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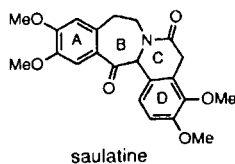
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Dedicated to the memory of Professor Roland K. Robins

A study directed toward the synthesis of saulatine (5,8,9,14a-tetrahydro-3,4,11,12-tetramethoxyisoquino[1,2-*b*]benzazepine-6,14-dione) is described. The successful synthetic route consists of three steps starting with 3,4-dimethoxyphenethylamine and 2-bromo-(3,4-dimethoxy-2-ethoxycarbonylphenyl)-acetate. It was found that the methoxy moieties present on the aromatic rings prohibit the use of the intramolecular Friedel-Crafts reaction with a Lewis acid catalyst for ring construction because of their demethylation tendency under the reaction conditions.

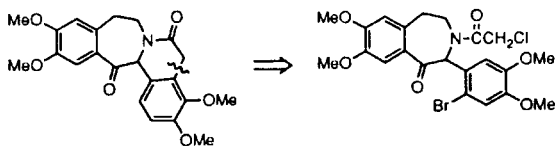
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Saulatine is an alkaloid having an unusual structural skeleton of isoquinolobenzazepine. It was first reported in 1984 by Hocquemiller *et al* as an alkaloid isolated from *Abuta bullata* [1], but Shamma and Rahimizadeh claimed that the compound may not be biogenetically formed but is an artifact generated from palmitine during the isolation process [2]. Nevertheless, the alkaloid and related compounds were of interest to us as potential pharmacological agents in view of the fact that many of tetrahydroisoquinolines and benzazepines are known to have interesting CNS activities [3-7]. This report describes the synthetic study made for the preparation of saulatine.



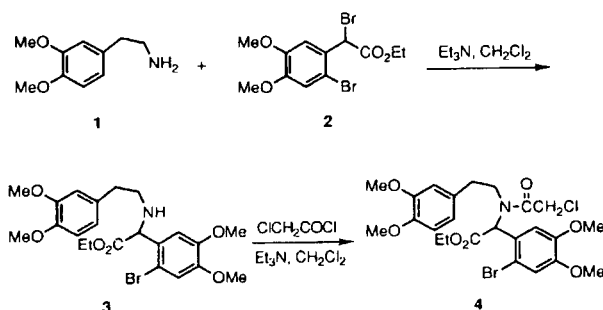
Our initial synthetic strategy consists of construction of the benzazepine portion of the alkaloid first, followed by the formation of the remaining partial structure of fused isoquinolone *via* the intramolecular Friedel-Crafts alkylation (Route 1). Accordingly, we prepared the key intermediate, **3** in this route by allowing 3,4-dimethoxyphenethylamine to react with **2**. The latter compound was, in turn,

Route 1



obtained from 3,4-dimethoxyphenylacetic acid ethyl ester (**5**) by bromination with *N*-bromosuccinimide. Thus, when **5** was treated with an equivalent molar quantity of *N*-bromosuccinimide in the presence of a catalytic

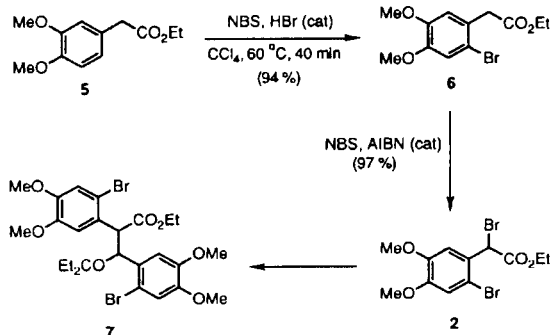
Scheme 1



amount of hydrobromic acid, a ring bromination occurred exclusively at the 2-position to give **6**, which upon treatment with *N*-bromosuccinimide under radical conditions gave **2** in an overall yield of 91%. We found that **2** undergoes a radical dimerization with a loss of bromine during storage. Thus when **2** was kept for an extended period, there was obtained a new compound tinted brown with the change in melting point from 40-41.5° to 110-111°. The dimeric structural assignment for the new compound is supported by elemental analysis and spectral data.

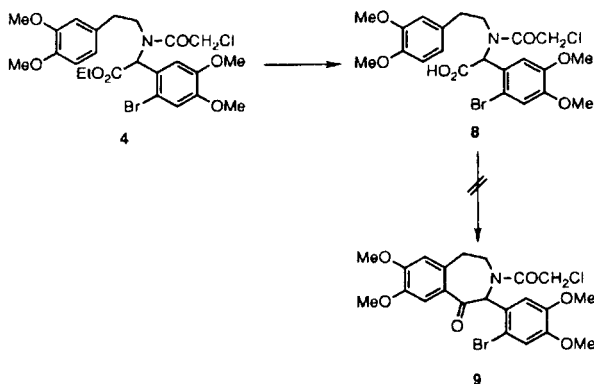
The bromine group on the ring of **2** would serve as a directing group in the intramolecular Friedel-Crafts alkylation reaction in the construction of ring C at the final stage of the synthesis. In the absence of the bromine, the ring formation reaction may also take place at the 5-position (where the bromine is positioned) as well, giving eventually a product isomeric to saulatine. Bromine was chosen on the basis of the fact that it can be removed readily after-

Scheme II



ward by the treatment with a tin hydride reagent. Treatment of **3** with chloroacetyl chloride gave **4**, which upon alkaline hydrolysis yielded the corresponding acid, **8**. Numerous attempts at the formation of the azepine ring to give **9** via the intramolecular acylation reaction of **8** under the Friedel-Crafts conditions, however, met with failure.

