A Facile Synthesis of 1,2,3,4-Tetrahydroisoquinolines through Cyclization of *O,N*-Acetals. II.[1] Syntheses of Isoquinolinequinone Antibiotics

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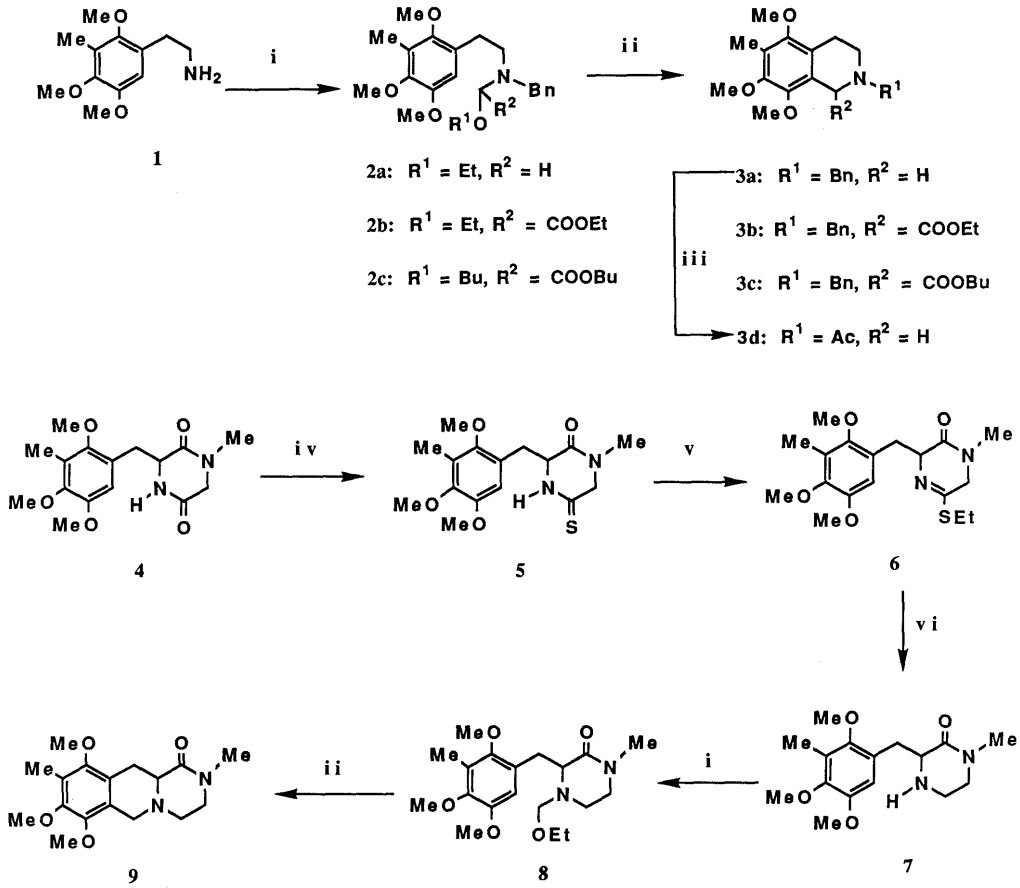
A mild and efficient method for the synthesis of 1,2,3,4-tetrahydroisoquinolines 3a—c and 9 by a modified Pictet–Spengler reaction involving Lewis acid-mediated cyclization of the *O,N*-acetals 2a—c and 8 is described. The synthetic utility of this reaction is demonstrated with a preparation of two isoquinolinequinone antibiotics, renierone (11) and mimocin (12), from the ester 3c.

Keywords modified Pictet–Spengler reaction; *O,N*-acetal; isoquinolinequinone; synthesis

The majority of isoquinoline syntheses involve acid-catalyzed ring closure to a benzene ring and benefit considerably from the presence of an electron-donating substituent.[2] Although the Pictet–Spengler reaction has proven to be an excellent method for the preparation of 1,2,3,4-tetrahydroisoquinolines,[3,4] the ring-closure reaction is sensitive to substituent effects. We have recently reported a mild and efficient method for the synthesis of 1,2,3,4-tetrahydroisoquinolines through cyclization of *O,N*-acetals.[1] This reaction was applicable to the syntheses of dimeric isoquinolinequinone antibiotics such as saframycin B.[5] We report here an additional synthetic utility of this reaction demonstrated by a preparation of two isoquinolinequinone antibiotics, renierone (**11**) and mimocin (**12**).

Reaction of the *N*-benzyl amine (**1**)[1] with paraformaldehyde in the presence of potassium carbonate in ethanol quantitatively afforded an *O,N*-acetal (**2a**), which was subsequently treated with trifluoroacetic acid at room temperature for 1 h to provide the 1,2,3,4-tetrahydroisoquinoline (**3a**) in 80% overall yield. Debenzylation of **3a** followed by treatment with acetic anhydride in pyridine afforded the *N*-acetyl derivative (**3d**) (64.8%), whose proton nuclear magnetic resonance (^{1}H-NMR) spectrum indicated a low-field shift of the signal of the methylene proton at position 1. The reaction of **1** with ethyl glyoxylate or butyl glyoxylate[6] in the presence of potassium carbonate in ethanol followed by treatment with trifluoroacetic acid afforded the 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid ester (**3b** or **3c**,



reagent: i, **2a** and **8**, paraformaldehyde, K_2CO_3, EtOH; **2b**, CHOCOOEt, K_2CO_3, EtOH; **2c**, CHOCOOBu, K_2CO_3, BuOH; ii, CF_3COOH:, iii, Pd/C, H_2, EtOH, followed by Ac_2O, pyridine; iv, Lawesson's reagent, dimethoxyethane; v, Meerwein reagent, CH_2Cl_2; vi, Al (Hg), THF-H_2O

