Synthesis of a Simple (±)-Dibenzocyclooctadiene Lignan, (±)-Normethylgomisin A

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(±)-Normethylgomisin A (3) was synthesized by the samarium-Barbier reaction of the phenylpropene 4 and the phenylacetone 5 to give the butanol 6, followed by oxidative aryl–aryl coupling reaction of the butanol.

Keywords synthesis; lignan; (±)-normethylgomisin A; samarium-Barbier reaction; oxidative aryl–aryl coupling reaction

Synthesis of dibenzocyclooctadiene lignans, constituents of the fruits of *Schizandra chinesis* BAILLON, is of interest not only because of their unique structure, but also because of their significant biological activities,[1] in particular, significant antihepatotoxic activity against liver injuries induced by various chemicals.[2] Although we reported syntheses of dibenzocyclooctadiene (DBCO) lignans, (±)-schizandrin (**1a**), (±)-gomisin A (**1b**), (±)-isoschizandrin (**2a**), (±)-isogomisin A (**2b**) and related stereoisomers, utilizing the samarium-Grignard and the samarium-Barbier reactions in the preceding papers,[3,4] there are practical difficulties in those syntheses with respect to chemical yield and stereochemical control. We wished to synthesize a normethyl derivative such as **3** for bological investigation.

The key intermediate **6** for the present synthesis was prepared by the samarium-Barbier reaction of the phenylethylene **4** with the phenylacetone **5** using SmI_2 in the presence of (HMPA) and *tert*-BuOH in tetrahydrofuran (THF) in a yield of 90%.[4] The butanol **6** transformed to the isobutyrate **7**, which was oxidized with reagent systems based on $Fe(ClO_4)_3$ to give the aryl–aryl coupling prod-

