New Synthesis of 2,6-Diaryl-4-oxo-3,7-dioxabicyclo[3.3.0]octanes: Synthesis of (±)-Styraxin

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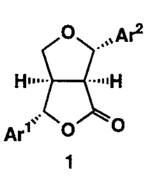
An efficient method for the stereocontrolled synthesis of the unsymmetrically substituted 4-oxofurofuran lignan **1** has been developed based on a stereocontrolled aldol reaction of the succinic anhydride derivative **20** with an aromatic aldehyde employing (±)-styraxin as a representative example.

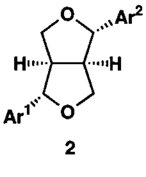
Considerable interest has been focused on the synthesis of lignans of the furofuran series **1**–**3** (2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes)[1] because of their wide range of biological activities,[2] e.g. antitumor activity, phosphodiesterase inhibition activity, and the effect on the central nervous systems. Although a number of methods for the synthesis of **2** and **3** have been reported,[3,4] only a few for the synthesis of the 4-oxofurofuran lignan **1** including that of the unsymmetrically substituted one ($Ar^1 \neq Ar^2$) have been reported.[5,6] However, these methods were not necessarily effective in terms of chemical yield and stereoselectivity. We recently reported the stereocontrolled syntheses of the four possible diastereoisomers of **3** based on the stereoselective aldol reaction of the succinic anhydride derivative with an aromatic aldehyde.[4e,f,g] We envisaged that our method would be applicable to the stereocontrolled synthesis of **1**, and now report the first stereocontrolled synthesis of the unsymmetrically substituted **1** adopting (±)-styraxin (**1a**) as a representative example.



1

styraxin (**1a**)

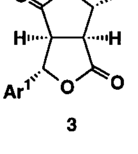
Ar^1 =3,4-methylenedioxyphenyl
Ar^2 = 4-hydroxy-3-methoxyphenyl



2

methyl piperitol (**2a**)

Ar^1 = 3,4-methylenedioxyphenyl
Ar^2 = 3,4-dimethoxyphenyl

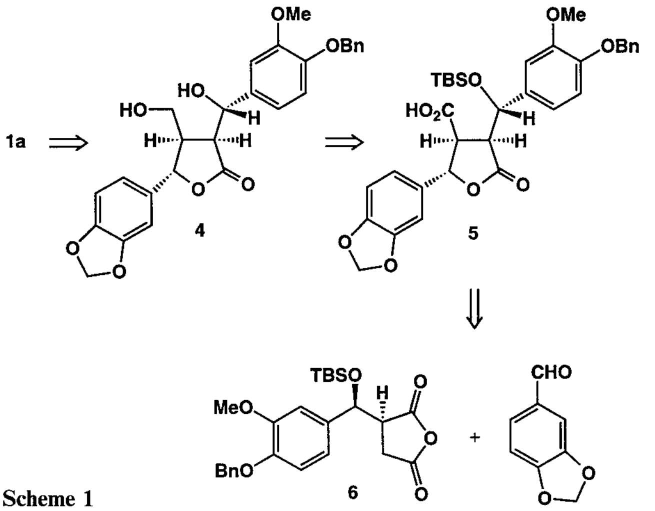


3

methyl 4,8-dioxopiperitol (**3a**)

Ar^1 = 3,4-methylenedioxyphenyl
Ar^2 = 3,4-dimethoxyphenyl

We first considered that **1a** could be synthesized from the diol **4** by the intramolecular cyclization reaction used in our synthesis of methyl piperitol (**2a**),[3i,k] and **4** could be obtained from **5**, which could be synthesized based on the stereoselective aldol reaction of the succinic anhydride **6** with piperonal [4f] (Scheme 1).

