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Total Synthesis of (±)-Clavizepine†

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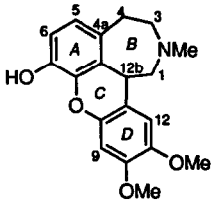
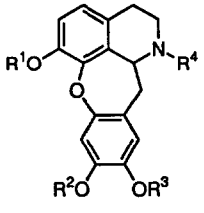
Abstract: The first total synthesis of benzopyranobenzazepine alkaloid (±)-clavizepine (**1**) has been achieved by using the Bradsher cyclization of the keto ester **16** (leading to **18**) and the Pummerer-type cyclization of the sulfoxide **25** (leading to **26**) as the key steps.

(-)-Clavizepine (**1**) is an alkaloid isolated in 1986 from *Corydalis claviculata* (L.) DC.[1] The structure of **1** was assigned through examination of its UV, ^{1}H and ^{13}C NMR, and mass spectral characteristics. The gross structure of **1** reveals a unique 1-benzopyrano-3-benzazepine skeleton bearing one asymmetric center (C_{12b}), though its absolute configuration is unknown. Another intriguing feature is the presence of a pharmacologically attractive 1-aryl-3-benzazepine moiety[2] as the structural subunit. From a biogenetic point of view, this alkaloid has been suggested to be the result of a rearrangement of the cularine system **2**.[3] In this paper, we present the details of our work on the first total synthesis of (±)-clavizepine.[4,5]



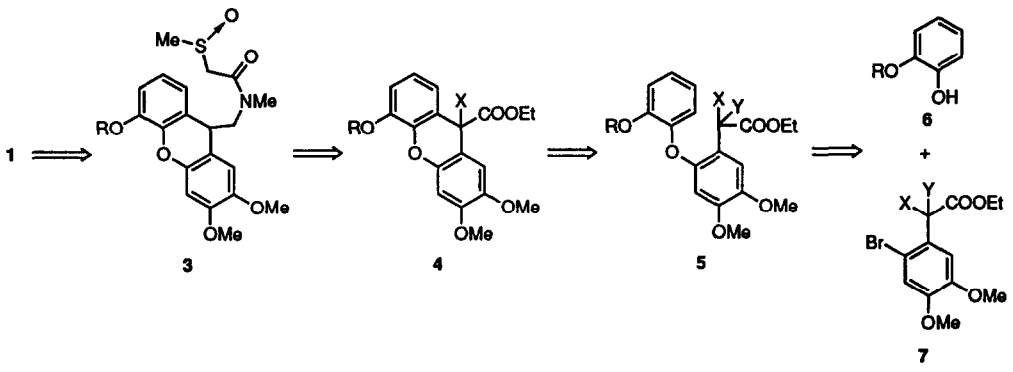
1



2

While a variety of possible strategies for the assembly of this alkaloid could be envisioned on the basis of a retrosynthetic analysis, we decided to employ our method of constructing the 3-benzazepine skeleton, which consists of an electrophilic aromatic substitution of α-sulfinylacetamides under the Pummerer rearrangement conditions,[6] to form the C_4-C_{4a} bond of **1** at the final stage. The synthesis of the requisite sulfoxide **3** was envisaged to arise from the xanthene-9-carboxylic ester **4**, which in turn was prepared by Ullmann condensation of **6** with **7** followed by cyclization of the resulting diphenyl ether **5**.

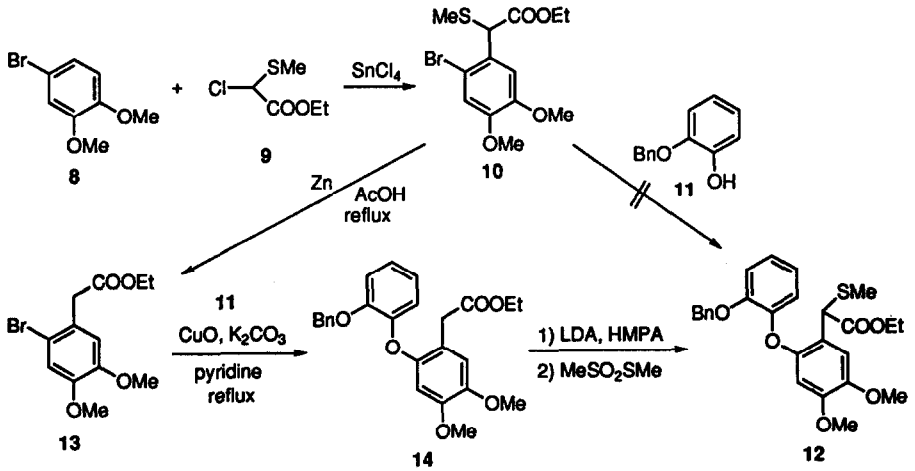
† Dedicated to Professor Emeritus Yasumitsu Tamura of Osaka University on the occasion of his 70th birthday.



Formation of A-C-D Rings of 1.

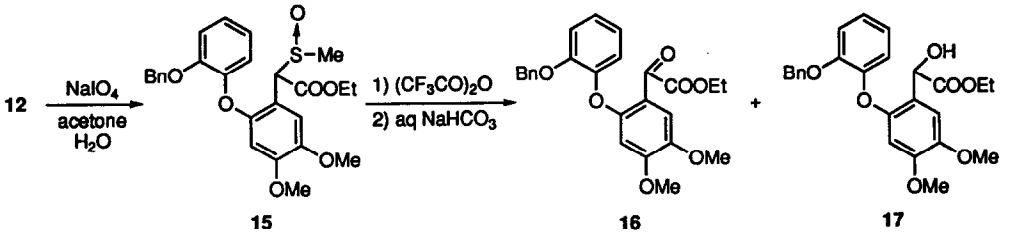
In considering how the xanthene derivative **4** might be formed, it occurred to us that the sulfoxide **15** should provide **4** (X = SMe, R = Bn) under the Pummerer rearrangement conditions, and the compound **4** (X = SMe, R = Bn) thus became our initial target.

