JOC Article

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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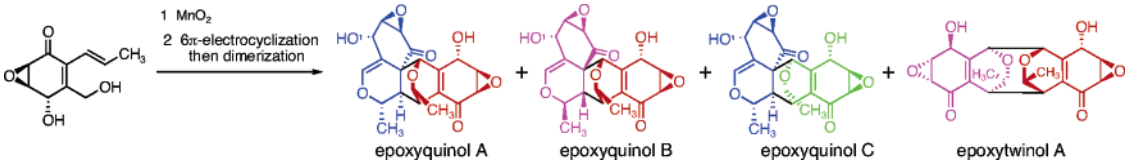

Full details of two versions of the total synthesis of epoxyquinols A, B, and C and epoxytwinol A (RKB-3564D) are described. In the first-generation synthesis, the $HfCl_4$-mediated diastereoselective Diels−Alder reaction of furan with Corey's chiral auxiliary has been developed. In the second-generation 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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(1) (a) Folkman, J. *J. Natl. Cancer Inst*. **1990**, *82*, 4. (b) Risau, W. *Nature* **1997**, *386*, 671. (c) Klagsbrum, M.; Moses, M. A. *Chem. Biol*. **1999**, *6*, R217. (d) Gasparini, G. *Drugs* **1998**, *58*, 17.

(2) Kakeya, H.; Onose, R.; Koshino, H.; Yoshida, A.; Kobayashi, K.; Kageyama, S.-I.; Osada, H. *J. Am. Chem. Soc*. **2002**, *124*, 3496.

(3) Kakeya, H.; Onose, R.; Yoshida, A.; Koshino, H.; Osada, H. *J. Antibiot.* **2002**, *55*, 829.

(4) Kakeya, H.; Osada, H. Unpublished work.

(5) (a) Osada, H.; Kakeya, H.; Konno, H.; Kanazawa, S. PCT Int. Appl. 2002, WO 02088137. (b) Kakeya, H., Onose, R. Koshino, H. Osada, H. A manuscript is in preparation.

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

(7) Asami, Y.; Kakeya, H.; Onose, R.; Chang, Y.-H.; Toi, M.; Osada, H. *Tetrahedron* **2004**, *60*, 7085.

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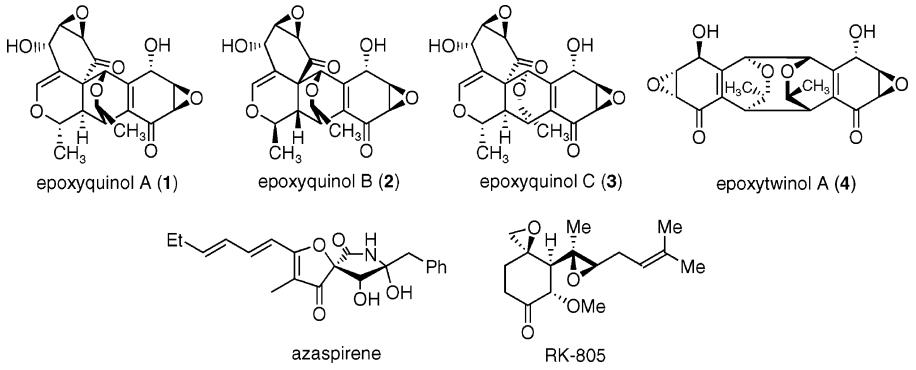
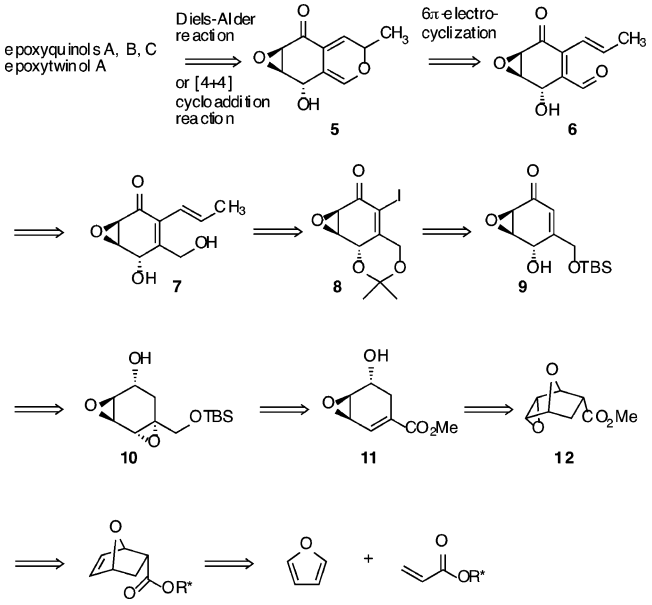


FIGURE 1. Epoxyquinols A, B, and C, epoxytwinol A, azaspirene, and RK-805.

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-

(8) (a) Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3192. (b) Shoji, M.; Kishida, S.; Takeda, M.; Kakeya, H.; Osada, H.; Hayashi, Y. *Tetrahedron Lett.* **2002**, *43*, 9155.

(9) 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.

(10) See: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: Chichester, UK, 1976; p 103.

