Chiral Synthesis of Lignan Lactones, (−)-Hinokinin, (−)-Deoxypodorhizone, (−)-Isohibalactone and (−)-Savinin by Means of Enantioselective Deprotonation Strategy

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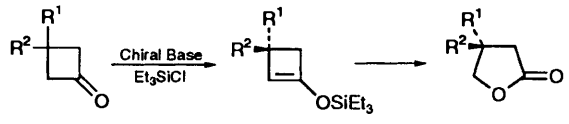
Chiral synthesis of lignan lactones, (−)-hinokinin, (−)-deoxypodorhizone, (−)-isohibalactone and (−)-savinin, has been achieved by employing an enantioselective deprotonation of 3-(3,4-methylenedioxybenzyl)cyclobutanone with lithium (*S,S'*)-α,α'-dimethyldibenzylamide, as a key step.

Chiral β-substituted γ-butyrolactones are an important class of compounds since this subunit is found in a variety of natural products, and they serve as valuable building blocks for the synthesis of various types of natural products and biologically important substances.[1] Recently we have established[2] a procedure for chiral synthesis of 3-substituted and 3,3-disubstituted γ-butyrolactones by utilizing an enantioselective deprotonation strategy,[3] in which cyclobutanones having a phenyl group at the 3-position were employed as the starting materials (Scheme 1).



Scheme 1

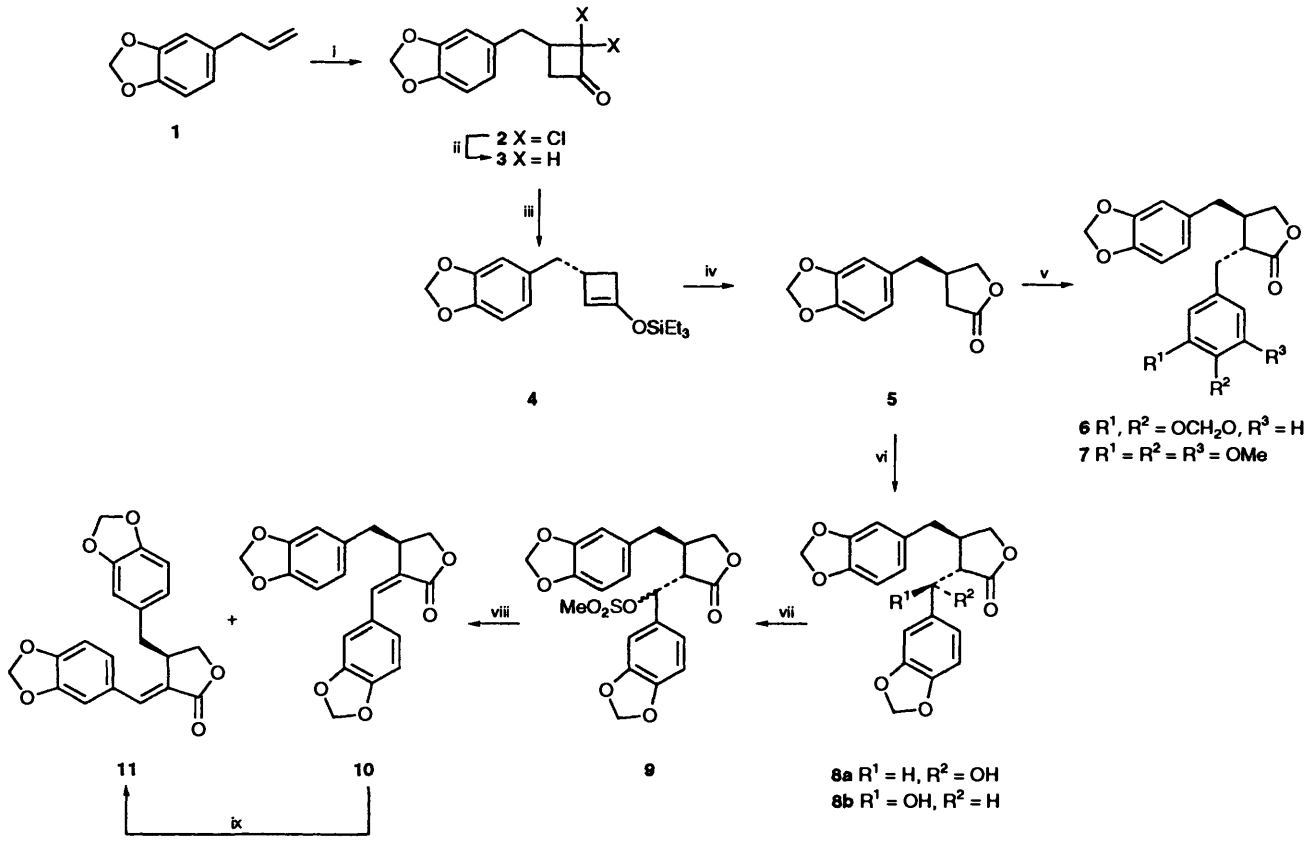
As part of an ongoing effort directed at the synthesis of natural products by an enantioselective deprotonation technique, we are interested in the chiral synthesis of β-alkyl-γ-butyrolactones. Among the natural products having a β-alkyl-γ-butyrolactone moiety, lignan lactones are one of the most important target compounds because of their interesting antileukaemic activity. We report here an enantiocontrolled synthesis of several lignan lactones.

