SYNTHESIS OF A NATURALLY OCCURRING BENZOCYCLOBUTENE, MUSCOMOSIN

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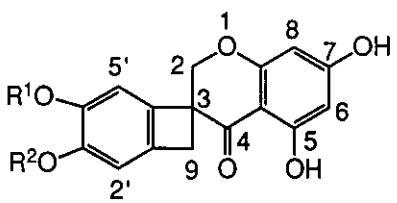
Abstract--- A naturally occurring benzocyclobutene, muscomosin (**2**) was synthesized from 1-cyanobenzocyclobutene derivative.

Although benzocyclobutene derivatives have been utilized as powerful synthons for the synthesis of various types of polycyclic compounds including natural products, the occurrence of benzocyclobutene derivatives in nature is somewhat uncommon. In 1973, the novel homoisoflavanone, scillascillin (**1**) was isolated from *Scila scilloides* Druce as the first naturally occurring benzocylobutene derivative[1] and its total synthesis was also reported by Cava in 1983.[2]

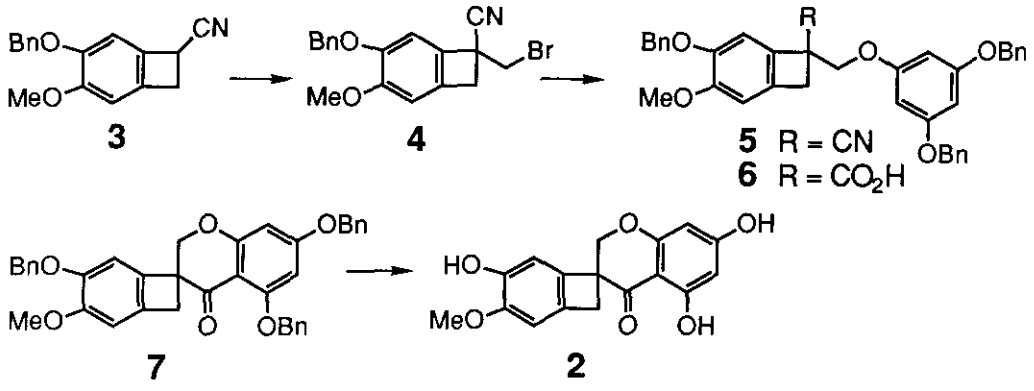


1 $R^1 + R^2 = CH_2$
2 $R^1 = H$, $R^2 = Me$

Recently a number of homoisoflavanone were isolated from *Muscari* species as additional members of natural benzocyclobutene derivatives[3] and we herein describe the synthesis of muscomosin (**2**),[3] one of this family of compounds, with the modification of Cava's procedure[2] as follows.

Alkylation of the benzocyclobutene (**3**)[4] with dibromomethane in *N,N*-dimethylformamide in the presence of sodium hydride afforded the bromide (**4**) in 95.6% yield, which on treatment with phloroglucinol dibenzyl ether[5]

and potassium carbonate in *N,N*-dimethylformamide at 100 °C gave the *O*-alkylated product (**5**) in 92.2% yield. Hydrolysis of the cyanide (**5**) was carried out in the usual manner to provide the carboxylic acid (**6**) in quantitative yield. Intramolecular Friedel-Crafts acylation of the acid (**6**) was successfully achieved by treatment with trifluoroacetic anhydride[6] in toluene at room temperature to afford the desired spiro-compound (**7**) in 49% yield. Finally reductive debenzylation of the ketone (**7**) with 10% palladium-carbon under hydrogen atmosphere furnished muscomosin, whose spectroscopic data were identical with those reported.[3]



Thus we could achieve the simple synthesis of muscomosin, and this synthetic route would be applicable to the synthesis of other homoisoflavanone derivatives.

EXPERIMENTAL SECTION

Mps were measured with a Yanagimoto MP apparatus and are uncorrected. Ir spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H-Nmr spectra were obtained in $CDCl_3$ on a JEOL PMX GSX 270 instrument, and chemical shifts are reported in ppm on the δ scale from internal Me_4Si. Mass spectra were measured with a JEOL JMS D-300 spectrometer.

