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Total Synthesis of Homochiral Kadsurin Having the Natural Configuration

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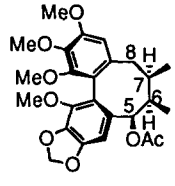
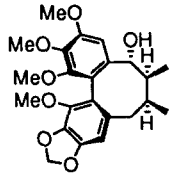
Abstract: The total synthesis of kadsurin was achieved in a stereoselective manner. The stereoselective hydrogenation of the homochiral enone (12), obtained from the known tetracyclic lactone (7), afforded known ketone (13), the conversion of which into kadsurin has already been reported.

Kadsurin (**1**) is the lignan isolated from *Kadsura japonica* Dunal (Schisandraceae), and the structure including absolute configuration has been determined by Yamamura's group in 1973.[1] Kadsurin possesses the dibenzocyclooctene skeleton which is closely related to the lignans isolated from *Schisandra chinensis* Bail (gomisin O (**2**) is shown here as a representative).[2] While the total synthesis of racemic kadsurin was achieved by Ghera in 1977,[3] synthesis of homochiral material remains to be achieved. For several years, we have been engaged in research directed at the total synthesis of dibenzocyclooctene lignans isolated from *Schisandra chinensis* and have succeeded in the establishment of the general strategy for their synthesis in homochiral form.[4] Because of the structural similarity of kadsurin with lignans isolated from *Schisandra chinensis* and the biological importance of the dibenzocyclooctene lignans with oxygen functionality on the eight membered ring,[6] we decided to investigate the stereoselective synthesis of homochiral kadsurin having the natural configuration. In this paper we describe the details of our route to homochiral kadsurin.

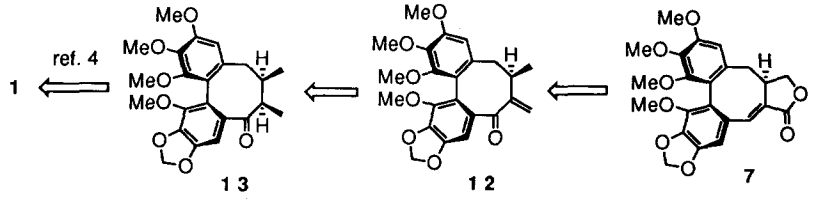


1: kadsurin



2: gomisin O

Our synthetic strategy is shown in Scheme 1. As the stereoselective reduction of ketone (**13**) followed by acetylation successfully resulted in the total synthesis of racemic kadsurin,[3] our main concern was focused on the stereoselective construction of homochiral **13** with the proper configuration. For this aim, we utilized the methodology which led to the total syntheses of homochiral lignans isolated from *Schisandra chinensis*.[4]



Scheme 1. Synthetic Strategy of **1**

The known homochiral lactone (**7**)[4c] was selected as the intermediate. By the reductive modification of α-alkylidene butyrolactone moiety, **7** was expected to afford enone (**12**), in which oxygen functionality had been introduced at C-5 position. The inspection of molecular models suggested that the most stable conformation of **12** is a twist-boat form as shown in Figure 1,[7] and hence the hydrogenation of **12** would provide the desired intermediate (**13**) by the attack of hydrogen from the α face of the molecule. Finally, the previously reported procedure[3] would result in the total synthesis of homochiral kadsurin (**1**).

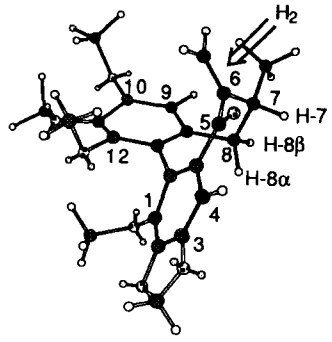
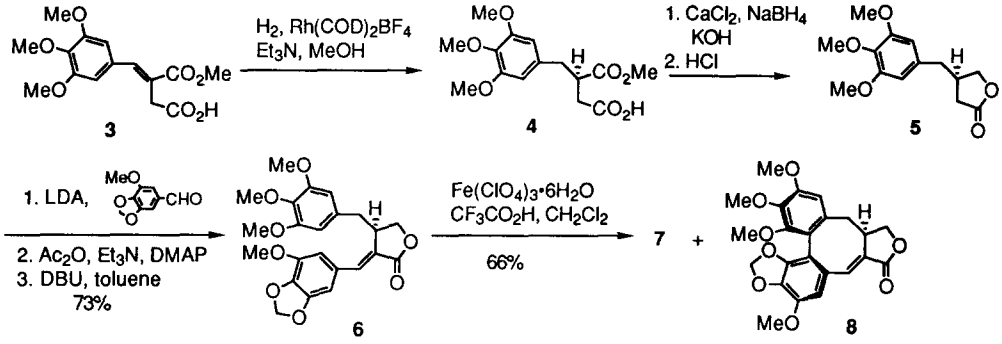


