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Enantiocontrolled synthesis of the epoxycyclohexenone moieties of scyphostatin, a potent and specific inhibitor of neutral sphingomyelinase

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Abstract—The epoxycyclohexenone moieties **2** and **3b** of scyphostatin (**1**), a potent and specific inhibitor of neutral sphingomyelinase, were synthesized in enantiomerically pure forms starting from (−)-quinic acid (**11**). The synthetic method features (i) the preparation of the olefin masked enones **25** and **29**, the precursors for the key aldol-type coupling reaction, (ii) the efficient and stereocontrolled aldol-type coupling reactions between **25** (or **29**) and benzaldehyde (**8**) and Garner's aldehyde analogue **9** to deliver alcohols **23** and **24**, respectively, both of which possess the requisite asymmetric quaternary carbon center at the C6 position, and (iii) the stereospecific S_N2-type epoxide ring formation of the mesylates **35** and **47** under mild basic conditions to produce the targeted compounds **2** and **3b**, respectively.

1. Introduction

Recently, sphingomyelinase (SMase) inhibitors have received considerable attention from the biological and pharmacuetical standpoints.[1] SMase is the enzyme that specifically hydrolyzes the phosphoester linkage of sphingomyelin (SM), one of the most abundant sphingolipid species, to generate ceramide and phoshocholine.[2,3] The SM-derived ceramide is believed to be an intracellular lipid second messenger in cell membranes and to play important roles in the regulation of cell proliferation, differentiation, and apoptosis.[2,3] SMase inhibitors, therefore, are considered as valuable tools for the investigation of the biological function of the enzyme and the catabolite ceramide in signal transduction.[3] In addition, selective SMase inhibitors are highly anticipated to be promising candidates for the treatment of ceramide-mediated pathogenic states such as AIDS,[4] inflammation,[5] and immunological and neurological disorders.[6]

In 1997, Ogita et al. at the Sankyo research group reported the isolation and structure elucidation of a novel natural product, scyphostatin (**1**, Fig. 1), from the mycelial extract of *Trichopeziza mollissima* SANK 13892.[7,8] This natural product was found to be a powerful and specific inhibitor of membrane-bound neutral sphingomyelinase (N-SMase).[8] It has been reported that **1** inhibits N-SMase and acidic SMase (A-SMase) with IC_{50} values of 1.0 and 49.3 μM, respectively.[7,8] Remarkably, scyphostatin is the most potent and specific one among the many low molecular weight N-SMase inhibitors of natural sources[9] or of synthetic substances[10] known to date.

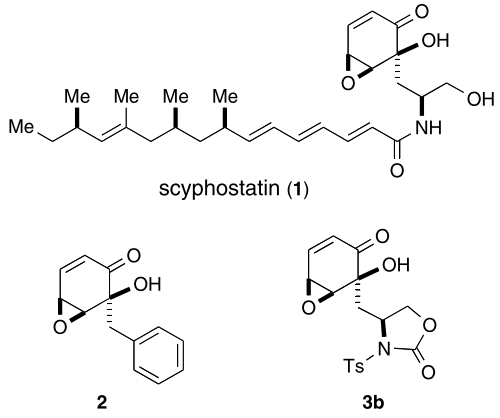

Figure 1. Structures of scyphostatin (**1**) and the epoxycyclohexeone moieties **2** and **3b**.

Keywords: Sphingomyelinase; Aldol-type coupling; Diels–Alder reaction.
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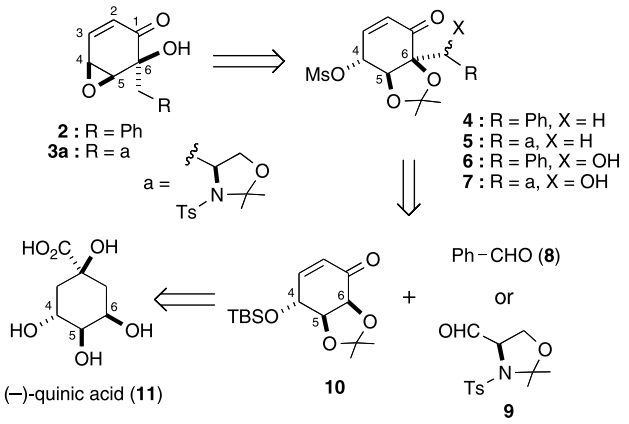
The gross structure of scyphostatin (**1**) was revealed by extensive and incisive spectroscopic studies.[7] It consists of a novel, highly oxygenated cyclohexenone ring incorporated with a C-20 unsaturated fatty acid-substituted aminopropanol side chain. This initial structure elucidation only established the relative and absolute stereochemistry of the cyclohexenone moiety of **1**.[7] In 2001, Kogen et al. at the Sankyo research group determined the relative and absolute configurations of the three stereogenic centers present in the fatty acid side chain.[11] At the almost same time, Hoye et al. disclosed an enantioselective synthesis of the C-20 unsaturated fatty acid moiety and provided alternative proof of its stereostructure including the absolute configuration.[12]

The remarkable biological properties and unique structural features make **1** an exceptionally intriguing and timely target for total synthesis. So far, a number of synthetic approaches toward scyphostatin (**1**) have been reported by Gurujar's group,[13] Taylor's group,[14] Ohkata's group,[15] Kita's group,[16] Maier's group,[17] Negishi's group,[18] and Pitsino's group.[19] We have already reported our own preliminary results concerning the enantioselective synthesis of the epoxycylohexenone substructures **2** and **3b**[20] (Fig. 1). Additionally, we have also disclosed an efficient method for the introduction of a fatty acid side chain at the amino propanol moiety.[21] In 2004, our assiduous endeavors culminated in the completion of the first total synthesis of (+)-**1**.[22] In this paper, we wish to disclose the full details of our first-generation synthesis of the epoxycyclohexenone moieties **2** and **3b** of scyphostatin (**1**).

