Photoinduced Molecular Transformations. 158. A Total Synthesis of (±)-Methyl Piperitol: An Unsymmetrically Substituted 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane Lignan[1]

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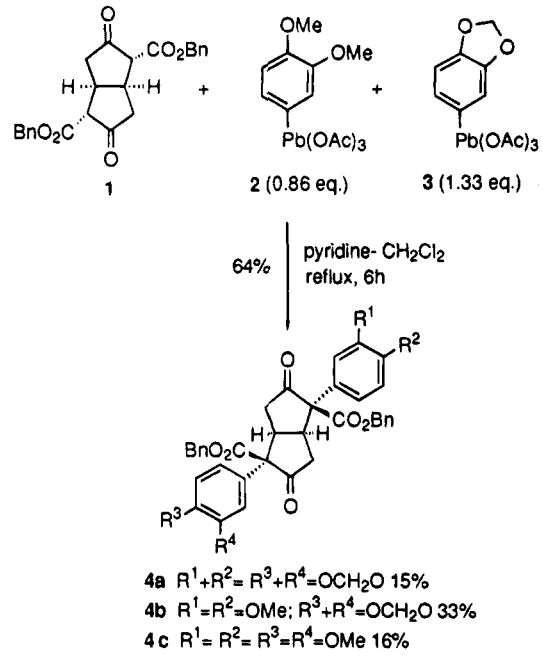
In the previous parts of this series of papers,[1-3] we have reported that a variety of molecules including natural products can be synthesized by several new reaction processes involving the selective β-scission of alkoxyl radicals generated by the photolysis of the hypoiodites of the corresponding alcohols as the key steps.

The 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes comprise one of the largest groups of lignans to which many biologically-active natural products belong.[4] As part of the project, we recently reported new total syntheses of naturally-occurring symmetrically substituted 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignans, (±)-sesamin and (±)-eudesmin, and the first total synthesis of (±)-yangambin according to a general method for replacing a carbonyl group of a cyclopentanone ring by an oxygen atom to give the corresponding tetrahydrofuran ring involving a regioselective β-scission of alkoxyl radicals.[1]

In this paper, we report a new total synthesis of (±)-methyl piperitol **10**, a representative *unsymmetrically* substituted 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignan according to the same route as previously reported for the symmetrically substituted lignans.[1] (+)-Methyl piperitol was isolated from Helichrysum bracteatum[5] by Höke and Hansel in 1972,[5a] and its racemic form was isolated by Pelter and colleagues in 1976.[5b] Although lignans possessing the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]-octane structure have been synthesized by a variety of methods,[6] only limited synthetic methods for *unsymmetrically* substituted lignans have been available. The total synthesis of (±)-methyl piperitol was first reported by Pelter and colleagues,[7a] and recently Iwasaki and colleagues[7b] reported its stereocontrolled synthesis.

Scheme 1



4a $R^1+R^2=R^3+R^4=OCH_2O$ 15%
4b $R^1=R^2=OMe$; $R^3+R^4=OCH_2O$ 33%
4c $R^1=R^2=R^3=R^4=OMe$ 16%

Results and Discussion

Schemes 1–3 outline the sequence of our synthesis of (±)-methyl piperitol. Thus, a preliminary experiment on the mixed arylation of dibenzyl 3,7-dioxobicyclo[3.3.0]-octane-2,6-dicarboxylate (**1**) with 1.1 equivalents of (3,4-dimethoxyphenyl)lead triacetate (**2**) and [3,4-(methylenedioxy)phenyl]lead triacetate (**3**) in dry CH_2Cl_2 in the presence of pyridine under ultrasonication (according to a modified procedure of Pinhey[8]) gave a 0.46:1:0.72 mixture of 2,6-dibenzyl 2,6-diaryl-3,7-dioxobicyclo[3.3.0]-octane-2,6-dicarboxylates **4a–c** (Scheme 1). This arylation indicated that aryllead triacetate **2** is more reactive than aryllead triacetate **3**. Thus, arylation of dibezyl ester with adjusted quantities of aryllead triacetates **2** (0.86 equiv) and **3** (1.33 equiv) under the above-mentioned conditions gave an enhanced yield of unsymmetrically arylated product **4b** (33%) with accompanying formation of symmetrically arylated products **4a** (15%) and **4c** (16%) in the ratio of 1:0.43:0.49.

