Pergamon

Tetrahedron 57 (2001) 1903–1908

TETRAHEDRON

Asymmetric synthesis of (−)- and (+)-eutipoxide B using a base-catalyzed Diels–Alder reaction

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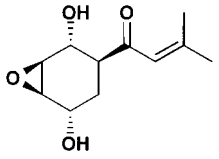
Received 28 November 2000; accepted 4 January 2001

Abstract—The asymmetric synthesis of eutipoxide B, a metabolite of the phytopathogenic fungus *Eutypa lata*, is described. Quick and efficient synthesis of each enantiomer was achieved through base-catalyzed asymmetric Diels–Alder reactions with 3-hydroxy-2-pyrone and chiral acrylates.

Eutipoxide B (**1**, Fig. 1) is a secondary metabolite of the phytopathogenic fungus *Eutypa lata*, which is responsible for 'vineyard die-back' disease. The first isolation of eutipoxide B and its first synthesis in racemic form were reported in 1992 by Tabacchi et al.[1] This compound features a highly oxygenated cyclohexene oxide, an important component of various biologically active compounds. For example, (+)-crotepoxide[2] (isolated from the fruit of *Croton macrostachys*), (+)-cyclophellitol[3] (obtained from a *Phellinus* sp. mushroom) and eupenoxide[4] (produced by a fungus of the genus *Eupenicilliu*) are typical naturally occurring cyclohexene oxides displaying various, strong biological activities. Although the biological functions and the absolute stereochemistry of **1** are not known at this time, a strong interest in the synthesis of **1** has developed, in part because of its structural resemblance to the biologically active compounds described above and in part because of a general interest in methods for synthesis of highly substituted cyclohexene oxides. After the first synthesis of *dl*-**1**,[1] asymmetric syntheses of (−)- and (+)-**1** were reported by Ogasawara et al. in 1993[5] and Maycock et al. in 1997,[6] respectively. The former asymmetric synthesis was achieved by an efficient asymmetric induction using lipase hydrolysis of a *meso* substrate with a rigid tricyclic structure and the latter synthesis was attained by stereoselective 1,4-addition on an optically active cyclohexene derivative obtained from (−)-quinic acid.

We have previously reported a base-catalyzed Diels–Alder (DA) reaction of 3-hydroxy-2-pyrone (**2**) with electron-deficient dienophiles.[7–9] The mechanism of this reaction, which involves activation of the diene moiety by a base, is completely opposite to that of an ordinary DA reaction, which is generally catalyzed by a Lewis acid that activates a dienophile.[10] The DA adducts arising from the base-catalyzed reaction have various functional groups on the ridged bicyclolactone framework and are considered to be attractive starting materials for syntheses of complex molecules. In our continuing efforts to improve the synthetic utility of this reaction, we have further examined the base-catalyzed asymmetric DA reaction of **2**.[8,9] In particular, the reaction of **2** and the optically active acrylate derivative **3** to give **4** appears to be a useful method for preparing highly functionalized six-membered rings, due to the ready availability of the substrates and the near-complete stereoselectivity. Indeed, the efficient asymmetric synthesis of pseudo-sugars that have four oxygen functional groups and one alkyl substituent on a cyclohexane ring has been achieved from the optically active adduct **4**.[9]

An important consideration in achieving efficient asymmetric synthesis of **1** is the choice of the chiral starting material, which should have appropriate functional groups at appropriate positions. Since **1** contains four oxygen functional groups and one alkyl substituent, its structural features are essentially the same as those of pseudo-sugars. Therefore, we again choose **4** as the starting material for this asymmetric synthesis. Indeed, each functionality of **4** potentially corresponds to a functional group on **1**. For example, the oxygen functional groups at C-1 and C-4 and the double bond at C-5,6 of **4** potentially correspond to the epoxide and two hydroxyl groups of **1**, respectively. In



(-)-1: eutipoxide B

Figure 1.

Keywords: eutipoxide B; Diels–Alder reaction; asymmetric synthesis.

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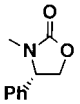
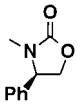
0040–4020/01/$ - see front matter
PII: S0040-4020(01)00032-1

Table 1. Stereoselective DA reaction of **2** and **3** in practical scale

Dienophile	Catalyst (equiv.)	Yield (%)	% de [(+)- or (−)-**4**]
X =  (-)-**3**	Cinchonine (0.2)	74	>95 (+)-**4**
X =  (+)-**3**	Cinchonidine (0.2)	82	>95 (−)-**4**

addition, the carbonyl group at C-8 of **4** provides a suitable footing to introduce the alkyl substituent of **1**. In this paper, we present this new efficient asymmetric synthesis of (+)- and (−)-**1** from **4**.

