4 (*t*), 56.6 (*q*), 38.7 (*t*), 26.9 (*t*); CIMS ($NH_3$): 196 (100, $[M+1]^+$), 195 (19, $M^{+\cdot}$).

**Reduction with $LiAlH_4$**: $LiAlH_4$ (1.2 g; 31 mmol) was suspended in dry THF (110 mL), and then heated to reflux under $N_2$. To this refluxing suspension, the solution of nitrostyrene (**3** ) (1.14 g; 5.1 mmol) in dry THF (20 mL) was added dropwise during 2 h and refluxed for 3 h under $N_2$. After cooling, sat. aq. sodium potassium tartrate solution was added and the mixture extracted with $Et_2O$ (6 x 30 mL). After drying of the organic phase ($Na_2SO_4$), it was evaporated to dryness to give a dark yellow oil, which was purified by acid/base treatment: 0.7 g (72%).

***N*-[2-(4-Methoxy-2,3-methylenedioxyphenyl)ethyl]-3,4-dimethoxyphenylacetamide (5).** 3,4-Dimethoxyphenylacetyl chloride, prepared from 3,4-dimethoxyphenylacetic acid (0.745 g; 3.8 mmol) and $SOCl_2$ (1.2 mL; 6.5 mmol) in $CHCl_3$ (15 mL), was dissolved in $Et_2O$ (5 mL) and added dropwise to the mixture of amine (**4** ) (0.7 g; 3.58 mmol) and 10% aq. NaOH (2 mL) in $Et_2O$ (20 mL) during 0.5 h. After the addition, the reaction was stirred at 20°C for an additional 3 h. The colorless precipitate was filtered, washed with $H_2O$ several times and dried : 1 g (77%); mp 99.7-100.3°C (AcOEt-hexane); IR (KBr): 3300, 2940, 2910, 1640*s*, 1610, 1595, 1540, 1515*s*, 1445*s*, 1420, 1375, 1355, 1340, 1290, 1265 1230, 1180, 1160, 1140, 1105, 1060, 1040, 1030; $^1$H-NMR ($CDCl_3$): 6.80 (*d*, *J* = 8.6, 1H), 6.69 (*m*, 2H), 6.43 (*d*, *J* = 8.5, 1H), 6.38 (*d*, *J* = 8.5, 1H), 5.85 (*s*, 2H), 5.50 (br *s*), 3.88 (*s*, 3H), 3.87 (*s*, 3H), 3.83 (*s*, 3H), 3.47 (*s*, 2H), 3.43 (*t*, *J* = 6.4, 2H), 2.67 (*t*, *J* = 6.4, 2H); $^{13}$C-NMR ($CDCl_3$): 172.8 (*s*), 150.8 (*s*), 149.8 (*s*), 144.3 (*s*), 128.8 (*s*), 122.8 (*d*), 121.5 (*d*), 112.4 (*d*), 111.4 (*d*), 107.4 (*d*), 101.0 (*t*), 56.4 (*q*), 55.8 (*q*), 55.7 (*q*), 43.4 (*t*), 39.3 (*t*), 28.8 (*t*); CIMS ($NH_3$): 391 (13, $[M+NH_4]^+$), 375 (20, $[M+2]^+$), 374 (100, $[M+1]^+$).

**7-Methoxy-1-(3,4-dimethoxybenzyl)-5,6-methylenedioxy-3,4-dihydroisoquinoline hydrochloride (6).** Amide (**5**) (1 g; 2.68 mmol) and $POCl_3$ (1.2 mL; 13.1 mmol) in dry MeCN (15 mL) were refluxed under argon. The excess of $POCl_3$ and MeCN were completely removed *in vacuo* yielding a brownish viscous residue which crystallized as pale yellow crystals from acetone: 0.85 g (82%); mp 127.4-128.1°C(MeOH); IR (KBr): 3210, 2970, 2900, 1665, 1635, 1600, 1520*s*, 1450*s*, 1430*s*, 1410, 1340, 1320*s*, 1265, 1240, 1210, 1160*s*, 1130*s*, 1040, 1025, 1005; $^1$H-NMR ($CD_3OD$) : 7.52 (*s*, 1H), 7.07 (*d*, *J* = 1.8, 1H), 7.03 (*d*, *J* = 8.2, 1H), 6.97 (*dd*, *J* = 8.2; 1.8, 1H), 6.26 (*s*, 2H), 4.53 (*s*, 2H), 3.99 (*s*, 3H), 3.95 (*t*, *J* = 7.8, 2H). 3.90 (*s*, 3H), 3.88 (*s*, 3H), 3.09 (*t*, *J* = 7.8, 2H); $^{13}$C-NMR ($CDCl_3$): 176.6 (*s*), 149.7 (*s*),

146.2 (*s*), 125.1 (*s*), 121.4 (*d*), 118.5 (*s*), 112.9 (*d*), 112.6 (*d*), 112.4 (*s*), 112.2 (*d*), 103.9 (*t*), 56.2 (*q*), 55.1 (*q*), 54.9 (*q*), 40.8 (*t*), 38.4 (*t*), 17.9 (*t*); CIMS ($NH_3$): 357 (21, $[M+2]^+$), 356 (100, $[M+1]^+$), 355 (4, $M^{+\cdot}$).

