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New Asymmetric Synthesis of a Pheromone Component of the Shield Bug *Cantao Parentum*

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Abstract—A novel procedure has been developed for the synthesis of (2*S*,4*R*,6*R*,8*S*)-2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane, a pheromone component of the shield bug *Cantao Parentum*, through intermediate cyclopropanol derivatives in the key stages of carbon chain construction and introduction of functional groups.

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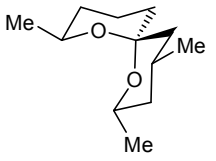
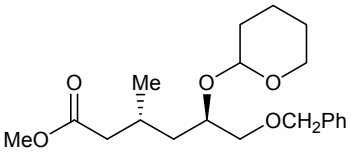
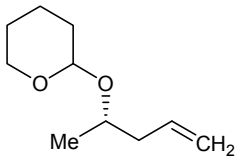
Structurally relatively simple spiro acetals are widespread in nature and are components of higher insect secretions. It has recently been found that the main component of the abdominal gland of the shield bug *Cantao Parentum* (White) is (2*S*,4*R*,6*R*,8*S*)-2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane (**I**), an unusual representative of methyl-substituted spiro acetals secreted by insects [1]. The synthesis of compound **I** was reported in a few publications [1–3].



I



II



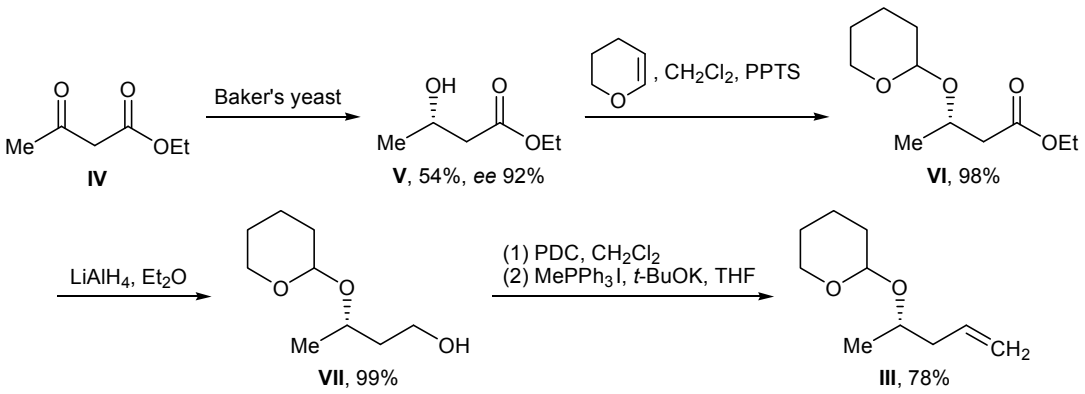
III

In the present work the carbon skeleton of molecule **I** was built up via reductive cyclopropanation with ligand exchange between key building block **II** and tetrahydropyran-protected alkenol **III**. Analogous cyclopropanol strategy was used previously to synthesize some bioactive compounds [4].

Compound **III** was prepared according to the known scheme of consecutive transformations [5–7] (Scheme 1). Enzymatic reduction of ethyl acetoacetate (**IV**) with baker's yeast gave hydroxy ester **V** which was treated with dihydropyran to protect the hydroxy group. The optical purity of ester **V** was determined by Mosher's method, from the intensity ratio of the signals of methoxy (δ 3.54 and 3.56 ppm) and methyl protons (δ 1.34 and 1.43 ppm) in the ^{1}H NMR spectrum of the acylation product of **V** with (*S*)- and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (Mosher's acid chloride) [8]. Tetrahydropyranyl ether **VI** was reduced with lithium tetrahydridoaluminate, alcohol **VII** thus obtained was carefully oxidized with pyridinium dichromate (PDC), and intermediate labile aldehyde was subjected to Wittig olefination. The overall yield of compound **III** in five steps was 41% (Scheme 1).

Key ester **II** was synthesized from accessible lactone **VIII** which was prepared in turn starting from ethyl 3,3-diethoxypropionate (**IX**) according to previously developed procedures [9] (Scheme 2). Cyclopropanation of **IX**, mesylation of **X**, and oxidation of the diethyl acetal moiety in **XI** afforded ethyl 2-(1-methanesulfonyloxycyclopropyl)acetate (**XII**). Cationic cyclopropyl–allyl rearrangement of the latter gave ester **XIII** having an allyl bromide fragment, and compound **XIII** was converted via mild Barbier allylation [10] into organotin derivative **XIV** [11]. Unsaturated lactone (*R*)-**XV** was obtained by modified asymmetric allylation according to Keck [12]. The high enantiomeric excess of (*R*)-**XV** was determined by Mosher's method [8] (from the intensity ratio of the signals of the methoxy groups, δ 3.41 and 3.57 ppm) after transformation of lactone **XV** into labile alcohol via successive reduction to the corresponding diol, ring closure

Scheme 1.