Chart 1

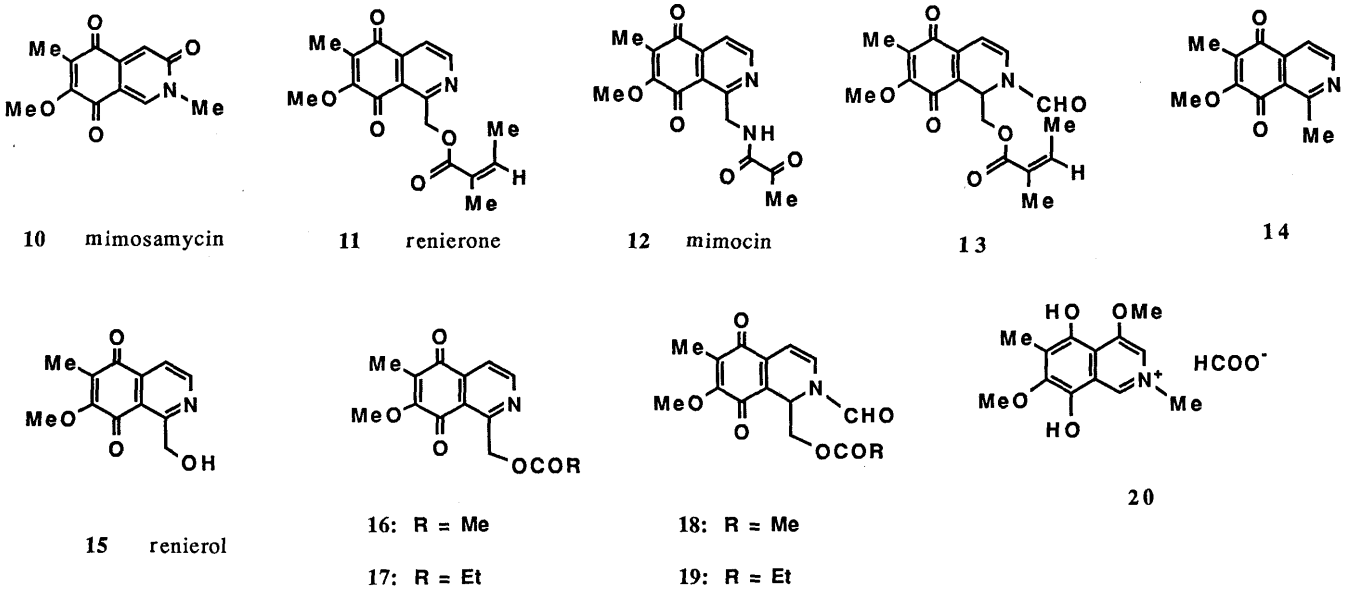


Fig. 1

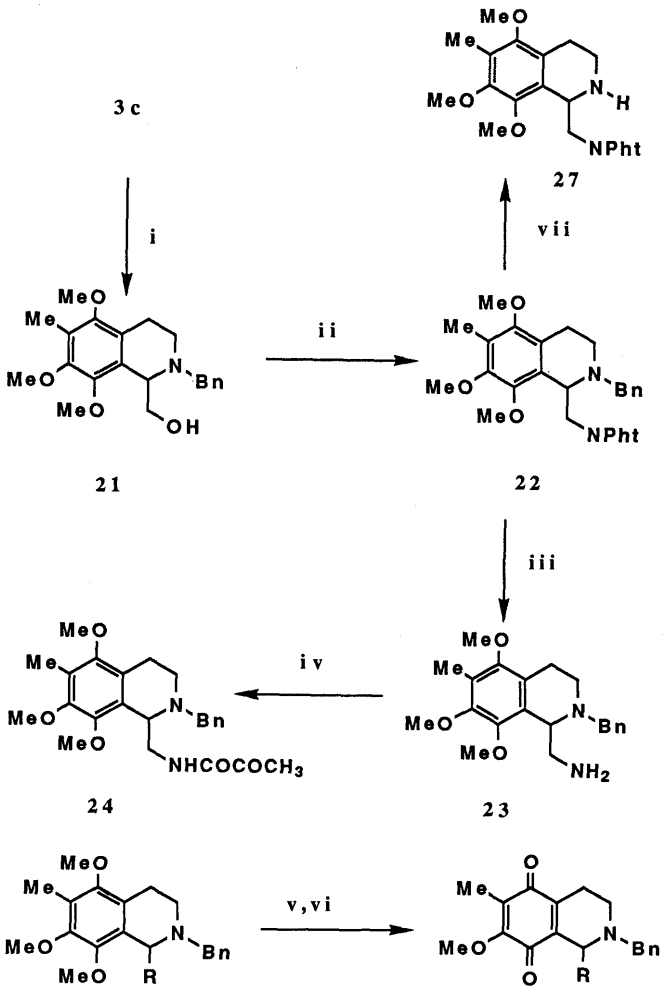
respectively).

In order to extend the synthetic usefulness of this cyclization, we decided to apply the method to the synthesis of the tricyclic lactam (**9**). The starting amine (**7**) was prepared *via* the following three steps. Treatment of the 2,5-piperazinedione (**4**)[7] with Lawesson's reagent[8] yielded the monothioamide (**5**) (91.7%) which was alkylated with Meerwein reagent[9] to afford the thioimidate ester (**6**) (71.4%). Reduction of **6** with aluminum amalgam afforded the amine (**7**) in 59% yield. The reaction of **7** with paraformaldehyde following the above two steps afforded the tricyclic lactam (**9**) in 65.8% overall yield.

Having established a general procedure for the synthesis of highly functionalized 1,2,3,4-tetrahydroisoquinolines, we wish to confirm the utility of the ester (**3c**) in the synthesis of simple isoquinolinequinone antibiotics.[10] Mimosamycin (**10**)[11,12] is a novel antibiotic discovered in the culture broth of *Streptomyces lavendulae* along with mimocin (**12**)[13] and saframycins. Over the last several years additional mimosamycin derivatives, namely, renierone (**11**)[14] and its derivatives (**13**—**19**),[15] and 5,8-dihydroxy-4,7-dimethoxy-2,6-dimethylisoquinolinium formate (**20**),[18] have been independently isolated from bacterial sources and marine sponges. The obvious structural similarities of **11**—**19** made it attractive to attempt their synthesis through **3c**.

As our first model we investigated the conversion of the ester to the aminomethyl group *via* the hydroxymethyl group. Reduction of **3c** with lithium aluminum hydride afforded the alcohol (**21**) in 72% yield. Although the alcohol could not be transformed to the corresponding amine (**23**) *via* the extremely unstable halide or tosylate of **21**,[19] this problem was solved by utilizing the Mitsunobu procedure.[20] Treatment of **21** with diethyl azodicarboxylate, triphenylphosphine, and phthalimide in tetrahydrofuran at 25 °C for 2 h gave the imide (**22**) (86%). Cleavage of the phthaloyl group with hydrazine hydrate afforded the amine (**23**) (100%), which was acylated with pyruvoyl chloride to give the pyruvamide (**24**) (77%).

Conversion of the polymethoxyarene (**24**) to a *p*-quinone



reagents: i, $LiAlH_4$, THF; ii, diethyl azodicarboxylate, PPh_3, PhtNH, THF; iii, NH_2NH_2–H_2O, EtOH; iv, MeCOCOCl, NEt_3, 4-(dimethylamino)pyridine, THF; v, BBr_3, CH_2Cl_2 −78°C; vi, ceric ammonium nitrate, MeCN–H_2O: vii, Pd/C, $HCOONH_4$, MeOH.

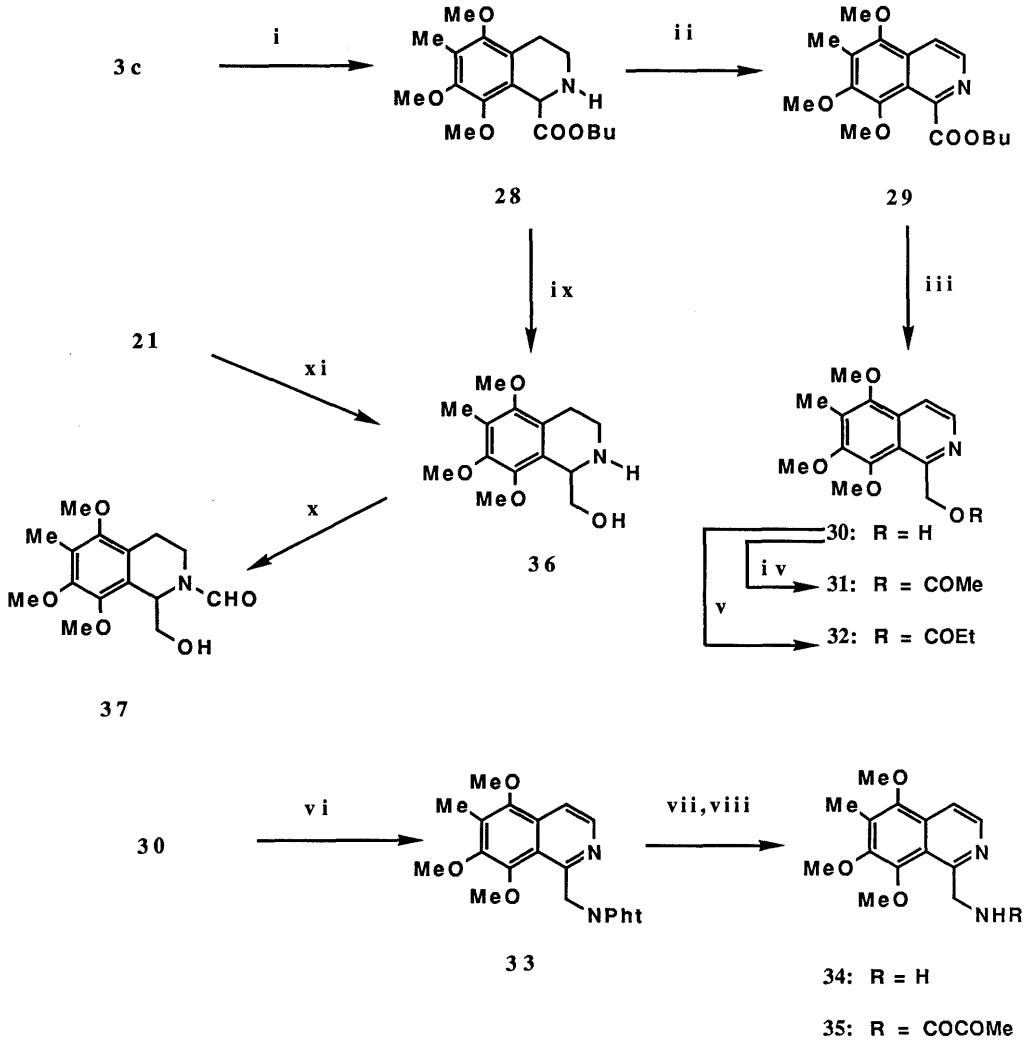
Chart 2

system was initiated by oxidative demethylation. All attempts at direct oxidative demethylation of the model compound (**3a**) employing the usual agents (*e.g.*, nitric acid,[21] ceric ammonium nitrate,[22] argentic oxide,[23] ceric ammonium nitrate-2,4,6-pyridine-tricarboxylic acid system,[24] silver(II) dipicolinate,[25] and nitric acid-impregnated manganese dioxide[26]) gave only a polar polymeric material. This problem was solved by using the partial demethylation and oxidative demethylation sequence. Treatment of **3a** with 1.0 eq of boron tribromide in dichloromethane at −78 °C for 1 h and then with ceric ammonium nitrate in acetonitrile and water at 0 °C for 1 h provided the *p*-quinone (**25**) in 28.1% yield. A similar partial demethylation and oxidative demethylation sequence of **24** gave the *p*-quinone (**26**) in 36.7% yield.

