First Asymmetric Total Synthesis of Synerazol (I), an Antifungal Antibiotic, and Determination of Its Absolute Stereochemistry.

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First Asymmetric Total Synthesis of Synerazol, an Antifungal Antibiotic, and Determination of Its Absolute Stereochemistry

Yujiro Hayashi,*,† Mitsuru Shoji,† Takasuke Mukaiyama,† Hiroaki Gotoh,† Shinpei Yamaguchi,† Munetaka Nakata,‡ Hideaki Kakeya,§ and Hiroyuki Osada§

Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Graduate School of BASE (Bio-Applications and Systems Engineering), Tokyo University of Agriculture and Technology, Naka-cho, Koganei, Tokyo 184-8588, and Antibiotics Laboratory, Discovery Research Institute, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan

hayashi@ci.kagu.tus.ac.jp

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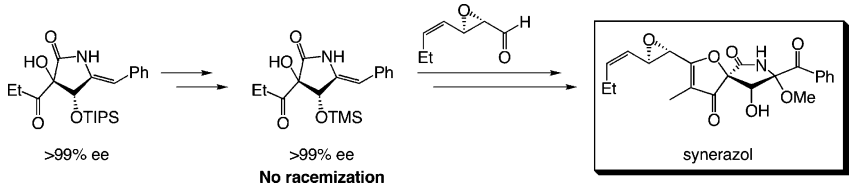

By synthesizing two possible diastereomers, the first asymmetric total synthesis of synerazol, an antifungal antibiotic, has been accomplished, allowing determination of its absolute stereochemistry. A more practical second generation route was also established. The key steps are racemization-free deprotection 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.

Introduction

Synerazol is an antifungal antibiotic isolated by Ando and co-workers in 1991 from the cultured broth of *Aspergillus fumigatus* SANK 10588.[1] Synerazol is active against *Candida albicans* and other fungi and shows marked synergistic activity with azole-type antifungal agents. Synerazol contains a highly oxygenated 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione skeleton with benzoyl and epoxyalkene substituents. The core structure, a hetero-spirocyclic γ-lactam, is also found in the pseurotins[2] and azaspirene.[3] Pseurotin A, isolated from a culture broth of *Pseudeurotium ovalis* (strain S2269/F) in 1976 by Bloch et al.,[2a] was reported to inhibit chitin synthase by Sterner et al. in 1993[2c] and also found to induce cell differentiation of PC12 cells by Komagata et al. in 1996.[2d] Its structure, including the absolute stereochemistry, has been unambiguously determined by a single-crystal X-ray analysis of its 12,13-dibromo derivative.[2b] Azaspirene, possessing the same core structure, has been isolated from the fungus *Neosartorya* sp. by Kakeya and Osada et al. in 2002[3] and found to inhibit endothelial migration induced by vascular endothelial growth factor. Because of the unprecedented, densely functionalized core structure of the pseurotins and azaspirene, their total synthesis poses a significant challenge.[4] We have completed the first total synthesis of a member of this class of compounds, that of azaspirene, in 2002.[5] Through this asymmetric total synthesis the absolute stereochemistry of azaspirene was determined. Our group also accomplished the asymmetric total syntheses of pseurotin A and of 8-*O*-demethylpseurotin A in 2003.[6] Recently Tadano's group reported the total syntheses of pseurotin A, 8-*O*-demethylpseurotin A, and azaspirene from D-glucose.[7] Despite

* To whom correspondence should be addressed. Phone: (+81)3-5228-8318. Fax: (+81)3-5261-4631.
† Tokyo University of Science.
‡ Tokyo University of Agriculture and Technology.
§ Discovery Research Institute, RIKEN.

(1) Ando, O.; Satake, H.; Nakajina, M.; Sato, A.; Nakamura, T.; Kinoshita, T.; Furuya, K.; Haneishi, T. *J. Antibiot*. **1991**, *44*, 382.

(2) (a) Bloch, P.; Tamm, C.; Bollinger, P.; Petcher, T. J.; Weber, H. P. *Helv. Chim. Acta* **1976**, *59*, 133. (b) Weber, H. P.; Petcher, T. J.; Bloch, P.; Tamm, C. *Helv. Chim. Acta* **1976**, *59*, 137. (c) Wenke, J.; Anke, H.; Sterner, O. *Biosci. Biotechnol. Biochem*. **1993**, *57*, 961. (d) Komagata, D.; Fujita, S.; Yamashita, N.; Saito, S.; Morino, T. *J. Antibiot*. **1996**, *49*, 958.