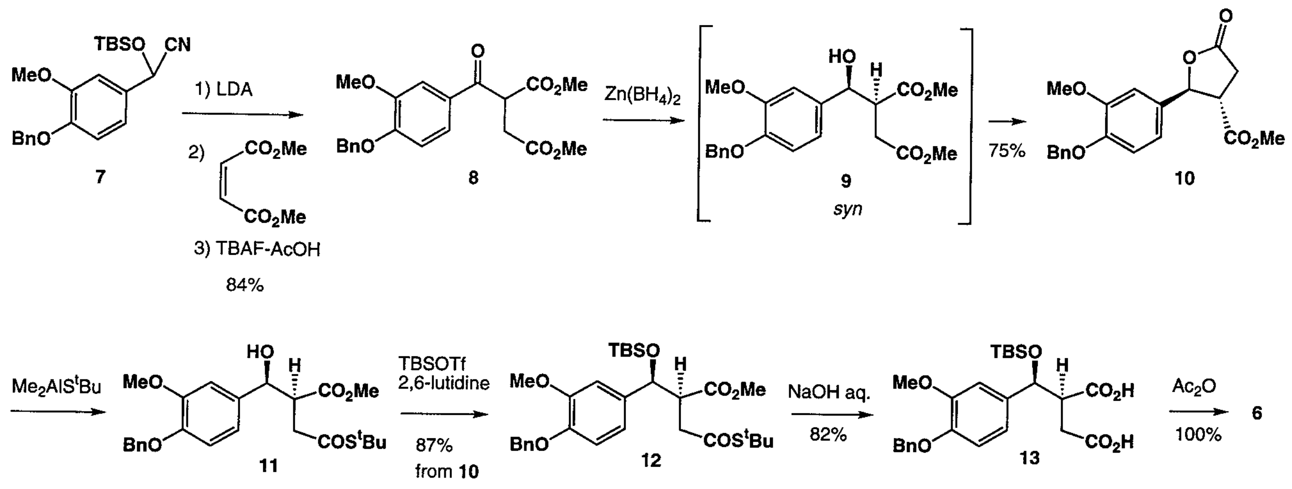


Scheme 1

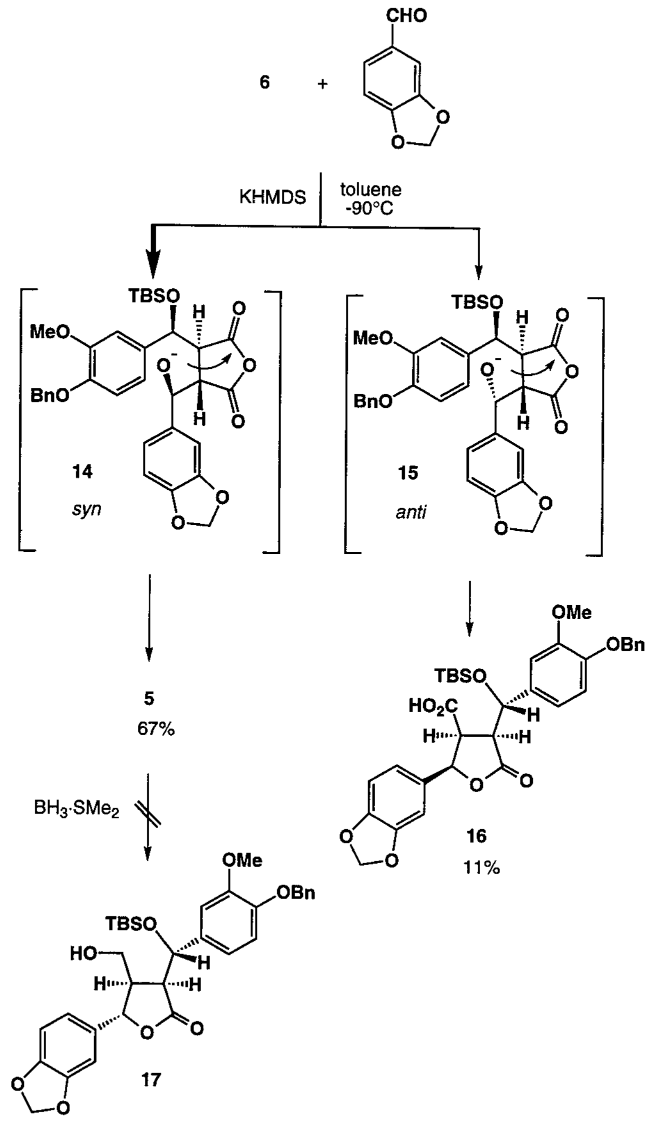
According to the strategy, the key intermediate **6** was first synthesized (Scheme 2). The Michael addition of the anion generated by treatment of the cyanohydrin **7** with LDA to dimethyl maleate in toluene at −70 °C, followed by treatment of the resulting adduct with tetrabutylammonium fluoride (TBAF)/acetic acid (1:1) in THF at room temperature afforded the benzoyl succinate **8** in 84 % yield. The benzoyl succinate **8** was stereoselectively converted into the lactone **10** in 75 % yield, via *syn*-alcohol **9**, with zinc borohydride.[7] Treatment of **10** with dimethylaluminum *tert*-butyl sulfide in dichloromethane at 0 °C afforded the thioester **11**. Without isolation, the crude **11** was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine to afford **12** in 87 % yield from **10**. The thioester **12** was saponified to give **13** in 82 % yield. The diacid **13** was heated in acetic anhydride at 60 °C to give the succinic anhydride **6** quantitatively.

The *syn*-selective aldol reaction of the succinic anhydride **6** with piperonal was achieved employing potassium hexamethyldisilazane (KHMDS) in toluene at −90 °C in the same manner as we have previously reported,[4f] to afford the γ-lactone **5** in 67 % yield along with 11 % of the diastereoisomer **16** (Scheme 3). Compound **5** was next treated with borane methyl sulfide complex in THF. However, the expected chemoselective reduction of the carboxyl group did not proceed, and the desired **17** was not obtained at all. The rather bulky neighboring group probably shields the carboxyl group from the attack of the reducing agent.