We began the synthesis of the sulfide **12** starting from 4-bromoveratrole (**8**). Friedel-Crafts reaction of **8** with ethyl chloro(methylthio)acetate (**9**)[7] in the presence of $SnCl_4$ gave **10** in nearly quantitative yield. The bromide **10** was then subjected to the Ullmann reaction with catechol monobenzyl ether **11**[8] in the presence of CuO and K_2CO_3 in refluxing pyridine.[9] This, however, brought about decomposition of the starting material **10**, probably due to the result of a tight complexation of the methylthio group of **10** with the copper catalyst used. Therefore, we were forced to examine a similar reaction with the desulfurized compound **13** which was readily obtained from **10** by treating with zinc in hot acetic acid. When a mixture of **13** (1 eq) and **11** (2 eq) was heated in refluxing pyridine in the presence of CuO (5 eq) and K_2CO_3 (4 eq) for 20 h, the expected Ullmann condensation product **14** was obtained in 61% yield (based on **13**). The compound **14** was then treated successively with lithium diisopropylamide (LDA) and methyl methanethiolsulfonate to give the desired sulfide **12** in 76% yield.



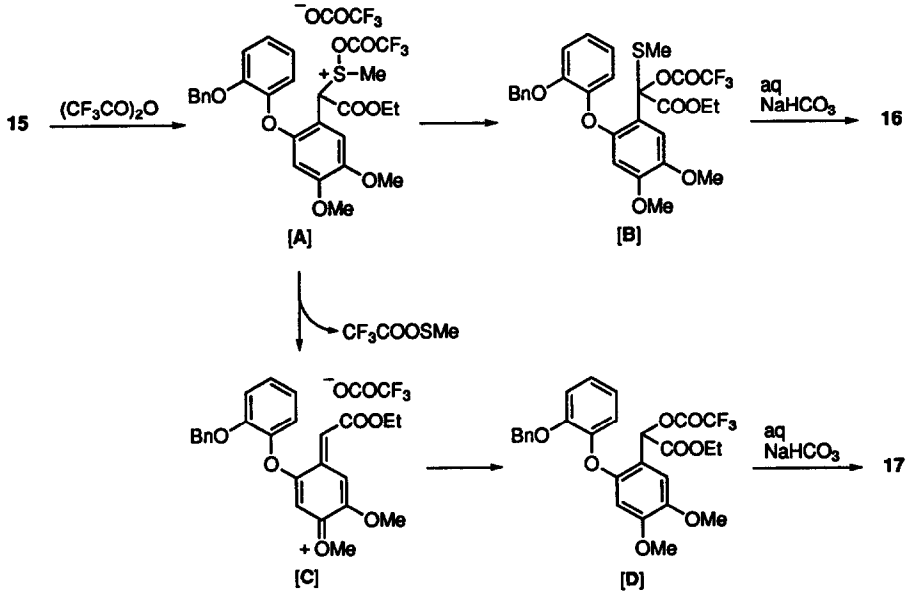
Scheme 1

With the requisite sulfide **12** in hand, we examined the cyclization of the corresponding sulfoxide **15**. Thus, treatment of **12** with $NaIO_4$ in aqueous acetone afforded the sulfoxide **15**, which was then exposed to trifluoroacetic anhydride (TFAA) in CH_2Cl_2 at 0°C to give the keto ester **16** and the hydroxy ester **17** in 45 and 20% yields, respectively. Unfortunately, no desired cyclization product **4** (X = SMe, R = Bn) was obtained.



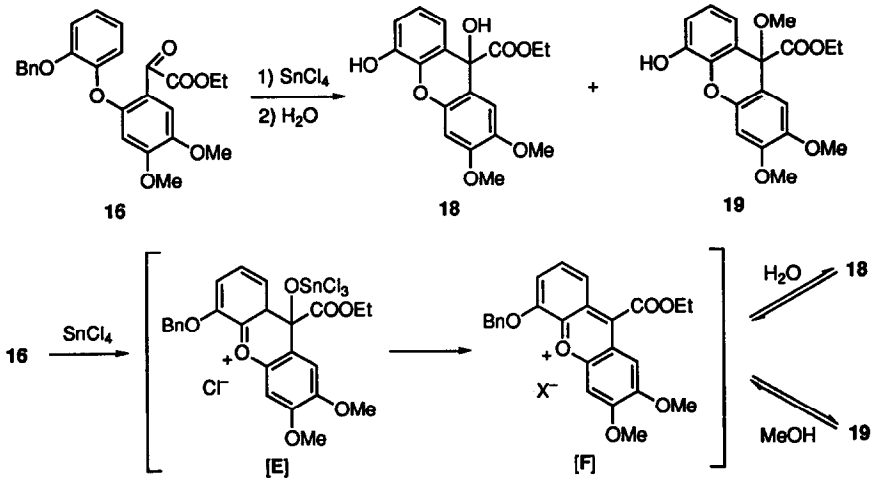
Scheme 2

Formation of **16** and **17** from **15** is considered to proceed *via* the discrete steps shown in Scheme 3. Thus, reaction of the sulfoxide **15** with TFAA gives initially the intermediacy of sulfonium ion **(A)**, which then undergoes the normal Pummerer rearrangement to give the trifluoroacetate **(B)**. On the other hand, elimination of $CF_3C(O)OSMe$ from the sulfonium ion **(A)**, promoted by an electron donating *p*-methoxy group, provides an ion pair **(C)**, which then recombines to give the trifluoroacetate **(D)**. When the resulting mixture is treated with an aqueous $NaHCO_3$ solution, the trifluoroacetates **(B)** and **(D)** are hydrolyzed to give **16** and **17**, respectively.



Scheme 3

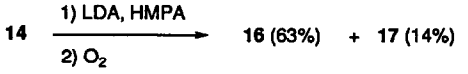
Although an attempt to cyclize the sulfoxide **15** failed, we considered that the keto ester **16** obtained from **15** might become an alternate precursor of the xanthene-9-carboxylic acid derivatives **4**. Indeed, when the compound **16** was treated with $SnCl_4$ and then with water in CH_2Cl_2, the cyclization product **18** was obtained in 36% yield together with the methoxy derivative **19** (30%), with concomitant debenzylation.