(3) Asami, Y.; Kakeya, H.; Onose, R.; Yoshida, A.; Matsuzaki, H.; Osada, H. *Org. Lett*. **2002**, *4*, 2845.

(4) For synthetic studies on the pseurotins, see: (a) Dolder, M.; Shao, X.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 63. (b) Shao, X.; Dolder, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 483. (c) Su, Z.; Tamm, C. *Helv. Chim. Acta* **1995**, *78*, 1278. (d) Su, Z.; Tamm, C. *Tetrahedron* **1995**, *51*, 11177. (e) Aoki, S.; Ohi, T.; Shimizu, K.; Shiraki, R.; Takao, K.; Tadano, K. *Heterocycles* **2002**, *58*, 57.

(5) Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc*. **2002**, *124*, 12078.

(6) Hayashi, Y.; Shoji, M.; Yamaguchi, S.; Mukaiyama, T.; Yamaguchi, J.; Kakeya, H.; Osada, H. *Org. Lett*. **2003**, *5*, 2287.

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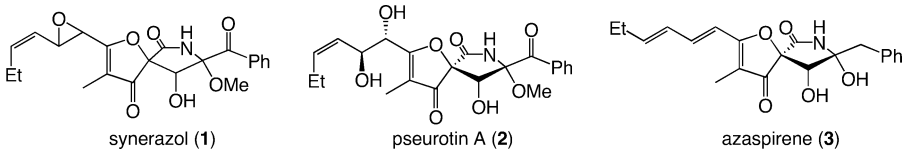


FIGURE 1. The structures of synerazol (**1**), pseurotin A (**2**), and azaspirene (**3**).

the similarity of their structures, the reported biological properties of synerazol, pseurotin A, and azaspirene are rather different as described above. Systematic comparison of the biological properties of these natural products and their derivatives is highly desirable, and a sufficient quantity of not only the natural products but also several derivatives is required for such biological study. As we had established a synthetic method for pseurotin A and azaspirene, we began to investigate the total synthesis of synerazol, the last member of this family of natural products remaining unsynthesized.The absolute stereochemistry of synerazol was unknown when we started this synthesis. We have determined this unambiguously by the first asymmetric total synthesis of synerazol as described in the first part of this paper[8] and in the second part a more practical synthesis of the natural isomer involving highly diastereoselective reactions. Recently Igarashi and co-workers have also determined the absolute stereochemistry using the modified Mosher's MTPA method on an alcohol derived from synerazol.[9]

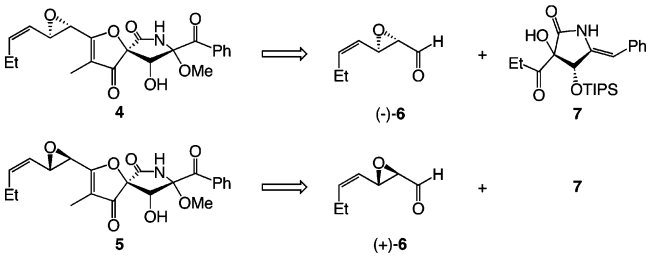
Results and Discussion

First Generation Synthesis of Synerazol. Retrosynthetic Analysis. While the absolute stereochemistry of synerazol was unknown, we postulated that the absolute stereochemistry of the 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione ring system would likely be the same as pseurotin A[2b] and azaspirene.[5] As there was no information on the side-chain epoxyalkene, we decided to synthesize both possible diastereomers, **4** and **5**.

Using the methodology developed for the synthesis of pseurotin A and azaspirene, we planned to prepare the diastereoisomers **4** and **5** from ketone **7** containing the lactam moiety and epoxyaldehydes (−)-**6** and (+)-**6**, respectively, by aldol condensation followed by functional group transformations (Scheme 1).