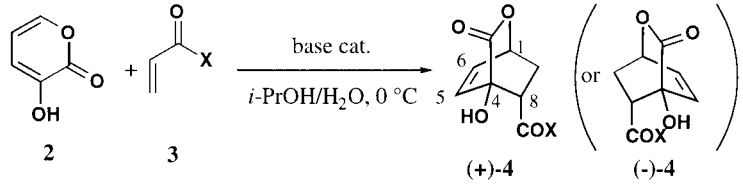
Before beginning the synthesis, we first sought a practical method of obtaining optically pure **4** in quantity (Scheme 1).[11] Fortunately, we found a very simple and practical method for obtaining (+)-**4**, as shown in Table 1. To a fine suspension of (−)-**3** (10.3 g, 47.4 mmol) and **2** (6.35 g, 56.7 mmol) in aqueous 2-propanol (*i*-PrOH/H_2O=95:5, 177 mL) at 0°C, powdered cinchonine (2.78 g, 9.44 mmol) was added. The mixture was continuously stirred for 2 h at 0°C, and the resulting precipitate was collected by vacuum filtration and washed with 2-propanol (ca. 30 mL×3). The washed precipitate was dried under vacuum for 3 h to yield (+)-**4** as a slightly yellow powder (11.5 g, 74%, single isomer).

Consequently, (−)-**4** was also obtained from (+)-**3** by a similar method, in which the catalyst was cinchonidine rather than cinchonine. The stereoselectivity of this reaction was approximately equal to that of the above-described reaction yielding (+)-**4**.

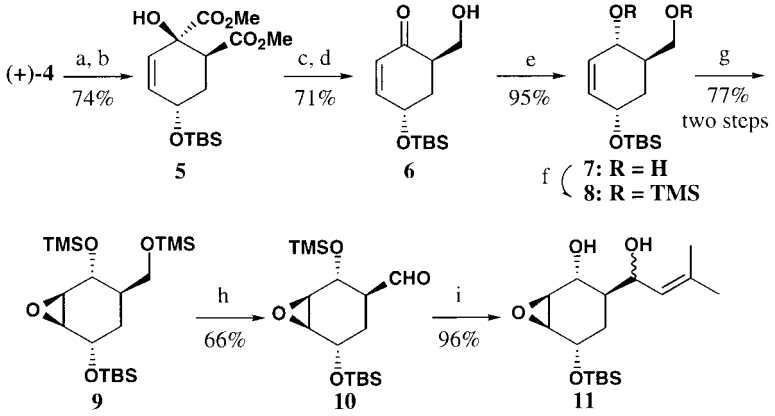
With sufficient quantities of optically pure starting materials in hand, we began the synthesis of (−)-**1** from (+)-**4a** (Scheme 2). First, methanolysis and subsequent TBS protection for the resulting secondary alcohol yielded silyl ether **5**. Then, reduction of two carbomethoxy groups of **5** and oxidative cleavage of the resulting 1,2-diol resulted in the desired unsaturated ketone **6** in good yield. Next, stereoselective reduction of the carbonyl group of **6** was achieved by $NaBH(OAc)_3$, and the 1,3-diol having the appropriate stereochemistry **7** was obtained as a single isomer.[12]

The next step was stereoselective epoxidation of the C–C double bond and chemoselective oxidation of the primary hydroxyl group to an aldehyde that could be a footing for introduction of the side-chain. Normally, direct and chemoselective oxidation of a 1,3-diol to give a hydroxyl aldehyde is difficult. Frequently, the reiteration of protection–deprotection processes is needed, such as (1) selective protection of the primary alcohol using a bulky reagent, (2) protection of the secondary alcohol, (3) selective deprotection of the primary group and (4) oxidation of the primary alcohol. Recently, however, Rodriguez et al.[13] reported chemoselective Swern oxidation of a primary silyl ether to an aldehyde in the presence of secondary silyl ethers. Using this method, the desired aldehyde could be prepared from a trisilyl ether that is easily derived from **7**. Furthermore, the bulky silyl ether neighboring the double bond was expected to promote stereoselective epoxidation. Indeed, epoxidation and subsequent Swern oxidation of silyl ether **8** resulted in epoxy aldehyde **10**, with complete stereoselectivity and in good yield.