2. Results and discussion

2.1. Primary synthetic plan for the epoxycyclohexenone moieties 2 and 3a

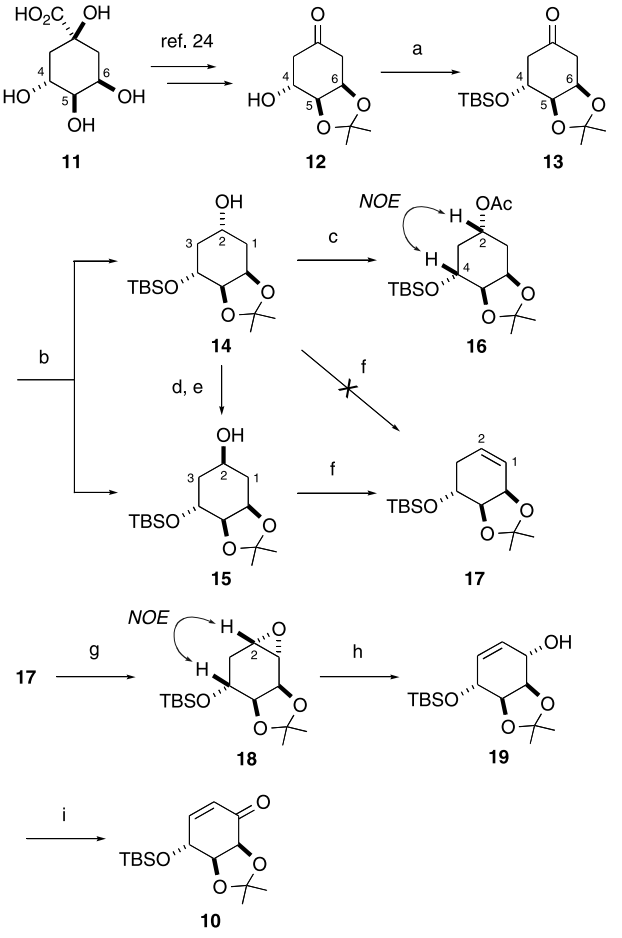
Our primary synthetic plan for the epoxycyclohexenone moieties **2** and **3a** is outlined in Scheme 1. The key feature of this plan is aldol-type coupling reactions between the cyclohexenone **10** and the aldehydes **8** and **9** to form the coupling products **6** and **7**, respectively (**10**+**8**→**6** and **10**+**9**→**7**). In these reactions, we envisioned that electrophiles **8** and **9** would approach exclusively from the less hindered α-face of the enolate, generated in situ from **10**, under the influence of the β-oriented *O*-isopropylidenedioxy moiety, thus leading to establishment of the requisite asymmetric quaternary carbon center at the C6 position (cyclohexeneone numbering)[23] in **6** and **7**. This type of coupling reaction is considerably challenging at the synthetic chemistry level, because the substrate **10** possesses unusual trihydroxy functionalities at the C4, C5, and C6 positions, and in addition, an electrophilic enone system. The coupling products **6** and **7** would be converted to the target molecules **2** and **3a** through the advanced key intermediates **4** and **5**, respectively, by sequential functional group manipulation and deprotection, or vice versa; the sequence involves deoxygenation of the secondary hydroxy group in the side chain and stereospecific S_N2-type epoxide ring formation as the crucial steps. The cyclohexenone **10** having three contiguous oxygen functionalities at the C4, C5, and C6 positions with correct stereochemistries would be derived from commercially available (−)-quinic acid (**11**).



Scheme 1. Primary synthetic plan for the epoxycyclohexeone moieties **2** and **3a**.

2.2. Synthesis of the intermediate 10

At first, as shown in Scheme 2, we pursued the synthesis of the intermediate **10**, a substrate for the key aldol-type coupling reaction, starting from commercially available (−)- quinic acid (**11**). The known cyclohexanone **12**[24] was



Scheme 2. Synthesis of the intermediate **10**. (a) TBSCL, imidazole, DMF, rt, 98%; (b) $NaBH_4$, THF–H_2O, −5 °C→rt, 53% for **14**, 44% for **15**; (c) Ac_2O, pyridine, DMAP, 0 °C→rt, 98%; (d) DEAD, Ph_3P, benzonic acid, THF, 0 °C→98%; (e) 2 M KOH–MeOH, rt, quant.; (f) DEAD, Ph_3P, THF, rt, 67% for **15**→**17**, 0% for **14**→**17**; (g) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C→rt, 92%; (h) Se_2Ph_2, $NaBH_4$, EtOH, 0 °C→reflux; H_2O_2, THF, 0 °C→reflux, 78%; (i) Dess–Martin periodinane, CH_2Cl_2, rt, 95%.

readily and sufficiently prepared from **11** in three steps [(1) dimethoxypropane/*p*-TsOH/acetone, reflux, 80%; (2) $LiAlH_4$/THF, reflux, quant.; (3) $NaIO_4$/*t*-BuOH–THF–AcOH, room temperature, quant.] according to the reported procedure.[24] After protection of the hydroxy group in **12** as its *t*-butyldimethylsilyl (TBS) ether, the carbonyl function of the resulting TBS ether **13** was subjected to reduction with sodium borohydride to furnish an epimeric mixture of the alcohols **14** (53%) and **15** (44%) that were separated by silica gel column chromatography. The newly formed C2 stereochemistry of the two isomers was assigned on the basis of spectroscopic studies. The NOESY experiment of the acetate **16** derived from **14** showed a clear interaction between C2–H and C4–H.

We next examined installation of an olefinic double bond by dehydration of **14** and **15**. Thus, reaction of **15** with diethyl azodicarboxylate (DEAD) and triphenylphosphine provided the desired olefin **17** in 67% yield with complete regioselectivity at the C1–C2 position. On the contrary, treatment of the C2 epimeric alcohol **14** under the same dehydration conditions afforded none of the desired olefinic product **17**, and the unreacted starting material **14** was recovered unchanged. Therefore, the alcohol **14** was converted to **15** by employing the Mitsunobu inversion procedure[25] (98% overall yield). The difference of the reactivity between **14** and **15** under the dehydration conditions can be rationalized by conformational analyses of both **14** and **15** (Fig. 2). Thus, the NOESY experiment of **15** indicated that the cyclohexane ring takes a boat-form, which places the C2 hydroxy group in an axial position; this conformation may facilitate E2 elimination to afford the desired $\Delta^{1,2}$ olefin **17**. On the other hand, the NOESY experiment of **14** indicated that the C2 hydroxy group is in equatorial orientation within the boat-formed cyclohexane ring; this conformation would preclude any possibility of E2 elimination.

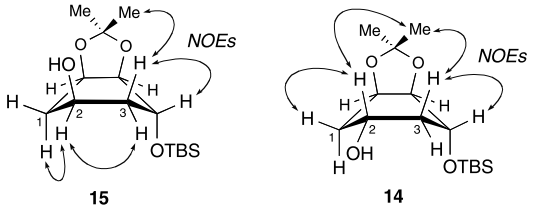
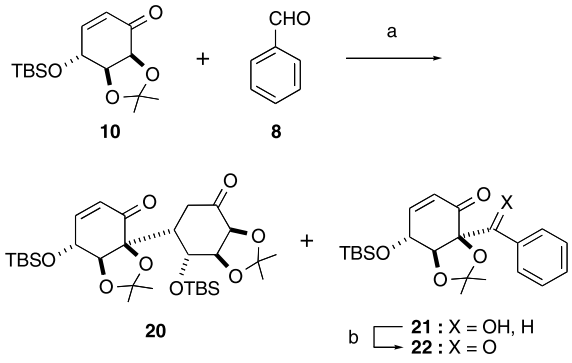


Figure 2. Conformational analyses of the alchohols **14** and **15**.

