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# Synthesis of (±)-Septicine

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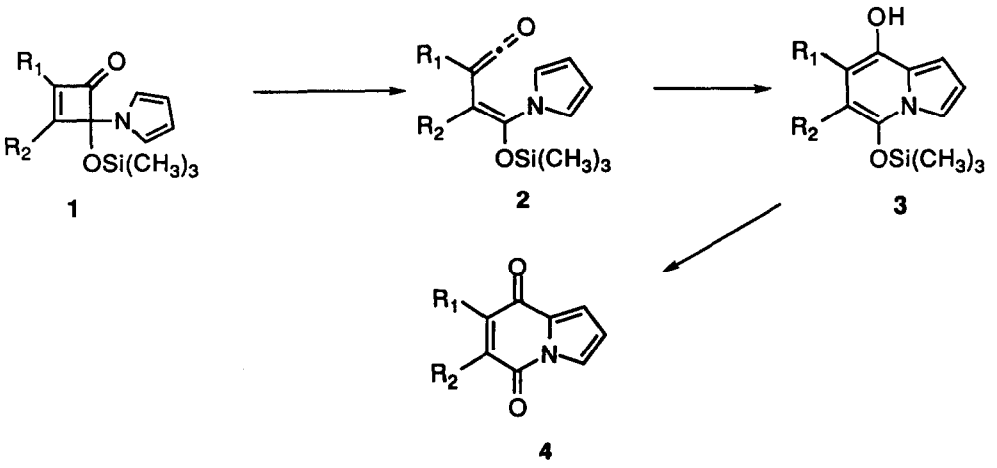
**Abstract:** The total synthesis of the indolizidine alkaloid, (±)-septicine **(5)** (27% overall yield) in 8 steps from dimethyl squarate is presented. The key step of the synthesis involves the ring expansion of 2,3-bis-(3,4-dimethoxyphenyl)-4-(1-pyrrolo)cyclobutenone **12** to the corresponding indolizine-5,8-dione **6**. The synthesis is highly convergent and thus could be used for the synthesis of a variety of analogs.

Reported here is an example of the synthetic utility of the recently described thermal ring expansion of 4-(1-pyrrolo)cyclobutenones to indolizine-5,8-diones.[1] Specifically, the use of this rearrangement as the key step in the synthesis of the indolizidine alkaloid, (±)-septicine (5) is presented.

Septicine, an alkaloid isolated from *Ficus septica*, is a member of a class of compounds believed to be precursors to the phenanthroindolizidine alkaloids in which the aryl rings are fused.[2] Since these alkaloids have interesting physiological effects on the respiratory system[3] as well as antibiotic,[4] antileukemic[5] and anticancer[6] activities, new strategies for their synthesis continue to surface.[7]