Figure 1. Expected conformation of **12** and stereochemical course of hydrogenation



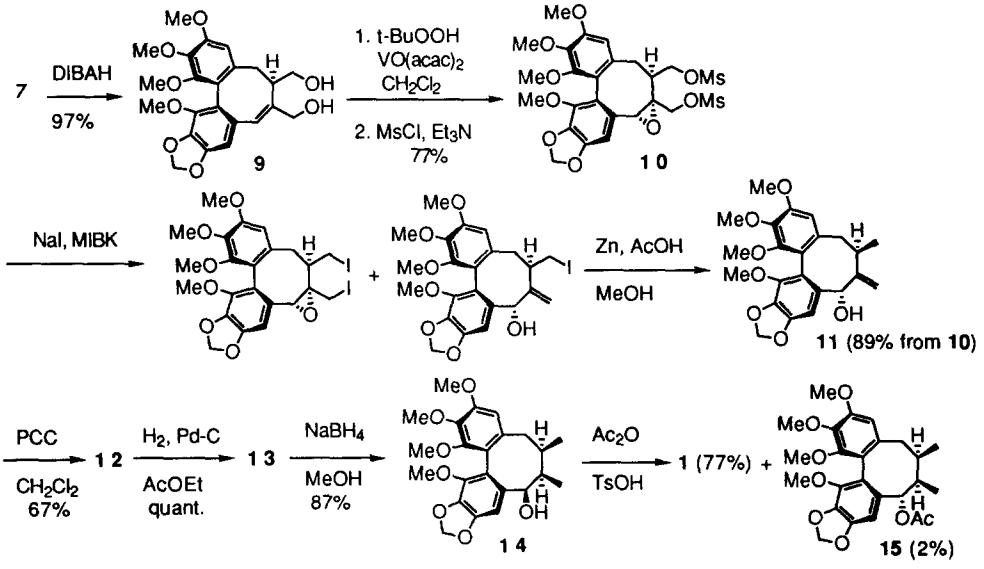
Scheme 2. Synthesis of the optically pure tetracyclic lactone (**7**)

In the event, the synthesis of kadsurin started with the preparation of the tetracyclic lactone ((+)-**7**) (Scheme 2). The homochiral butyrolactone ((+)-**5**),[4c,8] obtained by the asymmetric hydrogenation of **3**[9] and following ester reduction, was subjected to aldol condensation with 5-methoxy-3,4-methylenedioxybenzaldehyde affording (*E*)-alkylidenebutyrolactone ((-)-**6**). The iron perchlorate mediated oxidative coupling[10] of (-)-**6** proceeded in the moderate yield producing the regioisomeric mixture of (+)-**7** and **8**, in which the desired isomer ((+)-**7**) was the predominant product and could be isolated as a crystalline solid by the recrystallization.

For the transformation of (+)-**7** to enone ((-)-**12**), (+)-**7** was reduced with diisobutylaluminum hydride (DIBAH) to allylic alcohol ((+)-**9**) in 97% yield (Scheme 3). The stereoselective epoxidation of (+)-**9** with *t*-butyl hydroperoxide in the presence of vanadyl acetylacetonate followed by methanesulfonylation afforded epoxymesylate ((-)-**10**) as a single product (77%). Treatment of (-)-**10** with sodium iodide in refluxing methyl isobutyl ketone (MIBK) followed by zinc reduction afforded the single allylic alcohol ((-)-**11**) (89%) through the mixture of diiodide and oxirane ring opened monoiodide. Then the pyridinium chlorochromate (PCC) oxidation of (-)-**11** furnished the desired enone ((-)-**12**) in 45% overall yield from (+)-**7**.