Synthesis of the Epoxyaldehyde. The enantiomerically pure side-chain aldehyde has been prepared in a highly stereoselective manner (Scheme 2). The synthesis started from D-tartaric acid diethyl ester (−)-**8**, which was converted to epoxy diester (+)-**10** by Saito's procedure.[10] Careful optimization of the reaction conditions enabled the selective monoreduction of this diester to hydroxy ester (+)-**11** in reasonable yield (71%). Protection of the alcohol with TBSCl and imidazole, followed by reduction and oxidation, afforded aldehyde (+)-**14**. Wittig reaction provided the *Z*-olefin with excellent stereoselectivity (*Z*:*E*

SCHEME 1. First Generation Retrosynthetic Analysis



= >98:2). Deprotection and oxidation afforded side-chain aldehyde (−)-**6**, which was used immediately in the next reaction because it gradually decomposed. Starting from L-tartaric acid diethyl ester (+)-**8**, the enantiomer (+)-**6** was also prepared by the same route.

With side-chain epoxyaldehydes (−)-**6** and (+)-**6** in hand, their reaction with ketone **7**, prepared by our established method,[5,6] was examined.

The lithium enolate of **7** reacted with side-chain epoxy aldehyde (−)-**6**, affording the aldol product **17** in 45% yield (diastereomer ratio = 2:1) with recovery of ketone **7** in 49% yield (Scheme 3). Thus, the yield based on the recovered starting material (BRSM) was 88%. Oxidation of aldol **17** with the Dess−Martin periodinane (DMP)[11] in CH_2Cl_2 proceeded smoothly, providing the 1,3-diketone, which owing to the mild acidity of silica gel was transformed into azaspiro compound **18** via cyclization and dehydration reactions during purification with thin-layer chromatography (TLC).

When **18** was treated with dimethyldioxirane (DMD)[12] at low temperature, selective oxidation of the benzylidene was achieved, affording diol **19** in 40% yield with 33% recovery of **18**. As overoxidation proceeded on prolonged reaction time or at higher temperature, quenching the reaction at an early stage and repeating the oxidation on recovered **18** are recommended. A subsequent DMP oxidation afforded benzoyl derivative **20** in good yield (95%).

In our previous total synthesis of pseurotin A,[6] successful transformation of a hydroxy group into the corresponding methyl ether was accomplished by treatment of **23** with AcCl in MeOH to afford pseurotin A in 25% yield (eq 1, Scheme 4). When *N*,*O*-acetal **25**, prepared by removal of the TIPS group of **20**, was treated with AcCl in MeOH in order to convert the hydroxy group into a methoxy group and form **4**, decomposition occurred because of the acid instability of the epoxyalkene moiety (eq 2, Scheme 4). Even in the presence of a milder acid

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(8) We have orally presented the first synthesis of synerazol and determination of its absolute stereochemistry at the following meeting: Hayashi, Y.; Shoji, M.; Mukaiyama, T.; Yamaguchi, S.; Gotoh, H.; Kakeya, H.; Osada, H. *Abstracts of Papers*, 84 Annual Meeting of Japan Chemical Society, Kobe, Japan, March 27, 2004; p 981.

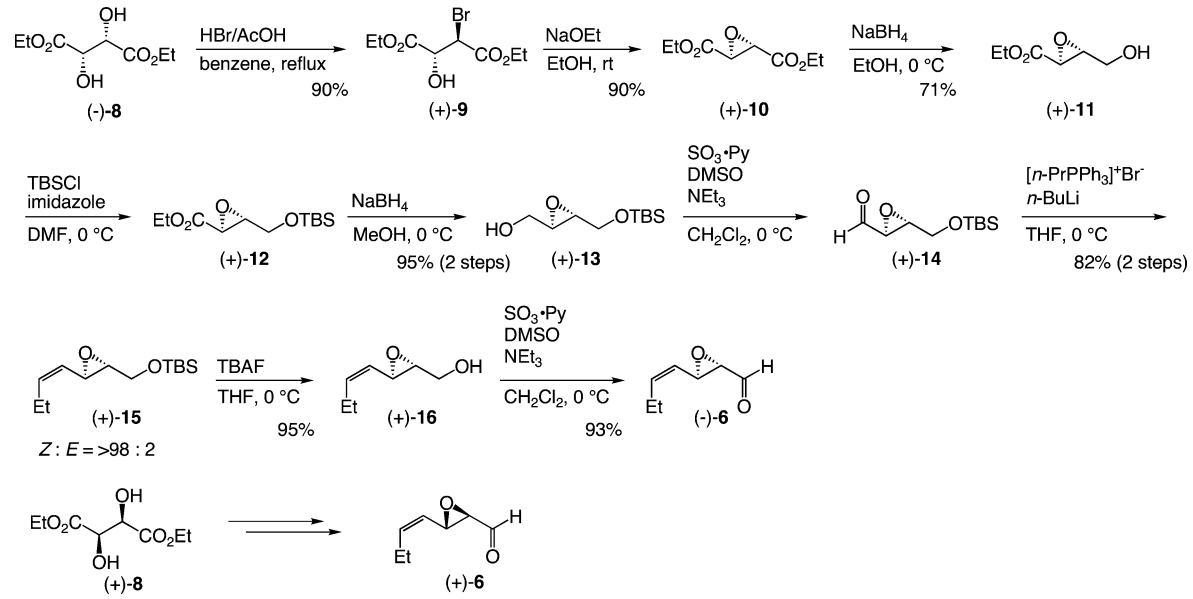
(9) Igarashi, Y.; Yabuta, Y.; Furumai, T. *J. Antibiot.* **2004**, *57*, 537.

