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Construction of the Pentacyclic Ring System of Apogeissoschizine

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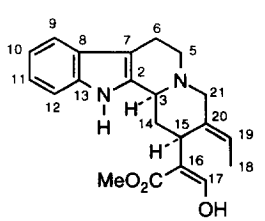
Abstract: The synthesis of pentacyclic apogeissoschizine-type compounds is reported. It involves the construction of the seven-membered E ring by addition of the enolate derived from methyl 1-indolepropionate to the γ-position of a pyridinium salt, with subsequent acid-promoted cyclization of the resulting 1,4-dihydropyridine, and the closure of the C ring by cyclization on the indole 3-position in the last synthetic step. Copyright © 1996 Elsevier Science Ltd

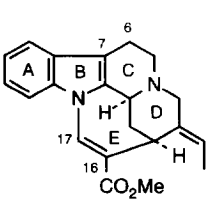
Apogeissoschizine is a degradation product of geissospermine[1] that is also formed by treatment of geissoschizine under acidic conditions.[1,2] It possesses an unusual pentacyclic skeleton that incorporates an indolo[2,3-*a*]quinolizidine ring system with an additional bridged seven-membered E ring linking C-17[3] and the indole nitrogen. Very recently, the alkaloid 2,7-dihydroxyapogeissoschizine, embodying the same pentacyclic skeleton, has been isolated from *Strychnos gossweileri*[4] (Figure 1). Apart from the above conversions from geissospermine and geissoschizine, no syntheses for the apogeissoschizine skeleton have been reported so far.

We present here the first synthetic entry to the bridged pentacyclic system of apogeissoschizine. Our approach involves i) the construction of the seven-membered E ring by nucleophilic addition of the enolate derived from methyl 1-indolepropionate to the γ-position of a pyridinium salt, followed by acid-promoted cyclization of the resulting 1,4-dihydropyridine,[5] and ii) the closure of the C ring in a late stage of the synthesis by formation of C_6-C_7 bond from an appropriately *N*-4 substituted tetracyclic system.[6]

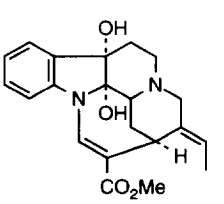
In a model experiment, interaction of the enolate derived from ester **1** with *N*-methylpyridinium iodide **2**, followed by treatment with anhydrous *p*-toluenesulfonic acid in benzene at 70 °C for 2 hours afforded tetracycle **6** as a nearly equimolecular mixture of C-16 epimers in 13% yield (Scheme 1). When the



Geissoschizine



Apogeissoschizine

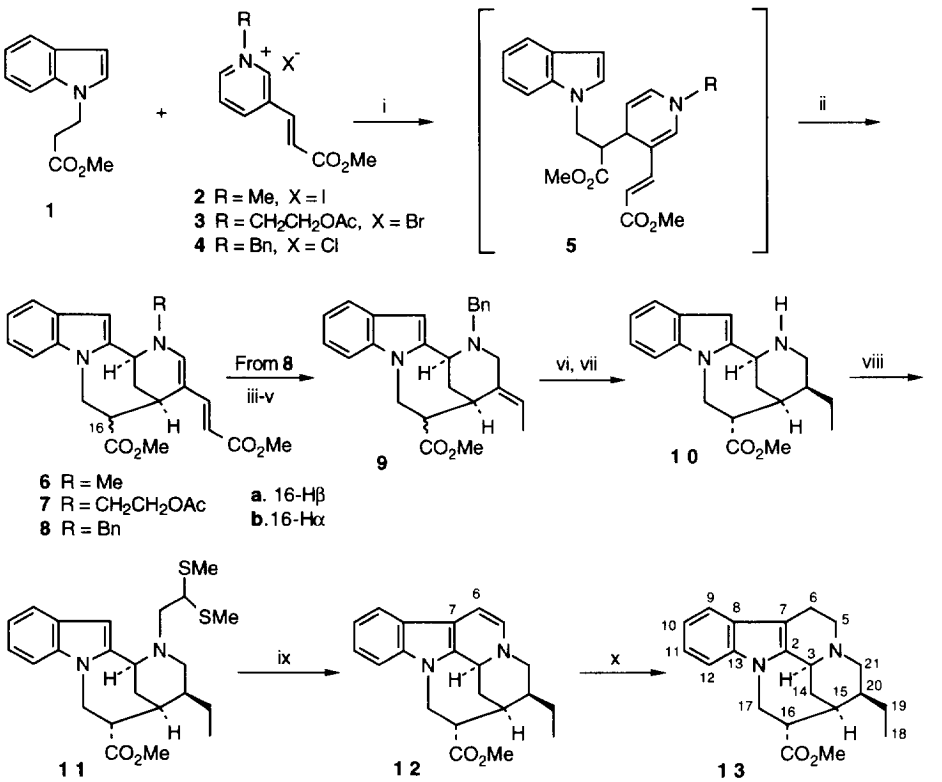


2,7-Dihydroxyapogeissoschizine

Figure 1

acidic treatment was omitted or when the cyclization was attempted under milder conditions (room temperature for 2 hours), the intermediate 1,4-dihydropyridine **5** (R = Me), which could be further cyclized under the above conditions, was isolated in 12% yield.

Once the applicability of the nucleophilic addition-cyclization sequence for the construction of the tetracyclic ABDE substructure of apogeissoschizine was established, our attention was focused on the preparation of a tetracyclic derivative bearing a two-carbon substituent on the piperidine nitrogen able to undergo cyclization on the indole ring. However, the use of the pyridinium salt **3** in the reaction with ester **1** led to the expected tetracycle **7** in only 6% yield. A more convenient result from the synthetic standpoint was obtained operating from pyridinium salt **4**, which incorporates an easily removable *N*-benzyl group. In this case, a 1:1 mixture of tetracycles **8a** and **8b** was isolated in 15% yield. The (tetrahydropyridyl)acrylate moiety of tetracycles **8a,b** was stereoselectively elaborated into the corresponding (*E*)-ethylidenepiperidine derivatives **9a,b** (23% yield, nearly equimolecular mixture of C-16 epimers) by the usual one-pot, three-step sequence consisting of treatment with refluxing aqueous HCl, reesterification of the C-16 carboxy group, and finally sodium borohydride reduction.[7]



Scheme 1. Reagents and Conditions: i) LDA, THF; ii) TsOH-C_6H_6, 70 °C, 2 h; iii) 2.5 N HCl, 100 °C, 2 h; iv) 0.2 N HCl-MeOH, rt, 20 h; v) $NaBH_4$, MeOH, 0 °C, 1 h; vi) separation of C-16 epimers; vii) H_2, $Pd(OH)_2$, MeOH, 18 h; viii) $(SMe)_2CHCHO$, $NaCNBH_3$, MeOH, rt, 16 h; ix) DMTSF, CH_2Cl_2; x) H_2, Pd-C, MeOH, rt, 12 h.