Next, we turned our attention to the conversion of *N*-benzyl-1,2,3,4-tetrahydroisoquinoline to the corresponding isoquinoline. Debenzylation of the imide (**22**) according to the procedure of Ram and Spicer[27] provided the secondary amine (**27**) (31%). Numerous efforts to dehydrogenate **27** were totally unsuccessful. As an alternative, dehydrogenation with chloranil of the ester (**28**), which was prepared from **3c** (80%), afforded the isoquinoline (**29**) in 61.2% yield.

Encouraged by the result of the above model conversion (Chart 2), we carried out a similar transformation of the ester (**29**) to the pyruvamide (**35**). Reduction of **29** with diisobutylaluminium hydride in tetrahydrofuran gave the alcohol (**30**), which has been transformed into renierone (**11**)[28,29] and the quinone (**14**).[29,30] Treatment of **30** under Mitsunobu conditions afforded the imide (**33**) (50%). Cleavage of the phthaloyl group afforded the amine (**34**), which was acylated to give the pyruvamide (**35**) (36.2%). Conversion of **35** to mimocin (**12**) using oxidative demethylation with argentic oxide has been reported by Matsuo *et al.*[31] and with ceric ammonium nitrate by us.[13,32] Finally, reduction of the ester (**28**) with lithium aluminum hydride afforded the alcohol (**36**) (56%), which was also obtained from the *N*-benzyl derivative (**21**) (52%). Formylation of **36** under the usual conditions gave the *N*-formyl compound (**37**) (85.6%), which was transformed into the quinone (**13**).[29]

Thus a formal synthesis of these isoquinolinequinone antibiotics has been accomplished. Application of the preparation of highly functionalized 1,2,3,4-tetrahydroisoquinolines through cylization of *O*,*N*-acetals is in



reagents: i, Pd/C, $HCOONH_4$, MeOH; ii, chloranil, *p*-xylene; iii, diisobutylaluminum hydride, THF; iv, Ac_2O, pyridine; v, $(EtCO)_2O$, pyridine; vi, diethyl azodicarboxylate, PPh_3, PhtNH, THF; vii, NH_2NH_2–H_2O, EtOH; viii, MeCOCOCl, NEt_3, 4-(dimethylamino)pyridine, THF; ix, $LiAlH_4$, THF; x, HCOOEt, MeOH: xi, Pd/C, EtOH, AcOH.

Chart 3

progress.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Ultraviolet (UV) spectra were determined in methanol with a Hitachi 340 spectrometer. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H-NMR spectra were measured on a JEOL GX 400 (operating at 400 MHz), or on a JNM-PMX60SI (operating at 60 MHz). ^{13}C-NMR spectra were measured on a JEOL GX 400 (operating at 100 MHz). NMR spectra were taken in $CDCl_3$ and chemical shifts are reported in δ_H values relative to internal $Si(CH_3)_4$. Mass spectra (MS) were recorded on a JEOL JMS-D 300 spectrometer. Elemental analyses were obtained by using a Perkin–Elmer model 240B elemental analyzer. All reactions except hydrogenation and oxygenation were run under an argon atmosphere. Anhydrous sodium sulfate was used for drying organic solvent extracts, and removal of the solvent was performed with a rotary evaporator and finally under high vacuum. Column chromatography was performed with E. Merck silica gel 60 (70—230 mesh).

2-Benzyl-6-methyl-5,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (3a) A solution of the secondary amine (**1**) (472.5 mg, 1.5 mmol) and anhydrous K_2CO_3 (828 mg, 6 mmol) in ethanol (0.26 ml) was stirred for 10 min at room temperature. Paraformaldehyde (60 mg, 2 mmol) was then added in one portion, and the mixture was stirred overnight at room temperature, then filtered. The filtrate was evaporated under reduced pressure to give the unstable *O,N*-acetal (**2a**) as a syrup, MS *m/z*: 328 (63%, $M-CH_2OCH_2CH_3$), 209 (13), 196 (49), 120 (61), 91 (100). IR ($CHCl_3$): 2930, 2820, 1590, 1485, 1450, 1415, 1340, 1235, 1120, 1090, 1015 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.13 (3H, t, J=7 Hz, CH_2CH_3), 2.10 (3H, s, $ArCH_3$), 2.75 (4H, br s, 2×CH_2), 3.30 (2H, q, J=7 Hz, CH_2CH_3), 3.50, 3.62, and 3.68 (each 3H, s, OCH_3), 3.78 (2H, s, NCH_2Ph), 4.08 (2H, s, NCH_2O), 6.38 (1H, s, ArH), 7.15 (5H, s, 5×ArH), which was used in the following reaction without further purification.

The *O,N*-acetal (**2a**) was treated with trifluoroacetic acid (3 ml) and this mixture was stirred at room temperature for 1 h, then concentrated. The remaining mixture was diluted with water (20 ml) and was made alkaline with saturated $NaHCO_3$ solution, and extracted with chloroform (50 ml×3). The combined extracts were dried and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with dichloromethane afforded the title compound (**3a**) (390 mg, 80%) as a colorless oil, bp 128—132 °C/1 Torr. *Anal.* Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.04; H, 7.85; N, 4.14. MS *m/z*: 327 (M^+, 74%), 326 (100), 296 (85), 208 (63), 193 (63), 165 (12), 91 (75). High-resolution MS Calcd for $C_{20}H_{25}NO_3$: 327.1834. Found: 327.1870. IR ($CHCl_3$): 2980, 2920, 2820, 1460, 1410, 1345, 1325, 1250, 1110, 1080, 1060 cm^{-1}. UV λ_{max} nm: 222 sh, 259, 265, 268, 280. ^{1}H-NMR (400 MHz) δ: 2.17 (3H, s, $ArCH_3$), 2.64 (2H, t, J=5.9 Hz, CH_2), 2.80 (2H, t, J=5.9 Hz, CH_2), 3.63 (2H, s, 1-H_2), 3.67 (3H, s, OCH_3), 3.71 (2H, s, $NCH_2C_6H_5$), 3.77 and 3.78 (each 3H, s, OCH_3), 7.24—7.40 (5H, m, 5×ArH).

2-Acetyl-6-methyl-5,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (3d) A solution of the 1,2,3,4-tetrahydroisoquinoline (**3a**) (311.3 mg, 0.95 mmol) in ethanol (5 ml) and acetic acid (0.1 ml) was hydrogenated over 20% palladium on carbon (100 mg) at 1 atm for 17 h. The catalyst was removed by filtration and washed with ethanol (50 ml). The combined filtrates were concentrated *in vacuo* to give the residue. A solution of this residue in dry pyridine (4 ml) was treated with acetic anhydride (2 ml), and the mixture was kept at room temperature for 1 h. After being diluted with water (20 ml), the mixture was extracted with chloroform (20 ml×3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give the title compound (**3d**) (171.2 mg, 64.8%) as a solid, which was recrystallized from AcOEt–ether to give colorless needles, mp 106—107 °C. *Anal.* Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.49; H, 7.88; N, 4.97. MS *m/z*: 279 (M^+, 100%), 264 (17), 248 (17), 236 (15), 208 (18), 206 (28), 193 (30), 43 (11). IR (KBr): 1650 (C=O) cm^{-1}. UV λ_{max} nm (log ε): 221 (4.19), 269 sh (2.94), 227 (2.90). ^{1}H-NMR (60 MHz) δ: 2.06 (3H, s, $ArCH_3$), 2.08 (3H, s, $COCH_3$), 2.50—2.90 (2H, m, CH_2), 3.50—3.80 (2H, m, CH_2), 3.60, 3.75, and 3.80 (each 3H, s, OCH_3), 4.50 (2H, s, CH_2).