Hydrogenolysis of crystalline 2,6-dibenzyl 2-(3,4-dimethoxyphenyl)-6-[3,4-(methylendioxy)phenyl]-3,7-dioxobicyclo[3.3.0]octane-2,6-dicarboxylate (**4b**) in ethyl acetate in the presence of 10% palladium on carbon under

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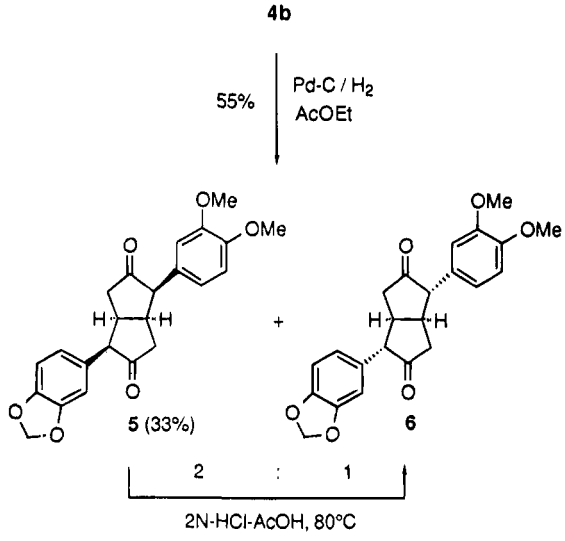
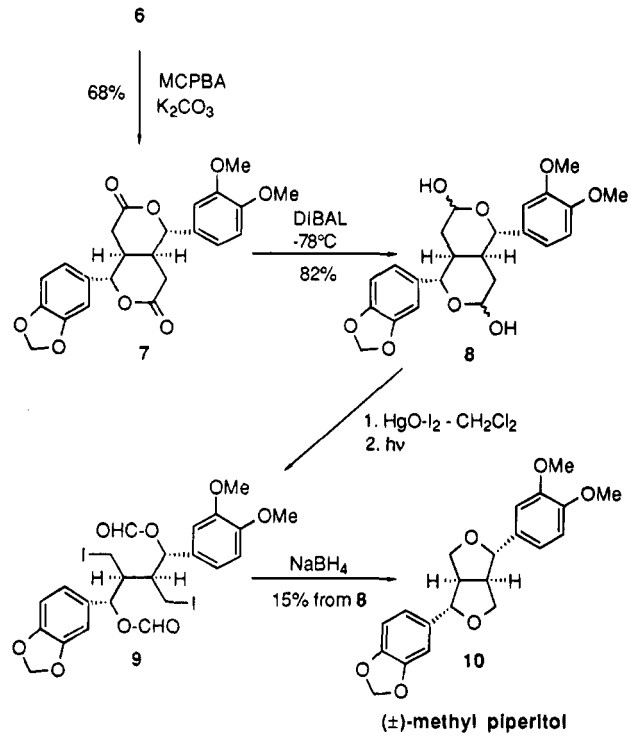
Scheme 2



