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PRACTICAL SYNTHESIS OF TRICYCLIC LACTAM MODEL OF ANTITUMOR RENIERAMYCIN-SAFRAMYCIN NATURAL PRODUCTS

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This paper is dedicated to Professor Dr. Lutz F. Tietze on the occasion of his 75th birthday.

Abstract – A practical synthesis of the tricyclic lactam model compound of antitumor renieramycin-saframycin natural product starting from 2-hydroxy-4,5-dimethoxy-3-methylbenzaldehyde in eleven steps was described. A tosyl group was used for protection of a phenol during this transformation. The overall yield of the target compound was 23%.

Natural products belonging to the bis-1,2,3,4-tetrahydroisoquinoline family and their reduced forms, including such marine natural products as renieramycins, cribrostatin 4 (renieramycin H), ecteinascidins, and saframycins, have received considerable attention for their potent biological activities and structural diversity, as well as their meager availability in nature (Figure 1).¹

In the course of our research on new metabolites, which involves the isolation and characterization of biologically active compounds and the synthesis of their respective analogues, we have examined partial structures that may mimic the biological action of natural products. Among a handful of studies of right-half model compounds containing a lactam ring, we have reported the formation of right-half model derivative (**1**) from phenol (**2**)^{2,3} via a three-step transformation (Scheme 1).⁴ The introduction of a cyano group improved cytotoxicity to human cancer cell lines in a series of right-half model compounds. This finding has stirred much excitement and inspired the search for simplified model compounds possessing

antitumor activities similar to or more potent than those displayed by parent natural products. We are very interested in the preparation of right-half model derivatives. We have reported the preparation of right-half model compound (**2**),² the structure of which was confirmed by X-ray crystallographic analysis.³ However, a more efficient synthetic route was required because both overall yield and reproducibility were surprisingly low when the synthesis was conducted on a large scale. The most serious problem was that regioselective demethylation of trimethoxy arene (**5**) with boron tribromide at the last step gave a wide range (20-70%). In this paper, we present a more efficient synthesis of phenol (**2**) from 2-hydroxy-4,5-dimethoxy-3-methylbenzaldehyde (**6**) in eleven steps. A tosyl group was chosen to protect the phenolic function in the sequence.

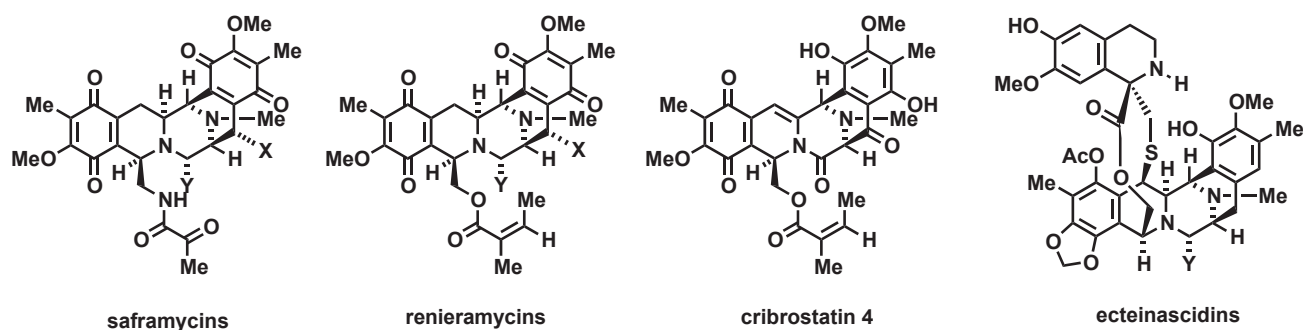
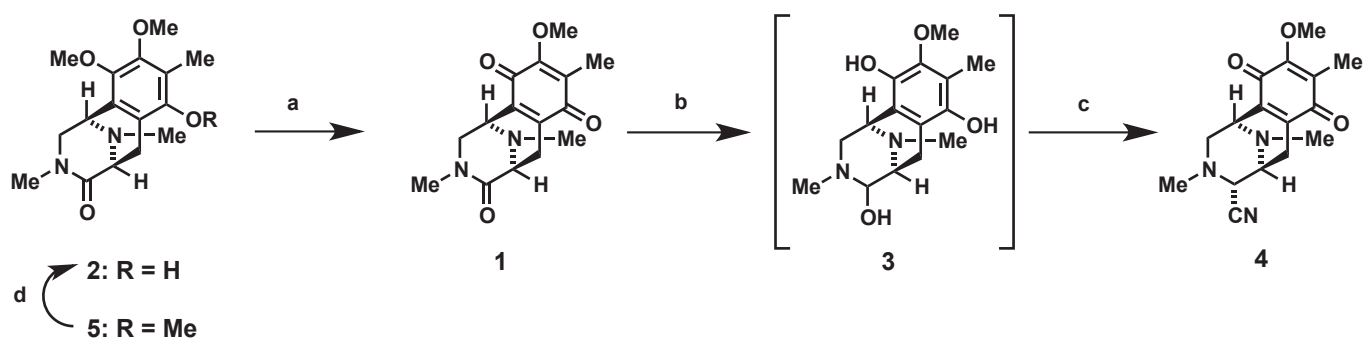


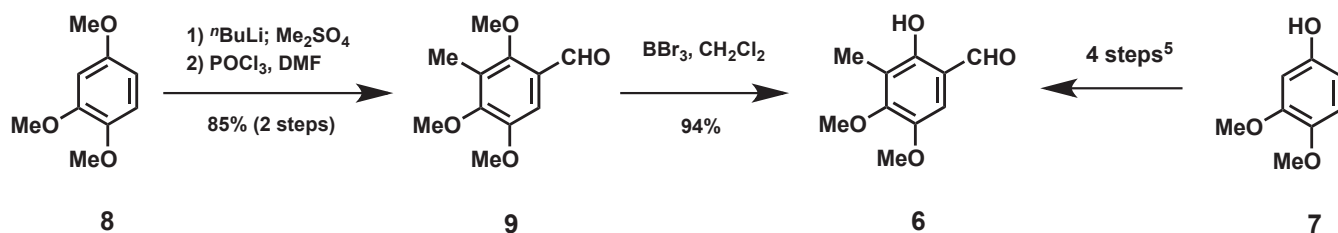
Figure 1. Structure of antitumor bis-1,2,3,4-tetrahydroisoquinoline natural products



Scheme 1. a) 10N HNO₃, 25 °C, 30 min (100%); b) Red-Al, 0 °C, 1 h; c) KCN/H₃O⁺, 25 °C, 1 h (74%, 2 steps); d) BBr₃, CH₂Cl₂, -78 °C (72%).