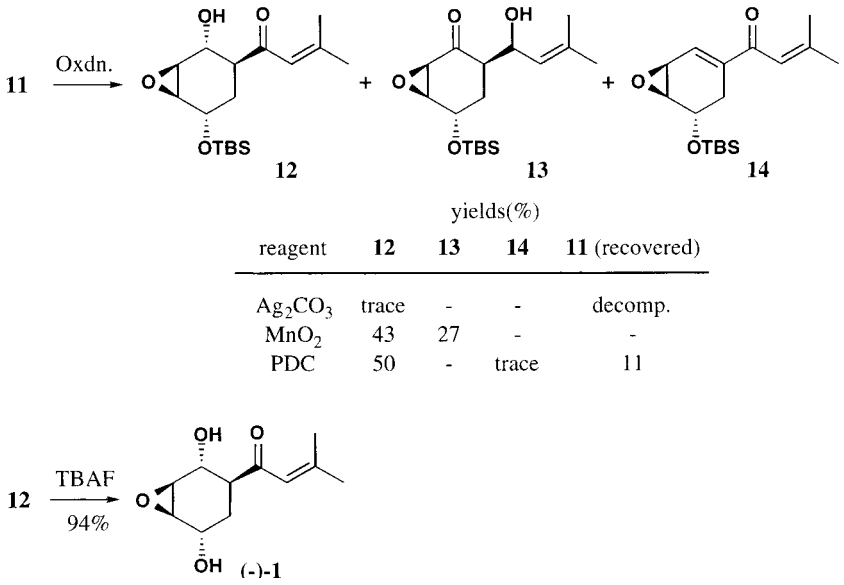
Introduction of the C4 side-chain and deprotection of the



Scheme 1.



Scheme 2. (a) MeONa, MeOH; (b) TBSCl, imidazole; (c) $LiAlH_4$, THF; (d) $NaIO_4$, THF/H_2O; (e) $NaBH(OAc)_3$; (f) TMSCl, Imidazole; (g) *m*CPBA; (h) DMSO, $(COCl)_2$, Et_3N; (i) 2-methylpropenyl magnesiumbromide.



Scheme 3.

remaining TMS ether were achieved by treatment with the corresponding Grignard reagent and subsequent acidic work-up, and diol **11** was obtained as a 1:1 diastereomeric mixture. This mixture was used for oxidation of the resulting hydroxyl group without separation.

Since the target hydroxyl group was an allylic alcohol, effective and selective oxidation was expected (Scheme 3). Surprisingly, Fetizone oxidation[14] of **11** afforded only a trace amount of **12** and the starting material was not recovered, probably due to its decomposition. Active-MnO_2 oxidation[15] of **11** was complete within 15 min, but provided an inseparable mixture of **12** and an alternative ketone **13**, which was obtained as a single isomer of undetermined stereochemistry. Although PDC oxidation[16] of **12** was relatively slow compared to MnO_2 oxidation, the desired ketone **12** was obtained along with a trace amount of dehydrated **14**, which could be removed by SiO_2 column chromatography. Therefore, we chose PDC as the oxidant for this step.

Finally, deprotection of the TBS ether of **12** yielded the target compound (−)-**1**, which was obtained as a colorless oil. Its spectroscopic properties, including optical rotation ($[\alpha]_D^{24}=-60$ (*c* 0.82, $CHCl_3$), lit.[5] $[\alpha]_D^{23}=-56.6$ (*c* 0.68, $CHCl_3$)), were fully identical to those previously reported.[1,5,6]

Since the enantiomeric starting material (−)-**4a**, as well as (+)-**4a**, was available, synthesis of the opposite enantiomer was also examined. This enantiomer was successfully produced with (−)-**4a**, using a procedure identical to that described above, with an optical rotation of $[\alpha]_D^{24}=+55$ (*c* 0.20, $CHCl_3$), lit.[6] $[\alpha]_D^{23}=+57.3$ (*c* 0.84, $CHCl_3$).

In conclusion, the efficient asymmetric synthesis of both enantiomers of **1** has been achieved from (+)- and (−)-**4a**, which were themselves obtained from a base-catalyzed asymmetric DA reaction of **2** and (−)- and (+)-**3a**, respectively. This synthesis demonstrates the synthetic utility of these adducts, which are readily available at high optical purity, for synthesis of various biologically active molecules including cyclohexane oxides. Further applications of (+)- and (−)-**4a** are currently being examined in our laboratory.

1. Experimental

1.1. General

All reagents and solvents were used as supplied commercially, except for THF and CH_2Cl_2, which were distilled from Na/Ph_2CO and CaH_2, respectively. Melting points were determined on a Yanagimoto micro melting point apparatus and were uncorrected. Infrared spectra were measured by JASCO FT/IR 5300 spectrophotometer: only diagnostic absorptions in the infrared spectrum were reported. ^1H and ^{13}C NMR spectra were measured by JEOL GSX400 spectrometer at 400 and 100 MHz, respectively. All chemical shifts (δ) were recorded in ppm, relative to tetramethylsilane (TMS). Mass spectra were recorded on a Shimazu QP-5000 mass spectrometer. High-resolution FAB mass spectra were obtained from JEOL JMX-SX/SX 102A spectrometer using *m*-nitrobenzyl alcohol matrix. Optical rotation was measured with a JASCO DIP-370S Digital Polarimeter. All reactions were carried out under inert atmosphere, if necessary. TLC analysis was performed on Silica gel 60 F_{254}-coated aluminum sheets (Merck). Visualization was accomplished with 254 nm UV light and phosphomolybdic acid ethanol solution as an indicator.