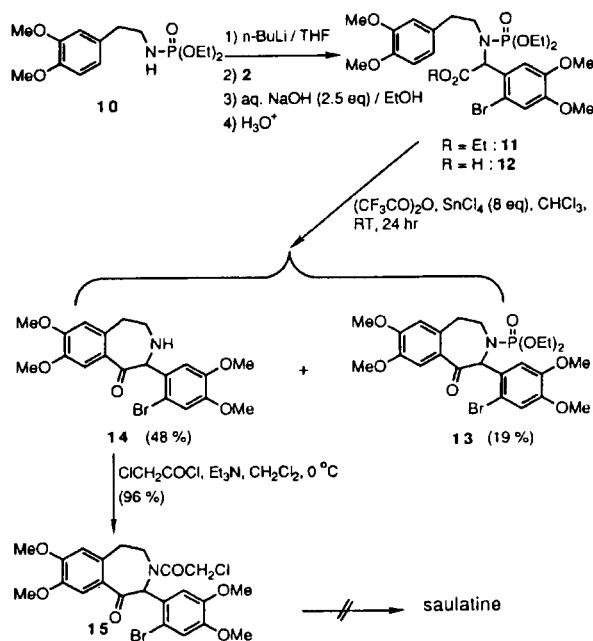
Scheme III



Zhao *et al* prepared a series of tetrahydro-3-benzazepin-1-ones from *N*-homopiperonylglycine derivatives [8,9]. They demonstrated that dialkyl phosphite is an effective *N*-protecting group for the benzazepine synthesis. The protecting group survives the harsh conditions of the Friedel-Crafts reaction, but on the other hand may be removed easily by treating with tetrahydrofuran solution saturated with hydrogen chloride gas at room temperature. The original synthetic scheme was, correspondingly, modified to make use of the literature method of Zhao *et al* [8,9] in the construction of the benzazepine ring (Scheme IV).

Treatment of **10** with an equivalent amount of *n*-butyllithium in tetrahydrofuran and the subsequent addition of **2** afforded **11** in a 81% yield, which was then hydrolyzed to give the corresponding acid, **12**. When **12** was subjected to the Friedel-Crafts alkylation reaction in trifluoroacetic anhydride using a large excess of stannic chloride

Scheme IV



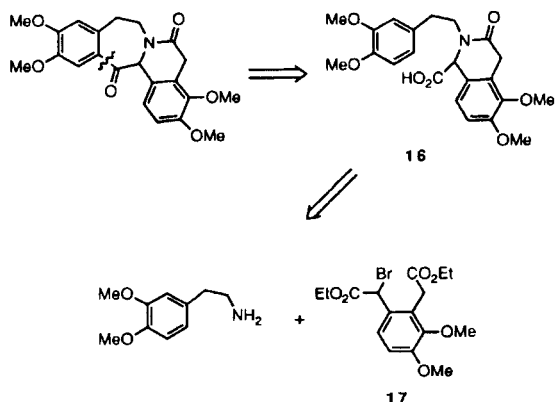
(8 equivalents), the dephosphorylated **14** was obtained as well as the expected **13** in a 48% and 19% yield, respectively, after chromatographic purification using a silica gel column. The isolation of **14** was a pleasant surprise for us because it was not only unexpected, but also attempted deprotection of the phosphoryl group following the literature method met with failure. The formation of ring C would complete the synthesis. To this end, **14** was treated with chloroacetyl chloride to give **15**, and the latter was subjected to the intramolecular Friedel-Crafts alkylation reaction. However, the reaction failed under a variety of conditions, giving only a complex mixture of products. The failure of the ring formation reaction may be attributable to the reduced reactivity caused by the bromine of the aromatic ring towards the Friedel-Crafts reaction. Consequently, demethylation may occur instead under the Friedel-Crafts conditions.

At this stage we came to realize that the construction of the tetrahydroisoquinolone ring of saulatine by the intramolecular Friedel-Crafts alkylation may not be readily attainable and we should seek an alternative approach for the ring construction. Consequently, a new strategy was formulated, which consisted of building the ring by an approach other than the Friedel-Crafts method first, then ring B under mild Friedel-Crafts conditions using polyphosphoric acid.

The successful synthetic route to saulatine, thus, encompasses the use of **16** as a key intermediate, which might be prepared by allowing 3,4-dimethoxyphenethylamine to react with **17** (Route II).

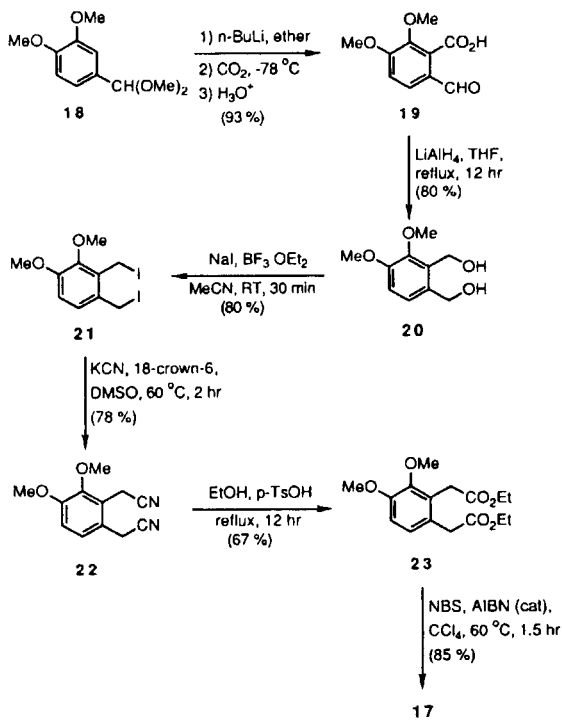
The synthesis of **17** is outlined in scheme V. 5,6-