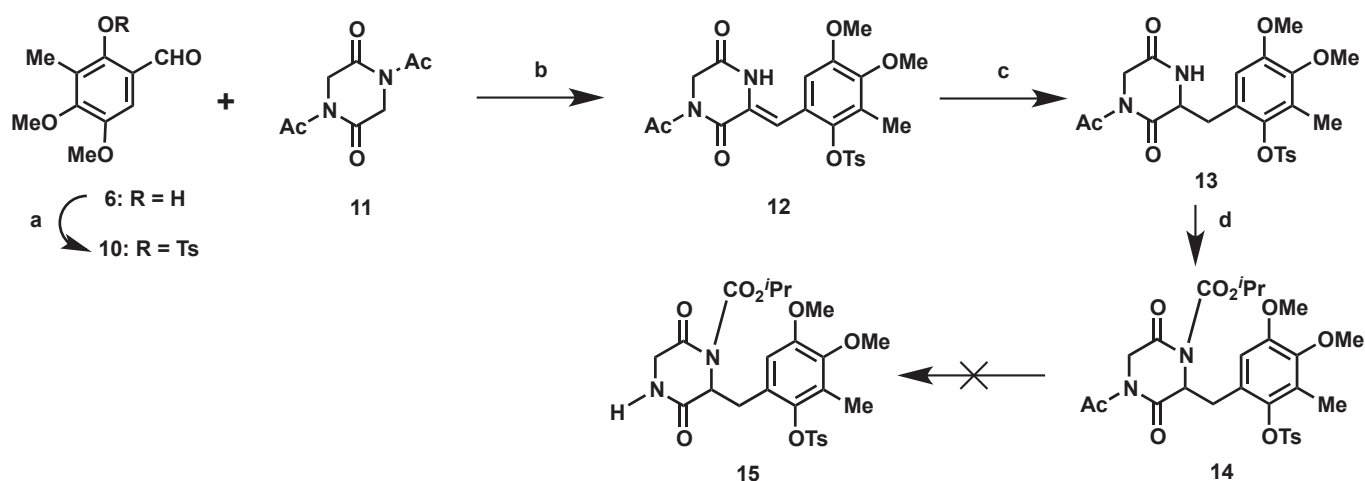
Our starting material for the large-scale production of **2** was 2-hydroxy-4,5-dimethoxy-3-methylbenzaldehyde (**6**), which was prepared from commercially available 3,4-dimethoxyphenol (**7**) according to the four-step procedure of Parker and Kang.^{5,6} However, compound (**7**) was not the best choice for the large-scale preparation because of its high cost. Thus, the nucleophilic substitution of 1,2,4-trimethoxybenzene (**8**) with *n*-BuLi and Me₂SO₄ followed by the Vilsmeier-Haack formylation was carried out, and 3-methyl-2,4,5-trimethoxybenzaldehyde (**9**) was obtained in 85% yield.⁷ Regioselective

demethylation of **9** was achieved by reacting with 1.0 equiv. of boron tribromide in dichloromethane at $-78\text{ }^{\circ}\text{C}$ for 30 min to give **6** in 94% yield (Scheme 2).



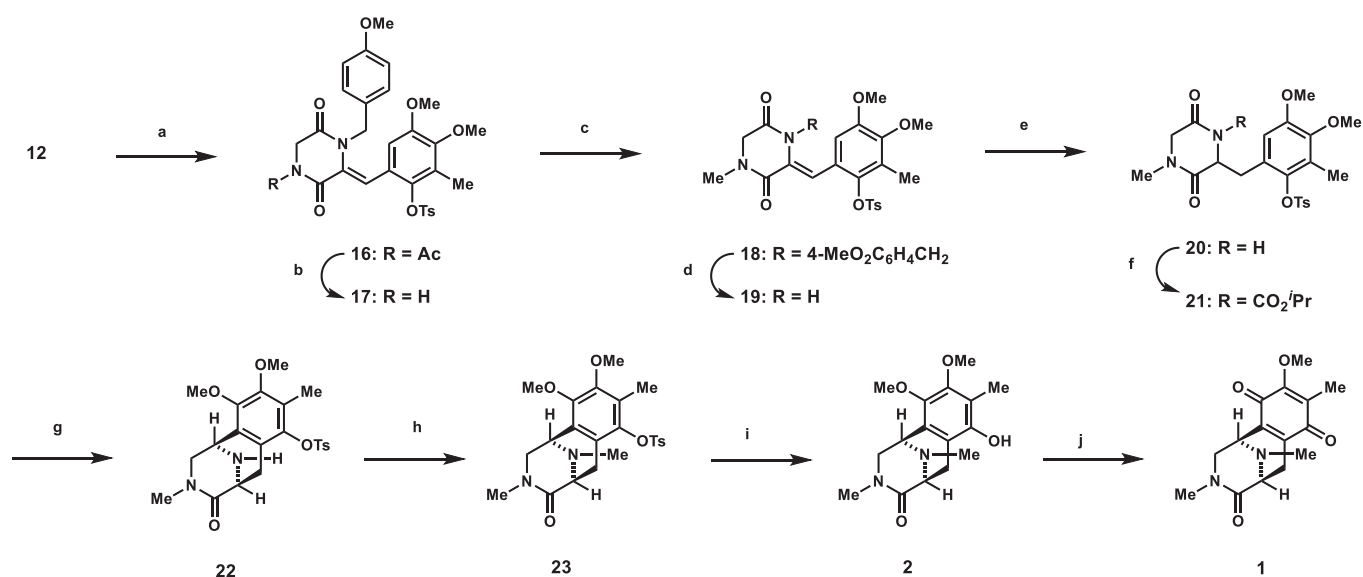
Scheme 2. Preparation of compound **6**

With an ample amount of starting material (**6**) in hand, we turned our attention to the transformation of **6** into right-half model **2**. Phenol (**6**) was protected with a *p*-toluenesulfonyl (Ts) group to afford tosylate (**10**) in 94% yield. The condensation of **10** with diacetate (**11**)⁸ in the presence of potassium *tert*-butoxide in dichloromethane gave product **12** in 88% yield (Scheme 3).^{7b,9,10} The geometric structure of **12** was confirmed from the chemical shift of the olefinic proton at δ 6.82. Reduction of the exo-double bond of **12** by catalytic hydrogenation in the presence of 5% Rh/C in 2-propanol occurred cleanly to give **13** in 93% yield. Treatment of **13** with isopropyl chloroformate in the presence of triethylamine (TEA) and 4-dimethylaminopyridine (DMAP) in dichloromethane gave imide (**14**) in 97% yield. We then investigated the transformation **14** into deacetylated compound (**15**). Numerous efforts for the chemoselective deacetylation of **14** under basic conditions were unsuccessful and afforded an inseparable mixture of degradation products.



Scheme 3. a) TsCl, TEA, CH_2Cl_2 (94%); b) $t\text{BuOK}/t\text{BuOH}$, CH_2Cl_2 (88%); c) H_2 , 5% Rh/C, $i\text{PrOH}$ (93%); d) ClCO_2^iPr , TEA, DMAP, CH_2Cl_2 (97%).