**Scheme-1**



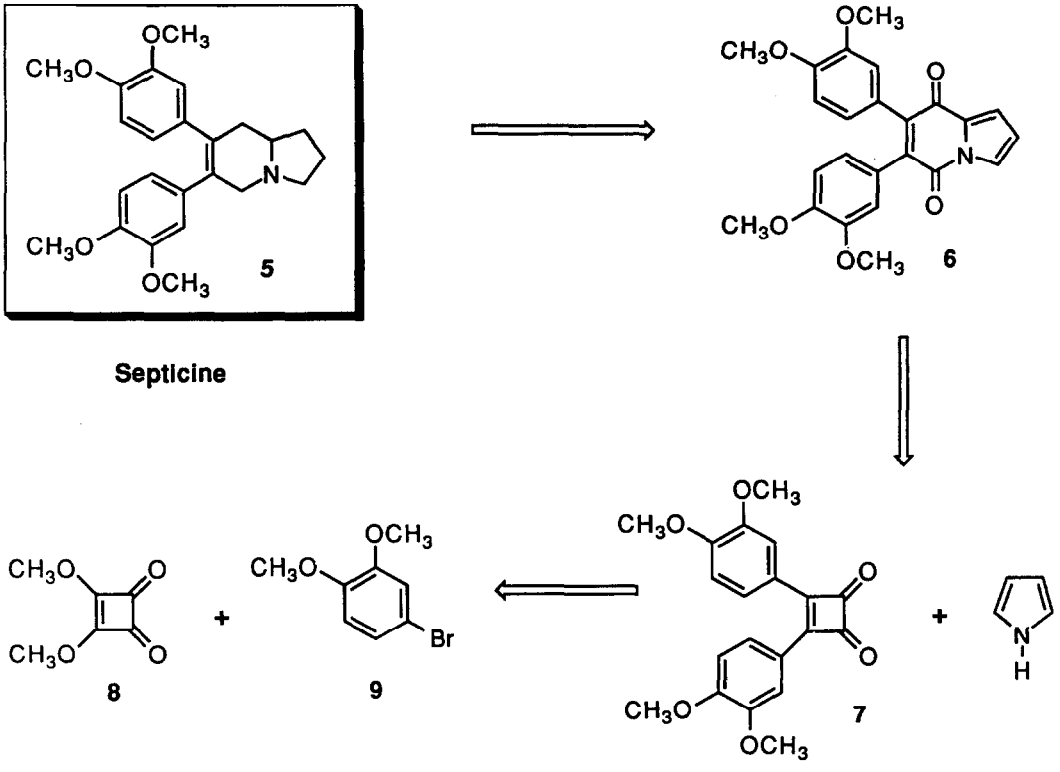

1 2 3 4

**Results and Discussion**

The synthesis of (±)-septicine described here relies on the rearrangement of a readily available 4-(1-pyrrolo)cyclobutenone to an indolizine-5,8-dione (Scheme-1).[8] The transformation is envisaged to involve electrocyclic ring opening of the cyclobutenone **1** to the conjugated ketene **2**. Subsequent ring closure of the ketene leads to the indolizine **3** and this provides the indolizinedione **4** upon oxidative work up.

A retrosynthetic analysis of septicine, which takes advantage of the above rearrangement, is outlined in Scheme-2. Refunctionalization of (±)-septicine to the indolizinedione **6** reveals the key disconnection to the symmetrical diaryl cyclobutenedione **7** and pyrrole. The cyclobutenedione then transforms to commercially available dimethyl squarate (**8**) and 4-bromoveratrole (**9**).

