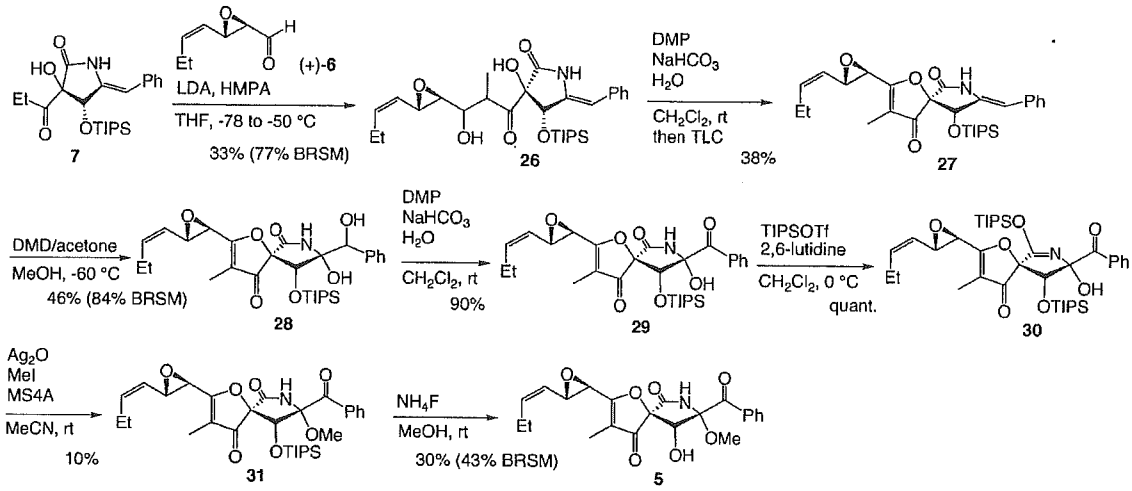
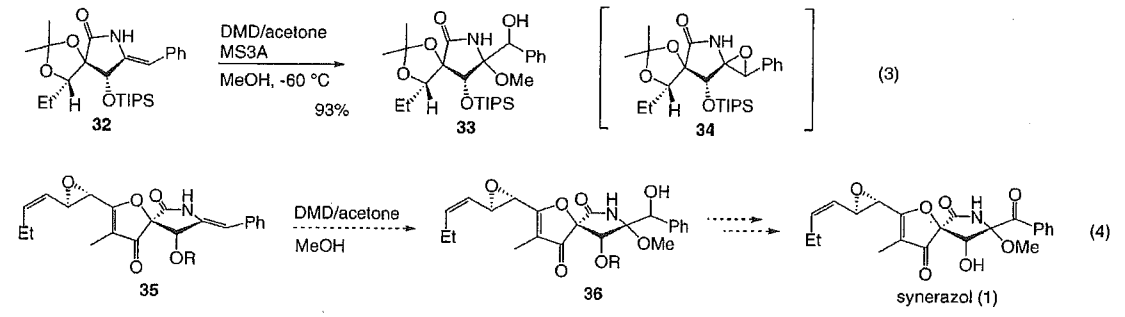
SCHEME 5. Synthesis of 5



SCHEME 6



lated **21** was formed quantitatively, the structure of which was assigned by IR analysis. The yield of the methyl ether **22** was poor (10%) when **21** was treated with Ag_2O and MeI.[13] Despite extensive experimentation on this methyl ether formation under several different reaction conditions using reagents such as MeI and NaH, decomposition occurred because of the instability of the epoxyalkene moiety and the yield did not exceed 10%. Even though the yield of **22** was not satisfactory, the first total synthesis of **4** was accomplished by deprotection of the TIPS group with NH_4F. Though the reaction was slow even in the presence of an excess amount of NH_4F (34 equiv), **4** was isolated in 55% yield with 30% recovery of **22** after 11 h at room temperature.

By the same synthetic procedure, starting from the enantiomeric aldehyde (+)-**6**, the diastereomer **5** was also synthesized as shown in Scheme 5.

The ^1H NMR and ^{13}C NMR spectra of **4**, **5**, and natural synerazol were very similar. Chiral HPLC analysis[14] showed that the retention time of natural synerazol is identical to that of the isomer **4** derived from D-tartaric acid diethyl ester. The optical rotation of synthetic **4** ($[\alpha]^{22}_D$ +22.6 (*c* 0.14, $CHCl_3$)) is in good agreement with that of literature data[1] for the natural product ($[\alpha]^{25}_D$ +22.9 (*c* 0.55, $CHCl_3$)). These results clearly indicate that **4** is the natural isomer of synerazol.

Though we had accomplished the first total synthesis of synerazol and thus determined its absolute stereochemistry, this synthetic route is not practical for large scale preparation and derivatization, because of the poor yield for formation of the methyl ether **22**. A more efficient route is therefore required.

Second Generation Synthesis. An interesting phenomenon was observed when oxidation of the benzylidene moiety in model **32** was examined. When **32** was treated with DMD in MeOH, methyl ether **33** was obtained in 93% yield (eq 3, Scheme 6). In this reaction the intermediate epoxide **34** was formed, which was trapped with MeOH to afford methyl ether **33**.

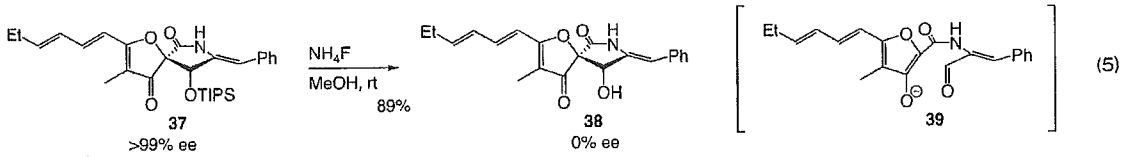
Should it be possible to oxidize the benzylidene moiety of azaspiro compound **35** with DMD to afford methyl ether **36** directly (eq 4, Scheme 6), the poor reaction for introducing the methyl ether in the first generation synthesis could be avoided.

Though oxidation of **18** with DMD was investigated under anhydrous conditions several times, only diol **19** was obtained without formation of the desired methyl ether (Scheme 3). The failure of the introduction of methyl ether would be explained as follows by the comparison between **18** and **32**. Because it would be more crowded around the benzylidene moiety in the case of **18**, MeOH could not react with the intermediate epoxide, but water, which is much smaller than MeOH and contaminated in the solvent, reacted with the epoxide, affording diol **19**. If this TIPS group can be substituted with a much smaller protecting group, such as triethylsilyl (TES) or

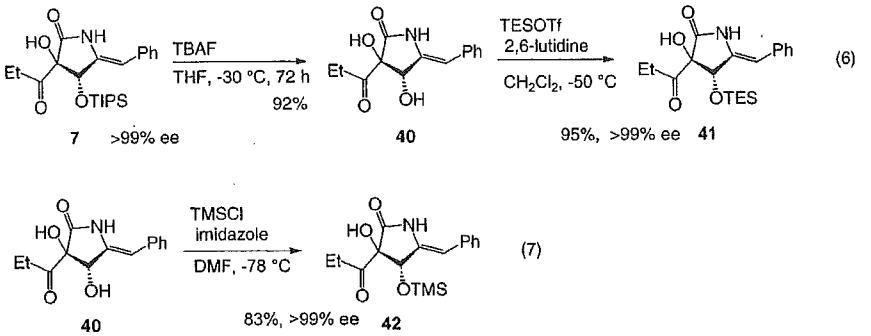
(13) Greene, A. E.; Drian, C. L.; Crabbe, P. *J. Am. Chem. Soc.* **1980**, *102*, 7583.

(14) HPLC analysis conditions: CHIRACEL AD-H column, 2-PrOH/hexane = 1/3, 1.0 mL/min; retention times, 12.82 min (**4** + natural synerazol), 13.00 min, 13.65 min (**5** + natural synerazol).

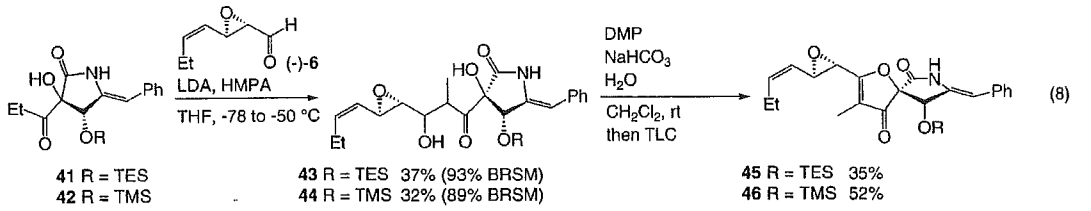
SCHEME 7



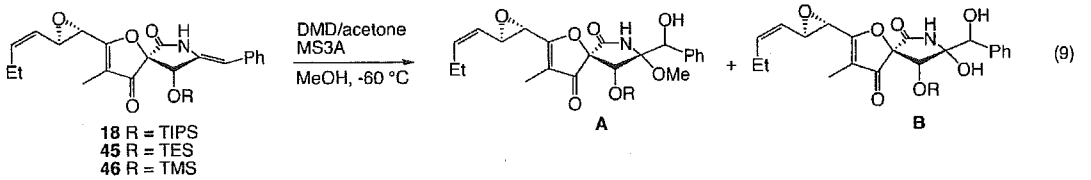
SCHEME 8



SCHEME 9



SCHEME 10



trimethylsilyl (TMS), introduction of the methyl ether might be possible. Exchanging the protecting group at the stage of **18** would be inadequate because of isomerization, which we observed in our previous total synthesis of azaspirene.[5] That is, when **37** was treated with NH_4F in MeOH at room temperature, complete racemization proceeded (eq 5, Scheme 7). As there is a β-ketoamide moiety in **38**, racemization can occur by the retro-aldol reaction via stable conjugated anion **39**. In fact isomerization occurred when **18** was treated with NH_4F.

Though a similar racemization might well be expected with the substrate **7**, which also has a β-ketoamide moiety, the racemization of **7** was in fact found to be slow (vide infra). That is, when **7** (>99% ee) was treated with tetrabutylammonium fluoride (TBAF) in THF at room temperature and the resulting alcohol **40** was then protected with TESOTf and 2,6-lutidine, mono TES ether **41** was obtained quantitatively in 84% ee. When the deprotection was carried out at lower temperature (−30 °C), the racemization was completely suppressed, and the TES ether **41** was obtained in excellent optical purity (>99% ee) (eq 6, Scheme 8). The corresponding TMS ether **42** was also prepared without racemization (>99% ee) (eq 7, Scheme 8).

TABLE 1. DMD Oxidation of Benzylidene Derivatives 18, 45, 46

			yield (%)[a]	
entry	R	time (h)	A	B
1	TIPS (**18**)	12	0	46
2	TES (**45**)	4	30	30
3	TMS (**46**)	4	65 (**47**)	10

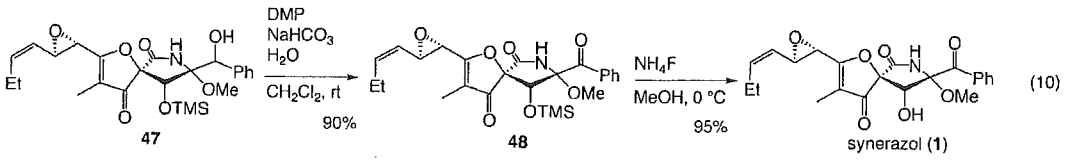
[a] Isolated yield.

By following the established two-step procedure, benzylidene derivatives **45** and **46** containing TES and TMS groups have been synthesized from **41** and **42** as shown in eq 8 (Scheme 9).

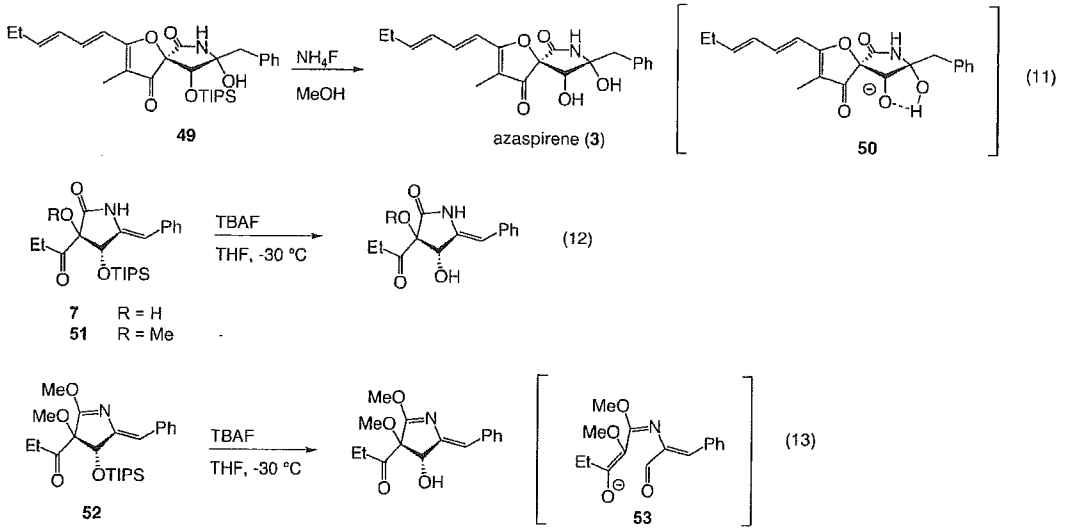
With the benzylidene derivatives **45** and **46** in hand, the oxidation with DMD was investigated. The benzylidene derivatives with different protecting groups were treated with DMD in MeOH in the presence of MS3A at low temperature (−60 °C), with the results summarized in Table 1.

The bulkiness of the silyl protecting group clearly affected the ratio of methyl ether **A** to diol **B** greatly (eq 9, Scheme 10). In the case of TIPS ether **18**, the reaction was slow, affording diol in 46% yield with 38% recovery

SCHEME 11



SCHEME 12



of the starting material **18**. None of the desired methyl ether was formed. The methyl ether and diol were formed in the same yield (30%) in the case of TES ether **45**. Unlike these unsuccessful results, methyl ether **47** was obtained in an acceptable yield (65%) when TMS ether **46** was oxidized.

As the desired methyl ether **47** had been obtained, the total synthesis was completed by carrying out the remaining two steps, oxidation with DMP and deprotection of the silyl group with NH_4F, affording synerazol (**1**) in good yield (eq 10, Scheme 11).

Racemization Mechanism. Though a practical total synthesis of synerazol has been accomplished, the different racemization behavior of substrates **37** and **7** during the deprotection of the TIPS group appears strange: whereas the azaspiro compound **37** completely racemizes, no racemization of γ-lactam **7** occurs at all (eqs 5 and 6). In our previous total synthesis of azaspirene, we found that hydroxy azaspiro compound **49** does not racemize and affords azaspirene in the last step of the total synthesis.[5] In this case, a hydrogen-bonding interaction as shown in **50** may prevent racemization (eq 11, Scheme 12).

As the hydroxy group of γ-lactam **7** might play a role, we examined the racemization of 3-methoxy γ-lactam **51**. We also investigated dimethoxy compound **52**. Their racemization behavior is summarized in Table 2. No racemization occurred in the cases of γ-lactam **7** and methoxy γ-lactam **51**, whereas dimethoxy derivative **52** completely racemized. Hence the 3-hydroxy does not affect the racemization. In the case of **52**, however, the anion generated by a retro-aldol reaction is very stable as a result of the delocalization shown in **53**, and this would be the driving force for the facile racemization.

TABLE 2. Racemization during Deprotection of TIPS Group

entry	SM[a]	time (h)	yield (%)[b]	ee[c] (%)
1	**7**	72	92	>99
2	**51**	20	50	>99
3	**52**	20	96	0

[a] Starting material. [b] Isolated yield. [c] Enantiomeric excess of alcohol.

The compounds **22**, **31**, and **48** did not isomerize at all, when the silyl protecting group was removed. This would be because of a hydrogen-bonding interaction as shown in **54**, which would be formed by trapping the intermediate alkoxide with solvent MeOH. As for the racemization,

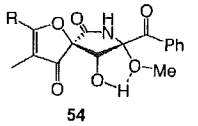


FIGURE 2. Hydrogen-bonding interaction in **54**.

which proceeded via retro-aldol reaction, the following has been determined: (1) When there is a hydrogen-bonding interaction, racemization dose not proceed as shown in **22**, **31**, **48**, and **49**. (2) When there is no hydrogen-bonding interaction and the generated anion is very stable owing to the delocalization such as in **39** and **53**, racemization is a facile process as shown in **18**, **37**, and **52**; otherwise it is a slow process as shown in **7** and **51**.

Conclusion

In summary, we have succeeded in the total syntheses of synerazol, an antifungal antibiotic, by two routes in a

highly stereoselective manner for the first time. In the first generation synthesis, two possible isomers were synthesized, and the absolute stereochemistry was determined. In the second generation synthesis, which is more practical than the first, the key steps are racemization-free deprotection of a TIPS group and introduction of a methyl ether by DMD oxidation of the benzylidene moiety in a substrate having a small protecting group. The present synthesis of synerazol combined with our previous total syntheses of the pseurotins and azaspirene makes possible their derivatization and large-scale preparation, which will pave the way for biological study of this class of natural products.

Experimental Section

(2*S*,3*R*)-2,3-Epoxy-4-hydroxybutanoic Acid Ethyl Ester ((+)-11). To a EtOH (380 mL) solution of (+)-**10** (20.6 g, 106 mmol) was added $NaBH_4$ (3.23 g, 85.1 mmol) at 0 °C. After stirring the reaction mixture for 2 h at that temperature, the reaction was quenched by the addition of pH 7.0 phosphate buffer, and the organic materials were extracted with chloroform three times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (ethyl acetate/hexane = 1:4−1:2) gave 11.0 g (71%) of alcohol (+)-**11** as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, J = 7.1 Hz), 1.79 (1H, bs), 3.33−3.39 (1H, m), 3.51 (1H, d, J = 2.0 Hz), 3.74 (1H, dd, J = 13.1, 3.3 Hz), 3.98 (1H, dd, J = 13.1 2.1 Hz), 4.14−4.29 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 50.1, 57.8, 60.0, 61.7, 168.8; FT-IR (neat) ν 3392, 2987, 1743, 1736, 1331, 1247, 1207, 1031, 781, 627 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_6H_{11}O_4$ 147.0657, found 147.0668; $[\alpha]^{18}_D$ +33.6 (*c* 1.33, $CHCl_3$); mp 43.0−44.0 °C.

