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Total synthesis of (+)-epiepoformin, (+)-epiepoxydon and (+)-bromoxone employing a useful chiral building block, ethyl (1*R*,2*S*)-5,5-ethylenedioxy-2-hydroxycyclohexanecarboxylate

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Abstract—Enantioselective total synthesis of (+)-epiepoformin **1**, (+)-epiepoxydon **2** and (+)-bromoxone **3** using a chiral building block, ethyl (1*R*,2*S*)-5,5-ethylenedioxy-2-hydroxycyclo- hexanecarboxylate **6**, is described. Since the synthesis afforded intermediates **18**, **2** and **25**, it accomplished a formal synthesis of (−)-theobroxide **19**, (−)-phyllostine **22**, (+)-herveynone **27** and (−)-asperpentyn **28**. The usefulness of **6** for the synthesis of natural epoxycyclohexene derivatives was demonstrated.

1. Introduction

Epiepoformin **1**, epiepoxydon **2** and bromoxone **3** are well known as typical oxygenated cyclohexenones with remarkable biological activities (Fig. 1). For example, epiepoformin **1** and epiepoxydon **2** being inhibitors of lettuce seed germination were isolated from the culture broth of an unidentified fungus separated from a diseased crapemyrtle leaf by Nagasawa and co-workers in 1978.[1] On the other hand, bromoxone **3** was isolated from marine acorn worm with its acetate by Higa and co-workers in 1987.[2] The acetate of bromoxone **3** shows potent antitumor activity against P388 cells in vitro. Several methods for their synthesis have already been reported.[3–5] In this paper, we describe a novel synthesis of epiepoformin **1**, epiepoxydon **2** and bromoxone **3**, using a common chiral building block, ethyl (1*R*,2*S*)-5,5-ethylenedioxy-2-hydroxycyclohexanecarboxylate **6**.

Our synthetic plan is shown in Scheme 1. We thought that all target compounds could be synthesized from the common intermediate, phenylselenoketone **4**, via introduction of the proper substituent and deprotection. The key intermediate **4** must be obtained from enone **5** by stereoselective epoxidation and regioselective introduction of the phenylselenyl group. The enone **5** could be derived from the chiral building block **6** via modification of functional groups including decarboxylation. We started the synthesis according to this plan.

The chiral building block **6** as the starting material was first synthesized in our laboratory in 1985,[6] and is now available in large quantities by simple operation via the high enantiomeric reduction with baker's yeast of β-ketoester **7**. We have already succeeded in total syntheses of a series of natural products using this building block; e.g. sporogen AO1,[7] polyoxygenated eremophilanes,[8] dendryphiellin C,[9]

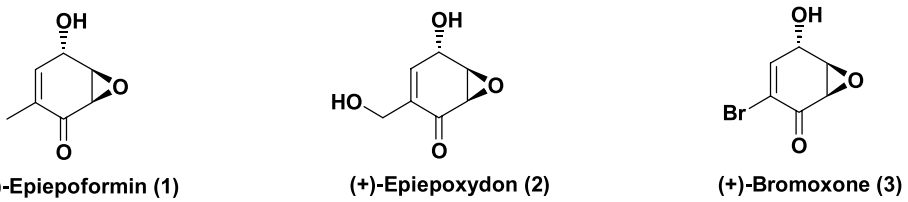

Figure 1.

Keywords: total synthesis; natural epoxycyclohexene derivatives; chiral building block.
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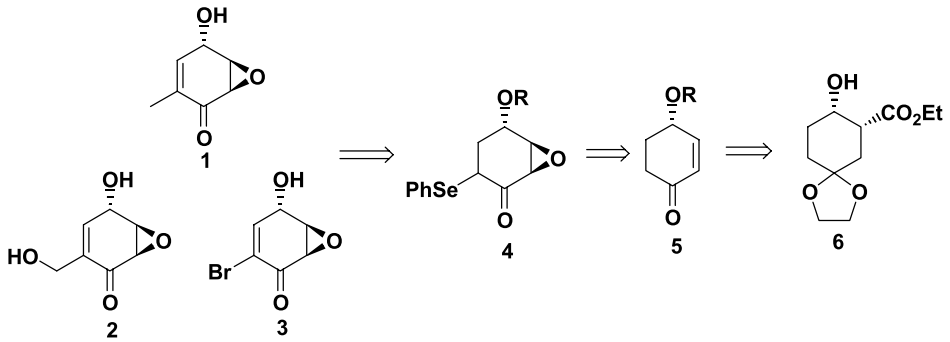
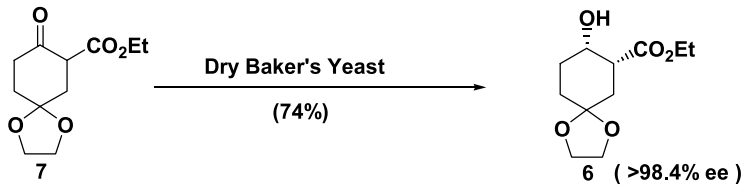


Scheme 1.



Scheme 2.