The relative configuration at C-16 in the above tetracycles was determined from the coupling constants between H-16 and H-17 (0-1.8 Hz and 3-4.1 Hz in series **a** and 0-3.3 Hz and 11-12 Hz in series **b**) in the ^{1}H-NMR spectra and by the shielding of C-14 in series **a** due to the γ-effect induced by the methoxycarbonyl group (Table 1).

Debenzylation of **9a** by hydrogenolysis took place with simultaneous hydrogenation of the ethylidene substituent to give the unstable secondary amine **10**, bearing a β-ethyl group at C-20. In contrast, the C-16 epimer **9b** showed to be reluctant to undergo debenzylation under the same conditions. However, this synthetic problem could be overcome since **9b** was epimerized to a 2:3 mixture of C-16 epimers **9a** and **9b** by treatment with potassium fluoride in refluxing methanol for two days.

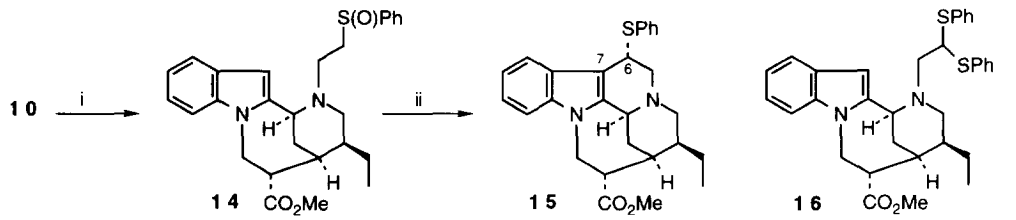
Three routes were explored for the introduction of the two-carbon tryptamine bridge of apogeissoschizine. The first uses an electrophilic cyclization on the indole 3-position of a thionium ion generated by DMTSF treatment of a dithioacetal.[8] The required dithioacetal **11** was prepared (32%) by reductive alkylation of the secondary amine **10** with bis(methylthio)acetaldehyde. As expected, dithioacetal **11** smoothly cyclized by treatment with DMTSF to give the pentacyclic enamine **12**, which was easily identified on the basis of their characteristic vinyl peaks at δ6.11 and 6.56 (J = 6.5 Hz). Catalytic hydrogenation of crude **12** gave tetrahydroapogeissoschizine (**13**) in 27% overall yield from **11**.

Table 1. Significant ^{13}C-NMR Data of Tetracyclic and Pentacyclic Apogeissoschizine-type Compounds.

	C-2	C-3	C-5	C-6	C-7	C-14	C-15	C-16[a]	C-17	C-18	C-19	C-20	C-21
6a	138.5	54.4	41.0		102.1	27.5	29.1	42.4	41.6	103.2	145.6	105.0	146.3
6b	137.5	54.1	41.0		102.7	31.7	31.6	47.3	41.1	102.9	146.7	101.6	146.8
7a	138.4	52.8	51.7	61.3	102.9	27.7	29.3	42.5	41.4	103.2	145.3	105.9	145.8
8a	136.2	51.2	56.4		102.8	27.7	29.5	42.5	41.5	103.3	145.1	105.3	145.9
8b	136.1	50.9	56.4		102.5	31.9	31.8	47.3	41.1	103.6	146.3	103.0	146.7
9a	138.5	56.2	59.1		100.8	28.2	32.5	47.2	42.0	12.9	121.0	137.9	52.4
9b	138.6	55.4	59.3		104.9	35.8	34.6	49.8	43.8	12.8	124.0	133.0	56.4
11	138.9	52.7	59.1	55.5	104.9	31.9	32.2	43.0	44.1	11.7	23.8	40.4	51.9
13	135.9	53.6	50.3	18.4	110.5	29.7	32.6	44.3	46.0	11.6	22.9	42.6	47.4
14	139.8	55.3	55.9	48.3	104.9	31.9	32.5	43.1	44.4	11.9	23.8	40.6	51.1
	139.0	54.7	55.3	47.1	105.1	32.0	32.4	43.0	44.1	11.8	23.7	40.5	51.5
15[b]	138.6	53.1	58.9	40.3	109.6	29.1	32.6	44.2	45.7	11.6	22.9	42.7	48.0
16[b]	134.2	55.1	59.7	57.6	104.8	31.9	32.4	43.1	44.5	11.8	23.7	40.6	53.4
17	137.0	43.8	164.7	41.5	104.1	29.6	33.2	45.9	41.4	11.4	22.8	41.8	44.1
18	94.7	55.6	172.7	35.9	48.9	26.0	31.8	41.0	42.2	11.2	24.0	39.8	41.2
19	c	49.0	178.0	34.7	c	25.3	32.0	45.0	44.7	12.1	23.1	40.0	41.8
20[b]	68.6	52.9	173.1	37.0	38.9	30.0	32.1	41.0	46.0	11.3	23.8	40.2	42.7

[a] 16-CO_2Me group (average values): 51.7 and 172.0. [b]Assignments confirmed by HMQC. [c] Not observed.