(10) Saito, S.; Komada, K.; Morowake, T. *Org. Synth.* **1995**, *73*, 184.

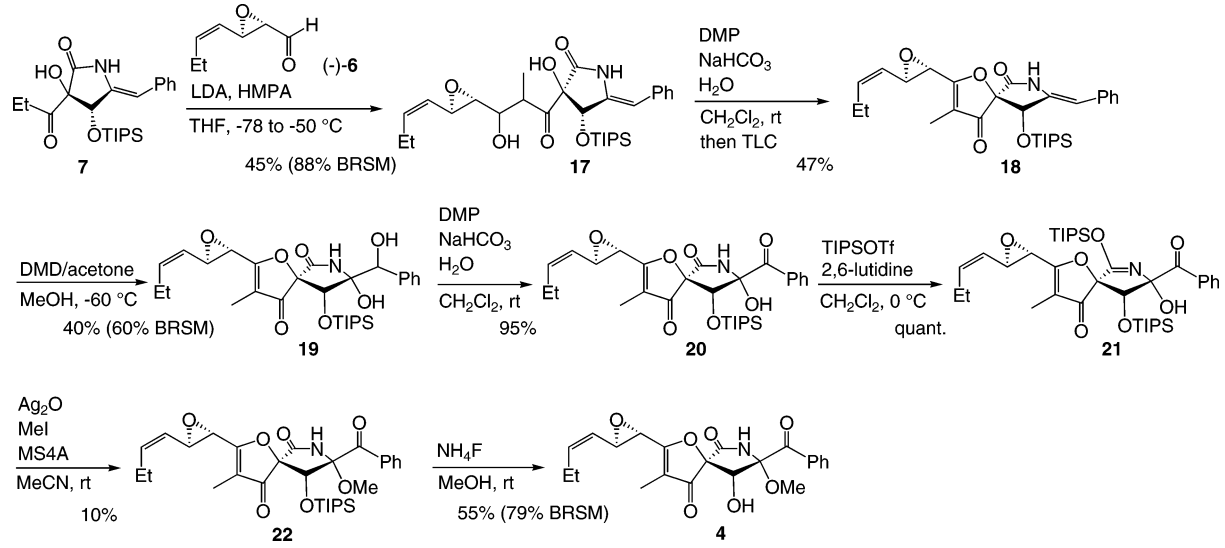
(11) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (d) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

(12) (a) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377. (b) Koseki, Y.; Kusano, S.; Ichi, D.; Yoshida, K.; Nagasaka, T. *Tetrahedron* **2000**, *56*, 8855.