Ethyl 2-Benzyl-6-methyl-5,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (3b) A solution of the secondary amine (**1**) (215 mg, 0.68 mmol) and anhydrous K_2CO_3 (469.2 mg, 3.4 mmol) in ethanol (5 ml) was stirred for 30 min at room temperature. A solution of ethyl glyoxylate (1.39 g, 13.6 mmol) in ethanol (5 ml) was then added dropwise over 30 min, and the mixture was stirred overnight at room temperature, and then filtered. The residue was washed with ethanol (50 ml). The combined filtrates were evaporated under reduced pressure to give the unstable *O,N*-acetal (**2b**) as a syrup, which was used in the following reaction without further purification.

The *O,N*-acetal (**2b**) was treated with trifluoroacetic acid (3 ml) and this mixture was stirred at room temperature for 1 h, then concentrated. The residue was diluted with water (20 ml), made alkaline with saturated $NaHCO_3$ solution, and extracted with chloroform (50 ml×3). The combined extracts were dried and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with dichloromethane afforded the title compound (**3b**) (201.3 mg, 74%) as a colorless oil. *Anal.* Calcd for $C_{21}H_{29}NO_5 \cdot 0.5H_2O$: C, 67.63; H, 7.40; N, 3.43. Found: C, 67.69; H, 7.27; N, 3.38. MS *m/z*: 326 (100%, $M-COOCH_2CH_3$), 91 (35). IR ($CHCl_3$): 1715 (C=O) cm^{-1}. UV λ_{max} nm: 222 sh, 259, 265, 268, 280, ^{1}H-NMR (400 MHz) δ: 1.31 (3H, t, J=7.1 Hz, CH_2CH_3), 2.19 (3H, s, $ArCH_3$), 2.71—2.76 (3H, m), 3.00—3.09 (1H, m), 3.69 (3H, s, OCH_3), 3.71 (1H, d, J=13.7 Hz, NCHPh), 3.75 and 3.76 (each 3H, s, OCH_3), 3.96 (1H, d, J=13.7 Hz, NCHPh), 4.24 (2H, q, J=7.1 Hz, CH_2CH_3), 4.61 (1H, s, CH), 7.23—7.39 (5H, m, 5×ArH).

Butyl 2-Benzyl-6-methyl-5,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (3c) A solution of the secondary amine (**1**) (315 mg, 1 mmol) and anhydrous K_2CO_3 (690 mg, 5 mmol) in butanol (5 ml) was stirred for 30 min at room temperature. A solution of butyl glyoxylate (650 mg, 5 mmol) in butanol (5 ml) was then added dropwise over 30 min, and the mixture was stirred overnight at room temperature, then filtered. The residue was washed with chloroform (50 ml). The combined filtrates were evaporated under reduced pressure. The unstable *O,N*-acetal (**2c**) (containing butanol) was stirred with trifluoroacetic acid (3 ml) at room temperature for 1 h, then concentrated. The remaining mixture was diluted with water (20 ml) and was made alkaline with saturated $NaHCO_3$ solution, then extracted with chloroform (50 ml×3). The combined extracts were dried and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with hexane–AcOEt (10:1, v/v) afforded the title compound (**3c**) (315 mg, 74%) as a colorless oil. *Anal.* Calcd for $C_{25}H_{33}NO_5$: C, 70.23; H, 7.78; N, 3.28. Found: C, 70.03; H, 7.70; N, 3.30. MS *m/z*: 326 (100%, $M-COOC_4H_9$), 91 (29). IR ($CHCl_3$): 1715 (C=O) cm^{-1}. UV λ_{max} nm 222 sh, 259, 265, 268, 280. ^{1}H-NMR (400 MHz) δ: 0.93 (3H, t, J=7.6 Hz, CH_2CH_3), 1.40 (2H), 1.66 (2H), 2.19 (3H, s, $ArCH_3$), 2.72—2.75 (3H, m), 3.02—3.07 (1H, m), 3.69 (3H, s, OCH_3), 3.69 (1H, d, J=13.7 Hz, NCHPh), 3.75 and 3.76 (each 3H, s, OCH_3), 3.97 (1H, d, J=13.7 Hz, NCHPh), 4.17 (1H, t, J=6.6 Hz, OCH), 4.17 (1H, t, J=6.6 Hz, OCH), 4.62 (1H, s, CH), 7.23—7.39 (5H, m, 5×ArH).

1-Methyl-3-(3-methyl-2,4,5-trimethoxyphenylmethyl)-5-thioxo-2-piperazinone (5) A mixture of the 2,5-piperazinedione (**4**)[7] (1.095 g, 3.4 mmol) and Lawesson's reagent (1.031 g, 3.55 mmol) in dimethoxyethane (50 ml) was stirred at room temperature for 12 h. The solvent was removed *in vacuo*, then the residue was taken up in saturated $NaHCO_3$ (50 ml), and extracted with AcOEt (30 ml×3). The combined extracts were washed with water (30 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from AcOEt gave the title compound (**5**) (930 mg, 91.7%) as pale yellow needles, mp 130.5—132 °C. *Anal.* Calcd for $C_{16}H_{22}N_2O_4S$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.91; H, 6.63; N, 8.18. MS *m/z*: 338 (M^+, 13%), 196 (13), 195 (100), 165 (16). IR (KBr): 3220, 3160, 3040, 1650 (C=O) cm^{-1}. UV λ_{max} nm (log ε): 230 sh (3.90), 278 (4.15). ^{1}H-NMR (60 MHz) δ: 2.17 (3H, s, $ArCH_3$), 2.88 (3H, s, NCH_3), 3.15 (2H, t like, $ArCH_2CH$), 3.65 (3H, s, OCH_3), 3.75 (6H, s, 2×OCH_3), 4.00 (2H, ABq, J=17 Hz, S=C-CH_2N), 4.20 (1H, m, 3-H), 6.50 (1H, s, ArH), 8.90 (1H, br s, NH).

1-Methyl-3-(3-methyl-2,4,5-trimethoxyphenylmethyl)-2-piperazinone (7) A mixture of the thioamide (**5**) (676 mg, 2 mmol) and Meerwein reagent (1.9 g, 10 mmol) in dry dichloromethane (40 ml) was stirred at room temperature for 1 h. The solvent was removed *in vacuo*, then the residue was taken up in saturated $NaHCO_3$ (40 ml), and extracted with dichloromethane (30 ml×3). The combined extracts were washed with water (30 ml), dried, and concentrated *in vacuo* to give the residue, which was chromatographed on silica gel (40 g) using hexane–AcOEt (1:1, v/v) to give the thioimidate ester (**6**) (523 mg, 71.4%) as a colorless oil. MS *m/z*: 366 (M^+, 10), 196 (16), 195 (100), 165 (13). ^{1}H-NMR (400 MHz) δ: 1.24 (3H, t, J=7.5 Hz, CH_2CH_3), 2.17 (3H, s, $ArCH_3$), 2.85 (3H, s, NCH_3), 2.95 (1H, m), 3.00 (2H, m), 3.09 (2H, q, J=7.5 Hz, OCH_2), 3.54 (1H, m), 3.63, 3.78, and 3.78 (each 3H, s, OCH_3), 4.56 (1H, m, 1-H), 6.54 (1H, s, ArH), which was used immediately in the following reaction.