(11) Li, C.; Bardhan, S.; Pace, E. A.; Liang, M.-C.; Gilmore, T. D.; Porco, J. A., Jr. *Org. Lett.* **2002**, *4*, 3267.

(12) Li, C.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 1310.

(13) (a) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2003**, *44*, 3569. (b) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2004**, *45*, 3611.

(14) Imada, S.; Kuwahara, S. *Abstracts of Annual Meeting of Japan Society for Bioscience, Biotechnology, and Agrochemistry, Hiroshima, Japan,* March 30th, 2004, p 274.

(15) (a) Lee, J. C.; Yang, X.; Schwartz, M.; Strobel, G.; Clardy, J. *Chem. Biol.* **1995**, *2*, 721. (b) Lee, J. C.; Strobel, G. A.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 3232. (c) Jarvis, B. B. *Chemtracts: Org. Chem.* **1997**, *10*, 10.

(16) (a) Li, C.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10484. (b) Li, C.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 5095.

(17) Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1741.

(18) (a) Shoji, M.; Kishida, S.; Kodera, Y.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *Tetrahedron Lett.* **2003**, *44*, 7205. (b) Shoji, M.; Imai, H.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *J. Org. Chem.* **2004**, *69*, 1548.

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.

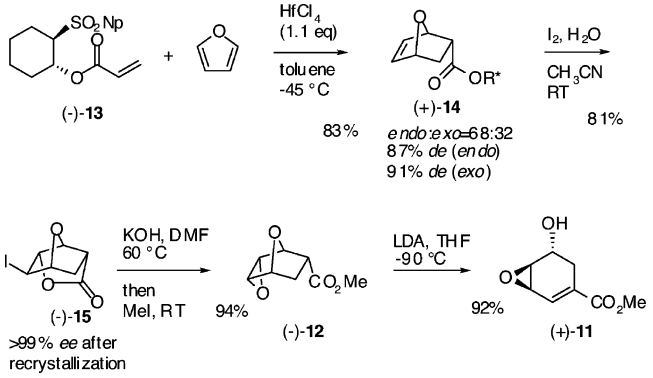
In this retrosynthetic analysis, there are several noteworthy features that should be pointed out: Synthesis of derivatives with different side-chains should be accessible because the side-chain is introduced at a late stage of the monomer synthesis by a Suzuki coupling reaction. All the carbon atoms 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

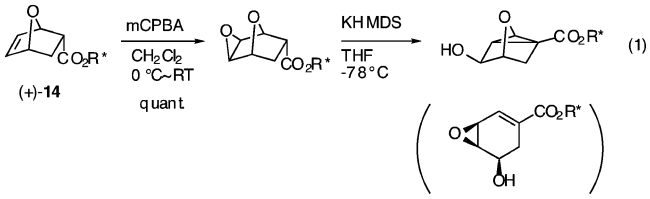
(20) Recent review of asymmetric Diels−Alder reactions: Hayashi, Y. *Catalytic Asymmetric Diels−Alder Reactions* in *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2001, pp 5−56. Review of Diels−Alder reaction of furan: Kappe, C. O.; Murphree, 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%).

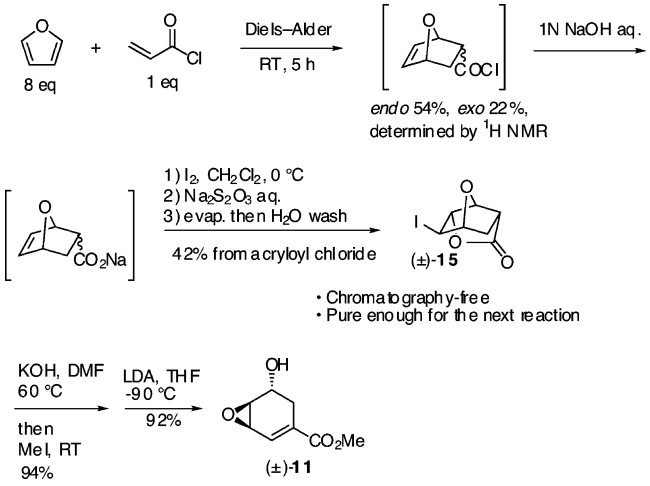


Exposure of (−)-**12** to LDA at −90 °C for 30 min led to β-elimination, affording hydroxyester (+)-**11**. Low temperature and an exact equivalent of LDA are both essential for high yield in this step; otherwise, Michael addition of diisopropylamine to (+)-**11** occurs, generating a β-aminoester as 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 (^{1}H 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.