To continue the synthesis, the olefin **17** was oxidized with *m*-chloroperbenzoic acid (*m*CPBA) to give the epoxide **18** as a single diastereomer in 92% yield, whose stereochemistry was assigned based on the NOE experiment. The stereoselectivity can be explained by the consideration that the oxidizing reagent (*m*CPBA) accessed exclusively from the less hindered α-face of the molecule under the influence of the β-oriented *O*-isopropylidenedioxy moiety. Conversion of the epoxide **18** to the allyl alcohol **19** was successfully achieved by employing a reliable Sharpless protocol.[26] Thus, treatment of **18** with the phenylselenyl anion, generated in situ from diphenyl diselenide and sodium borohydride, caused the regioselective epoxide ring opening at the sterically and electrostatically favored C2 position to form the corresponding phenylselenide, which was then oxidized by excess 30% aqueous hydrogen peroxide to provide the allyl alcohol **19** in 95% overall yield via elimination of the intermediary phenylselenoxide. Finally, Dess–Martin oxidation[27] of **19** furnished the requisite intermediate **10** in 95% yield.

2.3. Initial attempts to achieve the coupling reaction of the cyclohexenone 10 with benzaldehyde (8)

Having obtained the intermediate **10**, we next investigated the crucial aldol-type coupling reaction between **10** and benzaldehyde (**8**) as shown in Scheme 3. Initial attempts to achieve this coupling reaction, unfortunately, turned out to be fruitless. Thus, reaction of the lithium enolate of **10**, generated in situ by reaction with $LiN(SiMe_3)_2$, with **8** in THF at −78 °C resulted in the predominant formation of the unexpected dimerized product **20** (38%) as a single stereo isomer and the desired coupling product **21** (12%) as an epimeric mixture with respect to the benzilic hydroxy group. Since the coupling product **21** was very unstable during isolation and purification by silica gel column chromatography, assignment of the structure and stereochemistry of **21** was performed by spectroscopic analyses (COSY, HMBC, and NOESY experiments) of the corresponding carbonyl compound **22**, readily prepared by Dess–Martin oxidation (78%).

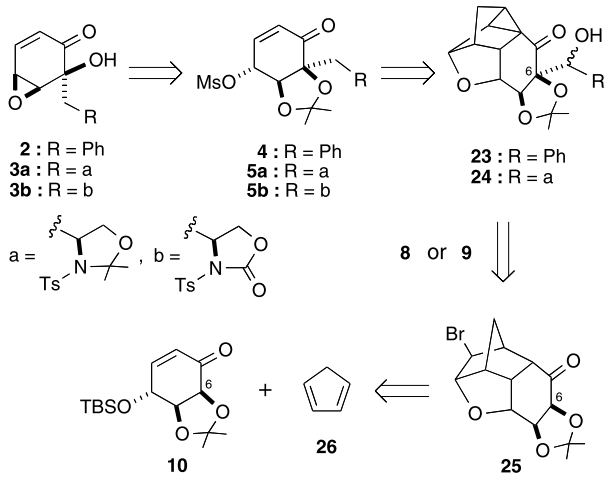


Scheme 3. Aldol-type coupling reaction of the cyclohexenone **10** and benzaldehyde (**8**). (a) $LiN(SiMe_3)_2$, THF, −78 °C, 38% for **20**, 12% for **21**; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 78%.

These preliminary studies demonstrated that the enone olefin function present in **10** was extremely susceptible to nucleophilic attack of the enolate generated from **10** itself. In order to circumvent this problem, we decided to mask the highly reactive enone system of **10** in the form of the bromo ether **25** (cf. Scheme 4) during the aldol-type coupling reaction. We anticipated that **25** would behave as a promising substrate for the designed coupling reaction. Further investigations concerning the synthesis of **25** and subsequent coupling reaction with the aldehydes **8** and **9** are the subject of the following sections.

2.4. Modified synthetic plan for the epoxycyclohexenone moieties 2 and 3a

Our initial attempts to achieve the direct coupling between the cyclohexenone **10** and benzaldehyde (**8**) met with failure; therefore, we settled on modifying our original synthetic plan. Thus, as shown in Scheme 4, the bromo ether

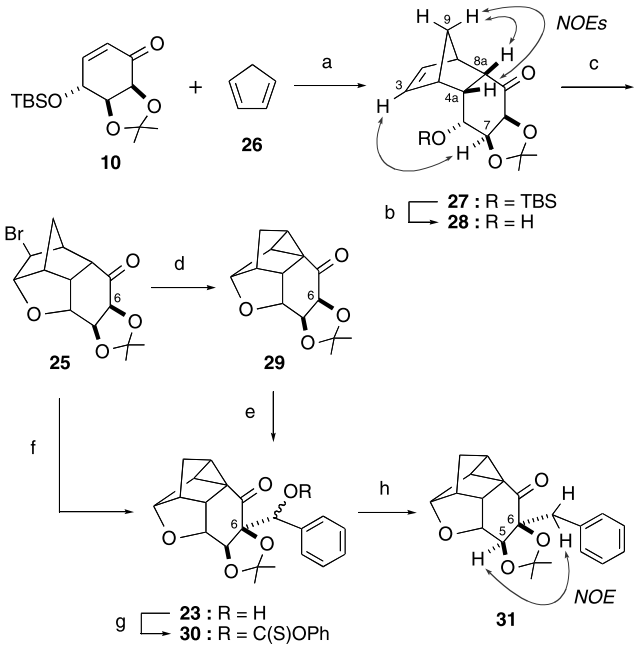


Scheme 4. Modified synthetic plan for the epoxycyclohexenone moieties **2** and **3**.

25, a synthetically equivalent of the cyclohexenone **10**, was envisaged to be prepared by Diels–Alder reaction of **10** with cyclopentadiene (**26**) followed by desilylation and bromo etherification. The crucial aldol-type reaction of **25** with the aldehydes **8** and **9** would produce the coupling products **23** and **24**, respectively, with correct stereochemistry at the C6 position. The intermediates **23** and **24** would be converted to the cyclohexenones **4** and **5**, the potential key intermediates of the target molecules **2** and **3**, via sequential functional group manipulation. As will be mentioned later (cf. Sections 2.7 and 2.8), the *N*,*O*-isopropylidene group at the C6 side chain in **24** turned out to be labile during the regeneration of the enone olefin moiety (cf. **24**→**5a**); therefore, the *N*,*O*-isopropylidene group was replaced with a sturdy cyclic carbamate group (cf. **5b**).