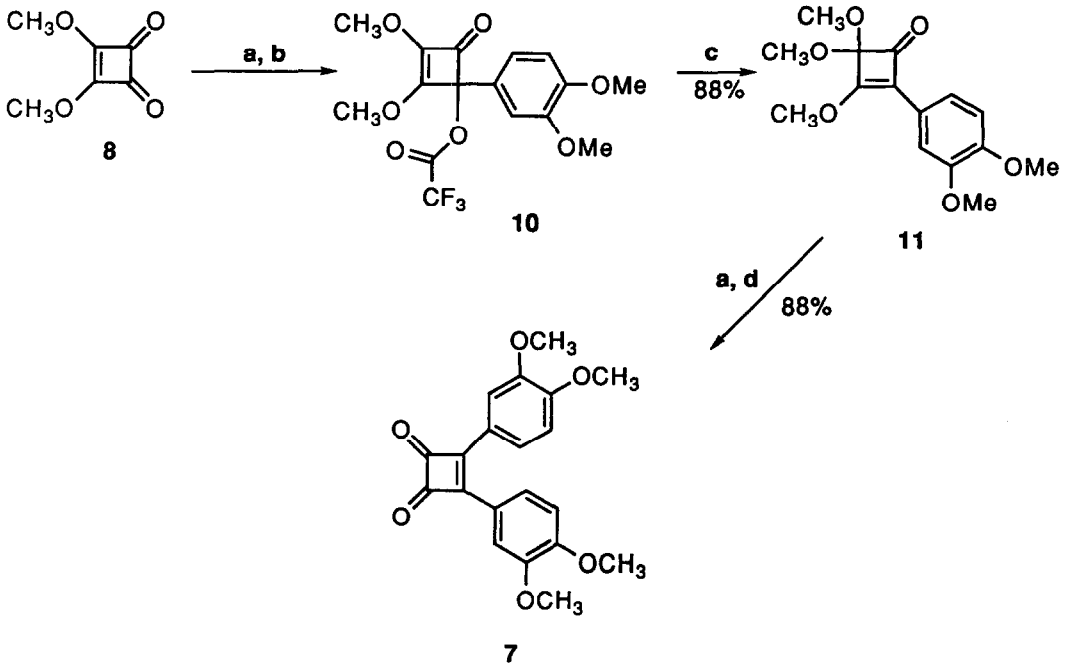
**Scheme-2**




The synthesis begins by treating dimethyl squarate (**8**) with the lithium salt of 4-bromoveratrole. Addition of trifluoroacetic anhydride to the reaction solution presumably gave trifluoroacetate **10** which was directly converted to the cyclobutenedione monoketal **11** in 88%

overall yield upon treatment with dry methanol.[9] Addition of the lithium salt of 4-bromoveratrole to 11 followed by work up with 10% HCl then gave the diaryl cyclobutenedione 7 in 88% isolated yield. This transformation is noteworthy since it illustrates a potentially general route to symmetrical and unsymmetrical cyclobutenediones.

**Scheme-3**



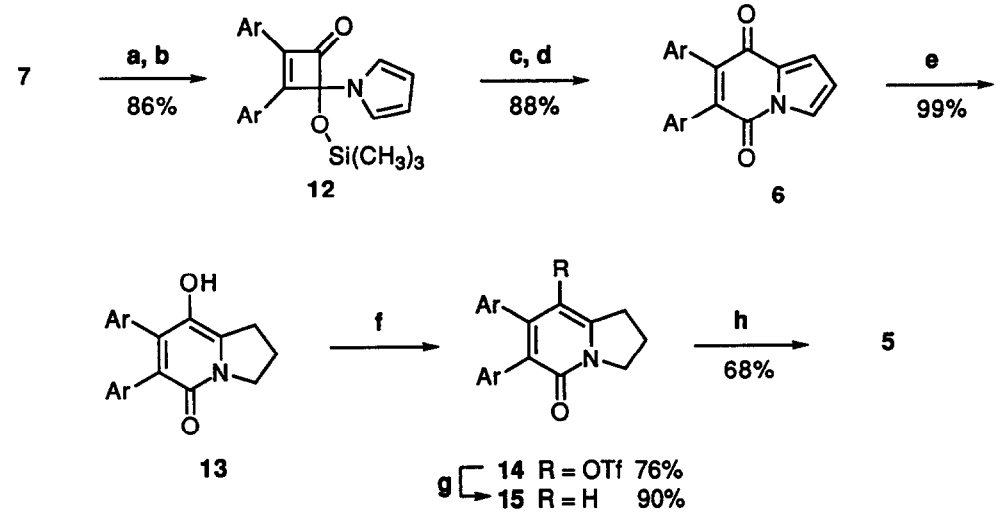

**a**) 1,2-$CH_3O$-$C_6H_3$-4-Li, **b**) TFAA, **c**) $CH_3OH$, **d**) 10% HCl

Addition of 1-lithiopyrrole to **7** followed by a trimethylsilyl chloride quench gave the cyclobutenone **12** in 84% yield. This was subjected to thermolysis in refluxing *p*-xylene and the crude reaction product was oxidized with ferric chloride to afford the desired indolizinedione **6** in 88% yield.

A series of reductions was then employed to convert the indolizinedione to the natural product. Catalytic hydrogenation[10] of **6** gave an essentially quantitative yield of the tetrahydro derivative **13**. Unfortunately, all attempts to further reduce **13** failed to give satisfactory results. As a result, the hydroxyl group was removed by conversion to the triflate **14** (76%) followed by treatment with

$Pd(OAc)_2$/DPPP and triethyl ammonium formate[11] to gave the pyridone 15 in 90% yield. Finally, treatment of 15 with LAH/$AlCl_3$[12] gave (±)-septicine (5) in 68% yield. Its spectral data and melting point are in accord with analogous data reported for the racemic natural product.