Accordingly, the 4-methoxybenzyl group protection of the NH group in **12** and the sequence of transformation into **2** were studied (Scheme 4). Alkylation of **12** with 4-methoxybenzyl chloride in the presence of sodium hydride (NaH) in DMF furnished **16**, and successive treatment with hydrazine monohydrate afforded **17** in 82% overall yield. Methylation of **17** with methyl iodide in the presence of NaH in DMF afforded **18** in 75% yield. Deprotection of **18** with trifluoroacetic acid (TFA) and H₂SO₄ produced compound **19** in 83% yield. Catalytic hydrogenation of **19** over 5% Rh/C on carbon in 2-propanol occurred cleanly to give 1-methyl-2,5-piperazinedione **20** in 95% yield. Treatment of **20** with isopropyl chloroformate furnished imide **21** in 91% yield. Partial reduction of the activated lactam carbonyl group of **21** followed by protic acid treatment afforded cyclization product **22** in 77% yield. Reductive *N*-methylation of **22** with formalin and formic acid gave **23** in 91% yield, and its tosyl group was subjected to deprotection with hydrazine monohydrate in ethanol to afford phenol **2**, which was identical with the authentic sample based on comparison of spectroscopic and thin layer chromatography (TLC) data.³ Oxidative demethylation of **2** in 10 N HNO₃ gave *p*-quinone lactam **1** in a quantitative yield.



Scheme 4. a) NaH, 4-MeOC₆H₄CH₂Cl, DMF, 25 °C, 14 h; b) NH₂NH₂·H₂O, EtOH, 25 °C, 15 h (82%, 2 steps); c) NaH, MeI, DMF, 25 °C, 15 h (75%); d) H₂SO₄, TFA, 25 °C, 3 h (83%); e) H₂, 5% Rh/C, ⁱPrOH, 25 °C, 19 h (95%); f) ClCO₂ⁱPr, TEA, DMAP, CH₂Cl₂, 25 °C, 6.5 h (91%); g) Li(O^tBu)₃AlH, THF, 0 °C, 1.5 h, and then H₂SO₄, TFA, 25 °C, 15 h (79%); h) 37% HCHO·H₂O, HCO₂H, 70 °C, 1 h (91%); i) NH₂NH₂·H₂O, EtOH, reflux, 15 h (89%); j) 10N HNO₃, 25 °C, 30 min (100%).

In conclusion, we succeeded in the large-scale preparation of key intermediate **2**, which could be converted into a variety of right-half model derivatives, including **3**. The tosyl protecting group was very useful for the synthesis of antitumor renieramycin-saframycin type natural products. To extend the scope of this strategy, we performed the total synthesis of marine natural products, such as cribrostatin 4, renieramycin I,¹¹ and renieramycin T.¹²

EXPERIMENTAL

All melting points were determined with a Yanagimoto micromelting points apparatus and uncollected. IR spectra were obtained with a Shimadzu Prestige 21/IRAffinity-1 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 500 FT NMR spectrometer at 500 MHz for ^1H and 125 MHz for ^{13}C ; a JEOL JNM-AL 400 NMR spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C ; and a JEOL JNM-AL 300 NMR spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C (ppm, J in Hz with TMS as internal standard). All proton and carbon signals were assigned by extensive NMR measurements using COSY, HMBC, and HMQC techniques. Mass spectra were recorded on a JEOL JMS 700 instrument with a direct inlet system operating at 70 eV. Elemental analyses were conducted on a YANACO MT-6 CHN CORDER elemental analyzer. Dry solvents such as THF and CH_2Cl_2 , were obtained using standard procedure.

2,4,5-Trimethoxy-3-methylbenzaldehyde (9)

$n\text{BuLi}$ (1.60 mol/L in n hexane, 225 mL, 360 mmol) was added dropwise into a stirred solution of 1,2,4-trimethoxybenzene **8** (50.46 g, 300 mmol) in THF (240 mL) at 0 °C over 2 h. The reaction mixture was stirred at 0 °C for 1 h. A solution of dimethyl sulfate (34.1 mL, 360 mmol) in THF (60 mL) was added to the reaction mixture over 2 h. The reaction mixture was stirred for 1 h at 25 °C. The reaction mixture was diluted with H_2O (200 mL) and then extracted with CHCl_3 (3×200 mL). The combined extracts were washed with aqueous 5% NaHCO_3 solution (200 mL), dried, and concentrated in vacuo to give a residue (60.09 g), which was used in the next step without further purification.

Phosphoryl chloride (POCl_3 ; 55.9 mL, 600 mmol) was added to a stirred solution of the above residue in DMF (46.5 mL, 600 mmol) at 0 °C for 7 min, and the reaction mixture was heated for 2.5 h at 100 °C. The reaction mixture was carefully neutralized with saturated aqueous sodium acetate, and the mixture was diluted with H_2O (500 mL) and extracted with CH_2Cl_2 (3×500 mL). The combined extracts were washed with aqueous 5% NaHCO_3 solution (2×500 mL), dried, and concentrated in vacuo to give a residue (69.25 g). The residue was purified by distillation at 139 °C (3.5 mmHg) to give **9** (53.65 g, 85%, 2 steps). All spectral data were identical with those of an authentic sample described previously.^{7a,b}

δ_{H} (300 MHz, CDCl_3) 10.29 (1H, s, CHO), 7.23 (1H, s, ArH), 3.89 (3H, s, ArOCH_3), 3.88 (3H, s, ArOCH_3), 3.84 (3H, s, ArOCH_3), 2.23 (3H, s, ArCH_3).

2-Hydroxy-4,5-dimethoxy-3-methylbenzaldehyde (6)

A solution of BBr_3 in CH_2Cl_2 (1.0 mol/L in CH_2Cl_2 , 100 mL, 0.1 mol) was added dropwise into a stirred solution of **9** (21.0 g, 0.1 mol) in CH_2Cl_2 (500 mL) at 0 °C, and the reaction mixture was stirred for 30 min at 25 °C. The reaction mixture was diluted with aqueous saturated NaHCO_3 solution (1.0 L) and then

extracted with CHCl_3 (3×1.0 L). The combined extracts were washed with aqueous brine (1.0 L), dried, and concentrated in vacuo to give a solid (19.33 g), recrystallization of which from Et_2O afforded **6** (18.4 g, 94%) as colorless needles, mp 76-77 °C. All spectral data were identical with those of an authentic sample described previously.^{6b}

δ_{H} (300 MHz, CDCl_3) 11.29 (1H, s, Ar-OH), 9.75 (1H, s, CHO), 6.86 (1H, s, ArH), 3.91 (3H, s, ArOCH₃), 3.86 (3H, s, ArOCH₃), 2.17 (3H, s, ArCH₃).

6-Formyl-3,4-dimethoxy-2-methylphenyl 4-methylbenzenesulfonate (10)

A solution of **9** (18.88 g, 96 mmol) and TEA (17.6 mL, 125 mmol) in CH_2Cl_2 (160 mL) was cooled with ice water, and TsCl (23.84 g, 125 mmol) was added over 30 min. The reaction mixture was stirred for 2 h at 25 °C. Thereafter, the mixture was diluted with brine (160 mL) and extracted with CH_2Cl_2 (3×300 mL). The combined extracts were washed with H_2O (300 mL), dried, and concentrated in vacuo to give a solid (39.68 g), recrystallization of which from benzene gave **10** (31.73 g, 94%) as colorless prisms, mp 147-148 °C

γ_{max} (KBr) 2970, 1692, 1364, 1206 cm^{-1} . δ_{H} (400 MHz, CDCl_3) 9.79 (1H, s, CHO), 7.76 (2H, d, $J = 8.2$ Hz, ArH), 7.37 (2H, d, $J = 8.2$ Hz, ArH), 7.30 (1H, s, ArH), 3.91 (3H, s, Ar-OCH₃), 3.88 (3H, s, Ar-OCH₃), 2.49 (3H, s, ArCH₃), 2.06 (3H, s, ArCH₃). δ_{C} (100 MHz, CDCl_3) 187.1 (d), 153.2 (s), 151.6 (s), 146.2 (s), 144.5 (s), 131.9 (s), 130.1 (d), 128.5 (d), 127.9 (s), 125.9 (s), 107.6 (d), 60.5 (q, OCH₃), 56.0 (q, OCH₃), 21.7 (q, ArCH₃), 10.4 (q, ArCH₃). EIMS m/z (%) 350 (M^+ , 27), 195 (100). HR-EI-MS m/z 350.0825 [M^+] (calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_6\text{S}$, 350.0824). Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{O}_6\text{S}$: C 58.27, H 5.18. Found: C 58.44, H 5.17.