(2*S*,3*R*)-2,3-Epoxy-4-(*tert*-butyldimethylsiloxy)-butanoic Acid Ethyl Ester ((+)-12). To a DMF (295 mL) solution of (+)-**11** (17.8 g, 122 mmol) and imidazole (16.9 g, 248 mmol) was added TBSCl (27.6 g, 183 mmol) at 0 °C. After stirring the reaction mixture for 1.5 h at that temperature, the reaction was quenched by the addition of pH 7.0 phosphate buffer, the organic materials were extracted with ethyl acetate three times, and the combined organic extracts were washed with brine three times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. The crude (+)-**12** (40.8 g) was directly used in the next reaction: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 1.28 (3H, t, J = 7.1 Hz), 3.27−3.31 (1H, m), 3.40 (1H, d, J = 1.9 Hz), 3.76 (1H, dd, J = 12.3, 3.6 Hz), 3.89 (1H, dd, J = 12.3, 2.6 Hz), 4.15−4.26 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −5.4, 14.1, 18.3, 25.8, 50.3, 58.2, 61.4, 61.6, 169.1; FT-IR (neat) ν 2956, 2931, 2857, 1755, 1739, 1473, 1198, 838, 779 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{12}H_{25}O_4Si$ 261.1522, found 261.1522; $[\alpha]^{16}_D$ +18.8 (*c* 1.09, $CHCl_3$).

(2*R*,3*R*)-2,3-Epoxy-4-(*tert*-butyldimethylsiloxy)butan-1-ol ((+)-13). To a MeOH (440 mL) solution of crude (+)-**12** (40.8 g) was added $NaBH_4$ (13.9 g, 367 mmol) at 0 °C. After 30 min, the reaction mixture was warmed to room temperature and stirred for 1.5 h at that temperature. The reaction was quenched by the addition of pH 7.0 phosphate buffer, and the organic materials were extracted with chloroform three times, dried over anhydrous $MgSO_4$, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (ethyl acetate/hexane = 1:9−1:1) gave 25.3 g (95%, two steps) of alcohol (+)-**13** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.03 (3H, s), 0.85 (9H, s), 2.30 (1H, bs), 3.02−3.10 (2H, m), 3.59 (1H, dd, J = 12.7, 4.2 Hz), 3.66 (1H, dd, J = 12.0, 4.3 Hz), 3.83 (1H, dd, J = 12.0, 2.7 Hz), 3.88 (1H, dd, J = 12.7, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.6, −5.3, 25.7, 25.9, 55.7, 55.9, 61.3, 62.7; FT-IR(neat) ν 3435, 2929, 2858, 1736, 1473, 1464, 1254, 1111, 870, 779 cm^{-1}; HRMS (FAB) [M − C_4H_9]$^+$ calcd for $C_6H_{13}O_3Si$ 161.0634, found 161.0630; $[\alpha]^{21}_D$ +21.6 (*c* 1.41, $CHCl_3$).

(2*S*,3*R*)-2,3-Epoxy-4-(*tert*-butyldimethylsiloxy)-butanal ((+)-14). To a CH_2Cl_2 (95 mL) and DMSO (95 mL) solution of (+)-**13** (20.5 g, 93.9 mmol) and NEt_3 (40 mL, 282 mmol) was added SO_3·Py (26.9 g, 169 mmol) at 0 °C. After stirring the reaction mixture for 1 h at that temperature, the reaction was quenched by the addition of pH 7.0 phosphate buffer, the organic materials were extracted with diethyl ether four times, and the combined organic extracts were washed with brine three times, dried over anhydrous $MgSO_4$, and concentrated in vacuo after filtration. The crude aldehyde (+)-**14** (23.3 g) was directly used in the next experiment: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.86 (9H, s), 3.32 (1H, dd, J = 6.3, 1.7 Hz), 3.33−3.37(1H, m), 3.75 (1H, dd, J = 12.3, 3.8 Hz), 3.95 (1H, dd, J = 12.3, 2.4 Hz), 9.04 (1H, d, J = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, 25.8, 31.6, 56.2, 56.7, 61.3, 198.0; FT-IR (neat) ν 2956, 2929, 2858, 1731, 1473, 1254, 1132, 1107, 839, 779 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{10}H_{21}O_3Si$ 217.1260, found 217.1226.

(2*R*,3*R*)-(*Z*)-2,3-Epoxy-4-(*tert*-butyldimethylsiloxy)-hept-4-ene ((+)-15). To a THF (235 mL) solution of [*n*-PrPPh$_3$]$^+$-Br$^-$ (42.0 g, 109 mmol) was added a hexane solution of *n*-BuLi (2.44 M, 40 mL, 98.6 mmol) at 0 °C, and the reaction mixture was stirred for 30 min. To the reaction mixture was added a THF solution (40 mL) of crude aldehyde (+)-**14** (23.3 g) at 0 °C, and the reaction mixture was stirred for 30 min. The reaction was quenched by the addition of pH 7.0 phosphate buffer, the organic materials were extracted with diethyl ether four times, and the combined organic extracts were washed with brine three times, dried over anhydrous $MgSO_4$, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (diethyl ether/pentane = 1:4) gave 18.9 g (82%, *Z*/*E* = >98/2, two steps) of olefin (+)-**15** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.02 (3H, t, J = 7.5 Hz), 2.05−2.25 (2H, m), 2.95−3.00 (1H, m), 3.51 (1H, dd, J = 9.0, 1.9 Hz), 3.72 (1H, dd, J = 11.9, 4.5 Hz), 3.83 (1H, dd, J = 11.9, 3.3 Hz), 5.03 (1H, ddt, J_d = 11.0, 9.1 Hz, J_t = 1.4 Hz), 5.70 (1H, dt, J_d = 11.0 Hz, J_t = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, −5.3, 14.2, 18.3, 21.1, 25.9, 51.8, 60.0, 63.2, 125.8, 138.5; FT-IR (neat) ν 2958, 2929, 2858, 1473, 1464, 1255, 1140, 1107, 837, 777 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{13}H_{27}O_2Si$ 243.1780, found 243.1792; $[\alpha]^{23}_D$ +9.4 (*c* 1.17, $CHCl_3$).

(2*R*,3*R*)-(*Z*)-2,3-Epoxyhept-4-en-1-ol (+)-16. To a THF (90 mL) solution of (+)-**15** (16.4 g, 67.7 mmol) was added a THF solution of TBAF (1.0 M, 88 mL, 88 mmol) at 0 °C. After stirring the reaction mixture for 15 min at that temperature, the reaction was quenched by the addition of pH 7.0 phosphate buffer, and the organic materials were extracted with diethyl ether four times, dried over anhydrous $MgSO_4$, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (diethyl ether/pentane = 1:10−1:1) gave 8.22 g (95%) of alcohol (+)-**16** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, t, J = 7.5 Hz), 2.10−2.32 (2H, m), 3.05 (1H, t, J = 2.4 Hz), 3.61−3.73 (2H, m), 3.95 (1H, ddd, J = 12.6, 5.1, 2.4 Hz), 5.04 (1H, ddt, J_d = 10.9, 9.1 Hz, J_t = 1.5 Hz), 5.73 (1H, dt, J_d = 11.0 Hz, J_t = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.0, 51.4, 59.9, 61.2, 125.2, 139.0; FT-IR (neat) ν 3410, 2962, 2925, 2854, 1458, 1074, 874, 727 cm^{-1}; HRMS (FAB) calcd for $C_7H_{12}O_2$ 128.0837, found 128.0836; $[\alpha]^{21}_D$ +78.1 (*c* 1.44, $CHCl_3$).

(2*S*,3*R*)-(*Z*)-2,3-Epoxyhept-4-enal ((−)-6). To a CH_2Cl_2 (4 mL) and DMSO (4 mL) solution of alcohol (+)-**16** (500 mg, 3.90 mmol) and NEt_3 (1.65 mL, 11.7 mmol) was added SO_3·Py (1.18 mg, 7.41 mmol) at 0 °C. After stirring the reaction mixture for 1 h at that temperature, the reaction was quenched by the addition of pH 7.0 phosphate buffer, the organic materials were extracted with diethyl ether four times, and the combined organic extracts were washed with brine three times, dried over anhydrous $MgSO_4$, and concentrated in vacuo after

filtration. Purification by silica gel column chromatography (diethyl ether/pentane = 1:5) gave 458 mg (93%) of aldehyde (−)-**6** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.5 Hz), 2.07−2.32 (2H, m), 3.25 (1H, dd, J = 6.0, 1.5 Hz), 3.87 (1H, d, J = 8.4 Hz), 4.96 (1H, dd, J = 10.7. 9.2 Hz), 5.80 (1H, dt, J_d = 10.7 Hz, J_t = 7.5 Hz), 9.05 (1H, d, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.1, 52.4, 60.4, 122.9, 140.8, 197.5; FT-IR (neat) ν 2968, 2935, 2875, 1728, 1668, 1633, 1066, 818, 735, 536 cm^{-1}; HRMS (FAB) calcd for $C_7H_{10}O_2$ 126.0681, found 126.0668; $[\alpha]^{21}_D$ −296.7 (*c* 1.04, $CHCl_3$).

(3*S*,4*S*)-5-(*Z*)-Benzylidene-3-((4*R*,5*R*)-(*Z*)-4,5-epoxy-3-hydroxy-2-methylnon-6-enoyl)-3-hydroxy-4-triisopropylsiloxypyrrolidin-2-one (17). To a THF solution (4.0 mL) of diisopropylamine (0.75 mL, 5.30 mmol) and HMPA (0.90 mL, 5.17 mmol) was added a hexane solution of *n*-BuLi (2.4 M, 1.75 mL, 4.27 mmol) at 0 °C, and the reaction mixture was stirred for 10 min. To the reaction mixture was added a THF solution (4.0 mL) of ketone **7** (430 mg, 1.04 mmol) at −78 °C, and the reaction mixture was stirred for 1.5 h. Aldehyde (−)-**6** (380 mg, 3.02 mmol) was added to the reaction mixture at −78 °C, and then the reaction temperature was raised to −50 °C over 1 h. The reaction was quenched by the addition of pH 7.0 phosphate buffer, and the organic materials were extracted with ethyl acetate three times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (diethyl ether/hexane = 1:4, ethyl acetate/hexane = 1:4−1:3) gave 250 mg (45%) of a 2:1 diastereomeric mixture of aldol **17** along with the recovery of the ketone **7** (210 mg, 49%). A mixture of diastereomers was employed in the next experiment, but careful TLC separated the major isomer, which shows the following spectral data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.5 Hz), 1.05−1.21 (21H, m), 1.23 (3H, d, J = 6.8 Hz), 1.96−2.20 (2H, m), 2.74 (1H, bs), 2.87 (1H, dd, J = 2.2, 3.8 Hz), 3.28−3.41 (1H, m), 3.45 (1H, dd, J = 9.0, 1.6 Hz), 3.65 (1H, bd, J = 3.4 Hz), 4.77 (1H, s), 4.89 (1H, t, J = 9.2 Hz), 5.17 (1H, d, J = 1.6 Hz), 5.66 (1H, dt, J_d = 10.8, J_t = 7.7 Hz), 5.95 (1H, s), 7.18−7.39 (5H, m), 8.77 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 12.6, 14.2, 17.8, 17.9, 21.6, 46.8, 52.1, 60.4, 71.6, 79.7, 88.5, 104.0, 124.7, 127.2, 127.5, 129.2, 134.6, 135.8, 139.2, 169.4, 205.8; FT-IR (neat) ν 3417, 2945, 2870, 1747, 1684, 1452, 1134, 883, 816, 683 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{30}H_{46}O_6NSi$ 544.3094, found 544.3071.

(5*S*,9*S*)-8-(*Z*)-Benzylidene-2-((1*S*,2*R*)-(*Z*)-1,2-epoxyhex-3-enyl)-3-methyl-9-triisopropylsiloxy-1-oxa-7-azaspiro-[4.4]non-2-ene-4,6-dione (18). To a CH_2Cl_2 solution (12.2 mL) of a mixture of diastereomer of aldol **17** (250 mg, 0.462 mmol) and $NaHCO_3$ (356 mg, 4.24 mmol) was added Dess−Martin periodinane (494 mg, 1.16 mmol) at 0 °C. After 5 min, the reaction mixture was warmed to room temperature and a solution of a mixture (9.1 mL, 0.508 mmol) of CH_2Cl_2 and H_2O (1000:1) was added. After stirring the reaction mixture for 1 h at that temperature, the reaction was quenched by the addition of saturated $NaHCO_3$ and diluted with ethyl acetate. The organic materials were extracted with ethyl acetate three times, and the combined organic extracts were washed with saturated $NaHCO_3$ twice, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Crude organic materials were charged on the TLC and were left for 20 min. After extraction of the organic materials from silica gel, the crude materials were purified by silica gel column chromatography (ethyl acetate/hexane = 1:5−1:2), affording 178 mg (47%) of azaspiro[4.4]nonenedione **18** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00−1.16 (24H, m), 1.77 (3H, s), 2.14−2.37 (2H, m), 3.76 (1H, s), 4.11 (1H, d, J = 8.8 Hz), 5.08 (1H, dd, J = 10.5, 8.8 Hz), 5.41 (1H, s), 5.84 (1H, dt, 10.5, 7.8 Hz), 7.13−7.36 (5H, m), 8.00 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1, 12.7, 14.0, 17.8, 17.9, 21.3, 29.7, 52.8, 54.7, 75.1, 92.3, 104.4, 114.4, 123.7, 126.9, 127.7, 128.9, 134.2, 134.9, 141.2, 164.8, 180.4, 194.9; FT-IR (neat) ν 3255, 2945, 2868, 1743, 1712, 1695, 1641, 1452, 1186, 1140, 1070, 883 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{30}H_{42}O_5NSi$ 524.2832, found 524.2824; $[\alpha]^{19}_D$ +98.8 (*c* 0.60, $CHCl_3$).

(5*S*,8*R*,9*R*)-2-((1*S*,2*R*)-(*Z*)-1,2-epoxyhex-3-enyl)-8-hydroxy-8-(hydroxy-phenyl-methyl)-3-methyl-9-triisopropylsiloxy-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (19). To a MeOH solution (22.5 mL) of azaspiro[4.4]nonenedione **18** (197 mg, 0.376 mmol) was added an acetone solution of dimethyl dioxirane (0.084 M, 45 mL, 3.76 mmol) at −60 °C, and the reaction mixture was stirred for 16 h. The reaction was quenched by the addition of Me_2S (0.83 mL, 11.3 mmol) and concentrated in vacuo after filtration. Purification by silica gel column chromatography (ethyl acetate/hexane = 1:9−1:4) gave 84 mg (40%) of diol **19** as a colorless oil with the recovery of **18** (66 mg, 33%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−1.16 (24H, m), 1.75 (3H, s), 2.17−2.35 (2H, m), 2.51 (1H, bs), 3.75 (1H, s), 4.11 (1H, bd, J = 6.9 Hz), 4.88 (1H, s), 5.06 (1H, t, J = 9.8 Hz), 5.35 (1H, s), 5.74 (1H, s), 5.84 (1H, dt, J_d = 10.8, J_t = 7.7 Hz), 6.19 (1H, bs), 7.30−7.45 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0, 12.6, 14.0, 17.8, 17.8, 21.3, 52.8, 55.0, 71.6, 71.7, 86.6, 94.7, 114.4, 123.6, 127.0, 128.5, 138.2, 141.3, 164.4, 183.2, 199.4; FT-IR (neat) ν 3348, 2943, 2870, 1736, 1693, 1624, 1458, 1196, 1068, 883, 825, 698 cm^{-1}; HRMS (FAB) [M − OH]$^+$ calcd for $C_{30}H_{42}O_6NSi$ 540.2781, found 540.2733; $[\alpha]^{19}_D$ −71.4 (*c* 0.46, $CHCl_3$).

(5*S*,8*S*,9*R*)-8-Benzoyl-2-((1*S*,2*R*)-(*Z*)-1,2-epoxyhex-3-enyl)-8-hydroxy-3-methyl-9-triisopropylsiloxy-1-oxa-7-azaspiro-[4.4]nonene-4,6-dione (20). To a CH_2Cl_2 solution (0.73 mL) of diol **19** (8.1 mg, 0.0146 mmol) and $NaHCO_3$ (21 mg, 0.219 mmol) was added Dess−Martin periodinane (37 mg, 0.0871 mmol) at 0 °C. After 5 min, the reaction mixture was warmed to room temperature and a solution of a mixture (0.29 mL, 0.0161 mmol) of CH_2Cl_2 and H_2O (1000:1) was added. After stirring the reaction mixture for 7.5 h at that temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and diluted with ethyl acetate. The organic materials were extracted with ethyl acetate three times, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ twice, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (ethyl acetate/hexane = 1:10−1:3) gave 7.7 mg (95%) of benzoyl product **20** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94−1.01 (21H, m), 1.05 (3H, t, J = 7.5 Hz), 1.81 (3H, s), 2.18−2.35 (2H, m), 3.77 (1H, bd, J = 1.8 Hz), 4.11 (1H, ddd, J = 9.2, 1.8, 1.0 Hz), 5.08 (1H, bt, J = 10.8 Hz), 5.47 (1H, s), 5.86 (1H, dt, J_d = 10.8 Hz, J_t = 7.5 Hz), 6.40 (1H, s), 6.73 (1H, bs), 7.47 (2H, dd, J = 7.8, 7.6 Hz), 7.61 (1H, bt, J = 7.4 Hz), 8.31 (2H, bdd, J = 8.1, 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1, 12.3, 14.0, 17.7, 21.3, 52.8, 55.1, 72.5, 88.2, 93.5, 114.4, 123.4, 128.7, 130.7, 132.9, 134.1, 141.5, 163.9, 183.4, 191.8, 199.3; FT-IR (neat) ν 3263, 2927, 2866, 1736, 1693, 1624, 1462, 1242, 1188, 1072, 883, 822, 687 cm^{-1}; HRMS (FAB): [M − OH]$^+$ calcd for $C_{30}H_{40}O_6NSi$ 538.2625, found 538.2652; $[\alpha]^{21}_D$ −50.1 (*c* 0.77, $CHCl_3$).

(5*S*,8*S*,9*R*)-8-Benzoyl-2-((1*S*,2*R*)-(*Z*)-1,2-epoxyhex-3-enyl)-8-hydroxy-3-methyl-6,9-bis-triisopropylsilanyloxy-1-oxa-7-azaspiro[4.4]nona-2,6-dien-4-one (21). To a CH_2Cl_2 solution (0.35 mL) of **20** (10.5 mg, 0.0190 mmol) was added 2,6-lutidine (0.015 mL, 0.129 mmol) and TIPSOTf (0.015 mL, 0.0569 mmol) at 0 °C. After stiiring the reaction mixture for 30 min at that temperature, the reaction was quenched by the addition of cold saturated $NaHCO_3$, and the organic materials were extracted with ethyl acetate three times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. As **21** was labile, it was purified by a very short column of florisil in a short time and was immediately used in the next experiment: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−1.09 (42H, m), 1.80 (3H, s), 2.15−2.33 (2H, m), 3.74 (1H, bd, J = 1.7 Hz), 4.04 (1H, bdd, J = 7.0, 1.0 Hz), 5.08 (1H, bt, J = 9.1 Hz), 5.17 (1H, s), 5.69 (1H, s), 5.85 (1H, dt, J_d = 11.0 Hz, J_t = 7.6 Hz), 7.40 (2H, t, J = 7.8 Hz), 7.50 (1H, t, J = 7.4 Hz), 8.28 (2H, d, J = 7.7 Hz); FT-IR (neat) ν 3460, 2943, 2867, 1701, 1633, 1464, 1383, 1367, 1252, 1186, 1051, 804, 677 cm^{-1}.

