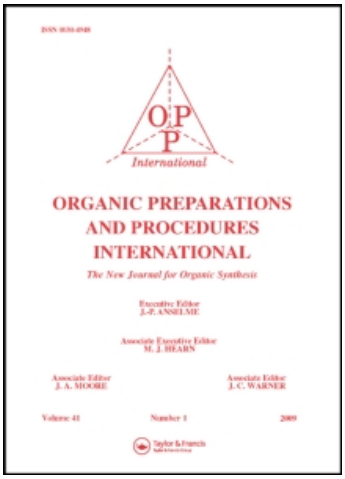

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A CONVENIENT PREPARATION OF DIBENZO[a,e]CYCLOOCTATRIENE USING FRIEDEL-CRAFTS INTRAMOLECULAR ACYLATION†

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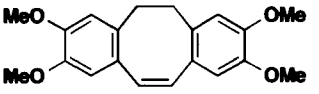
A large number of natural alkaloids, which possess a dibenzocyclooctadiene ring system, such as pavine (**1a**)[1] and argenonine (**1b**),[2] have shown potent and varied biological activity.[3]

1

a) R = H; b) R = Me



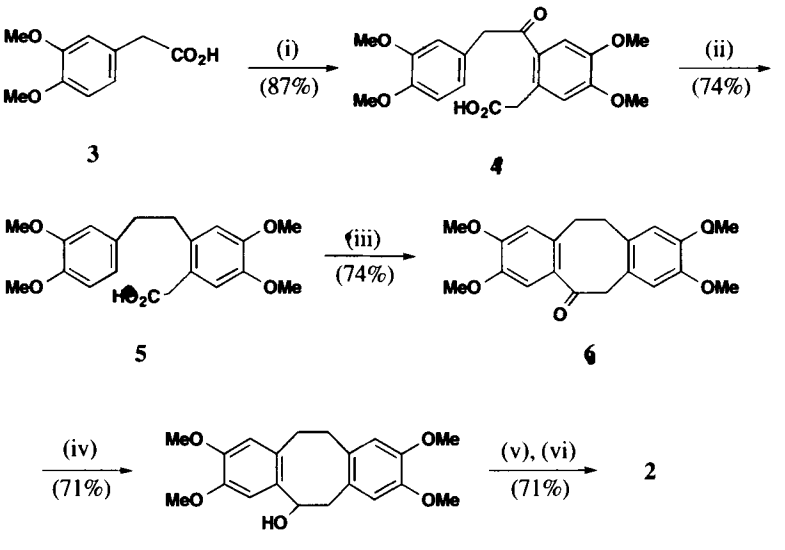
2

Although the preparation of key intermediates, dibenzocyclooctadiene and dibenzocyclooctatetraene derivatives for these compounds, has been described by several workers,[4-6] there are few reports of synthetic approaches to construct the above basic structures *via* Friedel-Crafts intramolecular acylation.[5,6] We now report the preparation of 2,3,8,9-tetramethoxy-5,6-dihydrodibenzo[*a,e*]cyclooctatriene (**2**) in five steps from readily available homoveratric acid by intramolecular Friedel-Crafts acylation followed by reduction and dehydration of alcohol **7**.