(Z)-6-((4-Acetyl-3,6-dioxopiperazin-2-ylidene)methyl)-3,4-dimethoxy-2-methylphenyl 4-methylbenzenesulfonate (12)

A solution of KO^tBu (1 M ^tBuOH solution, 36 mL, 36 mmol) was added to a stirred solution of **10** (10.51 g, 30 mmol) and diacetate **11** (5.9 g, 30 mmol) in dry CH_2Cl_2 (120 mL) at 0 °C over 1 h, and the reaction mixture was stirred for 1.5 h at 25 °C. The reaction mixture was poured into saturated aqueous NH_4Cl solution (150 mL) at 0 °C and extracted with CH_2Cl_2 (3×120 mL). The combined extracts were washed with brine (120 mL), dried, and concentrated in vacuo to give a solid (14.29 g), recrystallization of which from benzene gave **12** (12.92 g, 88%) as colorless prisms, mp 186-187 °C.

γ_{max} (KBr) 1705, 1360, 1175 cm^{-1} . δ_{H} (300 MHz, CDCl_3) 8.01 (1H, br s, NH), 7.74 (2H, d, $J = 8.3$ Hz, ArH), 7.30 (2H, d, $J = 8.3$ Hz, ArH), 6.82 (1H, s, 6a-H), 6.64 (1H, s, 5-H), 4.29 (2H, s, 5'-H), 3.84 (3H, s, 4-OCH₃), 3.83 (3H, s, 3-OCH₃), 2.62 (3H, s, NAc), 2.40 (3H, s, Ar-CH₃), 2.14 (3H, s, Ar-CH₃). δ_{C} (67.8

MHz, CDCl₃) 172.2 (s), 162.4 (s, C-3'), 159.0 (s, C-6'), 151.5 (s, C-4), 148.7 (s, C-3), 145.4 (s), 139.9 (s, C-1), 133.5 (s), 129.7 (d), 128.7 (s, C-2), 128.2 (d), 126.1 (s), 122.2 (s), 115.9 (d, C-6a), 109.6 (d, C-5), 60.3 (q, 3-OCH₃), 55.9 (q, 4-OCH₃), 46.0 (t, C-5'), 27.1 (q, NCOCH₃), 21.5 (q, ArCH₃), 10.9 (q, Ar-CH₃). EIMS *m/z* (%): 488 (M⁺, 17), 333 (38), 91 (100), 234 (24), 206 (18). HR-EIMS *m/z* 488.1250 [M⁺] (calcd for C₂₃H₂₄N₂O₈S, 488.1253). Anal. Calcd for C₁₈H₂₂N₂O₇-1/6 C₆H₆: C 57.48, H 5.02, N 5.59. Found: C 57.37, H 5.02, N 5.31.

6-((4-Acetyl-3,6-dioxopiperazin-2-yl)methyl)-3,4-dimethoxy-2-methylphenyl 4-methylbenzenesulfonate
(13)

A solution of **12** (2.4 g, 5.0 mmol) in *i*PrOH (100 mL) was hydrogenated over 5% Rh/C (1.0 g) for 3 h at 25 °C. The catalyst was removed by filtration and washing was carried out with MeOH and CHCl₃. The combined filtrates were concentrated in vacuo to give a solid (2.71 g), recrystallization of which from AcOEt/*n*-hexane gave **13** (2.3 g, 93%) as colorless prisms, mp 179-180 °C.

γ_{\max} (KBr) 3252, 1713, 1697, 1686, 1368, 1246, 1070 cm⁻¹. δ_{H} (400 MHz, CDCl₃) 7.85 (2H, d, *J* = 8.5 Hz, 2''-H), 7.38 (2H, d, *J* = 8.5 Hz, 3''-H), 6.60 (1H, s, 5-H), 6.59 (1H, br-s, NH), 4.28 (1H, ddd, *J* = 7.9, 5.0, 2.7 Hz, 2'-H), 4.27 (1H, d, *J* = 18.0 Hz, 5'-H), 3.85 (1H, d, *J* = 18.0 Hz, 5'-H), 3.81 (3H, s, 4-OCH₃), 3.76 (3H, s, 3-OCH₃), 3.33 (1H, dd, *J* = 14.5, 5.0 Hz, 6a-H), 3.16 (1H, dd, *J* = 14.5, 7.9 Hz, 6a-H), 2.54 (3H, s, NAc), 2.48 (3H, s, 4''-CH₃), 1.92 (3H, s, 2-CH₃). δ_{C} (100 MHz, CDCl₃) 171.7 (s, 4-COCH₃), 168.0 (s, C-3'), 166.1 (s, C-6'), 151.6 (s, C-4), 147.6 (s, C-3), 145.7 (s, C-4''), 140.9 (s, C-1), 133.4 (s, C-1''), 130.0 (d, C-3''), 128.2 (d, C-2''), 127.8 (s, C-2), 124.6 (s, C-6), 111.7 (d, C-5), 60.4 (q, 3-OCH₃), 57.3 (d, C-2'), 56.0 (q, 4-OCH₃), 45.5 (t, C-5'), 34.9 (t, C-6a), 27.0 (q, 4-COCH₃), 21.7 (q, 4''-CH₃), 11.0 (q, 2-CH₃). EIMS *m/z* (%) 490 (M⁺, 17), 335 (100), 293 (24), 271 (43), 36 (13), 180 (91). HR-EIMS *m/z* 490.1409 [M⁺] (calcd for C₂₃H₂₆N₂O₈S, 490.1410). Anal. Calcd for C₂₃H₂₆N₂O₈S: C 56.32, H 5.34, N 5.71. Found: C 56.33, H 5.29, N 5.55.

Isopropyl 4-acetyl-2-(4,5-dimethoxy-3-methyl-2-(tosyloxy)benzyl)-3,6-dioxopiperazine-1-carboxylate
(14)

A solution of **13** (245.0 mg, 0.5 mmol), TEA (140 μ L, 1.0 mmol), and DMAP (122.0 mg, 1.0 mmol) in dry CH₂Cl₂ (15 mL) was cooled with ice water, and ClCO₂*i*Pr (230 μ L, 2.0 mmol) was added over 20 min at 0 °C. The reaction mixture was stirred for 1 h at 25 °C. The reaction mixture was poured into water (150 mL) and extracted with CHCl₃ (3 \times 150 mL). The combined extracts were washed with aqueous 1 N HCl solution (150 mL) and 5% aqueous NaHCO₃ solution (150 mL), dried, and concentrated in vacuo.