Results and Discussion

The starting cyclobutanone **3** was prepared by adopting the literature procedure[4] as follows. [2 + 2] Cycloaddition of safrole **1** with trichloroacetyl chloride and phosphoryl chloride in diethyl ether in the presence of zinc–copper couple gave the dichlorocyclobutanone **2**, in 66% yield, which on treatment with zinc powder in refluxing acetic acid provided the desired cyclobutanone **3**, in 93% yield (Scheme 2). Based on the consideration of our earlier work,[2] an enantioselective deprotonation of the cyclobutanone **3** was carried out by using the chiral base, lithium (*S,S'*)-α,α'-dimethyldibenzylamide,[5] at −78 °C in tetrahydrofuran (THF) and the resulting enolate was trapped by triethylsilyl chloride to provide the silyl enol ether **4** in 77% yield. Although the enantiomeric excess of the silyl enol ether **4** could not be determined at this stage, it was further converted into the γ-butyrolactone **5** by ozonolysis, followed by sodium borohydride reduction of the ozonide. The optical purity of the γ-butyrolactone **5** was determined to be 67% by comparison of its specific optical rotation, $[\alpha]_D$ +3.5 (*c* 0.8, $CHCl_3$) with that reported {lit.,[6] $[\alpha]_D$ +5.22 (*c* 1.13, $CHCl_3$); lit.,[7] $[\alpha]_D$ +5.02 (*c* 1.07, $CHCl_3$)}. When this enantioselective deprotonation reaction was carried out at −100 °C in THF, the optical purity of the γ-butyrolactone **5** (75% yield), $[\alpha]_D$ +4.1 (*c* 1.0, $CHCl_3$), was increased to 80%. The relatively poor asymmetric induction observed here, compared with the case of 3-phenylcyclobutanone is obviously due to the introduction of a sterically less hindered alkyl group, a methylene unit, at the 3-position, and similar results were also obtained in the enantioselective deprotonation of 4-substituted cyclohexanones.[8]

Since we had established a chiral synthetic procedure for the β-alkyl-γ-butyrolactone ring system with reasonable optical purity, this strategy was applied to the synthesis of naturally occurring α,β-dibenzyllignan lactones and α-benzylidene-β-benzyllignan lactones.