A mixture of the thioimidate ester (**6**) (183 mg, 0.5 mmol) and aluminum amalgam[33] (prepared from 0.2 g of aluminum foil) in 10% tetrahy-

drofuran (THF)–H_2O (10 ml) was stirred at 0 °C for 4 h. The gray slurry was filtered through Celite pad and washed with chloroform (50 ml). The combined filtrates were concentrated *in vacuo*, and the residue was diluted with 5% $NaHCO_3$ (20 ml), and extracted with chloroform (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give a residue which was subjected to chromatography on silica gel (10 g) using dichloromethane–methanol (50 : 1, v/v) to give the title compound (**7**) (90.9 mg, 59%) as a colorless oil. MS *m/z*: 308 (M^+, 4%), 196 (100), 195 (76), 181 (16), 165 (18), 150 (10), 113 (48). High-resolution MS Calcd for $C_{16}H_{24}N_2O_4$: 308.1736. Found: 308.1710. IR ($CHCl_3$): 3600—3200 (NH), 1640 (C=O) cm^{-1}. UV λ_{max} nm: 222 sh, 265, 268, 280. ^{1}H-NMR (400 MHz) δ: 1.72 (1H, br s, NH), 2.22 (3H, s, $ArCH_3$), 2.81 (1H, dd, J=13.7, 10.3 Hz), 2.92 (1H, ddd, J=12.5, 9.8, 4.2 Hz), 2.98 (3H, s, NCH_3), 3.12 (1H, ddd, J=12.5, 4.6, 3.7 Hz), 3.18 (1H, ddd, J=11.5, 3.7, 3.7 Hz), 3.42 (2H, m), 3.66 (1H, dd, J=10.5, 3.2 Hz), 3.69, 3.79, and 3.81 (each 3H, s, OCH_3), 6.65 (1H, s, ArH).

2,9-Dimethyl-7,8,10-trimethoxy-1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino-[1,2-*b*]isoquinolin-1-one (9) A solution of the secondary amine (**7**) (30.7 mg, 0.104 mmol) and anhydrous K_2CO_3 (220.8 mg, 5 mmol) in ethanol (0.5 ml) was stirred for 30 min at room temperature. Paraformaldehyde (24 mg, 0.8 mmol) was then added in one portion, and the mixture was stirred overnight at room temperature and then filtered. The residue was washed with chloroform (50 ml). The combined filtrates were evaporated under reduced pressure. The unstable *O,N*-acetal (**8**) was stirred with trifluoroacetic acid (1 ml) at room temperature for 1 h, then concentrated. The remaining mixture was diluted with water (10 ml), made alkaline with saturated $NaHCO_3$ solution, and extracted with chloroform (20 ml × 3). The combined extracts were dried and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with AcOEt–methanol (50 : 1, v/v) afforded the title compound (**9**) (21 mg, 65.8%) as a pale yellow oil. MS *m/z*: 320 (M^+, 48%), 234 (11), 220 (17), 208 (100), 193 (63), 165 (11). High-resolution MS Calcd for $C_{17}H_{24}N_2O_4$: 320.1736. Found: 320.1764. IR ($CHCl_3$): 1645 (C=O) cm^{-1}. UV λ_{max} nm: 222 sh, 265, 268, 280. ^{1}H-NMR (400 MHz) δ: 2.18 (3H, s, $ArCH_3$), 2.60—2.73 (2H, m), 2.94 (1H, dd, J=11.7, 3.9 Hz, 11a-H), 3.02 (3H, s, NCH_3), 3.12 (1H, m), 3.20 (1H, m), 3.33 (1H, dd, J=15.4, 0.5 Hz, 6-Hα), 3.50 (1H, ddd, J=17.1, 3.9, 0.5 Hz, 11-Hβ), 3.68 (1H, m), 3.68, 3.79, and 3.82 (each 3H, s, OCH_3), 4.12 (1H, d, J=15.4 Hz, 6-Hβ). ^{13}C-NMR (100 MHz) δ: 9.2 (q, $ArCH_3$), 27.4 (t, 11-C), 34.4 (q, NCH_3), 48.1 (t), 50.4 (t), 59.9 (q, OCH_3), 59.9 (q, OCH_3), 60.1 (q, OCH_3), 61.6 (d, 11a-C), 123.3 (s), 123.4 (s), 125.1 (s), 145.4 (s), 149.6 (s), 152.7 (s), 168.8 (s, C=O).

2-Benzyl-1-hydroxymethyl-6-methyl-5,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (21) Lithium aluminum hydride (500 mg, 13.2 mmol) was added to a stirred solution of **3c** (1.043 g, 2.61 mmol) in dry THF (50 ml), and the mixture was heated at reflux for 2 h. The reaction was quenched at 0 °C by addition of water, and the mixture was filtered. The filter cake was carefully washed with chloroform (200 ml). The combined filtrates were concentrated *in vacuo*. The residue was subjected to chromatography [silica gel, 30 g, elution with benzene–AcOEt (3 : 1—2 : 1, v/v)] to give the title compound (**21**) (672 mg, 72%) as a colorless oil. *Anal.* Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.26; H, 7.78; N, 3.83. MS *m/z*: 339 (13%, M–H_2O), 326 (100), 91 (55). IR (Nujol): 3700—3200 (OH) cm^{-1}. UV λ_{max} nm: 258, 264, 269, 279. ^{1}H-NMR (400 MHz) δ: 2.20 (3H, s, $ArCH_3$), 2.55 (1H, m), 2.80—2.92 (2H, m), 2.86 (1H, s, OH), 3.15 (1H, m), 3.47 (1H, t, J=9.9 Hz, CHOH), 3.71 (3H, s, OCH_3), 3.74 (1H, dd, J=9.9, 4.8 Hz, CHOH), 3.76 (1H, d, J=13.2 Hz, NCHPh), 3.78 and 3.79 (each 3H, s, OCH_3), 3.81 (1H, d, J=13.2 Hz, NCHPh), 3.98 (1H, dd, J=9.9, 4.8 Hz, 1-H), 7.28—7.35 (5H, m, 5 × ArH).

2-Benzyl-6-methyl-5,7,8-trimethoxy-1-phthalimidomethyl-1,2,3,4-tetrahydroisoquinoline (22) A solution of diethyl azodicarboxylate (0.5 ml, 3.71 mmol) in dry THF (1 ml) was added dropwise to a solution of **21** (226.2 mg, 0.63 mmol), phthalimide (466 mg, 3.17 mmol), and triphenylphosphine (831 mg, 3.17 mmol) in dry THF (5 ml) at room temperature. The solution was stirred at room temperature for 2 h, then the solvent was removed *in vacuo*. The residue was diluted with water (30 ml) and extracted with chloroform (30 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give the residue, which was chromatographed on silica gel (40 g) using hexane–AcOEt (8 : 1, v/v) to give the title compound (**22**) (264.1 mg, 86%) as a solid, mp 140—141.5 °C (ether). *Anal.* Calcd for $C_{29}H_{30}N_2O_5$: C, 71.58; H, 6.22; N, 5.76. Found: C, 71.45; H, 6.25; N, 5.70. MS *m/z*: 326 (100%, M–CH_2NPht), 91 (34). IR (KBr): 1765, 1710 cm^{-1}. UV λ_{max} nm (log ε): 218 (4.74), 270 (3.26), 281 (3.30), 298 (3.23). ^{1}H-NMR (400 MHz) δ: 2.22 (3H, s, $ArCH_3$), 2.59 (1H, dd, J=17.6, 4.4 Hz), 2.79 (1H, ddd, J=17.6, 12.9, 6.1 Hz), 2.99 (1H, dd, J=14.4, 6.1 Hz), 3.47 (1H, d, J=12.9 Hz, NCHPh), 3.54 (1H, m), 3.67 (1H, d, J=12.9 Hz, NCHPh), 3.74, 3.79, and 3.82 (each 3H, s, OCH_3), 3.91 (2H, m), 4.35 (1H, dd, J=9.3, 5.4 Hz, 1-H), 6.85 (2H, t like), 6.92 (2H, d like), 7.03 (1H, t like), 7.73 (2H, m), 7.81 (2H, m).

***N*-[(2-Benzyl-6-methyl-5,7,8-trimethoxy-1,2,3,4-tetrahydro-1-isoquinolyl)methyl]-2-oxopropanamide (24)** Hydrazine monohydrate (0.1 ml) was added to a stirred solution of **22** (185 mg, 0.38 mmol) in ethanol (4 ml), the resulting solution was heated under reflux for 2 h, then concentrated *in vacuo*. The residue was dissolved in benzene (20 ml) and extracted with 1 N HCl (10 ml × 3). The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give the amine (**23**) (140.1 mg, 100%) as a solid. An analytical sample was obtained by crystallization from methanol–AcOEt, mp 222—223 °C (dec.). *Anal.* Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.50; H, 7.35; N, 7.62. MS *m/z*: 326 (100%, M–CH_2NH_2), 296 (11), 91 (54). IR (KBr): 3480 (NH), 1505, 1465, 1415, 1315, 1260, 1118, 1080 cm^{-1}. UV λ_{max} nm (log ε): 222 sh (4.12), 272 sh (3.01), 278 (3.03). ^{1}H-NMR (400 MHz) δ: 2.20 (3H, s, $ArCH_3$), 2.32 (2H, br s, NH_2), 2.48 (1H, m), 2.72—2.88 (4H, m), 3.12—3.19 (1H, m), 3.68 (1H, d, J=13.4 Hz, NCHPh), 3.71 (3H, s, OCH_3), 3.71 (1H, m), 3.76 (1H, d, J=13.4 Hz, NCHPh), 3.76 and 3.79 (each 3H, s, OCH_3), 7.23—7.36 (5H, m, 5 × ArH).