**7-Methoxy-1-(3,4-dimethoxybenzyl)-5,6-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (7).** To an ice cooled solution of dihydroisoquinoline (**6**) (0.8 g; 2.04 mmol) in MeOH (70 mL), $NaBH_4$ (0.6 g; 16 mmol) was added portionwise during 1 h. Then the reaction was stirred at 20°C for 1 h. Following evaporation of the solvent to dryness, $H_2O$ (50 mL) was added to the residue and it was extracted with $CH_2Cl_2$ (6x25 mL). After drying the combined organic phase ($Na_2SO_4$), it was evaporated to dryness to give compound (**7**) as a colorless oil: 0.6 g (82%); IR (KBr): 2950, 2945, 2930, 2840, 1640, 1605, 1590, 1500*s*, 1460*s*, 1440*s*, 1375, 1335, 1315, 1260*s*, 1155, 1130*s*, 1025; $^1$H-NMR ($CDCl_3$): 6.80 (*m*, 3H), 6.37 (*s*, 1H), 5.95 (*s*, 2H), 4.08 (*dd*, *J* = 9.2; 4.0, 1H), 3.87 (*s*, 3H), 3.86 (*s*, 3H), 3.85 (*s*, 3H), 3.17 (*m*, 2H), 2.85 (*m*, 2H), 2.63 (*m*, 2H); $^{13}$C-NMR ($CDCl_3$): 148.9 (*s*), 147.7 (*s*), 146.3 (*s*), 141.7 (*s*), 133.0 (*s*), 131.3 (*s*), 121.3 (*d*), 112.4 (*d*), 111.3 (*d*), 111.1 (*s*), 105.1 (*d*), 101.3 (*t*), 57.0 (*d*), 56.7 (*q*), 55.8 (*q*), 55.7(*q*), 42.2 (*t*), 40.1 (*t*), 23.2 (*t*); CIMS ($NH_3$): 359 (20, $[M+2]^+$), 358 (100, $[M+1]^+$).

**7-Methoxy-1-(3,4-dimethoxybenzyl)-5,6-methylenedioxyisoquinoline (8).** Tetrahydroisoquinoline (**7**) (0.535 g; 1.49 mmol) was dissolved in toluene (18 mL). Pd/C (10%, 0.27 g) was added to this solution under a constant argon flow and refluxed for 6 h at 125-130°C. After cooling, the catalyst was filtered off through Celite® which was washed several times with $CH_2Cl_2$. The solvent was evaporated to dryness *in vacuo* and the residue was crystallized from MeOH: 0.35 g (67%); mp 175.5-177°C (colorless); IR (KBr): 2990, 2960, 2930, 2840, 1650, 1600, 1530*s*, 1515*s*, 1470*s*, 1455*s*, 1430*s*, 1395*s*, 1340, 1330, 1280*s*, 1260*s*, 1235*s*, 1200*s*, 1160*s*, 1140*s*, 1130*s*, 1070, 1050*s*, 1025*s*; $^1$H-NMR ($CDCl_3$): 8.34 (*d*, *J* = 5.7, 1H), 7.46 (*d*, *J* = 5.7, 1H), 7.14 (*s*, 1H), 6.80 (*m*, 2H), 6.76 (*d*, *J* = 8.6, 1H), 6.21 (*s*, 2H), 4.51 (*s*, 2H), 3.91 (*s*, 3H), 3.82 (*s*, 3H), 3.77 (*s*, 3H); $^{13}$C-NMR ($CDCl_3$): 158.7 (*s*), 149.0 (*s*), 147.5 (*s*), 145.2 (*s*), 142.1 (*s*), 139.9 (*d*), 137.2 (*s*), 131.9 (*s*), 123.7 (*s*), 120.4 (*d*), 118.9 (*s*), 111.8 (*d*), 111.2 (*d*), 102.9 (*t*), 100.6 (*d*), 56.0 (*q*), 55.8 (*q*), 55.7 (*q*), 42.6 (*t*); CIMS ($NH_3$): 355 (22, $[M+2]^+$), 354 (100, $[M+1]^+$).