(5*S*,8*S*,9*R*)-8-Benzoyl-2-((1*S*,2*R*)-(*Z*)-1,2-epoxyhex-3-enyl)-8-methoxy-3-methyl-9-triisopropylsioxy-1-oxa-7-azaspiro-[4.4]non-2-ene-4,6-dione (22). A MeCN solution (0.45 mL) of **21** (13.5 mg, 0.0190 mmol) and MS4A (27 mg, 200 wt %) was stirred for 1.5 h at room temperature, and then to the reaction mixture were added Ag_2O (618 mg, 2.05 mmol) and MeI (0.09 mL, 1.57 mmol) at that temperature in the dark. After 40 min, the reaction mixture was filtered through a pad of Celite, and the volatile organic materials were removed under reduced pressure. Purification by thin-layer chromatography (ethyl acetate/hexane = 1:3) gave 1.1 mg (10%) of methyl ether **22** and alcohol **20** (3.7 mg, 35%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88−1.05 (24H, m), 1.79 (3H, s), 2.14−2.34 (2H, m), 3.62 (1H, bs), 3.74 (3H, s), 4.06 (1H, ddd, J = 8.8, 2.0, 0.9 Hz), 5.05 (1H, bdd, J = 10.3, 9.6 Hz), 5.47 (1H, s), 5.82 (1H, dt, J_d = 10.2, J_t = 7.6 Hz), 6.66 (1H, bs), 7.46 (2H, t, J = 7.3 Hz), 7.60 (1H, bt, J = 7.4 Hz), 8.16 (2H, bdd, J = 7.4, 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.2, 12.6, 14.0, 17.7, 21.3, 52.3, 52.7, 54.6, 75.2, 91.4, 115.0, 123.6, 128.9, 130.4, 133.2, 134.1, 141.3, 166.2, 179.8, 192.9, 195.3; FT-IR (neat) ν 2927, 2868, 1734, 1712, 1645, 1464, 1238, 1182, 1090, 1039, 883, 687; HRMS (FAB) [M + H]$^+$ calcd for $C_{31}H_{44}O_7NSi$ 570.2887, found 570.2861; $[\alpha]^{22}_D$ −26.2 (*c* 0.23, $CHCl_3$).

(+)-Synerazol. To a MeOH solution (0.1 mL) of methyl ether **22** (1.0 mg, 0.00176 mmol) was added NH_4F (2.2 mg, 0.0594 mmol) at 0 °C. After 1 h, the reaction mixture was warmed to room temperature and stirred for 11 h at that temperature, the volatile organic materials were removed under reduced pressure, and purification by thin-layer chromatography (ethyl acetate/hexane = 1:1) gave 0.4 mg (55%) of synerazol with the recovery of **22** (0.3 mg, 30%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, t, J = 7.5 Hz), 1.81 (3H, s), 2.17−2.35 (2H, m), 3.37 (3H, s), 3.74 (1H, bd, J = 1.7 Hz), 4.01 (1H, bd, J = 12.1 Hz), 4.08 (1H, bddd, J = 9.0, 1.7, 1.0 Hz), 4.62 (1H, d, J = 11.9 Hz), 5.06 (1H, bdd, J = 10.9, 9.0 Hz), 5.83 (1H, bdt, J_d = 11.0, J_t = 7.6 Hz), 7.28 (1H, bs), 7.46 (2H, t, J = 7.6 Hz), 7.62 (1H, bt, J = 7.4 Hz), 8.25 (2H, bdd, J = 8.6, 1.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 5.2, 14.0, 21.3, 51.7, 52.6, 55.1, 73.8, 89.4, 91.8, 114.3, 123.5, 128.7, 130.5, 132.2, 134.7, 141.5, 165.1, 182.1, 194.3, 196.7; FT-IR (neat) ν 3475, 3261, 2925, 1738, 1705, 1631, 1107, 1024, 791; HRMS (FAB) [M + H]$^+$ calcd for $C_{22}H_{24}O_7N$ 414.1553, found 414.1537; $[\alpha]^{22}_D$ +22.6 (*c* 0.14, $CHCl_3$).

(3*S*,4*S*)-5-(*Z*)-Benzylidene-3-((4*S*,5*S*)-(*Z*)-4,5-epoxy-3-hydroxy-2-methylnon-6-enoyl)-3-hydroxy-4-triisopropylsiloxy-pyrrolidin-2-one (26). To a THF solution (5.0 mL) of diisopropylamine (0.95 mL, 6.71 mmol) and HMPA (1.15 mL, 6.71 mmol) was added a hexane solution of *n*-BuLi (2.44 M, 2.3 mL, 5.61 mmol) at 0 °C, and the reaction mixture was stirred for 10 min. To the reaction mixture was added a THF solution (5.0 mL) of ketone **7** (557 mg, 1.34 mmol) at −78 °C, and the reaction mixture was stirred for 1.5 h. Aldehyde (+)-**6** (415 mg, 3.30 mmol) was added to the reaction mixture at −78 °C, and then the reaction temperature was raised to −55 °C over 1 h. The reaction was quenched by the addition of pH 7.0 phosphate buffer, and the organic materials were extracted with ethyl acetate three times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (diethyl ether/hexane = 1:4, ethyl acetate/hexane = 1:4−1:3) gave 235 mg (33%) of a 2:1 diastereomeric mixture of aldol **26** as a colorless oil along with the recovery of the ketone **7** (317 mg, 57%). A mixture of diastereomers was employed in the next reaction, but careful TLC separated the major isomer, which shows the following spectral data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.5 Hz), 0.93−1.06 (21H, m), 1.09 (3H, d, J = 7.0 Hz), 2.02−2.15 (2H, m), 2.74 (1H, bt, J = 2.4 Hz), 2.90 (1H, bs), 3.24−3.37 (1H, m), 3.55 (1H, bd, J = 9.3 Hz), 3.76 (1H, bs), 4.73 (1H, s), 4.82 (1H, dd, J = 10.6, 9.4 Hz), 5.01 (1H, bd, J = 1.9 Hz), 5.61 (1H, dt, J_d = 10.9, J_t = 7.6 Hz), 5.87 (1H, bd, J = 1.9 Hz), 7.06−7.29 (5H, m), 8.56 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 12.8, 14.7, 18.2, 18.3, 21.5, 45.5, 52.3, 60.5, 69.7, 80.1, 88.5, 104.7, 125.3, 127.6, 127.9, 129.5, 135.0, 136.4, 139.9, 170.0, 205.7; IR (neat) ν 3440, 2964, 2945, 2870, 1740, 1693, 1454, 1363, 1182, 1136, 1012, 883, 816, 683 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{30}H_{46}O_6NSi$ 544.3094, found 544.3098.

(5*S*,9*S*)-8-(*Z*)-Benzylidene-2-((1*R*,1*S*)-(*Z*)-1,2-epoxyhex-3-enyl)-3-methyl-9-triisopropylsiloxy-1-oxa-7-azaspiro-[4.4]non-2-ene-4,6-dione (27). To a CH_2Cl_2 solution (3.8 mL) of a mixture of the diastereomer of aldol **26** (58 mg, 0.107 mmol) and $NaHCO_3$ (93 mg, 1.11 mmol) was added Dess−Martin periodinane (156 mg, 0.367 mmol) at 0 °C. After 5 min, the reaction mixture was warmed to room temperature and a solution of a mixture (2.1 mL, 0.118 mmol) of CH_2Cl_2 and H_2O (1000:1) was added. After stirring the reaction mixture for 1 h at that temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and diluted with ethyl acetate. The organic materials were extracted with ethyl acetate three times, and the combined organic extracts were washed with saturated $NaHCO_3$ twice, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (ethyl acetate/hexane = 1:5−1:2) gave 26 mg (38%) of azaspiro[4.4]nonenedione **27** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03−1.13 (24H, m), 1.77 (3H, s), 2.14−2.35 (2H, m), 3.73 (1H, bd, J = 9.5 Hz), 4.11 (1H, bd, J = 9.0 Hz), 5.09 (1H, bt, J = 10.5 Hz), 5.43 (1H, bd, J = 1.7 Hz), 5.86 (1H, bdt, J_d = 11.0, J_t = 7.5 Hz), 5.94 (1H, s), 7.18−7.39 (5H, m), 7.79 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1, 12.7, 14.1, 17.8, 17.9, 21.3, 53.3, 54.6, 75.0, 92.3, 104.4, 114.3, 123.6, 127.0, 129.0, 134.1, 134.9, 141.2, 164.6, 180.3, 195.0; FT-IR (neat) ν 3273, 2943, 2868, 1743, 1714, 1695, 1645, 1456, 1186, 1068, 883, 812, 685 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{30}H_{42}O_5NSi$ 524.2832, found 524.2799; $[\alpha]^{32}_D$ +79 (*c* 0.61, $CHCl_3$).

(5*S*,8*R*,9*R*)-2-((1*R*,2*S*)-(*Z*)-1,2-Epoxyhex-3-enyl)-8-hydroxy-8-(hydroxy-phenyl-methyl)-3-methyl-9-triisopropylsiloxy-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (28). To a MeOH solution (9.5 mL) of azaspiro[4.4]nonenedione **27** (134 mg, 0.180 mmol) was added an acetone solution of dimethyl dioxirane (0.094 M, 19 mL, 1.80 mmol) at −60 °C, and the reaction mixture was stirred for 14 h. The reaction was quenched by the addition of Me_2S (0.45 mL, 6.13 mmol) and concentrated in vacuo after filtration. Purification by silica gel column chromatography (ethyl acetate/hexane = 1:9−1:4) gave 66 mg (46%) of diol **28** as a colorless oil with the recovery of **27** (60 mg, 45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00−1.19 (24H, m), 1.76 (3H, s), 2.13−2.36 (3H, m), 3.74 (1H, bd, J = 1.2 Hz), 4.10 (1H, bd, J = 8.7 Hz), 4.91 (1H, bs), 5.09 (1H, bt, J = 10.3 Hz), 5.39 (1H, s), 5.74 (1H, s), 5.77 (1H, s), 5.87 (1H, dt, J_d = 10.8, J_t = 7.7 Hz), 6.13 (1H, bs), 7.31−7.50 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1, 12.7, 14.1, 17.8, 21.3, 53.1, 55.0, 71.5, 71.7, 86.5, 94.8, 114.2, 123.6, 126.9, 128.6, 128.8, 138.1, 141.3, 164.0, 183.0, 199.3; FT-IR (neat) ν 3381, 2945, 2868, 1736, 1693, 1626, 1464, 1456, 1194, 1068, 883, 813 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{30}H_{44}O_7NSi$ 558.2887, found 558.2875; $[\alpha]^{21}_D$ −84.5 (*c* 0.43, $CHCl_3$).

(5*S*,8*S*,9*R*)-8-Benzoyl-2-((1*R*,2*S*)-(*Z*)-1,2-epoxyhex-3-enyl)-8-hydroxy-3-methyl-9-triisopropylsiloxy-1-oxa-7-azaspiro-[4.4]nonene-4,6-dione (29). To a CH_2Cl_2 solution (2.6 mL) of diol **28** (29 mg, 0.0522 mmol) and $NaHCO_3$ (100 mg, 1.19 mmol) was added Dess−Martin periodinane (159 mg, 0.374 mmol) at 0 °C. After 5 min, to the reaction mixture was added to a solution of a mixture (1.0 mL, 0.0574 mmol) of CH_2Cl_2 and H_2O (1000:1). After stirring the reaction mixture for 6 h at that temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and diluted with ethyl acetate. The organic materials were extracted with ethyl acetate three times, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ twice, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (ethyl acetate/hexane = 1:9−1:2) gave 24.8 mg (90%) of benzoyl product **29** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91−1.07 (24H,

m), 1.81 (3H, bd, J = 0.9 Hz), 2.10−2.36 (2H, m), 3.75 (1H, bs), 4.11 (1H, bd, J = 8.8 Hz), 5.09 (1H, bt, J = 9.5 Hz), 5.52 (1H, s), 5.87 (1H, bdt, J_d = 10.1 Hz, J_t = 8.2 Hz), 6.38 (1H, s), 6.76 (1H, bs), 7.48 (2H, t, J = 7.0 Hz), 7.61 (1H, bt, J = 6.8 Hz), 8.29 (2H, bd, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0, 12.3, 14.1, 17.7, 21.3, 53.0, 55.0, 72.3, 88.1, 93.5, 114.2, 123.5, 128.7, 130.6, 132.8, 134.1, 141.4, 164.0, 183.6, 191.6, 199.3; FT-IR (neat) ν 3290, 2943, 2868, 1747, 1739, 1693, 1626, 1464, 1240, 1186, 1072, 883, 685 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{30}H_{42}O_7NSi$ 556.2731, found 556.2733; $[\alpha]^{22}_D$ −81.4 (c 0.19, $CHCl_3$).

(5*S*,8*S*,9*R*)-8-Benzoyl-2-((1*R*,2*S*)-(*Z*)-1,2-epoxyhex-3-enyl)-8-hydroxy-3-methyl-6,9-bis-triisopropylsiloxy-1-oxa-7-azaspiro[4.4]nona-2,6-dien-4-one (30). To a CH_2Cl_2 solution (0.47 mL) of **29** (9.6 mg, 0.0173 mmol) were added 2,6-lutidine (0.015 mL, 0.129 mmol) and TIPSOTf (0.015 mL, 0.0558 mmol) at 0 °C. After stirring the reaction mixture for 30 min at that temperature, the reaction was quenched by the addition of cold saturated aqueous $NaHCO_3$, and the organic materials were extracted with ethyl acetate three times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. As **30** was labile, it was purified by a very short column of florisil in a short time and was immediately used in the next experiment: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−1.09 (42H, m), 1.80 (3H, s), 2.17−2.35 (2H, m), 3.74 (1H, bd, J = 1.4 Hz), 4.08 (1H, bd, J = 8.0 Hz), 5.09 (1H, bt, J = 9.5 Hz), 5.21 (1H, s), 5.70 (1H, s), 5.86 (1H, dt, J_d = 11.0 Hz, J_t = 7.7 Hz), 7.41 (2H, t, J = 7.7 Hz), 7.51 (1H, t, J = 7.3 Hz), 8.28 (2H, d, J = 7.6 Hz).

(5*S*,8*S*,9*R*)-8-Benzoyl-2-((1*R*,2*S*)-(*Z*)-1,2-epoxyhex-3-enyl)-8-methoxy-3-methyl-9-triisopropylsiloxy-1-oxa-7-azaspiro-[4.4]non-2-ene-4,6-dione (31). A MeCN solution (0.3 mL) of **30** (12 mg, 0.0169 mmol) and MS4A (24 mg, 200 wt %) was stirred for 1.5 h at room temperature, and then to the reaction mixture were added Ag_2O (508 mg, 1.69 mmol) and MeI (0.048 mL, 0.843 mmol) at that temperature in the dark. After 40 min, the reaction mixture was filtered through a pad of Celite, and the volatile organic materials were removed under reduced pressure. Purification by thin-layer chromatography (ethyl acetate/hexane = 1:3) gave 1.0 mg (10%) of methyl ether **31** as a colorless oil along and alcohol **29** (3.0 mg, 32%).

(5*S*,8*S*,9*R*)-8-Benzoyl-2-((1*R*,2*S*)-(*Z*)-1,2-epoxyhex-3-enyl)-9-hydroxy-8-methoxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (5). To a MeOH solution (0.1 mL) of methyl ether **31** (1 mg, 0.00176 mmol) was added NH_4F (3 mg, 0.081 mmol) at 0 °C. After 1 h, the reaction mixture was warmed to room temperature and stirred for 8.5 h at that temperature, the volatile organic materials were removed under reduced pressure, and purification by thin-layer chromatography (ethyl acetate/hexane = 1:1) gave 0.2 mg (30%) of **5** as a colorless oil with the recovery of **31** (0.3 mg, 30%): $[\alpha]^{22}_D$ −49:2 (c 0.02, $CHCl_3$).

(4*S*,5*R*,8*R*,9*R*)-4-Ethyl-8-(hydroxyphenylmethyl)-8-methoxy-2,2-dimethyl-9-triisopropylsilanyloxy-1,3-dioxa-7-azaspiro[4.4]nonan-6-one (33). To a MeOH solution (19 mL) of lactam **32** (85 mg, 0.185 mmol) was added an acetone solution of dimethyl dioxirane (0.1 M, 9.5 mL, 0.925 mmol) at −60 °C, and the reaction mixture was stirred for 6 h. The reaction was quenched by the addition of Me_2S (0.2 mL, 2.78 mmol) and concentrated in vacuo after filtration. Purification by thin-layer chromatography (ethyl acetate/hexane = 1:3) gave 87 mg (93%) of methyl ether **33** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, t, J = 7.2 Hz), 1.13−1.22 (21H, m), 1.25−1.35 (2H, m), 1.46 (3H, s), 1.61 (3H, s), 3.23 (3H, s), 3.31 (1H, d, J = 6.5 Hz), 4.35 (1H, bdd, J = 11.1 Hz, 1.9 Hz), 4.84 (1H, d, J = 6.4 Hz), 4.93 (1H, s), 5.23 (1H, bs), 7.28−7.39 (5H, m).

(3*S*,4*S*)-5-(*Z*)-Benzylidene-3,4-dihydroxy-3-propyonylpyrrolidin-2-one (40). To a THF solution (2.0 mL) of the ketone **7** (76 mg, 0.183 mmol) was added THF solution of TBAF (1 M, 0.37 mL, 0.366 mmol) at −30 °C. After stirring for 72 h at that temperature, the reaction mixture was quenched by the addition of pH 7.0 phosphate buffer, and the organic materials were extracted with chloroform three times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by thin-layer chromatography (ethyl acetate/hexane = 1:1) gave 44 mg (92%) of diol **40** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, bt, J = 7.0 Hz), 2.49 (1H, bdq, J_d = 19.0, J_q = 7.0 Hz), 2.73 (1H, bdq, J_d = 19.0, J_q = 7.1 Hz), 4.24 (1H, bs), 4.99 (1H, s), 5.16 (1H, bs), 5.92 (1H, s), 7.17−7.32 (5H, m), 8.64 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.9, 32.1, 77.8, 86.9, 104.9, 127.1, 127.5, 129.0, 134.63, 134.65, 171.3, 205.2; FT-IR (neat) ν 3336, 2925, 1736, 1718, 1689, 1404, 1381, 1174, 1115, 956, 908, 758, 694, 644 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{14}H_{16}NO_4$ 262.1079, found 262.1099; $[\alpha]^{23}_D$ +203 (c 0.35, $CHCl_3$).