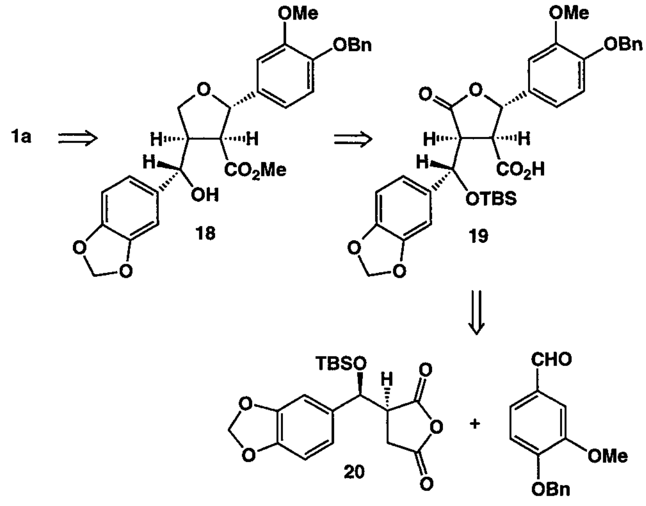
This result turned us to plan an alternative approach. Namely, **1a** could be obtained by lactonization of **18** which could be synthesized by chemoselective reduction of the carbonyl group of the γ-lactone **19** prepared from the acid anhydride **20** and benzylvanillin (Scheme 4).



Scheme 2



Scheme 3

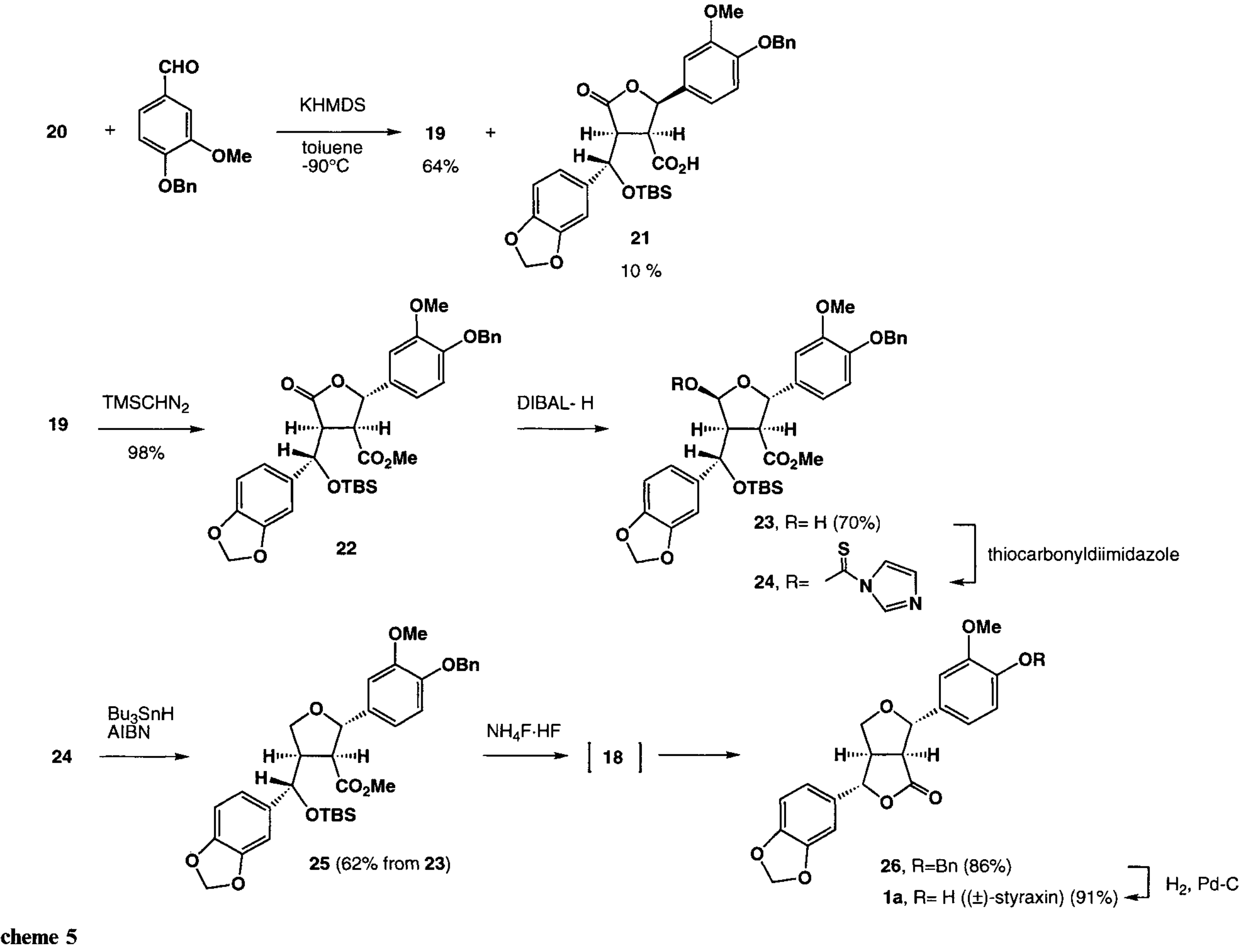


Scheme 4

Thus, the γ-lactone **19** was prepared in 64 % yield by the aldol reaction of **20** and benzylvanillin in the same manner as described above (Scheme 5). The γ-lactone **19** was treated with trimethylsilyldiazomethane (TMSCHN$_2$) in methanol to give **22** in 98 % yield. Reduction of **22** with diisobutylaluminium hydride (DIBAL-H) gave the lactol **23** in 70 % yield as a single isomer. Hydride seemed to attack from the less hindered α-side of the lactone ring. Then, treatment of **23** with thiocarbonyldiimidazole in refluxing 1,2-dichloroethane followed by reduction of the resulting thiocarbonyldiimidazole **24** with tributyltin hydride in refluxing xylene afforded **25** in 62 % yield from **23**. Removal of the TBS group and the lactonization proceeded in one-pot by treatment of **25** with ammonium hydrogen fluoride (NH$_4$F–HF) in DMF and *N*-methylpyrrolidone (NMP) (10 : 1) at room temperature to afford (±)-benzylstyraxin (**26**) in 86 % yield. Deprotection of the phenolic hydroxyl group by hydrogenation by using palladium on carbon provided (±)-styraxin (**1 a**) in 91 % yield. The spectral data including ^{1}H NMR were in good accordance with those of the natural styraxin.[8]