The stereoselective alkylation of the γ-butyrolactone **5** with 3,4-methylenedioxybenzyl bromide under similar reaction conditions to those reported by Tomioka and Koga[6] afforded (−)-hinokinin **6**, $[\alpha]_D$ −28.1 (*c* 0.7, $CHCl_3$) {lit.,[6] $[\alpha]_D$ −35.1 (*c* 0.701, $CHCl_3$); lit.,[7] $[\alpha]_D$ −35.0 (*c* 1.72, $CHCl_3$); lit.,[9] $[\alpha]_D$ −35 (*c* 1.00, $CHCl_3$)} in 78% yield. (−)-Deoxypodorhizone **7**, $[\alpha]_D$ −19.4 (*c* 1.3, $CHCl_3$) {lit.,[10] $[\alpha]_D$ −25.2 (*c* 0.410, $CHCl_3$); lit.,[11] $[\alpha]_D$ −21.6 (*c* 0.4, $CHCl_3$); lit.,[12] $[\alpha]_D$ −25.5 (*c* 0.35, $CHCl_3$)} was also synthesized by using 3,4,5-trimethoxybenzyl bromide as an alkylating agent in 74% yield with *ca.* 80% optical purity. Moreover, the reaction of the γ-butyrolactone with 3,4-dimethoxybenzaldehyde in the presence of lithium diisopropylamide (LDA) in THF gave the alcohols as a mixture of the *threo*-**8a** and *erythro*-isomers **8b** in the ratio of *ca.* 1:1. The stereochemistry of the alcohols **8a** and **8b** was determined by their NMR spectra which showed the resonances for the benzylic protons at δ 4.77 as a double doublet with coupling constants of *J* 1.2 and 8.5 Hz for the *threo*-isomer and at δ 5.26 as a double doublet with coupling constants of *J* 3.1 and 4.9 Hz for the *erythro*-isomer.[13] The mixture of the alcohols **8a** and **8b** was treated with methanesulfonyl chloride in dichloromethane in the presence of triethylamine to provide the methanesulfonate **9** as a mixture of the diastereoisomers, which without purification, was treated with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in acetonitrile at room temperature to furnish (−)-isohibalactone **10**, m.p. 149 °C (benzene), $[\alpha]_D$ −110.4 (*c* 0.2, $CHCl_3$) {lit.,[14] $[\alpha]_D$ +86 ($CHCl_3$) for its antipode} as a major product together with (−)-savinin, m.p. 127 °C (benzene) {lit.,[15] m.p. 147 °C (benzene)}, $[\alpha]_D$ −67.3 (*c* 0.2, $CHCl_3$) {lit.,[15] $[\alpha]_D$ −82 (*c* 2.5, $CHCl_3$)}, in 63 and 17% yields, respectively, whose spectroscopic data were identical with those reported. Although (−)-isohibalactone is not a naturally occurring lignan lactone, its antipodal form, gadain, was isolated from *Jatropha gossypifolia*,[14] and (+)-γ-butyrolactone *ent*-**5** is also readily available by application of this procedure using lithium (*R,R'*)-α,α'-dimethyldibenzylamide as the chiral base, this synthesis, therefore, provides access to a chiral synthesis of gadain.



Scheme 2 *Reagents and conditions:* i, CCl_3COCl, $POCl_3$, Zn–Cu, Et_2O, room temp. (65.6%); ii, Zn, AcOH, reflux (93.2%); iii, (*S,S'*)-α,α'-dimethyldibenzylamine, BuLi, THF then Et_3SiCl, −78 °C (76.9%); iv, O_3, MeOH, −78 °C then $NaBH_4$ then 2 mol dm^{-3} HCl (75.4%); v, LDA, piperonyl bromide, THF, −78 °C for **6** (77.5%) or LDA, 3,4,5-trimethoxybenzyl bromide, THF, −78 °C for **7** (73.5%); vi, LDA, piperonal, THF, −78 °C (85%); vii, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C (85.2%); viii, DBU, MeCN, room temp. (63.4% for **10** and 17.3% for **11**); ix, Bu_3SnH, AIBN, benzene, reflux (81.6%)

Finally the major product, (−)-isohibalactone obtained from the above reaction, was isomerized into (−)-savinin by treatment with tributyltin hydride in the presence of azoisobutyronitrile (AIBN) in refluxing benzene in 82% yield.[16]

Thus, we have established a chiral synthetic strategy for lignan lactones and this procedure should be applicable to the synthesis of other types of lignan lactones such as podophyllotoxin and steganacin.