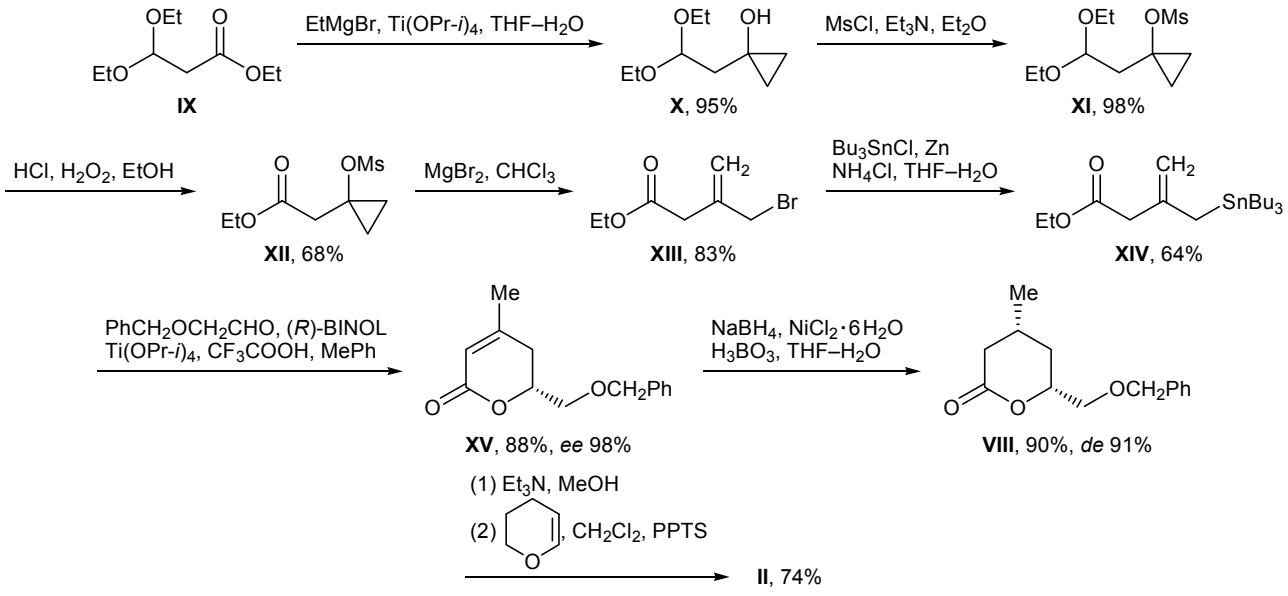
of the latter to unsaturated pyran, and removal of the benzyl protecting group (see the procedure for the synthesis of the *S* isomer [9]).

Diastereoselective reduction of the prochiral double bond in lactone **XV** [9] gave key lactone **VIII** which was subjected to column chromatography on silica gel; as a result, the ratio of the *cis* and *trans* isomers of **VIII** increased from 10:1 to 20:1. Treatment of **VIII** with triethylamine in methanol produced intermediate hydroxy ester, and the hydroxy group in the latter was protected by transformation into tetrahydropyranyl ether (Scheme 2). In this way, the second building block **II** was isolated in an overall yield of 20% (9 steps) starting from readily accessible ethyl 3,3-diethoxypropionate (**IX**).

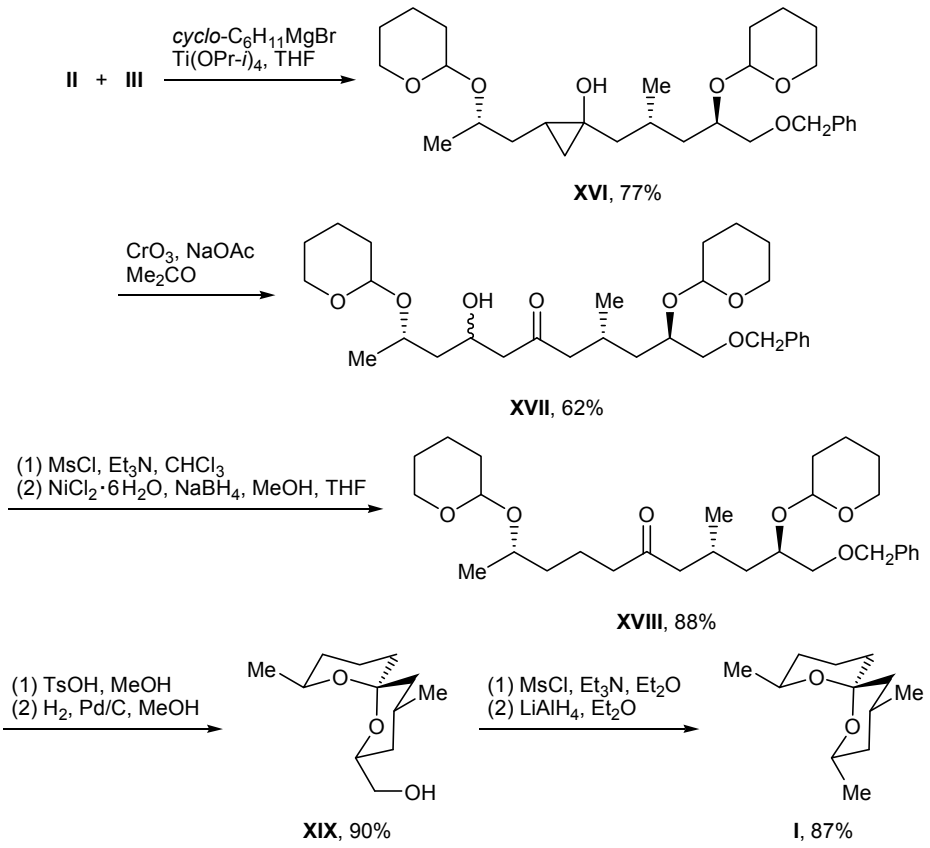
Reductive cyclopropanation of **II** with the use of cyclohexylmagnesium bromide and an equivalent amount of titanium tetraisopropoxide and ligand exchange with alkene **III** afforded disubstituted cyclopropanol **XVI** as a mixture of diastereoisomers in a moderate yield (Scheme 3). Oxidative cleavage of the cyclopropane ring in **XVI** at the C^1–C^2 bond by the action of chromium(VI) oxide in acetone at 0°C [13] gave hydroxy ketone **XVII**. The hydroxy group in the latter was removed via mesylation, and subsequent reduction of the double C=C bond led to ketone **XVIII**. Addition of methanol in the reduction process improved the solubility and facilitated separation of products resulting from side reduction of the carbonyl group.