Route II



Dimethoxyphthalaldehyde (**19**) [10,11] was prepared from the dimethyl acetal of 3,4-dimethoxybenzaldehyde (**18**) by following the method described by Napolitano *et al* [11]. Reduction of **19** with lithium aluminium hydride gave **20**, the hydroxyl groups of which were then converted to ethoxycarbonyls to yield **23** by a sequence of reactions as shown in Scheme V. The conversion of the hydroxyl groups in **20** to the corresponding iodides was effected by the procedure reported by Vanker and Rao [12]. Bromination on **23** under radical conditions using *N*-bromosuccinimide took place regioselectively at the less hindered benzylic carbon to give the desired com-

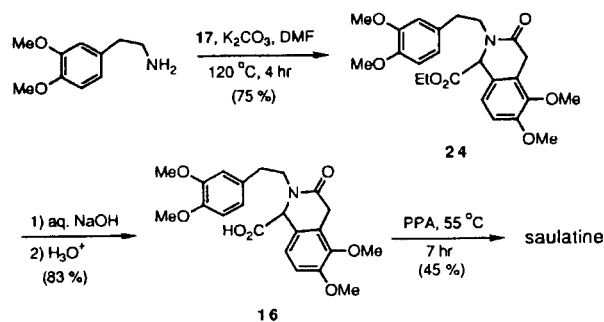
Scheme V



pound **17** in an 85% yield.

Treatment of **17** thus obtained with 3,4-dimethoxyphenethylamine for 4 hours at 120° in dimethylformamide in the presence of potassium carbonate afforded

Scheme VI



24, which was converted by alkaline hydrolysis of the ester moiety to give **16**, the key intermediate. The last step of the synthesis which involves the azepine ring formation was achieved by heating **16** with a large amount of polyphosphoric acid at 55° for 7 hours, thus obtaining finally saultatine in a 45% yield (Scheme VI). Attempted ring formation under a variety of other conditions using a Lewis acid catalyst such as stannic chloride gave invariably a complex mixture of products, from which no desired product could be isolated. The spectral data as well as physical properties of the product thus synthesized are in complete agreement with those reported for saultatine by Hocquemiller *et al* [1].

In conclusion, we have synthesized saultatine in three steps starting with 3,4-dimethoxyphenethylamine and ethyl 2-bromo-(3,4-dimethoxy-2-ethoxycarbonylphenyl)acetate after making several unsuccessful attempts. The intramolecular Friedel-Crafts conditions using a Lewis acid as the catalyst were found to be not usable for the construction of ring C as well as ring B of saultatine because of the undesirable demethylation of the methoxy groups present on the ring under these reaction conditions [13]. It appears that the facile oxidation of the hydroxyl groups follows under the conditions once the demethylation takes place [7], leading to the generation of a complex mixture of products.

EXPERIMENTAL

Melting points were taken in capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. The nmr spectra were determined on Bruker FT-NMR (300 MHz) in deuteriochloroform and are expressed as a downfield shift from internal tetramethylsilane. Infrared absorption spectra were obtained in a potassium bromide pellet unless otherwise indicated using a Perkin-Elmer Model 843 FT-IR. Mass spectra were recorded on a Kratos MS 25 spectrometer. Elemental analyses were performed by the Korea Basic Science Center.

Ethyl (2-Bromo-4,5-dimethoxyphenyl)acetate (6).

To the solution obtained by dissolving 17.24 g (77 mmoles) of ethyl (3,4-dimethoxyphenyl)acetate in carbon tetrachloride (100 ml) were added 13.66 g (77 mmoles) of *N*-bromosuccinimide and several drops of hydrobromic acid, and the resulting mixture was heated at 40° for 50 minutes. The reaction mixture was chilled; succinimide that formed was removed by filtration, and the combined filtrate and washings were evaporated under reduced pressure. The solid residue thus obtained was recrystallized from ethanol to give 21.84 g (94%) of the product, mp 64-65°; ¹H nmr: δ 1.27 (t, 3H), 3.71 (s, 2H), 3.86 (s, 6H), 4.18 (q, 2H), 6.80 (s, 1H), 7.03 ppm (s, 1H); ir: ν 1729 cm⁻¹ (C=O).

Anal. Calcd. for C₁₂H₁₅BrO₄: C, 47.54; H, 4.99. Found: C, 47.24; H, 5.03.

Ethyl 2-Bromo-2-(2-bromo-4,5-dimethoxyphenyl)acetate (2).

A mixture of 6 (19.90 g, 65.8 mmoles), *N*-bromosuccinimide (11.72 g, 65.8 mmoles), carbon tetrachloride (100 ml), and azobisisobutyronitrile (0.1 g) was refluxed for 1 hour, and cooled to room temperature. Succinimide that was formed was removed by filtration, and the filtrate was evaporated under reduced pressure to dryness. The evaporation residue was purified by column chromatography (silica gel), then recrystallized from petroleum ether to give 24.4 g (97%) of the product, mp 40-41.5°; ¹H nmr: δ 1.32 (t, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.26 (t, 2H), 5.84 (s, 1H), 6.99 (s, 1H), 7.34 ppm (s, 1H); ir (neat): ν 1740 cm⁻¹ (C=O).