**Scheme-4**




**a)** $C_4H_4NLi$, **b)** TMSCl, **c)** *p*-xylene, **d)** $FeCl_3$, **e)** $H_2$/Pd-C, **f)**, $Tf_2O$, **g)** $Pd(OAc)_2$, DPPP, $Et_3N$, $HCO_2H$, **h)** LAH, $AlCl_3$

## Conclusions

In conclusion, we note that the synthesis described here provides a new and convergent route to functionalized indolizidine alkaloids. (±)-Septicine was synthesized in 8 steps from dimethyl squarate in 27% overall yield. This compares favorably in efficiency to the other septicine syntheses reported in the literature.[7] It has a particular advantage in being highly convergent and stems from readily available starting materials. It thus lends itself towards the construction of a variety of related natural products and analogs.

## Experimental Section

**2,2-Dimethoxy-4-(3,4-dimethoxyphenyl)-3-methoxycyclobuteneone (11).** 4-Bromoveratrole (11.14 ml, 77.5 mmol) was dissolved in THF (350 ml) at -78°C and *n*-BuLi (50.6 ml, 81.0 mmol, 1.6 M) was added in 5 portions via syringe. The solution was allowed to stir for 15 min (becoming cloudy after 5 min) and then added to dimethyl squarate (10.0 g, 70.4 mmol) as a

cloudy suspension in THF (350 ml) via cannula at -78°C. The solution was stirred for 20 min and then TFAA (11.9 ml, 84.5 mmol) was added causing initial darkening which went to light yellow after complete addition. After stirring for 15 min MeOH (15 ml) was added and the ice bath was removed. After warming to ca. 0°C the solvent was removed *in vacuo* and the residue was purified by flash chromatography (750g florisil, 4:1 hex:EtOAc) to obtain the dimethyl ketal as an oily solid which was crystallized ($Et_2O$/Hex 4:1) to a white solid (12.045g). Chromatographing the mother liquor afforded an additional 6.263g for 18.305g overall (88%, mp 84-85°C): IR ($CCl_4$) 3002, 2955, 2836, 1759, 1639, 1516, 1463, 1370, 1254, 1106, 1034 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 6H), 3.90 (s, 3H), 3.92 (s, 3H), 4.25 (s, 3H), 6.87 (d, $J$ = 8.1 Hz, 1H), 7.40 (m, 2H); $^{13}C$ NMR (300 MHz, $CDCl_3$) δ 53.70, 55.69, 55.70, 59.97, 109.66, 110.81, 115.14, 120.31, 120.80, 129.11, 148.65, 149.21, 179.21, 189.52; EIMS m/e (rel int) 294 (97), 279 (100), 263 (32), 251 (53), 235 (56), 191 (48), 178 (68), 165 (82), 149 (58); exact mass calc for $C_{15}H_{18}O_6$ = 294.1103, found 294.1121. Anal. calc 61.20 % C, 6.17 % H, found 61.38 % C, 5.97 % H.

**3,4-Bis-dimethoxyphenylcyclobutenedione (7).** 4-Bromoveratrole (8.71 ml, 60.55 mmol) was dissolved in THF (400 ml) at -78°C and *n*-BuLi (39.5 ml, 63.18 mmol, 1.6 M) was added via syringe. The solution was allowed to stir for 10 min and then added to 2,2-dimethoxy-4-(3,4-dimethoxyphenyl)-3-methoxycyclobutenone (15.48 g, 52.65 mmol) in THF (200 ml) via cannula at -78°C. The solution was stirred for 20 min and then TFAA (8.92 ml, 63.18 mmol) was added. The solution was stirred for 20 min at -78°C and then poured into a separatory funnel containing HCl (10%, 200 ml). The organic layer was separated and washed with HCl (10%, 2 X 100 ml), $H_2O$ (1 X 100 ml), brine (200ml) and then dried over $MgSO_4$. The solvent was removed and the yellow solid was washed with ether (100 ml) to obtain a yellow solid. The mother liquor was concentrated *in vacuo* to afford more compound for a total of (16.43 g, 88%, mp 216-217°C): IR ($CDCl_3$) 1779, 1762, 1596, 1500, 1355, 1267, 1149, 1022 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.99 (s, 3H), 7.00 (d, $J$ = 8.4 Hz, 1H), 7.64 (d, $J$ = 2.1 Hz, 1H), dd, $J$ = 8.4, 1.8 Hz, 1H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 56.17, 110.75, 111.26, 121.38, 122.38, 149.36, 153.34, 184.52, 196.13; CIMS (m/e) 355, 139, 112, 97, 81, 71; exact mass calc for $C_{20}H_{18}O_6$ = 354.1103, found 354.1075. Anal. calc 67.78 % C, 5.12 % H, found 67.93 % C, 5.11 % H.