Scheme 4

Formation of **18** and **19** from **16** may be explained as follows. The ketone **16** cyclizes with the aid of $SnCl_4$ to give the xanthylium salt (**F**) *via* the intermediate (**E**) (Bradsher reaction).[10] When the reaction mixture is treated with water, the salt (**F**) reacts with water to give the hydroxy ester **18**. The product **18** thus formed is considered to give an equilibrium mixture with the xanthylium salt (**F**) under the acidic conditions, so that the salt (**F**) reacts with methanol, which is contained as a stabilizer in CH_2Cl_2 used as an extraction solvent, to give the methoxy derivative **19**. In fact, when methanol-free CH_2Cl_2 was used for extraction, only the hydroxy ester **18** was obtained in 66% yield. On the other hand, when a solution of **18** in methanol containing a catalytic quantity of *p*-toluenesulfonic acid was allowed to stand at room temperature, the methoxy derivarive **19** was obtained in 95% yield.

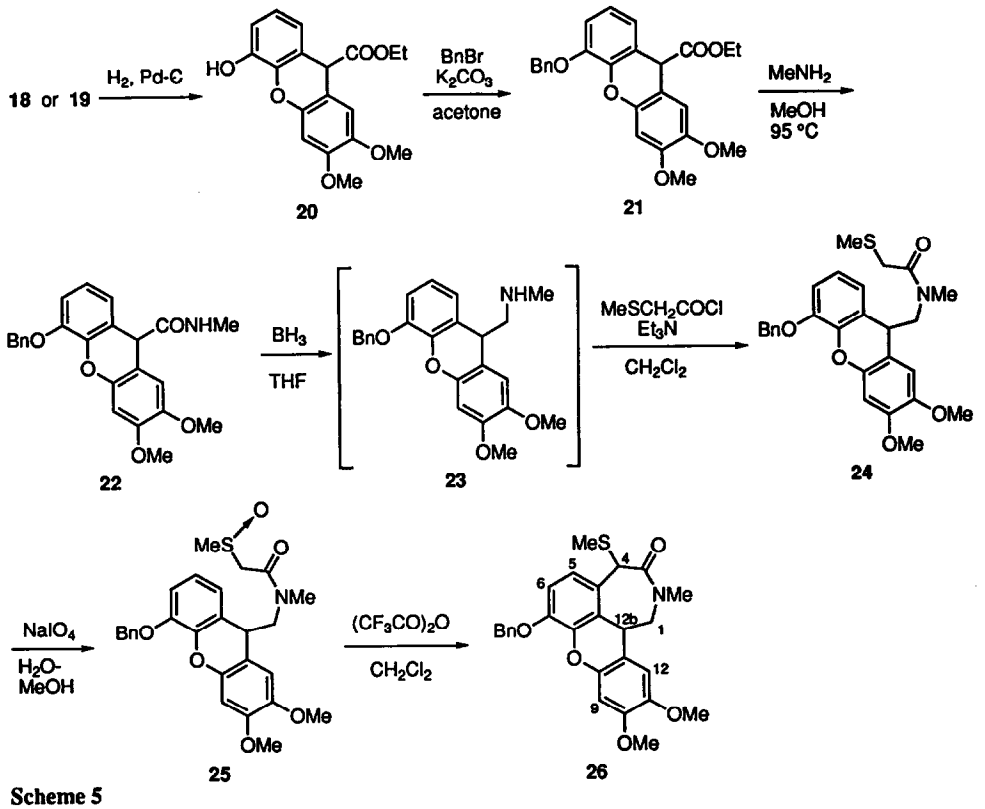
As shown above, the keto ester **16** has proved to be a good precursor of the xanthene-9-carboxylic ester **18** or **19**. However, the synthesis of **16** from **14** required three chemical operations (**14** → **12** → **15** → **16**), so we examined an alternate short synthesis of **16** from **14**. Thus, the ester **14** was treated successively with LDA and a molecular oxygen to give directly the keto ester **16** in 63% yield, along with the hydroxy ester **17** (14%).[11]



Synthesis of (±)-Clavizepine.

With the requisite xanthene derivatives **18** and **19** so conveniently assembled, we then examined a transformation of these materials to the sulfoxide **25**, a key intermediate for the construction of the B ring of clavizepine.

The hydrogenolysis of **18** over palladium catalyst proceeded very slowly even under medium pressure. The desired deoxygenated compound **20** was obtained in 86% yield after a period of one week. On the other hand, the deoxygenation of the methoxy derivative **19** completed within two days to give **20** in 94% yield.



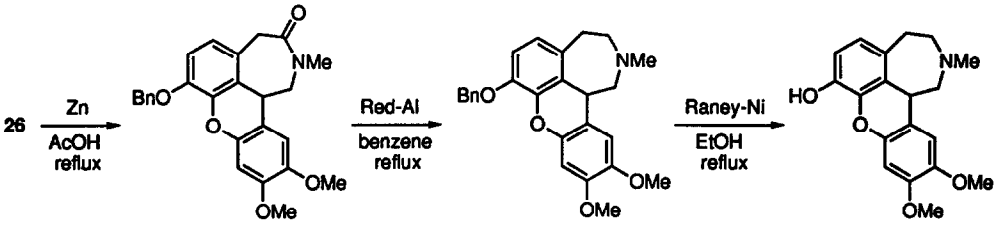
Scheme 5

The phenolic hydroxy group of **20** was reprotected with benzyl bromide to give the benzyl ether **21**, which was heated with excess methylamine in methanol at 95 °C in a sealed tube to give the amide **22** in 92% yield. Reduction of **22** to the amine **23** with diborane in THF was very sluggish, but continuous refluxing of the mixture for 10 days afforded **23** in nearly quantitative yield. Acylation of **23** with (methylthio)acetyl chloride followed by oxidation of the resulting sulfide **24** with $NaIO_4$ provided the sulfoxide **25** in an excellent yield.