Because we have already developed an efficient method for the stereoselective syntheses of the isomers of γ-lactone **19**,[4e,f,g] the present method should find wide application in the synthesis of a variety of derivatives of (±)-styraxin (**1 a**) involving those having different stereochemistry at the two benzylic positions and different substituents on the two aromatic rings.

Melting points were measured on a Büchi 535 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400II analyser. IR spectra were recorded on a Perkin-Elmer 1640 spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker AC-200 (200 MHz) spectrometer in CDCl$_3$ with TMS as an internal standard. Mass spectra were recorded on a Hitachi M-2000A and JMS-HX200 spectrometer. Column chromatography was carried out on silica gel (Kieselgel 60, 230–400 mesh, E. Merck).



Scheme 5

Dimethyl 2-[(4-Benzyloxy-3-methoxy)benzyol]succinate (8):

To a solution of LDA (32 mmol) in toluene (150 mL) were added dropwise successively the cyanohydrin **7** (11.2 g, 29 mmol) in toluene (20 mL) and dimethyl maleate (4.2 g, 29 mmol) in toluene (20 mL) at −70 °C under a N_2 atmosphere. The mixture was stirred for 20 min at the same temperature, then quenched by the addition of AcOH (15 %, 30 mL, 76 mmol). The organic layer was separated, and the aqueous layer extracted with EtOAc (200 mL). The combined organic layers were washed with brine (100 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was dissolved in THF (200 mL), and then AcOH (2.3 mL, 38 mmol) and TBAF (1 M in THF, 35 mL) were added to the solution at r.t. After 30 min, the solution was washed with H_2O (100 mL), 10 % citric acid (100 mL) and brine (100 mL), and then dried ($MgSO_4$). After evaporation of the solvent in vacuo, the residue was purified by silica gel column chromatography using hexane/EtOAc (1 : 1) as an eluent to afford **8** (9.5 g, 84 %); mp 119–120 °C.

IR (film): $\nu = 1730, 1666, 1593, 1420, 1262\ cm^{-1}$.

^1H NMR: $\delta = 3.05$ (d, 2 H, $J = 7.2$ Hz), 3.68 (s, 6 H), 3.94 (s, 3 H), 4.84 (t, 1 H, $J = 7.2$ Hz), 5.24 (s, 2 H), 6.92 (d, 1 H, $J = 8.4$ Hz), 7.31–7.48 (m, 5 H), 7.58–7.67 (m, 2 H).

MS: $m/z = 386$ (M^+), 354, 242, 91.

Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.03; H, 5.71.

trans-3-Methoxycarbonyl-4-[(4-benzyloxy-3-methoxy)phenyl]butyrolactone (10):

To a suspension of $NaBH_4$ (760 mg, 20 mmol) in Et_2O (50 mL) was added $ZnCl_2$ (1 M in Et_2O, 10 mL, 10 mmol) at r.t. The mixture was stirred for 5 h and the insoluble materials were filtered off. The filtrate was poured into a solution of **8** (3.8 g, 9.8 mmol) in Et_2O (200 mL) at −20 °C. The solution was allowed to warm to 0 °C and stirred for 2 h. The reaction was quenched by the addition of AcOH (2.4 mL, 40 mmol). The mixture was washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel using hexane/EtOAc (2 : 1) as an eluent to afford **10** (2.6 g, 75 %) and the *anti*-isomer of **9** (0.23 g, 6 %).

Compound **10**:

IR (film): $\nu = 1787, 1726, 1517, 1455, 1265\ cm^{-1}$.

^1H NMR: $\delta = 2.90$ (dd, 1 H, $J = 5.1$, 16.9 Hz), 2.99 (dd, 1 H, $J = 8.8$, 16.9 Hz), 3.17 (m, 1 H), 3.61 (s, 3 H), 3.98 (s, 3 H), 4.82 (d, 1 H, $J = 8.0$ Hz), 5.14 (s, 2 H), 6.70–6.95 (m, 3 H), 7.27–7.47 (s, 5 H).

MS: $m/z = 356$ (M^+), 244, 142, 91.

HRMS: m/z Calcd for $C_{20}H_{20}O_6 + H$ [$(M+H)^+$]: 357.1338; Found: 357.1342.

The *anti*-isomer of **9**: mp 75–76 °C.

IR (KBr): $\nu = 1743, 1592, 1513, 1437, 1262\ cm^{-1}$.