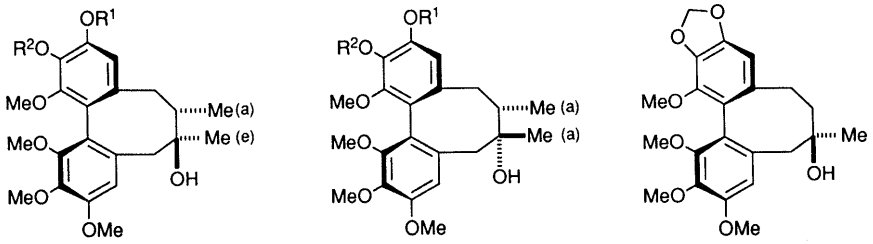


Chart 1

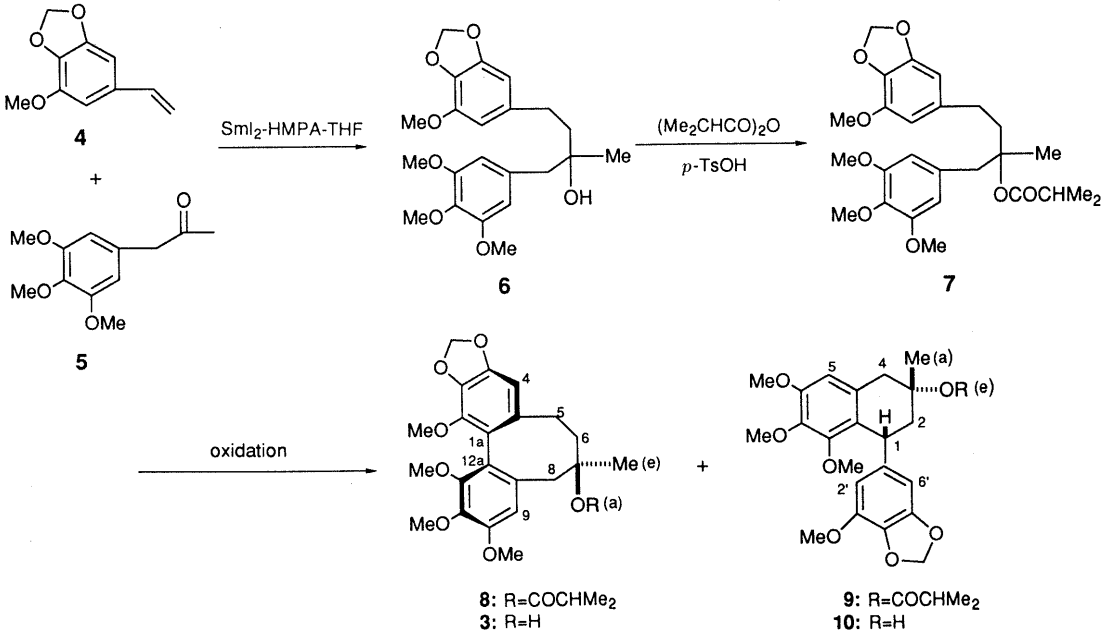


Chart 2

duct. Oxidation of **7** with the reagent system $Fe(ClO_4)_3 \cdot 9H_2O$–CH_2Cl_2–MeCN gave the aryl–aryl coupling product **8** and a 1-aryltetralin **9** in a total yield of 34%. Alkaline hydrolysis of **8** and **9** afforded the desired normethyl derivative **3**, mp 148—149 °C, and a 1-aryltetralin **10** in yields of 83.4 and 9.4%, in the ratios of 9 : 1, respectively. The product yields of **8** and **9** were increased to 64% when reaction was carried out with the same reagent system in the presence of CF_3CO_2H, but the product ratios of **3** and **10** were 74.5% and 18.4%, respectively.

The structures of **3** and **10** were elucidated by means of ^{1}H-NMR and ^{1}H-nuclear Overhauser effect (^{1}H-NOE) experiments. The aryl–aryl coupling position of **3** was confirmed to be between C(1a) and C(12a) by the observations that when the signal of C(9)-H at δ 6.57 was irradiated, a 14.9% increment of the C(10)-OMe signal was observed, but irradiation of C(4)-H at δ 6.45 had no influence on any of the aromatic-OMe signal. The stereochemistry of **3** was also revealed by the following ^{1}H-NOE results. Namely, (a) upon irradiation of the signal of C(9)-H at δ 6.57, 7.3% and 5.6% increments of the signals of C(8)-αH and C(7)-OH, respectively, were observed, but irradiation of C(7)-Me had no influence, (b) upon irradiation of the signal of C(4)-H at δ 6.45, the signal of C(5)-βH was increased 4.3%, (c) upon irradiation of the signal of C(6)-αH at δ 1.45, a 4.3% increment of the signal of C(4)-H was obsereved, (d) the dihedral angle between C(5)-βH and C(6)-αH may be about 90° because the coupling constant between these two protons was 0 Hz, and the dihedral angle between C(5)-αH and C(6)-αH may be about 180° because the coupling constant between these two protons was 13 Hz. Thus, the DBCO ring of **3** is considered to have a twist-boat-chair form and the conformation of the C(7)-Me group may be equatorial as shown in Chart 3.

Finally, the structure of the tetralin **10** was also elucidated by analysis of the a ^{1}H-NMR data and a ^{1}H-NOE experiment (Chart 3). Namely, (a) upon irradiation of the signal of C(5)-H at δ 6.25, 10.2% and 4.0% increments of the signals of C(6)-OMe and C(4)-βH, respectively, were observed, (b) upon irradiation of the signal of C(2′)-H at δ 6.46, 11.4% and 7.4% increments of the signals of C(3′)-OMe and C(1)-βH were observed, (c) upon irradiation of the signal of C(4)-βH at δ 2.58, a 6.1% increment of the signal of C(5)-H was observed. These analyses imply that the structure of the 1-aryltetralin **10** may be represented as shown in Chart 3.

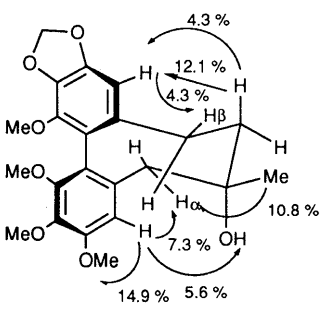
Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IR-700 spectrometer, and ^{1}H- and ^{13}C-NMR spectra with JEOL JNM-EX90, JNM-GX270 and JNM-GSX500 spectrometers with tetramethylsilane as an internal standard ($CDCl_3$ and C_6D_6 solution). Mass spectra were recorded on a JEOL JMS-D300 spectrometer. Elemental analyses were done with a Yanaco CHN-MT-3. Wako Silica gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254} were used for column chromatography and thin-layer chromatography (TLC), respectively. Organic extract were dried over Na_2SO_4.