1.1.1. (1*S*,4*R*,8*S*)-4-Hydroxy-3-oxo-8-[(4*S*)-4-phenyloxazolidin-2-one-3-carbonyl]-2-oxabicyclo[2.2.2]oct-5-ene [(−)-4a]. See text. R_f 0.51 (hexane/AcOEt, 3:7). Mp 120.0–121.5°C. $[\alpha]_D^{20}=+73$ (*c* 0.45, $CHCl_3$). IR (KBr): 3478, 3416, 1775, 1707, 1638, 1618, 766, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.27–7.40 (m, 5H); 6.35–6.38 (m, 2H); 5.43 (dd, *J*=8.8 Hz, 1H); 5.26 (d, *J*=4.0 Hz, 1H); 4.73 (t, *J*=8.8 Hz, 1H); 4.29–4.33 (m, 2H); 3.77 (s, –O*H*); 2.71

(ddd, J=13, 9.5, 3.7 Hz, 1H); 1.83 (dd, J=13, 3.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 173.9, 169.8, 153.8, 138.8, 135.0, 129.3, 129.2, 128.9, 125.9, 75.8, 74.0, 70.1, 58.1, 40.2, 32.5. Anal. Calcd for $C_{17}H_{15}NO_6$: C 62.00, H 4.59, N 4.25. Found: C 62.01, H 4.56, N 4.29.

1.1.2. Dimethyl (1*S*,2*R*,5*S*)-5-*tert*-butyldimethylsilyloxy-2-hydroxy-3-cyclohexene-1,2-dicarboxylate (5). To a solution of adduct (+)-**4a** (5.00 g, 15.2 mmol) in MeOH (100 mL), a solution of NaOMe 4.9 M in MeOH (9.3 mL, 45.6 mmol) at 0°C was added dropwise. The reaction was complete for approximately 30 min. The resulting solution was quenched with aqueous diluted H_3PO_4 (5.0%, 50 mL) and water (50 mL), evaporated under reduce pressure to remove MeOH. The resulting solution was extracted with ethyl acetate (40 mL) for three times, and the combined organic layer was washed with aqueous saturated solution of $NaHCO_3$, and brine, evaporated to give crude product which was used without further purification in the next step.

To a solution of the above product (4.95 g) in DMF (30 mL) at 60°C imidazole (1.14 g, 16.7 mmol) and TBDMSCl (2.30 g, 15.2 mmol) were added. After stirring for 10 h at the same temperature, the reaction mixture was poured into water and extracted with ethyl acetate (30 mL) for three times. The combined organic layer was dried over $MgSO_4$, filtered through a glass filter, and evaporated under reduce pressure. Purification by column chromatography gave **5** (3.80 g, 74% from (+)-**4a**) as a colorless oil. R_f 0.33 (hexane/AcOEt, 7:3). $[\alpha]_D^{20}$=−69 (c 0.76, $CHCl_3$). IR (neat): 3495, 2955, 2888, 2859, 1746, 1439, 1256, 1065, 837, 777 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.97 (dd, J=9.9, 5.1 Hz, 1H); 5.61 (d, J=9.5 Hz, 1H); 4.29 (brs, 1H); 3.85 (s, –O*H*); 3.84 and 3.70 (each s, 3H); 3.59 (dd, J=12, 4.4 Hz, 1H); 2.04–2.13 (m, 2H); 0.90 (s, 9H); 0.084 and 0.096 (each s, 3H). ^{13}C NMR ($CDCl_3$): δ 175.5, 173.2, 132.5, 127.7, 72.1, 63.1, 53.4, 52.0, 42.1, 29.5, 25.8, 18.1, −4.52, −4.78. HRFABMS m/z. Calcd for $C_{16}H_{29}O_6Si$ $(M+H)^+$: 345.1761. Found 345.1733.