(3*S*,4*S*)-5-(*Z*)-Benzylidene-3-hydroxy-3-propyonyl-4-trimethylsilanyloxy-pyrrolidin-2-one (42). To a DMF solution (0.5 mL) of diol **40** (12 mg, 0.0459 mmol) and imidazole (15.6 mg, 0.0230 mmol) was added TMSCl (10 μL, 0.081 mmol) at −78 °C. After stirring for 5 min at that temperature, the reaction was quenched by the addition of pH 7.0 phosphate buffer, the organic materials were extracted with ethyl acetate three times, and the combined organic extracts were washed with brine three times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by thin-layer chromatography (ethyl acetate/hexane = 1:2) gave 12.7 mg (83%) of ketone **42** as a colorless oil. Enantiomeric excess was determined as >99.5% by chiral HPLC analysis [HPLC conditions: Chiralpak AS-H column, 2-propanol/hexane = 1:20, 1.0 mL/min, retention times, 10.51 min (major), 8.12 min (minor)]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (9H, s), 0.98 (3H, t, J = 7.1 Hz), 2.33 (1H, dq, J_d = 18.5, J_q = 7.1 Hz), 2.66 (1H, dq, J_d = 18.5, J_q = 7.1 Hz), 4.59 (1H,s), 4.88 (1H, bd, J = 2.0 Hz), 5.68 (1H, bd, J = 1.6 Hz), 7.14−7.30 (5H, m), 7.90 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.094, 7.0, 31.6, 78.4, 86.4, 103.9, 127.1, 127.4, 129.1, 134.7, 135.7, 170.3, 203.6; FT-IR (neat) ν 3448, 3265, 2966, 1747, 1732, 1691, 1354, 1254, 1136, 881, 846, 754, 694 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{17}H_{24}O_4NSi$ 334.1475, found 334.1498; $[\alpha]^{22}_D$ +204 (c 0.35, $CHCl_3$).

(3*S*,4*S*)-5-(*Z*)-Benzylidene-3-((4*R*,5*R*)-(*Z*)-4,5-epoxy-3-hydroxy-2-methylnon-6-enoyl)-3-hydroxy-4-trimethylsiloxypyrrolidin-2-one (44). To a THF solution (0.68 mL) of diisopropylamine (0.1 mL, 0.707 mmol) and HMPA (0.11 mL, 0.608 mmol) was added a hexane solution of n-BuLi (1.51 M, 0.37 mL, 0.554 mmol) at 0 °C, and the reaction mixture was stirred for 10 min. To the reaction mixture was added a THF solution (1.2 mL) of ketone **42** (45 mg, 0.135 mmol) at −78 °C, and the reaction mixture was stirred for 1 h. Aldehyde (−)-**6** (92 mg, 0.730 mmol) was added to the reaction mixture at −78 °C, and then the reaction temperature was raised to −50 °C over 1 h. The reaction was quenched by the addition of pH 7.0 phosphate buffer, and the organic materials were extracted with chloroform three times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (diethyl ether/hexane =1:4) gave 20 mg (32%) of a 2:1 diastereomeric mixture of aldol **44** as a colorless oil along with the recovery of the ketone **42** (22 mg, 49%) and 5.3 mg (15%) of diol **40**. A mixture of diastereomers was employed in the next reaction, but careful TLC separated the major isomer, which shows the following spectral data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (9H, s), 0.954 (3H, t, J = 7.4 Hz), 1.21 (3H, d, J = 6.7 Hz), 2.01−2.27 (2H, m), 2.90 (1H, s), 3.29 (1H, quint, J = 6.2 Hz), 3.51 (1H, d, J = 8.9 Hz), 3.67 (1H, bs), 4.75 (1H, bs, 4.92 (1H, t, J = 9.8 Hz), 4.97 (1H, s), 5.68 (1H, dt, J_d = 10.4, J_t = 7.9 Hz), 5.75 (1H, s), 7.21−7.37 (5H, m), 8.47 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.1, 12.5, 14.2, 21.0, 46.9, 52.0, 60.2, 71.3, 79.0, 88.0, 103.6, 124.7, 127.1, 127.4, 129.1, 134.7, 135.6, 139.4, 169.5, 206.4; FT-IR (neat) ν 3423, 2962, 1735, 1689, 1456, 1373, 1254, 1182, 1136, 876, 847, 754, 694 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{24}H_{34}O_6NSi$ 460.2155, found 460.2155; $[\alpha]^{19}_D$ +168 (c 0.79, $CHCl_3$).

(5*S*,9*S*)-8-(*Z*)-Benzylidene-2-((1*S*,2*R*)-(*Z*)-1,2-epoxyhex-3-enyl)-3-methyl-9-trimethylsiloxy-1-oxa-7-azaspiro[4.4]-non-2-ene-4,6-dione (46). To a CH_2Cl_2 solution (0.63 mL) of a mixture of diastereomer of aldol **44** (7.0 mg, 0.0152 mmol) and $NaHCO_3$ (25 mg, 0.300 mmol) was added Dess−Martin periodinane (39 mg, 0.0914 mmol) at 0 °C. After 5 min, the reaction mixture was warmed to room temperature and added to a solution of a mixture (0.3 mL, 0.0167 mmol) of CH_2Cl_2 and H_2O (1000:1). After stirring for 30 min at that temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and diluted with ethyl acetate. The organic materials were extracted with ethyl acetate three times, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ twice, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by thin-layer chromatography (ethyl acetate/hexane = 1:2) gave 3.5 mg (52%) of azaspiro[4.4]nonenedione **46** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (9H, s), 1.04 (3H, t, J = 7.5 Hz), 1.80 (3H, s), 2.20−2.35 (2H, m), 3.79 (1H, bd, J = 1.9 Hz), 4.17 (1H, ddd, J = 9.0, 1.9, 1.0 Hz), 5.08 (1H, dd, J = 10.7, 9.4 Hz), 5.20 (1H, bd, J = 1.9 Hz), 5.80 (1H, bd, J = 1.9 Hz), 5.85 (1H, dt, J_d = 11.0, J_t = 7.4 Hz), 7.19−7.27 (3H, m), 7.35 (2H, t, J = 7.5 Hz), 7.76 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.1, 5.0, 14.1, 21.4, 52.6, 54.9, 74.5, 91.8, 104.0, 114.5, 123.7, 127.1, 127.7, 129.4, 134.0, 135.0, 141.3, 164.7, 180.4, 195.4; FT-IR (neat) ν 3265, 2962, 2852, 1739, 1714, 1697, 1637, 1448, 1254, 1184, 1136, 1068, 879, 847, 752, 696 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{24}H_{30}O_5NSi$ 440.1893, found 440.1893; $[\alpha]^{19}_D$ +165 (*c* 0.22, $CHCl_3$).

(5*S*,8*R*,9*R*)-2-((1*S*,2*R*)-(*Z*)-1,2-Epoxyhex-3-enyl)-8-(hydroxy-phenyl-methyl)-8-methoxy-3-methyl-9-trimethylsiloxy-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (47). To a MeOH solution (0.7 mL) of azaspiro[4.4]nonenedione **46** (3.1 mg, 0.00705 mmol) was added MS3A (12 mg) and an acetone solution of dimethyl dioxirane (0.1 M, 0.35 mL, 0.0353 mmol) at −60 °C, and the reaction mixture was stirred for 4 h. The reaction was quenched by the addition of Me_2S (0.02 mL, 0.272 mmol) and concentrated in vacuo after filtration. Purification by thin-layer chromatography (ethyl acetate/hexane = 1:2) gave 2.2 mg (65%) of methyl ether **47** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03 (9H, s), 1.04 (3H, t, J = 7.4 Hz), 1.76 (3H, s), 2.18−2.35 (2H, m), 3.51 (3H, m), 3.62 (1H, bs), 3.73(1H, bd, J = 1.8 Hz), 4.07 (1H, ddd, J = 8.2, 1.8, 1.0 Hz), 4.65 (1H, bs), 4.90 (1H, s), 5.06 (1H, bt, J = 9.9 Hz), 5.83 (1H, dt, J_d = 11.1, J_t = 7.5 Hz), 6.17 (1H, bs), 7.33−7.45 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 0.26, 5.1, 14.1, 21.3, 52.6, 52.6, 54.7, 74.9, 76.3, 89.8, 91.7, 114.7, 123.7, 127.8, 128.5, 128.8, 137.8, 141.1, 166.6, 179.6, 196.1; FT-IR (neat) ν 3419, 3271, 2956, 2923, 2852, 1732, 1709, 1645, 1456, 1254, 1196, 1078, 1043, 877, 845 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{25}H_{34}O_7NSi$ 488.2105, found 488.2124; $[\alpha]^{32}_D$ −4.7 (*c* 0.14, $CHCl_3$).

(5*S*,8*S*,9*R*)-8-Benzoyl-2-((1*S*,2*R*)-(*Z*)-1,2-epoxyhex-3-enyl)-8-methoxy-3-methyl-9-trimethylsilanyloxy-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (48). To a CH_2Cl_2 solution (0.16 mL) of methyl ether **47** (2.0 mg, 4.10 μmol) and $NaHCO_3$ (7.1 mg, 0.0845 mmol) was added Dess−Martin periodinane (11.1 mg, 0.0261 mmol) at 0 °C. After 5 min, the reaction mixture was warmed to room temperature and added to a solution of a mixture (0.1 mL, 5.64 μmol) of CH_2Cl_2 and H_2O (1000:1). After stirring for 30 min at that temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and diluted with ethyl acetate. The organic materials were extracted with ethyl acetate three times, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ twice, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by thin-layer chromatography (ethyl acetate/hexane = 1:2) gave 1.8 mg (90%) of benzoyl product **48** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.12 (9H, s), 1.03 (3H, t, J = 7.5 Hz), 1.80 (3H, s), 2.17−2.35 (2H, m), 3.43 (3H, s), 3.74 (1H, bd, J = 1.6 Hz), 4.12 (1H, ddd, J = 9.0, 1.6, 0.9 Hz), 4.52 (1H, s), 5.05 (1H, dd, J = 10.1, 9.8 Hz), 5.83 (1H, dt, J_d = 10.9, J_t = 7.6 Hz), 7.08 (1H, bs), 7.45 (2H, t, J = 7.8 Hz), 7.62 (1H, bt, J = 7.6 Hz), 8.37 (2H, d, J = 7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ −0.3, 5.2, 14.1, 14.1, 21.3, 51.9, 52.4, 54.8, 75.3, 91.9, 115.5, 123.6, 128.7, 131.3, 133.0, 134.6, 141.4, 165.3, 179.5, 194.7, 194.8; FT-IR (neat) ν 3294, 2960, 2925, 2852, 1743, 1716, 1685, 1645, 1448, 1254, 1142, 872, 850 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{25}H_{32}O_7NSi$ 486.1948, found 486.1925; $[\alpha]^{30}_D$ +12.5 (*c* 0.15, $CHCl_3$).

(+)-Synerazol. To a MeOH solution (0.2 mL) of benzoyl product **48** (1.8 mg, 0.0037 mmol) was added NH_4F (2.2 mg, 0.0594 mmol) at 0 °C. After stirring for 15 min, the volatile organic materials were removed under reduced pressure, and purification by thin-layer chromatography (ethyl acetate/hexane = 1:1) gave 1.5 mg (95%) of synerazol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, t, J = 7.5 Hz), 1.81 (3H, s), 2.17−2.35 (2H, m), 3.37 (3H, s), 3.74 (1H, bd, J = 1.7 Hz), 4.01 (1H, bd, J = 12.1 Hz), 4.08 (1H, bddd, J = 9.0, 1.7, 1.0 Hz), 4.62 (1H, d, J = 11.9 Hz), 5.06 (1H, bdd, J = 10.9, 9.0 Hz), 5.83 (1H, bdt, J_d = 11.0, J_t = 7.6 Hz), 7.28 (1H, bs), 7.46 (2H, t, J = 7.6 Hz), 7.62 (1H, bt, J = 7.4 Hz), 8.25 (2H, bdd, J = 8.6, 1.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 5.2, 14.0, 21.3, 51.7, 52.6, 55.1, 73.8, 89.4, 91.8, 114.3, 123.5, 128.7, 130.5, 132.2, 134.7, 141.5, 165.1, 182.1, 194.3, 196.7; FT-IR (neat) ν 3475, 3261, 2925, 1738, 1705, 1631, 1107, 1024, 791 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{22}H_{24}O_7N$ 414.1553, found 414.1537; $[\alpha]^{22}_D$ +22.6 (*c* 0.14, $CHCl_3$).

(5*S*,8*R*,9*R*)-2-((1*S*,2*R*)-(*Z*)-1,2-Epoxyhex-3-enyl)-8-(hydroxy-phenyl-methyl)-8-methoxy-3-methyl-9-triethylsiloxy-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (45A). To a MeOH solution (0.72 mL) of azaspiro[4.4]nonenedione **45** (3.5 mg, 0.00727 mmol) were added MS3A (12 mg) and an acetone solution of dimethyl dioxirane (0.1 M, 0.36 mL, 0.0363 mmol) at −60 °C, and the reaction mixture was stirred for 4 h. The reaction was quenched by the addition of Me_2S (0.02 mL, 0.272 mmol) and concentrated in vacuo after filtration. Purification by thin-layer chromatography (ethyl acetate/hexane = 1:2) gave 1.2 mg (30%) of methyl ether **45A** and 1.1 mg (30%) of diol **45B** with the recovery of **45** (1.0 mg, 30%).

(5*S*,8*R*,9*R*)-2-((1*S*,2*R*)-(*Z*)-1,2-Epoxyhex-3-enyl)-8-(hydroxy-phenyl-methyl)-8-methoxy-3-methyl-9-triethylsiloxy-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (45A): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.51 (6H, q, J = 8.0 Hz), 0.91 (9H, t, J = 8.0 Hz), 1.05 (3H, t, J = 7.5 Hz), 1.76 (3H, s), 2,17−2.36 (2H, m), 3.49 (3H, s), 3.73 (1H, bd, J = 1.8 Hz), 4.06 (1H, bdd, J = 8.9, 1.1 Hz), 4.69 (1H, s), 5.06 (1H, bt, J = 10.3 Hz), 5.09 (1H, s), 5.83 (1H, dt, J_d = 10.9, J_t = 7.5 Hz), 5.93 (1H, bs), 7.31−7.43 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.6, 5.1, 6.5, 14.1, 21.3, 52.7, 52.8, 54.6, 75.1, 75.7, 90.1, 91.8, 114.4, 123.9, 127.5, 128.4, 128.7, 138.1, 141.0, 166.8, 179.8, 196.1; FT-IR (neat) ν 3402, 2952, 2920, 2875, 2850, 1732, 1711, 1637, 1458, 1406, 1194, 1041, 731 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{28}H_{40}O_7NSi$ 530.2574, found 530.2562; $[\alpha]^{21}_D$ −64 (*c* 0.04, $CHCl_3$).

(5*S*,8*R*,9*R*)-2-((1*S*,2*R*)-(*Z*)-1,2-Epoxyhex-6-enyl)-8-hydroxy-8-(hydroxy-phenyl-methyl)-3-methyl-9-triethylsiloxy-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (45B): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (6H, dq, J_d = 3.2, J_q = 8.0 Hz), 0.93 (9H, t, J = 7.9 Hz), 1.05 (3H, t, J = 7.5 Hz), 1.78 (3H, s), 2.19−2.35 (2H, m), 3.77 (1H, bd, J = 1.7 Hz), 4.14 (1H, bdd, J = 8.0, 1.1 Hz), 4.83 (1H, s), 5.08 (1H, bt, J = 10.0 Hz), 5.11 (1H, s), 5.79 (1H, s), 5.86 (1H, dt, J_d = 10.8, J_t = 7.8 Hz), 6.12 (1H, bs), 7.33−7.52 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.7, 5.1, 6.5, 14.0, 21.3, 52.7, 55.1, 71.2, 72.6, 86.4, 94.3, 114.5, 123.6, 127.1, 128.6, 128.8, 138.1, 141.4, 164.2, 183.1, 199.1; FT-IR (neat) ν 3346, 2958, 2877, 2854, 1732, 1697, 1625, 1456, 1412, 1379, 1194, 1068, 827, 729 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{27}H_{38}O_7NSi$ 516.2418, found 516.2427; $[\alpha]^{21}_D$ −130 (*c* 0.04, $CHCl_3$).

(5*S*,9*S*)-8-(*Z*)-Benzylidene-2-((2*S*,3*R*)-(*Z*)-3-but-1-enyl oxiranyl)-3-methyl-9-triethylsiloxy-1-oxa-7-azaspiro[4.4]-non-2-ene-4,6-dione (45): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65

(6H, quint., J = 7.6 Hz), 0.95 (9H, t, J = 7.9 Hz), 1.06 (3H, t, J = 7.5 Hz), 1.88 (1H, s), 2.18–2.37 (2H, m), 3.78 (1H, bd, J = 1.9 Hz), 4.15 (1H, bdd, J = 9.0, 1.2 Hz), 5.09 (1H, bdd, J = 10.7, 9.1 Hz), 5.23 (1H, bd, J = 2.0 Hz), 5.84 (1H, bs), 5.85 (1H, bdt, J_d = 15.0, J_t = 7.5 Hz), 7.20–7.37 (5H, m), 7.72 (1H, bs); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.7, 5.1, 6.6, 14.1, 21.3, 52.7, 54.8, 74.6, 92.0, 104.0, 114.5, 123.7, 127.0, 127.7, 129.0, 134.1, 135.0, 141.3, 164.7, 180.5, 195.2; FT-IR (neat) ν 3276, 2958, 2935, 2877, 1743, 1712, 1697, 1641, 1452, 1408, 1184, 1137, 1068, 827, 746 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{27}H_{36}O_5NSi$ 482.2363, found 482.2388; $[\alpha]^{32}_D$ +146 (c 0.17, $CHCl_3$).

(3*S*,4*S*)-5-(*Z*)-Benzylidene-3-methoxy-3-propionyl-4-triisopropylsiloxy-pyrrolidin-2-one (51). To a solution of ketone **7** (9.0 mg, 0.0217 mmol) and Ag_2O (251 mg, 1.09 mmol) in CH_3CN (0.7 mL) was added iodomethane (0.12 mL, 2.17 mmol), and the mixture was stirred at 0 °C for 5 h in the dark. The reaction mixture was filtered through a pad of Celite and washed AcOEt. The filtrate was concentrated in vacuo, and the residue was purified by preparative thin-layer chromatography (diethyl ether:chloroform = 1:7) and afforded methyl ether **51** (2.9 mg, 31%) as a colorless oil along with the recovery of the ketone **7** (2.7 mg, 30%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, t, J = 7.2 Hz), 1.09–1.19 (21H, m), 2.54 (1H, dq, J_d = 19.1, J_q = 7.1 Hz), 2.69 (1H, dq, J_d = 19.1, J_q = 7.2 Hz), 3.59 (3H, s), 5.16 (1H, bd, J = 1.6 Hz), 5.84 (1H, s), 7.19–7.25 (3H, m), 7.36 (2H, t, J = 7.7 Hz), 7.75 (1H, bs); ^{13}C NMR (150 MHz, $CDCl_3$) δ 6.7, 12.6, 17.8, 17.9, 33.2, 54.0, 75.3, 91.9, 103.8, 127.0, 127.5, 129.1, 135.0, 136.0, 169.2, 203.5; FT-IR (neat) ν 3230, 2945, 2868, 1738, 1722, 1684, 1464, 1186, 1138, 883, 808, 679 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{24}H_{38}O_4NSi$ 432.2570, found 432.2582; $[\alpha]^{25}_D$ +117 (c 0.19, $CHCl_3$).