**7-Methoxy-1-(3,4-dimethoxybenzyl)-2-methyl-5,6-methylenedioxyisoquinolinium iodide (9).** Isoquinoline (**8**) (0.35 g; 0.99 mmol) and MeI (3.5 mL; 56 mmol) in DMF (6 mL) was heated to 150°C and refluxed for 2 h under argon. After cooling, the excess MeI was removed *in vacuo* and crystallized after adding $Et_2O$. The crystals were filtered and washed with $Et_2O$ several times and dried: 47 g (96%); mp 194°C(decomp) (MeOH); IR (KBr): 3000, 1640, 1625, 1590, 1545*s*, 1520*s*, 1470*s*, 1440*s*, 1415*s*,

1350, 1335, 1300*s*, 1260*s*, 1240, 1210, 1190, 1155*s*, 1145*s*, 1090, 1050*s*, 1025*s*; $^1$H-NMR ($CDCl_3$): 8.65 (*d*, *J* = 6.9, 1H), 7.98 (*d*, *J* = 6.9, 1H), 7.49 (*s*, 1H), 7.05 (*d*, *J* = 2, 1H), 6.69 (*d*, *J* = 8.2, 1H), 6.44 (*s*, 2H), 6.24 (*dd*, *J* = 8.2; 2, 1H), 5.17 (*s*, 2H), 4.57 (*s*, 3H), 4.06 (*s*, 3H), 3.87 (*s*, 3H), 3.81 (*s*, 3H); $^{13}$C-NMR ($CDCl_3$): 157.9 (*s*), 149.8 (*s*), 148.7 (*s*), 143.3 (*s*), 142.9 (*s*), 135.3 (*d*), 125.6 (*s*), 124.7 (*s*), 119.3 (*d*), 118.9 (*s*), 116.5 (*d*), 112.1 (*d*), 111.7 (*d*), 104.9 (*t*), 104.1 (*d*), 57.2 (*q*), 56.5 (*q*), 55.9 (*q*), 47.9 (*q*), 36.2 (*t*); ESIMS: 368 ($M^{+\cdot}$).

**7-Methoxy-1-(3,4-dimethoxybenzyl)-2-methyl-5,6-methylenedioxy-1,2-dihydroisoquinoline (10).** Isoquinoline (**9**) (0.45 g; 0.91 mmol) was added portionwise to the suspension of $NaBH_4$ (0.15 g; 4 mmol) in pyridine (6.5 mL). After obtaining a clear solution, first $CH_2Cl_2$ (20 mL), and then $H_2O$ (25 mL) were added. After separation of organic phase, the aq. layer was extracted with additional $CH_2Cl_2$ (5x20 mL), washed with $H_2O$ (15 mL) and dried ($Na_2SO_4$). After evaporation of the $CH_2Cl_2$, the remaining pyridine was removed at rt under high vacuum. Colorless crystals from EtOH: 0.24 g (71%); mp 118.5-118.8°C; IR ($CHCl_3$): 3000, 2940, 2840, 1645, 1640, 1590, 1510*s*, 1490 1465*s*, 1425*s*, 1365, 1320, 1290, 1260, 1230 1155, 1140*s*, 1070; $^1$H-NMR ($CDCl_3$): 6.74 (*d*, *J* = 8.1, 1H), 6.53 (*dd*, *J* = 8.1; 1.9, 1H), 6.40 (*d*, *J* = 1.9, 1H), 6.07 (*dd*, *J* = 7.2; 1.2, 1H), 5.94 (*d*, *J* = 1.4, 1H), 5.93 (*d*, *J* = 1.4, 1H), 5.61 (*s*, 1H), 5.30 (*d*, *J* = 7.2, 1H), 4.20 (*m*, 1H), 3.84 (*s*, 3H), 3.77 (*s*, 3H), 3.60 (*s*, 3H), 2.89 (*dd*, *J* = 12.8; 5.4, 1H), 2.87 (*s*, 3H), 2.74 (*dd*, *J* = 12.8; 8.1, 1H); $^{13}$C-NMR ($CDCl_3$): 148.5 (*s*), 147.5 (*s*), 140.3 (*s*), 134.7 (*d*), 133.9 (*s*), 131.1 (*s*), 123.0 (*s*), 121.8 (*d*), 113.3 (*d*), 110.9 (*d*), 110.1 (*s*), 106.2 (*d*), 101.14 (*t*), 89.9 (*d*), 56.5 (*q*), 55.9 (*q*), 55.8 (*q*), 40.9 (*q*), 36.2 (*t*); CIMS ($NH_3$): 371 (21, $[M+2]^+$), 370 (100, $[M+1]^+$).