The tetrahydropyranyl protecting groups were removed from **XVIII** by treatment with methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid, and the intermediate cyclic acetal thus formed was subjected to reductive debenzylation by hydrogenolysis over Pd/C in methanol. The major diastereo-

Scheme 2.



Scheme 3.



isomer of **XIX** was isolated by column chromatography, and its spectral characteristics completely coincided with those reported in [3]. Successive mesylation and exhaustive reduction of the intermediate methanesulfonate with lithium tetrahydridoaluminate in diethyl ether at room temperature afforded target pheromone component **I** whose spectral parameters were identical to those given in [3]. The overall yield of **I** in the 17-step synthesis starting from ester **IX** was 7%.

The described methodology for the synthesis of a secretion component of the shield bug *Cantao Parentum* is advantageous due to high yields, simple experimental procedures, and the use of cheap and accessible reagents; it requires no expensive or toxic catalysts and ensures convenient combination of complex polyfunctional building blocks into the target carbon skeleton.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded from solutions in chloroform-*d* on a Bruker AC 400 spectrometer at 400 and 100 MHz, respectively. The IR spectra of solutions in carbon tetrachloride were measured on a Bruker Vertex 70 spectrometer. The optical rotations were determined at room temperature on an SM-3 polarimeter (scale mark 0.05°). The pure products were isolated by chromatography on silica gel (70–230 mesh). All solvents were dried according to standard methods and distilled before use.

Ethyl (3*S*)-3-hydroxybutanoate (V). Dry baker's yeast, 25 g, was dispersed in 300 mL of water at 30°C, 50 g of saccharose was added, the mixture was vigorously stirred for 10 min to initiate fermentation, and 3 g (23 mmol) of freshly distilled ethyl acetoacetate (**IV**) was added. The mixture was vigorously stirred for 12 h at a bath temperature of 35–38°C, 100 mL of diethyl ether was added, and the mixture was filtered through a layer of alumina. The organic phase was separated, the aqueous phase was extracted with diethyl ether (3×30 mL), the extracts were combined with the organic phase, washed with brine (150 mL), and dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was subjected to chromatography using petroleum ether–ethyl acetate (40:1 to 5:1) as eluent. Yield 1.64 g (54%). The spectral parameters of ester **V** were consistent with those reported in [7].

Ethyl (3*S*)-3-(tetrahydro-2*H*-pyran-2-yloxy)-butanoate (VI). Hydroxy ester **V**, 0.70 g (5.3 mmol), was dissolved in 10 mL of anhydrous methylene chloride, 0.56 g (6.6 mmol) of 3,4-dihydro-2*H*-pyran and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) were added, and the mixture was heated for 2.5 h under reflux. When the reaction was complete (TLC), the mixture was washed with a saturated solution of $NaHCO_3$ (100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to obtain a compound **VI** as a colorless oily substance. Yield 1.12 g (98%). The spectral parameters of the product were consistent with those reported in [14].

(3*S*)-3-(Tetrahydro-2*H*-pyran-2-yloxy)butan-1-ol (VII). A solution of 1.30 g (6.0 mmol) of protected hydroxy ester **VI** in 6 mL of anhydrous diethyl ether was added under stirring to a suspension of 0.12 g (3 mmol) of $LiAlH_4$ in 6 mL of anhydrous diethyl ether. The mixture was stirred for 1 h and diluted with 30 mL of diethyl ether, 0.5 mL of water was added, the mixture was filtered, and the precipitate was washed with diethyl ether (15 mL). The organic phases were combined, dried over Na_2SO_4, and evaporated under reduced pressure to isolate compound **VII** as a mixture of diastereoisomers. Yield 1.03 g (99%). IR spectrum, ν, cm^{-1}: 3401, 1076, 1023. ^1H NMR spectrum, δ, ppm: 1.14 d (3H, CH_3, J = 6.1 Hz), 1.26 d (3H, CH_3, J = 6.4 Hz), 1.43–1.55 m (8H, $CH_2CH_2C\mathbf{H}_2CHO$, $CH_2C\mathbf{H}_2CH_2CHO$), 1.58–1.66 m (1H, $C\mathbf{H}_2CH_2OH$), 1.68–1.81 m (7H, $C\mathbf{H}_2CH_2OH$, $C\mathbf{H}_2CH_2CH_2CHO$), 2.52 br.s (1H, OH), 3.27 br.s (1H, OH), 3.45–3.51 m (2H, $CH_3C\mathbf{H}OCH$), 3.62–3.71 m (2H, $CH_2C\mathbf{H}_2O$), 3.73–3.85 m (2H, $CH_2C\mathbf{H}_2O$), 3.86–3.96 m (3H, CH_2OH), 3.98–4.06 m (1H, $C\mathbf{H}_2OH$), 4.54–4.56 m (1H, OCHO), 4.66–4.68 m (1H, OCHO). ^{13}C NMR spectrum, δ_C, ppm: 20.2, 20.3, 21.2, 22.0, 25.4, 25.6, 31.5, 31.6, 39.0, 39.3, 60.0, 60.4, 63.2, 64.6, 70.8, 74.0, 98.1, 99.6. Found, %: C 62.06; H 10.39. $C_9H_{18}O_3$. Calculated, %: C 62.04; H 10.41.