Experimental

General Methods.—M.p.s were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX 270 instrument (270 MHz), chemical shifts are reported in ppm on the δ scale from internal Me_4Si, and *J* values are given in Hz. Mass spectra were measured with a JEOL JMS D-300 spectrometer. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. All new compounds described in the Experimental section were homogeneous on TLC.

2,2-Dichloro-3-(3,4-methylenedioxybenzyl)cyclobutanone **2**.—To a stirred solution of safrole **1** (1.0 g, 6.17 mmol) in diethyl ether (30 cm^3) in the presence of zinc–copper couple (4.0 g) was added a solution of trichloroacetyl chloride (1.9 g, 10.45 mmol) and phosphoryl chloride (1.6 g, 10.43 mmol) in diethyl ether (15 cm^3) at ambient temperature over the period of 1.5 h and the mixture was further stirred at the same temperature for 1 h. After removal of the insoluble material by filtration, the filtrate was concentrated to about one fourth of the volume and then diluted with the same volume of hexane. The mixture was decanted to separate the solution from the insoluble material precipitated and the solution was washed with saturated sodium hydrogen carbonate and brine, and then dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (9:1, v/v) afforded the 2,2-dichlorocyclobutanone **2** (1.1 g, 66%) as a colourless solid, m.p. 60 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1820; δ 2.72 (1 H, dd, *J* 7.9 and 13.4, $ArCH_2CHCH_2CO$), 3.0–3.35 (4 H, m, $ArCH_2CHCH_2CO$), 5.95 (2 H, s, OCH_2O) and 6.66–6.78 (3 H, m, Ar-H); *m/z* 272 (M^+) (Found: M^+, 272.0015. $C_{12}H_{10}Cl_2O_3$ requires *M*, 272.0007).

3-(3,4-Methylenedioxybenzyl)cyclobutanone **3**.—A mixture of the 2,2-dichlorocyclobutanone **2** (9.3 g, 34.2 mmol), zinc powder (22.4 g, 0.34 mol) and acetic acid (80 cm^3) was heated at reflux with stirring for 1 h. The insoluble material was removed by filtration and the filtrate was diluted with large excess of diethyl ether. The organic layer was washed with saturated sodium hydrogen carbonate and brine, and then dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (4:1, v/v) afforded the cyclobutanone **3** (6.5 g, 93%) as a colourless oil (Found: C, 70.4; H, 5.9. $C_{12}H_{12}O_3$ requires C, 70.55; H, 5.9%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780; δ 2.62–2.83 (5 H, m, $ArCH_2CHCH_2CO$ and 2 × $ArCH_2CHCH_2CO$), 3.10–3.17 (2 H, m, $ArCH_2CH$), 5.93 (2 H, s, OCH_2O) and 6.61–6.76 (3 H, m, Ar-H); *m/z* 204 (M^+) (Found: M^+, 204.0778. $C_{12}H_{12}O_3$ requires *M*, 204.0785).

(+)-3-(3,4-Methylenedioxybenzyl)-1-triethylsiloxycyclobut-1-ene **4**.—To a stirred solution of (*S,S'*)-α,α'-dimethyldibenzylamine (143 mg, 0.64 mmol) in dry THF (15 cm^3) was added