2.5. Synthesis of the intermediate 31 for the epoxycyclohexenone moiety 2: preparation of the masked enone 25 and subsequent aldol-type coupling reaction with benzaldehyde (8)

As shown in Scheme 5, we next carried out the synthesis of the intermediate **31** for the first target compound **2**; the sequence involved the preparation of the olefin masked cyclohexenone **25** and subsequent coupling reaction with benzaldehyde (**8**) as the crucial steps. Diels–Alder reaction of **10** with cyclopentadiene (**26**) in the presence of diethylaluminium chloride proceeded smoothly and cleanly in a completely diastereofacial- and *endo*-selective manner to provide the corresponding cycloadduct **27** as a single isomer in almost quantitative yield (97%). The structure and stereochemistry of the Diels–Alder adduct **27** was assigned based on the NMR spectral analysis including NOESY experiments; thus, clear NOE interactions between C9–H and C8a–H, C4a–H and between C3–H and C7–H were observed, respectively. After deprotection of the TBS group of **27** with tetrabutylammonium fluoride (TBAF) (75%), the resulting alcohol **28** was subjected to bromo etherification using *N*-bromosuccinimide (NBS)[28] to provide the desired tetracyclic bromo ether **25** in 86% yield.



Scheme 5. Aldol-type coupling reaction of the masked enone **25** with benzaldehyde (**8**) and the synthesis of the intermediate **31**. (a) Et_2AlCl, CH_2Cl_2, −78→0 °C, 97%; (b) TBAF, THF, 0 °C→rt, 75%; (c) NBS, CH_2Cl_2, 0 °C→rt, 86%; (d) $LiN(SiMe_3)_2$, THF, 98%; (e) $LiN(SiMe_3)_2$, THF, −78 °C; at −78 °C add. benzaldehyde (**8**), 98%; (f) $LiN(SiMe_3)_2$, THF, −78 °C; at −78 °C add. benzaldehyde (**8**), 98%; (g) phenyl chlorothionoformate, DMAP, MeCN, rt, 92%; (h) *n*-Bu_3SnH, AIBN, toluene, 110 °C, 79%.

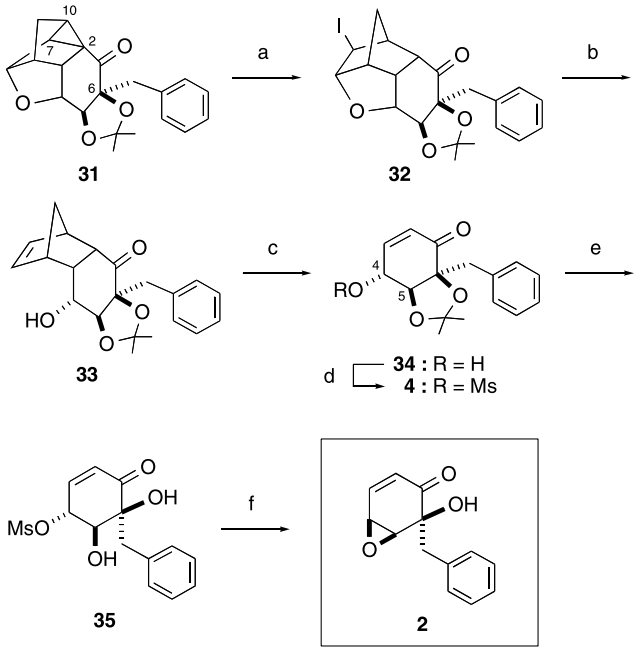
The crucial aldol-type coupling reaction between **25**[29] and benzaldehyde (**8**) was next conducted to establish the requisite C6 asymmetric quaternary carbon center. During the optimization of the reaction conditions, we found that the bromo ether **25** exhibited an interesting and unprecedented reactivity. Thus, treatment of **25** with 1.1 equiv of $LiN(SiMe_3)_2$ in THF at −78 °C for 30 min resulted in the formation of the unexpected cyclopropane derivative **29** in almost quantitative yield (98%), whose structure was confirmed by extensive spectroscopic studies including COSY, HMBC, and NOESY experiments in the 500 MHz NMR spectra. Subsequent treatment of **29** with 1.1 equiv of $LiN(SiMe_3)_2$ in THF at −78 °C followed by addition of benzaldehyde (**8**) (2.2 equiv) afforded the desired coupling product **30** in excellent yield (98%) as a hardly separable mixture of the epimeric alcohols (6:1 by 500 MHz ^{1}H NMR). The C6 stereochemistry of the product **23** turned out to be completely controlled as we expected; the assignment was later confirmed by NOE study of the transformed compound **31** (vide infra).

Encouraged by these successful results, we next examined a more efficient one-pot procedure for the direct coupling of **25** and **8**. Thus, treatment of **25** with 2.2 equiv of $LiN(SiMe_3)_2$ followed by reaction with 2.2 equiv of **8** furnished the requisite coupling product **23** in 98% yield. The secondary hydroxy group in **23** was deleted by using Robin's modification[30] of the Barton method.[31] Thus, treatment of **23** with phenyl thionochloroformate in acetonitrile in the presence of 4-dimethylaminopyridine (DMAP) at ambient temperature afforded the corresponding phenoxythionocarbonate **30** in 92% yield. Compound **30**

was then allowed to react with tri-*n*-butyltin hydride in toluene in the presence of a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) at 110 °C, giving rise to the desired deoxygenated product **31** in 79% yield. At this stage, the C6 stereochemistry could be unambiguously confirmed by NOESY experiments in the 500 MHz ^{1}H NMR spectrum of **31**, in which a clear NOE interaction between C5–H and the benzylic proton was observed.

2.6. Synthesis of the epoxycyclohexenone moiety 2

Having succeeded in introduction of the benzyl substituent at the C6 position with the correct stereochemistry, we next executed conversion of **31** into the epoxycyclohexenone moiety **2** (Scheme 6); the sequence involved regeneration of the enone system and subsequent epoxide ring formation as the pivotal steps. Regioselective cleavage of the cyclopropane ring in **31** was successfully achieved by treatment with trimethylsilyl iodide (TMSI)[32] in carbon tetrachloride at −20→−10 °C to give the desired γ-iodo ketone **32** in 89% yield as the sole product. The regioselectivitiy observed for this ring opening reaction can be explained by the so-called stereoelectronic effect. Thus, the σ_{C2-C7} orbital efficiently overlaps with the $\pi_{C=O}$ orbital, while the overlap between the σ_{C2-C10} orbital and the $\pi_{C=O}$ orbital is insufficient due to the geometrical factor. An attack of the iodo anion, therefore, occurred predominantly at the C7 position in **31**. Conversion of the γ-iodo ketone **32** to the requisite cyclohexenone **34** was effectively achieved by applying the Ogasawara procedure.[28] Thus, treatment of **32** with zinc powder in methanol containing a small amount of acetic acid gave the tricyclic compound **33** in 91% yield, which was then subjected to retro-Diels–Alder reaction by heating at 230 °C in diphenyl ether to produce **34** in 81% yield.