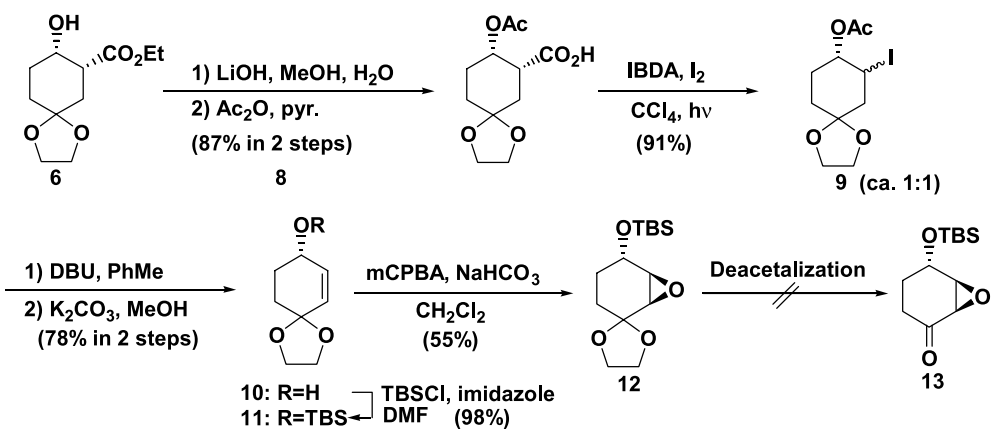
pironetin[10] and key intermediates of both enantiomers of epibatidine[11] (Scheme 2).

2. Results and discussion

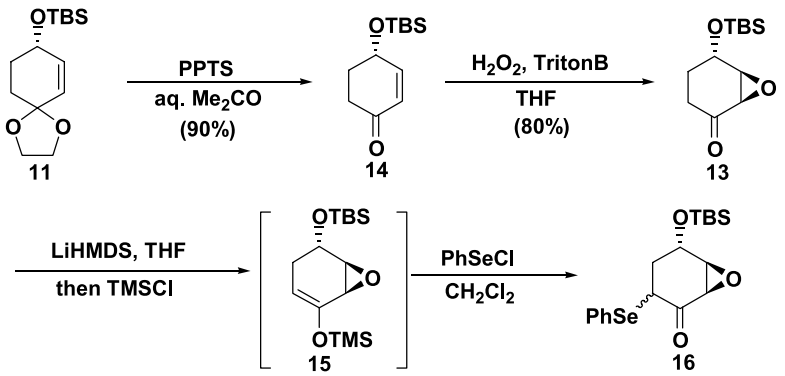
Hydrolysis of **6**, followed by acetylation of the hydroxyl group gave carboxylic acid **8**. Oxidative decarboxylation[12] of **8** with iodobenzene diacetate (IBDA) and iodine in carbon tetrachloride afforded iodide **9** as an inseparable diastereomeric mixture of 1:1. Dehydroiodination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and subsequent hydrolysis of **9** gave allylic alcohol **10**. After TBS protection of the hydroxyl group of **10**, epoxidation of the resulting compound **11** with *m*-chloroperbenzoic acid (*m*CPBA) gave epoxide **12**. Deacetalization of **12** under various conditions afforded no desired compound (Scheme 3).

On the other hand, deacetalization of compound **11** with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone gave enone **14**[13] in excellent yield. Epoxidation of enone **14** proceeded stereoselectively by using Triton B as a base[3e,14] to give epoxyketone **13**. Next, we investigated regioselective introduction of the phenylselenyl group to the α-position of the ketone **13**. At first, enolate was prepared with lithium diisopropylamide (LDA), then we attempted to introduce the phenylselenyl group to enolate directly. But, only a complex mixture was obtained. Therefore, we attempted stepwise introduction of the phenylselenyl group. Trapping the enolate with trimethylsilyl chloride (TMSCl) gave silyl enol ether **15**, which was treated with phenylselenenyl chloride in dichloromethane to afford phenylselenyl compound **16** as a diastereomeric mixture (Scheme 4).

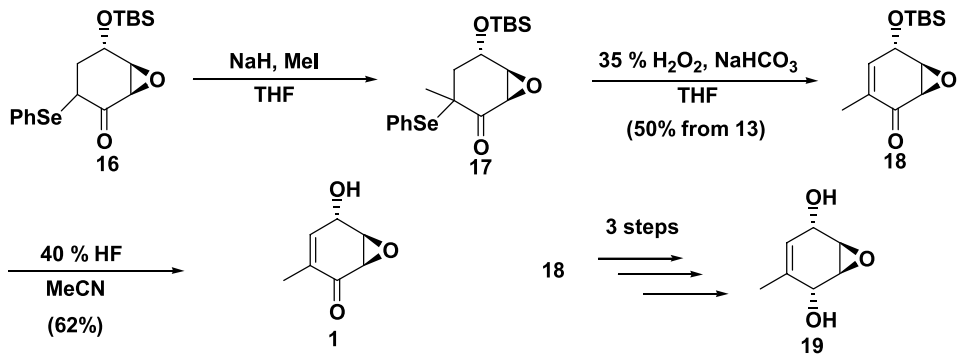
Introduction of a methyl group to **16** with sodium hydride as a base and methyl iodide gave compound **17**. Successive oxidative elimination of the phenylselenenyl group with 35% hydrogen peroxide in the presence of sodium hydrogen carbonate gave enone **18**. Finally, deprotection of the TBS group[15] with 40% hydrofluoric acid in acetonitrile gave epiepoformin. The overall yield of epiepoformin was 13.5%



Scheme 3.



