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Synthesis of Monoterpene Lactones, (+)-Boschnialactone and (+)-Isoiridomyrmecin, Starting from L-(+)-Arabinose

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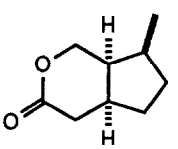
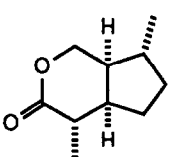
Abstract: A new method for the preparation of optically active γ-substituted α,β-unsaturated δ-lactones as the useful chiral building blocks for natural product synthesis, starting from L-(+)-arabinose and synthesis of two monoterpene lactones, (+)-boschnialactone and (+)-isoiridomyrmecin, by the use of these building blocks are described.

Use of carbohydrates as an important chiral pool for the synthesis of natural products has been extensively investigated because of their low prices and availability of both enantiomers in some cases.[1] On the other hand, optically active γ-substituted α,β-unsaturated δ-lactones seem to be potent chiral building blocks for the synthesis of natural products having a δ-lactone moiety in the molecule, although such chiral synthons have been rather rare so far. It is well-known that there are a large number of monoterpene lactones showing biologically characteristic activities. We are aiming at synthesizing these lactones in enantiomerically pure form by the use of carbohydrates, *inter alia* arabinose since both the enantiomers are readily available. We report here a new method for the synthesis of optically active γ-substituted α,β-unsaturated-δ-lactones from L-(+)-arabinose and synthesis of monoterpene lactones, (+)-boschnialactone (**1**) [2] and (+)-isoiridomyrmecin (**2**) [3], both the enantiomers of natural products, by the use of these chiral building blocks.