A solution of the crude **23** (140.1 mg), triethylamine (0.106 ml, 0.76 mmol), and 4-(dimethylamino)pyridine (92.8 mg, 0.76 mmol) in dry dichloromethane (4 ml) was cooled with ice-water, and a carbon tetrachloride solution of pyruvoyl chloride[34] (1.0 M, 1.57 ml, 1.57 mmol) was added dropwise over 10 min. The reaction mixture was stirred for 1 h at 25 °C, then diluted with water (10 ml) and extracted with dichloromethane (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo*. The residue was subjected to chromatography [silica gel, 8 g; elution with benzene–AcOEt 10 : 1 (v/v)] to give the title compound (**24**) (124.5 mg, 77% from **22**) as a solid, which was recrystallized from ether to give colorless needles, mp 125.5—127 °C. *Anal.* Calcd for $C_{24}H_{30}N_2O_5 \cdot 0.2H_2O$: C, 67.02; H, 7.12; N, 6.51. Found: C, 67.03; H, 7.22; N, 6.40. MS *m/z*: 326 (100%, M–$CH_2NHCOCOCH_3$), 91 (42). IR (KBr): 3380 (NH), 1710 (C=O), 1685 (C=O) cm^{-1}. UV λ_{max} nm (log ε): 210 (4.57), 226 (4.00), 258 (3.24), 265 (3.21), 268 (3.20), 279 (3.12). ^{1}H-NMR (400 MHz) δ: 2.20 (3H, s, $ArCH_3$), 2.54 (3H, s, $COCH_3$), 2.54 (1H, ddd, J=17.6, 3.2, 1.0 Hz), 2.84 (1H, ddd, J=17.6, 11.7, 6.1 Hz), 2.96 (1H, dd, J=13.9, 5.4 Hz), 3.14 (1H, dd, J=13.7, 10.0 Hz), 3.17 (1H, m), 3.64 (1H, d, J=12.9 Hz, NCHPh), 3.71 (3H, s, OCH_3), 3.72 (1H, d, J=12.9 Hz, NCHPh), 3.77 and 3.78 (each 3H, s, OCH_3), 3.80—3.90 (2H, m), 7.25—7.36 (5H, m, 5 × ArH), 7.67 (1H, br s, NH).

2-Benzyl-6-methyl-7-methoxy-1,2,3,4-tetrahydro-5,8-isoquinolinedione (25) A solution of **3a** (130.8 mg, 0.4 mmol) in dry dichloromethane (8 ml) was cooled at −78 °C, and a dichloromethane solution of boron tribromide (1.0 M, 0.4 ml, 0.4 mmol) was added. After being kept at the same temperature for 1 h, and then at 0 °C for 1 h, the reaction mixture was poured into ice-water. The aqueous layer was extracted with chloroform (20 ml × 2). The combined extracts were washed with brine (20 ml) and concentrated *in vacuo*. A stirred solution of the residue (125 mg) in acetonitrile (4 ml) was cooled with ice-water, an aqueous solution (4 ml) containing ceric ammonium nitrate (549 mg) was added dropwise over 10 min, and then stirring was continued at 0 °C for 1 h. The reaction mixture was diluted with water (10 ml) and extracted with chloroform (20 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo*. The residue was subjected to chromatography on preparative layer silica gel plates [Merck 5715, solvent hexane–AcOEt 2 : 1 (v/v)] to afford the title compound (**25**) (33.4 mg, 28.1%) as a pale yellow amorphous powder. MS *m/z*: 297 (M^+, 25%), 296 (19), 282 (18), 180 (30), 91 (100). High-resolution MS Calcd for $C_{18}H_{19}NO_3$: 297.1395. Found: 297.1372. IR ($CHCl_3$): 1685, 1655 (C=O) cm^{-1}. UV λ_{max} nm: 268, 368. ^{1}H-NMR (60 MHz) δ: 1.92 (3H, s, C=C–CH_3), 2.53 (2H, br s), 3.27 (2H, br s), 3.63 (2H, s, NCH_2Ph), 3.92 (3H, s, OCH_3), 7.20 (5H, br s, 5 × ArH).

***N*-[(2-Benzyl-6-methyl-7-methoxy-5,8-dioxo-1,2,3,4,5,8-hexahydro-1-isoquinolyl)methyl]-2-oxopropanamide (26)** A solution of **24** (63.9 mg, 0.15 mmol) in dry dichloromethane (3 ml) was cooled at −78 °C, and a dichloromethane solution of boron tribromide (1.0 M, 0.3 ml, 0.3 mmol) was added. After being kept at the same temperature for 1 h, and then at 0 °C for 1 h, the reaction mixture was poured into ice-water. The aqueous layer was extracted with chloroform (10 ml × 2). The combined extracts were washed with brine (10 ml) and concentrated *in vacuo*. A solution of the residue (65 mg) in acetonitrile (1.5 ml) was added an aqueous solution (1.5 ml) containing ceric ammonium nitrate (206 mg), and stirring was continued at 0 °C for 1 h. The reaction mixture was diluted with water

(5 ml) and extracted with chloroform (20 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo*. The residue was subjected to chromatography on preparative layer silica gel plates [Merck 5715, solvent hexane–AcOEt 1 : 1 (v/v)] to afford the title compound (**26**) (21.8 mg, 36.7%) as a pale yellow amorphous powder. MS *m/z*: 396 (M^+, 0.5%), 298 (31), 296 (64), 91 (100). High-resolution MS Calcd for $C_{22}H_{24}N_2O_5$: 396.1685. Found: 396.1661. IR ($CHCl_3$): 3400 (NH), 1725 (C=O), 1685 (C=O), 1655 (C=O) cm^{-1}: UV λ_{max} nm: 268, 368. ^{1}H-NMR (400 MHz) δ: 1.95 (3H, s, C=C–CH_3), 2.34 (1H, ddd, J= 19.8, 3.9, 2.0 Hz), 2.44 (3H, s, $COCH_3$), 2.55 (1H, dddd, J=19.8, 10.0, 5.9, 1.4 Hz), 2.86 (1H, ddd, J=13.9, 5.9, 2.0 Hz), 3.06 (1H, ddd, J=13.9, 10.0, 3.9 Hz), 3.25 (1H, ddd, J=13.7, 8.8, 4.8 Hz), 3.62 (1H, ddd, J=13.7, 6.3, 3.9 Hz), 3.66 (1H, ABq, J=13.2 Hz, NCH_2Ph), 3.68 (1H, ddd, J=8.8, 6.3, 1.4 Hz, 1-H), 4.02 (3H, s, OCH_3), 7.20—7.30 (5H, m, 5 × ArH), 7.44 (1H, dd, J=4.8, 3.9 Hz, NH). ^{13}C-NMR (100 MHz): 8.6 (q, C–$\underline{C}H_3$), 18.3 (t), 24.4 (q, O=C–$\underline{C}H_3$), 40.6 (t, $CH\underline{C}H_2NH$), 42.0 (t, NCH_2Ph), 54.4 (d), 57.7 (t), 60.9 (q, OCH_3), 127.6 (d), 128.3 (s), 128.6 (d), 128.8 (d), 137.8 (s), 138.2 (s), 142.8 (s), 155.8 (s), 159.9 (s, NC=O), 182.2 (C=O), 186.9 (C=O), 196.7 (O=$\underline{C}$–CH_3).