butyllithium (1.63 mol dm^{-3} in hexane solution; 0.38 cm^3, 0.61 mmol) at −78 °C under argon and the resulting solution was allowed to warm to room temperature over 10 min. The solution was cooled to −100 °C and triethylsilyl chloride was added to this solution. To this mixture was added a solution of the cyclobutanone **3** (100 mg, 0.49 mmol) in THF (1 cm^3) at the same temperature and the solution was further stirred for 10 min. After addition of triethylamine (1.0 cm^3) and saturated sodium hydrogen carbonate, the mixture was concentrated to leave a residue, which was extracted with hexane. The extract was washed with saturated sodium hydrogen carbonate and brine, and then dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (99:1, v/v) afforded the silyl enol ether **4** (120 mg, 77%) as a colourless oil; $[\alpha]_D$ +27.7 (*c* 1.3, $CHCl_3$) (Found: C, 67.95; H, 8.4. $C_{18}H_{26}O_3Si$ requires C, 67.9; H, 8.25%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1620; δ 0.68 (6 H, q, *J* 7.9, 3 × $SiCH_2$), 0.98 (9 H, t, *J* 7.9, 3 × $SiCH_2CH_3$), 2.17 (1 H, dd, *J* 1.2 and 12.8, $CHHCOSiEt_3$), 2.56 (1 H, m, $ArCH_2CHCH_2$), 2.60–2.63 (2 H, m, $ArCH_2CH$), 2.69 (1 H, dd, *J* 4.3 and 12.8, $CHHCOSiEt_3$), 4.70 (1 H, s, $CH{=}COSiEt_3$), 5.92 (2 H, s, OCH_2O) and 6.60–6.74 (3 H, m, Ar-H).

(+)-4-(3,4-*Methylenedioxybenzyl*)*dihydrofuran*-2(3H)-*one* **5**.—A stream of ozone was bubbled through a stirred solution of the silyl enol ether **4** (100 mg, 0.31 mmol) in methanol (10 cm^3) at −78 °C until disappearance of the starting material on TLC. The reaction mixture was flushed with argon and treated with sodium borohydride (59 mg, 1.56 mmol) at the same temperature. The resulting mixture was allowed to warm to room temperature over 1 h, and further stirred for 1 h. After evaporation of the solvent, the residue was treated with hydrochloric acid (2 mol dm^{-3}) and extracted with ethyl acetate. The extract was washed with 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–ethyl acetate (1:1, v/v) afforded the γ-butyrolactone **5** (52 mg, 75%) as a colourless oil; $[\alpha]_D$ +4.1 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1770; δ 2.27 (1 H, dd, *J* 6.7 and 17.7, $CHHCO$), 2.60 (1 H, dd, *J* 7.9 and 17.7, $CHHCO$), 2.67–2.82 (3 H, m, $ArCH_2CH$), 4.02 (1 H, dd, *J* 6.1 and 9.2, $CHHOCO$), 4.33 (1 H, dd, *J* 6.7 and 9.2, $CHHOCO$), 5.95 (2 H, s, OCH_2O) and 6.58–6.77 (3 H, m, Ar-H); *m/z* 220 (M^+) (Found: M^+, 220.0726. $C_{12}H_{12}O_4$ requires *M*, 220.0734).

(−)-*Hinokinin* **6**.—To a stirred solution of LDA [prepared from diisopropylamine (0.10 cm^3, 0.68 mmol) and butyllithium (1.63 mol dm^{-3} in hexane; 0.39 cm^3, 0.63 mmol)] in dry THF (7 cm^3) under argon was added a solution of the γ-butyrolactone **5** (100 mg, 0.45 mmol) in THF (2.5 cm^3) at −78 °C and the solution was stirred for a further 15 min. A solution of piperonyl bromide (135 mg, 0.59 mmol) in THF (3 cm^3) and hexamethylphosphoric triamide (0.1 cm^3) was added to the above solution at −78 °C and the resulting mixture was further stirred for 4 h at the same temperature. The reaction mixture was treated with saturated ammonium chloride and concentrated to leave a residue, which was extracted with ethyl acetate. The organic layer was washed with 10% hydrochloric acid, saturated sodium hydrogen carbonate and brine, and then dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (7:3, v/v) afforded (−)-hinokinin **6** (125 mg, 78%) as a colourless oil; $[\alpha]_D$ −28.1 (*c* 0.7, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1770; δ 2.41–2.61 (4 H, m, $ArCH_2CHCHCO$), 2.84 (1 H, dd, *J* 6.7 and 14.0, $ArCHHCHCO$), 2.99 (1 H, dd, *J* 4.9 and 14.0, $ArCHHCHCO$), 3.86 (1 H, dd, *J* 6.7 and 9.2, $CHHOCO$), 4.13 (1 H, dd, *J* 6.7 and 9.2, $CHHOCO$), 5.93 (4 H, s, 2 × OCH_2O) and 6.45–6.74 (6 H, m, Ar-H); *m/z* 354 (M^+) (Found: M^+, 354.1101. $C_{20}H_{18}O_6$ requires *M*, 354.1101). These spectroscopic data were identical with those reported.[4,5,7]