(**1**) (+)-Boschnialactone



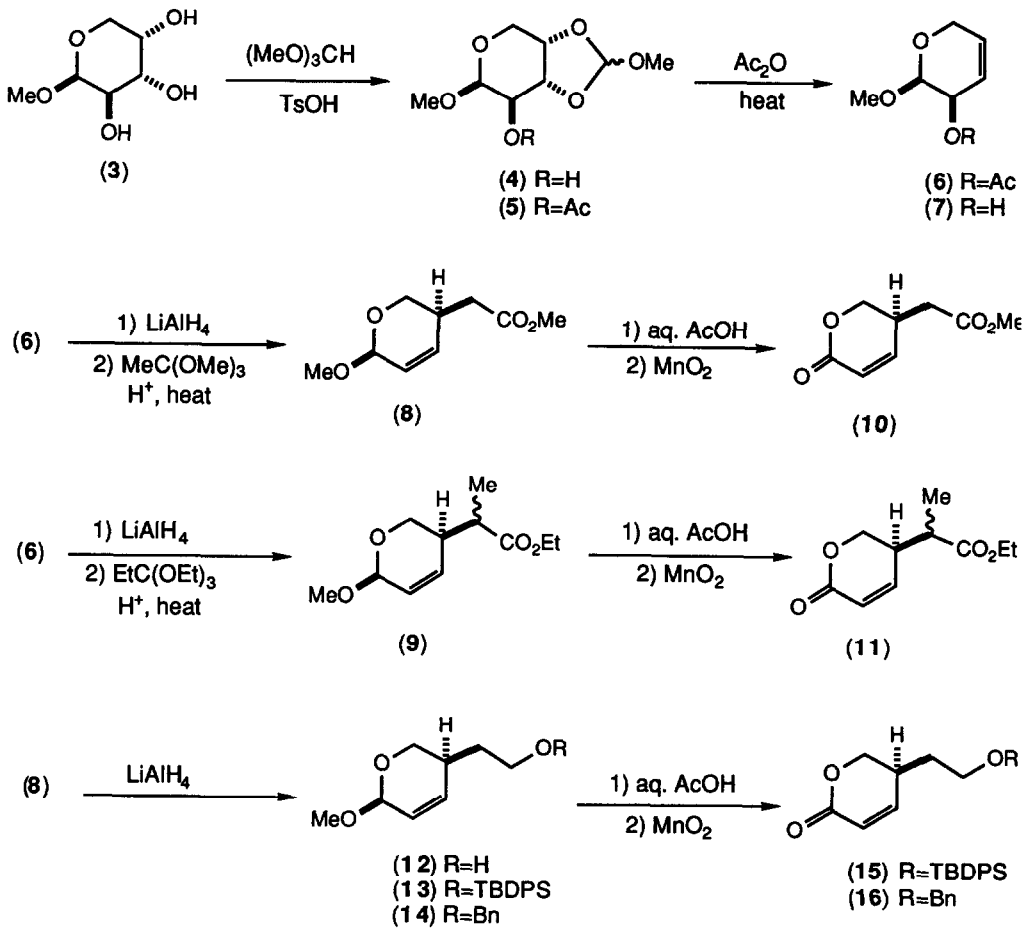
(**2**) (+)-Isoiridomyrmecin

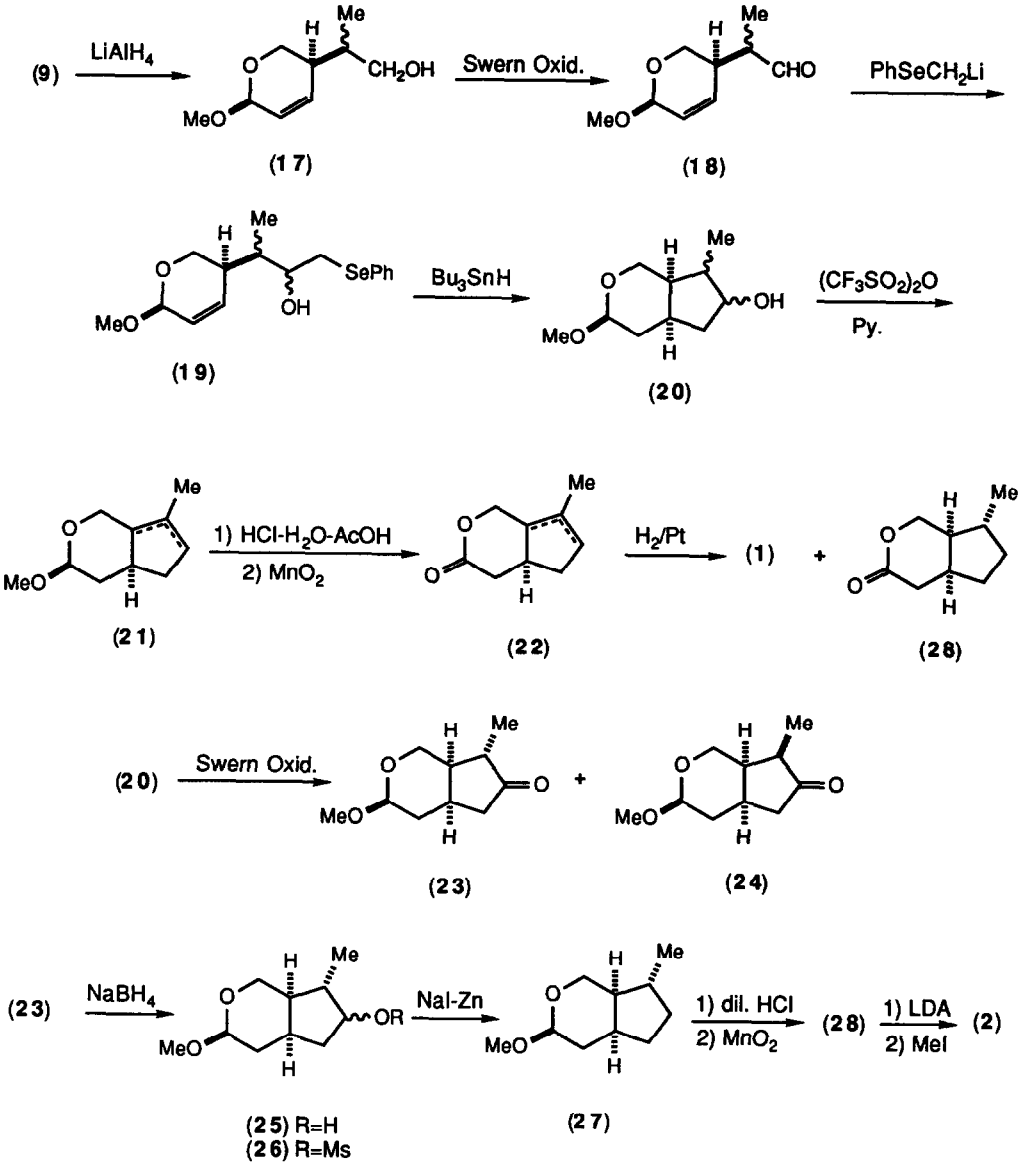
We started the investigation with L-(+)-arabinose. Treatment of the methyl L-(+)-arabinoside (**3**) with trimethyl orthoformate in the presence of *p*-toluenesulfonic acid followed by acetic anhydride in pyridine gave the acetate **5**. Application of the Ando's protocol [4] to **5** to convert the orthoester moiety to a double bond using acetic anhydride afforded the unsaturated acetate **6** in 80% overall yield from **3**.[5] After removal of an acetyl group of **6** with lithium aluminum hydride, the Claisen rearrangement of the resulting alcohol **7** by heating in trimethyl orthoacetate in the presence of a catalytic amount of (±)-10-camphorsulfonic acid at 180 °C in a sealed glass tube with occasional removal of methanol produced gave the olefinic ester **8** in 69% yield. On the Claisen

rearrangement, the use of triethyl orthopropionate in place of orthoacetate gave the corresponding olefinic homo-ester **9** as an inseparable 1:1 mixture of stereoisomers concerning a secondary methyl group, which was revealed by its ^{1}H-NMR spectrum.

Acidic hydrolysis of the acetal group in **8** with aqueous acetic acid gave the hemiacetal, but the product was found to be unstable under the usual workup conditions. Then the hydrolyzate of **8** with aqueous acetic acid was submitted to lyophilization and the residue was oxidized with manganese(IV) oxide in methylene chloride, furnishing the lactone **10** in acceptable yield. Application of the same procedure to the homo-ester **9** gave the corresponding lactone **11** as a mixture of diastereoisomers. Some attempts to isolate each stereoisomer of **11** in pure form were unsuccessful.

On the other hand, reduction of **8** with lithium aluminum hydride gave the alcohol **12**, which was transformed into the lactones **15** and **16** by the following reaction sequence: 1) protection of the primary hydroxyl group as *t*-butyldiphenylsilyloxy (**13**) or benzyloxy group (**14**); 2) hydrolysis of an acetal moiety with aqueous acetic acid; 3) oxidation with manganese(IV) oxide.