Scheme 4.



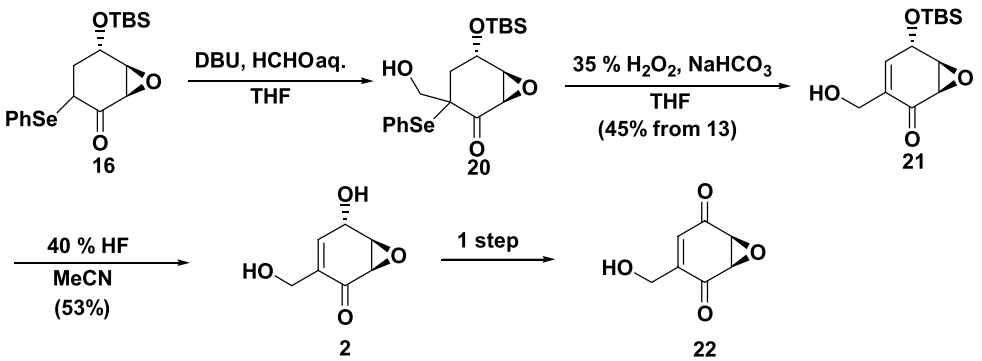
Scheme 5.

in total 13 steps. The analytical data of our synthetic epiepoformin were identical with those of the authentic product.[3] The conversion from the intermediate **18** to theobroxide **19**,[16] a potato micro-tuber inducing substance, was reported by Ogasawara and co-workers in 1995.[3c] Thus, we accomplished total synthesis of (+)-epiepoformin and the formal synthesis of (−)-theobroxide (Scheme 5).

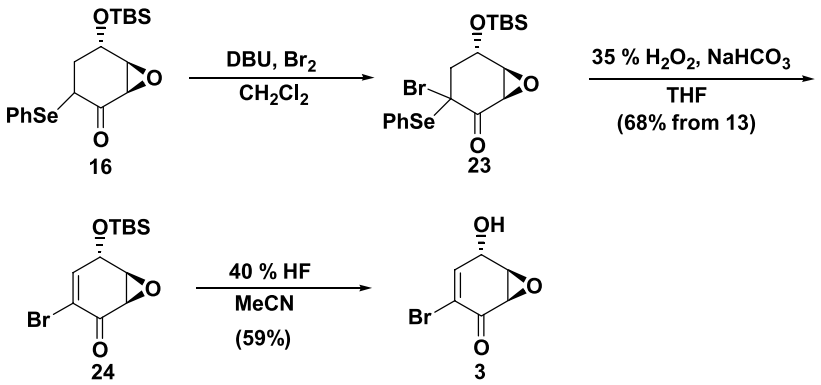
On the other hand, treatment of **16** with DBU as a base and 35% formalin gave hydroxymethyl compound **20**. Oxidative elimination of the resulting compound **20** was achieved in a similar manner as above to give enone **21**. Then deprotection of the TBS group gave epiepoxydon. Epiepoxydon was yielded 10.4% overall in 13 steps. The analytical data of our synthetic epiepoxydon were identical with those of the authentic product.[4] The conversion from epiepoxydon to phyllostine **22**,[17] a phytotoxin, was reported by Ogasawara and co-workers in 1996.[4f] Now, we have achieved total synthesis of (+)-epiepoxydon and the formal synthesis of (−)-phyllostine, too (Scheme 6).

On the other hand, treatment of **16** with DBU and bromine gave bromo analog **23**. In the same manner, oxidative elimination gave enone **24**. Then deprotection of the TBS group afforded bromoxone **3**, which was synthesized in 17.5% overall yield through 13 steps. The analytical data of our synthetic bromoxone were identical with those of the authentic product[5] (Scheme 7).

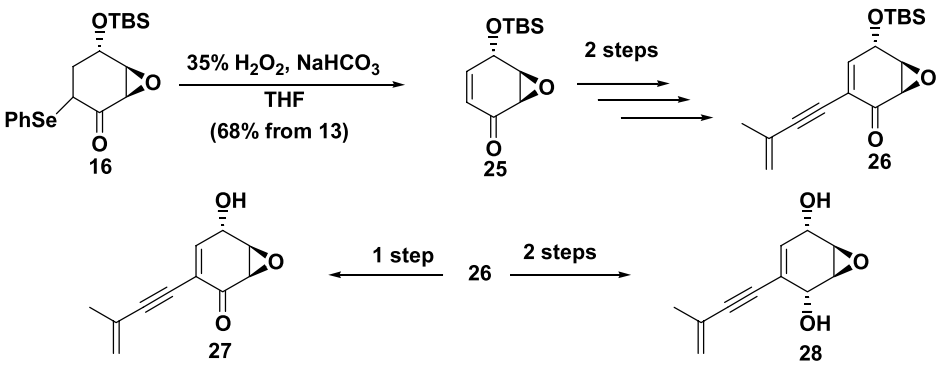
Oxidative elimination of phenylselenoketone **16** gave enone **25**. The analytical data of our synthetic enone were identical with those of the authentic product.[3d] The conversion from



Scheme 6.