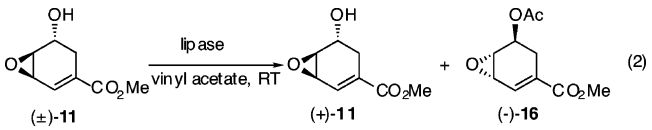


TABLE 1. Kinetic Resolution of Cyclohexenol (±)-11 Using Various Lipases[a]

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

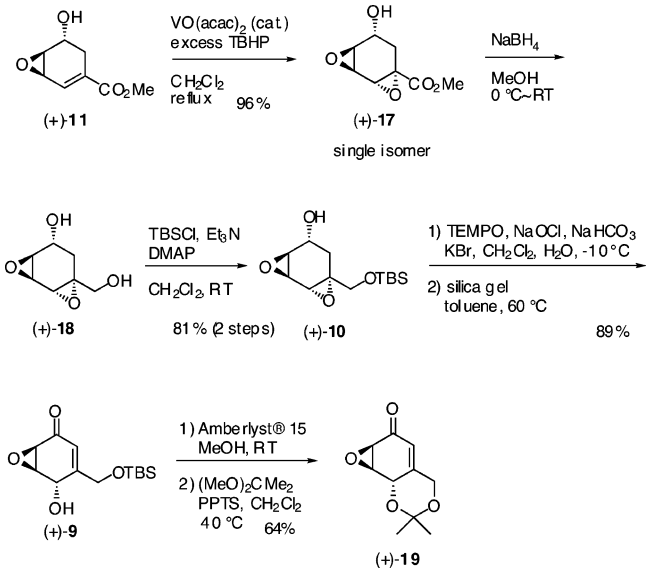
[a] Reaction was performed with 10 wt % lipase TL. [b] Determined by ^{1}H NMR. [c] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel OD-H column. [d] Once-recycled lipase TL was employed. [e] Twice-recycled lipase TL was employed.

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

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

(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.

(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.

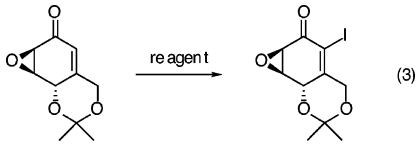


TABLE 3. α-Iodonation of (+)-19 under Various Reaction Conditions

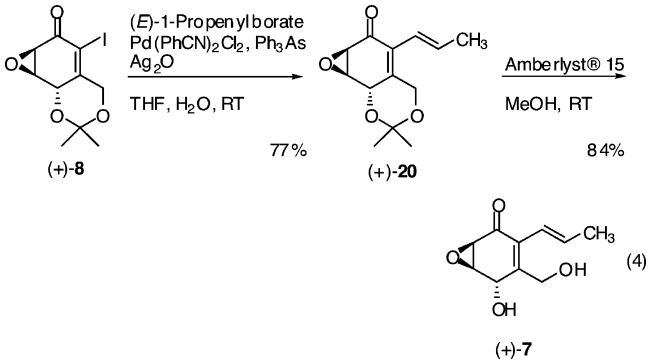
entry	reagent	temp (°C)	time (h)	yield (%)[a]
1	I_2, $PhI(OCOCF_3)_2$, pyridine	23	4	10
2	I_2, $PhI(OCOCF_3)_2$, pyridine	23	6	52
3	I_2, $PhI(OCOCF_3)_2$, pyridine	23	6.5	<5[b]
4	I_2, $PhI(OCOCF_3)_2$, pyridine, cat BHT	23	20	86
5	I_2, DMAP, pyridine	23−70	30	0[c]
6	NaN_3, ICl	−23−23	22	0[b]
7	I_2, CH_3CO_2Ag,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



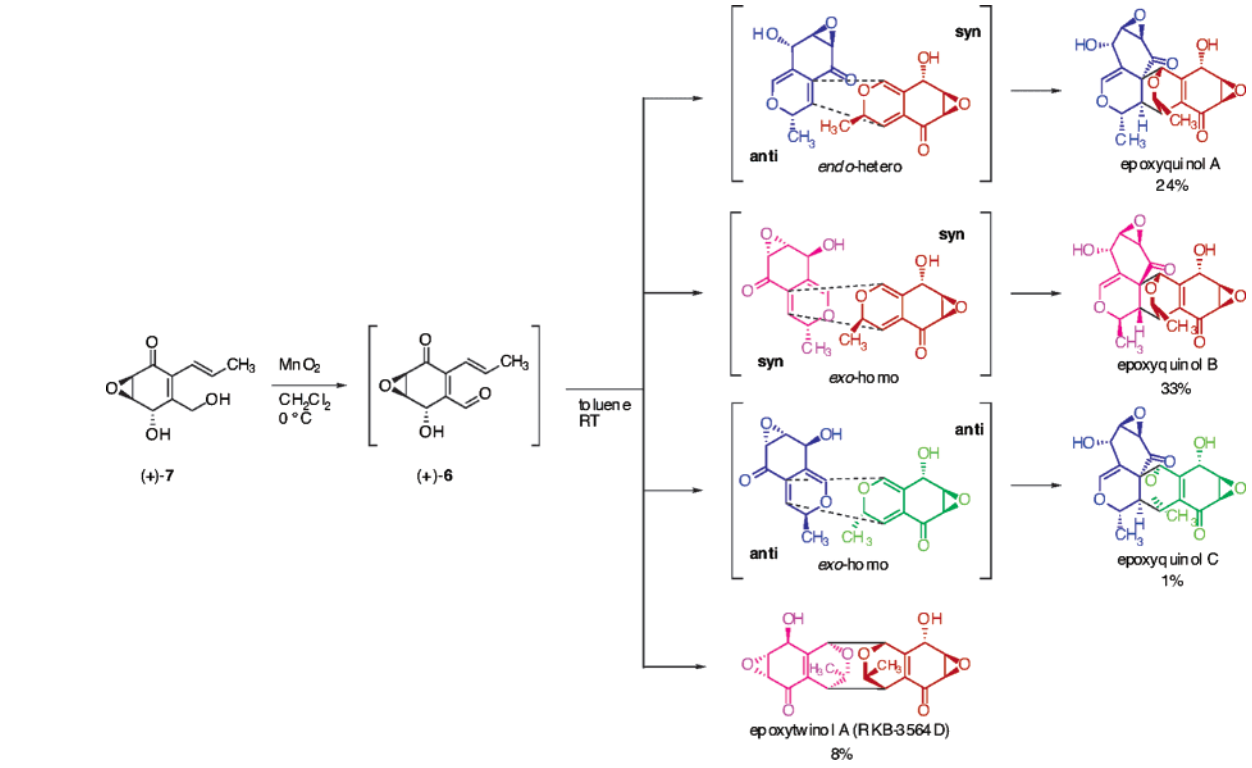
Biomimetic, Oxidative Dimerization of Monomer (+)-7. With the monomer (+)-**7** in hand, we examined its dimerization. In our previous paper, we reported the first total synthesis of epoxyquinols A and B, which resulted from the biomimetic transformation involving a cascade of reactions composed of oxidation, 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.