^1H NMR: $\delta = 2.90$ (dd, 1 H, $J = 9.7$, 17.7 Hz), 2.99 (dd, 1 H, $J = 8.8$, 17.7 Hz), 3.34 (m, 1 H), 3.76 (s, 3 H), 3.90 (s, 3 H), 5.16 (s, 2 H), 5.58 (d, 1 H, $J = 7.5$ Hz), 6.78–6.90 (m, 3 H), 7.29–7.46 (s, 5 H).

MS: $m/z = 388$ (M^+), 356, 243, 91.

Anal. Calcd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23. Found: C, 64.88; H, 6.22.

S-tert-Butyl {(3*S**,4*S**)-4-[(4-Benzyloxy-3-methoxy)phenyl]-4-(*tert*-butyldimethylsiloxy)-3-methoxycarbonyl}butanethioate (12):

To a solution of Me_3Al (2 M in hexane, 2.7 mL, 5.4 mmol) in CH_2Cl_2 (30 mL) was added 2-methylpropane-2-thiol (0.73 mL, 5.4 mmol) at 0 °C under a N_2 stream. The mixture was stirred at r.t. for 20 min. The obtained aluminum reagent was added to a solution of **10** (1.6 g, 4.5 mmol) in CH_2Cl_2 (20 mL) via a cannula. After the solution was stirred at r.t. for 2 h, the reaction was quenched by H_2O (30 mL). The organic layer was washed with 1 N NaOH (20 mL, 20 mmol) and brine (50 mL), and dried ($MgSO_4$). After removal of the $MgSO_4$ by filtration the mixture was poured into a stirred mixture of TBSOTf (3.1 mL, 13.5 mmol) and 2,6-lutidine (2.8 mL, 24 mmol) in CH_2Cl_2 (50 mL) at r.t. After 1 h, the mixture was washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. Silica gel column chromatography of the residue using hexane/EtOAc (4 : 1) as an eluent afforded **12** (2.2 g, 87 %).

IR (film): $\nu = 1741, 1684, 1514, 1364, 1263\ cm^{-1}$.

^1H NMR: $\delta = -0.25$ (s, 3 H), −0.02 (s, 3 H), 0.89 (s, 9 H), 1.39 (s, 9 H), 2.59 (d, 1 H, $J = 13.0$ Hz), 2.96–3.24 (m, 2 H), 3.61 (s, 3 H), 3.88 (s, 3 H), 5.08 (d, 1 H, $J = 3.9$ Hz), 5.30 (s, 2 H), 6.72 (dd, 1 H, $J = 1.7$, 8.2 Hz), 6.82 (d, 1 H, $J = 8.2$ Hz), 6.87 (d, 1 H, $J = 1.7$ Hz), 7.28–7.46 (m, 5 H).

MS: $m/z = 503$ [$(M - t\text{-Bu})^+$], 357, 91, 73.

HRMS: m/z Calcd for $C_{30}H_{44}O_6SSi + Na$ [$(M+Na)^+$]: 583.2526. Found: 583.2534.

(2*S**)-2-[(4-Benzyloxy-3-methoxy)phenyl-α*S**-(*tert*-butyldimethylsiloxy)]methylsuccinic Acid (13):

A mixture of **12** (1.2 g, 2.1 mmol) in MeOH (12 mL) and 2 N NaOH (4.2 mL, 8.4 mmol) was heated at 50 °C for 2 h. The mixture was concentrated under reduced pressure to remove MeOH and the wet solid was redissolved in 2 N NaOH (4.2 mL, 8.4 mmol) and the solution was stirred at 50 °C for 2 h. The mixture was poured into a mixture of H_2O (50 mL) and Et_2O (50 mL). The aqueous layer was separated, acidified with 2 N HCl (9 mL, 18 mmol) and extracted with EtOAc (200 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was crystallized from diisopropyl ether to give **13** (833 mg, 82 %); mp 110 °C.

IR (KBr): $\nu = 3380, 1713, 1590, 1514, 1259\ cm^{-1}$.

^1H NMR: $\delta = -0.18$ (s, 3 H), 0.02 (s, 3 H), 0.88 (s, 9 H), 2.29 (d, 1 H, $J = 16.5$ Hz), 2.80–3.21 (m, 2 H), 3.89 (s, 3 H), 5.11 (s, 2 H), 5.19 (br s, 1 H), 6.72–6.90 (m, 3 H), 7.28–7.43 (m, 5 H).

MS: $m/z = 417$ [$(M - t\text{-Bu})^+$], 357, 91, 73.

Anal. Calcd for $C_{25}H_{34}O_7Si$: C, 63.27; H, 7.22. Found: C, 63.15; H; 7.20.

(2*S**)-2-[(4-Benzyloxy-3-methoxy)phenyl-α*S**-(*tert*-butyldimethylsiloxy)]methylsuccinic Anhydride (6):

A solution of **13** (648 mg, 1.37 mmol) in Ac_2O (6 mL) was stirred at 60 °C for 20 min. The solvent was removed under reduced pressure to give **6** (623 mg, 100 %).

IR (film): $\nu = 1784, 1593, 1513, 1464, 1259\ cm^{-1}$.