Anal. Calcd. for C₁₂H₁₄O₄Br₂: C, 37.72; H, 3.69. Found: C, 37.86; H, 3.61.

Diethyl 2,3-Bis(2-Bromo-4,5-dimethoxyphenyl)succinate (7)

Compound 6 changed color during storage from white to light brown. The new compound tinted brown was recrystallized from ether, mp 110-111°; ¹H nmr: δ 1.19 (t, 6H), 3.74 (s, 6H), 3.85 (s, 6H), 4.12 (m, 4H), 4.98 (s, 2H), 6.80 (s, 2H), 6.88 ppm (s, 1H); ¹³C nmr: δ 14.0, 51.3, 55.9, 56.0, 61.3, 111.1, 115.2, 115.5, 126.9, 148.3, 148.6, 172.5 ppm; ms: m/z 606, 604, 602; ir: ν 1725 cm⁻¹ (C=O).

Anal. Calcd. for C₂₄H₂₈O₈Br₂: C, 47.70; H, 4.67. Found: C, 47.44; H, 4.71.

Ethyl 2-[2-(3,4-Dimethoxyphenyl)ethylamino]-2-(2-bromo-4,5-dimethoxyphenyl)acetate (3).

Ethyl-2-bromo-2-(2-bromo-4,5-dimethoxyphenyl)acetate (2, 6.70 g, 17.62 mmoles) was added to a mixture of 3,4-dimethoxyphenethylamine (1, 9.68 g, 24.43 mmoles) and triethylamine (6.26 ml) in methylene chloride (100 ml) under nitrogen atmosphere, and the resulting mixture was stirred at room temperature for 1 hour, then the solvent was removed under reduced pressure after washing with water. The crude product was then purified by column chromatography (silica gel) to give 11.78 g (95%) of 3 as an oil; ¹H nmr: δ 1.19 (t, 3H), 2.27-2.89 (m, 4H), 3.78 (s, 3H), 3.84-3.86 (d, 9H), 4.12-4.22 (m, 2H), 4.85 (s, 1H), 6.72 (dd, 2H), 6.79 (d, 1H), 6.82 (s, 1H), 7.01 ppm (s, 1H); ir (neat): ν 3340 (N-H), 1743 cm⁻¹ (C=O). The compound was used for the reaction with chloroacetyl chloride without further purification.

2-[*N*-Chloromethylcarbonyl-*N*-2-(3,4-dimethoxyphenyl)ethylamino]-2-(2-bromo-4,5-dimethoxyphenyl)acetic Acid (8).

To the ice chilled mixture of 3 (11.47 g, 23.83 mmoles) and triethylamine (6 ml) in methylene chloride (100 ml) was added dropwise with stirring chloroacetyl chloride (3.80 ml, 47.66

mmoles) dissolved in a small amount of methylene chloride. The stirring was continued for 3 hours. After washing the reaction mixture with water several times, it was dried (magnesium sulfate), and evaporated under reduced pressure to dryness. The residue was recrystallized from ethanol to give 12.83 g (93%) of ethyl 2-[*N*-chloromethylcarbonyl-*N*-2-(3,4-dimethoxyphenyl)ethylamino]-2-(2-bromo-4,5-dimethoxyphenyl)acetate (4), mp 112-113°; ¹H nmr: δ 1.28 (t, 3H), 2.52-2.79 (m, 2H), 3.46 (t, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 3.86 (s, 2H), 3.90 (s, 3H), 4.27 (q, 2H), 5.94 (s, 1H), 6.53 (s, 1H), 6.60 (d, 1H), 6.67 (d, 1H), 6.95 (s, 1H), 7.10 ppm (s, 1H); ir: ν 1731 (C=O), 1654 cm⁻¹ (amide C=O).

Anal. Calcd. for C₂₄H₂₉O₇NCIBr: C, 51.58; H, 5.23; N, 2.51. Found: C, 51.71; H, 5.09; N, 2.28.

A mixture of 4 (2.20 g, 4.04 mmoles), pyridine (4 ml), and 0.5 *N* aqueous sodium hydroxide solution (8.50 ml) was stirred for 5 hours, then acidified with dilute hydrochloric acid to pH 4.5. Product was extracted with ether several times. The combined extracts were dried and evaporated to dryness, and the residue was recrystallized from ethanol to give 8 (1.40 g, 65%), mp 79-81°; ¹H nmr: δ 2.33 (m, 1H), 2.60 (m, 1H), 3.40 (t, 2H), 3.73 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 3.96 (s, 2H), 5.63 (s, 1H), 6.35 (s, 1H), 6.47 (d, 1H), 6.69 (d, 1H), 6.81 (d, 1H), 6.94 (s, 1H); ir: ν 3600-2500 (O-H, bs), 1735 (C=O), 1640 cm⁻¹ (amide C=O).

Anal. Calcd. for C₂₂H₂₅O₇NCIBr: C, 49.78; H, 4.75; N, 2.64. Found: C, 50.12; H, 5.06; N, 2.90.

Ethyl [*N*-Diethylphosphoryl-*N*-2-(3,4-dimethoxyphenyl)ethylamino]-2-(2-bromo-4,5-dimethoxyphenyl)acetate (11).