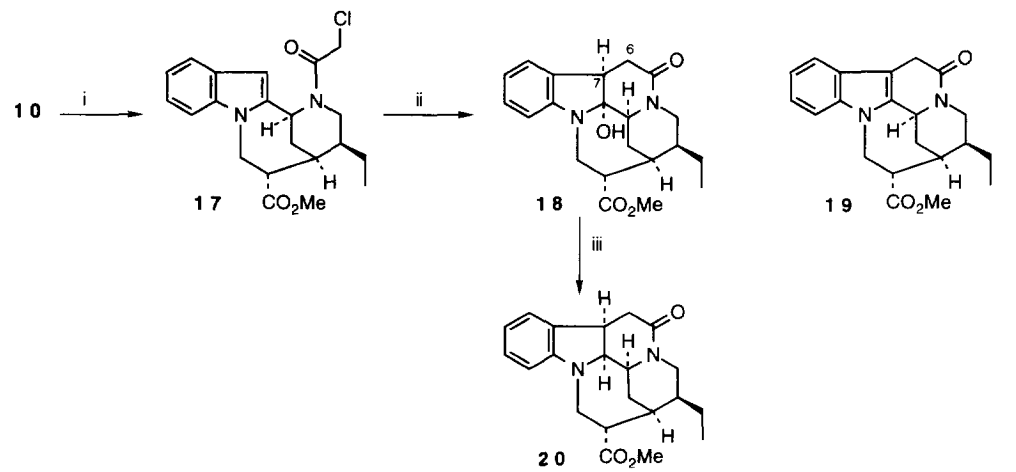
The second route involves the Pummerer cyclization[9] of sulfoxide **14** , which was prepared as a 1:1 mixture of diastereomers (33%) by alkylation of amine **10** with phenyl vinyl sulfoxide (Scheme 2). This cyclization was attempted under a variety of conditions. The expected pentacyclic sulfide **15** was only obtained, although in very low yield (6%), when the reaction was conducted with trimethylsilyl triflate in the presence of diisopropylethylamine. However, under these conditions, dithioacetal **16** was isolated as the major product.[10]



Scheme 2. Reagents and Conditions: i) CH_2=CHS(O)Ph, MeOH, reflux, 4 h; ii) TMSOTf, DIPEA, CH_2Cl_2, rt, 1h.

Alternatively, closure of C ring was investigated by photocyclization[11] of chloroacetamide **17**, which was accessible (77%) by acylation of amine **10** with chloroacetyl chloride (Scheme 3). Photocyclization of **17** in a diluted 1:1 MeOH-H_2O solution in the presence of sodium carbonate gave the pentacyclic 2-hydroxyindoline **18** in 14% yield. This compound underwent dehydration to the unstable indole **19** on storage or during column chromatography, but could be reduced to the pentacyclic indoline **20** by treatment with sodium cyanoborohydride in methanol.

Finally, the low stability of most of the tetracyclic and pentacyclic apogeissoschizine-type compounds prepared in this work is worth mentioning. The loss of material that generally occurs during purification accounts for the low yields reported in the Experimental Section.



Scheme 3. Reagents and Conditions: i) $ClCH_2COCl$, Et_3N, THF, 0 °C, 1 h; ii) hv, MeOH-H_2O, 0.5 mg/ml, rt, 15min; iii) $NaCNBH_3$, MeOH-HCl, 0 °C, 1 h.

EXPERIMENTAL SECTION

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 (200 and 50.3 MHz, respectively) or 300 (300 and 74.5 MHz, respectively) instrument. Chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer or on a Autospec-VG (HRMS). Column and flash chromatography were carried out on SiO_2 (silica gel 60, SDS, 0.06-0.2 mm and 0.04-0.06 mm, respectively). Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Centro de Investigación y Desarrollo (CSIC), Barcelona.

Methyl 3-(1-Indolyl)propionate (1). Method A. A suspension of indole (5 g, 0.04 mol) and KOH (11.5 g) in DMSO (68 ml) was stirred at room temperature for 1.5 h. Then, methyl 3-bromopropionate (3 ml, 0.03 mol) was added, and the resulting suspension was stirred at room temperature for 4 h. The reaction mixture was diluted with H_2O, washed with Et_2O, acidified with concentrated HCl, and extracted with Et_2O. The ethereal extracts were dried and evaporated, and the resulting residue was treated overnigth at room temperature with a 0.04 N MeOH solution of dry HCl (65 ml). The solvent was removed and the residue was chromatographed (flash, 8:2 Et_2O-hexane) to give ester **1** (4.7 g, 78%): IR (NaCl) 1739 (CO); ^1H-NMR (200 MHz) 2.88 (t, J = 6.8 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 4.50 (t, J = 6.8 Hz, 2H, CH_2N), 6.64 (d, J = 3.3 Hz, 1H, indole 3-H), 7.23 (d, J = 3.3 Hz, 1H, indole 2-H), 7.25-7.45 (m, 3H, indole), 7.80 (d, J = 8 Hz, 1H, indole 4-H); ^{13}C-RMN 34.6 (CH_2), 41.7 (CH_2N), 51.8 (OCH_3), 101.5 (C-3), 108.9 (C-7), 119.4 (C-4), 120.9 (C-5), 121.5 (C-6), 127.8 (C-2), 128.6 (C-3a), 135.5 (C-7a), 171.5 (CO). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.44; N, 6.89. Found: C, 70.98; H, 6.43; N, 6.92.

Method B.A solution of indole (2 g, 17 mmol) in DMF (40 ml) was slowly added to a suspension of NaH (55%, 1.48 g, 35 mmol) in DMF (35 ml), and the resulting mixture was stirred at room temperature for 30 min. Then, methyl 3-bromopropionate (4.5 ml, 45 mmol) was added, and the mixture was stirred for 4 h. The reaction mixture was diluted with H_2O and extracted with Et_2O. Evaporation of the dried extracts followed by flash chromatography of the residue gave ester **1** (1.86 g, 54%).