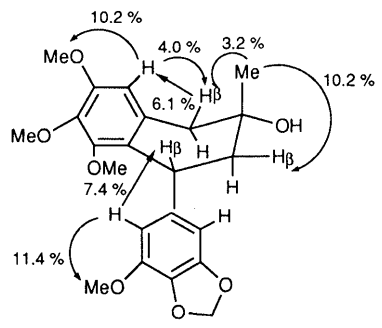
3-Methoxy-4,5-methylenedioxystyrene (4) A 0.1 M solution of 15% *n*-BuLi (6 ml) was added under a nitrogen atmosphere to a cooled solution of methyltriphenylphosphonium iodide (2.42 g, 6 mmol) in THF (100 ml). Then, a solution of 3-methoxy-4,5-methylenedioxybenzaldehyde (900 mg, 5 mmol) in THF (100 ml) was added slowly and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel column chromatography. The eluate with hexane–$CHCl_3$ (3 : 1, v/v) gave 712 mg (80%) of **4**, as a colorless oil. IR (neat): 1634 and 1617 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.91 (3H, s, Ar-OMe), 5.05—5.75 (3H, m, olefinic-H), 5.96 (2H, s, OCH_2O), 6.64 (1H, d, J = 1.4 Hz, Ar-H), 6.54 (1H, d, J = 1.4 Hz, Ar-H). MS *m/z*: 178 (M^+).

4-(3-Methoxy-4,5-methylenedioxyphenyl)-2-methyl-1-(3,4,5-trimethoxyphenyl)-2-butanol (6) A solution of the styrene **4** (712 mg, 4 mmol) and the ketone **5** (224 mg, 1 mmol) in dry THF (2 ml) and *tert*-BuOH (0.2 ml) was added over 1—2 min to a 0.1 M solution of SmI_2 in THF (20 ml)[6] and HMPA (4 ml). The reaction mixture was stirred at 25°C for 5 min, then the reaction was quenched with 0.5 N HCl (6 ml) and the whole was extracted with hexane–ether (1 : 1). The organic extracts were combined and washed with H_2O, and brine. The organic layer was dried and concentrated. The residue was subjected to silica gel column chromatography using CH_3CO_2Et–hexane (1 : 2, v/v) to give 364 mg (90%) of **6** as an oil. IR (neat): 3450, 1628, 1598 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, s, C2-Me), 1.69 (1H, br s, C2-OH), 1.72—1.85 (2H, m, C3-H), 2.67—2.77 (2H, m, C4-H), 2.69 (1H, d, J = 13.4 Hz, C1-H), 2.79 (1H, d, J = 13.4 Hz, C1-H), 3.85 (9H, s, 3 × Ar-OMe), 3.88 (3H, s, Ar-OMe), 5.93 (2H, s, OCH_2O), 6.36 (1H, d, J = 2.2 Hz, Ar-H), 6.39 (1H, d, J = 2.2 Hz, Ar-H), 6.44 (2H, s, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 30.6 (C4), 30.9 (C2-Me), 44.0 (C3), 48.5 (C1), 56.1, 56.2, 56.6 and 60.8 (each Ar-OMe), 72.2 (C2), 101.2 (OCH_2O), 102.3, 107.5, 107.6, 132.6, 136.8, 137.0, 143.5, 148.8 and 153.0 (each Ar-C). MS *m/z*: 404 (M^+).

2-Isopropylcarbonyloxy-4-(3-methoxy-4,5-methylenedioxyphenyl)-2-methyl-1-(3,4,5-trimethoxyphenyl)butane (7) *p*-Toluenesulfonic acid (400 mg) was added to a solution of the *erythro*-butanol **6** (808 mg, 2 mmol) in isobutyric anhydride (15 ml), and the mixture was stirred at room temperature for 1.5 h, then poured into ice-water and extracted with ether. The ether layer washed with saturated $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel column chromatography. The eluate with CH_3CO_2Et–hexane (1 : 3, v/v) gave 891 mg (94%) of **7** as an oil. IR (neat): 1712, 1613 and 1588 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, d, J = 7.0 Hz, $CHMe_2$), 1.16 (3H, d, J = 7.0 Hz, $CHMe_2$), 1.24 (3H, s, C2-Me), 1.65 (1H, br s, C2-OH), 1.72—