To the ice chilled solution of *N*-2-(3,4-dimethoxyphenyl)ethyl-*N*-diethylphosphoramidate [8] (10, 23.77 g, 74.9 mmoles) in dried tetrahydrofuran (100 ml) was added under an argon atmosphere *n*-butyllithium (2.5 *M* solution in hexane, 39 ml, 97.4 mmoles), and the resulting mixture was stirred at 0° for 1 hour, then the chilling source was removed. Ethyl 2-bromo-2-(2-bromo-4,5-dimethoxyphenyl)acetate (2, 28.62 g, 74.9 mmoles) dissolved in dried tetrahydrofuran (30 ml) was added under stirring to the mixture over a period of 30 minutes at room temperature, and the stirring was continued for 2 hours. The reaction mixture was treated with a large amount of water, and the product was extracted with ether several times. The combined ether extracts were dried and evaporated under reduced pressure to give an oily residue which was purified chromatographically using a silica gel column and the ethyl acetate(1)/*n*-hexane(1) eluent to give 37.66 g (81%) of the product; ¹H nmr: δ 1.28 (t, 3H), 1.35 (t, 6H), 2.03 (m, 1H), 2.68 (m, 1H), 3.22 (m, 2H), 3.80 (s, 12H), 3.89 (s, 3H), 4.18 (q, 6H), 5.65 (d, 1H), 6.38 (d, 1H), 6.42 (dd, 1H), 6.72 (d, 1H), 6.95 (s, 1H), 7.08 ppm (s, 1H); ir: ν 1732 (C=O), 1255 cm⁻¹ (P=O); ms: m/z 620 (M⁺), 538, 466, 382, 301, 256, 164, 97.

Anal. Calcd. for C₂₆H₃₇NO₉PBr: C, 50.49; H, 6.03; N, 2.26. Found: C, 50.42; H, 5.68; N, 2.09.

[*N*-Diethylphosphoryl-*N*-2-(3,4-dimethoxyphenyl)ethylamino]-2-(2-bromo-4,5-dimethoxyphenyl)acetic Acid (12).

A mixture of 11 (14.91 g, 24.11 mmoles), 0.5 *N* aqueous sodium hydroxide solution (120 ml, 60.3 mmoles), and a small amount of ethanol was heated under reflux for 2 hours. After cooling to room temperature, the reaction mixture was acidified with 2.5 *N* hydrochloric acid to pH 3. The product was extracted with ethyl acetate. The combined extracts were evaporated under reduced pressure to give a solid residue which was recrystallized from ethyl acetate, affording 12 (11.81 g, 83%), mp 137-

139°; ^1H nmr: δ 1.23-1.36 (tt, 6H), 2.09 (m, 1H), 2.65 (m, 1H), 3.25 (m, 2H), 3.76 (s, 1H), 3.81 (s, 1H), 3.83 (s, 1H), 3.88 (s, 1H), 4.13-4.22 (m, 4H), 5.70 (d, 1H), 6.32 (d, 1H), 6.40 (dd, 1H), 6.68 (d, 1H), 7.07 ppm (s, 1H); ir: ν 3600-2400 (O-H, bs), 1747 cm^{-1} (C=O).

Anal. Calcd. for $\text{C}_{24}\text{H}_{33}\text{NO}_9\text{PBr}$: C, 48.82; H, 5.63; N, 2.37. Found: C, 48.55; H, 5.63; N, 2.36.

2-(3,4-Dimethoxyphenyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-*N*-(diethoxyphosphinyl)-3-benzazepin-1-one (**13**) and 2-(3,4-Dimethoxyphenyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-3-benzazepin-1-one (**14**).

Trifluoroacetic anhydride (0.48 ml, 3.38 mmoles) was added to a mixture of **12** (1.0 g, 1.69 mmoles) and dried chloroform (30 ml) under a nitrogen atmosphere, and the resulting mixture was stirred at room temperature for 0.5 hour. Stannic chloride (1.39 ml, 11.83 mmoles) was added. The reaction mixture was stirred at room temperature for 24 hours. Tin-complex was decomposed by the addition of ammonium hydroxide (100 ml), and the product was extracted with chloroform. The combined chloroform extracts were dried and evaporated to dryness under reduced pressure. The residue was purified using a silica gel column eluting with methylene chloride(30)/methanol(1) to give **13** (0.18 g, 19%) and **14** (0.35 g, 48%).

Compound **13** was recrystallized from *n*-hexane, mp 143-145°; ^1H nmr: δ 1.00 (t, 3H), 1.15 (t, 3H), 2.97 (m, 1H), 3.11-3.35 (m, 3H), 3.61-3.77 (m, 4H), 3.82 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 5.68 (d, 1H), 6.68 (s, 1H), 6.87 (s, 1H), 7.09 (s, 1H), 7.41 ppm (s, 1H); ^{13}C nmr: δ 15.9, 16.0, 34.4, 43.1, 56.0, 56.1, 61.9, 62.0, 62.3, 62.4, 68.4, 112.4, 113.9, 114.0, 116.0, 116.1, 126.5, 131.0, 132.0, 147.7, 147.9, 149.3, 152.5, 203.2 ppm; ir: ν 1682 (C=O), 1280 (P=O), 1180, 1150 cm^{-1} (P-OEt); ms: m/z 573 (M^+), 533, 487, 464, 436, 408, 343, 259, 244, 223, 211, 149, 119, 97.