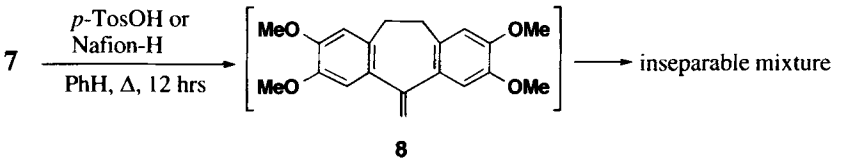
Self-condensation of homoveratric acid (**3**) catalyzed by polyphosphoric acid (PPA) carried out at 90-95° for 30 min according to a modification of the reported procedure[7] gave (2-homo- veratroyl-4,5-dimethoxyphenyl)acetic acid (**4**) in 87% yield. Clemmensen reduction of **4** afforded the desired product (**5**) in 74% yield. The attempted Friedel-Crafts intramolecular acylation of **5**, carried out under various conditions in the presence of protic or Lewis acids, such as perfluorinated sulfonic acid resin (Nafion-H),[8] $TiCl_4$, and $AlCl_3$, failed. However, treatment of **5** with PPA at 105-110° for 2 hrs resulted in intramolecular acylation to give the ketone derivative **6** in 74% yield. Reduction of **6** with sodium borohydride in ethanol at reflux gave the corresponding alcohol **7**. Attempted dehydration of **7** in benzene under reflux in the presence of *p*-toluenesulfonic acid or Nafion-H failed, only an inseparable mixture was obtained. Michael *et al.* reported the rearrangement of dibenzocyclooctatrienyl systems to substituted methyl- dibenzoheptatrienyl systems.[6] Thus, it is possible that the same rearrangement might occur to form *exo*-methylenedibenzocycloheptadiene (**8**), which would further polymerize in acid.

Consequently, alcohol **7** was dehydrated by thermolysis of the corresponding *N*-*p*-tosylcarbamate[6] formed from **7** and *p*-tosyl isocyanate to furnish the desired dibenzocyclooctatriene **2** in 70%

yield. Studies of the properties and chemical behavior of **2** are currently under investigation.



i) PPA, 90-95°, 0.5 hr; *ii*) Zn (Hg)/HCl/toluene, reflux, 6 hrs;
iii) PPA, 105-110°, 2 hrs; *iv*) $NaBH_4$/EtOH, reflux, 1 hr;
v) p-tosyl isocyanate/diglyme, room temp., 1 hr; *vi*) reflux, 16 hrs



EXPERIMENTAL SECTION

All melting points are uncorrected. ^{1}NMR spectra were recorded on a Nippon Denshi JEOL FT-270 NMR spectrometer in $CDCl_3$ with TMS as an internal reference. IR spectra were measured as KBr pellets or as liquid films on NaCl plates in a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct inlet system. Commercial polyphosphoric acid was used.

Preparation of (2-Homoveratryl-4,5-dimethoxyphenyl)acetic Acid (4).- A mixture of homoveratric acid (4.0 g, 20 mmol) and polyphosphoric acid (40 g) was heated at 90-95° while stirring by hand. After 30 min., the reaction mixture was quenched with cold water (100 mL). The mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the extract was washed with water (2 x 100 mL), dried (Na_2SO_4) and concentrated at reduced pressure to leave a pale brown solid, which was washed with hot hexane (3 x 10 mL) to give **4** (3.3 g, 87%) as a pale brown powder, mp. 133-134°, lit.[7] mp. 152-

153°. NMR ($CDCl_3$): δ 3.79 (2 H, s), 3.82 (3 H, s), 3.85 (3 H, s), 3.88 (3 H, s), 3.93 (3 H, s), 4.19 (2 H, s), 6.75-6.82 (4 H, m), 7.37 (1 H, s). Although the different melting point from the reference was observed, product **4** was used for the following reaction without further purification.

Clemmensen Reduction of 4 to 5.- A suspension of zinc (13.5 g, 0.21 mol) and $HgCl_2$ (1.35 g, 5 mmol) in conc. HCl (0.68 mL) and water (22.5 mL) was stirred at room temperature. After decantation of the reaction mixture, water (8.5 mL), conc. HCl (20 mL), toluene (12 mL) and **4** (3g, 8.32 mmol) was added and the reaction mixture was refluxed for 6 hrs. The mixture was extracted with ether (3 x 100 mL) and the extract was washed with water (2 x 100 mL), dried (Na_2SO_4) and concentrated at reduced pressure to afford **5** (2.21 g, 74%) as a pale brown solid. Crystallization from hexane gave **5** as a pale brown prisms, mp. 92-94°. NMR ($CDCl_3$): δ 2.70-2.90 (4 H, m), 3.51 (3 H, s), 3.80 (3 H, s), 3.81 (3 H, s), 3.85 (6 H, s), 6.60 (1 H, s), 6.61 (1 H, s), 6.67 (1 H, dd, J = 2.0, 8.3 Hz), 6.71 (1 H, s), 6.77 (1 H, d, J = 8.3 Hz); mass spectrum: *m/e* 360 (M^+).