3



10

Chart 3. ^{1}H-NOE Data for Synthetic Lignans **3** and **10** in C_6D_6

1.85 (2H, m, C4-H), 1.95—2.79 (5H, m, C3-H, C4-H and –CHMe$_2$), 2.78 (1H, d, J=13.7 Hz, C1-H), 3.21 (1H, d, J=13.7 Hz, C1-H), 3.82 (6H, s, 2×Ar-OMe), 3.83 (3H, s, Ar-OMe), 3.88 (3H, s, Ar-OMe), 5.92 (2H, s, OCH$_2$O), 6.31 (1H, s, Ar-H), 6.36 (1H, s, Ar-H), 6.41 (2H, s, Ar-H), ^{13}C-NMR (CDCl$_3$) δ: 19.2 (–COCHMe$_2$), 23.9 (C2-Me), 30.3 (C4), 35.1 (–COCH), 40.4 (C3), 44.8 (C1), 56.1, 56.6 and 60.9 (each Ar-OMe), 83.5 (C2), 101.2 (OCH$_2$O), 102.4, 107.5, 107.8, 132.6, 136.5, 143.5, 148.8 and 152.7 (each Ar-C), 176.6 (–COCH). MS m/z: 474 (M$^+$).

Oxidation of 7 with Fe(ClO$_4$)$_3$·9H$_2$O–CH$_2$Cl$_2$–MeCN and Hydrolysis of the Coupling Products A solution of the ester **7** (190 mg, 0.4 mmol) in dry MeCN (1 ml) was CH_2Cl_2 (1 ml) was added to a solution of Fe(ClO$_4$)$_3$·9H$_2$O (516 mg, 1 mmol) in dry MeCN (3 ml) and CH_2Cl_2 (3 ml), and the whole was stirred at room temperature for 1 min. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The eluate with CH_3CO_2Et–hexane–$CHCl_3$ (2:20:1, v/v) gave 65 mg (34.4%) of a mixture of **8** and **9**. A solution of the above mixture (65 mg) in 10% alcoholic KOH (20 ml) was refluxed for 24 h. The reaction mixture was poured into ice-water, acidified with aqueous 10% HCl and then extracted with chloroform. The organic layer was washed with H_2O, dried and concentrated. The residue was subjected to silica gel column chromatography. The first eluate with CH_3CO_2Et–$CHCl_3$ (1:2, v/v) gave 46 mg (83.4%) of 5,6,7,8-tetrahydro-7-hydroxy-1,10,11,12-tetramethoxy-7-methyl-2,3-methylenedioxydibenzo[*a*,*c*]cyclooctene (**3**) as colorless crystals ($CHCl_3$–ether–hexane), mp 148—149 °C. IR (KBr): 3566, 1614, 1591 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.28 (3H, s, C7-Me), 1.57 (1H, dd, J=13.0, 14.3 Hz, C6-αH), 1.89 (1H, br s, C7-OH), 2.00 (1H, dd, J=7.9, 14.3 Hz, C6-βH), 2.18 (1H, t, J=13.0 Hz, C5-αH), 2.40 (1H, dd, J=7.9, 13.0 Hz, C5-αH), 2.57 (2H, s, C8-H), 3.60, 3.86, 3.90 and 3.91 (12H, each s, 4×Ar-OMe), 5.95 and 5.96 (each 1H, d, J=1.5 Hz, OCH$_2$O), 6.48 (1H, s, C4-H), 6.65 (1H, s, C9-H). ^{1}H-NMR (C_6D_6) δ: 1.18 (3H, s, C7-Me), 1.45 (1H, dd, J=13.0, 14.3 Hz, C6-αH), 1.65 (1H, br s, C7-OH), 1.87 (1H, dd, J=7.9, 14.3 Hz, C6-βH), 2.15–2.33 (1H, m, C5-αH), 2.15–2.33 (1H, m, C5-βH), 2.48 (1H, dd, J=1.3, 13.1 Hz, C8-αH), 2.63 (1H, d, J=13.1 Hz, C8-βH), 3.37, 3.60, 3.87 and 3.88 (12H, each s, Ar-OMe), 5.28 and 5.34 (each 1H, d, J=1.5 Hz, OCH$_2$O), 6.45 (1H, s, C4-H), 6.57 (1H, s, C9-H). ^{13}C-NMR (CDCl$_3$) δ: 27.9 (C5), 32.2 (C7-Me), 44.4 (C8), 44.9 (C6), 56.0, 59.6, 60.6 and 60.9 (each Ar-OMe), 68.7 (C7), 100.8 (OCH$_2$O), 103.0, 110.2, 121.2, 124.1, 131.2, 134.7, 137.4, 140.7, 140.9, 148.9, 152.0 and 152.4 (each Ar-C). *Anal.* Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.71; H, 6.69. MS m/z: 402 (M$^+$).