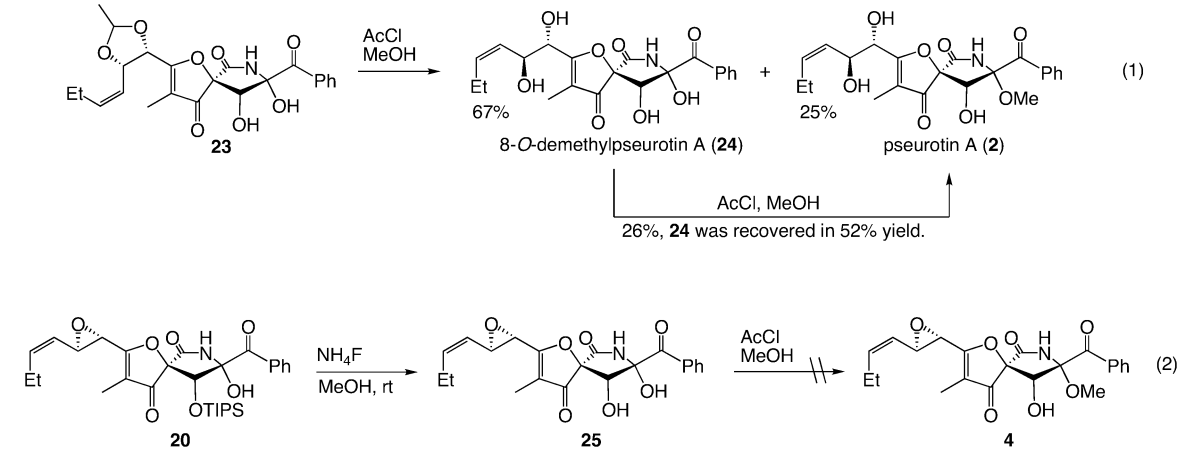
SCHEME 2. Synthetic Scheme of Epoxyaldehyde (−)-6 and (+)-6