Based on the above results, we focused our attention on the synthesis of monoterpene lactones, (+)-boschnialactone (**1**) and (+)-isoiridomyrmecin (**2**), both of which are enantiomeric to the natural products, since we used L-(+)-arabinose as a starting material. Conversion of the ester **9**, a mixture of diastereoisomers as mentioned above, to the aldehyde **18** was easily accomplished by lithium aluminum hydride reduction followed by the Swern oxidation of the resulting alcohol **17**. Treatment of **18** with phenylselenomethyllithium, prepared *in situ* from diphenylselenomethane and butyllithium,[6] gave the hydroxy selenide **19** as a diastereoisomeric mixture, which was, without further purification, subjected to a radical cyclization with tributyltin hydride in the

presence of azobisisobutyronitrile (AIBN) in refluxing benzene. Purification of the product by silica gel column chromatography gave the cyclization product **20** as a mixture of diastereoisomers in 65% overall yield from **18**. Dehydration reaction of the mixture with trifluoromethanesulfonic anhydride in the presence of pyridine gave a *ca.* 3:2 mixture of olefins **21** in 59% yield, in which the trisubstituted double bond isomer was predominant from the observation of ^{1}H-NMR spectrum; two singlets due to two methoxyl groups at δ 3.39 and 3.48 and integration ratios between these signals and the signals due to an olefinic methyls and an olefinic proton. Several attempts to improve the yield of **21** were made by using phosphorous oxychloride in pyridine, or mesylation of the cyclization product **20** followed by treatment with some organic bases, but they were fruitless. Hydrolysis of **21** with aqueous acetic acid containing hydrochloric acid and oxidation of the resulting hemiacetal with manganese(IV) oxide gave a mixture of the olefinic lactones **22** in 63% yield. Hydrogenation of **22** over platinum oxide in ethanol gave a 92:8 mixture of (+)-boschnialactone (**1**) and (+)-7-*epi*-boschnialactone (**28**) in 90% yield. The ^{1}H-NMR spectrum (400 MHz in $CDCl_3$) of **1** thus obtained was identical with that of natural (-)-boschnialactone,[2f] indicating an accomplishment of the synthesis of the terpene, though it is the enantiomer of the natural product. The absolute value of the optical rotation ($[\alpha]_D$ +17.4 ° (*c* 0.35, $CHCl_3$)) of the synthetic compound was almost identical with that of the natural compound ($[\alpha]_D$ -18.2 °(*c* 2.10, $CHCl_3$)), confirming its optical purity.

Swern oxidation of the alcohol **20** gave a mixture of two ketones **23** and **24** in 81% yield. The former was predominant and isolated in pure form by silica gel chromatography. Treatment of the latter with aluminum oxide in benzene gave the former by epimerization of the secondary methyl group. Reduction of **23** with sodium borohydride gave the alcohol **25** as a diastereoisomeric mixture which was smoothly converted to the mesylate **26**. Reduction of **26** with sodium iodide and zinc powder in dimethoxyethane gave the acetal **27** in 80% yield. Conversion of the acetal moiety to the corresponding lactone was accomplished by the same way as for **21**, giving rise to (+)-7-*epi*-boschnialactone (**28**) in 87% yield. Its ^{1}H-NMR spectrum was identical with that of **28** obtained by hydrogenation of **22**. Methylation at the α-position of the lactone **28** in a conventional way furnished (+)-isoiridomyrmecin (**2**) (mp 57-58 °C, lit[3i] mp 57.5-58 °C) stereoselectively, which showed identical spectroscopic properties. Its value of the optical rotation ($[\alpha]_D$ +51.6 ° (*c* 0.16, $CHCl_3$)) showed an opposite sign of the natural lactone and the absolute value is same as that of natural compound ($[\alpha]_D$ -56° (*c* 1.09 $CHCl_3$)).

Experimental

All operations were carried out under an argon atmosphere with oven-dried glassware. IR spectra were recorded on a Shimadzu IR-408 spectrophotometer in chloroform unless otherwise stated. ^{1}H-NMR spectra and ^{13}C-NMR spectrum were recorded on a JEOL FX 90Q (90 MHz) spectrometer using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO DIP-181 digital polarimeter and high-resolution mass spectra (HR-MS) were recorded on a JEOL JMS-DX 303 instrument. Merck Kieselgel Art. 9385 was used for flash column chromatography, and Merck Kieselgel precoated plates 60 F-254 were used for preparative thin layer chromatography.

(2*S*,3*R*)-3-Acetoxy-2,3-dihydro-2-methoxy-6*H*-pyran (6)

A solution of methyl L-(+)-arabinopyranoside (**3**) (3.08 g, 18.70 mmol), trimethyl orthoformate (5.82 g, 54.80 mmol), and a catalytic amount of *p*-toluenesulfonic acid in methylene chloride (50 mL) was stirred at

room temperature for 1 h and 5.82 g more of trimethyl orthoformate was added, and the whole was stirred for 2 h at room temperature. The catalyst was removed by passing through a short silica gel column by the aid of ethyl acetate and the eluate was concentrated to leave the orthoester **4**: ^{1}H-NMR: 2.28 (1H, br s, OH), 3.35 (3H in total, s), 3.45 (3H, s), 4.71 (1H, d, J=3.5 Hz), and 5.81 (1H, s each). MS: m/z 206 (M^+).