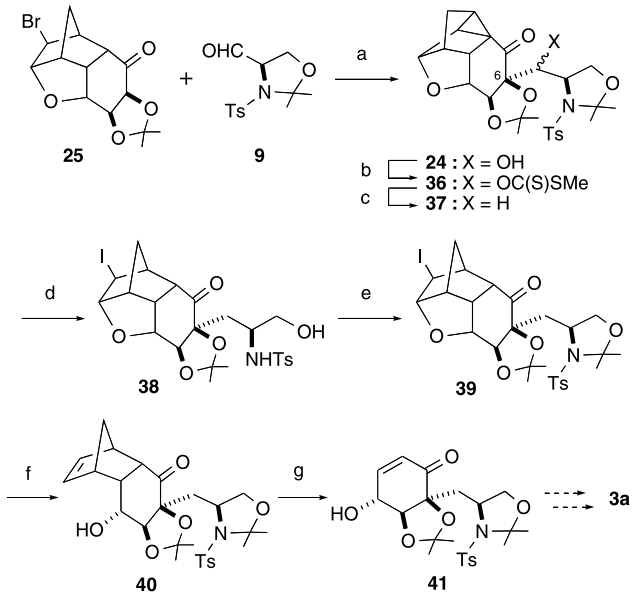
Scheme 6. Synthesis of the epoxycyclohexenone moiety **2**. (a) TMSI, CCl_4, −20→−10 °C, 89%; (b) Zn, AcOH, MeOH, 60 °C, 91%; (c) Ph_2O, 230 °C, 81%; (d) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C→rt, 85%; (e) TFA, H_2O, 0 °C, 85%; (f) 0.2 M NaOH, Et_2O, 0 °C, 90%.

The remaining task to complete the synthesis of the first target compound **2** involved the critical epoxide ring formation utilizing the two oxygen functionalities at the C4 and C5 positions in **34**. Toward this end, mesylation of the hydroxy group in **34** under the standard conditions (MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C→room temperature) (85%) followed by hydrolysis of the acetonide moiety of the resulting mesylate **4** by treatment with aqueous trifluoroacetic acid (TFA), furnished the desired diol **35** in 85% yield. Finally, the expected epoxide ring formation was successfully achieved by brief exposure of **35** to 0.2 M sodium hydroxide in ether at 0 °C for 10 min, providing the epoxycyclohexenone moiety **2** in 90% yield.

2.7. Initial attempts on the synthesis of the fully functionalized epoxycyclohexenone moiety 3a

Having established the synthetic route to the epoxycyclohexenone moiety **2**, we next undertook the synthesis of the fully functionalized epoxycyclohexenone moiety **3a** (cf. Scheme 4), which possesses the *N*,*O*-protected amino propanol side chain and the requisite asymmetric carbon centers. We envisaged that the targeted compound **3a** would be elaborated starting from the bromo ether **25** and D-serinal derivative **9**[33] [(*R*)-*N*-(*p*-toluenesulfonyl)-*N*,*O*-isopropylidene serinal], readily accessible from D-serine, based on the explored synthetic route to the epoxycyclohexenone moiety **2**.

As shown in Scheme 7, the synthesis started with the crucial aldol coupling reaction between **25** and **9**. The enolate anion, generated in situ by treatment of **25** with $LiN(SiMe_3)_2$ (2.2 equiv) in THF at −78 °C, was allowed to react with **9** (2.5 equiv) to furnish an excellent yield



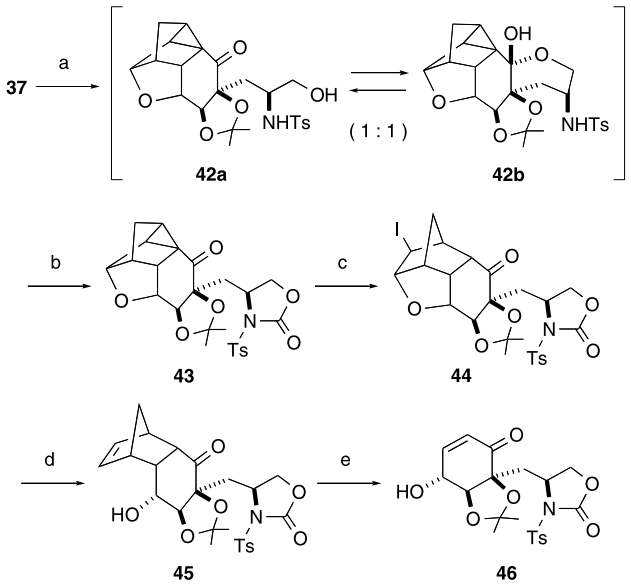
Scheme 7. Initial attempts on the synthesis of the intermediate **41** for the epoxycyclohexenone moiety **3a**. (a) $LiN(SiMe_3)_2$, THF, −78 °C; at −78 °C, add. (*R*)-*N*-(*p*-toluenesulfonyl)-*N*,*O*-isopropylidene serinal (**9**), 98%; (b) $NaN(SiMe_3)_2$, THF, −78 °C; CS_2, −78→−50 °C; MeI, −78→−50 °C, 88%; (c) *n*-Bu_3SnH, Et_3B, toluene, rt, 95%; (d) TMSI, CCl_4, −10 °C, 91%; (e) 2,2-dimethoxypropane, *p*-TsOH, benzene, 60 °C, 83%; (f) Zn, AcOH, MeOH, 60 °C, 98%; (g) Ph_2O, 230 °C, 25%.

(98%) of the desired coupling product **24** as an inseparable mixture of the epimeric alcohols (9:1 by 500 MHz ^{1}H NMR). Removal of the hydroxy group in **24** was initially attempted by employing the same reaction conditions [ClC(S)OPh, DMAP, MeCN] described for the preparation of **30** from **23** (cf. Scheme 5), which, unfortunately, ended in failure and the starting material **24** was recovered unchanged even under heating conditions. This is presumably due to the steric hindrance around the hydroxy group in **24**. Therefore, we looked at the Barton procedure[31] to achieve the requisite deoxygenation of the sterically hindered hydroxy group. Employing the original Barton conditions (NaH, CS_2, THF; MeI, 0 °C→room temperature), the reaction gave a poor yield (~30%) of the desired methyl xanthate **36**. In order to improve the yield, some modifications were made of the reaction conditions. After several trials, to our delight, we found that treatment of **24** with $NaN(SiMe_3)_2$ (1.2 equiv) in THF at −78 °C followed by addition of carbon disulfide (10 equiv) and iodomethane (10 equiv) at the same temperature furnished the methyl xanthate **36** in 88% yield. The resulting methyl xanthate **36** was further treated with tri-*n*-butyltinhydride and triethylborane[34] in toluene at ambient temperature to afford the requisite deoxygenated product **37** in 95% yield.