hydrogen at room temperature gave a mixture of 2,6-diaryl 3,7-dioxobicyclo[3.3.0]octanes by spontaneous loss of CO_2 (Scheme 2). Analysis of the mixture by ^1H NMR spectroscopy indicated that the mixture comprised of 2β-(3,4-dimethoxyphenyl)-6β-[3,4-(methylenedioxy)phenyl]-3,7-dioxobicyclo[3.3.0]octane (**5**) and its 2α,6α-isomer in the ratio of 2:1. Recrystallization of the mixture from dichloromethane–ethanol gave the 2β,6β-isomer **5** in 33% yield. NOE measurement established the *cis* disposition of the two aryl groups attached to the 3,7-dioxobicyclo-[3.3.0]octane **5** and *trans* disposition of aryl groups and the angular hydrogens of the bicyclooctane **5**; irradiation of the signals at δ 3.38 (1α- and 5α-H) resulted in an enhancement of the signal area at δ 3.92 (2α- and 6α-H). The reason for the predominant formation of the sterically more crowded 2β,6β-isomer **5** in this palladium-catalyzed hydrogenolysis is obscure. We found that this kinetically controlled formation of the less stable isomer **5** took place when fresh and more active palladium catalyst was used.[9] Heating of a solution of the mixture of the 2β,6β-isomer **5** and the 2α,6α-isomer **6** obtained by hydrogenolysis in a mixture of glacial acetic acid and 2 N HCl solution at 80 °C for 30 min gave the 2α,6α-isomer **6** in 90% yield (55% crystals) while the attempted isomerization of the mixture in 5% sodium hydroxide solution–methanol at room temperature or at reflux temperature gave an intractable mixture of products.

The selective Baeyer–Villiger oxidation of the 2α,6α-isomer **6** with *m*-CPBA in the presence of K_2CO_3[10] was complete within 2 h and gave the δ-lactone **7** in 68% yield while similar oxidation in the presence of $NaHCO_3$[11] took 56 h for completion and gave the δ-lactone **7** in 55% yield (Scheme 3). We also tried to prepare the δ-lactone corresponding to the 2β,6β-isomer **5** by Baeyer–Villiger oxidation. No δ-lactone, however, was obtained under the conditions mentioned above.

Scheme 3



The reduction of δ-lactone **7** with DIBAL in CH_2Cl_2 at −78 °C for 2 h gave crystalline dilactol **8** in 82% yield The dilactol **8** in CH_2Cl_2 was treated *in situ* with mercury(II) oxide and iodine (6 equiv), and the solution of the resulting hypoiodite was irradiated with Pyrex-filtered light generated by a 100-W high pressure mercury arc for 5 h (according to the general procedure for the β-scission reaction of alkoxyl radicals[2]) to give an oily iodo formate **9**. Subsequent heating of a solution of **9** and $NaBH_4$ in MeOH under reflux for 2 h gave (±)-methyl piperitol (**10**) which was identical with an authentic specimen[7b] (^1H NMR, IR, mp, and mixed mp). The yield of **10** (15%) from **8** was not as high as those in the corresponding processes in the synthesis of the lignans reported in the previous paper.[1] The modest yield of **10** from **8** is mainly due to the inefficient cyclization of **9**.

The advantage of this new synthetic route to 2,6-diaryl 3,7-dioxabicyclo[3.3.0]octane lignans compared to the several existing synthetic methods was discussed in the previous paper.[1] As described in the previous paper,[1] the present method provided a versatile and relatively short step synthesis of *symmetrically* substituted 2,6-diaryl 3,7-dioxabicyclo[3.3.0]octane lignans from easily accessible starting material without using strong acid or base. The synthesis reported in this paper revealed that our general method is also applicable to the synthesis of *unsymmetrically* substituted lignans under mild conditions even though the arylation step gives a statistical mixture of intermediates **4a–c** in modest yields.

Experimental Section

General Method. For descriptions of the instruments and general experimental procedures, see ref 1.

Dibenzyl 3,7-Dioxobicyclo[3.3.0]octane-2,6-dicarboxylate (1). This compound was prepared by transesterification of the corresponding dimethyl ester with benzyl alcohol in the presence of DMAP as described in the previous paper.[1]

2,6-Dibenzyl 2-(3,4-Dimethoxyphenyl)-6-[(3,4-methylenedioxy)phenyl]-3,7-dioxobicyclo[3.3.0]octane-2,6-dicarboxylate (4b). A mixture of dibenzyl 3,7-dioxobicyclo[3.3.0]-

(9) Similar 1:2 stereoisomeric mixture of α,α- and β,β-2,6-bis(3,4-dimethoxyphenyl)-3,7-dioxobicyclo[3.3.0]octanes was obtained when 2,6-[bis(3,4-dimethoxyphenyl)-3,7-dioxobicyclo[3.3.0]octane-2,6-dicarboxylate (an intermediate to (±)-eudesmin[1]) was subjected to hydrogenolysis with this fresh and active 10% Pd catalyst. The results are contrasted to those[1] concerning the hydrogenolysis of the 2,6-dicarboxylate with Pd–C, in which the α,α-2,6-bis(3,4-dimethoxyphenyl)-3,7-dioxobicyclo[3.3.0]octane was formed exclusively.