(3*S*,4*R*)-1-(5-(*Z*)-Benzylidene-2,3-dimethoxy-4-triisopropylsiloxy-4,5-dihydro-3*H*-pyrrol-3-yl)-propan-1-one (52). To a solution of ketone **7** (9.8 mg, 0.0236 mmol) and Ag_2O (270 mg, 1.17 mmol) in CH_3CN (0.5 mL) was added iodomethane (0.14 mL, 2.36 mmol), and the mixture was stirred at room temperature for 10 h in the dark. The reaction mixture was filtered through a pad of Celite and washed withAcOEt. The filtrate was concentrated in vacuo, and the residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:5) and afforded dimethoxy product **52** (5.6 mg, 53%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.1 Hz), 1.04–1.18 (2H, m), 2.30 (1H, dq, J_d = 18.7, J_q = 7.0 Hz), 2.57 (1H, dq, J_d = 18.7, J_q = 7.2 Hz), 3.47 (3H, s), 4.05 (3H, s), 5.27 (1H, bd, J = 1.5 Hz), 6.00 (1H, bd, J = 1.2 Hz), 7.18 (1H, t, J = 7.3 Hz), 7.32 (2H, t, J = 7.6 Hz), 7.81 (2H, d, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.9, 12.7, 17.8, 17.9, 32.8, 54.0, 56.2, 81.0, 94.0, 113.5, 126.5, 128.2, 129.0, 136.4, 147.9, 172.8, 202.1; FT-IR (neat) ν 2942, 2927, 2868, 1732, 1653, 1604, 1595, 1464, 1327, 1122, 883, 818, 692 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{25}H_{40}O_4NSi$ 446.2727, found 446.2743; $[\alpha]^{29}_D$ +183 (c 0.25, $CHCl_3$).

(3*S*,4*S*)-5-(*Z*)-Benzylidene-4-hydroxy-3-methoxy-3-propionyl-pyrrolidin-2-one (51′). To a THF solution (0.3 mL) of the methyl ether **51** (2.5 mg, 0.0580 mmol) was added a THF solution of TBAF (1 M, 0.015 mL, 0.015 mmol) at −20 °C. After stirring for 20 h at that temperature, the reaction mixture was quenched by the addition of pH 7.0 phosphate buffer, and the organic materials were extracted with chloroform three times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by thin-layer chromatography (ethyl acetate/hexane = 1:2) gave 0.8 mg (50%) of alcohol **51′** as a colorless oil along with the recovery of **51** (1.0 mg, 40%). Enantiomeric excess of **51′** was determined as >99.5% by chiral HPLC analysis [HPLC conditions: Chiralpak AD-H column, 2-propanol/hexane = 1:20, 1.0 mL/min, retention times, 21.09 min (major), 23.85 min (minor)]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, t, J = 7.1 Hz), 2.69–2.95 (2H, m), 3.32 (1H, bd, J = 1.4 Hz), 3.55 (3H, s), 5.04 (1H, bdd, J = 9.1, 1.0 Hz), 5.92 (1H, s), 7.17–7.38 (5H, m), 7.72 (1H, bs); ^{13}C NMR (150 MHz, $CDCl_3$) δ 6.7, 32.5, 54.1, 69.7, 90.6, 103.1, 127.1, 127.4, 129.1, 134.8, 136.1, 167.3, 210.2; FT-IR (neat) ν 3338, 2924, 2852, 1734, 1716, 1689, 1452, 1180, 1118, 758 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{15}H_{18}O_4N$ 276.1236, found 276.1227.

(3*S*,4*R*)-1-(5-(*Z*)-4-Hydroxy-2,3-dimethoxy-4,5-dihydro-3*H*-pyrrol-3-yl)-propan-1-one (52′). To a THF solution (0.2 mL) of the dimethoxy product **52** (3.9 mg, 0.0875 mmol) was added a THF solution of TBAF (1.0 M, 0.02 mL, 0.02 mmol) at −20 °C. After stirring for 20 h at that temperature, the reaction mixture was quenched by the addition of pH 7.0 phosphate buffer, and the organic materials were extracted with chloroform three times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by thin-layer chromatography (ethyl acetate/hexane = 1:3) gave 2.4 mg (96%) of a two diastereomer mixture of **52′** as a colorless oil. Enantiomeric excess of **52′** was determined as 0.3% by chiral HPLC analysis [HPLC conditions: Chiralpak AD-H column, 2-propanol/hexane = 1:40, 1.0 mL/min, retention times 10.51, 8.12, and 21.88 min, 28.33 min]: FT-IR (neat) ν 3475, 2925, 2852, 1716, 1606, 1595, 1441, 1338, 1076, 1012, 694 cm^{-1}.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR and IR of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Total Synthesis of Epoxyquinols A, B, and C and Epoxytwinol A and the Reactivity of a 2*H*-Pyran Derivative as the Diene Component in the Diels–Alder Reaction

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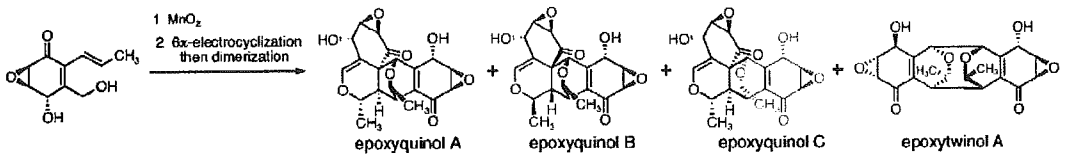

Full details of two versions of the total synthesis of epoxyquinols A, B, and C and epoxytwinol A (RKB-3564D) are described. In the first-generation synthesis, the $HfCl_4$-mediated diastereoselective Diels–Alder reaction of furan with Corey's chiral auxiliary has been developed. In the second-generation synthesis, a chromatography-free preparation of an iodolactone, by using acryloyl chloride as the dienophile in the Diels–Alder reaction of furan, and the lipase-mediated kinetic resolution of a cyclohexenol derivative have been developed. This second-generation synthesis is suitable for large-scale preparation. A biomimetic cascade reaction involving oxidation, 6π-electrocyclization, and then Diels–Alder dimerization is the key reaction in the formation of the complex heptacyclic structure of epoxyquinols A, B, and C. Epoxytwinol A is synthesized by the cascade reaction composed of oxidation, 6π-electrocyclization, and formal [4 + 4] cycloaddition reactions. A 2*H*-pyran, generated by oxidation/6π-electrocyclization, acts as a good diene, reacting with several dienophiles to afford polycyclic compounds in one step. An azapentacyclic compound is synthesized by a similar cascade reaction composed of the four successive steps: oxidation, imine formation, 6π-azaelectrocyclization, and Diels–Alder dimerization.

Introduction

The inhibition of angiogenesis is a promising method for treating angiogenesis-related diseases such as cancer and rheumatoid arthritis.[1] We have recently isolated and determined the structures of epoxyquinols A (**1**)[2], B (**2**),[3] and C (**3**)[4] and epoxytwinol A (RKB-3564D) (**4**)[5] (Figure 1) from an unknown soil fungus and azaspirene[6] and RK-805[7] from the fungus *Neosartorya* sp. With the exception of RK-805, these small natural products have structures quite distinct from those of known angiogenesis inhibitors, making their mechanism of action a matter of considerable interest. A sufficient quantity of the natural products is needed for biological investigations, and the study of structure–reactivity relationships requires derivatives. For these purposes an efficient and flexible total synthesis is highly desirable, and recently we have accomplished the first total synthesis of epoxyquinols A and B[8] and azaspirene.[9]

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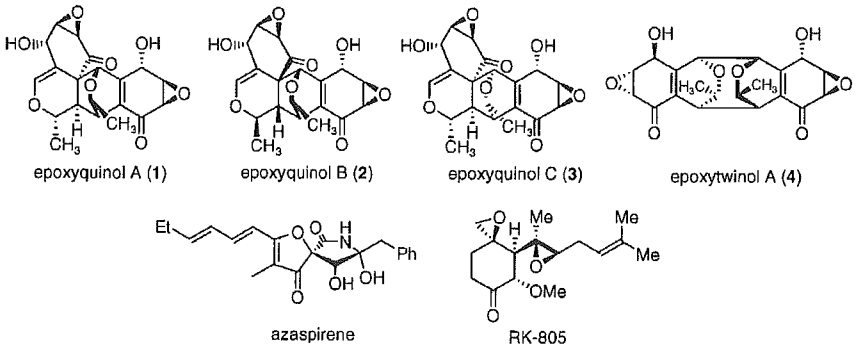
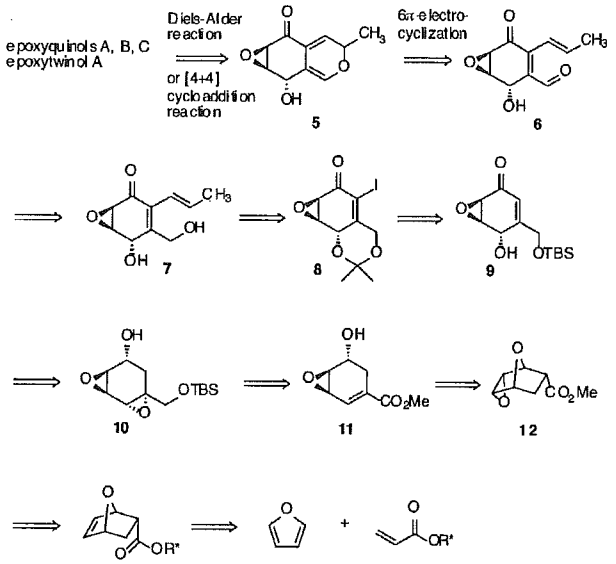


FIGURE 1. Epoxyquinols A, B, and C, epoxytwinol A, azaspirene, and RK-805.

SCHEME 1. Retrosynthetic Analysis of Epoxyquinols A, B, and C and Epoxytwinol A



Epoxyquinols A, B, and C are novel pentaketides, with complex, highly oxygenated, heptacyclic structures containing 12 chiral centers, which are biosynthetically generated from the epoxyquinol monomer **7** by a cascade reaction sequence of oxidation, 6π-electrocyclization,[10] and Diels–Alder reaction. That is, diol monomer **7** is oxidized to aldehyde **6**, from which 6π-electrocyclization proceeds, affording 2*H*-pyran derivative **5** (Scheme 1). Diels–Alder dimerization of 2*H*-pyran **5** proceeds to provide epoxyquinols A, B, and C. Several other diastereomers have also been isolated along with epoxyquinols A, B, and C from the same soil fungus, the structure determination of which will be the subject of future studies. We have isolated not only Diels–Alder dimers but also epoxytwinol A from the same fungus. Epoxytwinol A possesses the 3,8-dioxatricyclo[4.2.2.2^{2,5}]dodeca-9,11-diene skeleton, a completely different structure from those of epoxyquinols A, B, and C. It is postulated that epoxytwinol A is biosynthetically generated by a formal [4 + 4] cycloaddition reaction as used in the construction of the same key 2*H*-pyran intermediate **5** of epoxyquinols A, B, and C. Because of these compounds' important biological properties and synthetically challenging structures, several research groups, including ours,[8] have investigated these compounds total synthesis: Porco et al. have published an elegant total synthesis of epoxyquinols A and B[11] and just recently completed the first total synthesis of epoxytwinol A using alkoxysilanol methodology to promote formal [4 + 4] dimerization.[12] Mehta et al.[13] and Kuwahara et al.[14] have also succeeded in the total synthesis of epoxyquinols A and B. The related epoxyquinoid Diels–Alder dimer, Torreyanic acid, with selective cytotoxicity against human cancer cell lines,[15] was isolated by Lee and co-workers from the fungus *Pestalotiopsis* and has been synthesized by Porco and co-workers.[16]

Our group has completed the first asymmetric total synthesis of epoxyquinols A and B,[8a] thus determining their absolute stereochemistry. An $HfCl_4$-mediated Diels–Alder reaction of furan with Corey's chiral auxiliary[17] and a biomimetic, oxidative dimerization were developed as key reactions. We have uncovered the importance of hydrogen-bonding in the Diels–Alder reaction forming epoxyquinol B using the combined use of synthetic organic chemistry and theoretical chemistry.[18] We have also developed a practical total synthesis with a kinetic resolution using lipase as a key step.[8b] In a study on the large-scale preparation of epoxyquinols A and B, we carefully investigated the minor isomers of the key oxidative dimerization and have isolated and identi-

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fied epoxyquinol C and epoxytwinol A from the crude reaction mixture. These results are disclosed in this paper along with the full details of the total synthesis of epoxyquinols A and B.

In the key oxidative Diels–Alder reaction, oxidation of dienol **7** and subsequent 6π-electrocyclization affords 2*H*-pyran derivative **5**, which dimerizes to afford epoxyquinols A and B. 2*H*-Pyran derivatives are seldom employed in organic synthesis, and their reactivity has not been systematically investigated because of difficulty in generating them due to their easy isomerization into dienals.[19] As we found a simple method for generation of 2*H*-pyran intermediates by oxidation and 6π-electrocyclization during the synthesis of epoxyquinols A and B, we have investigated their reactivity as the diene component in the Diels–Alder reaction, and these results will also be presented here.

Encouraged by the facile generation of a 2*H*-pyran intermediate by oxidation and 6π-oxaelectrocyclization, the dimerization of 1,2-dihydropyridine, a nitrogen analogue of 2*H*-pyran, generated by the cascade reaction of oxidation, imine formation, and 6π-azaelectrocyclization has been investigated for the synthesis of azapentacycles and will also be described here.

In summary, in this paper we disclose the full details of our total synthesis of epoxyquinols A, B, and C and epoxytwinol A, as well as the results of our work on the reactivity of a 2*H*-pyran derivative as a diene in the Diels–Alder reaction with several dienophiles, and the formation of an azapentacycle via a cascade reaction.

Retrosynthesis. Our retrosynthetic analysis of epoxyquinols A, B, and C and epoxytwinol A is summarized in Scheme 1. Epoxyquinols A, B, and C and epoxytwinol A would be synthesized from the same monomer **7** by the postulated biosynthetic pathway involving an oxidation/6π-electrocyclization/Diels–Alder reaction cascade for epoxyquinols A, B, and C or an oxidation/6π-electrocyclization/[4 + 4] cycloaddition cascade for epoxytwinol A. The monomer **7** could be synthesized from iodocyclohexenone **8** by the Suzuki coupling reaction. Iodocyclohexenone **8** was to be prepared by the α-iodination of cyclohexenone **9**, which should be available from bisepoxy cyclohexenol **10**. Chiral cyclohexenol **10** would be formed from the Diels–Alder reaction between furan and a chiral acrylate derivative, followed by functional group transformations.

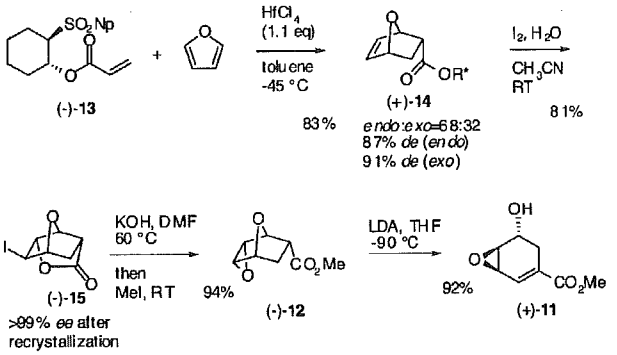
In this retrosynthetic analysis, there are several noteworthy features that should be pointed out: Synthesis of derivatives with different side-chains should be accessible because the side-chain is introduced at a late stage of the monomer synthesis by a Suzuki coupling reaction. All the carbon atoms except the side-chain are introduced in the first Diels–Alder reaction, and the remainder of the reactions are functional group transformations except for the Suzuki coupling reaction. Chirality is introduced at the stage of the initial Diels–Alder reaction, and highly diastereoselective synthesis of the monomer is possible by exploiting neighboring-group participation.

(19) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980.

Results and Discussion

First-Generation Monomer Synthesis. On the basis of the above retrosynthetic analysis, the Diels–Alder reaction of furan,[20] which is a difficult cycloaddition due to the facile retro-Diels–Alder reaction and low reactivity of furan as a diene due to its aromatic character, is the first step of our total synthesis. Although there are a number of methods for the diastereoselective Diels–Alder reaction of a chiral acrylate ester with furan,[21] few of these are synthetically useful with high *endo*/*exo*- and/or diastereoselectivities. Recently, we have found that $HfCl_4$ is a highly efficient Lewis acid in the Diels–Alder reaction of furan, and enables the reaction to proceed at low temperature.[22] The $HfCl_4$-mediated Diels–Alder reaction of furan was applied to chiral acrylate esters, and the choice of the chiral auxiliary was found to be important. While a chiral Evans' acrylate derivative, 3-acryloyl-4-benzyl-1,3-oxazolidin-2-one,[23] gave poor diastereoselectivity, high selectivity was obtained with the acrylate ester derived from Corey's chiral auxiliary ((−)-(1*R*,2*R*)-2-(naphthalene-2-sulfonyl)cyclohexanol).[17] That is, in the presence of 1.1 equiv of $HfCl_4$, the acrylate ester (−)-**13** reacted with furan in toluene at low temperature (−45 °C) for 34 h, giving the cycloadducts (+)-**14** in good yield with moderate *endo*/*exo*- and high diastereoselectivities.

SCHEME 2. Synthesis of (+)-11



Direct epoxidation of (+)-**14** with MCPBA gave stereoselectively the *exo*-epoxide,[24] which when reacted with

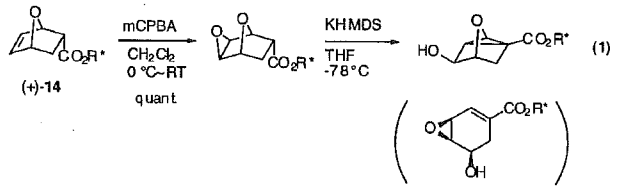
(20) Recent review of asymmetric Diels–Alder reactions: Hayashi, Y. *Catalytic Asymmetric Diels–Alder Reactions* in *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2001, pp 5–56. Review of Diels–Alder reaction of furan: Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179. Review of optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives: Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173.

(21) Catalytic asymmetric reaction by the use of a chiral Lewis acid; (a) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979. (b) Yamamoto, I.; Narasaka, K. *Chem. Lett.* **1995**, 1129. (c) Evans, D. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57. Diastereoselective reaction by the use of chiral dienophile; (d) Takayama, H.; Iyobe, A.; Koizumi, T. *J. Chem. Soc., Chem. Commun.* **1986**, 771. (e) Fraile, J. M.; Garcia, J. I.; Gracia, D.; Mayoral, J. A.; Pires, E. *J. Org. Chem.* **1996**, *61*, 9479. (f) Adrio, J.; Carretero, J. C.; Ruano, J. L. G.; Cabrejas, L. M. M. *Tetrahedron: Asymmetry* **1997**, *8*, 1623. (g) Arjona, O.; Iradier, F.; Medel, R.; Plumet, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2237. (h) Burke, M. J.; Allan, M. M.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **2000**, *11*, 2733 and references therein.

(22) Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4079.