2-[(2*S*)-Pent-4-en-2-yloxy]tetrahydro-2*H*-pyran (III). A solution of 1.03 g (5.9 mmol) of alcohol **VII** in 10 mL of anhydrous methylene chloride was added in one portion to a suspension of 3.22 g (8.8 mmol) of pyridinium dichromate in 15 mL of anhydrous methylene chloride, and the mixture was stirred for 10 h until the reaction was complete. The mixture was filtered through a layer of silica gel, and the filtrate was evaporated under reduced pressure. The residue was dissolved in 50 mL of diethyl ether, the solution was filtered through a layer of silica gel, and the solvent was removed under reduced pressure. The aldehyde thus obtained (1.21 g) was used in the next step without additional purification. A suspension of 2.34 g (5.8 mmol) of methyltriphenylphosphonium iodide in 12 mL of THF was cooled to −78°C, 0.62 g (5.5 mmol) of potassium *tert*-butoxide was added, the mixture was stirred for 1.5 h, a solution of 1.21 g (5.3 mmol) of the aldehyde in 6 mL of THF was slowly added over a period of 1 h at −5°C, and the mixture was stirred for 2 h. The mixture was diluted with water (30 mL), the aqueous phase was extracted with chloroform (3×15 mL), the extracts were combined and dried over $MgSO_4$, the solvent was distilled off under reduced pressure, and the product was isolated by chromatography on silica gel using petroleum ether–ethyl acetate (100:1) as eluent. Yield 0.78 g (78%). IR spectrum, ν, cm^{-1}: 1261, 1021. ^1H NMR spectrum, δ, ppm: 1.08 d and 1.19 d (1.5H each, CH_3, J = 6.1 Hz), 1.42–1.84 m (6H, $OCHC\mathbf{H}_2C\mathbf{H}_2C\mathbf{H}_2$), 2.11–2.37 m (2H, $C\mathbf{H}_2CH{=}CH_2$), 3.43–3.55 m (1H, $CH_3C\mathbf{H}OCH$), 3.76–3.95 m (2H, CH_2O), 4.54–4.78 m (1H, OCHO), 4.91–5.07 m (2H, $CH_2{=}$), 5.71–5.86 m (1H, CH=). ^{13}C NMR spectrum, δ_C, ppm: 19.6, 19.9, 20.5, 21.1, 25.4, 25.5, 30.9, 31.1, 40.7, 41.9 62.3, 62.6, 70.8, 72.6, 97.9, 98.3, 116.6, 116.8, 134.8, 135.3. Found, %: C 70.59; H 10.62. $C_{10}H_{18}O_2$. Calculated, %: C 70.55; H 10.66.

1-(2,2-Diethoxyethyl)cyclopropanol (X). A solution of 9.5 g (50 mmol) of ester **IX** and 2.8 mL (10 mmol) of Ti(OPr-*i*)$_4$ in 50 mL of THF–Et_2O (1:1) was cooled to 10°C, a solution of 150 mmol of ethylmagnesium bromide in 150 mL of THF–Et_2O (1:1) was added under stirring over a period of 6 h, and the mixture was stirred for 24 h. The solvent was removed under reduced pressure, the residue was treated with 200 mL of diethyl ether and 15 mL of a saturated aqueous solution of ammonium chloride under efficient cooling, the mixture was filtered, the precipitate was washed with diethyl ether (3×50 mL), and the organic phase was washed with brine (100 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to isolate 8.27 g (95%) of compound **X** whose spectral parameters were consistent with those reported in [15].

1-(2,2-Diethoxyethyl)cyclopropyl methanesulfonate (XI). A solution of 5.38 g (31 mmol) of compound **X** in 40 mL of anhydrous diethyl ether was cooled to 0°C, 8.6 mL (62 mmol) of triethylamine was added under stirring, and a solution of 3.6 mL (37 mmol) of methanesulfonyl chloride in 40 mL of anhydrous diethyl ether was added dropwise. The mixture was stirred for 2 h and treated with a saturated

aqueous solution of $NaHCO_3$ (100 mL), the organic layer was separated, the aqueous layer was extracted with diethyl ether (3×25 mL), and the extracts were combined with the organic phase, washed with brine (50 mL), and dried over Na_2SO_4. Removal of the solvent gave methanesulfonate **XI** which was brought into the next step without additional purification. Yield 7.66 g (98%). IR spectrum, ν, cm^{-1}: 1331, 1171, 1145. ^1H NMR spectrum, δ, ppm: 0.78–0.82 m (2H, CH_2, cyclopropyl), 1.19 t (6H, C**H**$_3$CH$_2$O, J = 7.0 Hz), 1.21–1.25 m (2H, CH_2, cyclopropyl), 2.13 d (2H, CHC**H**$_2$C, J = 5.4 Hz), 3.00 s (3H, CH_3SO_2), 3.49–3.57 m (2H, CH$_3$C**H**$_2$O), 3.62–3.70 m (2H, CH$_3$C**H**$_2$O), 4.78 t (1H, OCHO, J = 5.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 11.6 (2C), 15.2 (2C), 39.8, 40.3, 62.1, 63.8 (2C), 100.9. Found, %: C 47.66; H 7.94. $C_{10}H_{20}O_5S$. Calculated, %: C 47.60; H 7.99.