^1H NMR: $\delta = -0.12$ (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 2.61 (dd, 1 H, $J = 9.6$, 18.4 Hz), 3.06–3.26 (m, 2 H), 3.89 (s, 3 H), 5.14 (s, 2 H), 5.37 (d, 1 H, $J = 1.6$ Hz), 6.75–6.90 (m, 3 H), 7.15–7.45 (m, 5 H).

MS: $m/z = 399$ [$(M - t\text{-Bu})^+$], 357, 91, 73.

HRMS Calcd for $C_{25}H_{32}O_6Si + Na$ [$(M+Na)^+$]: 479.1866. Found: 479.1864.

(2*S**,3*S**,4*S**)-2-[(4-Benzyloxy-3-methoxy)phenyl-α*S**-(*tert*-butyldimethylsiloxy)]methyl-3-carboxy-4-[(3,4-methylenedioxy)phenyl]butyrolactone (5) and (2*S**,3*S**,4*R**)-2-[(4-Benzyloxy-3-methyl)phenyl-α*S**-(*tert*-butyldimethylsiloxy)]methyl-3-carboxy-4-[(3,4-methylenedioxy)phenyl]butyrolactone (16):

To a mixture of **6** (303 mg, 0.66 mmol) and piperonal (108 mg, 0.73 mmol) in toluene (8 mL) was added KHMDS (0.5 M in toluene, 1.5 mL, 0.73 mmol) at −90 °C. The mixture was stirred at the same temperature for 30 min and then quenched with AcOH (0.5 mL, 8 mmol) in toluene (2 mL) and warmed to r.t. The mixture was diluted with EtOAc (30 mL) and the organic layer was washed with H_2O (30 mL). The aqueous layer was extracted with EtOAc (30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated to dryness in vacuo. The residue was chromatographed on silica gel using $CHCl_3$/MeOH (100 : 1) as an eluent to afford **5** (271 mg, 67 %) and **16** (45 mg, 11 %).

Compound **5**:

IR (film): $\nu = 3300, 1780, 1713, 1507, 1255\ cm^{-1}$.

^1H NMR: $\delta = -0.14$ (s, 3 H), 0.02 (s, 3 H), 0.85 (s, 9 H), 3.13–3.26 (m, 2 H), 3.84 (s, 3 H), 5.07 (s, 2 H), 5.40 (br s, 1 H), 5.86 (br s, 1 H), 5.93 (s, 2 H), 6.68–6.87 (m, 6 H), 7.08–7.75 (m, 5 H).

MS: $m/z = 549$ [$(M - t\text{-Bu})^+$], 531, 357, 91.

HRMS: m/z Calcd for $C_{33}H_{38}O_9Si+Na$ [$(M+Na)^+$]: 629.2183. Found: 629.2178.

Compound **16**:

IR (film): $\nu = 3300, 1792, 1710, 1500, 1259$ cm^{-1}.

^{1}H NMR: $\delta = -0.37$ (s, 3 H), 0.08 (s, 3 H), 0.79 (s, 9 H), 3.34 (dd, 1 H, $J = 6.7, 7.7$ Hz), 3.72 (dd, 1 H, $J = 5.2, 6.7$ Hz), 3.91 (s, 3 H), 5.09 (d, 1 H, $J = 7.7$ Hz), 5.15 (s, 2 H), 5.45 (d, 1 H, $J = 5.2$ Hz), 5.94 (s, 2 H), 6.70–7.05 (m, 6 H), 7.29–7.47 (m, 5 H).

MS: $m/z = 549$ [$(M-t\text{-Bu})^+$], 531, 357, 91.

HRMS: m/z Calcd for $C_{33}H_{38}O_9Si+Na$ [$(M+Na)^+$]: 629.2183. Found: 629.2170.

(2S,3S*,4S*)-4-(4-Benzyloxymethoxyphenyl)-2-[αS*-(tert-butyldimethylsiloxy)-(3,4-methylenedioxy)phenyl]methyl-3-carboxybutyrolactone* (**19**) *and (2S*,3S*,4R*)-4-(4-Benzyloxy-3-methoxyphenyl)-2-[αS*-(tert-butyldimethylsiloxy)-(3,4-methylenedioxy)phenyl]-methyl-3-carboxybutyrolactone* (**21**):

The lactones **19** (64%) and **21** (10%) were obtained from **20** and benzylvanillin in the same manner as described above.

Compound **19**:

IR (film): $\nu = 3400, 1778, 1711, 1517, 1255$ cm^{-1}.

^{1}H NMR: $\delta = -0.19$ (s, 3 H), 0.02 (s, 3 H), 0.88 (s, 9 H), 3.18 (dd, 1 H, $J = 4.2, 8.7$ Hz), 3.34 (dd, 1 H, $J = 5.2, 8.7$ Hz), 3.88 (s, 3 H), 5.14 (s, 2 H), 5.31 (d, 1 H, $J = 4.2$ Hz), 5.78 (d, 1 H, $J = 5.2$ Hz), 5.87 (d, 1 H, $J = 1.4$ Hz), 5.89 (d, 1 H, $J = 1.4$ Hz), 6.68 (d, 1 H, $J = 7.9$ Hz), 6.72–6.90 (m, 5 H), 7.28–7.42 (m, 5 H).

MS: $m/z = 549$ [$(M-t\text{-Bu})^+$], 531, 265, 91.