6-Methyl-5,7,8-trimethoxy-1-phthalimidomethyl-1,2,3,4-tetrahydroisoquinoline (27) Anhydrous ammonium formate (189 mg, 3 mmol) was added to a stirred suspension of **22** (291.6 mg, 0.6 mmol) and 10% palladium on carbon (291.6 mg) in dry methanol (20 ml), and the mixture was heated at reflux for 27 h. The catalyst was removed by filtration through a celite pad, which was then washed with chloroform (100 ml). The combined organic filtrates were concentrated *in vacuo*. The residue was subjected to chromatography [silica gel, 7 g, elution with hexane–AcOEt 1 : 2 (v/v)] to give the title compound (**27**) (73.7 mg, 31%) as a solid, mp 178—179 °C. *Anal.* Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.49; H, 6.13; N, 6.97. MS *m/z*: 237 (M^+ − 159, 15%), 236 (100). IR (KBr): 3700—3200 (NH), 1775, 1725 (C=O) cm^{-1}. UV λ_{max} nm (log ε): 222 (4.90), 240 sh (3.99), 280 (3.38), 300 sh (3.28). ^{1}H-NMR (400 MHz) δ: 1.62 (1H, br s, NH), 2.20 (3H, s, $ArCH_3$), 2.63 (1H, ddd, J= 17.1, 11.0, 6.4 Hz), 2.78 (1H, ddd, J=17.1, 4.6, 2.2 Hz), 3.00 (1H, ddd, J= 13.5, 6.4, 2.2 Hz), 3.28 (1H, ddd, J=13.5, 11.0, 6.4 Hz), 3.69, 3.78, and 3.94 (each 3H, s, OCH_3), 3.98 (1H, dd, J=13.7, 10.3 Hz, CHNPht), 4.08 (1H, dd, J=13.7, 4.2 Hz, CHNPht), 4.48 (1H, dd, J=10.3 and 4.2 Hz, 1-H), 7.72 (2H, m, 2 × ArH), 7.85 (2H, m, 2 × ArH).

Butyl 6-Methyl-5,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (28) Anhydrous ammonium formate (2.25 g, 35.7 mmol) was added to stirred suspension of **3c** (3.05 g, 7.14 mmol) and 10% palladium on carbon (3 g) in dry methanol (200 ml), and the mixture was heated at reflux for 1 h. The catalyst was removed by filtration through a celite pad, which was then washed with chloroform (300 ml). The combined organic filtrates were concentrated *in vacuo* to give the title compound (**28**) (1.926 g, 80%) as a colorless oil. *Anal.* Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.06; N, 4.15. Found: C, 63.74; H, 8.33; N, 3.94. MS *m/z*: 236 (M^+ − 101, 100%). IR (neat): 3320 (NH), 1725 (C=O) cm^{-1}. UV λ_{max} nm: 272, 280. ^{1}H-NMR (400 MHz) δ: 0.92 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.38 (2H), 1.64 (2H), 2.19 (1H, br s, NH), 2.19 (3H, s, $ArCH_3$), 2.68—2.79 (2H, m), 2.99—3.10 (2H, m), 3.68, 3.77, and 3.78 (each, 3H, s, OCH_3), 4.16 (2H, t, J= 6.6 Hz, OCH_2), 4.71 (1H, s, 1-H).

Butyl 6-Methyl-5,7,8-trimethoxyisoquinoline-1-carboxylate (29) A mixture of **28** (1.292 g, 3.83 mmol) and chloranil (5.66 g, 23 mmol) in *p*-xylene (40 ml) was heated at 150 °C for 12h. The mixture was concentrated *in vacuo* to give the residue which was subjected to chromatography on silica gel [100 g, elution with hexane–AcOEt 1 : 1 (v/v)] afforded the title compound (**29**) (781.8 mg, 61.2%) as a colorless oil. *Anal.* Calcd for $C_{18}H_{23}NO_5 \cdot 0.2H_2O$: C, 64.16; H, 7.00; N, 4.16. Found: C, 63.96; H, 6.89; N, 3.92. MS *m/z*: 333 (M^+, 100%), 318 (33), 260 (19), 232 (30), 230 (57), 218 (31), 217 (16), 203 (10), 202 (28), 174 (12). High-resolution MS Calcd for $C_{18}H_{23}NO_5$: 333.1576. Found: 333.1559. IR (neat): 1745 (C=O) cm^{-1}. UV λ_{max} nm: 216, 243, 292, 305, 342. ^{1}H-NMR (400 MHz) δ: 0.97 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.49 (2H, m), 1.80 (2H, m), 2.40 (3H, s, $ArCH_3$), 3.86, 3.91, and 3.94 (each 3H, s, OCH_3), 4.45 (2H, t, J=6.7 Hz, OCH_2), 7.89 (1H, d, J=5.6 Hz, ArH), 8.44 (1H, d, J=5.6 Hz, ArH).

1-Hydroxymethyl-6-methyl-5,7,8-trimethoxyisoquinoline (30) A stirred solution of the ester (**29**) (684.4 mg, 2.07 mmol) in dry THF (30 ml) was cooled with ice-water, a toluene solution of diisobutylaluminum hydride (1.0 M, 4.14 ml, 4.14 mmol) was added dropwise over 10 min, and then stirring was continued at 0 °C for 1 h. The reaction was quenched by addition of methanol (0.2 ml), and the reaction mixture was concentrated *in vacuo* to give the residue. The residue was subjected to chromatography [silica gel, 20 g, elution with benzene–AcOEt 5 : 1 (v/v)] to give the title compound (**30**) (220 mg, 40.4%) as a pale yellow oil. ^{1}H-NMR (60 MHz) δ: 2.36 (3H, s, $ArCH_3$), 3.85, 3.91, and 3.96 (each 3H, s, OCH_3), 5.27 (2H, s, $C\underline{H}_2OH$), 7.71 (1H, d, J=6 Hz, ArH), 8.34 (1H, d, J=6 Hz, ArH). Decomposition occurred during attempts to further purify the product by chromatography or crystallization. An analytical sample was obtained as follows.

A mixture of the acetate (**31**) (183 mg, 0.6 mmol) and 85% KOH (80 mg) in methanol (2 ml) was heated under reflux for 2 h. The solvent was removed *in vacuo* and water (10 ml) was added. The pricipitated crystals were collected and recrystallization of which from ether give the title compound (**30**) (158 mg, 100%) as colorless prisms, mp 89—90 °C, whose spectra were identical with those of an authentic sample described earlier.[29]

Acylation of the Alcohol (30) (a) Acetic anhydride (0.5 ml) was added to a solution of the crude alcohol (**30**) (57.8 mg, 2.20 mmol) in dry pyridine (2 ml), and the mixture was left to stand at room temperature for 1 h. After being diluted with water (10 ml), the mixture was extracted with chloroform (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give the residue, which was subjected to chromatography on silica gel [7 g, elution with hexane–AcOEt 2 : 1 (v/v)] to afford (6-methyl-5,7,8-trimethoxy-1-isoquinolyl)methyl acetate (**31**) (47.0 mg, 70.1%) as a pale yellow oil. MS *m/z*: 305 (M^+, 44%), 263 (21), 262 (100), 248 (32), 232 (13), 216 (24), 204 (13), 190 (10). High-resolution MS Calcd for $C_{16}H_{19}NO_5$: 305.1263. Found: 305.1236. IR: 1735 (C=O) cm^{-1}. UV λ_{max} nm: 212, 236, 288, 298, 324 sh, 336. ^{1}H-NMR (60 MHz) δ: 2.05 (3H, s, $COCH_3$), 2.12 (3H, s, $ArCH_3$), 3.72, 3.80, and 3.97 (each 3H, s, OCH_3), 5.48 (2H, s, CH_2O), 7.43 (1H, d, J=5 Hz, ArH), 8.03 (1H, d, J=5 Hz, ArH).

(b) Propionic anhydride (0.5 ml) was added to a solution of the crude alcohol (**30**) (57.8 mg, 2.20 mmol) in dry pyridine (2 ml), and the mixture was left to stand at room temperature for 1 h. After being diluted with water (10 ml), the mixture was extracted with chloroform (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give the residue which was subjected to chromatography on silica gel [7 g, elution with hexane–AcOEt 4 : 1 (v/v)] to afford (6-methyl-5,7,8-trimethoxy-1-isoquinolyl)methyl propionate (**32**) (48.2 mg, 68.8%) as a pale yellow oil. MS *m/z*: 319 (M^+, 31%), 263 (25), 262 (100), 248 (23), 232 (11), 204 (12). High-resolution MS Calcd for $C_{17}H_{21}NO_5$: 319.1420. Found: 319.1440. IR: 1750 (C=O) cm^{-1}. UV λ_{max} nm: 212, 236, 288, 298, 324 sh, 336. ^{1}H-NMR (60 MHz) δ: 1.17 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.15 (3H, s, $ArCH_3$), 2.17 (2H, q, J=7 Hz, $OC\underline{H}_2CH_2$), 3.75, 3.82, and 3.88 (each 3H, s, OCH_3), 5.60 (2H, s, CH_2O), 7.50 (1H, d, J= 5 Hz, ArH), 8.33 (1H, d, J=5 Hz, ArH).