With the intermediate **37** possessing the requisite *N*,*O*-protected amino propanol side chain and the correct stereochemistry in hand, our next efforts were devoted to regeneration of the cyclohexenone olefin moiety. Toward this end, regioselective cleavage of the cyclopropane ring in **37** was conducted by treatment with TMSI to give the iodo ether **38** in 91% yield. In this reaction, the *N*,*O*-isopropylidene group was simultaneously hydrolyzed; therefore, regeneration of the *N*,*O*-isopropylidene moiety of the resulting aminopropanol **38** was carried out under conventional conditions (2,2-dimethoxypropane, *p*-TsOH, benzene, 60 °C) to furnish the acetonide **39** in 83% yield. Further treatment of **39** with zinc powder in methanol containing acetic acid at 60 °C furnished the tricyclic compound **40** in 98% yield. Retro-Diels–Alder reaction of **40** by the thermolysis at 230 °C in diphenyl ether, to our disappointment, provided a poor yield (25%) of the cyclohexenone derivative **41**. This is presumably due to the instability of the *N*,*O*-isopropylidene group under the harsh reaction conditions. Fortunately, this problem was solved by replacement of the *N*,*O*-isopropylidene group with a robust cyclic carbamate group prior to subjection to the retro-Diels–Alder reaction (cf. Scheme 8). This is the subject of the following section.

2.8. Successful synthesis of the fully functionalized epoxycyclohexenone moiety 3b

The synthesis of the fully functionalized epoxycyclohexenone moiety **3b** was successfully achieved by exchanging the *N*,*O*-isopropylidene moiety in **37** with the corresponding cyclic carbamate functionality. Thus, as shown in Scheme 8, the *N*,*O*-isopropylidene moiety in **37** was selectively deprotected by exposure to aqueous hydrogen chloride in THF at 55 °C, which furnished an equilibrium mixture of the *N*-Ts-β-amino alcohol **42a** and the cyclic hemiacetal **42b** (ca. 1:1 by ^{1}H NMR). This equilibrium mixture was then treated with phosgene dimer

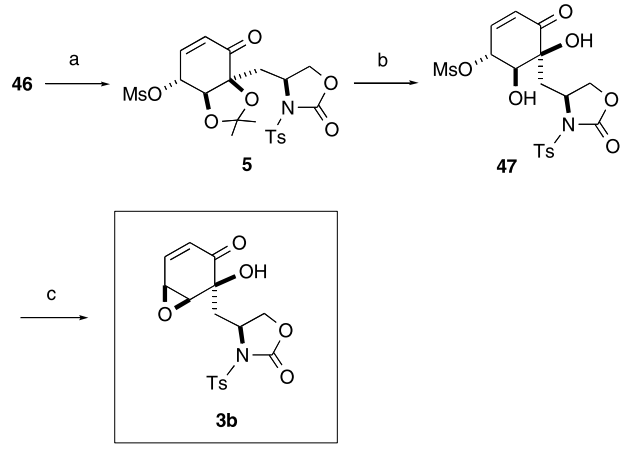


Scheme 8. Synthesis of the intermediate **46** for the epoxycyclohexenone **3**. (a) 1.0 M HCl, THF, 55 °C; (b) phosgen dimer, pyridine, THF, rt, 67% (two steps); (c) TMSI, CCl_4, −20 °C, 74%; (d) Zn, AcOH, MeOH, 60 °C, 95%; (e) Ph_2O, 230 °C, 59%.

(trichloromethyl chloroformate) in the presence of pyridine in THF, providing the desired cyclic carbamate **43** in 67% yield for the two steps.

To forward the synthesis, regeneration of the cyclohexenone olefin moiety was next investigated. Thus, regioselective cleavage of the cyclopropane ring in **43** by reaction with TMSI afforded the expected iodide **44** in 74% yield. Further treatment of **44** with zinc powder in methanol containing acetic acid furnished the alcohol **45** in 95% yield. Retro-Diels–Alder reaction of **45** proceeded effectively by thermolysis at 230 °C in diphenyl ether. The desired cyclohexenone **46** was obtained in an acceptable 59% yield.

The final route that led to completion of the synthesis of the targeted molecule **3** is summarized in Scheme 9. The hydroxy group in **46** was mesylated under standard conditions (MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C→room



Scheme 9. Synthesis of the intermediate **3b**. (a) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C→rt, 83%; (b) TFA, H_2O, 0 °C, quant.; (c) 0.2 M NaOH, Et_2O, 0 °C, 75%.

temperature) to give the corresponding mesylate **5** in 83% yield. The *O*-isopropylidene moiety of **5** was then hydrolyzed by reaction with aqueous trifluoroacetic acid at 0 °C to provide the requisite diol **47** in quantitative yield. Finally, brief exposure of **47** to aqueous sodium hydroxide in ether at 0 °C, led to the formation of **3b** in 75% yield. The structure and stereochemistry of **3b** were unambiguously confirmed by single X-ray crystallographic analysis as depicted in Figure 3.[35]

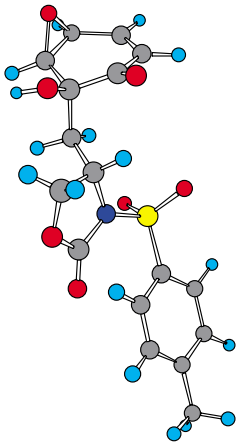


Figure 3. X-ray structure of the epoxycyclohexenone moiety **3b**. Red, O; navy, N; yellow, S; blue, H.

3. Conclusion

In conclusion, we have succeeded in developing an efficient and enantioselective synthetic pathway to the epoxycyclohexenone moieties **2** and **3b** of scyphostatin (**1**). The explored method features (i) the preparation of the key intermediate cyclohexene **10** and its olefin masked enone **25** starting from commercially available (−)-quinic acid (**11**), (ii) the aldol-type coupling reaction of the ketone **25** with benzaldehyde (**8**) or Garner's aldehyde analogue **9** to install the requisite asymmetric quaternary carbon center at the C6 position with complete stereoselectivity (**25**+**8**→**23** and **25**+**9**→**24**), and (iii) the facile epoxide ring formation of the β-hydroxymesylates **35** and **47** under mild basic conditions (**35**→**2** and **47**→**3b**). Further investigation toward the synthesis of scyphostatin analogues based on the present study is now in progress and will be reported in due course.

4. Experimental

4.1. General methods

All reactions involving air- and moisture-sensitive reagent were carried out using oven-dried glassware and standard syringe-septum cap techniques. Routine monitorings of reaction were carried out using glass-supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 40–50 μm) with the solvents indicated.

All solvents and reagents were used as supplied with the following exceptions. Tetrahydrofuran (THF) and ether were freshly distilled from sodium/benzophenone under argon. Dichloromethane, acetonitrile, and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride under argon.