**(±)-Thalimonine** (6,7,12,13-Tetrahydro-4,9,10-trimethoxy-14-methylbenzo[5,6]cycloocta[1,2-*e*]-1,3-benzodioxole-6,12-imine, **1**). Dihydroisoquinoline (**10**) (0.3 g; 0.813 mmol) was dissolved in a mixture of HCOOH (2.25 mL) and $H_3PO_4$ (0.82 mL). The solution was heated at 100-105°C for 2 h under argon. After cooling, it was poured into $H_2O$ (50 mL), the aq. solution was washed with $Et_2O$ (3x15 mL) and basicified with 10% NaOH (pH ≈ 9). The $CH_2Cl_2$ (6x20 mL) extract was dried ($Na_2SO_4$) and evaporated to dryness to give a brownish residue which was purified by flash chromatography ($CH_2Cl_2$/isopropanol 19:1) to give **(±)-1**: 0.18 g (60%). UV (EtOH): $\lambda_{max}$ 287 nm (log ε 3.67); IR ($CHCl_3$): 3000, 2940, 2900, 2840, 1650, 1610, 1510*s*, 1465, 1450, 1375, 1350, 1170, 1130*s*; $^1$H-NMR ($CDCl_3$): 6.60 (*s*, 1H), 6.45 (*s*, 1H), 6.31 (*s*, 1H), 5.91 (*d*, *J* = 1.4, 1H), 5.84 (*d*, *J* = 1.4, 1H), 4.04 (*d*, *J* = 5.8, 1H), 4.01 (*d*, *J* = 5.6, 1H), 3.86 (*s*, 3H), 3.84 (*s*, 3H), 3.78 (*s*, 3H), 3.41 (*dd*, *J* = 16.2; 5.8, 1H), 3.19 (*dd*, *J* = 16.4; 5.9, 1H), 2.59 (*d*, *J*

= 16.4, 2H), 2.53 (*s*, 3H); $^{13}$C-NMR ($CDCl_3$): 147.9 (*s*), 147.5 (*s*), 146.2 (*s*), 142.2 (*s*), 132.4 (*s*), 129.6 (*s*), 123.8 (*s*), 111.3 (*d*), 110.0 (*d*), 107.7 (*s*), 105.9 (*d*), 101.3 (*t*), 56.6 (*d*), 56.4 (*d*), 55.9 (*q*), 55.6 (*q*), 55.4 (*q*), 40.8 (*q*), 34.1 (*t*), 27.5 (*t*); CIMS ($NH_3$): 371 (21, $[M+2]^+$), 370 (100, $[M+1]^+$).

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**REFERENCES**

1. B. Gözler, *The Alkaloids: Pavine and Isopavine Alkaloids*, Vol. 31, ed. by A. Brossi, Academic Press, Inc., New York, 1987, pp. 317-389.
2. N. Fujiwara, Y.Ueda, and N. Ohashi, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 743; L. Chen, M. J. Su, M. H.Wu, and S. S. Lee, *J. Cardiovasc. Pharmacol.*, 1996, **27**, 740.
3. M. P.Velcheva, R. R. Petrova, S. Danghaaghiin, and Z. Yansanghiin, *J. Nat. Prod.*, 1992, **55**, 679; T. L. Varadinova, S. A. Shishkov, N. D. Ivanovska, M. P. Velcheva, S. Danghaaghiin, Z. Samadanghiin, and Z. Yansanghiin, *Phytother. Res.*, 1996, **10**, 414.
4. H. C. Chen, T. O. Soine, and K. H. Lee, *J. Pharm. Sci.*, 1971, **60**, 1634; K. C. Rice, W. C. Ripka, J. Reden, and A. Brossi, *J. Org. Chem.*, 1980, **45**, 601.
5. B. A. McKittrick and R. Stevenson, J. *Chem. Soc., Perkin Trans. 1*, 1984, 709.
6. V. I. Vinogradova and M. S.Yunusov, *Chem. Nat. Prod.*, 1986, 777.
7. S. F. Dyke, *Advances in Heterocyclic Chemistry: 1,2-Dihydroisoquinolines*, Vol. 14, ed. by A. R. Katritzky and A. J. Boulton, Academic Press, Inc., New York, 1972, pp. 279-329.
8. V. Pabuccuoglu and B. Gözler, *Doga-Tr. J. of Pharmacy*, 1991, **1**, 138; M. P. Velcheva, S. Danghaaghiin, Z. Samdanghiin, Z.Yansanghiin, and M. Hesse, *Phytochemistry*, 1995, **39**, 683; B. Gözler, M. A. Onur, S. Bilir, and M. Hesse, *Helv. Chim. Acta*, 1992, **75**, 260.

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