(−)-*Deoxypodorhizone* **7**.—Essentially the same procedure as that used for the preparation of (−)-hinokinin using the γ-butyrolactone **5** (100 mg, 0.45 mmol) and 3,4,5-trimethoxybenzyl bromide (154 mg, 0.59 mmol) was applied to the synthesis of (−)-deoxypodorhizone **7** (133 mg, 74%) as a colourless oil; $[\alpha]_D$ −19.4 (*c* 1.3, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1760; δ 2.47–2.64 (4 H, m, $ArCH_2CHCHCO$), 2.91 (2 H, dd, *J* 3.1 and 5.5, $ArCH_2CHCHCO$), 3.83 (9 H, s, 3 × OMe), 3.88 (1 H, dd, *J* 7.3 and 9.2, $CHHOCO$), 4.18 (1 H, dd, *J* 6.7 and 9.2, $CHHOCO$), 5.93 (2 H, s, OCH_2O), 6.36 (2 H, s, Ar-H) and 6.45–6.71 (3 H, m, Ar-H); *m/z* 400 (M^+) (Found: M^+, 400.1521. $C_{22}H_{24}O_7$ requires *M*, 400.1521). These spectroscopic data were identical with those reported.[8,9]

trans-3-(α-*Hydroxy*-3,4-*methylenedioxybenzyl*)-4-(3,4-*methylenedioxybenzyl*)*dihydrofuran*-2(3H)-*one* **8a** *and* **8b**.—To a stirred solution of LDA [prepared from diisopropylamine (0.13 cm^3, 0.91 mmol) and butyllithium (1.63 mol dm^{-3} in hexane; 0.56 cm^3, 0.91 mmol)] in dry THF (10 cm^3) under argon was added a solution of the γ-butyrolactone **5** (200 mg, 0.91 mmol) in THF (5 cm^3) at −78 °C and the solution was stirred for a further 15 min. A solution of piperonal (150 mg, 1.0 mmol) in THF (3 cm^3) was added to the above solution at −78 °C and the resulting mixture was further stirred for 2 h at the same temperature. The reaction mixture was treated with saturated ammonium chloride and concentrated to leave a residue, which was extracted with dichloromethane. The organic layer was washed with 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–ethyl acetate (7:3, v/v) afforded the alcohols **8a** and **8b** (286 mg, 85%) as a mixture of diastereoisomers; $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 and 1760; δ 2.12–2.83 (4 H, m, $ArCH_2CHCHCO$), 3.84–4.35 (2 H, m, CH_2OCO), 4.77 (0.5 H, dd, *J* 1.2 and 8.5, $ArCHOH$), 5.26 (0.5 H, dd, *J* 3.1 and 4.9, $ArCHOH$), 5.90–5.97 (4 H, m, 2 × OCH_2O) and 6.31–6.93 (4 H, m, Ar-H); *m/z* 370 (M^+) (Found: M^+, 370.1051. $C_{20}H_{18}O_7$ requires *M*, 370.1051).