Reaction of Ester 1 with Pyridinium Iodide 2. LDA (5.9 mmol) was added to a solution of the ester **1** (1 g, 4.9 mmol) in THF (50 ml) cooled at -70°C, and the resulting solution was stirred at - 70°C for 45 min. Then, pyridinium iodide **2** (1.5 g, 4.9 mmol) was added in portions, and the mixture was allowed to rise to -30°C and stirred at this temperature for 1.5 h. Enough of a saturated C_6H_6 solution of dry TsOH was added dropwise to bring the pH to 3.5-4, and the reaction mixture was heated at 70°C for 2 h. The reaction mixture was poured into a saturated aqueous Na_2CO_3 solution and extracted with Et_2O. Evaporation of the ethereal extracts, followed by column chromatography (hexane-AcOEt, increasing polarity) of the residue, gave **methyl 2α(and 2β)-(methoxycarbonyl)-6-methyl-2,3,6,7-tetrahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole-4(*E*)-acrylate (6a** and **6b)**: 250 mg (5:6 mixture, 13%); mp 220°C (Et_2O-acetone); IR (film) 1733 (CO) 1586 (C=C); ^1H-NMR (300 MHz, isomer **6a**) 2.20 (dm, J =14 Hz, 1H, 14-H), 2.37 (d, J = 14 Hz, 1H, 14-H), 2.96 (s, 3H, NCH_3), 3.02 (br s, 1H, 16-H), 3.52 (masked, 1H, 15-H), 3.52 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.93 (dd, J =14.8, 1.8 Hz, 1H, 17-H), 4.40 (d, J =6.2 Hz, 1H, 3H), 4.73 (dd, J = 14.8, 4.1 Hz, 1H, 17-H), 5.39 (d, J = 15.1 Hz, 1H, 18-H), 6.41 (s, 1H, 7-H), 6.76 (s, 1H, 21-H), 7.10-7.45 (m, 4H, indole, 19-H),

7.55 (d, J = 8 Hz, 1H, 9-H); ^{1}H-NMR (300 MHz, isomer **6b**) 2.16 (br d, J = 13.5 Hz, 1H, 14-H), 2.33 (m, 1H, 14-H), 2.73 (dt, J = 11, 2 Hz, 1H, 16-H), 2.92 (s, 3H, NCH_3), 3.56 (br s, 1H, 15-H), 3.69 and 3.72 (2s, 6H, OCH_3), 3.98 (dd, J = 15.3, 11 Hz, 1H, 17-H), 4.44 (d, J = 6 Hz, 1H, 3-H), 4.56 (d, J = 15.3 Hz, 1H, 17-H), 5.29 (d, J = 15.2 Hz, 1H, 18-H), 6.45 (s, 1H, 7-H), 6.80 (s, 1H, 21-H), 7.10-7.35 (m, 4H, indole, 19-H), 7.55 (d, J = 8 Hz, 1H, 9-H); ^{13}C-NMR, Table 1. Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.35; N, 7.36. Found: C, 69.41; H, 6.40; N, 7.22.

When the acidic treatment was omitted, **methyl 4-[2-(1-indolyl)-1-(methoxycarbonyl)ethyl]-1-methyl-1,4-dihydropyridine-3(*E*)-acrylate [5** (R=Me), 220 mg, 12%] was isolated after flash chromatography (Et_2O): IR (NaCl) 1732, 1703 (CO), 1575 (C=C); ^{1}H NMR (300 MHz) 3.02 (s, 3H, NCH_3), 3.29 (dt, J = 10.6, 3 Hz, 1H, $CHCOOCH_3$), 3.65 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.03 (dd, J = 5, 3 Hz, pyr 4-H), 4.25 (dd, J = 14.4, 3 Hz, 1H, CH_2N), 4.53 (dd, J = 14.4, 10.6 Hz, 1H, CH_2N), 4.73 (dd, J = 7.9, 5 Hz, 1H, pyr 5-H), 5.70 (d, J = 15.6 Hz, 1H, CH=), 6.02 (dd, J = 7.9, 1.3 Hz, 1H, pyr 6-H), 6.38 (dd, J = 3.2, 0.8 Hz, 1H, indole 3-H), 6.51 (d, J = 1.3 Hz, 1H, pyr 2-H), 7.02-7.20 (m, 4H, indole), 7.40 (d, J = 15.6 Hz, 1H, CH=), 7.59 (d, J = 7.5 Hz, 1H, indole 4-H); ^{13}C-NMR 35.0 (pyr C-4), 40.0 (NCH_3), 44.2 (CH_2N), 47.4 (CH), 51.2, 51.0 (OCH_3), 100.3 (=$CHCO_2CH_3$), 100.9 (indole C-3), 106.8 (pyr C-3), 108.3 (pyr C-5), 109.0 (indole C-7), 119.2 (indole C-4), 119.2 (indole C-5), 121.3 (indole C-6), 128.5 (indole C-3a), 128.8 (indole C-2), 131.2 (pyr C-6), 135.7 (indole C-7a), 141.1 (=CH), 144.6 (pyr C-2), 168.4, 172.7 (CO).

Methyl 6-(2-Acetoxyethyl)-2-(methoxycarbonyl)-2,3,6,7-tetrahydro-1*H*-3,7-methano[1,4]diazonino-[1,2-*a*]indole-4(*E*)-acrylate (7). Operating as above, from ester **1** (1 g, 4,9 mmol) and pyridinium bromide **3** (1.6 g, 4,9 mmol) a 2:1 mixture of tetracycles **7a** and **7b** (130 mg, 6%) was obtained: mp 166°C (Et_2O-acetone); IR (KBr) 1734 (CO) 1588 (C=C); ^{1}H-NMR (300 MHz, major isomer **7a**) 1.94 (s, 3H, CH_3CO), 2.20 (m, 1H, 14-H), 2.38 (d, J = 13.5 Hz, 1H, 14-H), 3.05 (br s, 1H, 16-H), 3.30 (m, 2H, 5-H), 3.51 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.95 (d, J = 15 Hz, 1H, 17-H), 4.20 (m, 2H, 6-H), 4.60 (masked, 1H, 3-H), 4.75 (dd, J = 15, 3 Hz, 1H, 17-H), 5.45 (d, J = 15 Hz, 1H, 18-H), 6.39 (s, 1H, 7-H), 6.79 (s, 1H, 21-H), 7.07-7.40 (m, 4H, indole, 19-H), 7.52 (d, J = 8 Hz, 1H, 9-H); ^{13}C-NMR, Table 1. Anal. Calcd for $C_{25}H_{28}N_2O_6$: C, 66.36; H, 6.23; N, 6.19. Found: C, 66.20; H, 6.27; N, 6.20.