Inspection of the ^{1}H-nmr spectrum of (-)-**12** in chloroform-*d* showed coupling constants of 9 Hz between H-8α and H-7, and 3 Hz between H-8β and H-7, suggesting the dihedral angles (ϕ) as follows, $\phi_{7\text{-}8\alpha}\cong30°$ and $\phi_{7\text{-}8\beta}\cong90°$. On the basis of these results, the expected conformation of (-)-**12** shown in Figure 1 was supported.

Then, the critical step of the synthesis was carried out. Palladium catalyzed hydrogenation of (-)-**12** proceeded stereoselectively affording a single product . By the comparison of the ^{1}H-nmr spectroscopic data with that reported by Ghera,[7] the product turned out to possess the desired structure ((-)-**13**) as expected from the conformational analysis of (-)-**12**. Now that the preparation of ketone ((-)-**13**) had been accomplished, the final manipulations to kadsurin were carried out by the reported sequences. The sodium borohydride reduction of (-)-**13** afforded a single product ((-)-**14**) as in the case with lithium aluminum hydride reduction.[3] Finally, acetylation of (-)-**14** with acetic anhydride in the presence of *p*-toluenesulfonic acid completed the synthesis of (-)-kadsurin (**1**) (77%) accompanied by a small amount of C-5 isomerized product (**15**) (2%). Melting point (154-156°C) and spectroscopic data (^{1}H-nmr, ^{13}C-nmr, ir, and ms) of synthetic (-)-**1** were identical with those of natural product, and the specific rotation value ($[\alpha]_D^{27}$ -26 (c=0.58, $CHCl_3$)) of synthetic **1** was close to the reported values (-39[1a] and -19.7[1b]).



Scheme 3. Total synthesis of kadsurin (**1**)

In conclusion, the synthesis of homochiral (-)-kadsurin was achieved utilizing the methodology developed for the synthesis of lignans isolated from *Schisandra chinensis*. The successful result reported here demonstrates that the methodology is useful for the synthesis of the variety of dibenzocyclooctene lignans with oxygen functionalities on the eight membered ring.

Experimental Section

(*R*)-3-(3,4,5-trimethoxybenzyl)butyrolactone (5) A solution of $Rh(COD)_2BF_4$ (66 mg, 0.16 mmol), and (*R,R*)-MOD-DIOP (133 mg, 0.18 mmol) in freshly distilled MeOH (20 ml) was stirred at room temperature for 10 min under argon, then added to a solution of **3** (23.1 g, 0.75 mole) and triethylamine (10.3 ml, 0.74 mole) in freshly distilled MeOH (120 ml). The mixture was stirred at room temperature under atmospheric pressure of hydrogen for 51 h. 0.5N NaOH solution was added, and the mixture was extracted with CH_2Cl_2. The aqueous layer was acidified with 6N HCl solution, extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, **4** was obtained as a pale yellow oil (23.1 g). To a solution of **4** (22.0 g) and KOH (85%, 4.6 g) in EtOH (150 ml), $CaCl_2$ (15.0 g) and $NaBH_4$ (10.3 g) was added, and the mixture was stirred at 0 °C for 14 h. After addition of 6N HCl solution, the mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent and recrystallization of the residue from AcOEt gave **5** as a colorless prisms (14.7 g, 74 %). m.p. 101.5-102.5 °C (colorless prisms). $[\alpha]_D^{25}$ +6.82 (c=1.07, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) 2.30 (1H, dd, J = 7, 17 Hz), 2.63 (1H, dd, J = 8, 17 Hz), 2.71 (2H, d, J = 9 Hz), 2.79-2.94 (1H, m), 3.83 (3H, s), 3.85 (6H, s), 4.05 (1H, dd, J = 6, 9 Hz), 4.36 (1H, dd, J = 7, 9 Hz), 6.36 (2H, s). IR ν_{max} (KBr) 2992, 2972, 2928, 1770, 1594 cm^{-1}. EI-MS *m/z* 266 (M^+), 181 (base). Anal Calcd for $C_{14}H_{18}O_5$; C:63.14, H:6.81. Found; C:62.93, H:6.61.