1.1.3. (4*S*,6*R*)-4-*tert*-Butyldimethylsilyloxy-6-hydroxymethyl-2-cyclohexenone (6). To a solution of **5** (3.66 g, 10.6 mmol) in THF (50 mL) was carefully added lithium aluminum hydride (LAH) (806 mg, 21.2 mmol) at 0°C, and after stirring for 3 h, the reaction mixture was quenched with water (1.0 mL), aqueous NaOH (15%, 1.0 mL) and H_2O (3.0 mL). A diluted H_3PO_4 (5.0%, 50 mL) was added to the resulting suspension to dissolve the precipitate. The clear solution was extracted with ether (30 mL) for three times, the extracts were washed with brine, and dried over $MgSO_4$. After filtered through a glass filter, the residue was evaporated under reduce pressure to give triol (2.72 g, 89%) as a white solid. R_f 0.47 (AcOEt). Mp. 72.5–73.5°C. $[\alpha]_D^{20}$=−120 (c 0.55, $CHCl_3$). IR (KBr): 3416, 2955, 2888, 1638, 1618, 1472, 1399, 837, 775 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.85 (dd, J=10, 4.4 Hz, 1H); 5.60 (d, J=10 Hz, 1H); 4.21 (brq, J=4.4 Hz, 1H); 3.80 (dd, J=11, 8.1 Hz, 1H); 3.74 (dd, J=11, 2.9 Hz, 1H); 3.69 (d, J=11 Hz, 1H); 3.47 (d, J=11 Hz, 1H); 3.25–3.83 (br, 3H); 2.17 (m, 1H); 1.87 (ddd, J=14, 9.5, 4.4 Hz, 1H); 1.56 (dt, J=14, 4.4 Hz, 1H); 0.88 (s, 9H); 0.067 and 0.071 (each s, 3H). ^{13}C NMR ($CDCl_3$): δ 133.1, 130.9, 72.2, 68.9, 64.3, 64.2, 38.8, 32.6, 25.8, 18.2, −4.56, −4.68. Anal. Calcd for $C_{14}H_{28}O_4Si$: C 58.29, H 9.78. Found: C 58.30, H 9.77.

To a stirring solution of the triol (2.25 g, 7.80 mmol) in THF/H_2O (1:1, 40 mL) $NaIO_4$ (1.84 g, 8.58 mmol) was added. The reaction was complete within 20 min. The resulting mixture was quenched with a few drops of ethylene glycol, extracted with ethyl acetate (25 mL) for three times, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered through a glass filter and concentrated under reduce pressure. The resulting residue was purified by silica gel column chromatography to give α,β -unsaturated ketone **6** (1.61 g, 80%) as a colorless oil. R_f 0.36 (hexane/AcOEt, 7:3). $[\alpha]_D^{20}$=−137 (c 0.88, $CHCl_3$). IR (neat): 3445, 1678, 1385, 1254, 1076, 999, 777 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.80 (ddd, J=9.9, 4.8, 1.1 Hz, 1H); 5.94 (d, J=9.9 Hz, 1H); 4.48 (dd, J=8.4, 4.0 Hz, 1H); 3.84–3.72 (m, 2H); 2.98 (ddd, J=16, 6.6, 4.8 Hz, 1H); 2.68 (dd, J=8.1, 4.8 Hz, –O*H*); 2.10–1.97 (m, 2H); 0.91 (s, 9H); 0.11 and 0.12 (each s, 3H). ^{13}C NMR ($CDCl_3$): δ 202.6, 148.7, 129.0, 63.3, 63.2, 43.8, 34.1, 25.7, 18.1, −4.64, −4.82. HRFABMS m/z. Calcd for $C_{13}H_{25}O_3Si$ $(M+H)^+$: 257.1575. Found 257.1573.

1.1.4. (1*S*,4*S*,6*R*)-4-*tert*-Butyldimethylsilyloxy-6-hydroxymethyl-2-cyclohexenol (7). To a solution of ketone **6** (120 mg, 0.468 mmol) in CH_3COOH (4.7 mL) $NaBH(OAc)_3$ was added at room temperature. After stirring for 30 min, the reaction mixture was poured into aq. saturated solution of $NaHCO_3$ (20 mL) and the whole mixture was extracted with AcOEt (20 mL) for three times. The combined organic layer was dried over $MgSO_4$, filtered through a glass filter, and evaporated. The resulting residue was purified by silica gel column chromatography, and alcohol **7** (115 mg, 95%) was obtained as a colorless oil. R_f 0.38 (hexane/AcOEt, 3:7). Mp 70.0–71.5°C. $[\alpha]_D^{21}$=−92 (c 0.55, $CHCl_3$). IR (KBr): 3252, 1618, 1470, 1254, 941, 880 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.73 (brd, J=10 Hz, 1H); 5.71 (brd, J=10 Hz, 1H); 4.18 (brd, J=2.6 Hz, 1H); 4.08 (dd, J=8.4, 5.1 Hz, 1H); 3.78 (ddd, J=10, 5.9, 4.4 Hz, 1H); 3.68 (dt, J=10, 4.0 Hz, 1H); 3.11 (d, J=5.5 Hz, –O*H*); 2.73 (dd, J=5.5, 4.4 Hz, –O*H*); 2.13–2.06 (m, 1H); 1.59 (br d, J=14 Hz, 1H); 1.41 (dt, J=4.0, 14 Hz, 1H); 0.89 (s, 9H); 0.71 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 132.8, 129.6, 72.5, 67.7, 63.7, 38.3, 32.4, 25.9, 18.2, −4.57, −4.76. Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C 60.37, H 10.27.