The crude material (296.0 mg) was purified by silica gel chromatography with hexane/AcOEt (3:2) to give **14** (280.0 mg, 97%) as a colorless amorphous powder.

γ_{\max} (CHCl₃) 2983, 2941, 1784, 1721, 1489, 1375, 1261, 1067 cm⁻¹. δ_{H} (500 MHz, CDCl₃) 7.83 (2H, d, $J = 8.2$ Hz, ArH), 7.39 (2H, d, $J = 8.2$ Hz, ArH), 6.61 (1H, s, 6'-H), 5.06 (1H, br t, $J = 6.7$ Hz, 2-H), 4.99 (1H, sep, $J = 6.4$ Hz, CH(CH₃)₂), 4.80 (1H, d, $J = 18.9$ Hz, 5-H), 3.83 (3H, s, ArOCH₃), 3.77 (3H, s, ArOCH₃), 3.47 (1H, d, $J = 18.9$ Hz, 5-H), 3.43 (1H, dd, $J = 14.0, 7.0$ Hz, 2a-H), 3.28 (1H, dd, $J = 14.0, 6.4$ Hz, 2a-H), 2.49 (3H, s, ArCH₃), 2.48 (3H, s, Ac), 1.91 (3H, s, ArCH₃), 1.28 (3H, d, $J = 6.4$ Hz, CH(CH₃)₂), 1.25 (3H, d, $J = 6.4$ Hz, CH(CH₃)₂). δ_{C} (125 MHz, CDCl₃) 171.1 (s, COCH₃), 167.1 (s, C-3), 163.5 (s, C-6), 151.6 (s, C-5'), 151.1 (s), 147.8 (s, C-4'), 145.7 (s), 141.0 (s, C-2'), 133.4 (s), 130.0 (d), 128.2 (d), 127.2 (s, C-3'), 124.2 (s, C-1'), 111.8 (d, C-6'), 72.6 (d, CH(CH₃)₂), 61.3 (d, C-2), 60.5 (q, OCH₃), 56.0 (q, OCH₃), 46.4 (t, C-5), 33.9 (t, C-2a), 26.8 (q, COCH₃), 21.7 (q, ArCH₃), 21.6 (q, CH(CH₃)₂), 21.5 (q, CH(CH₃)₂), 11.0 (q). EIMS m/z (%) 576 (M⁺, 38), 335 (100), 293 (39), 271 (26), 236 (26), 181 (34). HR-EIMS m/z 576.1776 [M⁺] (calcd for C₂₇H₃₂N₂O₁₀S, 576.1778).

(Z)-3,4-Dimethoxy-6-((1-(4-methoxybenzyl)-3,6-dioxopiperazin-2-ylidene)methyl)-2-methylphenyl 4-methylbenzenesulfonate (17)

Sodium hydride (60% oil dispersion, 342 mg, 8.55 mmol) was added to a stirred solution of **12** (3.48 g, 7.12 mmol) in dry DMF (140 mL) at 0 °C, and stirring was continued for 30 min at 25 °C. 4-Methoxybenzyl chloride (1.34 g, 8.55 mmol) in dry DMF (20 mL) was added dropwise over 20 min, and the reaction mixture was stirred for 14 h at 25 °C. Hydrazine monohydrate (3.24 mL) was added to the stirred reaction mixture at 0 °C in one portion, and the resulting mixture was stirred at 25 °C for 2 h. After the solution was concentrated in vacuo, the residue was diluted with H₂O (300 mL) and extracted with CHCl₃ (3 × 200 mL). The combined extracts were washed with brine (180 mL), dried, and concentrated in vacuo to give a residue. Chromatography on a silica gel column with hexane/AcOEt (1:5) gave **17** (3.30 g, 82%) as a pale brown amorphous powder.

γ_{\max} (KBr) 3206, 2938, 1699, 1352, 1175, 860 cm⁻¹. δ_{H} (400 MHz, CDCl₃) 7.77 (2H, d, $J = 8.3$ Hz, ArH), 7.34 (2H, d, $J = 8.3$ Hz, ArH), 7.10 (1H, br s, NH), 6.99 (1H, s, 6a-H), 6.82 (2H, d, $J = 8.8$ Hz, ArH), 6.69 (2H, d, $J = 8.8$ Hz, ArH), 6.61 (1H, s, 5-H), 4.49 (2H, s, NCH₂), 4.13 (2H, s, 5'-H), 3.82 (3H, s, 3-OCH₃), 3.81 (3H, s, 4-OCH₃), 3.72 (3H, s, ArOCH₃), 2.45 (3H, s, ArCH₃), 1.90 (3H, s, 2CH₃). δ_{C} (100 MHz, CDCl₃) 165.3 (s, C-3'), 164.7 (s, C-6'), 158.9 (s), 151.0 (s, C-4), 148.4 (s, C-3), 145.5 (s), 140.3 (s, C-1), 133.7 (s), 130.8 (s, C-2'), 129.9 (d), 128.9 (d), 128.3 (d), 128.2 (s), 127.1 (s, C-2), 124.7 (s, C-6), 117.6 (s, C-6a), 113.6 (d), 110.5 (d, C-5), 60.5 (q, 3-OCH₃), 55.9 (q, 4-OCH₃), 55.2 (q, ArOCH₃),

47.0 (t, NCH_2), 45.4 (t, C-5'), 21.7 (q, $TsCH_3$), 10.7 (q, 2- CH_3). EI-MS m/z (%): 566 (M^+ , 0.4), 395 (33), 394 (84), 121 (100). HR-EIMS m/z 566.1719 [M^+] (calcd for $C_{29}H_{30}N_2O_8S$, 566.1723).

(Z)-3,4-Dimethoxy-6-((1-(4-methoxybenzyl)-4-methyl-3,6-dioxopiperazin-2-ylidene)methyl)-2-methylphenyl 4-methylbenzenesulfonate (18)

Sodium hydride (60% oil dispersion, 127.2 mg, 3.18 mmol) was added to a stirred solution of **17** (1.50 g, 2.65 mmol) in DMF (15 mL) at 0 °C, and the reaction mixture was stirred for 30 min at 25 °C. Methyl iodide (198 μ L, 3.18 mmol) was added in one portion, and the reaction mixture was stirred for 15 h at 25 °C. The reaction was diluted with H_2O (150 mL) and extracted with $CHCl_3$ (3×150 mL). The combined extracts were washed with brine (150 mL), dried, and concentrated in vacuo to give a residue. Chromatography on a silica gel column with CH_2Cl_2 /acetone (25:1) gave **18** (1.16 g, 75%) as a pale yellow amorphous powder.