(23) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

KHMDS affords an undesired cyclopropane derivative (eq 1).[25] As a result, it was necessary to find an alternative route that would result in the preparation of the *endo* epoxide isomer. After some experimentation, selective formation of the *endo* epoxide was accomplished via iodolactone (−)-**15**. Though the usual two-step procedure (hydrolysis and iodolactonization) afforded iodolactone (−)-**15** in good yield, the chiral auxiliary was recovered in only 40% yield along with 55% yield of 1-(naphthalene-2-sulfonyl)cyclohexene. On the other hand, direct treatment of *endo* Diels–Alder adduct (+)-**14** with I_2 in aqueous CH_3CN afforded iodolactone (−)-**15** in 81% yield with recovery of the chiral auxiliary in 94% yield. After recrystallization, optically pure lactone (−)-**15** was obtained, and its absolute stereochemistry was determined by comparing its optical rotation with that reported in the literature.[26] Though the direct transformation of iodolactone (−)-**15** to epoxy methyl ester (−)-**12** in MeOH under a variety of basic conditions was unsuccessful, a two-step conversion (hydrolysis and esterification) worked well: Hydrolysis and epoxide formation occurred on treatment of (−)-**15** with KOH in DMF at 60 °C for 10 h, followed by esterification with MeI under sonication conditions for 1 h, furnished epoxyester (−)-**12** in one pot and high yield (94%).

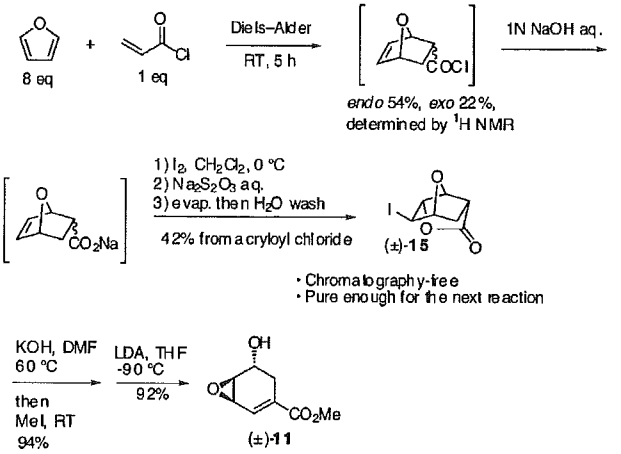


Exposure of (−)-**12** to LDA at −90 °C for 30 min led to β-elimination, affording hydroxyester (+)-**11**. Low temperature and an exact equivalent of LDA are both essential for high yield in this step; otherwise, Michael addition of diisopropylamine to (+)-**11** occurs, generating a β-aminoester as a side product.

The first total synthesis of epoxyquinols A and B was accomplished using (+)-**11** (vide infra). Though our $HfCl_4$-mediated, highly diastereoselective Diels–Alder reaction using a chiral auxiliary is suitable for the construction of optically active cyclohexanol derivatives, at least equimolar amounts of the auxiliary and $HfCl_4$ are necessary. To circumvent this problem, we have developed a more efficient and practical synthetic route to this key intermediate (+)-**11** for epoxyquinols A, B, and C and epoxytwinol A.

Second-Generation Monomer Synthesis. We chose as the key reaction of our new strategy the kinetic resolution of racemic cyclohexenol (±)-**11** using lipase,[27] as such reactions are known to be readily scalable. However, preparation of this intermediate itself proved to be difficult, because while the Diels–Alder reaction of furan and acrylate derivatives is a powerful means of synthesizing this class of compounds,[20,28] no method suitable for large-scale preparation of the *endo*-isomer has yet been described. Establishing such a route was our first goal. Instead of using a Lewis acid to promote the Diels–Alder reaction, we focused on the use of acryloyl chloride as a reactive dienophile, which is reported to react with furan in the presence of a hydrogen chloride scavenger, propylene oxide, over 48 h, providing the Diels–Alder adducts in 76.5% overall yield after conversion of the adduct to the corresponding ester. Under these conditions, the thermodynamically stable *exo*-isomer predominates (*endo*:*exo* = 3:7).[28a] After careful experimentation, it was found that the kinetically favored *endo*-isomer was generated predominately in the early stages of the reaction. The Diels–Alder reaction of acryloyl chloride and furan (8 equiv) proceeds in 5 h at room temperature, providing the *endo*- and *exo*-cycloadducts in 54 and 22% yields, respectively (^1H NMR yield). Though at this stage the starting material, acryloyl chloride, still remained, the yield of the *endo*-isomer did not increase further due to its conversion into the thermodynamically stable *exo*-isomer after longer reaction times. Hydrolysis of the acid chloride to the sodium salt of the acid was carried out by treatment with aqueous 1.5 M NaOH. On addition of I_2 and CH_2Cl_2 to the aqueous phase, iodolactonization proceeded efficiently, providing (±)-**15** in 42% yield as a white solid, which is pure enough to be used in the next experiment. Unreacted acryloyl chloride and the *exo*-Diels–Alder adduct could be easily separated from iodolactone (±)-**15**, as they both remained in the aqueous phase as the sodium salts of the corresponding acids. Though the yield was moderate, an efficient, chromatography-free proce-

SCHEME 3. Synthesis of (±)-11



(24) (a) Campbell, M. M.; Kaye, A. D.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron Lett.* **1984**, *25*, 1629. (b) Campbell, M. M.; Kaye, A. D.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron* **1984**, *40*, 2461. (c) Rajapaksa, D.; Keay, B. A.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 826.

(25) Rajapaksa, D.; Keay, B. A.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 826.

(26) Literature data: $[\alpha]^{25}_D$ −113 (*c* 1.04, $CHCl_3$). Ogawa, S.; Yoshikawa, M.; Taki, T. *J. Chem. Soc., Chem. Commun.* **1992**, 406. Synthetic **15**: $[\alpha]^{23}_D$ −114 (*c* 0.906, $CHCl_3$).

(27) (a) Sugai, T. *Curr. Org. Chem.* **1999**, *3*, 373. (b) Fuhshuku, K.; Oda, S.; Sugai, T. *Recent Res. Devel. Org. Chem.* **2002**, *6*, 57.

(28) Diels–Alder reaction of methyl acrylate and furan: (a) Kotsuki, H.; Asao, K.; Ohnishi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3339. (b) Moore, J. A.; Partain, E. M., III. *J. Org. Chem.* **1983**, *48*, 1105. (c) Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299. (d) Fraile, J. M.; Garcia, J. I.; Massam, J.; Mayoral, J. A.; Pires, E. *J. Mol. Catal. A: Chem.* **1997**, *123*, 43. (e) Ager, D. J.; East, M. B. *Heterocycles* **1994**, *37*, 1789. The Diels–Alder reaction under high pressure: (f) Kotsuki, H.; Nishizawa, H.; Ochi, M.; Matsuoka, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 496. (g) Dauben, W. G.; Krabbenhoft, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992. The Diels–Alder reaction of acrylic acid and furan: (h) Suami, T.; Ogawa, S.; Nakamoto, K.; Kasahara, I. *Carbohydr. Res.* **1977**, *58*, 240 and references therein.

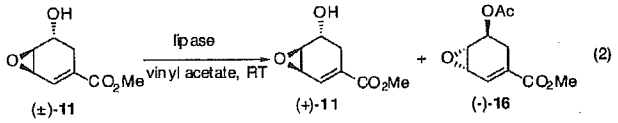


TABLE 1. Kinetic Resolution of Cyclohexenol (±)-11 Using Various Lipases[a]

entry	lipase	wt %	ratio of **11**:**16**[b]	**11** (% ee)[c]	**16** (% ee)[c]	k_{fast}/k_{slow}
1	lipase TL	40	50:50	96	97	215
2	lipase QL	50	53:47	85	98	128
3	lipase QLM	50	47:53	99	95	80
4	lipase PL	90	55:45	75	94	52
5	lipase PS	50	83:17	19	97	32
6	lipase SL	100	82:18	19	98	17
7	chirazyme L-2	40	42:58	70	60	6.1

[a] Reaction was performed using 0.12 mmol of (±)-**11** for 18 h at room temperature. [b] Ratio was determined by ^{1}H NMR. [c] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel OD-H column.

TABLE 2. Large-Scale Kinetic Resolution Using Recovered Lipase TL[a]

entry	scale (g)	time (h)	ratio of **11**:**16**[b]	**11** (% ee)[c]	**16** (% ee)[c]	k_{fast}/k_{slow}
1	8	36	49:51	99	96	211
2[d]	14	40	49:51	99	93	201
3[e]	21	36	49:51	99	94	195

[a] Reaction was performed with 10 wt % lipase TL. [b] Determined by ^{1}H NMR. [c] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel OD-H column. [d] Once-recycled lipase TL was employed. [e] Twice-recycled lipase TL was employed.

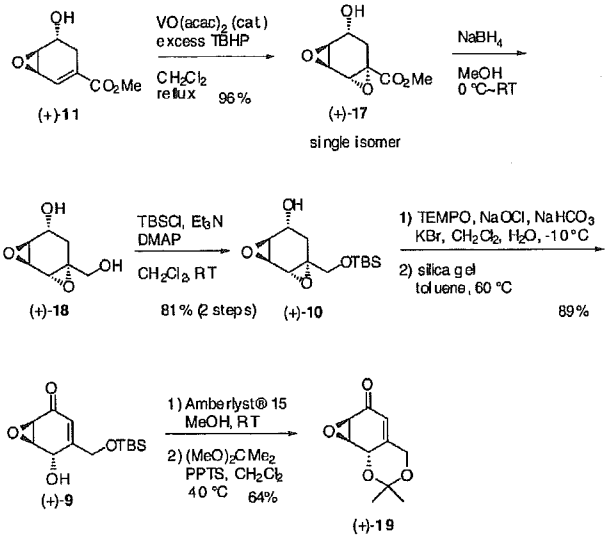
dure for the synthesis of iodolactone (±)-**15** has been developed,[29] and the reaction could easily be scaled up to 90 g.

After conversion of iodolactone (±)-**15** to cyclohexenol (±)-**11** by the same procedure described in Scheme 2, the kinetic resolution of (±)-**11** was examined (eq 2) with the results summarized in Table 1. The reaction was performed at room temperature in the presence of several lipases (40–100 wt/%) using vinyl acetate as a solvent. Among the lipases examined, the *Pseudomonas stutzeri* lipase (Meito TL) was found to be most efficient: When (±)-**11** was treated with a catalytic amount of lipase TL (40 wt %) in vinyl acetate at room temperature for 18 h, acetate (−)-**16** was obtained in 50% yield with 97% ee, while the desired alcohol (+)-**11** was recovered in 50% yield with 96% ee, indicating a very high selectivity (k_{fast}/k_{slow} = 215).

Next, the large-scale kinetic resolution was examined using recovered lipase TL, the results being summarized in Table 2. The reaction proceeded efficiently even with 10 wt % of the lipase TL, with a very high value of k_{fast}/k_{slow}, though a longer reaction time was necessary. The activity of recovered lipase did not decrease, and it worked as efficiently as fresh batches. The absolute configuration of (+)-**11** was determined by comparison of its optical rotation with that of previously synthesized (+)-**11**, as well as by using the advanced Mosher's MTPA

(29) Holmes and Jennings-White et al. elegantly synthesized *cis*-maneonene A using a similar sequence involving the Diels–Alder reaction of furan and fumaryl chloride, followed by hydrolysis and bromo-lactonization; see: Jennings-White, C. L. D.; Holmes, A. B.; Raithby, P. R. *J. Chem. Soc., Chem. Commun.* **1979**, 542.

SCHEME 4. Synthesis (+)-19



method.[30] As acetate (−)-**16** was easily converted to alcohol (−)-**11** on treatment with K_2CO_3 in MeOH, providing (−)-**11** in 97% yield, both enantiomers of alcohol **11** could be synthesized in large quantities and with high optical purity. This kinetic resolution is suitable for producing both optically active cyclohexenols (+)-**11** and (−)-**11** on a gram-scale, not only because high selectivity is achieved but also because only a catalytic amount of lipase is necessary and can be recycled.

Hydroxyl-directed epoxidation of homoallylic alcohol (+)-**11** using a catalytic amount of $VO(acac)_2$ and excess *tert*-butylhydroperoxide (TBHP) under reflux in CH_2Cl_2 [31] proceeded to give diepoxide (+)-**17** as a single isomer in high yield. Although reduction of ester (+)-**17** with DIBAL proceeded smoothly, the recovered yield of the diol (+)-**18** was quite low due to its water solubility. A nonaqueous workup was examined: Reduction with $NaBH_4$ in MeOH at room temperature for 15 min, removal of solvent, and flash column chromatography afforded the diol (+)-**18**. The primary alcohol of diol (+)-**18** was selectively protected with TBSCl, affording (+)-**10** in 81% yield over two steps. Though the oxidation of (+)-**10** with SO_3·pyridine[32] afforded 2-(*tert*-butyldimethylsilyloxymethyl)-5,6-epoxy-2-cyclohexene-1,4-dione from over-oxidation of (+)-**9**, TEMPO-oxidation[33] gave the desired β,γ-epoxyketone without formation of this byproduct. Isomerization occurred on treatment of the β,γ-epoxyketone with silica gel at 60 °C in toluene for 4 h,[34] affording α,β-unsaturated ketone (+)-**9** in 89% yield over two steps. The α-iodination of cyclohexenone (+)-**9** was problematic, and the choice of diol protecting group and

(30) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(31) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. (b) Meier, R.-M.; Tamm, C. *Helv. Chim. Acta* **1991**, *74*, 807.

(32) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(33) In our previous paper,[8a] the Dess–Martin periodinane was employed as the oxidant, which gave the desired product in good yield. TEMPO oxidation is suitable for large-scale preparation. Anelli, P. L.; Montanari, F.; Quici, S. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, p 367.

(34) Yadagiri, P.; Lumin, S.; Mosset, P.; Capdevila, J.; Falck, J. R. *Tetrahedron Lett.* **1986**, *27*, 6039.

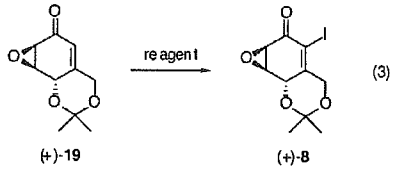


TABLE 3. α-Iodonation of (+)-19 under Various Reaction Conditions

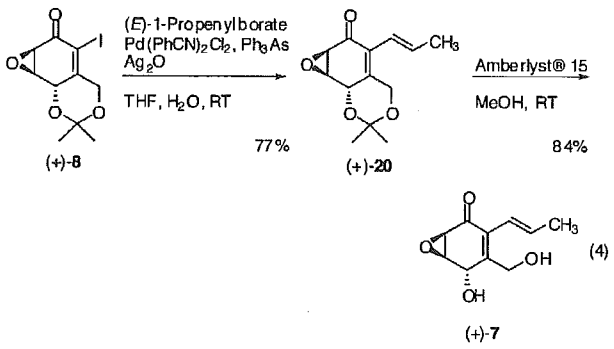
entry	reagent	temp (°C)	time (h)	yield (%)[a]
1	I_2, $PhI(OCOCF_3)_2$, pyridine	23	4	10
2	I_2, $PhI(OCOCF_3)_2$, pyridine	23	6	52
3	I_2, $PhI(OCOCF_3)_2$, pyridine	23	6.5	<5[b]
4	I_2, $PhI(OCOCF_3)_2$, pyridine, cat BHT	23	20	86
5	I_2, DMAP, pyridine	23−70	30	0[c]
6	NaN_3, ICl	−23−23	22	0[b]
7	I_2, CH_3CO_2Ag, pyridine	0−23	20	0[b]

[a] Isolated yield. [b] Complex mixture. [c] No reaction.

iodination reagent was found to be important for the success of this reaction: None of the desired product was obtained on treatment of hydroxy ketone (+)-**9** with I_2/DMAP,[35] I_2/$TMSN_3$,[36] or NaN_3/ICl,[37] while the secondary alcohol was oxidized, affording epoxyquinone in the reaction using I_2/$PhI(OCOCF_3)_2$/pyridine.[38]

The low reactivity and side reaction of (+)-**9** can be attributed to steric hindrance caused by the *tert*-butyldimethylsiloxymethyl group at the C3 position and nonprotected hydroxy group at the C4 position, respectively, and so the sterically smaller protecting group had to be employed. Acetonide derivative (+)-**19** was prepared in 64% yield from (+)-**9** over two steps by TBS group deprotection with Amberlyst in MeOH and protection of the resulting 1,3-diol with 2,2-dimethoxypropane. Unlike the result obtained with (+)-**9**, the reaction of (+)-**19** proceeded in the presence of I_2/$PhI(OCOCF_3)_2$/pyridine, affording (+)-**8**, but unreproducibly. After careful examination, it was found that the iodination proceeded only after a certain induction period and that, once generated, (+)-**8** began to decompose after a further induction period as shown in entries 1−3 of Table 3. On the basis of our speculation that the side reaction was radical in nature, we carried out the reaction in the dark in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenger, conditions that gave reproducible results, providing (+)-**8** in 86% yield, though a longer reaction time was required (entry 4).

As iodinated cyclohexenone (+)-**8** was labile, it was immediately subjected to the Suzuki coupling reaction with (*E*)-1-propenyl borate[39] under C. R. Johnson's conditions,[40] affording dienone (+)-**20** in 77% yield. Cleavage of the acetonide under acidic conditions provided monomer (+)-**7** in 84% yield.