(*R*)-(*E*)-3-(3,4,5-trimethoxybenzyl)-2-(3,4-methylenedioxy-5-methoxy)butyrolactone (6) *n*-BuLi (1.63 M solution in hexane, 30 ml, 49 mmole) was added to a solution of diisopropylamine (7.0 ml, 50 mmole) in THF (100 ml) at -70°C. A solution of **5** (10.65 g, 40 mmole) in THF (100 ml) was added to this mixture, and the resultant mixture was stirred at -70°C for 30 min. To this mixture a solution of 5-methoxy-3,4-methylenedioxybenzaldehyde (9.38 g, 52 mmole) in THF (200 ml) was added, the mixture was stirred at -70°C for 20 min, and the reaction was quenched by NH_4Cl solution. AcOEt was added, the separated organic layer was washed successively with 2N HCl solution, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was taken up into CH_2Cl_2 (100 ml), acetic anhydride (10 ml, 106 mmole), triethylamine (15 ml, 107 mmole), and 4-dimethylaminopyridine (15 mg, 0.12 mmole) were added, and the resultant mixture was stirred at room temperature for 16 h. The mixture was washed successively with 2N HCl solution, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was heated with DBU (15 ml) in toluene (200 ml) at 50°C for 3 h. AcOEt was added, washed successively with 2N HCl solution, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. Solvent was evaporated, then the residue was chromatographed (silica gel, AcOEt-hexane 1:2) to give **6** as a pale yellow solid (12.5 g, 73 %). m.p. 122.5-124.5°C (pale yellow prisms from AcOEt-hexane). $[\alpha]_D^{24}$ -121 (c=0.945, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) 2.62 (1H, dd, J = 10, 14 Hz), 3.00 (1H, dd, J = 4.0, 14 Hz), 3.69-3.80 (1H, m), 3.81 (3H, s), 3.86 (3H, s), 4.29 (1H, dd, J

= 2.0, 12 Hz), 4.31 (1H, d, J = 6.0 Hz), 6.04 (2H, s), 6.42 (2H, s), 6.75 (1H, d, J = 1.2 Hz), 6.82 (1H, d, J = 1.2 Hz), 7.48 (1H, d, J = 2.0 Hz). IR ν_{max} (KBr) 2980, 2940, 1750, 1636, 1604 cm^{-1}. EI-MS *m/z* 428 (M^+), 181 (base). Anal. Calcd for $C_{22}H_{20}O_8$; C: 64.48, H: 5.65. Found; C: 64.34, H: 5.69.

(3a*R*,*S*-Biar)-3a,4-Dihydro-6,7,8,9-tetramethoxy-10,11-methylenedioxydibenzo[4,5:6,7]-cycloocta[1,2-c]furan-1(3H)-one (7) A mixture of **6** (1.01 g, 2.4 mmole), iron perchlorate (2.51 g, 5.4 mmole), and trifluoroacetic acid (7 ml) in CH_2Cl_2 (50 ml) was stirred at room temperature for 2 h. AcOEt was added, the mixture was washed with 2N HCl solution, water, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (silica gel, CH_2Cl_2-AcOEt 20:1) to give **7** as a colorless solid (0.67 g, 66 %). m.p. 225-235°C (dec., colorless needles from CH_2Cl_2-hexane). $[\alpha]_D^{26}$ +417 (c=0.63, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) 2.44 (1H, dd, J = 1, 14 Hz), 3.05 (1H, dd, J = 6.8, 14 Hz), 3.44-3.56 (1H, m), 3.57 (3H, s), 3.85 (3H, s), 3.88 (6H, s), 4.09 (1H, dd, J = 9, 10 Hz), 4.46 (1H, t, J = 9 Hz), 6.03 (2H, s), 6.41 (1H, s), 6.49 (1H, d, J = 0.8 Hz), 7.46 (1H, d, J=3.6 Hz). IR ν_{max} (KBr) 2932, 1742, 1672, 1618, 1478, 1222, 1108, 1080 cm^{-1}. EI-MS 426 (M^+, base). Anal. Calcd for $C_{23}H_{22}O_8$: C; 64.78, H; 5.20. Found: C; 64.53, H; 5.18