**2,3-Bis-(3,4-dimethoxyphenyl)-4-(1-pyrrolo)-4-trimethylsiloxycyclobutenone (12).** *n*-Butyl lithium (4.05 ml, 6.48 mmol, 1.6 M) was added to pyrrole (436 ml, 6.36 mmol) in THF (100 ml) at -78° C. After stirring at -78° C for 25 min, the lithiopyrrole was added via cannula to a flask containing 3,4-bis-dimethoxyphenylcyclobutenedione (450 mg, 1.27 mmol) in THF (600 ml) at -78° C. After stirring for 1 h, trimethylsilyl chloride (865 ml, 6.86 mmol) was added. The reaction mixture was stirred for 3 h at -78° C and then allowed to slowly warm up to 25° C. The solution was concentrated *in vacuo* and purified by flash chromatography (silica gel, 2:1 hex : EtOAc) to give a yellow foam (525 mg, 84%): IR ($CDCl_3$) 2963, 2937, 2841, 1755, 1597, 1508, 1464, 1356, 1259, 1083 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 9 H), 3.76 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3 H),

6.18 (t, $J$ = 2.1 Hz, 2 H), 6.90 (m, 4H), 7.28 (d, $J$ = 4.5 Hz, 1H), 7.37 (d, $J$ = 1.8 Hz, 1H), 7.48 (t, $J$ = 1.5 Hz, 1H), 7.51 (t, $J$ = 1.5 Hz, 1H); $^{13}C$ NMR (300 MHz, $CDCl_3$) δ 0.55, 55.66, 55.77, 101.88, 108.78, 110.43, 110.65, 110.93, 117.98, 121.10, 121.19, 122.06, 122.83, 1465.10, 148.82, 150.33, 152.01, 168.21, 189.49; CIMS (m/e) 493, 421, 392, 371, 298, 267, 178, 113; exact mass calc for $C_{27}H_{31}NO_6Si$ = 493.1920, found 493.1878.

**6,7-Bis-(3,4-dimethoxyphenyl)-indolizine-5,8-dione (6).** 2,3-Bis-(3,4-dimethoxyphenyl)-4-(1-pyrrolo)-4-trimethylsiloxycyclobutenone (135 mg, 0.27 mmol) was dissolved in *p*-xylene (125 ml) and refluxed under $N_2$ for 2.5 h. The orange solution was allowed to cool to room temperature and then poured into a separatory funnel. The solution was washed with $FeCl_3$ (3 X 50 ml, satd soln 1:1 $H_2O$ : MeOH) and the organic layers combined. The aqueous layer was back extracted with EtOAc (3 X 50 ml), the combined organic layer was washed with brine (2 X 50 ml) and then dried over $MgSO_4$. Filtration, solvent removal and purification by flash chromatography (silica gel, 1:1 hex : EtOAc) gave the product as a red solid (101 mg, 88%) which can be crystallized from $CH_2Cl_2/Et_2O$ to give red prisms (mp = 196-198° C): IR ($CHCl_3$) 3011, 2937, 2839, 1701, 1648, 1603, 1555, 1513, 1464, 1415, 1314, 1263, 1144, 1106, 1066, 1026, 908 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.63 (s, 3 H), 3.64 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 6.47 (t, $J$ = 3.3 Hz, 1 H), 6.56 (d, $J$ = 1.8 Hz, 1H), 6.62 (s, 1H), 6.73 (d, $J$ = 1.8 Hz, 1H), 6.75 (s, 1H), 6.78 (m, 2H), 7.23 (dd, $J$ = 3.6, 1.5 Hz,1 H), 7.66 (dd, $J$ = 3.0, 1.2 Hz, 1H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 55.64, 55.70, 110.31, 110.37, 113.88, 114.38, 120.36, 123.08, 123.80, 123.99, 124.71, 125.40, 129.60, 140.31, 146.50, 148.10, 148.16, 149.20, 158.81, 174.53; EIMS m/e (rel int) 419 (100), 388 (38), 360 (3), 311 (4), 165 (5), 94 (5); exact mass calc for $C_{24}H_{21}NO_6$ = 419.1369, found 419.1349.