4-Benzyloxy-7-bromomethyl-7-cyano-3-methoxybicyclo[4.2.0]octa-1,3,5-triene (**3**) --- Sodium hydride (60% in oil)(136 mg, 3.4 mmol) was added to a stirred solution of the benzocyclobutene (**3**)(300 mg, 1.13 mmol) in dry DMF (5 ml) at 0 °C, and the mixture was further stirred for 0.5 h at ambient temperature. To the solution was added dibromomethane (0.4 ml, 5.65 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 16 h. The mixture was poured into ice-cooled water and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and concentrated to leave a residue, which was purified by column chromatography on silica gel using hexane-AcOEt (4 : 1, v/v) as eluant to afford the bromide (**4**)(387 mg, 95.6%)

as colorless crystals, mp 140-141 °C; ir($CHCl_3$) 2250 cm^{-1}; ^{1}H-nmr($CDCl_3$)δ 3.32(1H, d, J=13.4 Hz, 8-H), 3.69(2H, s, CH_2Br), 3.75(1H, d, J=13.4 Hz, 8-H), 3.87(3H, s, OMe), 5.06, 5.11(each 1H, each d, J=13.0 Hz, O*CH*$_2$Ph), 6.76(1H, s, ArH), 6.92(1H, s, ArH), 6.26-7.46(5H, m, Ph); *m/z* 357(M^+)(Found 357.0365. $C_{18}H_{16}NO_2Br$ requires 357.0365). Anal. Calcd for $C_{18}H_{16}NO_2Br$: C, 60.45; H, 4.50; N, 3.69. Found: C, 60.34; H, 4.50; N, 3.91.

4-Benzyloxy-7-[(3,5-dibenzyloxyphenyl)oxy]methyl-7-cyano-3-methoxybicyclo[4.2.0]octa-1,3,5-triene (5) --- To a stirred mixture of phloroglucinol dibenzyl ether (14 mg, 0.372 mmol) and potassium carbonate (103 mg, 0.744 mmol) in dry DMF (1 ml) was added the bromide (**4**)(133 mg, 0.372 mmol) and the resulting mixture was heated at 100 °C for 15 h. After the mixture was cooled to room temperature, the insoluble material was filtered off and the filtrate was diluted with water and extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (4 : 1, v/v) gave the ether (**5**)(200 mg, 92.2%) as colorless needles, mp 107-109 °C; ir($CHCl_3$) 2250 cm^{-1}; ^{1}H-nmr($CDCl_3$)δ 3.35(1H, d, J=13.4 Hz, 8-H), 3.70(1H, d, J=13.4 Hz, 8-H), 3.87(3H, s, OMe), 4.19(2H, s, *CH*$_2$OAr), 5.00(4H, s, 2×O*CH*$_2$Ph), 5.08(2H, s, O*CH*$_2$Ph), 6.19(2H, d, J=1.8 Hz, ArH), 6.28(1H, t, J=1.8 Hz, ArH), 6.76(1H, s, ArH), 6.86(1H, s, ArH), 7.26-7.45(15H, m, 3×Ph); *m/z* 583(M^+)(Found 583.2363. $C_{38}H_{33}NO_5$ requires 583.2358).