A solution of the crude orthoester **4**, pyridine (15 mL), and acetic anhydride (3 mL, 31.80 mmol) in methylene chloride (30 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was taken up in ethyl acetate. The organic solution was washed with water, 5% copper(II) sulfate, water, and brine, dried over $MgSO_4$, and concentrated to give the acetate **5** as an oil, which was, without further purification, used for the forthcoming reaction. IR: 1730, 1370, 1230, 1120, and 1080 cm^{-1}. ^{1}H-NMR: 2.17 (3H, s), 3.36 (3H, s each), 3.39 (3H, s), 3.49-4.00 (2H, m), 4.22-4.55 (2H, m), 4.74-4.84 (2H, m), and 5.80 (1H, s each).

According to the Ando's protocol,[4] a solution of the foregoing acetate **5** in acetic anhydride (30 mL) was refluxed under argon overnight. The mixture was concentrated in vacuo to give an oily residue, which was chromatographed on silica gel (hexane-ethyl acetate (4:1)). The eluate was concentrated to give the unsaturated acetate **6** (2.58 g, 80% from **3**): $[\alpha]_D^{20}$ +84.1° (c 1.00, $CHCl_3$). IR: 1730, 1370, 1230, and 1050 cm^{-1}. ^{1}H-NMR: 2.12 (3H, s), 3.50 (3H, s), 4.09-4.22 (2H, m), 4.93 (1H, d, J=4.0 Hz), 5.22-5.37 (1H, m), 5.51-5.75 (1H, m), 5.96 (1H, dq, J=2.0, 10.4 Hz). Anal. calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.65; H, 7.01.

Methyl (2*S*,5*S*)-2-[5,6-Dihydro-2-methoxy-2*H*-pyran-5-yl]acetate (8) and Ethyl (2*S*,5*S*)-2-[5,6-Dihydro-2-methoxy-2*H*-pyran-5-yl]propionate (9).

A solution of the acetate **6** (1.00 g, 5.81 mmol) in ether (10 mL) was added to a suspension of lithium aluminum hydride (243 mg, 6.39 mmol) in ether (50 mL) and the whole was stirred at room temperature for 30 min. After decomposition of the excess reagent by adding wet ether and several drops of water, inorganic materials formed were filtered off. The filtrate was concentrated under reduced pressure to give allylic alcohol **7**: $[\alpha]_D^{25}$ +127.6° (c 1.00, $CHCl_3$). IR:3560, 1125, 1100, 1070, and 1050 cm^{-1}. ^{1}H-NMR: 2.28 (1H, br d, J=9.9 Hz), 3.53 (3H, s), 4.00-4.32 (3H, m), 4.77 (1H, d, J=3.5 Hz), 5.58-5.92 (2H, m).

The allylic alcohol **7** was heated in trimethyl orthoacetate (6 mL, 47. 2 mmol) in the presence of a catalytic amount of (±)-10-camphorsulfonic acid in a sealed glass tube at 180 °C for 3 days with occasional removal of methanol formed. The mixture was concentrated and the residue was chromatographed on silica gel in hexane-ethyl acetate (4:1). Elution with the same solvent gave the acetate **8** (743 mg, 69%). $[\alpha]_D^{23}$ +84.4° (c 1.01, $CHCl_3$). IR: 1730, 1440, 1260, 1045, and 960cm^{-1}. ^{1}H-NMR: 2.14 (1H, dd, J=13.7 and 0.8 Hz), 2.35 (1H, d, J=13.7 Hz), 2.80 (1H, m), 3.41 (3H, s), 3.69 (3H, s), 4.81 (1H, m), 5.73-5.91 (2H, m). Anal. calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.85; H, 7.49.

When triethyl orthopropionate was used for the Claisen rearrangement of **7** in place of trimethyl orthoformate, the homo-ester **9** was obtained in 67% overall yield from the acetate **6** as a mixture of diastereoisomers. **9**: IR: 1720, 1190, 1050, and 960 cm^{-1}; ^{1}H-NMR: 1.14 and 1.17 (3H in total, d each, J=7.0 Hz), 1.26 (3H, t, J=7.0 Hz), 2.15-2.28 (2H, m), 3.41 (3H, s), 3.64 (1H, d, J=2.9 Hz), 3.72 (1H, d, J=3.1 Hz), 4.15 (2H, q, J=7.0 Hz), 4.79 (1H, m), 5.60-6.04 (2H, m). Anal. calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.35; H, 8.38.

Methyl (5*R*)-2-[5,6-Dihydro-2-oxo-2*H*-pyran-5-yl]acetate (10) and Ethyl (5*R*)-2-[5,6-

Dihydro-2-oxo-2*H*-pyran-5-yl]propionate (11)

A solution of **7** (743 mg, 4.00 mmol) in 30% aqueous acetic acid (4 mL) was stirred at room temperature for 5 h and diluted with water. The aqueous solution was submitted to lyophilization to leave solids which were dissolved in methylene chloride (80 mL) and treated with manganese(IV) oxide (7.48 g, 86 mmol) at room temperature for 12 h. After filtration, the filtrate was concentrated to dryness to give an oily residue which was purified by silica gel flash chromatography (hexane-ethyl acetate (1:1)) to give the lactone **10** (516 mg, 76%). $[\alpha]_D^{23}$ +110.3° (*c* 1.05, $CHCl_3$). IR: 1725cm^{-1}. ^{1}H-NMR: 2.49 (1H, dd, *J*= 14.8 and 0.2 Hz), 2.63 (1H, d, *J*=14.8 Hz), 2.96 (1H, m), 3.72 (3H, s), 4.22 (1H, ddd, *J*=1.0, 5.8, and 11.2 Hz), 4.50 (1H, ddd, *J*= 0.7, 4.6, and 11.2 Hz), 6.02 (1H, dd, *J*=1.5 and 9.9 Hz), and 6.91 (1H, ddd, *J*=0.8, 3.4, and 9.9 Hz). Anal. calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.25; H, 5.95.