(7*R*,*S*-Biar)-7,8-Dihydro-6,7-bis(hydroxymethyl)-1,10,11,12-tetramethoxy-2,3-methylenedioxydibenzo[a,c]cyclooctene (9) To a solution of **7** (5.01 g, 11.8 mmole) in THF (150 ml) was added a solution of DIBAH (1.5 M solution in toluene, 30 ml, 45 mmole) at 0°C, the resultant mixture was stirred at 0°C for 15 min, and the reaction was quenched by the addition of $Na_2SO_4 \cdot 10H_2O$. After the mixture was stirred at room temperature for 1 h, the insoluble materials were filtered off. After evaporation of the solvent, the residue was chromatographed (silica gel, AcOEt-hexane 4:1) to give **9** as a colorless amorphous solid (4.90g, 97 %). $[\alpha]_D^{26}$ +201 (c=0.63, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) 1.94 (1H, brs), 2.47 (1H, dd, J = 6, 9 Hz), 2.77 (1H, brs), 2.88-3.04 (2H, m), 3.48 (3H, s), 3.68-3.80 (2H, m), 3.84 (3H, m), 3.87 (3H, m), 4.04 (1H, d, J = 7 Hz), 4.12 (1H, J = 7 Hz), 5.98 (1H, d, J = 1.4 Hz), 5.99 (1H, d, J = 1.4 Hz), 6.38 (1H, d, J = 0.8 Hz), 6.43 (1H, s), 6,45 (1H, s). IR ν_{max} ($CHCl_3$) 3432, 3000, 2936, 1596, 1108, 1060 cm^{-1}. EI-MS *m/z* 431 (M^++1), 430 (M^+, base). HRMS Calcd for $C_{23}H_{26}O_8$ (M^+): 430.16277 (M^+). Found: 430.16612.

(5*R*,6*R*,7*S*,*S*-Biar)-5,6-Epoxy-5,6,7,8-tetrahydro-6,7-bis(methanesulfonyloxymethyl)-1,10,11,12-tetramethoxy-2,3-methylenedixoydibenzo[a,c]cyclooctene (10) A mixture of **9** (4.72 g, 11.0 mmole), $VO(acac)_2$ (26 mg, 0.1 mmole), and *t*-BuOOH (3.0 M solution in 2,2,4-trimethylpentane, 10 ml, 30 mmole) in CH_2Cl_2 (100 ml) was stirred at room temperature for 1 h. The mixture was washed with saturated $Na_2S_2O_3$ solution and H_2O, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved into CH_2Cl_2 (50 ml), triethylamine (10 ml) and methanesulfonyl chloride (20 ml, 260 mmole) were added, and the resultant mixture was stirred at 0°C for 30 min. The mixture was washed successively with 2N HCl solution, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. The residue was chromatographed (silica gel, AcOEt-hexane 1:2) to give **10** as a colorless solid (5.07 g, 77 %). m.p. 176-178°C (colorless prisms from CH_2Cl_2-hexane). $[\alpha]_D^{25}$ -31 (c=0.54, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) 1.76-1.92 (1H, m), 2.43 (1H, dd, J = 8.3, 15 Hz), 2.99-3.12 (1H, m), 3.00 (3H, s), 3.07 (3H, s), 3.67 (1H, s), 3.68 (3H, s), 3.89 (6H, s), 3.90 (3H, s), 4.35-4,41 (4H, m), 6.02 (2H, s), 6.59 (1H,

s), 6.61 (1H, s). IR ν_{max} (KBr) 2936, 1358, 1326, 1176 cm^{-1}. EI-MS *m/z* 602 (M^+, base). HR-MS Calcd for $C_{25}H_{30}O_{13}S_2$ (M^+): 602.11279 (M^+). Found: 602.11282. Anal. Calcd for $C_{25}H_{30}O_{13}S_2 \cdot 1/2H_2O$: C; 49.09, H; 5.11. Found: C; 48.83, H; 4.92.