Methyl 6-Benzyl-2α(and 2β)-(methoxycarbonyl)-2,3,6,7-tetrahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole-4(*E*)-acrylate (8a and 8b). Operating as above, from ester **1** (1 g, 4.9 mmol) and pyridinium bromide **4** (1.4 g, 4.9 mmol) a 1:1 mixture of tetracycles **8a,b** (340 mg, 15%) was obtained after column chromatography (hexane-Et_2O, increasing polarity). **8a**: IR (film) 1737, 1696 (CO), 1578 (C=C); ^{1}H-NMR (300 MHz) 2.17 (m, 1H, 14-H), 2.35 (d, J = 14 Hz, 1H, 14-H), 3.05 (br s, 1H, 16-H), 3.50 (masked, 1H, 15-H), 3.52 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.99 (dd, J = 14.7, 1.8 Hz, 1H, 17-H), 4.26 and 4.35 (2d, J = 15.4 Hz, 2H, $CH_2C_6H_5$), 4.45 (d, J = 6.5 Hz, 1H, 3-H), 4.77 (dd, J = 14.7, 4 Hz, 1H, 17-H), 5.45 (d, J = 15.2 Hz, 1H, 18-H), 6.34 (s, 1H, 7-H), 6.97 (s, 1H, 21-H), 7.10-7.40 (m, 9H, Ar, 19-H), 7.55 (d, J = 8 Hz, 1H, 4-H); ^{13}C-NMR, Table 1. **8b**: mp 130° C (Et_2O-hexane); IR (film) 1737, 1696 (CO), 1579 (C=C); ^{1}H-NMR (300 MHz) 2.15 (dm, J = 13 Hz, 1H, 14-H), 2.24 (m, 1H, 14-H), 2.75 (dt, J = 11, 1.9 Hz, 1H, 16-H), 3.59 (br s, 1H, 15-H), 3.69 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.04 (dd, J = 15, 11 Hz, 1H, 17-H), 4.27 (s, 2H, $CH_2C_6H_5$), 4.48 (d, J = 6.3 Hz, 1H, 3-H), 4.58 (d, J = 15 Hz, 1H, 17-H), 5.32 (d, J = 15.4 Hz, 1H, 18-H), 6.35 (s, 1H, 7-H), 7.02 (s, 1H, 21-H), 7.08-7.36 (m, 9H, Ar, 19-H), 7.56 (d, J = 8 Hz, 1H, 4-H); ^{13}C-NMR, Table 1. Anal. Calcd for $C_{28}H_{28}N_2O_4.1/3\ H_2O$: C, 72.71; H, 6.24; N, 6.05. Found: C, 72.87; H, 6.17; N, 5.99.

Methyl 6-Benzyl-4(*E*)-ethylidene-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino [1,2-*a*]indole-2α(and 2β)carboxylate (9a and 9b). A suspension of tetracycles **8a,b** (0.35 g, 0.77 mmol) in MeOH (10 ml) and 2.5 N aqueous HCl (20 ml) was refluxed for 2 h and then evaporated. The residue was dissolved in a 0.2 N MeOH solution of dry HCl (30 ml) and stirred at room temperature overnight. The solvent was removed and the residue was dissolved in MeOH (30 ml), treated with $NaBH_4$ (0.3 g, 9 mmol) at 0°C, and stirred at this temperature for 1 h. The solvent was evaporated and the residue was partitioned between H_2O and Et_2O and extracted with Et_2O. The organic extracts were dried and evaporated to give a nearly equimolecular mixture of tetracycles **9a** and **9b** (70 mg, 23%). Both isomers were separated by column chromatography (hexane-Et_2O, increasing polarity). **9a**: IR (NaCl) 1735 ; ^{1}H-NMR (300 MHz) 1.62 (d, J = 6.8 Hz, 3H, 18-H), 2.06 (br d, 14.3 Hz, 1H, 14-H), 2.31 (m, 1H, 14-H), 3.01 (br s, 1H, 16-H), 3.10 (d, J =13.7 Hz, 1H, 21-H), 3.23 (br d, J =13.7 Hz, 1H, 21-H), 3.38 (d, J =13.7 Hz, 1H, $CH_2C_6H_5$), 3.49 (s, 3H, OCH_3), 3.59 (br s, 1H, 15-H), 3.93 (d, J = 13.7 Hz, 1H, $CH_2C_6H_5$), 3.96 (d, J = 5 Hz, 1 H, 3-H), 4.83 (dd, J = 14, 4 Hz, 1H, 17-H), 5.04 (d, J =14 Hz, 1H, 17-H), 5.30 (q, J = 6.8 Hz, 1H, 19-H), 6.29 (s, 1H, 7-H), 7.01-7.25 (m, 7H, Ar), 7.43 (d, J = 8.5 Hz, 1H, C_6H_5), 7.52 (d, J = 7.7 Hz, 1H, 9-H); ^{13}C-NMR, Table 1. **9b**: mp 150°C (MeOH); IR (KBr) 1735 (CO); ^{1}H-NMR (300 MHz) 1.56 (d, J = 6.9 Hz, 3H, 18-H), 2.04 (dt, J =13.5, 2.1 Hz, 1H, 14-H), 2.48 (dm, J = 13.5 Hz, 1H, 14-H), 2.99 (dt, J = 12, 3.3 Hz, 1H, 16-H), 3.22 (m, 2H, 21-H), 3.44 (d, J = 13.5 Hz, 1H, $CH_2C_6H_5$), 3.65 (d, J = 13.5 Hz, 1H, $CH_2C_6H_5$), 3.71 (d, J = 6 Hz, 1H, 15-H), 3.76 (s, 3H, OCH_3), 4.28 (dm, J = 4 Hz, 1H, 3-H), 4.49 (dd, J = 15, 12 Hz, 1H, 17-H), 4.66 (dd, J = 15, 3.3 Hz, 1H, 17-H), 5.58 (q, J = 6.9 Hz, 1H, 19-H), 6.35 (s, 1H, 7-H), 7.12-7.40 (m, 8H, Ar), 7.59 (d, J = 8 Hz, 1H, 9-H); ^{13}C-NMR, Table 1. Anal. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.04; N, 6.99. Found: C, 77.88; H, 7.02; N, 6.88.