SCHEME 3. Synthesis of 4



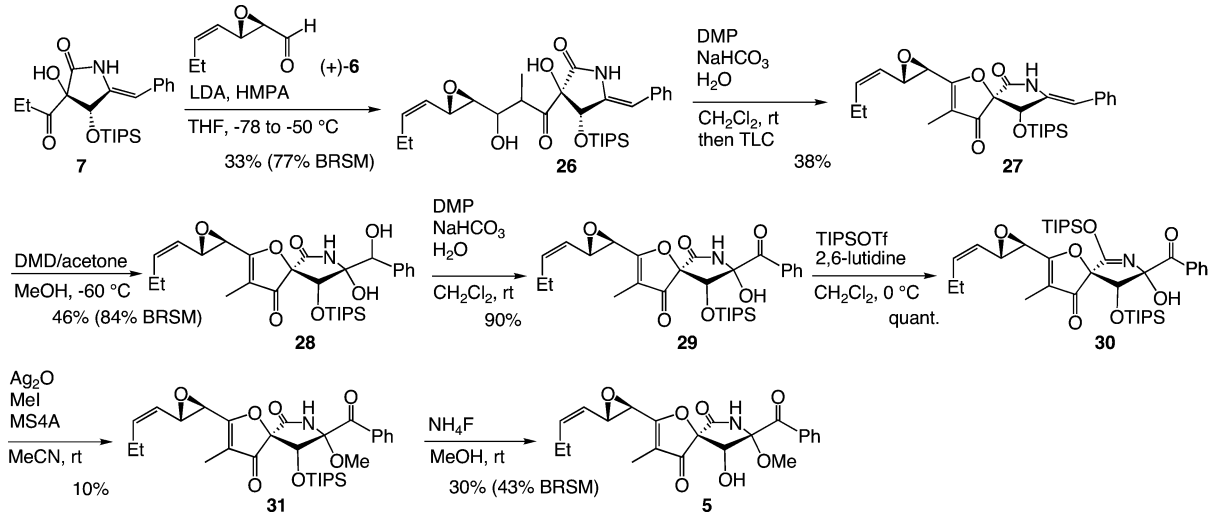
SCHEME 4



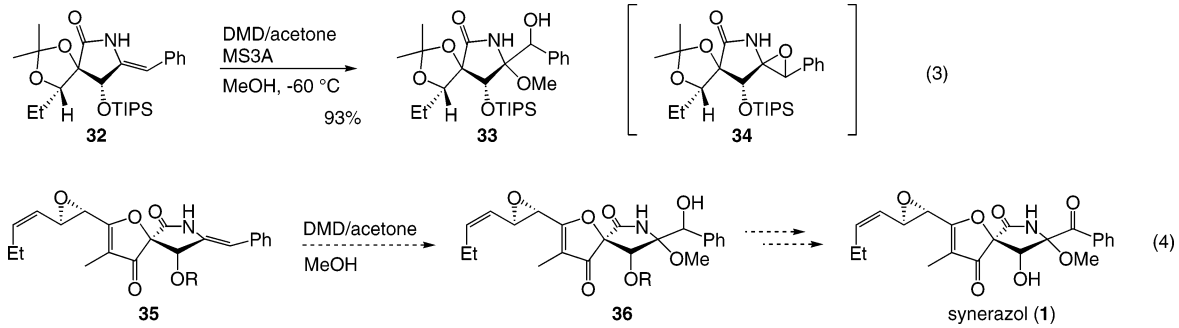
such as TsOH·H_2O or pyridinium *p*-toluenesulfonate (PPTS), decomposition also occurred without formation of **4**.

We next employed the Williamson ether synthesis. When **20** was treated with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) and 2,6-lutidine, *O*-sily-

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**.

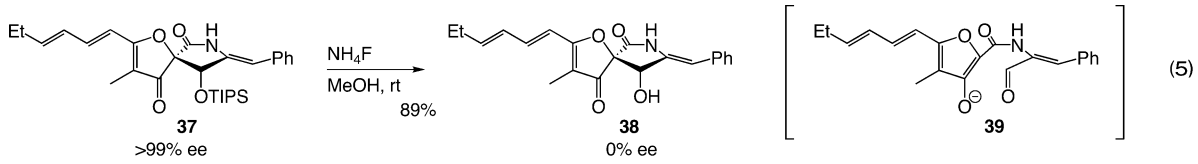
Should it be possible to oxidize the benzylidene moiety of azaspiro compound **35** with DMD to afford methyl ether **36** directly (eq 4, Scheme 6), the poor reaction for introducing the methyl ether in the first generation synthesis could be avoided.

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

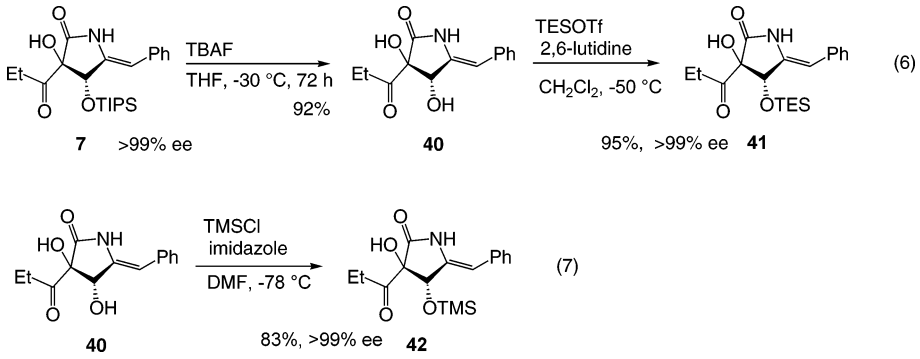
(13) Greene, A. E.; Drian, C. L.; Crabbe, P. *J. Am. Chem. Soc.* **1980**, *102*, 7583.

(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).