Treatment of **9** in the same manner as mentioned above gave the lactone **11** as a 1:1 mixture of diastereoisomers. IR: 1720cm^{-1}. ^{1}H-NMR: 1.20-1.36 (6H in total, m), 2.47-2.99 (2H, m), 4.17 and 4.18 (2H in total, q each, *J*=7.1 Hz), 4.26-4.57 (2H, m), 6.05 (1H, ddd, *J*=1.5, 3.0, 10. 0 Hz), 6.79-6.99 (1H, m). Anal. calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.33; H, 7.06.

(5*S*)-5-[2-(t-Butyldiphenylsilyloxyethyl)]-5,6-dihydropyran-2(2*H*)-one (15)

A solution of **8** (294 mg, 1.58 mmol) in ether (8 mL) was added to a suspension of lithium aluminum hydride (74 mg, 1.95 mmol) in ether (12 mL) and the resulting mixture was stirred at room temperature for 30 min. After decomposition of the excess reagent by adding wet ether and a few drops of water, inorganic precipitates were filtered off. The filtrate was concentrated under reduced pressure to give the alcohol **12** as an oil, which was treated with *t*-butyldiphenylsilyl chloride (399 mg, 1.45 mmol) in dimethylformamide (2 mL) in the presence of imidazole (222 mg, 3.30 mmol) at room temperature overnight. The reaction mixture was diluted with ethyl acetate and washed with half-saturated brine and saturated brine, and dried over $MgSO_4$. Removal of the solvent left an oil which was chromatographed on silica gel (hexane-ethyl acetate (8:1)) to give the silyl ether **13** (573 mg, 92%). $[\alpha]_D^{23}$ +39.1° (*c* 1.04, $CHCl_3$). IR: 2940, 1110, 1050, and 700cm^{-1}. ^{1}H-NMR: 1.05 (9H, s), 1.38-1.62 (2H, m), 2.55 (1H, m), 3.40 (3H, s), 3.51-3.77 (4H, m), 4.77 (1H, m), 5.65 (1H, dt, *J*=12.6 and 2.7 Hz), 5.90 (1H, br. d, *J*=12.6 Hz), 7.29-7.45 (6H, m), 7.57-7.73 (4H, m). Anal. calcd for $C_{24}H_{32}O_3Si$: C, 72.69; H, 8.13. Found: C, 72.43; H, 8.21. The silyl ether **13** was transformed into the lactone **15** in the same manner as for the preparation of **10** from **8**. **15** : $[\alpha]_D^{19}$ +50.6° (*c* 0.54, $CHCl_3$); IR; 1720cm^{-1}; ^{1}H-NMR: 1.06 (9H, s), 1.68 (2H, m), 2.76 (1H, m), 3.27 (2H, t, *J*=6.5 Hz), 4.11 (1H, ddd, *J*=0.7, 6.8, and 11.0 Hz), 4.40 (1H, ddd, *J*=0.9, 5.0, and 11.0 Hz), 5.94 (1H, dd, *J*=1.8 and 9.8 Hz), 6.82 (1H, dd, *J*=4.0 and 9.8 Hz), 7.31-7.48 (6H, m), and 7.52-7.69 (4H, m). Anal. calcd for $C_{23}H_{28}O_3Si$: C, 72.59; H, 7.42. Found: C, 72.67; H, 7.57.

(5*S*)-5-[2-Benzyloxyethyl]-5,6-dihydropyran-2(2*H*)-one (16)

A mixture of the crude alcohol **12** (1.61 mmol), obtained by lithium aluminum hydride reduction of **8** (300 mg, 1.61 mmol), sodium hydride (46 mg, 1.93 mmol), benzyl bromide (330 mg , 1.93 mmol), and tetrahydrofuran (20 mL) was heated at reflux for 7 h. After the excess sodium hydride was decomposed by a few drops of water, the reaction mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated brine and dried over $MgSO_4$. Removal of the solvent left an oily residue which was purified by silica gel flash chromatography (hexane-ethyl acetate (20:1-

8:1)) to give the benzyl ether **14** (342 mg, 86%). $[\alpha]_D^{19}$ +62.5° (*c* 1.00, $CHCl_3$). IR: 1104 and 1050 cm^{-1} ^{1}H-NMR: 1.56 (2H, m), 2.51 (1H, m), 3.41 (3H, s), 3.52 (2H, t, *J*=6.5 Hz), 3.41-3.85 (2H, m), 4.49 (2H, s),4.79 (1H, m), 5.69 (1H, dt, *J*=2.3 and 10.4 Hz), 5.87 (1H, br d, *J*=10.4 Hz), and 7.31 (5H, s). Anal. calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.41; H, 7.96.