The cyclization of the sulfoxide **25** was effected by treatment with TFAA in CH_2Cl_2 at room temperature to give the clavizepine skeleton **26** in 95% yield. Another possible cyclization product based on the attack on the C_{12} position of **26** was not formed. This is probably due to the presence of a sterically demanding *ortho*-

methoxy group. The ^1H NMR spectrum ($CDCl_3$) of **26** exhibited the signals due to the SMe protons at δ 2.29 and 2.17 in an integrated ratio of 8:1, which suggested the compound **26** to be a mixture of two diastereoisomers in a ratio of 8:1. Recrystallization of the mixture from hexane-AcOEt gave a major stereoisomer (mp 97-99 °C) of **26**, whose ^1H NMR spectrum (C_6D_6) exhibited an AB quartet (J = 8.3 Hz) centered at δ 6.55 due to the C_5 and C_6 protons, thereby confirming the structure **26**.

Transformation of **26** to (±)-clavizepine was accomplished in a straightforward manner. Thus, desulfurization of **26** with zinc in acetic acid gave, in 92% yield, the lactam **27**, which was then reduced by sodium bis(2-methoxyethoxy)aluminum hydride (Red Al) to afford the amine **28** in 62% yield. While the deprotection of the benzyl ether **28** by hydrogenolysis over Pd-C failed, treatment of **28** with Raney nickel in boiling ethanol furnished (±)-clavizepine (**1**), mp (dec) 218-219 °C (MeOH), in 93% yield. The ^1H and ^{13}C NMR spectra of this synthetic material were indistinguishable from those of natural (-)-clavizepine reported in the literature.[1]



27 28 (±)-1

Scheme 6

Thus, we succeeded in the first total synthesis of (±)-clavizepine (**1**) by using the Bradsher cyclization of the keto ester **16** (leading to **18**) and the Pummerer-type cyclization of the sulfoxide **25** (leading to **26**) as the key steps.

Experimental Section

Melting points are uncorrected. IR spectra were recorded with a JASCO IRA-100 spectrophotometer. ^1H (270 MHz) and ^{13}C NMR (67.8 MHz) spectra were measured on a JEOL JNM-EX 270 spectrometer, and δ values are quoted relative to tetramethylsilane. Exact MS determinations were obtained on a Hitachi M-80 instrument operating at 20 eV. Column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque, Inc.) under pressure.

Ethyl 2-Bromo-4,5-dimethoxy-α-(methylthio)phenylacetate (10). To a solution of 4-bromoveratrole (**8**) (23.6 g, 0.11 mol) and ethyl chloro(methylthio)acetate (**9**)[7] (18.3 g, 0.11 mol) in dry CH_2Cl_2 (700 ml) was added $SnCl_4$ (28.3 g, 0.11 mol) at 0 °C, and the mixture was stirred at room temperature for 30 min. Water (500 ml) was added to the reaction mixture, and the organic phase was dried ($MgSO_4$) and concentrated to give **10** (37.1 g, 98%) as a colorless oil, which was homogeneous by ^1H NMR spectroscoppy. IR ($CHCl_3$) ν 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (3H, t, J = 7.3 Hz), 2.13 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 4.18, 4.25 (1H each, both dq, J = 10.6, 7.3 Hz, OCH_2CH_3), 5.02 (1H, s), 7.01 (1H, s), 7.25 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.1, 15.1, 51.9, 56.1, 56.2, 61.8, 112.2, 114.6, 115.1, 127.5, 148.7, 149.2, 170.3. *Anal.* Calcd for $C_{13}H_{17}BrO_4S$: C, 44.71; H, 4.91. Found: C, 44.99; H, 4.72.

Ethyl 2-Bromo-4,5-dimethoxyphenylacetate (13). Zinc dust (49.0 g, 0.75 mol) was added to a solution of **10** (52.4 g, 0.15 mol) in acetic acid (50 ml), and the mixture was heated under reflux for 5 h.

CH_2Cl_2 (100 ml) was added to the reaction mixture, and the organic materials were removed by filtration. The filtrate was concentrated *in vacuo* to give **13** (43.5 g, 96%), mp 65.5-66.5 °C (from hexane) [lit.[12] mp 66-67 °C]. IR ($CHCl_3$) ν 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, t, J = 7.3 Hz), 3.71 (2H, s), 3.86 (6H, s), 4.19 (2H, q, J = 7.3 Hz), 6.80 (1H, s), 7.03 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.2, 41.2, 56.1, 56.2, 61.0, 113.9, 115.0, 115.5, 126.2, 148.4, 148.8, 170.8.

Ethyl 2-[2-(Benzyloxy)phenoxy]-4,5-dimethoxyphenylacetate (14). Potassium carbonate (5.53 g, 40 mmol) was added to a solution of **11**[8] (4.01 g, 20 mmol) and **13** (3.03 g, 10 mmol) in pyridine (45 ml), and the mixture was heated to 130 °C. To this was added copper (II) oxide (3.98 g, 50 mmol), and the mixture was heated under reflux for 20 h. $CHCl_3$ (150 ml) was added to the reaction mixture, and the inorganic materials were removed by filtration. The filtrate was washed successively with water, 10% NaOH, 10% HCl, and brine, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 5:1) to give **14** [2.56 g, 61% (based on **13**)] as an orange oil. IR ($CHCl_3$) ν 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (3H, t, J = 7.3 Hz), 3.61 (2H, s), 3.72 (3H, s), 3.89 (3H, s), 4.04 (2H, q, J = 7.3 Hz), 5.15 (2H, s), 6.46 (1H, s), 6.77-6.89 (2H, m), 6.83 (1H, s), 6.93-7.03 (2H, m), 7.27-7.37 (5H, m). ^{13}C NMR ($CDCl_3$) δ 14.1, 35.1, 56.0, 56.3, 60.7, 71.1, 103.6, 113.7, 115.4, 117.1, 118.6, 121.6, 123.4, 127.3, 127.8, 128.4, 137.1, 145.2, 147.7, 148.4, 148.9, 149.2, 171.6. *Anal.* Calcd for $C_{25}H_{26}O_6$: C, 71.07; H, 6.20. Found: C, 71.05; H, 6.06.