Ethyl [1-(methanesulfonyloxy)cyclopropyl]-acetate (XII). A solution of 20.92 g (83.0 mmol) of methanesulfonate **XI** in 130 mL of ethanol was cooled to 0°C, 10.6 mL of concentrated aqueous HCl and 14.5 mL of 33% hydrogen peroxide were added in succession, and the mixture was stirred for 1 h and kept for 5 h at 50–55°C. The mixture was cooled to 0°C, 7.1 mL of concentrated aqueous HCl and 9.7 mL of 33% hydrogen peroxide were added, and the mixture was heated again for 5 h at 50–55°C. The main part of the solvent was removed under reduced pressure, the residue was diluted with ethyl acetate (100 mL), the mixture was neutralized with an aqueous solution of $NaHCO_3$ (400 mL), the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3×50 mL). The extracts were combined with the organic phase and dried over Na_2SO_4, and the solvent was distilled off under reduced pressure to isolate compound **XII** which was used in the next step without additional purification. Yield 12.53 g (68%). IR spectrum, ν, cm^{-1}: 1740, 1358, 1175, 1037. ^1H NMR spectrum, δ, ppm: 0.88–0.91 m (2H, CH_2, cyclopropyl), 1.27 t (3H, C**H**$_3$CH$_2$O, J = 7.2 Hz), 1.36–1.40 m (2H, CH_2, cyclopropyl), 2.84 br.s (2H, CH_2CO), 3.03 s (3H, CH_3SO_2), 4.18 q (2H, CH$_3$C**H**$_2$O, J = 7.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 12.0 (2C), 14.1, 39.7, 41.1, 60.8, 62.2, 169.9. Found, %: C 43.27; H 6.30. $C_8H_{14}O_5S$. Calculated, %: C 43.23; H 6.35.

Ethyl 3-(bromomethyl)but-3-enoate (XIII). A solution of 29.7 mL (344 mmol) of 1,2-dibromoethane in 200 mL of anhydrous diethyl ether was slowly added dropwise to 8.06 g (336 mmol) of magnesium turnings in 100 mL of anhydrous diethyl ether, and the mixture was heated under reflux until magnesium dissolved completely. About 180 mL of diethyl ether was distilled off from the resulting solution of $MgBr_2$ to obtain a colorless viscous mixture, a solution of 37.30 g (168 mmol) of methanesulfonate **XII** in 200 mL of chloroform was added under stirring, and the mixture was heated for 8 h under reflux. The mixture was treated with 200 mL of water, the organic phase was separated, the aqueous phase was extracted with chloroform (3×75 mL), the extracts were combined with the organic phase and dried over $MgSO_4$, the solvent was distilled off under reduced pressure, and the product was isolated by chromatography on silica gel using petroleum ether–ethyl acetate (100:1) as eluent. Yield 16.23 g (83%). IR spectrum: ν 1740 cm^{-1}. ^1H NMR spectrum, δ, ppm: 1.26 t (3H, C**H**$_3$CH$_2$O, J = 7.2 Hz), 3.25 br.s (2H, CH_2CO), 4.11 br.s (2H, CH_2Br), 4.15 q (2H, CH$_3$C**H**$_2$O, J = 7.2 Hz), 5.11 br.s and 5.34 br.s (1H each, CH_2=). ^{13}C NMR spectrum, δ_C, ppm: 14.1, 36.1, 38.8, 60.9, 119.3, 138.7, 170.7. Found, %: C 40.64; H 5.33. $C_7H_{11}BrO_2$. Calculated, %: C 40.60; H 5.35.

Ethyl 3-[(tributylstannyl)methyl]but-3-enoate (XIV). Tributylstannyl chloride, 7 g (22 mmol), was dissolved in 10 mL of THF, 150 mL of a saturated aqueous solution of ammonium chloride and 1.68 g (26 mmol) of zinc were added under vigorous stirring, a solution of 5.38 g (26 mmol) of compound **XIII** in 26 mL of THF was added over a period of 20 min, 30 mL of a saturated aqueous solution of ammonium chloride and 1.68 g (26 mmol) of zinc were additionally added, and the mixture was vigorously stirred for 1 h and extracted with diethyl ether (3×75 mL). The combined extracts were dried over $MgSO_4$, the solvent was distilled off under reduced pressure, and the product was isolated by chromatography on silica gel using petroleum ether–ethyl acetate (120:1) as eluent. Yield 6.07 g (64%). The spectral parameters of the product were in agreement with those given in [11].