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octane-2,6-dicarboxylate (**1**) (2.542 g, 6.3 mmol), freshly prepared from (3,4-dimethoxyphenyl)lead triacetate (**2**) (2.794 g, 5.4 mmol), and [3,4-(methylenedioxy)phenyl]lead triacetate (**3**) (4.255 g, 8.4 mmol) in dry CH_2Cl_2 (160 mL) containing dry pyridine (1.095 g, 13.8 mmol) was heated under reflux for 6 h in an atmosphere of N_2 in an ultrasonic cleaner. The mixture was diluted with CH_2Cl_2 (200 mL), washed with 3 N H_2SO_4 solution (100 mL), 5% $NaHCO_3$ solution (100 mL × 2), and water (200 mL × 2), and dried (Na_2SO_4). Evaporation of the solvent gave an oil (4.90 g), which was subjected to preparative TLC on silica gel (7:1 benzene–diethyl ether) to give five fractions. Fraction 1 (R_f 0.67, 644 mg, 1.0 mmol) was 2,6-dibenzyl 2,6-bis[3,4-(methylenedioxy)phenyl]-3,7-dioxobicyclo[3.3.0]octane-2,6-dicarboxylate (**4a**) (594 mg), mp 148–150 °C, (from CH_2Cl_2–EtOH) identical with authentic sample. Fraction 2 (R_f 0.61, 61 mg) was unidentified material. Fraction 3 (R_f 0.55, 1.569 g, 2.4 mmol, 44%) was 2,6-dibenzyl 2-(3,4-dimethoxyphenyl)-6-[3,4-(methylenedioxy)phenyl]-3,7-dioxobicyclo[3.3.0]octane-2,6-dicarboxylate (**4b**) (1.383 g): mp 90–92 °C (from CH_2Cl_2–EtOH) as colorless crystals. IR ($CHCl_3$) 1764, 1726, 1610, 1590, 1240 cm^{-1}; ^1H NMR (270 MHz) δ 2.27(1H, dd, J = 17.9, 9.6 Hz), 2.29 (1H, dd, J = 22.1, 9.2 Hz), 2.71 (1H, dd, J = 20.1, 9.9 Hz), 2.74 (1H, dd, J = 20.1, 10.2 Hz), 3.49 (2H, m), 3.77, 3.90 (each 3H, s), 5.04, 5.14 (each 1H, AB type J = 12.2 Hz), 5.05, 5.10 (each 1H, AB type J = 12.5 Hz), 5.99, 6.00 (each 1H, AB type, J = 1.3 Hz), 6.75–6.95 (6H, m), and 7.13–7.35 (10H, m); EI-MS *m/z* (relative intensity) 662 (M^+, 4.2), 571 [$(M - CH_2C_6H_5)^+$, 1.6], for $C_{39}H_{34}O_{10}$: C, 70.68; H, 5.17. Found: C, 70.67; H, 5.02. Fraction 4 (R_f 0.47, 66 mg) was unidentified material. Fraction 5 (R_f 0.38, 767 mg, 1.1 mmol) was 2,6-dibenzyl 2,6-bis(3,4-dimethoxyphenyl)-3,7-dioxobicyclo[3.3.0]octane-2,6-dicarboxylate (**4c**) (683 mg), mp 183.5–185.5 °C (from CH_2Cl_2–EtOH) (authentic sample, mp 188–189 °C).