Scheme 7.



Scheme 8.

enone **25** to harveynone **27**[4e] and asperpentyn **28**,[18] which are phytotoxins, was reported by Barros and co-workers.[3d] Thus, the formal synthesis of (+)-harveynone and (−)-asperpentyn was established (Scheme 8).

In conclusion, we have succeeded in enantioselective total synthesis of (+)-epiepoformin, (+)-epiepoxydon and (+)-bromoxone, using the common chiral building block. Also, we could indicate the formal synthesis of (−)-theobroxide, (−)-phyllostine, (+)-herveynone and (−)-asperpentyn. As a result, our chiral building block **6** have been established to be a extremely versatile material for the synthesis of highly oxygenated cyclohexane natural products.

3. Experimental

3.1. General

All melting points (mps) were uncorrected. Melting points were recorded on a Yazawa BY-2. Infrared spectra (IR) were measured on a Jasco FT/IR-300E spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were recorded on a JEOL JNM-AL 300 or a JEOL JNM-LA 400 spectrometer. Chemical shifts are reported in parts per million (δ) relative to internal chloroform (δ 7.26 for ^{1}H). Optical rotations were measured on a HORIBA SEPA 200 polarimeter. HRMS were recorded with a HITACHI M-80B mass spectrometer. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm Merck silica gel 60 F_{254} precoated glass-backed plates. Compounds were visualized by ultraviolet light (254 nm), iodine vapor or phosphomolybdic acid spray reagent. Preparative TLC was carried out using 0.5 mm Merck silica gel 60 F_{254} precoated glass-backed plates. Column chromatography was performed on Merck silica gel 60 or Kanto Chemical silica gel 60N (neutral). All solvents were reagent grade. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium/benzophenone under argon. Dichloromethane was freshly distilled from calcium hydride under argon. Carbon tetrachloride, toluene and *N*,*N*-dimethylformamide were dried over 4A-molecular sieves. Methanol, acetonitrile and acetone were used without purification.

3.1.1. (1*R*,2*S*)-2-Acetoxy-5,5-ethylenedioxycyclohexanecarboxylic acid (8). To a solution of **6** (15.0 g, 65 mmol) in methanol (225 mL) at 0°C was added 1 M aqueous lithium hydroxide (75 mL, 75 mmol) over 10 min. After being stirred at room temperature for 3 h, the reaction mixture was concentrated in vacuo. The residue was diluted with toluene and concentrated in vacuo 3 times to give carboxylic acid lithium salt (15.7 g) as a white solid. This was employed in the next step without further purification.

To a solution of crude carboxylic acid lithium salt (15.7 g) in pyridine (52 g) at 0°C was added acetic anhydride (20 g, 196 mmol) over 10 min. After being stirred at room temperature for 3 days, the reaction mixture was concentrated in vacuo. The residue was added dil. hydrochloric acid to adjust pH 4, and extracted with ethyl acetate (200 mL×3). The combined organic phase was washed with brine (300 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was washed with

n-hexane to give **8** (13.8 g, 87% from **6**); colorless plates; mp 134–135°C; $[\alpha]_D^{20}=+37.9°$ (*c* 0.19, $CHCl_3$); IR (KBr) ν_{max} 2991, 1726, 1684, 1444, 1384, 1293, 1219, 1146, 1082, 1033, 972, 945, 913 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57–2.10 (6H, m), 2.04 (3H, s), 2.90 (1H, ddd, *J*=2.4, 2.7, 12.9 Hz), 3.90–4.04 (4H, m), 5.44 (1H, br s); HRMS (*m*/*z*) calcd for $C_9H_{12}O_4$ $[M-AcOH]^+$, 184.0736, found 184.0672.

3.1.2. (1*S*)-4,4-Ethylenedioxy-2-iodo-1-cyclohexyl acetate (9). A mixture of **8** (7.5 g, 31 mmol), iodobenzenediacetate (11.1 g, 34 mmol) and iodine (7.8 g, 31 mmol) in carbon tetrachloride (750 mL) was stirred and irradiated with tungsten-filament lamps at 60°C for 1.5 h. After cooling, the mixture was washed with aqueous sodium thiosulfate (300 mL×2), aqueous sodium hydrogen carbonate (300 mL) and brine (300 mL). The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (300 g) and eluted with *n*-hexane/ethyl acetate (10:1–4:1) to give **9** (9.12 g, 91%) as an inseparable diastereomeric mixture; colorless needles; mp 54–55°C; IR (KBr) ν_{max} 2959, 2885, 1739, 1363, 1245, 1070, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11–2.58 (6H, m), 2.09 and 2.13 (total 3H, each s), 3.90–3.96 (4H, m), 4.18 and 4.39 (total 1H, each ddd, *J*=4.6, 10.7, 13.0 Hz and 2.7, 4.5, 13.0 Hz), 4.90 and 5.19 (total 1H, dt *J*=4.7, 10.5 Hz and d, *J*=2.6 Hz); HRMS (*m*/*z*) calcd for $C_{10}H_{15}O_4$ $[M-I]^+$, 199.0970, found 199.0863.