HRMS: m/z Calcd for $C_{33}H_{38}O_9Si+Na$ [$(M+Na)^+$]: 629.2183. Found: 629.2153.

Compound **21**: mp 206–207 °C.

IR (KBr): $\nu = 3400, 1778, 1743, 1513, 1252$ cm^{-1}.

^{1}H NMR: $\delta = -0.38$ (s, 3 H), -0.10 (s, 3 H), 0.79 (s, 9 H), 3.35 (dd, 1 H, $J = 6.7, 8.3$ Hz), 3.74 (dd, 1 H, $J = 5.3, 6.7$ Hz), 3.86 (s, 3 H), 5.02 (d, 1 H, $J = 8.3$ Hz), 5.10 (s, 2 H), 5.48 (d, 1 H, $J = 5.3$ Hz), 5.95 (d, 1 H, $J = 1.4$ Hz), 5.98 (d, 1 H, $J = 1.4$ Hz), 6.77–6.87 (m, 3 H), 6.90–6.98 (m, 3 H), 7.29–7.42 (m, 5 H).

MS: $m/z = 549$ [$(M-t\text{-Bu})^+$], 531, 265, 91.

Anal. Calcd for $C_{33}H_{38}O_9Si$: C, 65.33; H, 6.31. Found: C, 65.16; H, 6.29.

(2*S**,4*S**)-4-(4-Benzyloxy-3-methoxyphenyl)-2-[α*S**-(*tert*-butyldimethylsiloxy)-(3,4-methylenedioxy)phenyl]methyl-3-methoxycarbonylbutyrolactone (22):

To a solution of **19** (2.9 g, 4.8 mmol) in MeOH (20 mL) was added dropwise TMSCHN$_2$ (2 M in Et$_2$O, 4.8 mL, 9.6 mmol) at 0 °C and the mixture stirred at r.t. for 30 min. After evaporation of the solvent in vacuo, the residue was purified on silica gel chromatography using hexane/EtOAc (2:1) as an eluent to afford **22** (2.9 g, 98%).

IR (film): $\nu = 1778, 1742, 1516, 1259, 1038$ cm^{-1}.

^{1}H NMR: $\delta = -0.17$ (s, 3 H), 0.05 (s, 3 H), 0.94 (s, 9 H), 3.19–3.35 (m, 2 H), 3.45 (s, 3 H), 3.88 (s, 3 H), 5.14 (s, 2 H), 5.30 (d, 1 H, $J = 3.7$ Hz), 5.81 (d, 1 H, $J = 6.2$ Hz), 5.95 (s, 2 H), 6.74–6.86 (m, 6 H), 6.28–7.42 (m, 5 H).

MS: $m/z = 620$ (M^+), 563, 265, 91.

HRMS: m/z Calcd for $C_{34}H_{40}O_9Si+Na$ [$(M+Na)^+$]: 643.2339. Found: 643.2339.

(2*S**,3*S**,4*S**,5*S**)-2-[(4-Benzyloxy-3-methoxy)phenyl]-4-[α*S**-(*tert*-butyldimethylsiloxy)-(3,4-methylenedioxy)phenyl]methyl-5-hydroxy-3-methoxycarbonyltetrahydrofuran (23):

To a solution of **22** (2.7 g, 4.3 mmol) in toluene (60 mL) was added dropwise DIBAL-H (1.5 M in toluene, 4.5 mL, 6.7 mmol) at −70 °C. The mixture was allowed to warm to 0 °C over 2 h and then quenched with H$_2$O (10 mL) and diluted with EtOAc (100 mL). The organic layer was washed with 1 N HCl (60 mL) and brine (60 mL), dried (MgSO$_4$), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel using hexane/EtOAc (3:1) as an eluent afforded **23** (1.9 g, 70%); mp 106–107 °C.

IR (KBr): $\nu = 3412, 1710, 1594, 1514, 1252$ cm^{-1}.

^{1}H NMR: $\delta = -0.40$ (s, 3 H), -0.08 (s, 3 H), 0.78 (s, 9 H), 2.72 (m, 1 H), 3.31 (dd, $J = 2.4, 8.0$ Hz), 3.86 (s, 3 H), 3.89 (s, 3 H), 4.85 (d, 1 H, $J = 10.5$ Hz), 4.92 (dd, 1 H, $J = 4.8, 12.6$ Hz), 5.16 (s, 2 H), 5.30 (d, 1 H, $J = 2.4$ Hz), 5.77 (d, 1 H, $J = 12.6$ Hz), 5.96 (s, 2 H), 6.72–6.89 (m, 6 H), 6.29–7.46 (m, 5 H).

MS: $m/z = 622$ (M^+), 265, 173, 91.

Anal. .Calcd for $C_{34}H_{42}O_9Si$: C, 65.57; H, 6.80. Found: C, 65.49; H, 6.84.