Epimerization of 9b. KF (170 mg, 2.7 mmol) was slowly added to a solution tetracycle **9b** (540 mg, 1.35 mmol) in MeOH-THF (5:1, 60ml), and the resulting mixture was refluxed for 2 days. The usual workup gave a 2:3 mixture of C-16 epimers **9a** and **9b** (500 mg, 93%), which were separated by column chromatography (1:9, Et_2O-hexane).

Methyl 4β-Ethyl-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole-2α-carboxylate (10). Compound **9a** (180 mg, 0.45 mmol) in MeOH (15 ml) was hydrogenated over $Pd(OH)_2$ (45 mg) at atmospheric pressure for 18 h. The catalyst was filtered off and the solvent was evaporated to give crude amine **10** (130 mg, 91%), which was used in the next step without further purification.

Methyl 6-[2,2-Bis(methylthio)ethyl]-4β-ethyl-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole-2α-carboxylate (11). Bis(methylthio)acetaldehyde[12] (0.07 ml, 0.52 mmol) and $NaCNBH_3$ (66 mg, 0.96 mmol) were added to a solution of crude amine **10** (100 mg, 0.32 mmol) in dry MeOH (5 ml). Then, a drop of 4 N MeOH solution of dry HCl was added and the resulting mixture was stirred at room temperature for 48 h. The solvent was evaporated and the residue was dissolved in H_2O and extracted with Et_2O. Evaporation of the dried extracts followed by flash chromatography of the residue (7:3 hexane-Et_2O) gave dithioacetal **11** (45 mg, 32%): ^{1}H-NMR (300 MHz) 1.02 (t, J = 7.3 Hz, 3H, 18-H), 1.48 (m, 2H, 19-H), 2.10 (masked, 3H, 14-H, 20-H), 2.11 and 2.14 (2 s, 6H, SCH_3), 2.42 (t, J = 11.6 Hz, 1H, 21-H), 2.56 (dd, J = 13.5, 6.8 Hz, 1H, 5-H), 2.80 (m, 2H, 15-H, 21-H), 3.04 (dd, J = 13.5, 7.3 Hz, 1H, 5-H), 3.11 (br, 1H, 16-H), 3.59 (s, 3H, OCH_3), 3.93 (dd, J = 7.3, 6.8 Hz, 1H, 6-H), 4.20 (br, 1H, 3-H), 4.34 (dd, J = 14.6, 2.5 Hz, 1H, 17-H), 4.92 (dd, J = 14.6, 3.8 Hz, 1H, 17-H), 6.38 (s, 1H, 7-H), 7.10 (t, J = 8 Hz, 1H, 10-H), 7.22 (t, J = 8 Hz, 1H,

11-H), 7.40 (d, J = 8 Hz, 1H, 12-H), 7.55 (d, J = 8 Hz, 1H, 9-H); ^{13}C-NMR, Table 1; MS (m/z, rel intensity) 432 (M^+, 1), 325 (100); HRMS calcd for $C_{23}H_{32}N_2O_2S_2$ 432.1905, found 432.1895.

(±)-16β,17,19,20α-Tetrahydroapogeissoschizine (13). A solution of dithioacetal **11** (50 mg, 0.11 mmol) in CH_2Cl_2 (3 ml) was slowly added under N_2 to a solution of DMTSF (47 mg, 0.22 mmol) in CH_2Cl_2 (25 ml) at -30 °C. The mixture was allowed to rise the room temperature and stirred at this temperature for 2 h. The reaction mixture was quenched with 10% aqueous Na_2CO_3 (25 ml) and stirred at room temperature for 30 min. The organic layer was dried and evaporated to give crude enamine **12** (30 mg): ^{1}H-NMR (300 MHz) 0.76 (t, J = 7.4 Hz, 3H, 18-H), 0.91 (m, 1H, 19-H), 1.08 (m, 1H, 19-H), 1.50 (t, J = 12.4 Hz, 1H, 21-H), 1.76 (m, 1H, 20-H), 2.32 (m, 2H, 14-H, 16-H), 2.53 (dd, J = 12.4, 4.1 Hz, 1H, 21-H), 2.72 (m, 1H, 15-H), 2.90 (dt, J = 14.6, 3 Hz, 1H, 14-H), 3.70 (s, 3H, OCH_3), 4.08 (br s, 1H, 3-H), 4.35 (dd, J = 14, 2 Hz, 1H, 17-H), 4.51 (dd, J = 14, 10.4 Hz, 1H, 17-H), 6.11 and 6.56 (2d, J = 6.5 Hz, 2H, 5-H and 6-H), 7.10-7.26 (m, 2H, indole), 7.34 (d, J = 8.2 Hz, 1H, 12-H), 7.59 (dm, J = 7.5 Hz, 1H, 9-H); MS (m/z, relative intensity) 336 (M^+, 10); HRMS calcd for $C_{21}H_{24}N_2O_2$ 336.1837, found 336.1844. Catalytic hydrogenation of **12** in MeOH (5 ml) over Pd-C (10%, 10 mg) at room temperature for 4 h gave pentacycle **13** (10 mg, 27%): ^{1}H-NMR (300 MHz) 0.68 (t, J = 7.3 Hz, 3H, 18-H), 0.80 (m, 1H, 19-H), 1.02 (m, 1H, 19-H), 1.76 (m, 1H, 20-H), 1.87 (t, J = 12 Hz, 1H, 21-H), 2.05 (m, 2H, 14-H, 16-H), 2.25 (dd, J = 12, 3 Hz, 1H, 21-H), 2.49 (m, 1H, 15-H), 2.59 (m, 1H, 6-H), 2.82 (m, 2H, 5-H, 14-H), 3.02 (m, 1H, 5-H), 3.35 (m, 1H, 6-H), 3.58 (s, 3H, OCH_3), 4.15 (br s, 1H, 3-H), 4.23 (dd, J = 14.3, 2.1 Hz, 1H, 17-H), 4.38 (dd, J = 14.3, 10.3 Hz, 1H, 17-H), 7.05-7.20 (m, 2 H, indole), 7.35 (d, J = 8 Hz, 1H, 12-H), 7.49 (d, J = 8 Hz, 1H, 9-H); ^{13}C-NMR, Table1; HRMS calcd for $C_{21}H_{26}N_2O_2$ 338.1994, found 338.1981.