trans-4-(3,4-*Methylenedioxybenzyl*)-3-(α-*methylsulfonyloxy*-3,4-*methylenedioxybenzyl*)*dihydrofuran*-2(3H)-*one* **9**.—A solution of the alcohols **8a** and **8b** (286 mg, 0.77 mmol), triethylamine (0.098 cm^3, 1.55 mmol) and methanesulfonyl chloride (0.12 cm^3, 1.55 mmol) in dichloromethane (5 cm^3) was stirred at ambient temperature for 1 h. The mixture was diluted with dichloromethane and washed with water and then dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (1:1, v/v) afforded the methanesulfonate **9** (295 mg, 85%) as a mixture of diastereoisomers; $\nu_{max}(CHCl_3)/cm^{-1}$ 1770; δ 2.34–3.05 (4 H, m, $ArCH_2CHCHCO$), 3.67 (3 H, s, OSO_2Me), 3.84–4.46 (2 H, m, CH_2OCO), 5.31 (0.5 H, d, *J* 4.3, $ArCHOSO_2$), 5.48 (0.5 H, d, *J* 3.1, $ArCHOSO_2$), 5.91–6.0 (4 H, m, 2 × OCH_2O) and 6.32–6.96 (6 H, m, Ar-H), which was used without further purification in the next reaction.

(−)-*Isohibalactone* **10** *and* (+)-*Savinin* **11**.—A solution of the methanesulfonate **9** (295 mg, 0.66 mmol) and DBU (0.1 cm^3, 0.66 mmol) in acetonitrile (7 cm^3) was stirred at ambient temperature for 5 h. The mixture was treated with water and extracted with dichloromethane. The extract was washed with water 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–ethyl acetate (4:1, v/v) afforded

(−)-isohibalactone **10** (147 mg, 63%) as colourless prisms; m.p. 148 °C (from benzene); $[\alpha]_D$ −110.4 (*c* 0.2, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1750 and 1600; δ 2.78 (1 H, dd, *J* 9.2 and 14.0, ArC*H*HCH), 2.92 (1 H, dd, *J* 7.3 and 14.0, ArC*H*HCH), 3.28 (1 H, m, $ArCH_2CH$), 4.10 (1 H, dd, *J* 3.7 and 9.2, CH_2OCO), 4.32 (1 H, dd, *J* 7.3 and 9.2, CH_2OCO), 5.95 (2 H, s, OCH_2O), 6.00 (2 H, s, OCH_2O), 6.59 (1 H, d, *J* 1.8, ArCH=C), 6.61–6.80 (4 H, m, Ar-H), 7.16 (1 H, dd, *J* 1.2 and 7.9, Ar-H) and 7.74 (1 H, d, *J* 1.2, Ar-H); *m/z* 352 (M^+) (Found: M^+, 352.0953. $C_{20}H_{16}O_6$ requires *M*, 352.0947). These data were identical with those reported.[12]

Further elution with the same solvent system afforded (−)-savinin **11** (40 mg, 17%) as colourless prisms; m.p. 127 °C (from benzene); $[\alpha]_D$ −67.3 (*c* 0.2, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740 and 1640; δ 2.60 (1 H, dd, *J* 10.4 and 14.6, ArC*H*HCH), 3.00 (1 H, dd, *J* 5.0 and 14.6, ArC*H*HCH), 3.73 (1 H, m, $ArCH_2CH$), 4.21–4.26 (2 H, m, CH_2OCO), 5.93 (2 H, s, OCH_2O), 6.04 (2 H, s, OCH_2O), 6.62–6.75 (3 H, m, Ar-H), 6.88 (1 H, d, *J* 8.5, ArCH=C), 7.04–7.09 (2 H, m, Ar-H) and 7.49 (1 H, s, Ar-H); *m/z* 352 (M^+) (Found: M^+, 352.0938. $C_{20}H_{16}O_6$ requires *M*, 352.0947). These data were identical with those reported.[13]

Isomerization of (−)-*Isohibalactone* **10** *into* (−)-*Savinin* **11**.—A solution of (−)-isohibalactone **10** (147 mg, 0.42 mmol) and tributyltin hydride (0.11 cm^3) in benzene (5 cm^3) in the presence of a catalytic amount of azoisobutyronitrile was heated at reflux for 1 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (4 : 1, v/v) afforded (−)-savinin **11** (120 mg, 82%), which was identical with the authentic specimen obtained above in all respects.

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