Ethyl 2-[2-(Benzyloxy)phenoxy]-4,5-dimethoxy-α-(methylthio)phenylacetate (12). To a solution of LDA, prepared from diisopropylamine (1.05 ml, 7.5 mmol) and butyllithium (1.6 M in hexane) (4.69 ml, 7.5 mmol), in THF (30 ml) was added a solution of **14** (1.27 g, 3 mmol) in THF (18 ml) at -78 °C, and the mixture was stirred at the same temperature for 30 min. HMPA (538 mg, 3 mmol) was then added, and stirring was continued for 30 min. A solution of methyl methanethiolsulfonate (1.89 g, 15 mmol) in THF (18 ml) was added to the solution, and the mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of 10% HCl, and the whole was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 7:1) to give **12** (1.35 g, 76%) as an yellow oil. IR ($CHCl_3$) ν 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (3H, t, J = 7.3 Hz), 2.06 (3H, s), 3.70 (3H, s), 3.91 (3H, s), 4.03, 4.14 (1H each, dq, J = 10.9, 7.3 Hz, OCH_2CH_3), 5.02 (1H, s), 5.14 (2H, s), 6.41 (1H, s), 6.82-6.90 (2H, m), 6.99-7.03 (2H, m), 7.20-7.35 (5H, m), 7.24 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.1, 15.2, 46.0, 56.0, 56.3, 61.4, 71.0, 102.7, 111.8, 115.3, 118.4, 119.2, 121.6, 123.8, 127.3, 127.9, 128.4, 136.9, 145.5, 147.2, 148.2, 149.4, 170.9. *Anal.* Calcd for $C_{26}H_{28}O_6S$: C, 66.65; H, 6.02. Found: C, 66.81; H, 5.89.

Ethyl 2-[2-(Benzyloxy)phenoxy]-4,5-dimethoxy-α-(methylsulfinyl)phenylacetate (15). A solution of sodium metaperiodate (321 mg, 1.5 mmol) in water (9 ml) was added to a solution of **12** (469 mg, 1 mmol) in acetone (6 ml) at 0 °C, and the mixture was stirred at room temperature for 15 h. Acetone was removed by evaporation, water (15 ml) was added to the residue, and the whole was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane-AcOEt, 1:2) to give **15** (441 mg, 91%) as a pale yellow oil. IR ($CHCl_3$) ν 1725, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21, 1.25 (total 3H, both t, J = 7.3 Hz), 2.30, 2.38 (total 3H, both s), 3.68, 3.70 (total 3H, both s), 3.88, 3.90 (total 3H, both s), 4.04-4.33 (2H, m), 5.06 (2H, s), 5.10, 5.27 (total 1H, both s), 6.37, 6.40 (total 1H, both s), 6.94-7.31 (10H, m). *Anal.* Calcd for $C_{26}H_{28}O_7S$: C, 64.45; H, 5.82. Found: C, 64.18; H, 5.99.

Ethyl 2-[2-(Benzyloxy)phenoxy]-4,5-dimethoxyphenylglyoxylate (16) and Ethyl 2-[2-(Benzyloxy)-phenoxy]-4,5-dimethoxy-α-hydroxyphenylacetate (17). From 15. To a solution of **15** (183 mg, 0.38 mmol) in CH_2Cl_2 (10 ml) was added TFAA (159 mg, 0.76 mmol) at 0 °C, and the mixture was stirred at room temperature for 24 h. The reaction mixture was washed with a saturated $NaHCO_3$ solution and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 4:1). The first eluate gave **16** (67 mg, 38%) as an yellow oil. IR ($CHCl_3$) ν 1740, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (3H, t, J = 7.3 Hz), 3.69 (3H, s), 3.91 (3H, s), 4.19 (2H, q, J = 7.3 Hz), 5.09 (2H, s), 6.20 (1H, s), 6.92-7.16 (4H, m), 7.25-7.31 (5H, m), 7.43 (1H, s). ^{13}C NMR ($CDCl_3$) δ 13.8, 56.2, 56.3, 61.7, 70.8, 100.2, 110.2, 115.3, 115.5, 121.3, 121.7, 125.6, 127.1, 127.9, 128.4, 136.5, 144.7, 145.3, 150.1, 155.3, 156.0, 165.7, 184.9. *Anal.* Calcd for $C_{25}H_{24}O_7$: C, 68.80; H, 5.54. Found: C, 68.54; H, 5.63. The second eluate gave **17** (34 mg, 19%) as an yellow oil. IR ($CHCl_3$) ν 3530, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (3H, t, J = 7.3 Hz), 3.49 (1H, s, OH), 3.70 (3H, s), 3.89 (3H, s), 4.03, 4.16 (1H each, both dq, J = 10.9, 7.3 Hz, OCH_2CH_3), 5.14 (2H, s), 5.38 (1H, s, CHOH), 6.40 (1H, s), 6.87-6.91 (2H, m), 6.89 (1H, s), 7.01-7.04 (2H, m), 7.28-7.34 (5H, m). *Anal.* Calcd for $C_{25}H_{26}O_7$: C, 68.48; H, 5.98. Found: C, 68.46; H, 6.15.

From 14. To a solution of LDA, prepared from diisopropylamine (0.34 ml, 2.4 mmol) and butyllithium (1.6 M in hexane) (1.5 ml, 2.4 mmol), in THF (10 ml) was added a solution of **14** (845 mg, 2 mmol) in THF (20 ml) at -78 °C, and the mixture was stirred at the same temperature for 30 min. HMPA (359 mg, 2 mmol) was added, and oxygen gas was bubbled through the solution at -78 °C for 1.5 h and then at room temperature for 10 min. The reaction was quenched by addition of 10% HCl, and the whole was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 5:1) to give **16** (592 mg, 63%) and **17** (124 mg, 14%).