Compound **14** was recrystallized from ether, mp 138-139°; ^1H nmr: δ 1.94 (bs, 1H), 2.76 (tt, 1H), 2.93 (m, 1H), 3.07 (m, 1H), 3.19 (m, 1H), 3.67 (s, 6H), 3.88 (s, 6H), 5.43 (s, 1H), 6.26 (s, 1H), 6.57 (s, 1H), 6.64 (s, 1H), 7.05 ppm (s, 1H); ^{13}C nmr: δ 29.3, 42.0, 55.8, 55.9, 56.0, 56.1, 59.8, 110.8, 111.5, 113.4, 114.5, 115.2, 127.9, 129.0, 135.8, 147.1, 147.7, 148.3 148.8 ppm; ir: ν 3360 (N-H), 1600 cm^{-1} (C=O); ms: m/z 438 (M^+), 422, 407, 392, 378, 349, 328, 299, 239, 192, 164, 149, 113, 95.

Anal. Calcd. for $\text{C}_{20}\text{H}_{22}\text{NO}_5\text{Br}$: C, 55.07; H, 5.08; N, 3.21. Found: C, 55.36; H, 5.29; N, 3.43.

2-(3,4-Dimethoxyphenyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-*N*-(chloroacetyl)-3-benzazepin-1-one (**15**).

To an ice chilled stirring mixture of **14** (1.1 g, 2.52 mmoles) and triethylamine (0.26 mg, 2.52 mmoles) in methylene chloride (10 ml) was added under a nitrogen atmosphere chloroacetyl chloride (0.34 g, 2.77 mmoles) dissolved in a small amount of methylene chloride, and the resulting reaction mixture was stirred at 0° for 20 minutes, then at room temperature for 10 minutes. It was washed with water several times, dried and evaporated on a rotary evaporator to dryness. The residue was recrystallized from ethyl acetate to give **15** (1.24 g, 96%), mp 169-171°; ^1H nmr: δ 2.85 (m, 2H), 3.01 (m, 2H), 3.63 (s, 3H), 3.72 (s, 3H), 3.84 (s, 6H), 4.06-4.10 (d, 2H), 6.44 (s, 1H), 6.54 (s, 1H), 6.63 (s, 1H), 7.05 ppm (s, 1H); ir: ν 1700 (C=O), 1660 cm^{-1} (amide C=O); ms: m/z 485 (M^+ -31), 450, 404, 368, 326, 284, 192, 177, 105, 85.

Anal. Calcd. for $\text{C}_{27}\text{H}_{23}\text{NO}_6\text{ClBr}$: C, 51.53; H, 4.52; N, 2.73. Found: C, 51.93; H, 4.88; N, 2.88.

(2-Hydroxymethyl-3,4-dimethoxyphenyl)ethanol (**20**).

To an ice chilled and stirring mixture of lithium aluminium hydride (2.71 g, 71.4 mmoles) and dried tetrahydrofuran (100 ml) was added dropwise 5,6-dimethoxyphthalaldehydic acid [**11**] (19, 10 g, 47.6 mmoles) dissolved in tetrahydrofuran (100 ml). After completion of the addition, the reaction mixture was heated under reflux for 12 hours. After cooling the reaction mixture to room temperature, it was treated with water (2.7 ml), with 15% aqueous sodium hydroxide solution (2.7 ml), then again with water (8.1 ml). Aluminium hydroxide thus formed was removed by filtration, and the combined filtrate and washings were evaporated on a rotary evaporator to dryness. The residue was recrystallized from ether to give **18** (7.54 g, 80%), mp 67-68°; ^1H nmr: δ 3.82 (s, 3H), 3.83 (s, 3H), 4.61 (s, 2H), 4.76 (s, 2H), 6.79 (d, 1H), 7.00 ppm (d, 1H); ir: ν 3362 (O-H), 3310 cm^{-1} (O-H); ms: m/z 198 (M^+), 180, 165, 149, 137, 122, 109, 94.

Anal. Calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_4$: C, 60.59; H, 7.12. Found: C, 60.68; H, 6.88.

(2-Iodomethyl-3,4-dimethoxy)benzyl Iodide (**21**).

Compound **20** (10.0 g, 50.4 mmoles) and sodium iodide (30.2 g, 202 mmoles) was dissolved in dry acetonitrile (200 ml) under a nitrogen atmosphere. The acetonitrile solution of borontrifluoride etherate obtained by dissolving 14.2 g (0.1 mole) of borontrifluoride etherate in 40 ml of dried acetonitrile was added dropwise over a period of 30 minutes. The resulting mixture was stirred at room temperature for 20 minutes, then poured into cold water (400 ml), whereby a precipitate was separated. The pale yellow precipitate was collected on a filter, and recrystallized from *n*-hexane to give the product (19.3 g, 80%), mp 69-71°; ^1H nmr: δ 3.85 (s, 3H), 3.98 (s, 3H), 4.55 (s, 2H), 4.67 (s, 2H), 6.77 (d, 1H), 7.03 ppm (d, 1H); ir: ν 1592, 1491, 1270, 1152 cm^{-1} ; ms: m/z 418 (M^+), 291, 245, 199, 164, 149, 121, 104. The compound is unstable and decomposes on standing in air.

1,2-Dicyanomethyl-3,4-dimethoxybenzene (**22**).