Anal. Calcd. for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.80; H, 6.89

Preparation of 2,3,8,9-Tetramethoxydibenzo[a,e]cyclooctene-5-one (6).- A mixture of **5** (500 mg, 1.46 mmol) and polyphosphoric acid (5 g) was heated at 105° while stirring by hand. After 2h, the reaction mixture was quenched with cold water (50 mL). The mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the extract was washed with water (2 X 30 mL), dried (Na_2SO_4) and concentrated at reduced pressure to leave a pale brown solid. Crystallization from hexane-benzene (1:1, v/v) gave **6** (370 mg, 74%) as a pale brown prisms, mp. 167-170°. IR (KBr): 1661 cm^{-1} (C=O); NMR ($CDCl_3$): δ 3.18-3.36 (4 H, m), 3.77 (3 H, s), 3.79 (3 H, s), 3.83 (3 H, s), 3.89 (3 H, s), 4.12 (2 H, s), 6.49 (1 H, s), 6.58 (1 H, s), 6.61 (1 H, s), 7.15 (1 H, s); mass spectrum: *m/e* 342 (M^+).

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.08; H, 6.29

Reduction of 5-Hydroxy-2,3,8,9-tetramethoxydibenzo[a,e]cyclooctene (7).- To a solution of **6** (500 mg, 1.46 mmol) in EtOH (7.5 mL) was gradually added $NaBH_4$ (500 mg, 13.2 mmol) and the mixture was refluxed for 1 hr. The reaction mixture was quenched with ice-water. The mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the extract was washed with water (2 x 30 mL), dried (Na_2SO_4) and concentrated at reduced pressure to leave a residue as a pale brown solid. Crystallization from benzene gave **7** (356.6 mg, 71%) as pale yellow prisms, mp. 176-178°. IR (KBr): 3487 cm^{-1} (OH); NMR ($CDCl_3$): δ 2.00 (1 H, broad s), 2.86-3.44 (6 H, m), 3.76 (3 H, s), 3.79 (3 H, s), 3.80 (6 H, s), 5.17 (1 H, t, J = 8.0 Hz), 6.45 (1 H, s), 6.49 (1 H, s), 6.51 (1 H, s), 6.77 (1 H, s); mass spectrum: *m/e* 344 (M^+).

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.80; H, 7.09

Preparation of 2,3,8,9-tetramethoxy-5,6-dihydrodibenzo[a,e]cyclooctatriene (2).- A solution of **7** (100 mg, 0.29 mmol) and *p*-tosyl isocyanate (969 mg, 0.35 mmol) in dry diglyme (5 mL) was stirred at room temperature for 1 hr under nitrogen. After the reaction mixture had been refluxed for 16 hrs, it was extracted with CH_2Cl_2 (3 x 20 mL). The extract was washed with water (2 x 10 mL), dried (Na_2SO_4) and concentrated at reduced pressure to leave a residue. The residue was subjected to silica-gel (Wako, C-300; 100 g) column chromatography using as eluent $CHCl_3$ to give a pale brown solid.

Crystallization from hexane:benzene 1:1 (v/v) afforded **2** (68 mg, 71%) as pale brown prisms, mp. 156.5-158°. NMR ($CDCl_3$) : δ 3.14 (4 H, s), 3.81 (6 H, s), 3.85 (6 H, s), 6.59 (2 H, s), 6.60 (2 H, s), 6.64 (2 H, s); mass spectrum: *m/e* 326 (M^+).

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.6; H, 6.79. Found: C, 73.8; H, 7.09

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