(6*R*)-6-(Benzyloxymethyl)-4-methyl-3,6-dihydro-2*H*-pyran-2-one (XV). A 0.1 M solution of Ti(OPr-*i*)$_4$, 5.8 mL (0.6 mmol), and 0.2 mL (20 μmol) of a 0.1 M solution of trifluoroacetic acid were added to a mixture of 0.34 g (1.2 mmol) of (*R*)-BINOL and 2.5 g of 4-Å molecular sieves (preliminarily calcined at 125–130°C in an oil-pump vacuum) in 20 mL of anhydrous toluene, and the mixture was stirred for 2.5 h at room temperature. The mixture was cooled to –30°C, a mixture of 7.76 g (18.0 mmol) of compound **XIV** and 1.76 g (12.0 mmol) of benzyloxyacetaldehyde [16] in 10 mL of anhydrous toluene was added, and the mixture was left to stand for 7 days in a refrigerator at

–15°C without stirring. The mixture was then treated under vigorous stirring with a saturated aqueous solution of $NaHCO_3$ (100 mL), the organic phase was separated, the aqueous phase was extracted with chloroform (3×30 mL), and the extracts were combined with the organic phase and dried over $MgSO_4$. The solvent was distilled off under reduced pressure, and the product was isolated by chromatography using petroleum ether–ethyl acetate (100:1 to 5:1) as eluent. Yield 1.22 g (88%), $[\alpha]_D$ = –120.7° (*c* = 1.2, $CHCl_3$). IR spectrum: ν 1731 cm^{-1}. ^1H NMR spectrum, δ, ppm: 1.98 s (3H, CH_3), 2.26 d.d (1H, C**H**$_2$CHO, *J* = 17.9, 4 Hz), 2.55 d.d (1H, C**H**$_2$CHO, *J* = 17.9, 11.7 Hz), 3.63–3.71 m (2H, CHC**H**$_2$OCH$_2$Ph), 4.53–4.57 m (1H, CH$_2$C**H**O), 4.59 br.s (2H, C**H**$_2$Ph), 5.80 br.s (1H, CHCO), 7.28–7.40 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 23.0, 31.3, 70.7, 73.6, 75.9, 116.2, 128.0 (2C), 128.3 (2C), 128.4, 131.6, 157.1, 164.5. Found, %: C 72.42; H 6.91. $C_{14}H_{16}O_3$. Calculated, %: C 72.39; H 6.94.

(4*R*,6*R*)-6-(Benzyloxymethyl)-4-methyltetrahydro-2*H*-pyran-2-one (VIII). An emulsion of 2.32 g (10 mmol) of compound **XV** in a mixture of 50 mL of THF and 50 mL of water was cooled to 0°C, 2.60 g (11 mmol) of $NiCl_2 \cdot 6H_2O$ and 2.34 g (40 mmol) of H_3BO_3 were added, and 0.84 g (22 mmol) of $NaBH_4$ was added in portions under stirring over a period of 10 min. The mixture was stirred for 0.5 h on cooling, 15 g of sodium chloride was added at room temperature, and the mixture was extracted with diethyl ether (4×25 mL). The combined extracts were dried over Na_2SO_4, the solvent was distilled off under reduced pressure, and the major (4*R*,6*R*)-diastereoisomer of **VIII** was isolated by chromatography using petroleum ether–ethyl acetate (40:1) as eluent. Yield 2.11 g (90%), $[\alpha]_D$ = –12.8° (*c* = 1.4, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1743, 1435, 1161. ^1H NMR spectrum, δ, ppm: 1.04 d (3H, C**H**$_3$CH, *J* = 6.4 Hz), 1.35–1.45 m (1H, CH$_3$C**H**), 1.93–1.98 m (1H, CC**H**$_2$CHO), 2.01–2.09 m (2H, CC**H**$_2$CHO, CH$_2$CO), 2.68 d.d.d (1H, CH$_2$CO, *J* = 12.6, 11.0, 2.1 Hz), 3.61 d.d.d (2H, CHC**H**$_2$OCH$_2$Ph, *J* = 14.9, 10.2, 4.6 Hz), 4.43–4.49 m (1H, CH$_2$C**H**O), 4.58 br.s (2H, C**H**$_2$Ph), 7.29–7.38 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 21.6, 26.6, 33.6, 38.2, 72.0, 73.6, 79.2, 127.7 (2C), 127.8, 128.4 (2C), 137.8, 170.8. Found, %: C 71.80; H 7.72. $C_{14}H_{18}O_3$. Calculated, %: C 71.77; H 7.74.