The benzyl ether **14** was transformed into the corresponding lactone **16** by the same procedure as for the preparation of **15** from **13**. **16:** $[\alpha]_D^{19}$ +78.6° (*c* 1.00, $CHCl_3$). IR: 1720 cm^{-1}. ^{1}H-NMR: 1.69-1.89 (2H, m), 2.72 (1H, m), 3.56 (2H, t, *J*=5.8 Hz), 4.16 (1H, ddd, *J*=0.7, 6.7, and 11.2 Hz), 4.42 (1H, ddd, *J*=0.7, 5.0, and 11.2 Hz), 4.50 (2H, s), 5.98 (1H, dd, *J*=1.8 and 9.8 Hz), 6.87 (1H, dd, *J*=4.0 and 9.8 Hz), and 7.32 (5H, s). Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.27; H, 6.93.

(+)-Boschnialactone (1)

(+)-Boschnialactone (**1**) was synthesized by the following eight-step reaction sequence from **9**, since all the intermediates were obtained as a mixture of inseparable diastereoisomers.

A solution of the ester **9** (729 mg, 3.41 mmol) in ether (5 mL) was added to a suspension of lithium aluminum hydride (140 mg, 3.68 mmol) in ether (25 mL) in an ice bath. After stirring at 0 °C for 30 min, the excess reagent was decomposed by adding wet ether and a few drops of water, and inorganic precipitates were filtered off. The filtrate was concentrated to give **17** as an oil, which was unstable and subjected to the next Swern oxidation without purification.

To a solution of oxalyl chloride (0.6 mL, 6.87 mmol) in methylene chloride (20 mL) was added at -70 °C under argon a solution of dimethylsulfoxide (1.0 mL, 14.1 mmol) in methylene chloride (5 mL) and the resulting mixture was stirred for 10 min at the same temperature. To this solution was added a solution of the foregoing crude alcohol **17** (3.41 mmol) in methylene chloride (5 mL) and the whole was stirred at -70 °C for 30 min. Then triethylamine (2.4 mL, 17.3 mmol) was added and the mixture was stirred at the same temperature for 10 min and allowed to warm to room temperature over 30 min. The reaction mixture was diluted with ethyl acetate and washed with half-saturated brine and saturated brine, dried over $MgSO_4$, and concentrated. Removal of the solvent in vacuo gave the aldehyde **18**: IR: 1720, 1050, 960, and 910cm^{-1}; ^{1}H-NMR: 1.12 (3H, d, *J*=7.3 Hz), 2.18-2.57 (1H, m), 2.57-2.95 (1H, m), 3.41 and 3.54 (3H in total, s each), 3.66 (1H, d, *J*=2.0 Hz), 3.75 (1H, d, *J*=2.2 Hz), 4.79-4.83 (1H, m), 5.79-5.84 (2H, m), 9.69 (1H, t, *J*=1.3 Hz).

A solution of the foregoing aldehyde **18** in tetrahydrofuran (THF, 5 mL) was added dropwise at -78°C to a solution of selenophenylmethyllithium in THF, which was prepared beforehand from diphenylselenomethane (1.25 g, 3.83 mmol) and butyllithium (2.2 mL of a 1.58 M hexane solution, 3.48 mmol) in THF (35 mL) at -78°C. After stirring for 30 min at the same temperature, the mixture was diluted with ether. The ethereal solution was washed with half-saturated brine, water, and saturated brine, and dried over $MgSO_4$. Evaporation of the solvent gave **19** as a mixture of four diastereoisomers, which was dissolved in benzene (20 mL) containing a catalytic amount of AIBN. To this solution was added dropwise under reflux a solution of tributyltin hydride (974 mg, 3.35 mmol) in benzene (25 mL) over a period of 2 h. The whole was further refluxed with stirring for an additional 4 h. After cooling, the mixture was concentrated and the residue was subjected to silica gel flash chromatography. The portion of ethyl acetate eluate was concentrated to give an oily residue which was again chromatographed on silica gel (hexane-ethyl acetate (10:1-2:1)) to give the bicyclic pyran **20** (413 mg, 65%) as a mixture of diastereoisomers.

To a solution of **20** (207 mg, 1.11 mmol) in methylene chloride (15 mL) containing pyridine (1.8 mL) was

added trifluoromethanesulfonic anhydride (1.35 mL, 8.0 mmol) at -78 °C. The whole was further stirred for an additional 1 h at the same temperature. After addition of potassium carbonate (3.07 g, 22.3 mmol), the reaction mixture was allowed to warm to room temperature over 1 h. The mixture was poured onto ice water and the product was extracted with ether. The ether extract was washed with aqueous cupper(II) sulfate, water, and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (pentane-ether (40:1-1:1)) to give a 3:2 mixture of the olefins **21** (113 mg, 59%). IR: 1445, 1385, 1135, 1085, and 1060 cm^{-1}. ^1H-NMR: 1.64 (3H, br s), 3.39 and 3.48 (1.8H and 1.2H, respectively, s each), and 5.36 (0.6H, m). HR-MS: Calcd for $C_{10}H_{16}O_2$: 168.1150. Found: 168.1150.