3.1.3. (1*S*)-4,4-Ethylenedioxy-2-cyclohexen-1-ol (10). A mixture of **9** (11.9 g, 37 mmol) and DBU (27.8 g, 183 mmol) in toluene (100 mL) was stirred at 100°C for 3.5 h. After cooling, the mixture was poured into cold water (100 mL) and extracted with ethyl acetate (200 mL×2). The combined organic phase was washed with brine (200 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (200 g) and eluted with *n*-hexane/ethyl acetate (20:1–4:1) to give acetate (6.58 g, 91%); colorless oil; $[\alpha]_D^{20}=-116°$ (*c* 1.40, $CHCl_3$); IR (film) ν_{max} 2958, 2883, 1733, 1372, 1117, 1019, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.76–2.15 (4H, m), 2.05 (3H, s), 3.93–4.02 (4H, m), 5.26 (1H, br s), 5.73 (1H, d, *J*=10.3 Hz), 5.88 (1H, dd, *J*=3.2, 10.3 Hz); HRMS (*m*/*z*) calcd for $C_8H_{10}O_2$ $[M-AcOH]^+$, 138.0681, found 138.0630.

A mixture of acetate (7.4 g, 37 mmol) and potassium carbonate (100 mg) in methanol (100 mL) was stirred at room temperature for 4.5 h. The mixture was concentrated in vacuo. The residue was chromatographed on silica gel (200 g) and eluted with *n*-hexane/ethyl acetate (4:1–2:3) to give **10** (5.02 g, 86%); colorless oil; $[\alpha]_D^{20}=-40.5°$ (*c* 1.24, $CHCl_3$); IR (film) ν_{max} 3399, 2951, 2882, 1114, 1011, 936 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57–1.62 (1H, m), 1.73–1.82 (2H, m), 1.93–1.99 (1H, m), 2.08–2.16 (1H, m), 3.90–4.03 (4H, m), 4.22 (1H, br s), 5.63 (1H, d, *J*=10.1 Hz), 5.95 (1H, dd, *J*=1.9, 10.1 Hz); HRMS (*m*/*z*) calcd for $C_8H_{10}O_2$ $[M-H_2O]^+$, 138.0681, found 138.0685.

3.1.4. (1*S*)-1-*tert*-Butyldimethylsilyloxy-4,4-ethylenedioxy-2-cyclohexene (11). To a solution of **10** (113 mg, 0.72 mmol) and imidazole (118 mg, 1.74 mmol) in *N*,*N*-dimethylformamide (3 mL) at 0°C was added *tert*-butyldimethylsilyl chloride (131 mL, 0.87 mmol). After being stirred at room temperature overnight, the mixture was poured into cold aqueous sodium hydrogen carbonate (5 mL) and extracted with diethyl ether (10 mL×2). The combined organic phase was washed with brine (20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (20 g) and eluted with *n*-hexane/ethyl acetate (20:1–5:1) to give **11** (191 mg, 98%); colorless oil; $[\alpha]_D^{20}=-54.9°$ (*c* 0.70, $CHCl_3$); IR (film) ν_{max} 2953, 2857, 1395, 1253, 1116, 1082, 1021, 870, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.88 (9H, s), 1.71–1.79 (2H, m), 1.93–1.97 (2H, m), 3.89–4.01 (4H, m), 4.17–4.25 (1H, m), 5.55 (1H, d, *J*=10.0 Hz), 5.86 (1H, dd, *J*=2.4, 10.0 Hz); HRMS (*m*/*z*) calcd for $C_{12}H_{22}O_3Si$ $[M-C_2H_4]^+$, 242.1338, found 242.1374.

3.1.5. (1*S*,2*S*,3*R*)-1-*tert*-Butyldimethylsilyloxy-2,3-epoxy-4,4-ethylenedioxycyclohexane (12). To a solution of **11** (500 mg, 1.85 mmol) and sodium hydrogen carbonate (840 mg, 10 mmol) in dichloromethane (50 mL) at 0°C was added *m*-chloroperbenzoic acid (1.6 g, 9.27 mmol). After being stirred at room temperature for 5 days, the mixture was poured into cold aqueous sodium hydrogen carbonate (50 mL) and extracted with diethyl ether (100 mL×2). The combined organic phase was washed with brine (200 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (20 g) and eluted with *n*-hexane/ethyl acetate (20:1–8:1) to give **12** (289 mg, 55%); colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.09 (3H, s), 0.89 (9H, s), 1.54–1.60 (3H, m), 1.74–1.78 (1H, m), 3.03 (1H, d, *J*=3.6 Hz), 3.17 (1H, d, *J*=3.6 Hz), 3.97–4.10 (5H, m).