Melting points were taken on a Yanaco MP-3 micro melting point apparatus and are uncorrected. Measurements of optical rotations were performed with a JASCO P-1020 automatic digital polarimeter. ^{1}H and ^{13}C NMR spectra were measured with a Brucker DRX-500 (500 MHz) spectrometer or a Brucker DRX-250 (250 MHz). Chemical shifts were expressed in ppm using tetramethylsilane ($\delta=0$) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low-resolution mass (MS) spectra was measured on Shimadzu GCMS-QP2010. High-resolution mass (HRMS) spectra was measured on JEOL MStation JMS-700 mass spectrometer. Elemental analyses were performed with a Perkin Elmer 2400II apparatus.

4.1.1. (1*R*,2*R*,3*R*)-3-*tert*-Butyldimethylsiloxy-1,2-(*O*-isopropylidenedioxy)cyclohexan-5-one (13). *tert*-Butyldimethylsilyl chloride (24.4 g, 0.16 mol) was added to a stirred solution of **12**[24] (10.0 g, 54 mmol) in dry DMF (120 ml) containing imidazole (14.7 g, 0.22 mol) at room temperature. After 15 h, the mixture was diluted with ethyl acetate (800 ml). The organic layer was successively washed with 3% aqueous hydrochloric acid (2×250 ml), saturated aqueous sodium hydrogen carbonate (2×250 ml), and brine (2×250 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 14:1) to give **13** (16.2 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ +105.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (3H, s, Si-Me), 0.09 (3H, s, Si-Me), 0.83 (9H, s, Si-*t*-Bu), 1.35 (3H, s, C-Me), 1.42 (3H, s, C-Me), 2.37 (1H, ddd, J=1.9, 3.5, 17.5 Hz, C4–H), 2.64 (1H, dd, J=2.2, 17.4 Hz, C4–H), 2.65 (1H, dd, J=2.5, 17.5 Hz, C6–H), 2.75 (1H, dd, J=3.5, 17.5 Hz, C6–H), 4.16 (1H, m, C3–H), 4.22 (1H, dt, J=2.2, 7.2 Hz, C2–H), 4.69 (1H, m, C1–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.06, −5.04, 17.9, 23.9, 25.6 (3 carbons), 26.3, 40.1, 41.9, 68.7, 72.4, 75.1, 108.7, 207.7; IR (neat) 440, 520, 690, 780, 810, 840, 870, 910, 980, 1010, 1060, 1090, 1140, 1180, 1210, 1250, 1380, 1470, 1720, 2860, 2930, 2960 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{14}H_{25}O_4Si$ [$(M-Me)^+$]: 285.1522, found 285.1253.

4.1.2. (1*R*,2*R*,3*R*,5*R*)- and (1*R*,2*R*,3*R*,5*S*)-3-*tert*-Butyldimethylsiloxy-5-hydroxy-1,2-(*O*-isopropylidenedioxy)-cyclohexane (14) and (15). Sodium borohydride (1.30 g, 34 mmol) in water (15 ml) was added dropwise to a stirred solution of **13** (9.40 g, 31 mmol) in THF (400 ml) at −5 °C, and stirring was continued for 1 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride (30 ml) at 0 °C, and then the mixture was diluted with ethyl acetate (1000 ml). The organic layer was washed with saturated aqueous ammonium chloride (2×300 ml) and brine (2×300 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was separated by column chromatography (hexane/ethyl acetate,

5:1→3:1) to give **14** (5.02 g, 53%) as a more polar product and **15** (4.16 g, 44%) as a less polar product.

Compound **14**. Colorless prism, mp 47–48 °C; $[\alpha]_D^{20}$ −41.7 (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (3H, s, Si-Me), 0.11 (3H, s, Si-Me), 0.89 (9H, s, *t*-Bu), 1.34 (3H, s, C-Me), 1.46 (3H, s, C-Me), 1.60 (1H, m, C4–H), 1.83 (1H, m, C6–H), 2.00 (1H, m, C4–H), 2.20 (1H, m, C6–H), 2.26 (1H, d, J=6.8 Hz, OH), 3.89–3.97 (2H, m, C2–H, C3–H), 4.02 (1H, br, C5–H), 4.40 (1H, dd, J=4.8, 9.8 Hz, C1–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.81, −4.72, 18.0, 25.8 (3 carbons), 25.9, 28.1, 35.5, 37.7, 65.1, 71.1, 72.7, 78.87, 108.5; IR (KBr) 510, 550, 630, 660, 690, 780, 840, 870, 920, 940, 960, 1020, 1040, 1060, 1120, 1190, 1220, 1240, 1260, 1370, 1380, 1460, 2860, 2890, 2930, 2990, 3420 cm^{-1}; CIMS (*m*/*z*) 303 $[(M+H)^+]$; HREIMS (*m*/*z*) calcd for $C_{14}H_{27}O_4Si$ $[(M-Me)^+]$: 287.1679, found 287.1682.

Compound **15**. Colorless oil. $[\alpha]_D^{20}$ −33.7 (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (3H, s, Si-Me), 0.10 (3H, s, Si-Me), 0.88 (9H, s, *t*-Bu), 1.35 (3H, s, C-Me), 1.52 (3H, s, C-Me), 1.73 (1H, m, C4–H), 1.90 (1H, ddd, J=3.9, 6.3, 13.7 Hz, C4–H), 2.04 (2H, t, J=4.4 Hz, C6–H), 2.27 (1H, d, J=8.2 Hz, OH), 3.90 (1H, t, J=5.2 Hz, C2–H), 4.04 (1H, dd, br, J=7.7, 10.7 Hz, C5–H), 4.09 (1H, m, C3–H), 4.41 (1H, dd, J=4.6, 9.7 Hz, C1–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.81, −4.72, 18.0, 25.7, 25.8 (3 carbons), 28.2, 33.8, 37.9, 65.3, 68.7, 74.1, 78.9, 108.6; IR (neat) 520, 660, 780, 840, 910, 940, 960, 1000, 1050, 1070, 1120, 1150, 1220, 1250, 1380, 1460, 2860, 2890, 2930, 2960, 2990, 3440 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{14}H_{27}O_4Si$ $[(M-Me)^+]$: 287.1679, found 287.1680.