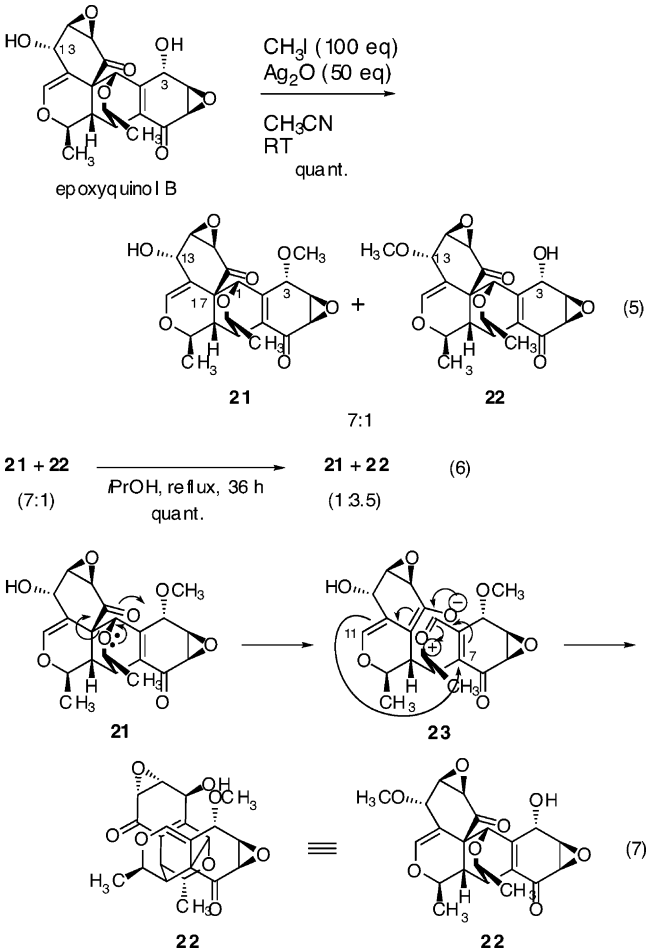
Isomerization Reaction of a Monomethyl Ether of Epoxyquinol B. As we had observed the facile transformation of epoxytwinol A into epoxyquinol B during isolation of the former from the unidentified fungus, we investigated whether the reverse, conversion of epoxyquinol B into epoxytwinol A, could be realized, 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

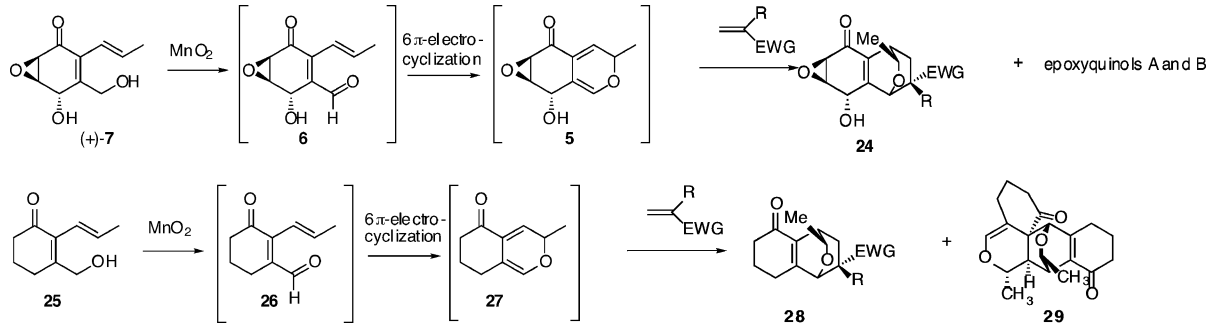
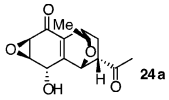
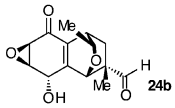
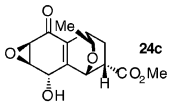
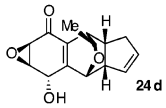
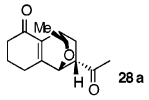
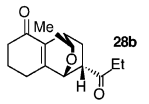
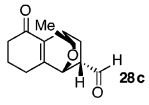
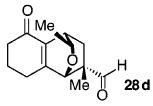
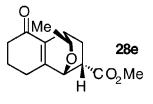
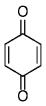
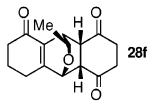
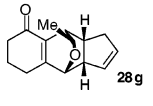