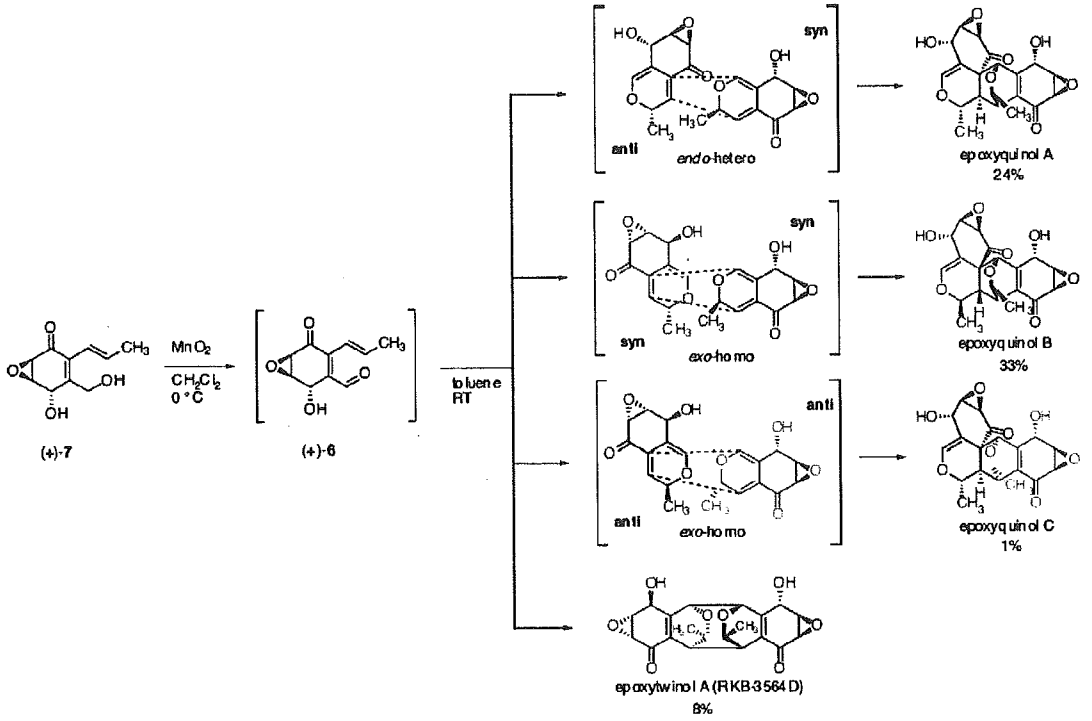
Biomimetic, Oxidative Dimerization of Monomer (+)-7. With the monomer (+)-**7** in hand, we examined its dimerization. In our previous paper, we reported the first total synthesis of epoxyquinols A and B, which resulted from the biomimetic transformation involving a cascade of reactions composed of oxidation, 6π-electrocyclization, and Diels−Alder reaction.[8a] This reaction was carried out on a 0.03 mmol scale. To search for other diastereomers in the crude reaction mixture, we examined the reaction on a 0.4 mmol scale. As there is a large solvent effect in this oxidative Diels−Alder reaction as reported in a previous paper,[18b] the present investigation was performed in toluene−2*H*-pyran **5**, which was obtained by the following three steps: (1) oxidation of alcohol (+)-**7** with MnO_2 in CH_2Cl_2, (2) filtration of the inorganic materials, and (3) removal of the volatile materials under reduced pressure, followed by dissolving the resulting mixture in toluene. Dimerization proceeded in 10 h at room temperature, and the crude material was carefully purified by column chromatography, affording epoxyquinols A and B in 24 and 33% yields, respectively, along with epoxyquinol C in 1% yield and epoxytwinol A in 8% yield. Epoxyquinol C, which is known to be formed from epoxyquinol A by microwave irradiation,[11] is a Diels−Alder reaction product of 2*H*-pyran **5** via the *exo-syn*(epoxide)-*anti*(Me)-homo reaction mode.[41] Theoretical calculations indicate that the energy for the transition state leading to epoxyquinol C is the lowest except for those leading to epoxyquinols A and B,[18b] which is in accord with the experimental results. As for epoxytwinol A, it is a formal [4 + 4] cycloaddition product of 2*H*-pyran **5** that gradually converted into epoxyquinol B. In addition to the total synthesis of these four compounds, we isolated all of them from the same soil fungus. The fact that the monomer (+)-**6** spontaneously dimerized to afford epoxyquinols A, B, and C and epoxytwinol A clearly indicates that an enzyme such as Diels−Alderase is not involved in this transformation.

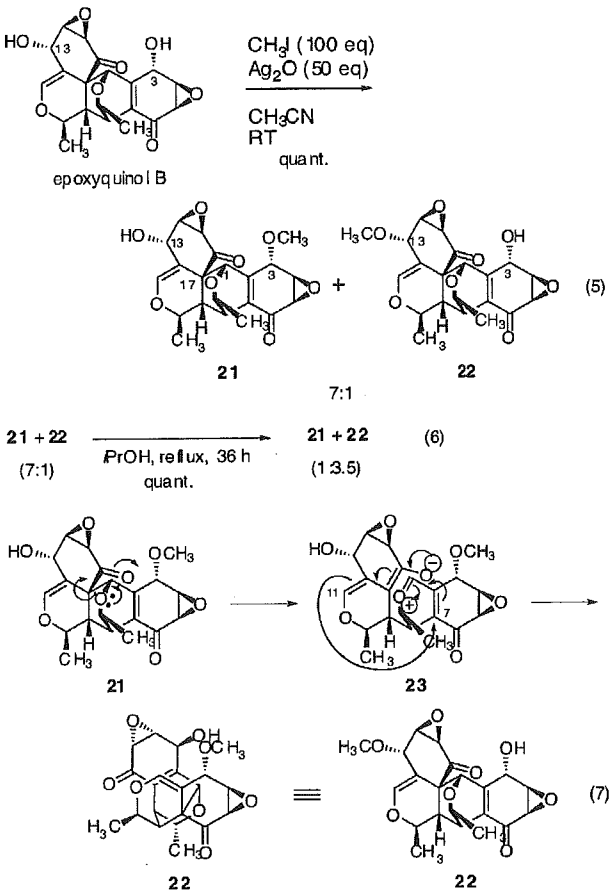
Isomerization Reaction of a Monomethyl Ether of Epoxyquinol B. As we had observed the facile transformation of epoxytwinol A into epoxyquinol B during isolation of the former from the unidentified fungus, we investigated whether the reverse, conversion of epoxyquinol B into epoxytwinol A, could be realized, but with disappointing results. Porco and co-workers have also failed to achieve this transformation.[12] During these studies, we have encountered an interesting phenomenon: When epoxyquinol B was treated with MeI

(35) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Chem. Eur. J.* **2000**, *6*, 3991.
(36) Sha, C.-K.; Huang, S.-J. *Tetrahedron Lett.* **1995**, *36*, 6927.
(37) McIntosh, J. M. *Can. J. Chem.* **1971**, *49*, 3045.
(38) Benhida, R.; Blanchard, P.; Fourrey, J.-L. *Tetrahedron Lett.* **1998**, *39*, 6849.
(39) (a) Lee, A. S.-Y.; Dai, W.-C. *Tetrahedron* **1997**, *53*, 859. (b) Matteson, D. S.; Jesthi, P. K. *J. Organomet. Chem.* **1976**, *110*, 25.
(40) Ruel, F. S.; Braun, M. P.; Johnson, C. R. *Org. Synth.* **1997**, *75*, 69.

(41) As for the classifications of the reaction modes, see ref 18b.

SCHEME 5. Synthesis of Epoxyquinols A, B, and C and Epoxytwinol A





and Ag_2O in CH_3CN, an inseparable mixture of monomethyl ethers of epoxyquinol B **21** and **22** was obtained in a 7:1 ratio, with 3-methyl ether **21** predominating. When this 7:1 mixture was refluxed in *i*-PrOH for 36 h, the diastereomeric ratio changed from 7:1 to 1:3.5, this time with the 13-methyl ether **22** as the major isomer. This isomerization is thought to proceed as follows: The C1–C17 bond of **21** was cleaved by the participation of an oxygen lone pair to afford intermediate **23** containing an oxonium ion and a vinylogous enolate, from which the C11–C7 bond was formed, affording **22**. Though this isomerization may also proceed in the case of epoxyquinol B itself, no reaction would be apparent as the starting material and transformed product are the same.

Reactivity of a 2*H*-Pyran Derivative. In the biomimetic oxidative dimerization of monomer (+)-**7**, the reactive intermediate, 2*H*-pyran (+)-**5**, is generated, which acts both as a diene and a dienophile. The cascade reaction of oxidation/6π-electrocyclyzation is a useful synthetic method for the formation of 2*H*-pyran derivatives, but no systematic study has been made of the reactivity of this reactive intermediate. Moreover, were the 2*H*-pyran derivative to react with another diene or dienophile instead of dimerizing, an efficient method for the synthesis of polycyclic compounds would be realized.

With this in mind, we examined the Diels–Alder reaction of a 2*H*-pyran derivative with several dienophiles and dienes. We choose epoxycyclohexenone (+)-**7** and cyclohexenone **25**, with and without the epoxide and a secondary hydroxy group as the monomers with which to investigate the reactivity of 2*H*-pyrans. The reactions using (+)-**7** and **25** were performed as follows: Alcohols (+)-**7** and **25** were oxidized with MnO_2 in CH_2Cl_2 at 0 °C and room temperature, respectively, for 1 h. After removal of inorganic materials by filtration, the solvent was carefully removed under reduced pressure at 0 °C

SCHEME 6. Synthesis of Various Polycyclic Compounds 24 and 28

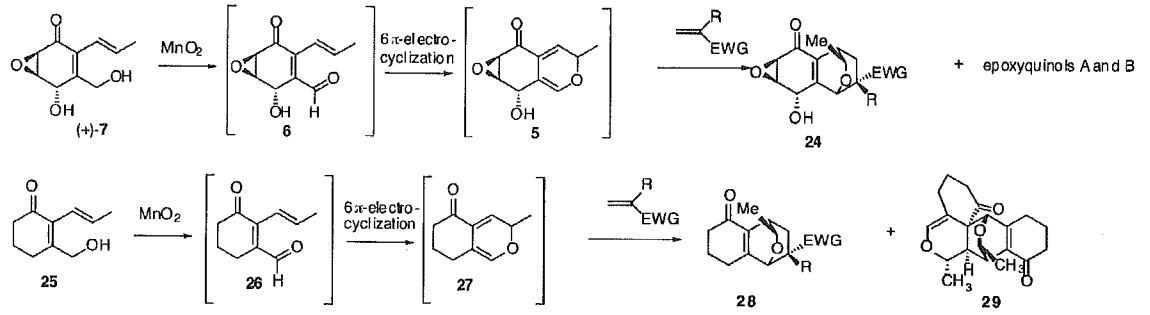


TABLE 4. Cascade Reaction of (+)-7 and 25 with Several Dienophiles

Entry	Cyclohexenone	Dienophile	Product	Yield/%[a]
1	(+)-7	COMe	24a	64
2	(+)-7	CHO	24b	69
3	(+)-7	CO_2Me	24c	56
4	(+)-7		24d	45
5	25	COMe	28a	76
6	25	COEt	28b	70
7	25	CHO	28c	52
8	25	CHO	28d	63
9	25	CO_2Me	28e	66
10[b]	25		28f	55
11	25		28g	49

[a] Isolated yield. [b] **28f** was isolated after hydrogenolysis of the Diels–Alder adduct.

to suppress the self-dimerization. Immediately after removal of the solvent, an excess of dienophile or diene was added to the reaction mixture, which was then stirred at room temperature.

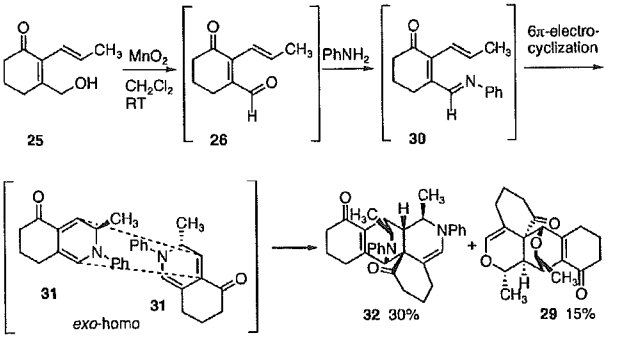
The 2*H*-pyrans **5** and **27**, acting as a diene, reacted with reactive dienophiles such as methyl vinyl ketone, ethyl vinyl ketone, acrolein, methacrolein, methyl acrylate, and benzoquinone, affording polycyclic compounds in moderate to good yield (52–76%) along with the self-dimerized product in 10–20% yield, the results of which are summarized in Table 4. In the case of benzoquinone, isolation and characterization were performed after hydrogenolysis of the Diels–Alder adduct due to the latter's instability. Only the *endo* Diels–Alder adducts were obtained stereoselectively in every reaction examined, and only *anti*(epoxide)-*anti*(Me) reaction was observed in the reaction of (+)-**7**. Though 2*H*-pyrans **5** and **27** also reacted with maleic anhydride, acryloyl chloride, and fumaryl chloride to provide Diels–Alder adducts quantitatively as single isomers as judged from ^{1}H NMR, attempts to isolate and characterize the products after conversion into the corresponding methyl esters were not successful. Less reactive dienophiles such as 2-cyclohexen-1-one and 2-cyclopenten-1-one did not react with 2*H*-pyran **27**, which instead generated the self-dimerization product **29**.[18b]

Next, the reaction with dienes was examined. Cyclopentadiene, known to be a reactive diene, reacted with 2*H*-pyrans **5** and **27** as a dienophile, affording a tetracyclic compound in moderate yield. Other dienes such as isoprene gave complex mixtures. The fact that cyclopentadiene reacted as a dienophile instead of a diene demonstrates the high reactivity of 2*H*-pyrans **5** and **27** as diene components.

Formation of an Azapentacycle via the Cascade Reaction. 1,2-Dihydropyridine **31**, a nitrogen analogue of 2*H*-pyran **27**, would be a useful synthetic intermediate for the formation of azacyclic compounds, should the same dimerization proceed. Though the 6π-azaelectrocyclization of a 1-azatriene to a 1,2-dihydropyridine is known, it usually requires harsh reaction conditions.[19,42] Recently, several 6π-azaelectrocyclizations that proceed at room temperature have been reported[43] and the asymmetric version has been elegantly applied to a formal total synthesis of 20-epiuleine.[44] Considering the facile 6π-oxaelectrocyclization of **6** to **5** and of **26** to **27**, the corresponding 6π-azaelectrocyclization of **30** to **31** was also expected to proceed under mild conditions.

Aldehyde **26**, generated by the MnO_2-mediated oxidation of monomer **25**, was treated with aniline, and the reaction mixture was stirred at room temperature for 30 h, affording azapentacyclic compound **32** in 30% yield along with the self-dimerization product **29** (15% yield) of 2*H*-pyran **27**. The structure of **32** was unambiguously determined by X-ray crystallographic analysis.[45] Azapentacycle **32** was thought to be generated by the self-dimerization of 1,2-dihydropyridine **31**, which is formed by the expected 6π-azaelectrocyclization. That is, the four successive reactions, oxidation, imine formation, 6π-azaelectrocyclization, and finally Diels–Alder dimerization, proceeded under mild conditions at room temperature. Though the yield was moderate, this is the first example of the Diels–Alder dimerization of a 1,2-dihydropyridine derivative. Azapentacycle **32** is the *exo*-Diels–Alder product, which is in marked contrast to the self-dimerization product **29** of 2*H*-pyran **27**, which is the *endo*-Diels–Alder product. In the dimerization of this 1,2-dihydropyridine, steric repulsion caused by the two phenyl groups makes the *endo*-Diels–Alder reaction unfavorable, and as a result, the *exo*-isomer was selectively obtained.

SCHEME 7. Synthesis of Azapentacycle 32



Conclusion

The total synthesis of epoxyquinols A, B, and C and epoxytwinol A has been accomplished by a biomimetic cascade reaction. Epoxyquinols A, B, and C were synthesized by the cascade reaction consisting of oxidation/6π-electrocyclization/Diels–Alder dimerization of the monomer **7** as a key step, while epoxytwinol A was generated by the cascade reaction of oxidation/6π-electrocyclization/formal [4 + 4] cycloaddition reaction of the monomer **7**. The monomer **7** has been synthesized by two different routes. In the first, the $HfCl_4$-mediated diastereoselective Diels–Alder reaction of furan with Corey's chiral auxiliary was developed, while chromatography-free preparation of an iodolactone and lipase-mediated kinetic resolution were key reactions in the second route. The present method is practical not only for synthesizing epoxyquinols in a large quantity but also preparing various derivatives with different side chains via Suzuki coupling of (+)-**8** and alkenyl borates. In fact, we synthesized several monomers, the biological activity of which is under investigation.[46] Another noteworthy feature described in the present paper is the high reactivity of 2*H*-pyrans **5** and **27** as dienes, used to prepare several polycyclic compounds by the Diels–Alder reaction. Azapentacycle **32** was also synthesized by the cascade reaction oxidation/imine formation/6π-azaelectrocyclization/Diels–Alder dimerization.

(42) Rodriguez-Otero, J. *J. Org. Chem.* **1999**, *64*, 6842.
(43) (a) de Lera, A. R.; Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 4051. (b) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099 and references therein.
(44) Tanaka, K.; Katsumura, S. *J. Am. Chem. Soc.* **2002**, *124*, 9660.
(45) A CIF file for the structure of **32** has been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 243000. Copies of the data can be obtained free of charge via the Internet at http://www.ccdc.cam.ac.uk or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44(1223)336033; email: deposit@ccdccam.ac.uk.
(46) Preliminary results have been published. Kakeya, H.; Miyake, Y.; Shoji, M.; Kishida, S.; Hayashi, Y.; Kataoka, T.; Osada, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3743.

Experimental Section

(1*R*,2*R*,4*R*)-7-Oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (1*R*,2*R*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (*endo*-14) and (1*R*,2*S*,4*R*)-7-Oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (1*R*,2*R*)-2-(Naphthalene-2-sulfonyl)-cyclohexyl Ester (*exo*-14). To a solution of $HfCl_4$ (70.0 mg, 0.219 mmol) in toluene (0.7 mL) was added (−)-**13** (70.1 mg, 0.203 mmol) at 0 °C, and the mixture was cooled to −45 °C. To the mixture was added furan (0.32 mL, 4.4 mmol), and the mixture was stirred for 34 h at that temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (aq) and filtered through a pad of Celite. The organic materials were extracted with AcOEt three times and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1) to *endo*-**14** (47.7 mg, 56%, 87% de) as a colorless solid and *exo*-**14** (22.4 mg, 27%, 91% de, inseparable mixture) as a colorless solid. ***endo*-14:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18−1.35 (4H, m), 1.49 (1H, qd, J = 12.1, 3.8 Hz), 1.66−1.80 (3H, m), 1.98−2.10 (2H, m), 2.77 (1H, ddd, J = 9.0, 4.8, 4.1 Hz), 3.36 (1H, ddd, J = 12.1, 10.1, 4.1 Hz), 4.91 (1H, br-d, J = 4.9 Hz), 5.12 (1H, td, J = 10.1, 4.9 Hz), 5.14 (1H, br-d, J = 4.9 Hz), 6.37 (2H, s), 7.62−7.72 (2H, m), 7.83 (1H, dd, J = 8.6, 1.7 Hz), 7.95 (1H, br-d, J = 7.8 Hz), 8.01 (2H, d, J = 8.3 Hz), 8.43 (1H, d, J = 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 24.1, 25.8, 28.5, 31.6, 42.8, 65.5, 70.5, 79.1, 79.2, 123.4, 127.8, 128.0, 129.3, 129.40, 129.41, 130.4, 132.1, 133.1, 135.3, 135.5, 136.4, 170.9; FT-IR (KBr) ν 3014, 2945, 2864, 1732, 1452, 1311, 1178, 1146, 1126, 1072, 1018, 756 cm^{-1}. Anal. Calcd for $C_{23}H_{24}O_5S$: C 66.97, H 5.86. Found: C 66.73, H 5.78. $[\alpha]^{25}_D$ +2.62 (*c* 1.00, $CHCl_3$). ***exo*-14:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.36 (4H, m), 1.49−1.60 (1H, m), 1.65−1.78 (3H, m), 1.79−1.88 (2H, m), 2.07−2.13 (1H, m), 2.26−2.34 (1H, m), 3.39 (1H, ddd, J = 12.1, 10.0, 4.1 Hz), 4.94 (1H, br-d, J = 4.1 Hz), 5.09 (1H, td, J = 10.0, 5.0 Hz), 5.12 (1H, br-s), 6.00 (1H, dd, J = 5.8, 1.3 Hz), 6.23 (1H, dd, J = 5.8, 1.5 Hz), 7.61−7.70 (2H, m), 7.84 (1H, dd, J = 8.6, 1.7 Hz), 7.92 (1H, br-d, J = 7.9 Hz), 7.98 (1H, d, J = 8.6 Hz), 8.01 (1H, d, J = 7.9 Hz), 8.44 (1H, br-s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 24.1, 25.1, 29.2, 31.5, 42.2, 65.7, 70.5, 77.6, 80.2, 123.5, 127.7, 127.9, 129.2, 129.3, 129.5, 130.4, 132.1, 134.6, 135.2, 135.6, 136.7, 172.5; FT-IR (KBr) ν 3012, 2943, 2864, 1736, 1308, 1144, 1126, 870, 758, 661 cm^{-1}.