3.1.6. (4*S*)-4-*tert*-Butyldimethylsilyloxy-2-cyclohexen-1-one (14). A mixture of **11** (300 mg, 1.11 mmol) and pyridinium *p*-toluenesulfonate (15 mg) in 90% aqueous acetone (5 mL) was stirred at reflux for 1 h. After cooling, the mixture was concentrated in vacuo. The residue was chromatographed on silica gel (20 g) and eluted with *n*-hexane/ethyl acetate (20:1–8:1) to give **14** (226 mg, 90%); colorless oil; $[\alpha]_D^{20}=-116.0°$ (*c* 0.70, $CHCl_3$), lit. $[\alpha]_D=-115.94°$ (*c* 1.06, $CHCl_3$);[13c] IR (film) ν_{max} 2954, 2857, 1691, 1472, 1382, 1253, 1102, 860, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.11 (3H, s), 0.12 (3H, s), 0.92 (9H, s), 2.00 (1H, ddt, *J*=4.0, 8.8, 12.8 Hz), 2.21 (1H, dqd, *J*=1.6, 4.4, 12.8 Hz), 2.34 (1H, ddd, *J*=4.4, 12.4, 16.8 Hz), 2.57 (1H, dtd, *J*=0.8, 4.4, 16.8 Hz), 4.52 (1H, ddd, *J*=2.4, 4.4, 9.2 Hz), 5.92 (1H, ddd, *J*=1.2, 2.0, 10.4 Hz), 6.83 (1H, dt, *J*=2.0, 10.4 Hz); HRMS (*m*/*z*) calcd for $C_{11}H_{19}O_2Si$ $[M-CH_3]^+$, 211.1154, found 211.1186.

3.1.7. (2*R*,3*S*,4*S*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-cyclohexan-1-one (13). To a solution of **14** (5.27 g, 23.3 mmol) in tetrahydrofuran (30 mL) at 0°C was added 35% hydrogen peroxide (11.3 g,.117 mmol) and triton B (1.05 mL, 2.33 mmol) over 10 min. After being stirred at the same temperature for 1.5 h, the mixture was poured into cold aqueous ammonium chloride (30 mL) and extracted with diethyl ether (50 mL×2). The combined organic phase was washed with aqueous sodium hydrogen carbonate (100 mL) and brine (100 mL), dried over anhydrous

magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (200 g) and eluted with *n*-hexane/ethyl acetate (20:1) to give **13** (4.52 g, 80%); colorless oil; $[\alpha]_D^{20}$=+57.3° (*c* 1.97, $CHCl_3$); IR (film) ν_{max} 2954, 2858, 1718, 1472, 1362, 1254, 1092, 982, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (3H, s), 0.12 (3H, s), 0.89 (9H, s), 1.70 (1H, ddd, *J*=4.0, 10.4, 14.0 Hz), 2.09 (1H, tq, *J*=3.2, 14.0 Hz), 2.29–2.44 (2H, m), 3.26 (1H, d, *J*=4.0 Hz), 3.46 (1H, dt, *J*=0.8, 3.4 Hz), 4.45 (1H, dd, *J*=3.2, 6.8 Hz); HRMS (*m/z*) calcd for $C_{11}H_{19}O_3Si$ $[M-CH_3]^+$, 227.1103, found 227.1075.

3.1.8. (2*R*,3*S*,4*S*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-phenylselenylcyclohexan-1-one (16). To a solution of **13** (1.0 g, 4.13 mmol) in tetrahydrofuran (10 mL) at-78°C was added 1 M lithium hexamethyldisilazane (4.95 mL, 4.95 mmol) over 30 min and the mixture was stirred for 30 min. Then to the mixture was added chlorotrimethylsilane (1.05 mL, 8.26 mmol) over 15 min and the mixture was stirred for 30 min. After being stirred at room temperature for 1 h, the mixture was concentrated in vacuo and dry *n*-pentane was added to the mixture. The pentane solution was filtered through a celite® pad and then concentrated in vacuo to give crude silyl enol ether **15** (1.33 g) as a pale-yellow oil. This was employed in the next step without further purification.

To a solution of crude **15** (1.33 g) in dichloromethane (50 mL) at −78°C was added a mixture of phenylselenenyl chloride (870 mg, 4.54 mmol) and dichloromethane (10 mL) over 30 min and the whole was stirred for 15 min. After being stirred at room temperature for 15 min, the mixture was concentrated in vacuo to give **16** (2.18 g) as a pale-yellow oil. This was employed in the next step without further purification.

3.1.9. (2*R*,3*S*,4*S*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methyl-5-cyclohexen-1-one (18). To a suspension of sodium hydride (25 mg, 0.65 mmol) in tetrahydrofuran (1 mL) at 0°C was added a mixture of crude **16** (82 mg) and tetrahydrofuran (1 mL) over 10 min. Then to the mixture at 0°C was added iodomethane (70 μL, 1.12 mmol) over 10 min. After being stirred at the same temperature overnight, the mixture was poured into cold water (3 mL) and extracted with diethyl ether (5 mL×2). The combined organic phase was washed with aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo to give crude **17** as a pale-yellow oil. This was employed in the next step without further purification.