(5*S*,7*R*,*S*-Biar)-5,6,7,8-Tetrahydro-1,10,11,12-tetramethoxy-7-methyl-6-methylene-2,3-methylenedioxydibenzo[a,c]cycloocten-5-ol (11) A mixture of **10** (4.72 g, 7.84 mmole) and NaI (40 g, 270 mmole) in MIBK (180 ml) was refluxed for 48 h. AcOEt was added, the mixture was washed with water, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved into MeOH (100 ml) and THF (100 ml), then acetic acid (2.5 ml, 44 mmole) and Zn (5 g, 76 mmole) were added. The resultant mixture was stirred at room temperature for 86 h. AcOEt was added, the mixture was washed successively with brine, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. The residue was chromatographed (silica gel, AcOEt-hexane 1:2) to give **11** as a colorless amorphous solid (2.88 g, 89 %). $[\alpha]_D^{29}$ -165 (c=0.63, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) 1.08 (3H, d, J = 7.3 Hz), 2.44-2.58 (2H, m), 2.68-2.84 (1H, m), 3.65 (3H, s), 3.82 (3H, s), 3.89 (3H, s), 3.91 (3H, s), 4.85 (2H, s), 5.36 (1H, s), 5.95 (1H, d, J = 1.5 Hz), 5.97 (1H, d, J = 1.5 Hz), 6.53 (1H, s), 6.95 (1H, s). IR ν_{max} ($CHCl_3$) 3596, 2996, 2932, 1620, 1596 cm^{-1}. EI-MS *m/z* 414 (M^+, base). HR-MS Calcd for $C_{23}H_{26}O_7$ (M^+): 414.16785 (M^+). Found: 414.16775.

(7*R*,*S*-Biar)-7,8-Dihydro-1,10,11,12-tetramethoxy-7-methyl-6-metylene-2,3-methylenedioxydibenzo[a,c]cycloocten-5(6H)-one (12) A mixture of **11** (2.77 g, 6.69 mmole) and PCC (3.5 g) in CH_2Cl_2 (200 ml) was stirred at room temperature for 4.5 h. Additional PCC (2 g) was added, and the mixture was stirred at room temperature for 30 min. Et_2O was added to the mixture, the insoluble materials were filtered off. The filtrate was washed successively with 2N HCl solution, H_2O, saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (silica gel, AcOEt-hexane 1:2) to give **12** as a colorless solid (1.85 g, 67 %). m.p. 139.5-141°C (colorless needles from CH_2Cl_2-hexane). $[\alpha]_D^{25}$ -27 (c=0.52, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) 1.18 (3H, d, J = 7 Hz), 2.28 (1H, dd, J = 3, 13 Hz), 2.68-2.84 (1H, m), 3.12 (1H, dd, J = 9, 13 Hz), 3.45 (3H, s), 3,83 (3H, s), 3,85 (3H, s), 3.88 (3H, s), 4.87 (1H, t, J = 1.2 Hz), 5.48 (1H, s), 6.06 (1H, d, J = 1.5 Hz), 6.06 (1H, d, J = 1.5 Hz), 6.38 (1H, s), 6.97 (1H, s). IR ν_{max} (KBr) 2940, 2904, 2836, 1666, 1608 cm^{-1}. EI-MS *m/z* 412 (M^+, base). Anal. Calcd for $C_{23}H_{24}O_7$: C; 66.98, H; 5.87. Found: C; 66.87, H; 5.86.

(6*R*,7*R*,*S*-Biar)-7,8-Dihydro-1,10,11,12-tetramethoxy-6,7-dimethyl-2,3-methylenedioxydibenzo[a,c]cycloocten-5(6H)-one (13) **12** (1.19 g, 2.89 mmole) was hydrogenated over 10% Pd-C (50% wet, 57 mg) in AcOEt (100 ml) under atmospheric pressure of hydrogen at room temperature for 4.5 h. After filtration of the reaction mixture, the filtrate was concentrated to give **13** as a colorless solid (1.21 g, quant). m.p. 145-147°C (colorless prisms from CH_2Cl_2-hexane). $[\alpha]_D^{26}$ -98 (c=0.52, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) 0.82 (3H, d, J = 7 Hz), 1.05 (3H, d, J = 7 Hz), 2.24-2.40 (1H, m), 2.58 (1H, dd, J = 4, 15 Hz), 2.85 (1H, dd, J = 4, 15 Hz), 2.91 (1H, dq, J = 5, 7 Hz), 3.56 (3H, s), 3.83 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 6.01 (1H, d, J = 1.2 Hz), 6.03 (1H, d, J = 1.2 Hz), 6.35 (1H, s), 6.44 (1H, s). IR ν_{max} (KBr) 2936, 1696, 1610, 1594 cm^{-1}. EI-MS *m/z* 414 (M^+, base). HR-MS Calcd for $C_{23}H_{26}O_7$ (M^+): 414.16785 (M^+). Found: 414.16784. Anal. Calcd for $C_{23}H_{26}O_7 \cdot 1/4H_2O$: C; 65.94, H; 6.38. Found: C; 66.00, H; 6.32.