TABLE 4. Cascade Reaction of (+)-7 and 25 with Several Dienophiles

Entry	Cyclohexenone	Dienophile	Product	Yield/%[a]
1	(+)-**7**		 **24a**	64
2	(+)-**7**		 **24b**	69
3	(+)-**7**		 **24c**	56
4	(+)-**7**		 **24d**	45
5	**25**		 **28a**	76
6	**25**		 **28b**	70
7	**25**		 **28c**	52
8	**25**		 **28d**	63
9	**25**		 **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.

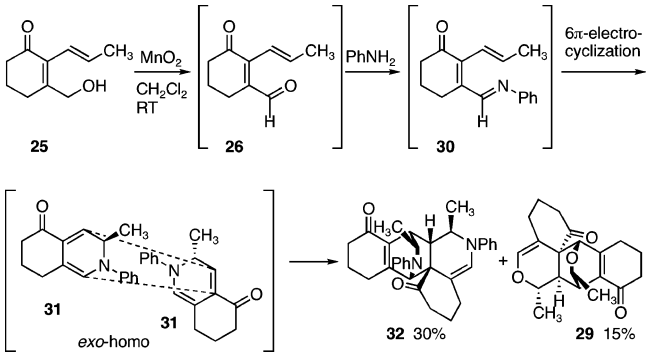
The 2*H*-pyrans **5** and **27**, acting as a diene, reacted with reactive dienophiles such as methyl vinyl ketone, ethyl vinyl ketone, acrolein, methacrolein, methyl acrylate, and benzoquinone, affording polycyclic compounds in moderate to good yield (52−76%) along with the self-dimerized product in 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*,7S)-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*,7S)-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,

848, 518 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{10}H_{12}O_4I$ 322.9780, found 322.9791; $[\alpha]^{27}_D$ +206 (*c* 1.35, MeOH).

(4*R*,6*R*,7S)-9,9-Dimethyl-2-(*E*)-propenyl-5,8,10-trioxatricyclo[5.4.0.0^{4,6}]undec-1-en-3-one ((+)-20). To a solution of iodoenone (+)-**8** (8.0 mg, 0.025 mmol), (*E*)-prppenyl borate (6.6 mg, 0.077 mmol) Ag_2O (18.4 mg, 0.079 mmol) and Ph_3As (1.5 mg, 0.0050 mmol) in THF−H_2O (10:1, 0.5 mL) was added $Pd(PhCN)_2Cl_2$ (1.0 mg, 0.0025 mmol) and stirred at room temperature for 11 h in the dark. To the reaction mixture was added saturated NH_4Cl (aq) (2 mL) and stirred for 1 h at that temperature. The reaction mixture was filtered through a pad of Celite 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 preparative thin-layer chromatography (Et_2O/benzne = 1/6) to afford dienone (+)-**20** (4.5 mg, 77%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.51 (3H, s), 1.82 (3H, dd, J = 6.5, 1.1 Hz), 3.48 (1H, d, J = 3.5 Hz), 3.69 (1H, d, J = 3.5 Hz), 4.59 (1H, d, J = 16.8 Hz), 4.64 (1H, d, J = 16.8 Hz), 4.88 (1H, s), 5.89 (1H, qd, J = 16.0, 6.5 Hz), 6.06 (1H, d, J = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 24.8, 25.5, 53.1, 57.1, 63.0, 63.8, 101.5, 121.0, 127.9, 134.8, 148.7, 190.9; FT-IR (neat) ν 2989, 2931, 2854, 1682, 1385, 1373, 1238, 1082, 1038, 858 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{13}H_{17}O_4$ 236.1049, found 236.1053; $[\alpha]^{25}_D$ +231 (*c* 0.73, MeOH).

(1*R*,5*S*,6*R*)-5-Hydroxy-4-hydroxymethyl-3-(*E*)-propenyl-7-oxabicyclo[4.1.0]hept-3-en-2-one ((+)-7). To a solution of acetonide (+)-**20** (9.0 mg, 0.038 mmol) in MeOH (0.8 mL) was added Amberlyst 15 (9 mg), and the mixture was stirred at room temperature for 40 min. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (AcOEt) to afford epoxycyclohexenol ((+)-**7**) (6.2 mg, 84%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 (3H, dd, J = 6.2, 1.0 Hz), 2.10 (1H, bs), 3.13 (1H, bd, J = 3.9 Hz), 3.56 (1H, dd, J = 3.9, 0.7 Hz), 3.82 (1H, dd, J = 3.9, 1.5 Hz), 4.49 (1H, d, J = 14.2 Hz), 4.77 (1H, d, J = 14.2 Hz), 5.00 (1H, bs), 5.96 (1H, qd, J = 16.0, 6.2 Hz), 6.06 (1H, d, J = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 53.4, 55.6, 63.0, 65.2, 121.6, 131.0, 135.3, 146.3, 194.3; FT-IR (neat) ν 3371, 2916, 1676, 1444, 1373, 1051, 968, 868 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{10}H_{12}O_4$ 196.0736, found 196.0732; $[\alpha]^{25}_D$ +285 (*c* 0.41, MeOH).