**8-Hydroxy-6,7-bis-(3,4-dimethoxy)-phenyl-1,2,3-trihydroindolizine-5-one (13).** 6,7-Bis-(3,4-dimethoxyphenyl)-indolizine-5,8-dione (300 mg, 0.71 mmol) was dissolved in ethanol (200 ml) and palladium on carbon catalyst (200 mg, 10% Pd/C) was added. $H_2$ was bubbled through the solution and stirred under balloon pressure for 3 h. The catalyst was filtered off to obtain a clear solution which was concentrated *in vacuo* to an oil (300 mg, 99%) which can be crystallized from $CHCl_3/Et_2O$ to obtain a light yellow solid (mp 184-185°C): IR ($CHCl_3$) 3542, 2963, 2937, 1663, 1580, 1516, 1464 cm-1; $^1H$ NMR (500 MHz, $CD_3OD$) δ 2.20 (m, 2 H), 3.13 (t, $J$ = 7.5 Hz, 2 H), 3.48 (s, 3 H), 3.49 (s, 3H), 3.66 (s, 3H), 3.68 (s, 3H), 4.14 (t, $J$ = 7.5 Hz, 2H), 6.48 (d, $J$ = 2.0 Hz, 1H), 6.49 (d, $J$ = 2.0 Hz, 1H), 6.55 (dd, $J$ = 8.0, 2.0 Hz, 1H), 6.61 (dd, $J$ = 8.5, 2.0 Hz, 1H), 6.67 (d, $J$ = 8.5 Hz, 1H), 6.74 (d, $J$ = 8.5 Hz, 1H); $^{13}C$ NMR (500 MHz, $CD_3OD$) δ 22.48, 30.00, 51.55, 56.37, 56.43, 112.20, 115.74, 116.61, 124.35, 125.16, 129.01,137.15, 148.02, 149.27, 149.62, 149.84, 149.99, 160.33; CIMS (m/e) 424, 257, 229, 146, 132; exact mass calc for $C_{24}H_{25}NO_6$ = 423.1682, found 423.1659 Anal. calc C, 68.06; H, 5.95; N, 3.31; found C, 68.21; H, 5.83; N, 3.21.

**6,7-Bis-(3,4-dimethoxyphenyl)-1,2,3-trihydro-8-trifluoromethylsulfonyl-indolizine-5-one (14).** 8-Hydroxy-6,7-bis-(3,4-dimethoxy)-

phenyl-1,2,3-trihydroindolizine-5-one (150 mg, 0.35 mmol) was dissolved in pyridine (3 ml) at 0°C under $N_2$. Trifluoromethanesulfonic anhydride (72 µl, 0.42 mmol) was added dropwise via syringe and the solution was stirred at 0°C for 3 h. The reaction mixture was poured into a separatory funnel containing EtOAc (25 ml), $Et_2O$ (25 ml) and HCl (10%, 25 ml). The aqueous layer was removed and the organic layer washed with HCl (10%, 25 ml), $H_2O$ (25 ml) and brine (25 ml) and then dried over $MgSO_4$. Solvent removal and purification by flash chromatography (silica gel, 98:2 $CHCl_3$:MeOH) gave the product as a yellow foam (148 mg, 76%): IR ($CHCl_3$) 3007, 1651, 1598, 1518, 1464, 1415, 1260, 1224, 1027 cm-1; $^1H$ NMR (500 MHz, $CDCl_3$) δ 2.32 (m, 2 H), 3.35 (t, $J$ = 7.5 Hz, 2 H), 3.62 (s, 3 H), 3.64 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 4.29 (t, $J$ = 7.0 Hz, 2H), 6.52 (s, 1H), 6.59 (s, 1H), 6.70 (m, 4H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 21.35, 30.65, 50.21, 55.56, 55.63, 55.67, 55.72, 110.39, 113.51, 114.04, 116.58, 119.14, 121.69, 122.94, 123.48, 125.09, 126.89, 129.21, 142.79, 145.05, 147.94, 148.41, 148.99, 159.80; CIMS (m/e) 556, 135, 123; exact mass calc for $C_{25}H_{24}NO_8SF_3$ = 555.1175, found 555.1180.