To a suspension of crude **17** and sodium hydrogen carbonate (50 mg, 0.6 mmol) in tetrahydrofuran (3 mL) at 0°C was added 35% hydrogen peroxide (50 μL, 0.5 mmol) over 10 min. After being stirred at room temperature for 1.5 h, the mixture was poured into water (5 mL) and extracted with diethyl ether (5 mL×2). The combined organic phase was washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC developed with *n*-hexane/ethyl acetate (5:1) to give **18** (20 mg, 50% from **13**) with inseparable unknown by-products; colorless oil; $[\alpha]_D^{20}$=+124.0° (*c* 0.59, $CHCl_3$); lit. $[\alpha]_D$+251.0° (*c* 1.17, $CHCl_3$),[3c] $[\alpha]_D$=+251.3° (*c* 1.40, $CHCl_3$),[3d] $[\alpha]_D^{31}$=+252° (*c* 0.815, $CHCl_3$);[3e] IR (film) ν_{max} 2954, 2930, 2858, 1685, 1092, 1074, 837, 778 cm^{-1}; ^1H NMR [300 MHz, $CDCl_3$, compound **18** could be assigned] δ 0.15 (3H, s), 0.17 (3H, s), 0.92 (9H, s), 1.84 (3H, s), 3.48 (1H, dd, *J*=1.2, 3.6 Hz), 3.62–3.64 (1H, m), 4.64 (1H, dd, *J*=1.2, 4.8 Hz), 6.27–6.30 (1H, m); HRMS (*m/z*) calcd for $C_{12}H_{19}O_3Si$ $[M-CH_3]^+$, 239.1103, found 239.1129.

3.1.10. (2*R*,3*R*,4*S*)-2,3-Epoxy-4-hydroxy-6-methyl-5-cyclohexen-1-one (epiepoformin 1). To a solution of **18** (8.8 mg, 0.035 mmol) in acetonitrile (1 mL) at 0°C was added 40% aqueous hydrofluoric acid (1 μL). After being stirred at room temperature for 1.5 h, the mixture was poured into aqueous sodium hydrogen carbonate (5 mL) and extracted with ethyl acetate (5 mL×5). The combined organic phase was washed with aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC developed with *n*-hexane/ethyl acetate (3:1) to give a white solid (5 mg), which was recrystallized from *n*-hexane/ethyl acetate to give **1** (3 mg, 62%); colorless plates; mp 80–81°C; lit. mp 87.5–88.5°C,[3c] 84–85°C;[3d] $[\alpha]_D^{20}$=+320.0° (*c* 0.06, EtOH); lit. $[\alpha]_D$+316.0° (*c* 0.37, EtOH),[3c] $[\alpha]_D$=+315.0° (*c* 0.49, EtOH),[3d] $[\alpha]_D^{27}$=+310° (*c* 0.46, EtOH);[3e] IR (KBr) ν_{max} 3416, 1667, 1436, 1376, 1274, 1129, 1040, 824, 725, 597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.86 (3H, s), 3.52 (1H, dd, *J*=1.2, 3.6 Hz), 3.77–3.79 (1H, m), 4.67 (1H, dd, *J*=1.2, 4.8 Hz), 6.44–6.47 (1H, m); HRMS (*m/z*) calcd for $C_7H_8O_3$ $[M]^+$, 140.0473, found 140.0567.

3.1.11. (2*R*,3*S*,4*S*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-hydroxymethyl-5-cyclohexen-1-one (21). To a suspension of crude **16** (100 mg) in tetrahydrofuran (1 mL) at 0°C was added DBU (76 mg, 0.5 mmol) and 35% formalin (108 mg, 1.25 mmol). After being stirred at the same temperature for 30 min, the mixture was poured into cold water (3 mL) and extracted with diethyl ether (5 mL×2). The combined organic phase was washed with aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo to give crude **20** as a pale-yellow oil. This was employed in the next step without further purification.

To a suspension of crude **20** and sodium hydrogen carbonate (100 mg, 1.2 mmol) in tetrahydrofuran (2 mL) at 0°C was added 35% hydrogen peroxide (100 μL, 1.0 mmol) over 10 min. After being stirred at room temperature for 2 h, the mixture was poured into water (5 mL) and extracted with diethyl ether (5 mL×2). The combined organic phase was washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (20 g) and eluted with *n*-hexane/ethyl acetate (20:1–4:1) to give a white solid (31 mg), which was recrystallized from *n*-hexane to give **21** (23 mg, 45% from **13**); colorless needles; mp 40–41°C; lit. mp 39.5–41°C;[4f] $[\alpha]_D^{20}$=+245.0° (*c* 0.49, $CHCl_3$); lit. $[\alpha]_D^{29}$=+233.5° (*c* 0.9, $CHCl_3$);[4f] IR (KBr) ν_{max} 3438, 2929, 1685, 1472, 1389, 1253, 1075, 843, 777, 717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.16 (3H, s), 0.19 (3H, s), 0.92 (9H, s), 1.98 (1H, br s), 3.48 (1H, dd, *J*=1.2, 3.6 Hz), 3.66–3.67 (1H, m), 4.26 (1H, d, *J*=14.4 Hz), 4.36 (1H, d,

J=14.4 Hz), 4.72 (1H, d, J=4.8 Hz), 6.50–6.51 (1H, m); HRMS (m/z) calcd for $C_9H_{13}O_4Si$ $[M-C_4H_9]^+$, 213.0583, found 213.0593.