(5*R*,6*R*,7*R*,*S*-Biar)-5,6,7,8-Tetrahydro-1,10,11,12-tetramethoxy-6,7-dimethyl-2,3-methylenedioxydibenzo[a,c]cycloocten-5-ol (14) To a solution of **13** (971 mg, 2.35 mmole) in THF (20 ml) and MeOH (40 ml) was added $NaBH_4$ (3.00 g, 79 mmole) at 0°C, the resultant mixture was stirred at 0°C for 1 h, and at room temperature for 2 h. AcOEt was added, the mixture was washed water and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (silica gel, AcOEt-hexane 1:2) to give **14** as a colorless solid (846 mg, 87 %). m.p. 140-141°C (colorless prisms from CH_2Cl_2-hexane). $[\alpha]_D^{27}$ -55 (c=0.56, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) 0.94 (3H, d, J = 7 Hz), 1.16 (3H, d, J = 7 Hz), 1.91 (1H, q, J = 7 Hz), 2.02-2.16 (1H, m), 2.64 (2H, d, J = 5 Hz), 3.66 (3H, s), 3.83 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 4.62 (1H, brs), 5.97 (2H, s), 6.34 (1H, s), 6.58 (1H, s). IR ν_{max} (KBr) 3560, 2940, 2876, 1614, 1594 cm^{-1}. EI-MS *m/z* 416 (M^+, base). Anal. Calcd for $C_{23}H_{28}O_7$: C; 66.33, H; 6.78. Found: C; 66.53, H; 6.77.

(5*R*,6*R*,7*R*,*S*-Biar)-5,6,7,8-Tetrahydro-1,10,11,12-tetramethoxy-6,7-dimethyl-2,3-methylenedioxydibenzo[a,c]cycloocten-5-yl acetate (kadsurin; 1) and (5*S*,6*R*,7*R*,*S*-Biar)-5,6,7,8-Tetrahydro-1,10,11,12-tetramethoxy-6,7-dimethyl-2,3-methylenedioxydibenzo[a,c]cycloocten-5-yl acetate (15) A mixture of **14** (103 mg, 0.25 mmole) and *p*-TsOH·H_2O (9 mg, 0.05 mmole) in acetic anhydride (5 ml) was stirred at room temperature for 3 h. H_2O and AcOEt were added, the mixture was washed with saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (silica gel, AcOEt-hexane 1:3) to give **1** as a colorless solid (87 mg, 77 %) and **15** as a colorless amorphous solid (1.6 mg, 2%). **1:** m.p. 154-156°C (colorless plates from AcOEt). $[\alpha]_D^{27}$ -26 (c=0.58, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) 0.91 (3H, d, J = 7 Hz), 1.06 (3H, d, J = 7 Hz), 1.57 (3H, s), 1.97-2.08 (2H, m), 2.64 (1H, d, J = 4 Hz), 2.65 (1H, d, J = 5 Hz), 3.62 (3H, s), 3.80 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 5.64 (1H, d, J = 1.1 Hz), 5.94 (1H, d, J = 1.1 Hz), 6.46 (1H, s), 6.56 (1H, s). IR ν_{max} (KBr) 2936, 2872, 1732, 1618 cm^{-1}. EI-MS *m/z* 458 (M^+, base). Anal. Calcd for $C_{25}H_{30}O_8$: C; 65.49, H; 6.6. Found: C; 65.43, H; 6.61. **15:** ^{1}H-NMR ($CDCl_3$) 0.81 (3H, d, J = 7 Hz), 1.00 (3H, d, J = 7 Hz), 1.4-1.7 (2H, m), 2.36 (1H, dd, J = 11, 16 Hz), 2.69 (1H, dd, J = 6, 16 Hz), 3.59 (3H, s), 3.87 (3H, s), 3.87 (3H, s), 3. 89 (3H, s), 4.23 (1H, d, J = 8 Hz), 5.98 (1H, d, J = 1.5 Hz), 5.99 (1H, d, J = 1.5 Hz), 6,47 (1H, s), 6.79 (1H, s). EI-MS *m/z* 416 (M^+). HR-MS Calcd for $C_{23}H_{28}O_7$ (M^+): 416.18350 (M^+). Found: 416.18476.

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