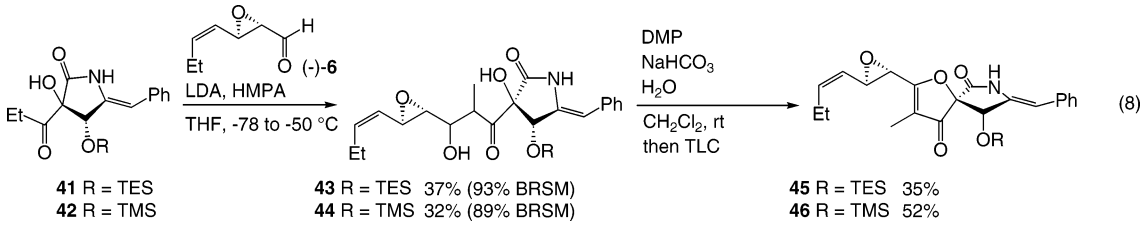
SCHEME 7



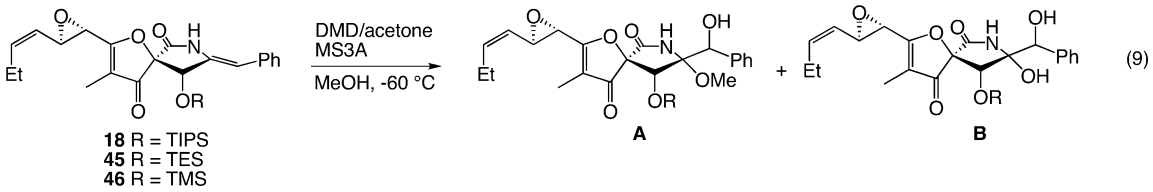
SCHEME 8



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

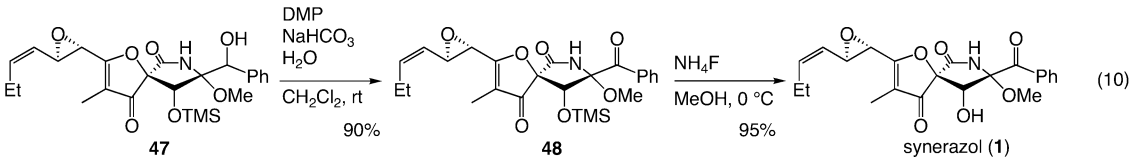
[a] Isolated yield.

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).

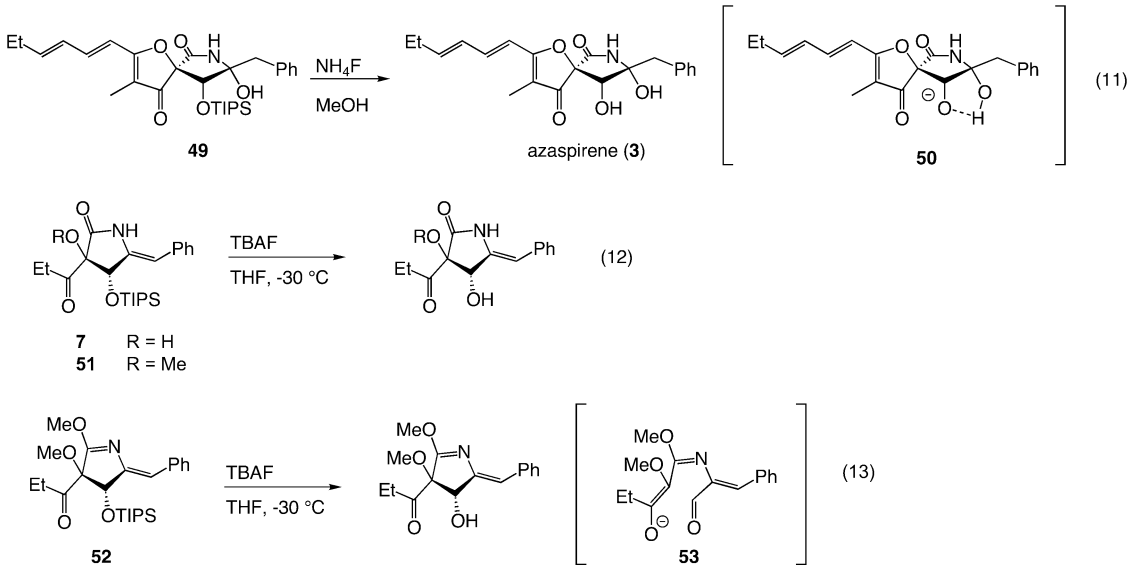
With the benzylidene derivatives **45** and **46** in hand, the oxidation with DMD was investigated. The benzylidene derivatives with different protecting groups were treated with DMD in MeOH in the presence of MS3A at low temperature (−60 °C), with the results summarized in Table 1.

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).

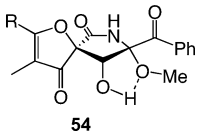
As the hydroxy group of γ-lactam **7** might play a role, we examined the racemization of 3-methoxy γ-lactam **51**. We also investigated dimethoxy compound **52**. Their racemization behavior is summarized in Table 2. No racemization occurred in the cases of γ-lactam **7** and methoxy γ-lactam **51**, 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,



54

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 $[n\text{-}PrPPh_3]^+$-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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