A mixture of powdered potassium cyanide (192 mg, 2.20 mmoles), 18-crown-6 (34.5 mg) and dimethyl sulfoxide (10 ml) was stirred at 60° under a nitrogen atmosphere for 20 minutes. To this reaction mixture was added compound **21** (548 mg, 1.31 mmoles), and the stirring was continued for 12 hours. After the reaction mixture was allowed to cool to room temperature, it was diluted with water by addition of 20 ml of water, and the product was extracted with ether. The combined ether extracts were dried and evaporated under reduced pressure to dryness. The residue was recrystallized from ethyl acetate to give 221 mg (78%) of the product, mp 85-87°; ^1H nmr: δ 3.75 (s, 2H), 3.79 (s, 2H), 3.88 (s, 3H), 3.92 (s, 3H), 6.91 (d, 1H), 7.13 ppm (d, 1H); ir: ν 2247 (C \equiv N), 1630, 1499, 1298 cm^{-1} ; ms: m/z 216 (M^+), 201, 190, 174, 146, 120.

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$: C, 66.65; H, 5.60; N, 12.96. Found: C, 66.87; H, 5.78; N, 12.26.

1,2-Diethoxycarbonylmethyl-3,4-dimethoxybenzene (**23**).

Compound **22** (1.1 g, 5.09 mmoles) was dissolved in anhydrous ethanol (10 ml). To the resulting solution was added *p*-toluenesulfonic acid (2.15 g, 2.2 mmoles). The reaction mixture was heated under reflux for 12 hours, then the excess ethanol was removed by evaporation under reduced pressure. The residue was dissolved in chloroform, and the chloroform solution was washed with water then with aqueous sodium bicarbonate solution. Evaporation of the chloroform under reduced

pressure gave an oily residue which was purified by column chromatography (silica gel-ethyl acetate(1)/methylene chloride(1)/*n*-hexane(3)) to give **23** as an oil (1.06 g, 67%); ¹H nmr: δ 1.25 (tt, 6H), 3.58 (s, 2H), 3.77 (s, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 4.13 (m, 4H), 6.81 (d, 1H), 6.96 ppm (d, 1H); ir (chloroform): ν 1727 cm⁻¹ (C=O); ms: m/z 310 (M⁺), 264, 237, 217, 207, 190, 175, 165, 155, 149, 130, 103; hrms: m/z 310.1419 (mass calcd. for C₁₆H₂₂O₆: 310.1416).

Ethyl 2-Bromo-(3,4-dimethoxy-2-ethoxymethylphenyl)acetate (**17**).

To the hot mixture of **23** (656 mg, 1.57 mmole) and *N*-bromosuccinimide (279 mg, 1.57 mmole) in carbon tetrachloride was added a catalytic amount of azobisisobutyronitrile. The reaction mixture was heated at 60° for 1.5 hours, then allowed to cool to room temperature. Succinimide that formed was removed by filtration, and the filtrate was evaporated under reduced pressure. The oily residue thus obtained was purified by column chromatography (silica gel-ethyl acetate(1)/methylene chloride(1)/*n*-hexane(3)) to give the product (519 mg, 85%) as a colorless oil; ¹H nmr: δ 1.27 (tt, 6H), 3.78 (d, 1H), 3.83 (s, 3H), 3.87 (s, 3H), 3.93 (d, 1H), 4.13-4.26 (m, 4H), 5.61 (s, 1H), 6.88 (d, 1H), 7.45 ppm (d, 1H); ir (chloroform): ν 1739 cm⁻¹ (C=O); ms: 387 (M⁺), 343, 308, 263, 234, 217, 206, 191, 179; hrms: m/z 388.0541 (mass calcd. for C₁₆H₂₁O₆Br: 388.0521).

1-Ethoxycarbonyl-5,6-dimethoxy-2-(3,4-dimethoxyphenyl)-3-oxo-1,2,3,4-tetrahydroisoquinoline (**24**), and 5,6-Dimethoxy-2-(3,4-dimethoxyphenyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-carboxylic Acid (**16**).

A mixture of 3,4-dimethoxyphenethylamine (113 mg, 0.623 mmole), **17** (237 mg, 0.623 mmole), and anhydrous potassium carbonate (94 mg) in dimethylformamide (6 ml) was stirred at 120° for 4 hours. After being cooled to room temperature, the reaction mixture was partitioned in chloroform and water. The organic layer was separated, washed with water, then with aqueous sodium bicarbonate solution, and dried. Evaporation of chloroform under reduced pressure gave an oily residue, from which the product was separated by flash column chromatography (silica gel-ethyl acetate(2)/*n*-hexane(1)) as an oil (207 mg, 75%); ¹H nmr: δ 1.18 (t, 3H), 2.83 (m, 2H), 3.12 (m, 1H), 3.55 (d, 1H), 3.64 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.91 (d, 1H), 4.10 (m, 2H), 4.15 (m, 1H), 4.61 (s, 1H), 6.60 (d, 1H), 6.61-6.88 ppm (m, 4H); ¹³C nmr: δ 14.0, 31.6, 33.7, 49.3, 55.5, 55.7, 55.8, 60.5, 61.9, 65.1, 110.8, 111.3, 111.9, 120.4, 121.9, 122.6, 126.7, 131.4, 145.3, 147.4, 148.7, 152.5, 169.3, 170.1 ppm; ir (chloroform): ν 1721 (C=O), 1654 (amide C=O) cm⁻¹; ms: m/z 447 (M⁺), 370, 264, 206, 190, 176, 164, 151, 135, 121, 105, 91, 77.