Ethyl 5,9-Dihydroxy-2,3-dimethoxyxanthene-9-carboxylate (18). To the solution of **16** (175 mg, 0.4 mmol) in dry CH_2Cl_2 (10 ml) was added $SnCl_4$ (209 mg, 0.8 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1 h and then at room temperature for 6 h. Water (10 ml) was added to the reaction mixture, the organic layer was separated, and the aqueous layer was further extracted with methanol-free CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane-AcOEt, 1:1) to give **18** (91 mg, 66%), mp 167-168 °C (from hexane-AcOEt). IR ($CHCl_3$) ν 3575, 3450, 3265, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (3H, t, J = 7.3 Hz), 3.88 (3H, s), 3.93 (3H, s), 4.11 (2H, q, J = 7.3 Hz), 4.85 (1H, s, OH), 5.68 (1H, s, OH), 6.77 (1H, s), 6.88 (1H, s), 6.96-7.07 (3H, m). *Anal.* Calcd for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.24; H, 5.22.

Ethyl 5-Hydroxy-2,3,9-trimethoxyxanthene-9-carboxylate (19). To the solution of **18** (60 mg, 0.17 mmol) in MeOH (1.5 ml) was added *p*-toluenesulfonic acid monohydrate (3 mg, 0.02 mmol), and the mixture was stirred at room temperature for 2 h. A saturated $NaHCO_3$ solution (2 ml) was added to the reaction mixture, and the whole was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 1:1) to give **19** (59 mg, 95%), mp 158-159 °C (from hexane-AcOEt). IR ($CHCl_3$) ν 3580, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (3H, t, J = 7.3 Hz), 2.93 (3H, s), 3.88 (3H, s), 3.94 (3H, s), 4.12 (2H, q, J = 7.3 Hz), 5.65 (1H, s, OH), 6.76 (1H, s), 6.92 (1H, s), 6.98-7.06 (3H, m). *Anal.* Calcd for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59. Found: C, 63.64; H, 5.88.

Ethyl 5-Hydroxy-2,3-dimethoxyxanthene-9-carboxylate (20). From 18. Compound **18** (300 mg, 0.87 mmol) was hydrogenolyzed in methanol (40 ml) over 5% Pd/C (300 mg) in a Paar apparatus at 6 kg/cm^2 of pressure for 7 days. The catalyst was filtered off, the solvent was removed by evaporation, and the residue was chromatographed on silica gel (hexane-AcOEt, 2;1) to give **20** (247 mg, 86%), mp 100.5-101 °C (from hexane-AcOEt). IR ($CHCl_3$) ν 3575, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (3H, t, J = 7.3 Hz), 3.86 (6H, s), 4.13 (2H, q, J = 7.3 Hz), 4.91 (1H, s, C_9-H), 5.81 (1H, br s, OH), 6.69 (1H, s), 6.74 (1H, s), 6.80-6.99 (3H, m). *Anal.* Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.43; H, 5.41.

From 19. In a manner similar to that described above for the reduction of **18**, compound **19** (59 mg, 0.16 mmol) was hydrogenolyzed in ethyl acetate (10 ml) over 5% Pd/C (15 mg) for 2 days. Workup gave **20** (50 mg, 94%).

Ethyl 5-Benzyloxy-2,3-dimethoxyxanthene-9-carboxylate (21). To a solution of **20** (765 mg, 2.32 mmol) in acetone (25 ml) were added successively potassium carbonate (960 mg, 6.95 mmol) and benzyl bromide (1.58 g, 9.26 mmol), and the mixture was heated under reflux for 2 h. After the solvent had been evaporated off, water (10 ml) was added to the residue, and the whole was neutralized with 10% HCl, then extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane-AcOEt, 5:1) to give **21** (897 mg, 92%), mp 102-103 °C (hexane-AcOEt). IR ($CHCl_3$) ν 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3H, t, J = 7.3 Hz), 3.86 (3H, s), 3.88 (3H, s), 4.11 (2H, q, J = 7.3 Hz), 4.92 (1H, s, C_9-H), 5.21 (2H, s), 6.73 (1H, s), 6.79 (1H, s), 6.85-6.97 (3H, m), 7.28-7.52 (5H, m). *Anal.* Calcd for $C_{25}H_{24}O_6$: C, 71.42; H, 5.75. Found: C, 71.45; H, 5.90.

5-Benzyloxy-2,3-dimethoxy-*N*-methylxanthene-9-carboxamide (22). To a solution of **21** (760 mg, 1.81 mmol) in methanol (8.5 ml) was added a 40% methylamine solution in methanol (1.5 ml), and the mixture was heated in a sealed tube at 95 °C for 5 h. The solvent and excess methylamine were evaporated off, and the residue was chromatographed on silica gel (hexane-AcOEt, 1:2) to give **22** (676 mg, 92%), mp 200-201 °C (hexane-AcOEt). IR ($CHCl_3$) ν 3450, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65, 2.66 (total 3H, both s, NMe), 3.85 (3H, s), 3.87 (3H, s), 4.82 (1H, s, C_9-H), 5.18 (2H, s), 5.40 (1H, br s, NH), 6.72 (1H, s), 6.83 (1H, s), 6.90 (1H, dd, J = 6.9, 2.6 Hz), 6.93-7.03 (2H, m), 7.30-7.51 (5H, m); ^{13}C NMR ($CDCl_3$) δ 26.7, 46.7, 56.1, 56.3, 71.2, 101.0, 109.4, 110.6, 113.4, 119.9, 121.5, 123.1, 127.4, 128.0, 128.6, 136.8, 141.3, 144.7, 145.6, 147.2, 149.6, 172.8. *Anal.* Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 71.07; H, 5.75; N, 3.46.