Methyl 4β-Ethyl-6-[2-(phenylsulfinyl)ethyl]-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole-2α-carboxylate (14). A mixture of amine **10** (75 mg, 0.24 mmol) and phenyl vinyl sulfoxide (0.06 ml, 0.48 mmol) in MeOH (5 ml) was refluxed for 4 h. The solvent was removed and the residue was diluted with H_2O and extracted with Et_2O. The organic extracts were dried and evaporated to give a 1:1 mixture of sulfoxides **14** (37 mg, 33%), which were separated by column chromatography (AcOEt). Less polar diastereomer: IR (film) 1732 (CO), 1033(SO); ^{1}H-NMR (300 MHz) 1.02 (t, J = 7.3 Hz, 3H, 18-H), 1.42 (m, 2H, 19-H), 1.74 (m, 1H, 20-H), 2.11 (dt, J = 14, 2.4 Hz, 1H, 14-H), 2.20 (m, 1H, 14-H), 2.30 (t, J = 11.8 Hz, 1H, 21-H), 2.48 (m, 1H, 6-H), 2.64 (dd, J = 11.8, 5.2 Hz, 1H, 21-H), 2.82 (br s, 1H, 16-H), 2.94-3.20 (m, 4H), 3.59 (s, 3H, OCH_3), 4.29 (m, 2H, 17-H and 3-H), 4.90 (dd, J = 15, 5 Hz, 1H, 17-H), 6.34 (s, 1H, 7-H), 7.00-7.70 (m, 9H, Ar); ^{13}C-NMR, Table 1. More polar diastereomer: IR (film) 1732 (CO), 1030 (SO); ^{1}H-NMR (300 MHz) 1.01 (t, J = 7.4 Hz, 3H, 18-H), 1.45 (m, 2H, 19-H), 1.64 (m, 1H, 20-H), 2.10 (m, 2H, 14-H), 2.35 (t, J = 12 Hz, 1H, 21-H), 2.70-3.10 (m, 7H), 3.59 (s, 3H, OCH_3), 4.06 (br s, 1H, 3-H), 4.24 (dd, J = 14.6, 2.8 Hz, 1H, 17-H), 4.89 (dd, J =14.6, 4.3 Hz, 1H, 17-H), 6.18 (s, 1H, 7-H), 7.05-7.70 (m, 9H, Ar); ^{13}C-NMR, Table 1; HMRS calcd for $C_{27}H_{32}N_2O_3S$ 464.2133, found 464.2147.

Pummerer Rearrangement of Sulfoxides 14. TMSOTf (0.04 mL, 0.22 mmol) was added to a solution of sulfoxides **14** (60 mg, 0.1 mmol) in CH_2Cl_2 (3 ml) containing diisopropylethylamine (0.04 ml, 0.22 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was poured into 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organics extracts were dried and evaporated, and the residue was chromatographed (flash, AcOEt). The initial elution gave dithioacetal **16** (10 mg, 17%): IR (film) 1732 (CO); ^{1}H-NMR (300 MHz) 0.98 (t, J = 7.2 Hz, 3H, 18-H), 1.40 (m, 3H, 19-H and 20-H), 2.03 (m, 1H, 14-H), 2.16

(m, 1H, 14-H), 2.41 (t, J = 11.8 Hz, 1H, 21-H), 2.63 (dd, J = 14, 7.1 Hz, 1H, 5-H), 2.75 (m, 2H, 15-H and 21-H), 3.06 (br s, 1H, 16-H), 3.14 (dd, J = 14, 7.1 Hz, 1H, 5-H), 3.57 (s, 3H, OCH_3), 4.08 (br s, 1H, 3-H), 4.27 (dd, J = 14.8, 2.7 Hz, 1H, 17-H), 4.57 (t, J = 7.1 Hz, 1H, 6-H), 4.86 (dd, J = 14.8, 4.3 Hz, 1H, 17-H), 5.96 (s, 1H, 7-H), 7.10-7.50 (m, 14H, Ar); ^{13}C-NMR, Table 1; MS, m/z (rel intensity) 556 (M^+, 1), 325 (100); HRMS calcd for $C_{33}H_{36}N_2O_2S_2$ 556.2218, found 556.2214. Further elution gave **(±)-6-(Phenylthio)-16β,17,19,20α-tetrahydroapogeissoschizine** (**15**, 3 mg, 6%): ^{1}H-NMR (300 MHz) 0.67 (t, J = 7.2 Hz, 3H, 18-H), 0.90 (m, 2H, 19-H), 1.72 (m, 1H, 20-H), 1.81 (t, J = 11.7 Hz, 1 H, 21-H), 1.95 (dt, J = 14.7, 3.9 Hz, 1 H, 14-H), 2.07 (m, 1H), 2.28 (dd, J = 10.8, 3.6 Hz, 1H), 2.47 (m, 1 H, 15-H), 2.72 (dt, J = 14.7, 3 Hz, 1H, 14-H), 3.40 (m, 2H), 3.60 (s, 3H, OCH_3), 3.85 (br s, 1H, 3-H), 4.27 (dd, J = 14.4, 2.7 Hz, 1H, 17-H), 4.35 (dd, J = 14.4, 9.9 Hz, 1H, 17-H), 4.58 (t, J = 7 Hz, 1H, 6-H), 7.05-7.50 (m, 8H, Ar), 7.66 (d, J = 8 Hz, 1H, 9-H); ^{13}C-NMR, Table 1; MS, m/z (rel intensity) 446 (M^+, 8), 336 (100).