γ_{max} (KBr) 3447, 2938, 1689, 1632, 1381, 1248, 1175, 1070 cm^{-1} . δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, $J = 8.2$ Hz, ArH), 7.34 (2H, d, $J = 8.2$ Hz, ArH), 7.01 (1H, s, 6a-H), 6.82 (2H, d, $J = 8.5$ Hz, ArH), 6.68 (2H, d, $J = 8.5$ Hz, ArH), 6.60 (1H, s, 5-H), 4.47 (2H, s, NCH_2), 4.07 (2H, s, 5'-H), 3.82 (3H, s, 3- OCH_3), 3.81 (3H, s, 4- OCH_3), 3.72 (3H, s, $ArOCH_3$), 3.03 (3H, s, NCH_3), 2.47 (3H, s, $ArCH_3$), 1.92 (3H, s, 2- CH_3). δ_C (100 MHz, $CDCl_3$) 164.7 (s, C-6'), 162.5 (s, C-3'), 158.9 (s), 151.0 (s, C-4), 148.3 (s, C-3), 145.4 (s), 140.2 (s, C-1), 133.9 (s), 131.2 (s, C-2'), 129.8 (d), 129.0 (d), 128.4 (s), 128.2 (d), 127.1 (s, C-2), 124.9 (s, C-6), 117.4 (d, C-6a), 113.6 (d), 110.5 (d, C-5), 60.5 (q, 3- OCH_3), 55.9 (q, 4- OCH_3), 55.2 (q, $ArOCH_3$), 52.3 (t, C-5'), 47.0 (t, NCH_2), 31.5 (q, NCH_3), 21.7 (q, $ArCH_3$), 10.7 (q, 2- CH_3). EIMS m/z (%) 580 (M^+ , 0.4), 423 (5), 410 (22), 409 (99), 408 (100), 121 (74). HR-EIMS m/z 580.1878 [M^+] (calcd for $C_{30}H_{32}N_2O_8S$, 580.1879).

(Z)-3,4-Dimethoxy-2-methyl-6-((4-methyl-3,6-dioxopiperazin-2-ylidene)methyl)phenyl 4-methylbenzenesulfonate (19)

Concentrated H_2SO_4 (720 μ L) was added to a stirred solution of **18** (2.44 g, 4.22 mmol) in TFA (14.0 mL) at 0 °C for 5 min, and the reaction mixture was stirred for 3 h at 25 °C. The reaction mixture was poured into brine (240 mL) and extracted with $CHCl_3$ (3×100 mL). The combined extracts were washed with aqueous 2 N NaOH solution (48 mL), dried, and concentrated in vacuo to give a residue. Chromatography on a silica gel column with ethyl acetate and then AcOEt/MeOH (100:1) afforded **19** (1.60 g, 83%) as a colorless amorphous powder.

γ_{max} (KBr) 3447, 3217, 2928, 1692, 1410, 1175, 1070, 876 cm^{-1} . δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, $J = 8.1$ Hz, ArH), 7.67 (1H, br s, NH), 7.31 (2H, d, $J = 8.1$ Hz, ArH), 6.65 (1H, s, 6a-H), 6.58 (1H, s, 5-H),

3.99 (2H, s, 5'-H₂), 3.83 (6H, s, ArOCH₃ × 2), 3.02 (3H, s, NCH₃), 2.44 (3H, s, 4''-CH₃), 2.23 (3H, s, 2-CH₃). δ_C (100 MHz, CDCl₃) 161.8 (s, C-6'), 157.1 (s, C-3'), 151.6 (s, C-4), 148.3 (s, C-3), 145.3 (s, C-4''), 139.3 (s, C-1), 133.7 (s, C-1''), 129.7 (d, C-3''), 128.9 (s, C-2), 128.3 (d, C-2''), 125.8 (s, C-2'), 122.7 (s, C-6), 112.4 (s, C-6a), 109.7 (d, C-5), 60.5 (q, ArOCH₃), 56.0 (q, ArOCH₃), 51.8 (t, C-5'), 34.2 (q, NCH₃), 21.7 (q, 4''-CH₃), 11.2 (q, 2-CH₃). EIMS *m/z* (%) 460 (M⁺, 14), 306 (18), 305 (100), 288 (34), 277 (32), 220 (28). HR-EIMS *m/z* 460.1302 [M⁺] (calcd for C₂₂H₂₄N₂O₇S, 460.1304).

3,4-Dimethoxy-2-methyl-6-((4-methyl-3,6-dioxopiperazin-2-yl)methyl)phenyl 4-methylbenzenesulfonate
(20)

A solution of **19** (1.61 mg, 3.6 mmol) in 2-propanol (70 mL) was hydrogenated over 5% Rh/C (720 mg) for 19 h at 25 °C. The catalyst was removed by filtration and washed with CHCl₃ and MeOH. The combined filtrates were concentrated in vacuo to furnish the crude material (1.55 g). Chromatography on a silica gel column with AcOEt/MeOH (100:1 – 10:1) afforded **20** (1.54 g, 95%) as a colorless amorphous powder.

γ_{max} (KBr) 3296, 2941, 1672, 1369, 1065 cm⁻¹. δ_H (300 MHz, CDCl₃) 7.86 (2H, d, *J* = 8.5 Hz, 2''-H), 7.38 (2H, d, *J* = 8.5 Hz, 3''-H), 6.62 (1H, s, 5-H), 6.33 (1H, br s, NH), 4.22-4.19 (1H, m, 2'-H), 3.82 (3H, s, 4-OCH₃), 3.76 (3H, s, 3-OCH₃), 3.70 (1H, d, *J* = 17.6 Hz, 5'-H), 3.44 (1H, d, *J* = 17.6 Hz, 5'-H), 3.32 (1H, dd, *J* = 14.4, 4.5 Hz, 6a-H), 3.13 (1H, dd, *J* = 14.4, 7.1 Hz, 6a-H), 2.91 (3H, s, NCH₃), 2.48 (3H, s, 4''-CH₃), 1.89 (3H, s, 2-CH₃). δ_C (100 MHz, CDCl₃) 165.4 (s, C-3'), 165.0 (s, C-6'), 151.4 (s, C-4), 147.1 (s, C-3), 145.6 (s, C-4''), 141.0 (s, C-1), 133.5 (s, C-1''), 130.1 (d, C-3''), 128.1 (d, C-2''), 127.5 (s, C-2), 125.3 (s, C-6), 111.2 (d, C-5), 60.3 (q, 3-OCH₃), 56.1 (d, C-2'), 55.9 (q, 4-OCH₃), 51.1 (t, C-5'), 35.4 (t, C-6a), 33.8 (q, NCH₃), 21.7 (q, 4''-CH₃), 11.0 (q, 2-CH₃). EIMS *m/z* (%) 462 (M⁺, 29), 335 (34), 307 (100), 290 (17), 271 (30), 181 (77). HR-EIMS *m/z* 462.1460 [M⁺] (calcd for C₂₂H₂₆N₂O₇S, 462.1461).

Isopropyl 2-(4,5-dimethoxy-3-methyl-2-(tosyloxy)benzyl)-4-methyl-3,6-dioxopiperazine-1-carboxylate
(21)

Isopropyl chloroformate (1.27 mL, 11.3 mmol) was added to a stirred solution of **20** (652 mg, 1.41 mmol), Et₃N (787 μL, 5.64 mmol), and DMAP (345 mg, 2.82 mmol) in CH₂Cl₂ (26.0 mL) at 0 °C for 10 min, and stirring was continued for 6.5 h at 25 °C. The reaction mixture was poured into 1 N aqueous HCl solution (20 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The combined extracts were washed with 5% aqueous NaHCO₃ solution (20 mL), dried, and concentrated in vacuo to give a residue (730 mg). Chromatography on a silica gel column with CH₂Cl₂/MeOH (1:100) gave **21** (703 g, 91%) as a colorless amorphous powder.