(2*S**,3*S**,4*S**)-2-[(4-Benzyloxy-3-methoxy)phenyl]-4-[α*S**-(*tert*-butyldimethylsiloxy)-(3,4-methylenedioxy)phenyl]methyl-3-methoxycarbonyltetrahydrofuran (25):

Thiocarbonyldiimidazole (159 mg, 0.90 mmol) was added to a solution of **23** (185 mg, 0.30 mmol) in 1,2-dichloroethane (10 mL) at r.t. and the mixture was refluxed for 3 h. The mixture was cooled to r.t. and directly charged on a silica gel column and eluted with hexane/EtOAc (4:1) to afford **24**. Compound **24** was dissolved in xylene (10 mL) and Bu$_3$SnH (0.25 mL, 0.90 mmol) and AIBN (10 mg, 0.06 mmol) were added at r.t. and the mixture was refluxed for 1 h. After addition of sat. aq KF (20 mL) at r.t. the solid was filtered and the filtrate was extracted with EtOAc (50 mL). The organic layer was dried (MgSO$_4$) and concentrated in vacuo. The residue was chromatographed on silica gel using hexane/EtOAc (8:1) as an eluent to afford **25** (112 mg, 62%).

IR (KBr): $\nu = 1734, 1598, 1514, 1255, 1041$ cm^{-1}.

^{1}H NMR: $\delta = -0.38$ (s, 3 H), -0.06 (s, 3 H), 0.79 (s, 9 H), 2.79 (m, 1 H), 3.17 (dd, $J = 3.3, 7.7$ Hz), 3.53 (dd, $J = 7.9, 8.0$ Hz), 3.77 (s, 3 H), 3.82 (dd, 1 H, $J = 5.2, 8.0$ Hz), 3.89 (s, 3 H), 4.84 (d, 1 H, $J = 9.7$ Hz), 5.10 (d, 1 H, $J = 3.3$ Hz), 5.15 (s, 2 H), 5.96 (s, 2 H), 6.65–6.88 (m, 6 H), 7.18–7.46 (m, 5 H).

MS: $m/z = 549$ [$(M-t\text{-Bu})^+$], 265, 91, 73.

HRMS: m/z Calcd for $C_{34}H_{42}O_8Si+Na$ [$(M+Na)^+$]: 629.2547. Found: 629.2546.

(1*S**,2*S**,5*S**,6*S**)-6-[(4-Benzyloxy-3-methoxy)phenyl]-2-[(3,4-methylenedioxy)phenyl]-4-oxo-3,7-dioxabicyclo[3.3.0]octane [26, (±)-Benzylstyraxin]:

To a solution of **25** (353 mg. 0.58 mmol) in DMF (20 mL) and NMP (2 mL) was added NH$_4$F · HF (132 mg, 2.3 mmol) at r.t. and the mixture was stirred for 3 d. The mixture was diluted with EtOAc (100 mL) and washed with brine (100 mL). The organic layer was dried (MgSO$_4$), and concentrated in vacuo. The residue was chromatographed on silica gel using hexane/EtOAc (10:1) as an eluent to afford **26** (230 mg, 86%); mp 142–143 °C.

IR (KBr): $\nu = 1771, 1592, 1510, 1490, 1257$ cm^{-1}.

^{1}H NMR: $\delta = 3.20$ (m, 1 H), 3.46 (dd, 1 H, $J = 3.7, 9.2$ Hz), 3.91 (s, 3 H), 4.02 (dd, 1 H, $J = 4.7, 9.2$ Hz), 4.33 (dd, 1 H, $J = 6.7, 9.4$ Hz), 5.15 (s, 2 H), 5.29 (d, 1 H, $J = 3.8$ Hz), 5.34 (d, 1 H, $J = 3.7$ Hz), 5.98 (s, 2 H), 6.70–6.90 (m, 5 H), 6.94 (s, 1 H), 7.28–7.45 (m, 5 H).

MS: $m/z = 460$ (M^+), 135, 161, 91.

Anal. Calcd for $C_{27}H_{24}O_7$: C, 70.43; H, 5.25. Found: C, 70.38; H; 5.20.

(1*S**,2*S**,5*S**,6*S**)-6-(4-Hydroxy-3-methoxyphenyl)-2-[3,4-(methylenedioxy)phenyl]-4-oxo-3,7-dioxabicyclo[3.3.0]octane [1a, (±)-Styraxin]:

To a solution of **26** (120 mg, 0.26 mmol) in EtOAc (20 mL) was added 10% Pd/C (20 mg) under a N$_2$ atmosphere. H$_2$ was bubbled into the mixture at r.t. for 1 h with stirring. The mixture was filtered through Celite pad and the filtrate was concentrated in vacuo. The residue was purified on silica gel chromatography using hexane/EtOAc (1:1) as an eluent to afford **1a** (88 mg, 91%); mp 154–155 °C.

IR (KBr): $\nu = 3494, 1762, 1608, 1516, 1456$ cm^{-1}.

^{1}H NMR: $\delta = 3.20$ (m, 1 H), 3.47 (dd, 1 H, $J = 3.7, 9.2$ Hz), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.02 (dd, 1 H, $J = 4.7, 9.2$ Hz), 4.33 (dd, 1 H, $J = 6.7, 9.4$ Hz), 5.30 (d, 1 H, $J = 3.7$ Hz), 5.34 (d, 1 H, $J = 3.6$ Hz), 5.61 (s, 1 H), 5.98 (s, 2 H), 6.70–6.94 (m, 6 H).

MS: $m/z = 370$ (M^+), 285, 161, 151.

Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 64.73; H, 4.84.

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