(1*R*,2*R*,3*R*,6*R*,7*S*)-2-Iodo-4,8-dioxatricyclo[4.2.1.0^{3,7}]-nonan-5-one (15). To a solution of *endo*-**14** (64.6 mg, 0.156 mmol) in CH_3CN (1.5 mL) and water (0.06 mL) was added I_2 (194 mg, 0.764 mmol) at room temperature, and the mixture was stirred for 5.5 h. To the reaction mixture was added saturated $Na_2S_2O_3$ (aq), and organic materials were extracted with $CHCl_3$ (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by thin-layer chromatography to afford **15** (33.7 mg, 81%) as a colorless solid along with the recovery of the chiral auxiliary (42.4 mg, 94%). Iodolactone **15** was recrystallized from benzene−hexane twice to give optically pure **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (1H, dd, J = 13.5, 3.2 Hz), 2.20 (1H, dd, J = 13.5, 10.4, 4.7 Hz), 2.77 (1H, ddd, J = 10.4, 4.7, 3.2 Hz), 3.94 (1H, s), 4.80 (1H, d, J = 4.7 Hz), 5.12 (1H, d, J = 4.9 Hz), 5.38 (1H, t, J = 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 36.1, 38.0, 81.9, 84.2, 87.5, 175.8; FT-IR (KBr) ν 2995, 1787, 1324, 1189, 1022, 661, 433 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_7H_8O_3I$ 266.9518, found 266.9514; $[\alpha]^{23}_D$ −114 (*c* 0.906, $CHCl_3$); lit.[26] $[\alpha]^{25}_D$ −113 (*c* 1.04, $CHCl_3$).

Synthesis of *rac*-15. To furan (580 mL, 8 mol) was added acryloyl chloride (80 mL, 0.98 mol) at room temperature under an argon atmosphere, and the ratio of the *endo* adduct was monitored by ^{1}H NMR. After 3.5 h, the reaction mixture was quenched with 2 N NaOH (aq) (445 mL, 0.89 mol) and saturated $NaHCO_3$ (aq) (700 mL) and then stirred vigorously for 1.5 h. To the separated aqueous phase was added CH_2Cl_2 (900 mL) and I_2 (125 g, 0.49 mol) at 0 °C, and the mixture was stirred vigorously for 2 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ (aq), and the organic phase was concentrated in vacuo. The residue was filtered and washed with water and then dried to afford iodolactone **15** (109 g, 42%) as a colorless solid. The crude product was used for next reaction without further purification.

***rel*-(1*R*,2*S*,4*R*,5*S*,6*R*)-6-Methoxycarbonyl-3,8-dioxatricyclo[3.2.1.0^{2,4}]octane (12).** To a solution of iodolactone **15** (30.3 g, 0.114 mol) in DMF (450 mL) was added KOH (16.0 g, 0.285 mol) and stirred for 17 h at 60 °C. To the reaction mixture was added CH_3I (21.3 mL, 0.342 mol) at room temperature, and the mixture was sonicated for 2 h. After removal of volatile materials in vacuo, 1 N HCl (aq) (18 mL) and saturated NH_4Cl (aq) (150 mL) were added. The organic materials were extracted with AcOEt (3 × 300 mL), and the combined organic phases were washed with brine and then dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by silica gel column chromatography (AcOEt/hexane = 1) to afford methyl ester **12** (17.5 g, 90%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (1H, td, J = 11.6, 5.1 Hz), 2.08 (1H, dd, J = 11.6, 4.2 Hz), 2.91 (1H, dt, J = 11.6, 4.6 Hz), 3.74 (3H, s), 4.01 (1H, dd, J = 4.5, 2.5 Hz), 4.10 (1H, dd, J = 4.5, 2.3 Hz), 4.51 (1H, dt, J = 5.0, 2.5 Hz), 4.69 (1H, dt, J = 5.1, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.2, 44.6, 51.5, 66.2, 66.4, 77.4, 78.0, 171.8; FT-IR (KBr) ν 3039, 2921, 1731, 1444, 1342, 1305, 1097, 956, 609 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_8H_{11}O_4$ 171.0657, found 171.0663. Anal. Calcd for $C_8H_{10}O_4$: C 56.47, H 5.92. Found: C 56.55, H 5.88.

***rel*-(1*R*,5*R*,6*S*)-3-Methoxycarbonyl-7-oxabicyclo[4.1.0]-hept-2-en-5-ol (11).** To a solution of diisopropylamine (1.17 mL, 8.32 mmol) in THF (6.3 mL) was added *n*BuLi solution (1.58 M in hexane, 4.21 mL, 6.66 mmol) dropwise at 0 °C, and the mixture was stirred for 10 min at that temperature. To a solution of methyl ester **12** (944 mg, 5.55 mmol) in THF (8.4 mL) was added the LDA solution prepared above dropwise at −90 °C, and the mixture was stirred for 10 min at that temperature. The reaction was quenched with pH 7 phosphate buffer, and organic materials were extracted with AcOEt (3 × 50 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by silica gel column chromatography (AcOEt/hexane = 1/3∼1/1) to afford alcohol **11** (869 mg, 92%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (1H, bs), 2.33 (1H, ddd, J = 17.6, 5.1, 3.4 Hz), 2.80 (1H, dt, J = 17.6, 1.8 Hz), 3.48 (1H, t, J = 4.8 Hz), 3.55−3.59 (1H, m), 3.75 (3H, s), 4.53−4.59 (1H, m), 7.13 (1H, t, J = 3.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.2, 46.2, 52.1, 56.0, 63.3, 130.7, 133.4, 166.6; FT-IR (neat) ν 3444, 2954, 1716, 1438, 1207, 819, 609, 509 cm^{-1}; HRMS (EI) [M]$^+$ calcd for $C_8H_{10}O_4$ 170.0579, found 170.0619.

Kinetic Resolution of Racemic Alcohol 11. To a solution of racemic alcohol **11** (2.80 g, 16.5 mmol) in vinyl acetate (30 mL) was added *Pseudomonas stutzeri* lipase (Meito TL, 0.28 g), and the mixture was stirred at room temperature for 40 h. The lipase was filtered off, and the filtrate was condensed in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/3∼1/1) to afford epoxy alcohol (+)-**11** (1.35 g, 49%, 99% ee) and acetate (−)-**16** (1.65 g, 48%, 96% ee) as a colorless oil. **(1*R*,5*R*,6*S*)-3-Methoxycarbonyl-7-oxabicyclo[4.1.0]hept-2-en-5-ol ((+)-11):** $[\alpha]^{26}_D$ +213 (*c* 0.56, MeOH). HPLC analysis conditions: CHIRALCEL OD-H column, 2-PrOH/hexane = 1/20, 1.5 mL/min; retention times 28.7 min (major), 11.1 min (minor). **(1*S*,5*S*,6*S*)-5-Acetoxy-3-methoxycarbonyl-7-oxabicyclo[4.1.0]hept-2-ene ((−)-16):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (3H, s), 2.36 (1H, ddd, J = 18.1, 5.3, 3.3 Hz), 2.82 (1H, dt, J = 18.1, 1.8 Hz), 3.49 (1H, t, J = 3.9 Hz), 3.60−3.63 (1H, m), 3.77 (3H, s), 5.62 (1H, dt, J = 5.4, 2.7 Hz), 7.14 (1H, t, J = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 26.4, 46.5, 52.1, 53.9, 65.6, 131.0, 133.0, 166.1, 170.3; FT-IR (neat) ν 2954, 2850, 1739, 1714, 1649, 1265, 1028, 818, 600 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{10}H_{13}O_5$ 213.0763, found 213.0772; $[\alpha]^{22}_D$ −226 (*c* 0.46, MeOH). HPLC analysis

conditions: CHIRALCEL OD-H column, 2-PrOH/hexane = 1/20, 1.5 mL/min; retention times 5.6 min (major), 6.0 min (minor).

(1*S*,5*S*,6*R*)-3-Methoxycarbonyl-7-oxabicyclo[4.1.0]hept-2-en-5-ol ((−)-11). To a solution of acetate (−)-**16** (198 mg, 0.93 mmol) in MeOH (1.0 mL) was added K_2CO_3 (13 mg, 0.093 mmol) at 0 °C, and the mixture was stirred for 1 h at that temperature. The reaction mixture was quenched with saturated NH_4Cl (aq) and concentrated in vacuo. The organic materials were extracted with AcOEt (3 × 10 mL), and the combined organic phases were washed with brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by silica gel column chromatography (AcOEt/hexane = 1/3~1/1) to afford alcohol **(−)-11** (154 mg, 97%) as a colorless oil.

(1*S*,2*R*,4*S*,6*R*,7*S*)-4-Methoxycarbonyl-3,8-dioxatricyclo-[5.1.0.0^{2,4}]octan-6-ol ((+)-17). To a solution of alcohol (+)-**11** (282 mg, 1.65 mmol) in CH_2Cl_2 (15 mL) was added $VO(acac)_2$ (22.0 mg, 0.083 mmol), and the mixture was stirred for 5 min at room temperature. To the reaction mixture was added *t*BuOOH (4.2 M in toluene, 2.0 mL), and the mixture was vigorously refluxed for 12 h. The reaction mixture was cooled to room temperature and quenched with saturated $Na_2S_2O_3$ (aq). Organic materials were extracted with AcOEt (3 × 30 mL), and the combined organic phases were washed with brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by silica gel column chromatography (AcOEt/hexane = 1/3~1/1) to afford diepoxide (+)-**17** (297 mg, 96%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (1H, bd, J = 16.0 Hz), 2.41 (1H, dd, J = 16.0, 4.4 Hz), 2.55 (1H, d, J = 12.0 Hz), 3.27 (1H, t, J = 3.4 Hz), 3.51 (1H, dd, J = 3.9, 2.8 Hz), 3.71 (3H, s), 3.80 (1H, d, J = 2.5 Hz), 4.13–4.21 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 50.3, 52.8, 53.7, 55.9, 57.5, 64.2, 168.5; FT-IR (neat) ν 3521, 2956, 1743, 1444, 1363, 1294, 1257, 1068, 863, 784 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_8H_{11}O_5$ 187.0606, found 187.0622; [α]$^{26}_D$ +60.9 (*c* 0.54, MeOH).

(1*R*,2*S*,4*S*,5*R*,7*R*)-7-Hydroxymethyl-3,8-dioxatricyclo-[5.1.0.0^{2,4}]octan-5-ol ((+)-18). To a solution of ester (+)-**18** (367 mg, 1.97 mmol) in MeOH (3 mL) was added $NaBH_4$ (223 mg, 5.91 mmol) at 0 °C, and the mixture was stirred for 30 min at room temperature. The volatile materials were evaporated in vacuo, and the residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1/10) to afford diol (+)-**18** (300 mg, 96%) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 2.05 (1H, dd, J = 15.6, 2.6 Hz), 2.08 (1H, dd, J = 15.6, 4.4 Hz), 3.22 (1H, bt, J = 3.5 Hz), 3.43 (1H, d, J = 12.4 Hz), 3.49 (1H, d, J = 2.5 Hz), 3.53 (1H, t, J = 3.2 Hz), 3.55 (1H, d, J = 12.4 Hz), 4.14 (1H, dt, J = 4.4, 3.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 29.3, 52.2, 55.2, 55.4, 62.1, 65.4, 65.5; FT-IR (neat) ν 3399, 3369, 2927, 1423, 1074, 1047, 809, 619 cm^{-1}; HRMS (FAB) [M + H]$^+$ Calcd for $C_7H_{11}O_4$: 159.0657, found: 159.0650; [α]$^{26}_D$ +11.1 (*c* 0.77, MeOH).

(1*R*,2*S*,4*S*,5*R*,7*R*)-7-(*tert*-Butyl-dimethyl-silanyloxy-methyl)-3,8-dioxatricyclo[5.1.0.0^{2,4}]octan-5-ol ((+)-10). To a solution of alcohol (+)-**18** (134 mg, 0.85 mmol), Et_3N (0.19 mL, 1.38 mmol), and 4-(dimethylamino)pyridine (10.3 mg, 0.085 mmol) in CH_2Cl_2 (2 mL) was added TBSCl (183 mg, 1.21 mmol) at 0 °C, and the mixture was stirred for 15 h at room temperature. The reaction was quenched with pH 7.0 phosphate buffer, and organic materials were extracted with AcOEt (3 × 10 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by silica gel column chromatography (AcOEt/hexane = 1/10~1/1) to afford TBS ether (+)-**10** (339 mg, 84%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.87 (9H, s), 2.02 (1H, dd, J = 15.4, 4.2 Hz), 2.10 (1H, d, J = 15.4 Hz), 2.82 (1H, d, J = 12.0 Hz), 3.29 (1H, bs), 3.47 (1H, d, J = 11.8 Hz), 3.48 (2H, s), 3.66 (1H, d, J = 11.8 Hz), 4.16 (1H, bd, J = 12.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.2, 25.7, 27.8, 50.9, 54.3, 54.5, 62.2, 94.9, 65.0; FT-IR (neat) ν 3517, 2954, 2929, 2857, 1116, 869, 688 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{13}H_{25}O_4Si$ 273.1522, found 273.1491; [α]$^{26}_D$ +14.0 (*c* 0.89, MeOH).

(1*R*,5*S*,6*R*)-4-(*tert*-Butyl-dimethylsiloxymethyl)-5-hydroxy-7-oxabicyclo[4.1.0]hept-3-en-2-one ((+)-9). To a solution of alcohol (+)-**10** (95.9 mg, 0.352 mmol), TEMPO (0.6 mg, 0.004 mmol), and KBr (4.2 mg, 0.035 mmol) in CH_2Cl_2–H_2O (10:3, 1.3 mL) was added NaOCl–$NaHCO_3$ (aq) (1.3 M, pH 9.5, 0.27 mL, 0.36 mmol) at −10 °C, and the mixture was stirred for 40 min at that temperature. The reaction was quenched with saturated $Na_2S_2O_3$ (aq), and organic materials were extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo. To the residue was added toluene (1.5 mL) and silica gel (0.5 g), and the mixture was stirred at 70 °C for 4.5 h. The reaction mixture was cooled to room temperature and condensed in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/3~1/1) to afford enone (+)-**9** (84.7 mg, 89%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (6H, s), 0.91 (9H, s), 3.29 (1H, bs), 3.43 (1H, s), 3.78 (1H, dd, J = 3.4, 0.9 Hz), 4.28 (1H, d, J = 15.6 Hz), 4.51 (1H, dd, J = 15.6, 1.6 Hz), 4.63 (1H, bs), 5.96 (1H, d, J = 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.2, 25.7, 52.7, 56.4, 64.1, 65.0, 121.1, 156.9, 193.6; FT-IR (neat) ν 3419, 2954, 2931, 2884, 1687, 1344, 1226, 1049, 879, 781 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{13}H_{23}O_4Si$ 271.1366, found 271.1368; [α]$^{25}_D$ +149 (*c* 0.56, MeOH).

(4*R*,6*R*,7*S*)-9,9-Dimethyl-5,8,10-trioxatricyclo[5.4.0.0^{4,6}]-undec-1-en-3-one ((+)-19). To a solution of TBS ether (+)-**9** (38.7 mg, 0.143 mmol) in MeOH (1 mL) was added Amberlyst 15 (11.3 mg), and the mixture was stirred for 5 h at room temperature. The reaction mixture was filtered, and the filtrate was condensed in vacuo. The residue was dissolved in CH_2Cl_2 (0.5 mL), and then 2,2-dimethoxypropane (0.35 mL, 2.85 mmol) and pyridinium *p*-toluenesulfonate (3.6 mg, 0.014 mmol) were added. After stirring for 4 h, the reaction mixture was poured into saturated $NaHCO_3$ (aq) and organic materials were extracted with AcOEt (3 × 10 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by neutral silica gel column chromatography (AcOEt/hexane = 1/10–1/3) to afford acetonide (+)-**19** (18.0 mg, 64%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, s), 1.60 (3H, s), 3.42–3.44 (1H, m), 3.67 (1H, d, J = 3.2 Hz), 4.26 (1H, d, J = 14.6 Hz), 4.58 (1H, dt, J = 14.6, 1.3 Hz), 4.81 (1H, s), 5.83 (1H, t, J = 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 27.1, 52.4, 57.3, 63.8, 64.0, 101.2, 120.1, 154.0, 190.9; FT-IR (neat) ν 1674, 1269, 1201, 1159, 1078, 881, 856, 779, 540 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{10}H_{13}O_4$ 197.0814, found 197.0818. Anal. Calcd for $C_{10}H_{12}O_4$: C 61.22, H 6.16. Found: C 61.38, H 6.23; [α]$^{25}_D$ +348 (*c* 0.10, $CHCl_3$); mp 93.0–94.0 °C.

(4*R*,6*R*,7*S*)-2-Iodo-9,9-dimethyl-5,8,10-trioxatricyclo-[5.4.0.0^{4,6}]undec-1-en-3-one ((+)-8). To a solution of iodine (23.4 mg, 0.092 mmol) and pyridine (11.2 μL, 0.14 mmol) in CH_2Cl_2 (0.3 mL) was added $PhI(OCOCF_3)_2$ (39.7 mg, 0.092 mmol), and the mixture was stirred at room temperature for 15 min in the dark. To the reaction mixture were added 2,6-di-*tert*-butyl-4-methylphenol (1.0 mg, 0.0045 mmol) and enone (+)-**19** (18.1 mg, 0.092 mmol), and the mixture was stirred for 22 h at that temperature. The reaction was quenched with saturated $Na_2S_2O_3$ (aq), and organic materials were extracted with AcOEt (3 × 10 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo, but not completely, and the residue was purified by neutral silica gel column chromatography (AcOEt/hexane = 1/30–1/10) to afford iodoenone (+)-**8** (25.5 mg, 86%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, s), 1.54 (3H, s), 3.63 (1H, dd, J = 3.4, 1.4 Hz), 3.76 (1H, d, J = 3.2 Hz), 4.35 (1H, dd, J = 18.3, 1.4 Hz), 4.40 (1H, dd, J = 18.3, 1.4 Hz), 4.72 (1H, d, J = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 25.7, 51.3, 57.4, 65.3, 69.6, 98.0, 102.8, 162.2, 184.3; FT-IR (neat) ν 2989, 2858, 1683, 1384, 1228, 1097,