ν_{\max} (KBr) 3601, 2984, 2940, 2361, 2342, 1780, 1732, 1676, 1267, 1244, 1066 cm^{-1} . δ_{H} (400 MHz, CDCl_3) 7.83 (2H, d, $J = 8.5$ Hz), 7.37 (2H, d, $J = 8.5$ Hz), 6.57 (1H, s, 6'-H), 4.97 (1H, sept, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 4.95 (1H, t, $J = 5.5$ Hz, 2-H), 3.82 (3H, s, 5'- OCH_3), 3.76 (3H, s, 4'- OCH_3), 3.60 (1H, d, $J = 18.3$ Hz, 5-H), 3.41 (1H, dd, $J = 14.3, 5.5$ Hz, 2a-H), 3.18 (1H, dd, $J = 14.3, 5.5$ Hz, 2a-H), 3.06 (1H, d, $J = 18.3$ Hz, 5-H), 2.81 (3H, s, NCH_3), 2.48 (3H, s, ArCH_3), 1.89 (3H, s, 3'- CH_3), 1.28 (3H, t, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.26 (3H, t, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_2$). δ_{C} (100 MHz, CDCl_3) 165.7 (s, C-6), 163.8 (s, C-3), 151.4 (s, C-5'), 150.9 (s, NCO_2), 147.5 (s, C-4'), 145.5 (s), 141.1 (s, C-2'), 133.4 (s), 129.8 (d), 128.3 (d), 127.7 (s, C-3'), 125.0 (s, C-1'), 111.6 (d, C-6'), 72.1 (d, $\text{CH}(\text{CH}_3)_2$), 60.4 (q, 4'- OCH_3), 59.8 (d, C-2), 55.9 (q, 5'- OCH_3), 52.2 (t, C-5), 33.8 (t, C-2a), 33.1 (q, NCH_3), 21.7 (q, ArCH_3), 21.6 (q, $\text{CH}(\text{CH}_3)_2$), 21.5 (q, $\text{CH}(\text{CH}_3)_2$), 11.0 (q, 3'- CH_3). EIMS m/z (%) 548 (M^+ , 28), 393 (9), 307 (100), 271 (11), 181 (19). HR-EIMS m/z 548.1824 [M^+] (calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_9\text{S}$, 548.1829).

(1R*,5S*)-9,10-Dimethoxy-3,8-dimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-epiminobenzo[*d*]azocin-7-yl 4-methylbenzenesulfonate (22)

A stirred solution of **21** (476 mg, 868 μmol) in dry THF (17 mL) was cooled in ice water, and tri-*tert*-butoxyaluminum hydride (883 mg, 3.47 mmol) was added over 10 min. The reaction mixture was stirred for 1.5 h at 0 °C. Anhydrous Na_2SO_4 (1.0 g) was added, and the reaction was quenched by the addition of water (1.0 mL). The reaction mixture was filtered through Celite pad, and the filtrate was diluted with brine (100 mL) and extracted with CHCl_3 (3 \times 50 mL). The combined extracts were washed with brine (500 mL), dried, and concentrated *in vacuo*, and the residue (980 mg) was used in the next step without further purification.

Concentrated H_2SO_4 (434 μL) was added to a stirred solution of the above residue in TFA (8.7 mL) at 0°C, and the reaction mixture was stirred for 15 h at 25 °C. After the reaction mixture was poured into H_2O (50 mL), the mixture was basified with 28% aqueous NH_4OH solution and then extracted with CHCl_3 (3 \times 50 mL). The combined extracts were washed with H_2O (50 mL), dried, and concentrated *in vacuo* to give a residue. Chromatography on a silica gel column with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (19:1) gave **22** (361 mg, 77%) as a colorless amorphous powder.

ν_{\max} (KBr) 3444, 3291, 2940, 2859, 1645, 1468, 1341, 1177, 1063, 754 cm^{-1} . δ_{H} (300 MHz, CDCl_3) 7.88 (2H, d, $J = 8.2$ Hz), 7.38 (2H, d, $J = 8.2$ Hz), 4.46 (1H, d, $J = 4.6$ Hz, 1-H), 3.92 (3H, s, 10- OCH_3), 3.89 (1H, dd, $J = 4.8, 2.4$ Hz, 5-H), 3.83 (1H, dd, $J = 11.8, 4.6$ Hz, 2-H), 3.78 (3H, s, 9- OCH_3), 3.17 (1H, dd, $J = 11.8, 1.0$ Hz, 2-H), 2.93 (1H, dd, $J = 17.6, 2.4$ Hz, 6-H), 2.86 (1H, dd, $J = 17.6, 4.8$ Hz, 6-H), 2.82 (3H, s, NCH_3), 2.48 (3H, s, ArCH_3), 2.13 (1H, s, NH), 2.12 (3H, s, 8- CH_3). δ_{C} (100 MHz, CDCl_3) 169.8 (s, C-4), 149.5 (s, C-9), 147.8 (s, C-10), 145.3 (s), 142.4 (s, C-7), 134.1 (s), 130.0 (d), 128.4 (s, C-10a),

127.9 (d), 127.0 (s, C-8), 124.4 (s, C-6a), 60.3 (q, 10-OCH₃), 60.1 (q, 9-OCH₃), 56.4 (t, C-2), 52.6 (d, C-5), 45.4 (d, C-1), 34.1 (q, NCH₃), 28.8 (t, C-6), 21.7 (q, ArCH₃), 11.0 (q, 8-CH₃). EIMS *m/z* (%) 446 (M⁺, 5), 375 (12), 374 (46), 291 (100), 220 (25), 204 (24). HR-EIMS *m/z* 446.1509 [M⁺] (calcd for C₂₂H₂₆N₂O₆S, 446.1512).

(1*R**,5*S**)-9,10-Dimethoxy-3,8,11-trimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-epiminobenzo[*d*]azocin-7-yl 4-methylbenzenesulfonate (23)

37% Aqueous formaldehyde solution (8.0 mL) was added to a stirred solution of **22** (260 mg, 583 μmol) in formic acid (4.5 mL) in 60 °C, and stirring was continued for 1 h at 70 °C. The reaction mixture was basified with 5% aqueous NaHCO₃ solution (200 mL) and extracted with CHCl₃ (3 × 200 mL). The combined extracts were washed with brine (200 mL), dried, and concentrated in vacuo to give a residue (271 mg). Chromatography on a silica gel column with CH₂Cl₂/MeOH (99:1) gave **23** (244 mg, 91%) as a colorless amorphous powder.