Methyl (3*R*,5*R*)-6-benzyloxy-3-methyl-5-(tetrahydro-2*H*-pyran-2-yloxy)hexanoate (II). Triethylamine, 7 mL (50.5 mmol), was added to a solution of 1.80 g (7.7 mmol) of lactone **VIII** in 30 mL of methanol, and the mixture was kept for 48 h. Excess methanol and triethylamine were removed under reduced pressure, the residue was diluted with 20 mL of anhydrous methylene chloride, 1.33 g (16 mmol) of 3,4-dihydro-2*H*-pyran and a catalytic amount of pyridinium *p*-toluenesulfonate were added, and the mixture was heated for 4 h under reflux. When the reaction was complete (TLC), a catalytic amount of triethylamine was added, the solvent was distilled off under reduced pressure, and the product was isolated by chromatography on silica gel using petroleum ether–ethyl acetate (100:1) as eluent. Yield 1.99 g (74%). IR spectrum, ν, cm^{-1}: 1738, 1077, 1026. ^1H NMR spectrum, δ, ppm: 0.83–0.90 m (4H, OCHC**H**$_2$CH$_2$), 0.95 d (3H, CHC**H**$_3$, *J* = 6.1 Hz), 0.98 d (3H, CHC**H**$_3$, *J* = 6.4 Hz), 1.10–1.86 m (14H, C**H**CH$_3$, CHC**H**$_2$CHO, OCH$_2$C**H**$_2$CH$_2$), 2.12–2.19 m (2H, CH$_2$CO), 2.33–2.41 m (2H, CH$_2$CO), 3.41–3.51 m (4H, C**H**$_2$OCH$_2$Ph), 3.66 s (6H, OCH$_3$), 3.63–3.67 m (1H, C**H**OCHCH$_2$), 3.77–3.84 m (1H, C**H**OCHCH$_2$), 3.86–3.98 m (4H, C**H**$_2$OCH), 4.52 d (2H, C**H**$_2$Ph, *J* = 2.1 Hz), 4.55 d (2H, C**H**$_2$Ph, *J* = 2.3 Hz), 4.63–4.66 m (1H, OCHO), 4.80–4.83 m (1H, OCHO), 7.28–7.36 m (10H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 19.4, 19.8, 22.6, 22.8, 25.4, 25.5, 26.9, 27.0, 31.0, 31.1, 39.3, 39.5, 42.0, 42.1, 51.3, 51.5, 62.5, 62.7, 72.4, 72.6, 73.0, 73.2, 75.2, 75.5, 94.6, 94.9, 127.5 (3C), 127.6 (3C), 128.2 (2C), 128.3 (2C), 138.3, 138.5, 173.4, 173.5. Found, %: C 68.59; H 8.60. $C_{20}H_{30}O_5$. Calculated, %: C 68.54; H 8.63.

1-[(2*R*,4*R*)-5-Benzyloxy-2-methyl-4-(tetrahydro-2*H*-pyran-2-yloxy)pentyl]-2-[(2*S*)-2-(tetrahydro-2*H*-pyran-2-yloxy)propyl]cyclopropan-1-ol (XVI). A solution of 45.0 mmol of cyclohexylmagnesium bromide in 45 mL of THF was added under stirring over a period of 4 h to a solution of 1.70 g (10.0 mmol) of compound **III**, 2.8 mL (10.0 mmol) of Ti(OPr-*i*)$_4$, and 2.45 g (7.0 mmol) of ester **II** in 10 mL of THF, and the mixture was stirred for 12 h. The solvent was evaporated under reduced pressure, the viscous residue was dissolved in 80 mL of diethyl ether, and 5 mL of water was added on cooling. The mixture was filtered, the precipitate was washed with diethyl ether (3×30 mL), and the organic extracts were combined, washed with saturated aqueous solutions of $NaHCO_3$ (50 mL) and NaCl (50 mL), and dried over Na_2SO_4. The solvent was distilled off under reduced pressure, and the product was isolated by chromatography using petroleum ether–ethyl acetate (30:1) as eluent. Yield 2.64 g (77%). IR spectrum, ν, cm^{-1}: 3390, 1076, 1024. ^1H NMR spectrum, δ, ppm: 0.07–0.18 m (1H, CH,

cyclopropyl), 0.82–0.98 m [20H, CH_2 in cyclopropyl, $CHCH_3$, $CHOCHCH_3$, $OCH(CH_2)_3$], 0.99–1.90 m (7H, $CHCH_3$, $CHCH_2CHO$, CH_2S, CH_3CHCH_2), 3.43–4.00 m (9H, OH, CH_2CH_2O, CH_2OCH_2Ph, $CHOCHCH_2$), 4.61–4.83 m (4H, OCHO, CH_2Ph), 7.24–7.37 m (5H, Ph). Found, %: C 80.04; H 9.41. $C_{29}H_{46}O_6$. Calculated, %: C 70.99; H 9.45.

(2*R*,4*R*,2*S*)-1-Benzyloxy-8-hydroxy-4-methyl-2,10-bis(tetrahydro-2*H*-pyran-2-yloxy)undecan-6-one (XVII). A solution of 2.45 g (5 mmol) of compound **XVI** in 10 mL of acetone was added dropwise under stirring at –15°C to a solution of 1.5 g (15 mmol) of CrO_3 and 0.41 g (3.0 mmol) of $NaOAc\cdot 3H_2O$ in a mixture of 8 mL of acetone and 0.3 mL of water. The mixture was stirred for 1 h, treated with 2.12 g (21 mmol) of triethylamine, and diluted with 60 mL of diethyl ether. The resulting suspension was filtered through a fine filter, and the precipitate was thoroughly washed with diethyl ether (3×10 mL). The inorganic material was dissolved in water (20 mL), and the aqueous phase was thoroughly extracted with diethyl ether (4×30 mL). The filtrates and organic extracts were combined, washed with brine (10 mL), and dried over Na_2SO_4. The solvent was distilled off under reduced pressure, and the product was isolated by chromatography using petroleum ether–ethyl acetate (45:1) as eluent. Yield 1.57 g (62%). IR spectrum, ν, cm^{-1}: 3474, 1710, 1373, 1119, 1076, 1014. ^1H NMR spectrum, δ, ppm: 0.90–1.82 m (23H, $CHCH_3$, $CHCH_3$, CH_2CHOCH, $CHOCHCH_3$, $OCHCH_2CH_2CH_2$, CH_2CHOH), 2.18–2.67 m (5H, CH_2CO, OH), 3.38–4.40 m (9H, $CHOCHCH_2$, CH_2CH_2O, CH_2OCH_2Ph, CHOH), 4.52–4.55 m (2H, CH_2Ph), 4.64–4.82 m (2H, OCHO), 7.24–7.36 m (5H, Ph). Found, %: C 68.77; H 9.12. $C_{29}H_{46}O_7$. Calculated, %: C 68.74; H 9.15.