2β-(3,4-Dimethoxyphenyl)-6β-[3,4-(methylenedioxy)phenyl]-3,7-dioxobicyclo[3.3.0]octane (5). A suspension of the above dibenzyl ester **4b** (993 mg, 1.5 mmol) and 10% Pd–C catalyst (155 mg) in AcOEt (180 mL) was stirred under hydrogen at room temperature for 1 h. The catalyst was removed by suction filtration through a Celite pad. Evaporation of the solvent from the filtrate gave a colorless solid (646 mg, 1:2 mixture of **6** and **5**). Addition of CH_2Cl_2–EtOH to it gave a crystalline β,β-diaryl diketone (227.4 mg), which contained 3% of the α,α- isomer (^1H NMR analysis). Its recrystallization from the same solvents gave β,β-diaryl diketone **5** (196 mg, 0.50 mmol, 33%): mp 179–180 °C (from CH_2Cl_2–EtOH); IR 1733 cm^{-1}; ^1H NMR (270 MHz) δ 2.05 (2H, dd, J = 19.6, 9.9 Hz), 2.38 (2H, dd, J = 19.6, 9.9 Hz), 3.38 (2H, m), 3.89 (6H, s),3.92 (2H, d, J = 6.6 Hz), 5.96 (2H, s), 6.65–6.88 (6H, m); EI-MS *m/z* (relative intensity) 394 (M^+, 100), 177 (76.8). Irradiation of the signals at δ 3.38 (1α- and 5α-H) resulted in an NOE enhancement of the signal areas at δ 3.92 (2α- and 6α-H). Anal. Calcd for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62. Found: C, 69.84; H, 5.61.

2α-(3,4-Dimethoxyphenyl)-6α-[3,4-(methylenedioxy)phenyl]-3,7-dioxobicyclo-[3.3.0]octane (6). The crude β,β-diphenyl diketone (561 mg, 1:2 mixture of **6** and **5**) was dissolved in a mixture of AcOH (130 mL) and 2 N HCl solution (50 mL), and the solution was heated at 80 °C for 30 min. The mixture was poured into water (300 mL), and the resultant mixture was extracted with CH_2Cl_2 (100 mL × 4). The combined extracts were washed successively with water (200 mL), 2.5% $NaHCO_3$ solution, and water (200 mL × 2) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a dark green oil (506 mg), which crystallized by adding EtOH to give α,α-diphenyl isomer (329 mg, 0.71 mmol, 55%), mp 192–193 °C. Its recrystallization from CH_2Cl_2–EtOH gave an analytical sample: mp 192.5–193 °C; IR 1731 cm^{-1}; ^1H NMR (270 MHz) δ 2.72 (2H, d, J =19.5 Hz), 2.75 (2H, dd, J =19.5, 3.3 Hz), 3.14 (2H, s), 3.15 (2H, d, J = 3.3 Hz), 3.88 (6H, s), 5.97 (2H, s), 6.60–6.90 (6H, m); EI-MS *m/z* (relative intensity) 394 (M^+, 97.6), 177 (100%). Anal. Calcd for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62. Found: C, 69.85; H, 5.58.

2α-(3,4-Dimethoxyphenyl)-7α-[3,4-(methylenedioxy)phenyl]-3,8-dioxabicyclo[4.4.0]decane-4,9-dione (7). A suspension of 2α-(3,4-dimethoxyphenyl)-6α-[3,4-(methylenedioxy)phenyl]-3,8-dioxobicyclo[3.3.0]octane (13.7 mg, 0.034 mmol), *m*-CPBA (59.4 mg, 0.275 mmol, 80%), and powdered K_2CO_3 (47.6 mg, 0.344 mmol) in CH_2Cl_2 (3.4 mL) was stirred at room temperature for 2 h and was filtered through a Celite pad. The filtrate was washed with aqueous 5% $Na_2S_2O_3$ (10 mL) and 5% $NaHCO_3$ solutions and water (10 mL × 2) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a solid (13.4 mg), which was recrystallized from CH_2Cl_2–EtOH to give dilactone **7** (10.0 mg, 0.023 mmol, 68%): mp 240.5–242 °C; IR 1736 cm^{-1}; ^1H NMR (400 MHz) δ 2.26 (2H, dd, J = 14.9, 6.6 Hz) and 2.37 (2H, dd, J =14.9, 11.2 Hz), 2.69 (2H, m), 3.91 (6H, s), 4.97 (2H, dd, J = 9.6, 7.9 Hz), 6.02 (2H, s), 6.76–6.92 (6H, m); EI-MS *m/z* (relative intensity) 426 (M^+, 80.8), 44 (100). Anal. Calcd for $C_{23}H_{22}O_8$: C, 63.49; H, 5.14. Found: C, 63.78; H, 5.20.