γ_{\max} (KBr) 2937, 1653, 1465, 1458, 1409, 1365, 1340, 1192, 1176, 1095, 1055, 1029, 881, 817, 756 cm⁻¹. δ_{H} (300 MHz, CDCl₃) 7.88 (2H, d, *J* = 8.3 Hz), 7.38 (2H, d, *J* = 8.3 Hz), 4.12 (1H, d, *J* = 4.9 Hz, 1-H), 3.92 (3H, s, 10-OCH₃), 3.92 (1H, dd, *J* = 12.2, 4.9 Hz, 2-H), 3.79 (3H, s, 9-OCH₃), 3.58 (1H, d, *J* = 6.8 Hz, 5-H), 3.06 (1H, d, *J* = 12.2 Hz, 2-H), 2.96 (1H, dd, *J* = 18.0, 6.8 Hz, 6-H), 2.81 (3H, s, 3-CH₃), 2.72 (1H, d, *J* = 18.0 Hz, 6-H), 2.48 (3H, s, ArCH₃), 2.45 (3H, s, 11-CH₃), 2.13 (3H, s, 8-CH₃). δ_{C} (100 MHz, CDCl₃) 169.6 (s, C-4), 149.7 (s, C-9), 148.5 (s, C-10), 145.3 (d), 142.1 (s, C-7), 134.1 (d), 129.9 (s), 127.9 (s), 127.0 (s, C-8), 126.1 (s, C-10a), 123.3 (s, C-6a), 60.3 (q, 10-OCH₃), 60.0 (q, 9-OCH₃), 58.4 (d, C-5), 53.7 (t, C-2), 51.2 (d, C-1), 39.8 (q, 11-CH₃), 33.9 (q, 3-CH₃), 23.4 (t, C-6), 21.7 (q, ArCH₃), 11.0 (q, 8-CH₃). EI-MS *m/z* (%) 460 (M⁺, 2), 388 (34), 306 (17), 305 (100), 233 (13), 218 (19). HR-EIMS *m/z*: 460.1667 [M⁺] (calcd for C₂₂H₂₈N₂O₆S, 460.1668).

(1*R**,5*S**)-7-Hydroxy-9,10-dimethoxy-3,8,11-trimethyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[*d*]azocin-4(1*H*)-one (2)

Hydrazine monohydrate (18.8 mL) was added to a stirred solution of **23** (437 mg, 0.95 mmol) in EtOH (9.4 mL) at room temperature, and the reaction mixture was heated for 15 h under reflux. The reaction mixture was diluted with aqueous saturated NH₄Cl solution (280 mL) and extracted with CHCl₃ (3 × 200 mL). The combined extracts were washed with brine (200 mL), dried, and concentrated in vacuo to give a residue (292 mg). Chromatography on a silica gel column with CH₂Cl₂/MeOH (30:1) gave **2** (258 mg, 89%) as a colorless amorphous powder. Colorless prisms were obtained by recrystallization from acetone and used for analysis, mp 201-202 °C (*Lit.*^{2b}, mp 199-201 °C).

ν_{\max} (KBr) 3238, 2967, 2940, 2924, 2866, 1643, 1456, 1338, 1310, 1298, 1227, 1111, 1070, 993, 962, 806, 725 cm^{-1} . δ_{C} (300 MHz, CDCl_3) 5.90 (1H, s, 7-OH), 4.12 (1H, d, $J = 4.9$ Hz, 1-H), 3.95 (1H, dd, $J = 11.6, 4.6$ Hz, 2-H), 3.85 (3H, s, 10-OCH₃), 3.79 (3H, s, 9-OCH₃), 3.70 (1H, d, $J = 6.4$ Hz, 5-H), 3.11 (1H, d, $J = 11.6$ Hz, 2-H), 2.93 (1H, dd, $J = 17.4, 6.4$ Hz, 6-H), 2.87 (3H, s, 3-CH₃), 2.85 (1H, d, $J = 17.4$ Hz, 6-H), 2.47 (3H, s, 11-CH₃), 2.16 (3H, s, 8-CH₃). δ_{C} (100 MHz, CDCl_3) 170.3 (s, C-4), 149.7 (s, C-9), 148.1 (s, C-10), 143.4 (s, C-7), 125.2 (s, C-8), 117.7 (s, C-10a), 114.9 (s, C-6a), 60.5 (q, 10-OCH₃), 60.2 (q, 9-OCH₃), 58.7 (d, C-5), 54.0 (t, C-2), 51.1 (d, C-1), 39.9 (q, 11-CH₃), 34.1 (q, 3-CH₃), 22.7 (t, C-6), 8.9 (q, 8-CH₃). EIMS m/z (%) 306 (M^+ , 24), 235 (18), 234 (100), 219 (9), 204 (8). HR-EIMS m/z 306.1579 [M^+] (calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_4$, 306.1580).

(1R*,5S*)-9-Methoxy-3,8,11-trimethyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[d]azocine-4,7,10(1H)-trione
(1)

A solution of **2** (153.0 mg, 0.15 mmol) in 10N HNO_3 (0.7 mL) was stirred for 30 min at 25 °C. After the reaction mixture was diluted with H_2O (100 mL), it was basified with saturated NaHCO_3 solution and extracted with CHCl_3 (3 \times 100 mL). The combined extracts were washed with brine (100 mL), dried, and concentrated in vacuo to give a solid, recrystallization of which from $\text{AcOEt-Et}_2\text{O}$ gave pure **1** (145.0 mg, 100%) as pale yellow prisms, mp 150.5-152 °C. All spectral data were identical with those of the authentic sample.²

ν_{\max} (KBr) 3007, 2943, 1657, 1614, 1315, 1304, 1233, 1150 cm^{-1} . δ_{H} (300 MHz, CDCl_3) 4.01 (3H, s, 9-OCH₃), 3.97 (1H, d, $J = 4.9$ Hz, 1-H), 3.90 (1H, dd, $J = 12.2, 4.9$ Hz, 2-H), 3.62 (1H, br d, $J = 5.6$ Hz, 5-H), 3.04 (1H, d, $J = 12.2$ Hz, 2-H), 2.89 (3H, s, 3-CH₃), 2.79 (1H, dd, $J = 20.2, 5.6$ Hz, 6-H), 2.72 (1H, dd, $J = 20.2, 2.0$ Hz, 6-H), 2.45 (3H, s, 11-CH₃), 1.96 (3H, s, 8-CH₃). δ_{C} (100 MHz, CDCl_3) 186.6 (s, C-10), 182.2 (s, C-7), 169.2 (s, C-4), 155.4 (s, C-9), 140.9 (s, C-8), 137.3 (s, C-10a), 129.5 (s, C-6a), 61.0 (q, 9-OCH₃), 58.2 (d, C-5), 51.1 (t, C-2), 49.7 (d, C-1), 39.8 (q, 11-CH₃), 33.8 (q, 3-CH₃), 24.0 (t, C-6), 8.8 (q, 8-CH₃). EI-MS m/z (%) 291 (16), 290 (M^+ , 100), 235 (20), 231 (17), 220 (10), 219 (22), 218 (58), 204 (50), 202 (11), 201 (12), 190 (16), 176 (22). HR-EIMS m/z 290.1265 [M^+] (calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4$, 290.1267). Anal. calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4$: C 62.05, H 6.25, N 9.65. Found: C 61.92, H 6.27, N 9.56.

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