1.1.5. (1*S*,2*S*,3*R*,4*R*,5*R*)-1-*tert*-Butyldimethylsilyloxy-2,3-epoxy-4-trimethylsilyloxy-5-trimethylsilyloxymethylcyclohexane (9). To a solution of diol **7** (405 mg, 1.57 mmol) and Et_3N (656 μL, 4.71 mmol) in CH_2Cl_2 (15 mL) TMSCl (500 μL, 3.92 mmol) was added at room temperature, and the mixture was stirred for 30 min. The reaction solution was poured into a mixture of aq. saturated solution of $NaHCO_3$ and H_2O (10 mL), and the whole mixture was extracted with ether (25 mL) for three times. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered through a glass filter, and evaporated to give crude TMS ether **8** (ca. 640 mg) as a colorless oil.

To a solution of **8** in CH_2Cl_2 (10 mL) was added *m*CPBA (541 mg, 3.17 mmol), and the solution was heated under

reflux. After 7 h, the excess *m*CPBA was quenched with aq. saturated solution of $Na_2S_2O_3$ and the mixture was extracted with ether (20 mL) for three times. The combined organic layer was washed with aq. saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered through a glass filter, and evaporated under reduced pressure. The residual oil was purified by silica gel column chromatography to give epoxide **9** (507 mg, 1.21 mmol, 77% from **7**) as a colorless oil. R_f 0.55 (hexane/ether, 10:1). $[\alpha]_D^{23}=+4.3$ (*c* 0.76, $CHCl_3$). IR (neat): 2957, 2859, 1472, 1254, 1088, 841 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.24 (brd, *J*=2.2 Hz, 1H); 3.69 (d, *J*=9.9 Hz, 1H); 3.55 (dd, *J*=9.9, 2.9 Hz, 1H); 3.45 (dd, *J*=9.9, 5.9 Hz, 1H); 3.08 (d, *J*=3.3 Hz, 1H); 3.05 (brd, *J*=1.1 Hz, 1H); 1.84–1.77 (m, 1H); 1.49 (brd, *J*=14 Hz, 1H); 1.34 (dt, *J*=14, 13, 2.9 Hz, 1H); 0.90 (s, 9H); 0.18 (s, 9H); 0.093 and 0.087 (each s, 3H); 0.073 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 67.0, 65.5, 63.1, 58.3, 55.5, 37.0, 28.3, 25.8, 18.1, 0.15, −0.57, −4.78, −4.82. HRFABMS *m/z*. Calcd for $C_{19}H_{43}O_4Si_3$ $(M+H)^+$: 419.2471. Found 419.2469.

1.1.6. (1*R*)-1-[(1*R*,2*R*,3*S*,4*S*,5*S*)-5-*tert*-Butyldimethylsilyloxy-3,4-epoxy-2-hydroxycyclohexyl]-3-methyl-2-butenol and (1*S*)-1-[(1*R*,2*R*,3*S*,4*S*,5*S*)-5-*tert*-butyldimethylsilyloxy-3,4-epoxy-2-hydroxy-cyclohexyl]-3-methyl-2-butenol (11). To a solution of oxalyl chloride (42 μL, 0.48 mmol) in CH_2Cl_2 (3.0 mL) was dropwisely added DMSO (68 μL, 0.96 mmol) at −78°C, and the solution was stirred for 30 min. A solution of **9** (134 mg, 0.32 mmol) in CH_2Cl_2 (0.5 mL) was then dropwisely added to the above solution at that temperature. After stirring for another 30 min, Et_3N (355 μL, 0.48 mmol) was added to the solution, and the resulting mixture was stirred and gradually warmed to room temperature for 2 h. The reaction solution was quenched with water (1.0 mL), the whole mixture was extracted with ether (10 mL) for three times. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered through a glass filter, and evaporated under reduced pressure to give crude product. The residue was purified by silica gel column chromatography to afford recovered **9** (19 mg, 14%), deprotected hydroxyaldehyde (5.0 mg, 7.2%), and aldehyde **10** (72 mg, 66%) as a colorless oil. R_f 0.52 (hexane/ether, 8:2). $[\alpha]_D^{23}=-5.9$ (*c* 0.91, $CHCl_3$). IR (neat): 2932, 1728, 1472, 1362, 1254, 1100, 839 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.70 (d, *J*=1.5 Hz, 1H); 4.28 (t, *J*=3.3 Hz, 1H); 4.16 (d, *J*=9.2 Hz, 1H); 3.12–3.09 (m, 2H); 2.70 (dddd, *J*=12, 9.2, 2.9, 1.5 Hz, 1H); 1.65 (dt, *J*=14, 3.3 Hz, 1H); 1.45 (ddd, *J*=14, 12.1, 2.9 Hz, 1H); 0.92 (s, 9H); 0.20 (s, 9H); 0.12 and 0.11 (each s, 3H). ^{13}C NMR ($CDCl_3$): δ 202.8, 65.8, 64.3, 57.1, 55.4, 48.1, 25.8, 25.1, 18.1, 0.156, −4.81, −4.85.