A solution of **21** (25 mg, 0.14 mmol) in 30% aqueous acetic acid (2 mL) containing a few drops of concentrated hydrochloric acid was stirred at room temperature for 30 min. After the reaction mixture was neutralized by aqueous sodium hydrogen carbonate, the product was extracted with methylene chloride. The extract was washed with brine, dried over $MgSO_4$, and concentrated. An oily residue was dissolved in methylene chloride (3 mL) and treated with manganese(IV) oxide (200 mg, 2.3 mmol) at room temperature overnight. The reaction mixture was filtered and the filtrate was concentrated to give a residue which was chromatographed on silica gel. Elution with hexane-ethyl acetate (2:1) furnished a *ca.* 4:1 mixture of the lactones **22** (14 mg, 63%). IR: 1740, 1250, and 1080cm^{-1}. ^1H-NMR: 1.62 (0.6H, br. s), 1.70 (2.4H, d, *J*=2.0 Hz), 1.80-3.08 (6H, m), 4.27 (1.6H, m), 4.7-5.2 (0.2H, m), and 5.41 (0.8H, m). HR-MS: Calcd for $C_9H_{12}O_2$: 152.0837. Found: 152.0838.

Hydrogenation of the lactones **22** (10 mg, 0.07 mmol) was carried out over platinum(IV) oxide (5 mg) in ethanol (1 mL) for 5 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give a 92:8 mixture (^1H-NMR) of (+)-boschnialactone (**1**) and (+)-7-*epi*-boschnialactone (**28**) (proposed from ^1H-NMR), the former of which was separated by preparative thin layer chromatography by means of repeat developments in hexane-ethyl acetate (7:1) and purified by recrystallization from hexane at -70°C (oil at room temperature). (+)-Boschnialactone (**1**) (7 mg, 70%): $[\alpha]_D^{21}$ +17.4° (*c* 0.35, $CHCl_3$). IR: 2960, 1735, 1460, and 1055cm^{-1}. ^1H-NMR:1.03 (3H, d, *J*=7.3 Hz), 1.35 (1H, dq, *J*=6.6, 11.7 Hz), 1.47-1.54 (1H, m), 1.69-1.76 (1H, m), 1.84-1.94 (1H, m), 2.10-2.22 (1H, m), 2.25-2.34 (1H, m), 2.42 (1H, dq, *J*=5.5, 8.8 Hz), 2.55-2.66 (1H, m), 4.12 (1H, dd, *J*=9.2, 11.4 Hz), and 4.22 (1H, dd, *J*=5.5 and 11.4 Hz). The ^1H-NMR spectral data was identical with those of natural (-)-boschnialactone[2f]. On the other hand, (+)-7-*epi*-boschnialactone (**28**) was so minute that it was characterized by ^1H-NMR spectrum of a 92:8 mixture after hydrogenation.

The Swern Oxidation of 20 and Subsequent Isomerization by Al_2O_3

To a solution of oxalyl chloride (0.047 mL, 0.54 mmol) in methylene chloride (3 mL) was added at -70 °C under argon a solution of dimethylsulfoxide (0.076 mL, 1.08 mmol) in methylene chloride (1 mL) and the resulting mixture was stirred for 10 min at the same temperature. To this solution was added a solution of the alcohol **20** (50 mg, 0.27 mmol) in methylene chloride (1 mL) and the whole was stirred at -70 °C for 30 min. Then triethylamine (0.19 mL, 1.35 mmol) was added and the mixture was stirred at the same temperature for 10 min and allowed to warm to room temperature over 30 min. The reaction mixture was diluted with ethyl acetate and washed with half-saturated brine and saturated brine, and dried over $MgSO_4$. Evaporation of the solvent left an oily residue which was stirred with basic aluminum oxide (500 mg) in benzene (5 mL) at room temperature for 12 h. The mixture was filtered and aluminum oxide was thoroughly washed with ethyl acetate. The filtrate and washings were combined and concentrated to give an oil which was purified by preparative thin layer

chromatography using hexane-ethyl acetate (3:1). The ketones **23** (32 mg, 65%) and **24** (8 mg, 16%) were obtained. **23:** Mp 77.5-78.5 °C (from hexane-ethyl acetate); $[\alpha]_D^{20}$ +136.4° (*c* 1.04, $CHCl_3$); IR:1730, 1140, and 1090cm^{-1}; ^{1}H-NMR: 1.09 (3H,d, *J*=7.0 Hz), 1.19-1.50 (1H, m), 1.58-2.09 (2H, m), 2.11-2.68 (4H, m), 3.48 (3H, s), 3.75 (1H, dd, *J*=3.4, 12.4 Hz), 4.03 (1H, dd, *J*=2.4, 12.4 Hz), 4.36 (1H, dd, *J*=2.5, 8.7 Hz). Anal. calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.15; H, 8.72. **24:** IR:1730, 1130, and 1075 cm^{-1}; ^{1}H-NMR: 1.00 (3H,d, *J*=6.8 Hz), 1.78-1.96 (2H, m), 2.00-2.89 (5H, m), 3.28 (3H, s), 3.30-3.76 (2H, m), 4.59-4.82 (1H, m). HR-MS: Calcd for $C_{10}H_{16}O_3$: 184.1099. Found: 184.1104.