The oily compound **24** (133 mg, 0.3 mmole) thus obtained was saponified with 0.1 *N* aqueous sodium hydroxide solution (7 ml) and a small amount (2 ml) of ethanol under reflux for 2.5 hours. The reaction mixture was then chilled, and acidified with dilute hydrochloric acid to pH 3, whereby a precipitate was separated to give **16** (100 mg, 83%), mp 212-214°; ¹H nmr (deuteriochloroform+dimethyl sulfoxide-d₆): δ 2.80 (m, 2H), 3.10 (m, 1H), 3.46 (d, 1H), 3.61 (s, 3H), 3.76 (d, 1H), 3.79 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.16 (m, 1H), 4.66 (s, 1H), 6.60 (d, 1H), 6.71 (d, 1H), 6.77 (d, 1H), 6.82 (d, 1H), 6.92 ppm (d, 1H); ¹³C nmr: δ 30.4, 32.3, 54.2, 54.6, 59.1, 63.4, 109.8, 110.3, 110.9, 119.4, 121.0, 122.3, 125.2, 130.3, 145.3, 147.4, 148.7, 152.5, 167.8, 170.4 ppm; ir: ν 3600-2800 (O-H, bs), 1770 (C=O), 1687 cm⁻¹ (amide C=O).

Anal. Calcd. for C₂₂H₂₅NO₇: C, 63.50; H, 6.07; N, 3.37. Found: C, 63.89; H, 6.20; N, 3.42.

Saulatine.

A mixture of **16** (100 mg, 0.25 mmole) and an excess amount of polyphosphoric acid (about 15 ml) was stirred under a nitrogen atmosphere using a mechanical stirrer while increasing the temperature of the oil bath slowly to 55°. The stirring was continued for 7 hours at the temperature. After cooling the reaction mixture to room temperature, ice-water was added, and product was extracted with chloroform. The combined extracts were dried and evaporated on a rotary evaporator, and the crude product thus obtained was purified by the chromatographic method using a silica gel column and a mixture of *n*-hexane(1)/methylene chloride(1)/ethyl acetate(2) as eluent, giving saulatine (43 mg, 45%). The analytical sample that was recrystallized from methanol melted at 227-228°, lit mp: 226-228° [1]; ¹H nmr: δ 3.03 (m, 1H), 3.06 (m, 1H), 3.30-3.39 (m, 2H), 3.84 (s, 1H), 3.82 (s, 3H), 3.85 (s, 3H), 3.89 (s, 1H), 3.95 (s, 3H), 4.62 (m, 1H), 5.20 (s, 1H), 6.74 (s, 1H), 6.69 (d, 1H), 7.04 (d, 1H), 7.73 ppm (s, 1H); ir: ν 1669 (C=O), 1625 cm⁻¹ (amide C=O); ms: m/z 397 (M⁺), 368, 354, 338, 310, 205, 191.

Anal. Calcd. for C₂₂H₂₃NO₆: C, 66.49; H, 5.83; N, 3.50. Found: C, 66.22; H, 6.07; N, 3.10.

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REFERENCES AND NOTES

- [1] R. Hocquemiller, A. Cave, and A. Fournet, *J. Nat. Prod.*, **47**, 539 (1984).
- [2] M. Shamma, and M. Rahimizadeh, *J. Nat. Prod.*, **49**, 398 (1986).
- [3] P. S. Charifson, *Drugs Future*, **14**, 1179 (1989).
- [4] F. R. Pfeiffer, J. W. Wilson, J. Weinstock, G. Y. Kuo, P. A. Chambers, K. G. Holden, R. A. Hahn, J. R. Wardell, A. J. Tobia, P. E. Setler, and H. M. Sarace, *J. Med. Chem.*, **25**, 352 (1982).
- [5] R. M. Riggs, D. E. Nichols, M. M. Foreman, and L. L. Truex, *J. Med. Chem.*, **30**, 1988 (1987).
- [6] G. L. Grunewald, V. M. Paradkar, D. M. Stillions, and F. Ching, *J. Heterocyclic Chem.*, **28**, 1587 (1991).
- [7] D. H. Kim, *J. Heterocyclic Chem.*, **29**, 11 (1992).
- [8] Y.-F. Zhao, S.-K. Xi, Y.-F. Tian, and A.-T. Song, *Tetrahedron Letters*, **24**, 1617 (1983).
- [9] Y.-F. Zhao, S.-K. Xi, A.-T. Song, and G.-J. Ji, *J. Org. Chem.*, **49**, 4549 (1984).
- [10] H. P. Paulmann, B. A. Keay, and R. Rodrigo, *Tetrahedron Letters*, **20**, 4921 (1979).
- [11] E. Napolitano, E. Giannone, R. Fiaschi, and A. Marsili, *J. Org. Chem.*, **48**, 3653 (1983).
- [12] Y. D. Vanker and C. T. Rao, *Tetrahedron Letters*, **26**, 2717 (1985).
- [13] There are numerous literature precedents of the demethylation of methoxy groups under Friedel-Crafts conditions: For example [a] F. Uhlig, *Angew. Chem.*, **66**, 435 (1954); [b] F.-H. Marquardt, *Helv. Chem. Acta*, **48**, 1476 (1965); [c] F.-H. Marquardt, *Helv. Chem. Acta*, **48**, 1486 (1965); [d] S. Dev, *J. Indian Chem. Soc.*, **33**, 703 (1965); [e] G. P. Schiemenz and U. Schmidt, *Liebigs Ann. Chem.*, 1509 (1982); [f] M. B. Floyd and G. R. Allen, Jr., *J. Org. Chem.*, **55**, 2647 (1970).