To a solution of **10** (160 mg, 0.46 mmol) in THF (5.0 mL) was added dropwise 2-methyl-1-propenylmagnesium bromide (1.0 M in THF, 0.69 mmol) at 0°C. After stirring for 2 h, the reaction was quenched with diluted HCl (5.0%, 2.0 mL), and the whole mixture was extracted with ethyl acetate (20 mL) for three times. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered through a glass filter, and evaporated to give crude product. Purification by column chromatography gave **11** as an almost 1:1 mixture of two isomers (total 146 mg, 96%). First diastereomer (white solid). R_f 0.48 (hexane/AcOEt, 6:4). Mp 100.5–102°C. $[\alpha]_D^{18}=-59$ (*c* 0.50, $CHCl_3$). IR (KBr): 3385, 2930, 1725, 1678, 1445, 1256, 1196, 1078, 912, 837 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.10 (dd, *J*=9.2, 1.1 Hz, 1H); 4.24–4.21 (m, 3H); 3.90 (d, *J*=9.2 Hz, 1H); 3.17 (d, *J*=3.3 Hz, 1H); 3.09 (s, 1H); 2.00 (brs, –O*H*); 1.83–1.70 (m, 1H); 1.73 (d, *J*=1.1 Hz, 3H); 1.66 (d, *J*=1.1 Hz, 3H); 1.25 (dt, *J*=13, 2.6 Hz, 1H); 1.10 (dt, *J*=2.6, 13 Hz, 1H); 0.91 (s, 9H); 0.083 and 0.064 (each s, 3H). ^{13}C NMR ($CDCl_3$): δ 137.4, 126.5, 74.3, 70.7, 65.3, 56.9, 55.0, 39.8, 26.6, 25.7, 25.6, 18.4, 18.1, −4.75, −5.00. Anal. Calcd for $C_{17}H_{32}O_4Si$: C 62.15, H 9.82. Found: C 62.05, H 9.82. Second diastereomer (white solid). R_f 0.33 (hexane/AcOEt, 6:4). Mp 129–130°C. $[\alpha]_D^{21}=-46$ (*c* 0.50, $CHCl_3$). IR (KBr): 3457, 2932, 1736, 1676, 1462, 1254, 1184, 1078, 905, 837 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.32 (dt, *J*=9.2, 1.5 Hz, 1H); 4.52 (dd, *J*=9.2, 3.7 Hz, 1H); 4.25 (dd, *J*=5.1, 2.6 Hz, 1H); 4.00 (brd, *J*=9.9 Hz, 1H); 3.63 (brs, –O*H*); 3.17 (d, *J*=3.7 Hz, 1H); 3.08 (t, *J*=2.6 Hz, 1H); 2.13 (ddd, *J*=9.9, 5.1, 4.8 Hz, 1H); 1.96 (brs, –O*H*); 1.74 (d, *J*=1.1 Hz, 3H); 1.68 (d, *J*=1.1 Hz, 3H); 1.22–1.18 (m, 2H); 0.91 (s, 9H); 0.10 and 0.092 (each s, 3H). ^{13}C NMR ($CDCl_3$): δ 137.3, 123.6, 71.6, 66.7, 65.4, 57.2, 54.9, 39.2, 26.8, 26.0, 25.8, 18.4, 18.1, −4.76, −4.87. Anal. Calcd for $C_{17}H_{32}O_4Si$: C 62.15, H 9.82. Found: C 61.92, H 9.78.

1.1.7. 1-[(1*S*,2*R*,3*S*,4*R*,5*S*)-5-*tert*-Butyldimethylsilyloxy-3,4-epoxy-2-hydroxycyclohexyl]-3-methyl-2-buten-1-one (12). To a solution of **11** (65 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) was added PDC (89 mg, 0.24 mmol) at 0°C. The reaction mixture was stirred and gradually warmed to rt for 2 h. The resulting mixture was filtered through a pad of silica gel and the pad was washed with ethyl acetate. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the starting material **11** (7.0 mg, 11%) and the desired product **12** (32 mg, 50%) as a colorless oil. R_f 0.40 (hexane/AcOEt, 7:3). $[\alpha]_D^{24}=-81$ (*c* 0.15, $CHCl_3$). IR (neat): 3463, 2930, 1686, 1618, 1445, 1254, 1076, 837 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.06 (t, *J*=1.1 Hz, 1H); 4.30 (dd, *J*=5.1, 2.6 Hz, 1H); 4.21 (dd, *J*=9.5, 4.4 Hz, 1H); 3.23 (d, *J*=3.7 Hz, 1H); 3.09 (brs, 1H); 2.73 (ddd, *J*=13, 9.5, 2.6 Hz, 1H); 2.61 (d, *J*=4.4 Hz, –O*H*); 2.16 (d, *J*=1.1 Hz, 3H); 1.91 (d, *J*=1.1 Hz, 3H); 1.65 (dt, *J*=14, 2.2 Hz, 1H); 1.44 (ddd, *J*=14, 13, 2.9 Hz, 1H); 0.95 (s, 9H); 0.142 and 0.138 (each s, 3H). ^{13}C NMR ($CDCl_3$): δ 202.3, 157.8, 122.4, 66.0, 65.3, 56.9, 54.8, 48.4, 28.4, 28.0, 25.7, 21.0, 18.1, −4.70, −4.89. Anal. Calcd for $C_{17}H_{30}O_4Si$: C 62.54, H 9.26. Found: C 62.71, H 9.20.