Epoxyquinols A (1), B (2), and C (3) and Epoxytwinol A (4). To a solution of (+)-**7** (78.9 mg, 0.402 mmol) in dry CH_2Cl_2 (8 mL) was added MnO_2 (700 mg, 75%, 6.03 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred for 1 h at that temperature. The reaction mixture was filtered through a pad of Celite, washed with AcOEt, and then concentrated in vacuo. The residue was diluted with toluene (8 mL) and allowed to stand at room temperature for 10 h and purified by silica gel column and preparative thin-layer chromatography (MeOH/$CHCl_3$ = 1/10) to afford epoxyquinol A (**1**) (18.9 mg, 24%, colorless solid), epoxyquinol B (**2**) (25.0 mg, 33%, colorless oil), epoxyquinol C (**3**) (0.8 mg, 1%, colorless oil), and epoxytwinol A (**4**) (6.0 mg, 8%, colorless oil). **(1*S*,2*R*,4*R*,6*R*,7*S*,11*S*,12*R*,13*S*,16*R*,18*R*,19*S*,22*R*)-7,19-Dihydroxy-11,22-dimethyl-5,10,17,21-tetraoxaheptacyclo[11.7.2.0^{2,8}.0^{2,12}.0^{4,6}.0^{14,20}.0^{16,18}]docosa-8,14(20)-diene-3,15-dione (Epoxyquinol A (1)):**[2] ^1H NMR (400 MHz, acetone-d_6) δ 0.71 (3H, d, J = 6.2 Hz), 1.00 (3H, d, J = 6.7 Hz), 2.44 (1H, bd, J = 1.3 Hz), 3.10 (1H, bd, J = 1.4 Hz), 3.38 (1H, d, J = 3.6 Hz), 3.43 (1H, bd, J = 4.5 Hz), 3.70−3.76 (2H, m), 4.30 (1H, qd, J = 6.2, 1.2 Hz), 4.42 (1H, qd, J = 6.7, 1.0 Hz), 4.63 (1H, bd, J = 8.8 Hz), 4.69 (1H, bd, J = 8.8 Hz), 4.89−4.97 (2H, m), 5.23 (1H, s), 6.73 (1H, d, J = 1.7 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 20.3, 20.9, 38.1, 39.3, 50.7, 53.6, 56.3, 58.8, 63.9, 64.2, 66.7, 67.0, 72.4, 74.8, 115.1, 134.4, 142.5, 153.5, 190.2, 200.7; $[\alpha]^{23}_D$ +63.1 (*c* 0.945, MeOH), lit.[2]) $[\alpha]^{21}_D$ +61.0 (*c* 0.146, MeOH).

(1*S*,2*S*,4*R*,6*R*,7*S*,11*R*,12*S*,13*S*,16*R*,18*R*,19*S*,22*R*)-7,19-Dihydroxy-11,22-dimethyl-5,10,17,21-tetraoxaheptacyclo[11.7.2.0^{2,8}.0^{2,12}.0^{4,6}.0^{14,20}.0^{16,18}]docosa-8,14(20)-diene-3,15-dione (Epoxyquinol B (2)):[3] ^1H NMR (400 MHz, acetone-d_6) δ 0.73 (3H, d, J = 6.4 Hz), 1.27 (3H, d, J = 6.4 Hz), 2.79 (1H, dd, J = 8.6, 3.0 Hz), 3.12 (1H, dd, J = 3.0, 1.0 Hz), 3.31 (1H, dq, J = 8.6, 6.4 Hz), 3.48 (1H, dd, J = 3.1, 0.7 Hz), 3.50 (1H, dd, J = 3.9, 0.8 Hz), 3.66 (1H, dd, J = 3.1, 1.8 Hz), 3.85 (1H, dd, J = 3.6, 1.6 Hz), 4.04 (1H, qd, J = 6.4, 1.0 Hz), 4.60 (1H, bs), 4.81 (1H, bs), 5.18 (1H, s), 5.78 (1H, bs), 5.84 (1H, bs), 6.61 (1H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 19.6, 20.5, 36.9, 42.2, 53.0, 53.3, 53.3, 55.4, 57.0, 64.4, 68.6, 70.5, 73.7, 74.9, 107.0, 133.0, 150.9, 151.9, 191.9, 200.0; $[\alpha]^{23}_D$ +151 (*c* 0.710, MeOH); lit.[3]) $[\alpha]^{21}_D$ +153 (*c* 0.315, MeOH).