The second eluate gave 5 mg (9.4%) of *c*-3-hydroxy-6,7,8-trimethoxy-*r*-1-(3-methoxy-4,5-methylenedioxyphenyl)-*t*-3-methyltetralin (**10**) as colorless oil. IR (neat): 3566, 1614 and 1591 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.24 (3H, s, C3-Me), 1.60—1.71 (1H, m, C2-βH), 1.67 (1H, s, C3-OH), 1.93 (1H, dd, J=7.3, 13.5 Hz, C2-αH), 2.74 (1H, d, J=15.8 Hz, C4-βH), 2.96 (1H, d, J=15.8 Hz, C4-αH), 3.37, 3.78, 3.83 and 3.87 (12H, each s, 4×Ar-OMe), 4.17 (1H, t, J=7.9 Hz, C1-H), 5.90 (2H, s, OCH$_2$O), 6.28 (1H, d, J=1.5 Hz, C6′-H), 6.30 (1H, d, J=1.5 Hz, C2′-H), 6.43 (1H, s, C5-H). ^{1}H-NMR (C_6D_6) δ: 1.12 (3H, s, C3-Me), 1.23 (1H, s, C3-OH), 1.86 (1H, dd, J=7.9, 13.1 Hz, C2-βH), 2.01 (1H, ddd, J=2.1, 7.9, 13.1 Hz, C2-αH), 2.58 (1H, dd, J=2.1, 15.8 Hz, C4-βH), 2.89 (1H, d, J=15.8 Hz, C4-αH), 3.37, 3.42, 3.46 and 3.68 (12H, each s, 4×Ar-OMe), 4.24 (1H, t, J=7.9 Hz, C1-H), 5.32 and 5.33 (each 1H, d, J=1.5 Hz, OCH$_2$O), 6.25 (1H, s, C5-H), 6.46 (1H, d, J=1.5 Hz, C2′-H), 6.50 (1H, d, J=1.5 Hz, C6′-H). ^{13}C-NMR (CDCl$_3$) δ: 27.4 (C3-Me), 40.7 (C1), 44.6 (C2 or C4), 46.9 (C2 or C4), 55.8, 56.6, 59.9 and 60.6 (each Ar-OMe), 70.1 (C3), 101.2 (OCH$_2$O), 101.6 (C5), 106.7 (C2′ or C6′), 107.4 (C2′ or C6′), 123.0, 131.7, 133.7, 140.7, 143.4, 148.8, 152.0 and 152.5 (each Ar-C). MS m/z: 402 (M$^+$).

Oxidation of 7 with Fe(ClO$_4$)$_3$·9H$_2$O–CF$_3$CO$_2$H–CH$_2$Cl$_2$–MeCN and Hydrolysis of the Coupling Products A solution of **7** (190 mg, 0.4 mmol) in dry MeCN (1 ml) and CH_2Cl_2 (1 ml) was added to a solution of Fe(ClO$_4$)$_3$·9H$_2$O (516 mg, 1 mmol) in dry MeCN (3 ml), CH_2Cl_2 (3 ml), and CF_3CO_2H (3 ml), and the whole was stirred at room temperature for 1 min. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with saturated aqueous NaHCO$_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel column chromatography to give 121 mg (64%) of a mixture of **8** and **9**. The above mixture (121 mg) was hydrolyzed and worked up as described above to give 77 mg (74.8%) of **3**, and 19 mg (18.4%) of **10**.

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