1.1.8. (−)-Eutipoxide B ((−)-1). To a solution of **12** (69 mg, 0.21 mmol) in THF (2.0 mL), was added tetrabutylammonium fluoride (1.0 M in THF, 0.42 mmol) at room temperature. After stirring for 30 min, the reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give (−)-eutipoxide B (**1**) (42 mg, 94%) as a very viscous and hygroscopic colorless oil. R_f 0.45 (AcOEt). $[\alpha]_D^{24}=-60$ (*c* 0.82, $CHCl_3$). IR (neat): 3418, 2932, 1680, 1615, 1445, 1383, 1250, 1115, 1044, 838, 799 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.15 (d, *J*=1.1 Hz, 1H); 4.38 (brd, *J*=2.2 Hz, 1H); 4.26 (dd, *J*=9.5, 4.4 Hz, 1H); 3.26 (d, *J*=3.3 Hz, 1H); 3.22 (br d, *J*=1.1 Hz, 1H); 2.87 (d, *J*=4.8 Hz, 1H); 2.67 (ddd, *J*=13, 9.5, 2.6 Hz, 1H); 2.20 (d, *J*=4.8 Hz, –O*H*); 2.16 (d, *J*=1.1 Hz, 3H); 1.92

(d, J=1.1 Hz, 3H); 1.80 (dt, J=13, 2.6 Hz, 1H); 1.50 (dt, J=2.6, 13 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 201.9, 158.4, 122.4, 65.8, 64.6, 56.7, 54.3, 48.3, 27.9, 27.7, 21.2. HRFABMS m/z. Calcd for $C_{11}H_{17}O_4$ $(M+H)^+$: 213.1131. Found 213.1127.

1.1.9. (+)-Eutipoxide B ((+)-1). In according to the above mentioned procedure, (+)-eutipoxide B ((+)-**1**) was also synthesized from (−)-**4a**. All the spectra showed completely identical with those of (−)-**1**, except for optical rotation. $[\alpha]_D^{24}$=+55 (c 0.20, $CHCl_3$).

Acknowledgements

The authors thank Dr Ryo Irie, Kyushu University, for elemental analyses and measurements of HRMS. We are also grateful to Professor Kunio Ogasawara, Tohoku University, for helpful advice to measure $[\alpha]_D$ of eutipoxide B.

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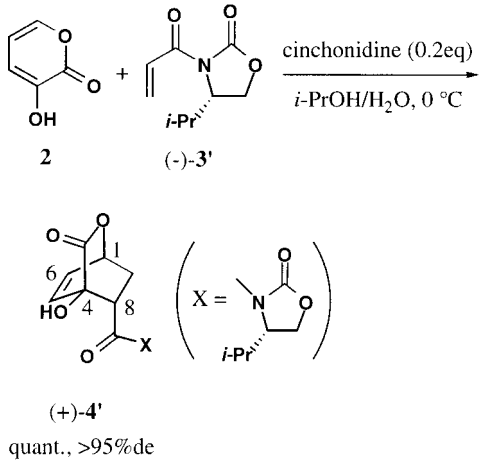
10. This type of reaction is very rare, and only one precedent, a base-catalyzed reaction of anthrone with electron deficient dienophile, was known at that present; (a) Koerner, M.; Rickborn, B. *J. Org. Chem.* **1989**, *54*, 6. (b) Koerner, M.; Rickborn, B. *J. Org. Chem.* **1990**, *55*, 2662–2672. (c) Riant, O.; Kagan, H. B.; Ricard, L. *Tetrahedron* **1994**, *50*, 4543–4554.
11. We have already reported a stereoselective synthesis of (+)-**4′**, which has essentially the same stereochemistry as (+)-**4**, by a reaction using (+)-**3′**. In this reaction, the resulting (+)-**4′** was obtained as a slightly gummy, intractable white powder, and thus (+)-**4** was used as a starting material (Scheme 4).



Scheme 4.

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