Methyl 6-(Chloroacetyl)-4β-ethyl-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino-[1,2-*a*]indole-2α-carboxylate (17). Chloroacetyl chloride (0.06 ml, 0.75 mmol) in THF (4 ml) was slowly added to a solution of crude amine **10** (180 mg, 0.57 mmol) and Et_3N (0.14 ml, 1.12 mmol) in THF (14 ml), and the resulting solution was stirred at 0°C for 1 h. The reaction mixture was washed with 10% aqueous Na_2CO_3 solution, dried, and evaporated. Flash chromatography (Et_2O) of the resulting residue gave chloroacetamide **17** (170 mg, 77%): mp 65-66°C (Et_2O); IR (KBr) 1732, 1659 (CO); ^{1}H-NMR (300 MHz, signals due to the major rotamer) 0.97 (t, J = 7.5 Hz, 3H, 18-H), 1.33 (m, 2H, 19-H), 1.91 (m, 1H, 20-H), 2.10 (dt, J = 14.9, 4.5 Hz, 1H, 14-H), 2.56 (dt, J =14.9, 2.4 Hz, 1H, 14-H), 2.94 and 3.04 (2m, 3H), 3.56 (dd, J = 13.6, 4.1 Hz, 1H, 21-H), 3.74 (s, 3H, OCH_3), 4.04 and 4.10 (2d, J = 12.1 Hz, 2H, CH_2Cl), 4.52 (m, 2H, 17-H), 6.26 (d, J = 5 Hz, 1H, 3-H), 6.58 (s, 1H, 7-H), 7.10-7.40 (m, 3 H, indole), 7.53 (d, J = 8 Hz, 1H, 9-H); ^{13}C-NMR, Table 1. Anal. Cald for $C_{21}H_{25}N_2O_3Cl$: C, 64.86; H, 6.47; N, 7.20. Found: C, 64.7; H, 6.53; N,7.13.

Photocyclization of Chloroacetamide 17. A solution of chloroacetamide **17** (60 mg, 0,15 mmol) in MeOH-H_2O (1:1, 120 ml) containing Na_2CO_3 (100 mg) was irradiated under N_2 at room temperature for 15 min using a 125 W medium-pressure mercury lamp in a quartz inmersion well reactor. The reaction mixture was evaporated to dryness, and the residue was chromatographed (flash, AcOEt) to give **(±)-2α-hydroxy-5-oxo-2,7α,16β,17,19,20α-hexahydroapogeissoschizine** (**18**, 8 mg, 14%): ^{1}H-NMR (300 MHz) 0.83 (t, J = 7.4 Hz, 3H, 18-H), 1.23 (m, 2H, 19-H), 1.60 (m, 1H, 20-H), 1.90 (m, 1H, 14-H), 2.20 (t, J = 11 Hz, 1H, 21-H), 2.67 (br s, 1H, 16-H), 2.72 (dd, J = 14.6, 2.2 Hz, 1H, 6-H), 2.84 (dd, J = 14.8, 2 Hz, 1H, 14-H), 3.01 (dd, J = 14.6, 5 Hz, 1H, 6-H), 3.60 (m, 3H, 17-H, 15-H), 3.75 (masked, 1H, 3-H), 3.77 (s, 3H, OCH_3), 3.90 (m, 1H), 6.35 (d, J = 7.5 Hz, 1H, 12-H), 6.67 (t, J = 7.5 Hz, 1H, 10-H), 7.02 (m, 2H, 9-H, 11-H); ^{13}C-NMR, Table 1. On storage in CH_2Cl_2 solution or during column chromatography, 2-hydroxyindoline **18** was slowly converted into indole **19**: ^{1}H-NMR (300 MHz) 0.82 (t, J = 7.5 Hz, 3H, 18-H), 0.96 (m, 1 H, 19-H), 1.20 (m, 1H, 19-H), 2.01 (m, 1H, 20-H), 2.38 (m, 1H, 14-H), 2.48 (m, 1H, 14-H), 2.84 (dm, J = 14 Hz, 1H), 2.93 (m, 1H), 3.16 (dd, J = 13.9, 7.3 Hz, 1H), 3.51 (dd, J = 13.9, 5.5 Hz, 1H), 3.70 (masked, 2H, 6-H), 3.71 (s, 3H, OCH_3), 4.40 (m, 2H, 17-H), 5.02 (br s, 1H, 3-H), 7.10-7.55 (m, 4H, indole); ^{13}C-NMR, Table 1.

(±)-5-Oxo-2α,7α,16β,17,19,20α-hexahydroapogeissoschizine (20). A MeOH solution of dry HCl 2N (0.05 ml) and $NaCNBH_3$ (5 mg, excess) were added to a solution of pentacycle **19** (20 mg, 0.056 mmol) in MeOH (2 ml), and the resulting mixture was stirred at 0°C for 1h. The solvent was evaporated, and the residue was partitioned between 10% aqueous $NaHCO_3$ and Et_2O and extracted with Et_2O. Evaporation of the dried

extracts followed by flash chromatography (Et_2O) gave indoline **20** (10 mg, 50%): IR (film) 1653, 1731 (CO); ^1H NMR (300 MHz) 0.85 (t, J = 7.4 Hz, 3H, 18-H), 1.21 (m, 2H, 19-H), 1.64 (m, 1H, 20-H), 2.12 (ddd, J = 14.8, 8.6, 3.6 Hz, 1H, 14-H), 2.36 (t, J = 13.4, 1H, 21-H), 2.50 (dd, J = 14.8, 3 Hz, 1H, 14-H), 2.69 (m, 3H, 6-H, 16-H, 15-H), 2.77 (dt, J = 15, 3.1 Hz, 1H, 6-H), 3.43 (m, 2H, 17-H), 3.70 (masked, 1H, 21-H), 3.76 (s, 3H, OCH_3), 3.80 (d, J = 7 Hz, 1H, 3-H), 3.97 (br s, 2H, 2-H, 7-H), 6.26 (d, J = 7.5 Hz, 12-H), 6.56 (t, J = 7.5 Hz, 10-H), 7.01 (m, 2H, 9-H, 11-H); ^{13}C-NMR, Table 1; MS, m/z (rel. intensity) 354 (M^+, 100), 295 (M-59, 11); HRMS calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1940.

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