3.1.12. (2*R*,3*R*,4*S*)-2,3-Epoxy-4-hydroxy-6-hydroxymethyl-5-cyclohexen-1-one (epiepoxydon 2). The deprotection of **21** (13 mg, 0.048 mmol) was performed as described above for **1** to give **2** (4 mg, 53%); colorless oil; $[\alpha]_D^{20}$=+256.1° (c 0.95, EtOH); lit. $[\alpha]_D$=+194° (c 1.57, EtOH),[1] $[\alpha]_D^{27}$=+256.4° (c 0.8, EtOH);[4f] IR (film) ν_{max} 3355, 1680, 1397, 1242, 1112, 1032, 821, 716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (1H, dd, J=1.2, 3.6 Hz), 3.81–3.84 (1H, m), 4.25 (1H, d, J=14.4 Hz), 4.43 (1H, d, J=14.4 Hz), 4.77 (1H, d, J=4.8 Hz), 6.67–6.70 (1H, m); HRMS (m/z) calcd for $C_7H_8O_4$ $[M]^+$, 156.0423, found 156.0438.

3.1.13. (2*R*,3*S*,4*S*)-6-Bromo-4-*tert*-butyldimethylsilyloxy-2,3-epoxy-5-cyclohexen-1-one (24). To a suspension of crude **16** (80 mg) in tetrahydrofuran (1 mL) at 0°C was added DBU (61 mg, 0.4 mmol) and bromine (32 mg, 0.2 mmol). After being stirred at the same temperature for 30 min, the mixture was poured into cold water (3 mL) and extracted with diethyl ether (5 mL×2). The combined organic phase was washed with aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo to give crude **23** as a pale-brown oil. This was employed in the next step without further purification.

To a suspension of crude **23** and sodium hydrogen carbonate (80 mg, 1.0 mmol) in tetrahydrofuran (2 mL) at 0°C was added 35% hydrogen peroxide (80 μL, 0.8 mmol) over 10 min. After being stirred at room temperature for 2 h, the mixture was poured into water (5 mL) and extracted with diethyl ether (5 mL×2). The combined organic phase was washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (20 g) and eluted with n-hexane/ethyl acetate (20:1–4:1) to give a white solid (39 mg), which was recrystallized from n-hexane/$CHCl_3$ to give **24** (33 mg, 68% from **13**); colorless needles; mp 49–50°C; $[\alpha]_D^{20}$=+98.9° (c 0.79, $CHCl_3$), IR (KBr) ν_{max} 2953, 2858, 1703, 1253, 1091, 877, 841, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (3H, s), 0.17 (3H, s), 0.93 (9H, s), 3.67–3.69 (1H, m), 3.65 (1H, dd, J=1.2, 3.6 Hz), 4.70 (1H, dt, J=1.2, 5.1 Hz), 6.96 (1H, dd, J=2.1, 5.1 Hz); HRMS (m/z) calcd for $C_8H_{10}BrO_3Si$ $[M-C_4H_9]^+$, 260.9583, found 260.9621.

3.1.14. (2*R*,3*R*,4*S*)-6-Bromo-2,3-epoxy-4-hydroxy-5-cyclohexen-1-one (bromoxone 3). The deprotection of **24** (7.9 mg, 0.025 mmol) was performed as described above for **1** to give a brown solid (5 mg), which was recrystallized from n-hexane/chloroform to give **3** (3 mg, 59%); pale-yellow needles; mp 124–125°C; lit. 123–127°C,[2] 138–139°C,[5b] 131–132°C;[5e] $[\alpha]_D^{20}$=+204.0° (c 0.21, acetone); lit. $[\alpha]_D^{22}$=+220° (c 0.09, $CHCl_3$),[2] $[\alpha]_D^{25}$=+203° (c 2.5, acetone);[5e] IR (KBr) ν_{max} 3467, 1688, 1610, 1254, 1046, 791, 613, 546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (1H, dd, J=1.2, 3.6 Hz), 3.84 (1H, br s), 4.75 (1H, d, J=5.2 Hz), 7.14 (1H, dd, J=2.4, 5.2 Hz); HRMS (m/z) calcd for $C_6H_5BrO_3$ $[M]^+$, 203.9422, found 203.9407.

3.1.15. (2*R*,3*S*,4*S*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-5-cyclohexen-1-one (25). To a solution of crude **16** (50 mg, 0.13 mmol) and sodium hydrogen carbonate (50 mg, 0.6 mmol) in tetrahydrofuran (1 mL) at 0°C was added 35% hydrogen peroxide (50 μL, 0.5 mmol) over 10 min. After being stirred at room temperature for 2 h, the mixture was poured into water (5 mL) and extracted with diethyl ether (5 mL×2). The combined organic phase was washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC developed with n-hexane/ethyl acetate (6:1) to give **25** (15.5 mg, 68% from **13**); colorless oil; $[\alpha]_D^{20}$=+335.9° (c 0.88, $CHCl_3$); lit. $[\alpha]_D^{28}$=+331.5° (c 1.22, $CHCl_3$);[3d] IR (film) ν_{max} 2955, 2930, 2858, 1692, 1260, 1090, 839, 806, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (3H, s), 0.18 (3H, s), 0.92 (9H, s), 3.44–3.46 (1H, m), 3.63–3.65 (1H, m), 4.66 (1H, dd, J=1.2, 4.2 Hz), 5.95 (1H, dt, J=1.6, 10.8 Hz), 6.52 (1H, ddd, J=2.8, 4.8, 10.8 Hz); HRMS (m/z) calcd for $C_{12}H_{20}O_3Si$ $[M]^+$, 240.1182, found 240.1090.

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