**6,7-Bis-(3,4-dimethoxyphenyl)-1,2,3-trihydroindolizine-5-one (15).** 6,7-Bis-(3,4-dimethoxyphenyl)-1,2,3-trihydro-8-trifluoromethylsulfonyl-indolizine-5-one (590 mg, 1.06 mmol) was dissolved in DMF (3 ml) and charged with palladium (II) acetate (36 mg, 0.16 mmol), 1,3-bis(diphenylphosphino)propane (72 mg, 0.17 mmol), triethyl amine (1.47 ml, 10.6 mmol) and formic acid (98%, 400 µl, 10.6 mmol) and heated to 90°C under $N_2$ for 3 h. After cooling it was extracted with brine and EtOAc, dried over $MgSO_4$ and chromatographed (silica gel, 95:5 $CHCl_3$:MeOH) to obtain the product as a light yellow solid (390 mg, 90%) which can be recrystallized from EtOAc/$Et_2O$ (mp = 198.5-200°C): IR ($CHCl_3$) 3005, 2963, 1641, 1587, 1515, 1465, 1257, 1138, 1027 cm-1; $^1H$ NMR (500 MHz, $CDCl_3$) δ 2.24 (m, 2 H), 3.15 (t, $J$ = 8.0 Hz, 2 H), 3.56 (s, 3 H), 3.67 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.21 (t, $J$ = 6.5 Hz, 2H), 6.27 (s, 1H), 6.54 (s, 1H), 6.73 (m, 5H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 21.48, 31.81, 49.07, 55.68, 55.79, 55.82(overlap), 103.51, 110.79, 110.92, 112.92, 114.92, 121.28, 123.90, 125.95, 128.72, 132.65, 147.85, 147.98, 148.32, 148.37, 148.55, 150.01, 161.50; EIMS m/e (rel int) 392(10), 406(36), 407(100); exact mass calc for $C_{24}H_{25}NO_5$ = 407.1732, found 407.1730

**(±) Septicine (5).** A suspension of $AlCl_3$ (20 mg, 0.15 mmol) in THF (50 ml) was added via cannula to a suspension of $LiAlH_4$ (8 mg, 0.2 mmol) in THF (50 ml) both at 0°C. After stirring for 5 min at 0°C the ice was removed for 15 min and then replaced. 6,7-Bis-(3,4-dimethoxyphenyl)-1,2,3-trihydroindolizine-5-one (25 mg, 6.14 x $10^{-5}$ mol) in THF (50 ml) was then added via cannula slowly with evolution of gas. The ice was removed and it was allowed to stir at rt for 1 h. The flask was equipped with reflux condenser and then refluxed under $N_2$ for 9 h. The light greenish-yellow solution was cooled to 0°C and then EtOH (1 ml) was added very slowly to quench the excess reagent. The reaction mixture was then poured onto ice and NaOH (10%) was added to raise the pH to >12. Extraction with $CHCl_3$, washing with Rochelle's salt, drying over $K_2CO_3$ and solvent removal gave a yellowish-green oil which was purified by column chromatography (silica gel, 98:2 $CHCl_3$:MeOH) to give an oil wich solidified on standing (16.2 mg, 68%). Recrystallization in EtOH

overnight at -15°C gave fine white needles (mp = 136-137°C, lit (nat) [7g] 135-136 and (racemic)[7b] 137-138°C); CIMS m/e (rel int): 396(100); EIMS (m/e): 395($M^+$), 326(M-$C_4H_4N$). Exact mass calc for $C_{24}H_{29}NO_4$ = 395.2096, found 395.2091. The $^1H$ NMR is in accord with the reported spectral data.[7b,c]

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