6-Methyl-5,7,8-trimethoxy-1-phthalimidomethylisoquinoline (33) A solution of diethyl azodicarboxylate (0.17 ml, 1.02 mmol) in dry THF (1 ml) was added dropwise to a solution of the crude alcohol (**30**) (90.6 mg, 0.34 mmol), phthalimide (150 mg, 1.02 mmol), and triphenylphosphine (267 mg, 1.02 mmol) in dry THF (5 ml) at room temperature. The solution was stirred at room temperature for 2 h, then the solvent was removed *in vacuo*. The residue was diluted with water (30 ml) and extracted with chloroform (30 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give the residue, which was chromatographed on silica gel (10 g) using hexane–AcOEt (7 : 1, v/v) to give the title compound (**33**) (66.0 mg, 50%) as a solid, mp 214.5—216 °C (AcOEt). *Anal.* Calcd for $C_{20}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.16; H, 5.02; N, 7.10. MS *m/z*: 392 (M^+, 95%), 377 (26), 232 (93), 230 (100). IR (KBr): 1775, 1725 cm^{-1}. UV λ_{max} nm (log ε): 220 (4.75), 238 (4.81), 277 sh (3.36), 291 (3.80), 336 (3.58). ^{1}H-NMR (400 MHz) δ: 2.39 (3H, s, $ArCH_3$), 3.82, 3.95, and 4.07 (each 3H, s, OCH_3), 5.65 (2H, s, CH_2NPht), 7.62 (1H, d, J=5.6 Hz, ArH), 7.75 (2H, m), 7.92 (2H, m), 8.15 (1H, d, J=5.6 Hz, ArH).

***N*-[(6-Methyl-5,7,8-trimethoxy-1-isoquinolyl)methyl]-2-oxopropanamide (35)** Hydrazine monohydrate (0.1 ml) was added to a stirred solution of **33** (105 mg, 0.25 mmol) in ethanol (4 ml), and the reaction mixture was heated under reflux for 1 h, and concentrated *in vacuo*. The residue was dissolved in benzene (20 ml) and extracted with 1 N HCl (10 ml × 3). The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give the unstable amine (**34**) (65.5 mg, 100%) as a syrup, which was used for the next step without further purification.

A solution of the crude **34** (65.5 mg), triethylamine (0.07 ml, 0.5 mmol), and 4-(dimethylamino)pyridine (61 mg, 0.5 mmol) in dry dichloromethane (2 ml) was cooled with ice-water, and a carbon tetrachloride solution of pyruvoyl chloride (1.0 M, 1.0 ml, 1.0 mmol) was added dropwise over 10 min. The reaction mixture was stirred for 1 h at 25 °C, diluted with

water (10 ml) and extracted with dichloromethane (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrared *in vacuo*. The residue was subjected to chromatography [silica gel, 3 g; elution with benzene–AcOEt 10 : 1 (v/v)] to give the title compound (**35**) (30.9 mg, 36.2% from **33**) as a solid, which was recrystallized from ether to give colorless needles, mp 149—150 °C, whose spectra were identical with those of an authentic sample described earlier.[13]

1-Hydroxymethyl-6-methyl-5,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (36) a) From **28**: Lithium aluminum hydride (151.6 mg, 4 mmol) was added to a stirred solution of **28** (674 mg, 2 mmol) in dry THF (20 ml), and the mixture was heated at reflux for 2 h. The reaction was quenched at 0 °C by addition of water, the mixture was filtered, and the filter cake was carefully washed with chloroform (200 ml). The combined filtrates were concentrated *in vacuo* to give a solid, recrystallization of which from AcOEt–ether gave the title compound (**36**) (299.2 mg, 56%) as colorless needles, mp 118—119 °C (lit.,[29] 120—121 °C). *Anal.* Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.77; H, 8.05; N, 5.14. MS *m/z*: 236 (100%, M–CH_2OH), 206 (17). IR (KBr): 3700—2400 (OH and NH) cm^{-1}. UV λ_{max} nm (log ε): 222 (4.05), 272 sh (2.83), 278 (2.89). ^{1}H-NMR (400 MHz) δ: 2.18 (3H, s, $ArCH_3$), 2.10—2.50 (2H, br s, NH and OH), 2.58 (1H, ddd, J=17.1, 10.8, 6.3 Hz), 2.74 (1H, ddd, J=17.1, 4.4, 2.2 Hz), 2.98 (1H, ddd, J=13.7, 10.8, 4.4 Hz), 3.06 (1H, ddd, J=13.7, 6.3, 2.4 Hz), 3.49 (1H, t, J=10.0 Hz), 3.67, 3.78, and 3.84 (each 3H, s, OCH_3), 3.85 (1H, dd, J=10.0, 4.6 Hz), 4.13 (1H, dd, J=10.0, 4.6 Hz).

b) From **21**: A solution of **21** (71.4 mg, 0.2 mmol) in ethanol (2 ml) and acetic acid (0.2 ml) was hydrogenated over 10% palladium on carbon (50 mg) at 1 atm for 30 h. The catalyst was removed by filtration and washed with ethanol (50 ml). The combined filtrates were concentrated *in vacuo* to give a solid, recrystallization of which from AcOEt–ether gave the title compound (**36**) (28 mg, 52%) as colorless needles, mp 118—119 °C, identical (IR, NMR, mass spectra and mixed mp 118—119 °C) with the sampel prepared by method a).

2-Formyl-1-hydroxymethyl-6-methyl-5,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (37) A solution of **36** (186.9 mg, 0.7 mmol) in ethyl formate (4 ml) and methanol (4 ml) was stirred at room temperature for 24 h. The solvent was removed *in vacuo*. The residue was diluted with water (20 ml) and extracted with chloroform (20 ml × 3). The combined extracts wre washed with 5% $NaHCO_3$ solution (20 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from AcOEt–ether gave the title compound (**37**) (176.7 mg, 85.6%) as colorless needles, mp 132—133 °C (lit.[29] 130—131 °C). This product was a mixture of two rotational isomers (ratio, 3 : 2). *Anal.* Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.24. Found: C, 60.64; H, 7.30; N, 4.65. MS *m/z*: 264 (100%, M–CH_2OH). IR (KBr): 3400 (OH), 1665 (C=O) cm^{-1}. UV λ_{max} nm (log ε): 222 (4.17), 272 sh (3.11), 278 (3.13). ^{1}H-NMR (400 MHz) δ: 2.18 (3H, s, $ArCH_3$, both isomers), 2.71—2.86 (1H, m, both isomers), 2.86 (3/5H, ddd, J=16.8, 5.1, 3.2 Hz, major), 2.94 (2/5H, ddd, J=16.8, 5.1, 3.2 Hz, minor), 3.05 (1H, br s, OH, both isomers), 3.12 (3/5H, dd, J=10.7, 5.1 Hz, major), 3.15 (2/5H, dd, J=10.7, 5.1 Hz, minor), 3.66 (9/5H, s, OCH_3, major), 3.67 (6/5H, s, OCH_3, minor), 3.69 (3/5H, d like major), 3.73 (2/5H, m, minor), 3.78 (9/5H, s, OCH_3, major), 3.79 (6/5H, s, OCH_3, minor), 3.85 (1H, m, both isomers), 3.89 (6/5H, s, OCH_3, minor), 3.90 (9/5H, s, OCH_3, major), 4.04 (2/5H, m, minor), 4.39 (3/5H, ddd, J=13.4, 6.6, 3.2 Hz, major), 4.75 (3/5H, dd, J=9.3, 3.9 Hz, major), 5.64 (2/5H, dd, J=8.1, 3.9 Hz, minor), 8.27 (2/5H, s, CHO, minor), 8.28 (3/5H, s, CHO, major).

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