(2*R*,4*R*,2*S*)-1-Benzyloxy-4-methyl-2,10-bis(tetrahydro-2*H*-pyran-2-yloxy)undecan-6-one (XVIII). A solution of 1.87 g (3.7 mmol) of alcohol **XVII** in 25 mL of anhydrous chloroform was cooled to 0°C, 1.1 mL (9.5 mmol) of triethylamine and 0.4 mL (5.5 mmol) of methanesulfonyl chloride in 3 mL of chloroform were added under stirring, and the mixture was stirred for 2 h and treated with a saturated aqueous solution of $NaHCO_3$ (25 mL). The organic phase was separated, the aqueous phase was extracted with chloroform (3×15 mL), the extracts were combined with the organic phase and dried over $MgSO_4$, and the solvent was distilled off under reduced pressure. The residue was dissolved in a mixture of 30 mL of methanol and 10 mL of THF, the solution was cooled to 0°C, 0.43 g (1.9 mmol) of $NiCl_2\cdot 6H_2O$ was added, and 0.28 g (2.2 mmol) of $NaBH_4$ was added in portions under stirring over a period of 5 min. The mixture was stirred for 1 h on cooling, diluted with 30 mL of water at room temperature, and extracted with diethyl ether (4×10 mL). The extracts were combined and dried over Na_2SO_4, the solvent was distilled off under reduced pressure, and the product was isolated by chromatography using petroleum ether–ethyl acetate (100:1) as eluent. Yield 1.60 g (88%). IR spectrum, ν, cm^{-1}: 1712, 1371, 1118, 1077, 1023. ^1H NMR spectrum, δ, ppm: 0.89 d and 0.93 d (1.5H each, $CHCH_3$, J = 6.4 Hz), 1.10 d and 1.22 d (1.5H each, CH_3CHO, J = 6.14 Hz), 1.39–1.89 m [19H, $CHCH_3$, CH_2CH-OCH, $OCH(CH_2)_3$, $(CH_2)_2CH_2CO$], 2.12–2.53 m (4H, CH_2CO), 3.41–3.95 m (8H, $CHOCHCH_2$, CH_2CH_2O, CH_2OCH_2Ph), 4.51–4.55 m (2H, CH_2Ph), 4.61–4.82 m (2H, OCHO), 7.24–7.37 m (5H, Ph). Found, %: C 80.03; H 9.42. $C_{29}H_{46}O_6$. Calculated, %: C 70.99; H 9.45.

[(2*S*,4*R*,6*R*,8*S*)-2,4,8-Trimethyl-1,7-dioxaspiro-[5.5]undec-2-yl]methanol (XIX). A catalytic amount of *p*-toluenesulfonic acid was added to a solution of 0.98 g (2 mmol) of ketone **XVIII** in 6 mL of methanol, and the mixture was heated for 2 h at 50°C. A few drops of triethylamine were added, the mixture was evaporated under reduced pressure, the residue was dissolved in 50 mL of diethyl ether, and the solution was filtered through a layer of silica gel. The filtrate was evaporated under reduced pressure, the residue was dissolved in 10 mL of methanol, 0.03 g of 5% $Pd(OH)_2/C$ was added, and the mixture was vigorously stirred for 4 h under a hydrogen atmosphere. The mixture was diluted with 30 mL of methylene chloride, the catalyst was filtered off and washed with 30 mL of methylene chloride, the solvent was removed under reduced pressure, and the target diastereoisomer was isolated by chromatography on silica gel using petroleum ether–ethyl acetate (35:1) as eluent. Yield 0.36 g (90%). The spectral parameters and specific optical rotation of the product were consistent with those reported in [3].

(2*S*,4*R*,6*R*,8*S*)-2,4,8-Trimethyl-1,7-dioxaspiro-[5.5]undecane (I). A solution of 0.84 g (4.2 mmol) of compound **XIX** in 4 mL of anhydrous diethyl ether was cooled to 0°C, 0.9 mL (6.3 mmol) of triethylamine and 0.5 mL (5.0 mmol) of methanesulfonyl chloride in 1 mL of anhydrous diethyl ether were added in succession, and the mixture was stirred for 2 h and treated with a saturated aqueous solution of $NaHCO_3$ (10 mL).

The organic phase was separated, the aqueous phase was extracted with diethyl ether Et_2O (3×10 mL), the extracts were combined with the organic phase, washed with brine (15 mL), and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was dissolved in 3 ml of anhydrous diethyl ether, the solution was added under stirring to a suspension of 0.16 g (4.2 mmol) of $LiAlH_4$ in 4 mL of anhydrous diethyl ether, and the mixture was stirred for 12 h. The mixture was diluted with 30 mL of diethyl ether, 1 mL of water was added on cooling, and the organic phase was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure, and compound **I** was isolated by chromatography on silica gel using petroleum ether–ethyl acetate (100:1) as eluent. Yield 0.67 g (87%). The spectral parameters of the product were consistent with published data [3].

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