(1*R*,2*R*,4*R*,6*R*,7*S*,11*S*,12*R*,13*R*,16*R*,18*R*,19*S*,22*S*)-7,19-Dihydroxy-11,22-dimethyl-5,10,17,21-tetraoxaheptacyclo[11.7.2.0^{2,8}.0^{2,12}.0^{4,6}.0^{14,20}.0^{16,18}]docosa-8,14(20)-diene-3,15-dione (Epoxyquinol C (3)):[11] ^1H NMR (400 MHz, acetone-d_6) δ 0.72 (3H, d, J = 6.4 Hz), 1.14 (3H, d, J = 6.4 Hz), 3.06 (1H, dd, J = 8.0, 3.0 Hz), 3.12 (1H, dd, J = 2.9, 1.2 Hz), 3.31 (1H, dq, J = 7.9, 6.4 Hz), 3.47 (1H, dd, J = 3.5, 1.0 Hz), 3.49 (1H, bd, J = 3.6 Hz), 3.80 (1H, d, J = 3.6 Hz), 3.83 (1H, dd, J = 3.5, 1.0 Hz), 3.97 (1H, qd, J = 6.4, 1.2 Hz), 4.57 (1H, bs), 5.00 (2H, bs), 5.27 (1H, s), 5.59 (1H, s), 6.64 (1H, d, J = 1.9 Hz).

(1*S*,2*S*,4*S*,5*R*,7*R*,10*S*,11*S*,14*R*,16*R*,17*S*,20*R*,22*R*)-4,17-Dihydroxy-20,22-dimethyl-6,15,19,21-tetraoxaheptacyclo[9.7.2.2^{2,10}.0^{3,9}.0^{5,7}.0^{12,18}.0^{14,16}]docosa-3(9),12(18)-diene-8,13-dione (Epoxytwinol A (4)):[5a] ^1H NMR (270 MHz, acetone-d_6) δ 0.77 (6H, d, J = 6.2 Hz), 3.21 (2H, bs), 3.53 (2H, dd, J = 3.7, 1.0 Hz), 3.85 (2H, dd, J = 3.7, 1.0 Hz), 4.20 (2H, q, J = 6.4 Hz), 4.38 (2H, d, J = 9.7 Hz), 4.60 (2H, bd, J = 9.7 Hz), 4.80 (2H, s).

(1*S*,2*S*,4*R*,6*R*,7*S*,11*R*,12*S*,13*S*,16*R*,18*R*,19*S*,22*R*)-7-Hydroxy-19-methoxy-11,22-dimethyl-5,10,17,21-tetraoxaheptacyclo[11.7.2.0^{2,8}.0^{2,12}.0^{4,6}.0^{14,20}.0^{16,18}]docosa-8,14(20)-diene-3,15-dione (21). To a solution of epoxyquinol B (3.0 mg, 0.0077 mmol) and iodomethane (48 μL, 0.77 mmol) in CH_3CN (0.5 mL) was added Ag_2O (90 mg, 0.39 mmol), and the mixture was stirred at room temperature for 5 h in the dark. The reaction mixture was filtered through a pad of Celite and washed with AcOEt. The filtrate was concentrated in vacuo, and the residue was purified by preparative thin-layer chromatography (AcOEt) to afford a 7:1 mixture of 3-methoxy epoxyquinol B (**21**) and 13-methoxy epoxyquinol B (**22**) (3.1 mg, 100%, colorless solid): ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (3H, d, J = 6.4 Hz), 1.27 (3H, d, J = 6.4 Hz), 2.76 (1H, dd, J = 6.1, 2.7 Hz), 3.12 (1H, br-d, J = 2.5 Hz), 3.46 (1H, d, J = 3.2 Hz), 3.54 (3H, s), 3.55−3.60 (2H, m), 3.66 (1H, br-t, J = 2.6 Hz), 3.88 (1H, d, J = 3.5 Hz), 4.18 (1H, br-q, J = 6.4 Hz), 4.25 (1H, s), 4.53 (1H, br-d, J = 1.8 Hz), 4.68 (1H, s), 5.13 (1H, s) 6.43 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 19.9, 37.3, 42.0, 52.5, 52.7, 54.1, 54.7, 55.9, 67.6, 70.6, 72.4, 73.0, 74.2, 78.3, 107.1, 135.2, 146.3, 148.6, 189.9, 199.3; HRMS (FAB) [M + H]$^+$ calcd for $C_{21}H_{23}O_8$ 403.1393, found 403.1399.