(3*S*,4a*S*,7*R*,7a*S*)-3-Methoxy-7-methyl-1,3,4,4a,5,6,7,7a-octahydrocyclopenta[*c*]pyran (27)

To a solution of the ketone **23** (123 mg, 0.67 mmol) in ethanol (12 mL) was added sodium borohydride (51 mg, 1.34 mmol) and the mixture was stirred at room temperature for 2.5 h. Cold water was added to the reaction mixture and the product was extracted with methylene chloride. The extract was washed with saturated brine, dried over $MgSO_4$, and concentrated to give the alcohol **25** as a diastereoisomeric mixture. The crude alcohol **25** was dissolved in methylene chloride (10 mL) and treated with pyridine (0.54 mL, 6.71 mmol) and methanesulfonyl chloride (615 mg, 5.37 mmol) at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate and the organic solution was washed with 5% copper(II) sulfate, water, and saturated brine, and dried over $MgSO_4$. Removal of the solvent gave the mesylate **26** (174 mg, 98%): IR 1360, 1340, 1180, 1090, and 960 cm^{-1}; ^{1}H-NMR: 1.12 (3H, d, *J*=6.8 Hz), 1.34-2.00 (4H, m), 2.00-2.62 (3H, m), 3.00 (3H, s), 3.44 (3H, s), 3.65 (1H, dd, *J*=4.6, 12.1 Hz), 3.86 (1H, dd, *J*=4.7, 12.1 Hz), 4.37 (1H, dd *J*=3.3, 7.9 Hz), and 4.55-4.77 (1H, m). A mixture of the crude mesylate **26** (174 mg, 0.66 mmol), sodium iodide (494 mg, 3.30 mmol), zinc powder (428 mg, 6.60 mmol), and dimethoxyethane (20 mL) was stirred at reflux for 1 h. The cooled reaction mixture was filtered and inorganic materials were thoroughly washed with ether. The filtrate and washings were combined and the solvents were distilled off at normal atmospheric pressure. The residual oil was dissolved in ether and washed with water and saturated brine, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel in hexane-ethyl acetate (40:1) to give **27** as a fairly volatile oil (88 mg, 77% from **23**) : IR: 2960, 1090, and 1050 cm^{-1}; ^{1}H-NMR: 0.97 (3H, d, *J*=6.2 Hz), 1.13-2.42 (9H, m), 3.43 (3H, s), 3.64 (1H, dd, *J*=4.4, 11.9 Hz), 3.83 (1H, dd, *J*=4.6, 11.9 Hz), 4.33 (1H, dd, *J*=3.3, 8.4 Hz). HR-MS: Calcd. for $C_{10}H_{17}O_2$ $(M-H)^+$ 169.1229. Found: 169.1236.

(+)-7-*Epi*-boschnialactone (28)

A solution of **27** (74 mg, 0.44 mmol) in aqueous THF (9 mL) (THF-water = 2:1 (v/v)) containing 7 drops of concentrated hydrochloric acid was stirred at 40 °C for 1 h. The cooled reaction mixture was extracted with methylene chloride. The extract was washed with aqueous sodium hydrogen carbonate, water, and saturated brine, and dried over $MgSO_4$. Evaporation of the solvent left an oil which was treated with manganese(IV) oxide (800 mg) in methylene chloride (10 mL) with efficient stirring at room temperature overnight. The mixture was filtered and inorganic materials were washed with methylene chloride. The filtrate and washings were combined and concentrated to leave a residue which was chromatographed on silica gel in hexane-ethyl acetate (3:1) to give (+)-7-epiboschnialactone (**28**) (58 mg, 87%): Mp 57-58 °C (hexane); IR: 1740 cm^{-1}; ^{1}H-NMR: 0.80-1.48 (2H, m), 1.06 (3H, d, *J*=5.9 Hz), 1.58-2.12 (4H, m), 2.21-2.85 (3H, m), 4.08 (1H, dd, *J*=4.4, 11.4 Hz), 4.29 (1H, dd, *J*=4.3, 11.4 Hz). HR-MS: Calcd for $C_9H_{14}O_2$: 154.0994. Found: 154.0999.

(+)-Isoiridomyrmecin (2)

A solution of **28** (15 mg, 0.09 mmol) in THF (1 mL) was added dropwise at -78 °C under argon to a solution of LDA, prepared from diisopropylamine (0.02 mL, 0.14 mmol) and butyllithium (0.09 mL of a 1.58 M hexane solution, 0.14 mmol) in THF (2 mL) at -78 °C, and the mixture was stirred at the same temperature for 30 min. Methyl iodide (0.018 mL, 0.29 mmol) was added and the whole was further stirred for 30 min at -78 °C, then allowed to warm to room temperature over 2 h. The reaction was quenched by aqueous ammonium chloride and the product was extracted with ether. The ethereal extract was washed with brine, dried over $MgSO_4$, and concentrated to leave an oil, which was submitted to preparative thin layer chromatography (hexane-ethyl acetate (2:1)) to give (+)-isoiridomyrmecin (**2**) (11 mg, 72%): IR: 2956, 1735, 1455, 1382, 1245, 1170, 1135, 1110, 1050 cm^{-1}; ^1H-NMR: 1.05 (3H, d, *J*=6.6 Hz), 1.20 (3H, d, *J*=6.6 Hz), 1.23-1.36 (2H, m), 1.58-1.73 (1H, m), 1.83-1.95 (1H, m), 1.95-2.17 (3H, m), 2.24-2.35 (1H, m), 3.96 (1H, t, *J*=11.3 Hz), 4.36 (1H, dd, *J*=5.9, 11.3 Hz). Mp 57-58°C (hexane). $[\alpha]_D^{21}$: +51.6° (*c* 0.16, $CHCl_3$).

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