4-Benzyloxy-7-[(3,5-dibenzyloxyphenyl)oxy]methyl-7-carboxyl-3-methoxybicyclo[4.2.0]-octa-1,3,5-triene (6) --- A mixture of the cyanide (**5**)(300 mg, 0.515 mmol) and potassium carbonate (116 mg, 2.06 mmol) in EtOH (3 ml) and water (3 ml) was refluxed for 48 h. Evaporation of the solvent gave a residue, which was dissolved in water. After acidified with 10% HCl, the mixture was extracted with AcOEt and the extract was washed with brine, dried over Na_2SO_4 and concentrated to give a residue, which was purified by column chromatography on silica gel. Elution with hexane-AcOEt (3 : 2, v/v) afforded the acid (**6**)(310 mg, 100%) as colorless amorphous powder; ir($CHCl_3$) 3450, 1720 cm^{-1}; ^{1}H-nmr($CDCl_3$)δ 3.17(1H, d, J=14.0 Hz, 8-H), 3.67(1H, d, 13.4 Hz, 8-H), 3.80(3H, s, OMe), 4.28, 4.38(each 1H, each d, J=9.1 Hz, CH_2O), 4.93(4H, s, 2×O*CH*$_2$Ph), 5.00, 5.03(each 1H, each d, J=12.2 Hz, O*CH*$_2$Ph), 6.19(1H, d, J=1.8 Hz, ArH), 6.23(1H, t, J=1.8 Hz, ArH), 6.73(1H, s, ArH), 6.88(1H, s, ArH), 7.25-7.42(15H, m, 3×Ph), 11.0(1H, br s, CO_2H). Anal. Calcd for $C_{38}H_{34}O_7 \cdot 0.1H_2O$: C, 75.73; H, 5.69. Found: C, 75.50; H, 5.70.

Tribenzylmuscomosin (7) --- A mixture of the acid (**6**)(260 mg, 0.432 mmol) and trifluoroacetic anhydride (0.61 ml, 4.32 mmol) in dry toluene (3 ml) was stirred at ambient temperature for 16 h. The mixture was poured into water and extracted with AcOEt. The extract was washed with saturated aqueous $NaHCO_3$ and brine and

dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (4 : 1, v/v) afforded tribenzylmuscomosin (**7**)(124 mg, 49%) as a pale yellow oil; ir($CHCl_3$) 1680 cm^{-1}; ^{1}H-nmr($CDCl_3$)δ 2.97(1H, d, J=13.4 Hz, 9-H), 3.67(1H, d, J=13.4 Hz, 9-H), 3.84(3H, s, OMe), 4.51(1H, d, J=11.0 Hz, 2-H), 4.55(1H, d, J=11.0 Hz, 2-H), 5.00, 5.03(each 1H, each d, J=11.6 Hz, OCH_2Ph), 5.08(2H, s, OCH_2Ph), 5.11(2H, s, OCH_2Ph), 6.22(1H, d, J=2.4 Hz, 6- or 8-H), 6.26(1H, d, J=2.4 Hz, 6- or 8-H), 6.69(1H, s, 2'-H), 6.80(1H, s, 5'-H), 7.24-7.56(15H, m, 3×Ph); *m/z* 584(M^+) (Found: 584.2192. $C_{38}H_{32}O_6$ requires 584.2197).

Muscomosin (2) --- A solution of the ketone (**7**)(100 mg, 0.171 mmol) in dry THF (5 ml) in the presence of 10% Pd-C (50 mg) under an atmosphere of hydrogen was stirred for 10 h at room temperature. After removal of the insoluble material by filtration, the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (7 : 3, v/v) provided muscomosin (**2**)(51 mg, 94.9%) as colorless crystals, mp 204-205 °C; ir($CHCl_3$) 1730 cm^{-1}; ^{1}H-nmr($CDCl_3$)δ 3.06(1H, d, J=13.4 Hz, 9-H), 3.59(1H, d, J=13.4 Hz, 9-H), 3.87(3H, s, OMe), 4.51(1H, d, J=11.3 Hz, 2-H), 4.58(1H, d, J=11.3 Hz, 2-H), 5.73(1H, br s, OH), 5.97(1H, d, J=2.1 Hz, 6- or 8-H), 5.99(1H, d, J=2.1 Hz, 6- or 8-H), 6.20-6.40(1H, br s, OH), 6.69(1H, s, 5'-H), 6.76(1H, s, 2'-H), 12.08(1H, s, 5-OH); *m/z* 314(M^+) (Found: 314.0784. $C_{17}H_{14}O_6$ requires 314.0789). Anal. Calcd for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49. Found: C, 64.51; H, 4.53.

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Received, 24th October, 1991