***N*-(5-Benzyloxy-2,3-dimethoxyxanthen-9-ylmethyl)-*N*-methyl-α-(methylthio)acetamide (24).** A 1 M solution of boran-THF complex in THF (23 ml, 23 mmol) was added to a solution of **22** (550 mg, 1.36 mmol) in THF (50 ml), and the mixture was heated under reflux for 10 days. A 20% HCl (10 ml) was added to the reaction mixture at 0 °C to destroy any excess diborane, and the solvent was removed by evaporation. A 10% NaOH solution (20 ml) was added to the aqueous phase, and the resulting alkaline mixture was extracted with diethyl ether. The organic phase was dried (K_2CO_3) and concentrated *in vacuo* to give the crude amine **23**, which was then immediately dissolved in CH_2Cl_2 (15 ml). Triethylamine (151 mg, 1.49 mmol) and (methylthio)acetyl chloride (186 mg, 1.49 mmol) were added successively to the above solution at 0 °C, and the mixture was stirred at room temperature for 9 h. Water (10 ml) was added to the reaction mixture, and the organic phase was separated. The aqueous phase was further extracted with CH_2Cl_2, and the combined organic phases were washed successively with 1 N HCl and a saturated $NaHCO_3$ solution, then dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 1:1) to give the amide **24** [632 mg, 97% (based on **22**)] as an oil. IR ($CHCl_3$) ν 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01, 2.26 (total 3H, both s, SMe), 2.51, 3.25 (total 2H, both s, SCH_2), 2.63, 3.03 (total 3H, both s, NMe), 3.39-3.50 (2H, m, NCH_2), 3.85 (3H, s), 3.88 (3H, s), 4.10, 4.35 (total 1H, both t, J = 7.3 Hz, C_9-H), 5.21, 5.22 (total 2H, both s, OCH_2), 6.52-7.0 (5H, m), 7.32-7.51 (5H, m). Exact MS *m/z*: Calcd for $C_{27}H_{29}NO_5S$: 479.1765. Found: 479.1782.

***N*-(5-Benzyloxy-2,3-dimethoxyxanthen-9-ylmethyl)-*N*-methyl-α-(methylsulfinyl)acetamide (25).** A solution of sodium metaperiodate (52 mg, 0.24 mmol) in water (5 ml) was added to a solution of **24** (406 mg, 1 mmol) in methanol (10 ml) at 0 °C, and the mixture was stirred at room temperature for 60 h. Water (20 ml) was added to the reaction mixture to dissolve the precipitated salts, and the whole was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (CH_2Cl_2-MeOH, 40:1) to give **25**, mp 72-74 °C (hexane-AcOEt). IR ($CHCl_3$) ν 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48, 2.50, 2.75 (total 3H, all s, SMe), 2.65, 2.66, 3.05, 3.06 (total 3H, all s, NMe), 2.85-3.81 (4H, m, SCH_2, NCH_2), 3.84, 3.86, 3.88, 3.90 (total 6H, all s, OMe x 2), 4.10, 4.32 (total 1H, both t, J = 7.3 Hz, C_9-H), 5.21, 5.23 (total 2H, both s, OCH_2), 6.46-7.03 (5H, m), 7.33-7.49 (5H, m). *Anal.* Calcd for $C_{27}H_{29}NO_6S \cdot 1/2H_2O$: C, 64.29; H, 5.95; N, 2.78. Found: C, 64.64; H, 6.10; N, 2.97.

7-Benzyloxy-2,3,4,12b-tetrahydro-10,11-dimethoxy-2-methyl-4-methylthio-1*H*-[1]benzopyrano-[4,3,2-ef][3]benzazepin-3-one (26). Trifluoroacetic anhydride (59 mg, 0.28 mmol) was added to a solution of **25** (720 mg, 0.14 mmol) in CH_2Cl_2 (4 ml) at 0 °C, and the mixture was stirred at room temperature for 59 h. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 2:1) to give **26** (64 mg, 95%) as a crystalline mixture of two diastereoisomers in a ratio of 8:1. ^1H NMR ($CDCl_3$) for the major isomer: δ 2.29 (3H, s, SMe), 2.98 (3H, s, NMe), 3.55-3.63 (2H, m, C_1-H), 3.89 (3H, s, OMe), 3.91 (3H, s, OMe), 4.60 (1H, s, C_4-H), 5.20 (2H, s, OCH_2), 5.55 (1H, dd, J = 8.9, 5.9 Hz, C_{12b}-H), 6.73 (1H, s, C_{10}-H or C_{11}-H), 6.75 (1H, s, C_{11}-H or C_{10}-H), 6.78 (2H, s, C_5-H, C_6-H), 7.29-7.51 (5H, m, ArH). Small peaks due to the SMe and NMe protons of the minor product appeared at δ 2.17 and 3.05, respectively. The mixture was recrystallized from hexane-AcOEt to give the major stereoisomer of **26**, mp 97-99 °C. IR (KBr) ν 1620 cm^{-1}; ^1H NMR (C_6D_6) δ 2.21 (3H, s, SMe), 2.69 (3H, s, NMe), 3.03-3.16 (2H, m, C_1-H), 3.20 (3H, s, OMe), 3.36 (3H, s, OMe), 4.83 (2H, s, OCH_2), 4.91 (1H, s, C_4-H), 5.83 (1H, dd, J = 11.6, 4.0 Hz, C_{12b}-H), 6.40 (1H, s, C_{10}-H or C_{11}-H), 6.51 (1H, d, J = 8.3 Hz, C_5-H or C_6-H), 6.59 (1H, d, J = 8.3 Hz, C_6-H or C_5-H), 6.62 (1H, s, C_{11}-H or C_{10}-H), 7.05-7.19 (3H, m, ArH), 7.38 (2H, br d, J = 6.9 Hz, ArH). *Anal.* Calcd for $C_{27}H_{27}NO_5S$: C, 67.90; H, 5.70; N, 2.93. Found: C, 67.52; H, 5.93; N, 2.74.