An attempted Baeyer–Villiger oxidation of β,β-diphenyl isomer under the same conditions as for the α,α-isomer did not give any corresponding dilactone, although the starting ketone was consumed. There was no signal around δ 5.0 assignable to C(2)- and C(7) protons in the ^1H NMR spectrum of the crude reaction products.

2α-(3,4-Dimethoxyphenyl)-7α-[3,4-(methylenedioxy)phenyl]-3,8-dioxabicyclo[4.4.0]decane-4,9-diol (8). To a stirred solution of dilactone **7** (21.3 mg, 0.05 mmol) in dry CH_2Cl_2 (8 mL) at −78 °C was added DIBAL (0.15 mL, 1.5 M, 0.225 mmol). The mixture was stirred for 2 h and warmed to room temperature. To the mixture was added water (5 mL), and the resultant suspension was filtered through a Celite pad. The filtrate was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a solid (21.8 mg), which was recrystallized from MeOH to give dilactol **8** (17.7 mg, 0.041 mmol, 82.3%): mp 208.5–210.5 °C; IR 3326 cm^{-1}; EI-MS *m/z* (relative intensity) 430 (M^+, 37), 262 [$(M - (MeO)_2C_6H_3CHO)^+$, 26], 167 [$(MeO)_2C_6H_3CHO$, 100%]. Anal. Calcd for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 63.88; H, 6.17.

3a,4,6,6a-Tetrahydro-1α-(3,4-dimethoxyphenyl)-4α-[3,4-(methylenedioxy)phenyl]-1*H*,3*H*-furo[3,4-*c*]furan: (±)-methyl piperitol. A stirred suspension of dilactol (**8**) (21.5 mg, 0.05 mmol), yellow HgO (65 mg, 0.30 mmol), and I_2 (76.1 mg, 0.30 mmol) in dry CH_2Cl_2 (67 mL) in a Pyrex test tube was irradiated under nitrogen with a 100-W high pressure Hg arc at room temperature for 5 h until most of the dilactol was consumed (TLC analysis). Precipitates (HgO and HgI_2) were then removed by suction filtration. The filtrate was washed with 0.5% $Na_2S_2O_3$ solution (20 mL), then water (20 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent gave an oily product (22.8 mg), whose ^1H NMR spectrum exhibited a singlet at δ 8.22 assignable to the formyl proton. The product was dissolved in MeOH (8 mL). To the solution was added $NaBH_4$ (3 mg, 0.08 mmol). The solution was stirred for 10 min at room temperature and then heated under reflux for 2 h. Evaporation of the solvent gave a product. To the product was added water (30 mL), and the mixture was extracted with CH_2Cl_2 (10 mL × 4). The solution was washed with water (20 mL) and dried over anhydrous Na_2SO_4. The oily crude product (12 mg) was purified by preparative TLC (2% MeOH–CH_2Cl_2). A band with R_f 0.42 gave (±)-methyl piperitol (**10**) (2.8 mg, 15% from the dilactol): mp 68.0–69.0 °C (from acetone–petroleum ether) [lit.[5b] mp 68–71 °C, lit.[7b] mp 69–72 °C]; ^1H NMR (270 MHz) δ 3.08 (2H, m), 3.85 (2H, m), 3.88 and 3.90 (each 3H, s), 4.26 (2H, m), 4.73 and 4.75 (each 1H, d, J = 4.3 Hz), 5.95 (2H, s), 6.79–6.90 (6H, m).

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