(1*S*,2*S*,4*R*,6*R*,7*S*,11*R*,12*S*,13*S*,16*R*,18*R*,19*S*,22*R*)-19-Hydroxy-7-methoxy-11,22-dimethyl-5,10,17,21-tetraoxaheptacyclo[11.7.2.0^{2,8}.0^{2,12}.0^{4,6}.0^{14,20}.0^{16,18}]docosa-8,14(20)-diene-3,15-dione (22). A solution of 3-methoxy epoxyquinol B and 13-methoxy epoxyquinol B (7:1 mxture, 1.5 mg) in 2-propanol (0.5 mL) was refluxed for 36 h. The reaction mixture was concentrated in vacuo to afford 3.5:1 mixture of **22** and **21**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (3H, d, J = 6.4 Hz), 1.33 (3H, d, J = 6.3 Hz), 2.86 (1H, dd, J = 8.9, 3.1 Hz), 3.11 (1H, br-d, J = 3.0 Hz), 3.29 (1H, dq, J = 8.9, 6.3 Hz), 3.48−3.53 (2H, m), 3.71 (3H, s), 3.73 (1H, dd, J = 2.9, 1.3 Hz), 3.82 (1H, dd, J = 3.6, 1.3 Hz), 4.10 (1H, br-q, J = 6.4 Hz), 4.11 (1H, s), 4.76 (1H, s), 4.88 (1H, s), 5.06 (1H, d, J = 1.3 Hz) 6.60 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 20.2, 35.9, 41.0, 51.0, 52.4, 52.6, 56.1, 58.0, 63.4, 63.8, 69.7, 72.8, 74.6, 78.3, 103.5, 132.3, 150.6, 152.4, 190.9, 197.9.

General Procedure of Table 4. To a solution of alcohol **25** (5.0 mg, 0.030 mmol) in dry CH_2Cl_2 (0.3 mL) was added MnO_2 (209 mg, 75%, 1.80 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred for 1 h at that temperature. The reaction mixture was filtered through a pad of Celite, washed with AcOEt, and then concentrated at 0 °C in vacuo. To the residue was added methyl vinyl ketone (0.25 mL, 3.0 mmol), and the mixture was allowed to stand at room temperature for 10 h. The mixture was concentrated in vacuo and purified by preparative thin-layer chromatography (AcOEt/hexane = 1/1) to afford **28a** (5.2 mg, 76%, colorless oil).

***rel*-(1*S*,8*R*,10*R*,12*S*)-12-Acetyl-10-methyl-9-oxatricyclo-[6.2.2.0^{2,7}]dodec-2(7)-en-3-one (28a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, d, J = 6.1 Hz), 1.26 (1H, ddd, J = 12.3, 6.5, 2.6 Hz), 1.97−2.20 (6H, m), 2.44 (2H, t, J = 6.6 Hz), 2.57 (2H, t, J = 6.0 Hz), 3.19 (1H, bs), 3.29−3.39 (1H, m), 3.95 (1H, q, J = 6.1 Hz), 4.46 (1H, d, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 23.1, 27.3, 28.4, 29.7, 31.4, 37.4, 51.7, 70.2, 72.1, 134.7, 161.2, 195.8, 207.7; FT-IR (neat) ν 2966, 2925, 2864, 1712, 1664, 1456, 1194, 1173, 1014, 876 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{14}H_{19}O_3$ 235.1334, found 235.1327.

***rel*-(1*S*,2*S*,10*R*,11*S*,12*S*,20*R*)-10,20-Dimethyl-9,19-diphenyl-9,19-diazapentacyclo[10.6.2.0^{2,7}.0^{2,11}.0^{13,18}]icosa-7,13-(18)-diene-3,14-dione (32).** To a solution of alcohol **25** (42.0 mg, 0.253 mmol) in dry CH_2Cl_2 (1.0 mL) was added MnO_2 (1.17 g, 75%, 10.1 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred for 1 h at that temperature. The reaction mixture was filtered through a pad of Celite, washed with AcOEt, and then concentrated at 0 °C in vacuo. To the residue was added aniline (0.47 mL, 5.1 mmol), and the mixture was allowed to stand at room temperature for 12 h. The mixture was concentrated in vacuo and purified by alumina column chromatography (AcOEt/hexane = 1/10) and further recrystallization from AcOEt to afford azapentacycle **32** (18.1 mg, 30%, yellow prisms): mp 197.0−198.0 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (3H, d, J = 6.0 Hz), 1.00 (3H, d, J = 6.7 Hz), 1.68 (1H, qt, J = 13.6, 4.0 Hz), 1.93−2.27 (5H, m), 2.33−2.42 (2H, m), 2.56 (1H, ddd, J = 18.0, 7.9, 5.0 Hz), 2.63−2.80 (3H, m), 3.27 (1H, s), 3.40 (1H, s), 3.94 (1H, qd, J = 6.0, 2.1 Hz), 3.99 (1H, q, J = 6.7 Hz), 5.20 (1H, s), 6.18 (1H, s), 6.64 (1H, t, J = 7.2 Hz), 6.72 (4H, d, J = 7.2 Hz), 6.82 (1H, t, J = 7.2 Hz), 7.15 (2H, t, J = 7.5 Hz), 7.21 (2H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 16.8, 22.9, 27.6, 29.2, 29.4, 37.0, 39.4, 40.5, 43.9, 52.7, 53.8, 58.9, 59.2, 113.8, 113.8, 114.1, 117.1, 119.7, 125.1, 129.3, 129.3, 133.6, 144.7, 145.4, 156.5, 195.2, 206.0; FT-IR (film) ν 3058, 2968, 2929, 2864, 1705, 1668, 1595, 1504, 1404, 1246, 1030, 748, 694 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{32}H_{35}N_2O_2$ 479.2699, found 479.2693.

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Supporting Information Available: Full characterization of compound **24** and **28**, ORTEP drawing of compound **32**, and 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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