7-Benzyloxy-2,3,4,12b-tetrahydro-10,11-dimethoxy-2-methyl-1*H*-[1]benzopyrano[4,3,2-ef][3]benz-azepin-3-one (27). Zinc dust (40 mg, 0.61 mmol) was added to a solution of **26** (29 mg, 0.06 mmol) in acetic acid (0.5 ml), and the mixture was heated under reflux for 5 h. CH_2Cl_2 (5 ml) was added to the reaction mixture, the inorganic materials were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane-AcOEt, 2:1) to give **27** (24 mg, 92%), mp 193-195 °C (hexane-AcOEt). IR ($CHCl_3$) ν 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.91 (3H, s), 3.48 (1H, t, J = 12.5 Hz, one of C_1-H), 3.62 (1H, d, J = 15.8 Hz, one of C_4-H), 3.63 (1H, dd, J = 12.5, 4.0 Hz, one of C_1-H), 3.89 (3H, s, OMe), 3.90 (3H, s, OMe), 4.07 (1H, d, J = 15.8 Hz, one of C_4-H), 4.65 (1H, dd, J = 12.5, 4.0 Hz, C_{12b}-H), 5.20 (2H, s, OCH_2), 6.72 (1H, s), 6.77 (1H, s), 6.81 (2H, s, C_5-H, C_6-H), 7.29-7.52 (5H, m). ^1H NMR (C_6D_6) δ 2.56 (3H, s), 2.80-2.96 (2H, m, C_1-H), 3.21 (3H, s, OMe), 3.52 (3H, s, OMe), 3.72, 3.79 (1H each, AB q, J = 15.5 Hz, C_4-H), 4.02 (1H, dd, J = 9.6, 7.3 Hz, C_{12b}-H), 4.84 (2H, s, OCH_2), 6.29 (1H, s), 6.55 (1H, d, J = 8.3 Hz), 6.660 (1H, d, J = 8.3 Hz), 6.663 (1H, s), 7.02-7.18 (3H, m), 7.38 (2H, br d, J = *ca.* 7 Hz). *Anal.* Calcd for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84; N, 3.25. Found: C, 72.26; H, 6.13; N, 3.44.

7-Benzyloxy-2,3,4,12b-tetrahydro-10,11-dimethoxy-2-methyl-1*H*-[1]benzopyrano[4,3,2-ef][3]benzazepine (28). To a solution of **27** (20 mg, 0.046 mmol) in dry benzene (2 ml) was added Red-Al (70% in toluene) (0.09 ml, 0.324 mmol), and the mixture was heated under reflux for 26 h. Water (1 ml) was added to the reaction mixture, and the whole was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*, and the residue was chromatographed on silica gel (CH_2Cl_2-MeOH, 40:1) to give **28** (12 mg, 62%) as a hygroscopic solid, which was used immediately in the next step. ^{1}H NMR ($CDCl_3$) δ 2.12 (1H, t, J = 11.9 Hz, one of C_3-H), 2.42 (3H, s, NMe), 2.47 (1H, dd, J = 12.2, 9.6 Hz, one of C_1-H), 2.71 (1H, dd, J = 14.9, 5.9 Hz, one of C_4-H), 3.05-3.23 (2H, m, one of C_3-H, one of C_4-H), 3.12 (1H, d, J = 12.2 Hz, one of C_1-H), 3.869 (3H, s, OMe), 3.875 (3H, s, OMe), 4.40 (1H, d, J = 9.6 Hz, C_{12b}-H), 5.19 (2H, s, OCH_2), 6.67 (1H, s), 6.71 (1H, d, J = 8.3 Hz), 6.74 (1H, d, J = 8.3 Hz), 6.79 (1H, s), 7.28-7.52 (5H, m). ^{13}C NMR ($CDCl_3$) δ 35.3, 37.4, 47.2, 56.1, 56.4, 57.2, 68.1, 71.5, 100.5, 111.2, 112.58, 112.63, 122.1, 124.0, 127.3, 127.8, 128.5, 134.6, 137.3, 140.4, 144.5, 145.3, 145.4, 148.8.

(±)-Clavizepine (1). Raney nickel (W-7) (*ca.* 1 g) was added to a solution of **28** (48 mg, 0.116 mmol) in ethanol (3 ml), and the mixture was heated under reflux for 5 h, then cooled to room temperature. Raney nickel was removed by filtration, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel (benzene-acetone, 1:1) to give (±)-clavizepine (**1**) (35 mg, 93%), mp 218-219 °C (dec.) (MeOH). IR ($CHCl_3$) ν 3575 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.17 (1H, t, J = 11.9 Hz, one of C_3-H), 2.46 (3H, s, NMe), 2.49 (1H, dd, J = 12.2, 9.6 Hz, one of C_1-H), 2.72 (1H, dd, J = 14.9, 5.9 Hz, one of C_4-H), 3.12-3.25 (2H, m, one of C_3-H and one of C_4-H), 3.20 (1H, d, J = 12.2 Hz, one of C_1-H), 3.886 (3H, s, C_{10}-OMe), 3.891 (3H, s, C_{11}-OMe), 4.42 (1H, d, J = 9.6 Hz, C_{12b}-H), 5.34 (1H, br s, OH), 6.60 (1H, s, C_9-H), 6.73 (1H, d, J = 7.9 Hz, C_5-H), 6.78 (1H, d, J = 7.9 Hz, C_6-H), 6.89 (1H, s, C_{12}-H). ^{13}C NMR ($CDCl_3$) δ 34.75 (C_4), 36.91 (C_{12b}), 46.99 (NMe), 56.06 (OMe), 56.48 (OMe), 57.14 (C_3), 67.40 (C_1), 99.84 (C_9), 111.66 (C_{12}), 113.06 (C_6), 122.78 (C_5, C_{12a}), 123.02 (C_{12c}), 132.92 (C_{4a}), 137.64 (C_{7a}), 142.53 (C_7), 143.92 (C_{8a}), 145.69 (C_{11}), 148.93 (C_{10}). Exact MS *m/z*: Calcd for $C_{19}H_{21}NO_4$: 327.1469. Found: 327.1459.

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