4.1.3. (1*R*,2*R*,3*R*,5*R*)-5-Acetoxy-3-*tert*-butyldimethylsiloxy-1,2-(*O*-isopropylidenedioxy)cyclohexane (16). Acetic anhydride (0.1 ml, 1.1 mmol) was added to a stirred solution of **14** (27 mg, 89 μmol) in pyridine (1.0 ml) containing 4-dimethylaminopyridine (1.0 mg, 8 μmol) at 0 °C, and stirring was continued for 3 h at room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (1 ml) at 0 °C, and the mixture was diluted with ether (30 ml). The organic layer was successively washed with 3% aqueous hydrochloric acid (2×15 ml), saturated aqueous sodium hydrogen carbonate (2×15 ml), and brine (2×10 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 7:1) to give **16** (30 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ −29.6 (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.07 (3H, s, Si-Me), 0.09 (3H, s, Si-Me), 0.89 (9H, s, Si-*t*-Bu), 1.34 (3H, s, C-Me), 1.45 (1H, m, C4–H), 1.46 (3H, s, C-Me), 1.82 (1H, m, C6–H), 2.03 (3H, s, Ac), 2.12 (1H, m, C4–H), 2.35 (1H, m, C6–H), 3.80 (1H, m, C3–H), 3.87 (1H, t, J=5.9 Hz, C2–H), 4.39 (1H, m, C1–H), 5.04 (1H, m, C5–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.85, −4.86, 18.0, 21.3, 25.4, 25.7 (3 carbons), 27.8, 31.2, 36.1, 66.8, 70.6, 73.0, 79.4, 108.5, 170.4; IR (neat) 410, 510, 610, 660, 700, 780, 840, 870, 900, 920, 940, 990, 1060, 1120, 1150, 1220, 1240, 1370, 1460, 1740, 2860, 2890, 2930, 2960, 2990 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{16}H_{29}O_5Si$ $[(M-Me)^+]$: 329.1784, found 329.1796.

4.1.4. Conversion of 14 to 15. Diethyl azodicarboxylate in toluene (40% solution, 14.5 ml, 34 mmol) was added dropwise to a stirred solution of **14** (5.00 g, 17 mmol) in dry THF (150 ml) containing triphenylphosphine (8.68 g, 34 mmol) and benzoic acid (4.15 g, 34 mmol) at 0 °C under argon. The mixture was stirred for 3 h at room temperature. Concentration of the mixture in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 13:1) to give the corresponding benzoate (6.61 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ +15.9 (*c* 1.06, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (3H, s, Si-Me), 0.10 (3H, s, Si-Me), 0.90 (9H, s, Si-*t*-Bu), 1.37 (3H, s, C-Me), 1.55 (3H, s, C-Me), 1.92–2.10 (3H, m, C4–H, C4–H, C6–H), 2.24 (1H, dt, J=5.1, 14.5 Hz, C6–H), 3.96 (1H, t, J=4.9 Hz, C2–H), 4.20 (1H, m, C3–H), 4.43 (1H, q, J=5.5 Hz, C1–H), 5.33 (1H, m, C5–H), 7.43 (2H, t, J=7.8 Hz, Ar-H), 7.55 (1H, t, J=7.4 Hz, Ar-H), 8.05 (2H, d, J=7.1 Hz, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.02, −4.84, 17.9, 25.7 (4 carbons), 30.9, 33.95, 33.99, 67.5, 68.8, 69.6, 72.8, 128.3 (2 carbons), 129.6 (2 carbons), 130.5, 132.9, 165.8, 207.1; IR (neat) 520, 710, 780, 840, 920, 940, 970, 1010, 1030, 1070, 1110, 1220, 1280, 1320, 1370, 1380, 1450, 1540, 1600, 1720, 1780, 2860, 2890, 2930 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{21}H_{31}O_5Si$ $[(M-Me)^+]$: 391.1941, found 391.1910.

2.0 M Potassium hydroxide solution (22.4 ml, 45 mmol) was added dropwise to a stirred solution of the above benzoate (6.50 g, 16 mmol) in methanol (280 ml) at 0 °C, and stirring was continued for 3 h at room temperature. The mixture was concentrated in vacuo to give a residue, which was diluted with ethyl acetate (800 ml). The organic layer was washed with brine (2×300 ml) and then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 3:1) to give **15** (4.82 g, quant.) as a colorless oil. The IR, ^1H NMR, and mass spectra of this material were identical with those recorded for preparation of **15** (see, Section 4.1.2).

4.1.5. (3*R*,4*R*,5*R*)-5-*tert*-Butyldimethylsiloxy-3,4-*O*-isopropylidenedioxy-1-cyclohexene (17). Diethyl azodicarboxylate in toluene (40% solution, 21.6 ml, 50 mmol) was added dropwise to a stirred solution of **15** (5.00 g, 17 mmol) in dry THF (150 ml) containing triphenylphosphine (13.1 g, 51 mmol) at room temperature. After 3 h, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 13:1) to give **17** (3.15 g, 67%) as a colorless oil. $[\alpha]_D^{20}$ −87.1 (*c* 1.05, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.07 (3H, s, Si-Me), 0.10 (3H, s, Si-Me), 0.89 (9H, s, Si-*t*-Bu), 1.38 (3H, s, C-Me), 1.46 (3H, s, C-Me), 2.01 (1H, m, C6–H), 2.28 (1H, m, C6–H), 3.83 (1H, m, C5–H), 3.98 (1H, t, J=6.8 Hz, C4–H), 4.60 (1H, d, J=6.2 Hz, C3–H), 5.80 (2H, m, C1–H, C2–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.5, 18.1, 25.8 (3 carbons), 26.1, 28.3, 31.9, 69.6, 72.8, 78.7, 108.6, 124.6, 128.5; IR (neat) 670, 780, 840, 910, 1010, 1060, 1120, 1220, 1250, 1380, 1460, 1690, 1730, 2860, 2930, 2960 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{14}H_{25}O_3Si$ $[(M-Me)^+]$: 269.1573, found 269.1570.

4.1.6. (1*S*,2*S*,3*R*,4*R*,5*R*)-5-*tert*-Butyldimethylsiloxy-1,2-epoxy-3,4-(*O*-isopropylidenedioxy)cyclohexane (18). 3-Chloroperoxybenzoic acid (*m*CPBA) (7.53 g, 45 mmol) was added in small portions to a stirred solution of **17** (4.95 g, 17 mmol) in dry dichloromethane (180 ml) containing sodium hydrogen carbonate (7.53 g, 45 mmol) at 0 °C, and stirring was continued for 24 h at room temperature. The reaction was diluted with ethyl acetate (400 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2×200 ml) and brine (2×200 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo affoded a residue, which was purified by column chromatography (hexane/ethyl acetate, 13:1) to give **18** (4.81 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ −29.1 (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (3H, s, Si-Me), 0.07 (3H, s, Si-Me), 0.88 (9H, s, Si-*t*-Bu), 1.38 (3H, s, C-Me), 1.46 (3H, s, C-Me), 1.90 (1H, ddd, *J*=1.6, 6.1, 15.6 Hz, C6–H), 2.18 (1H, ddd, *J*=4.0, 5.1, 15.4 Hz, C6–H), 3.14 (1H, d, *J*=3.6 Hz, C2–H), 3.23 (1H, s, C1–H), 3.87 (1H, dd, *J*=5.8, 11.2 Hz, C5–H), 3.94 (1H, m, C4–H), 4.53 (1H, d, *J*=5.6 Hz, C3–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.77, −4.75, 18.0, 25.7 (3 carbons), 26.0, 28.0, 29.4, 51.3, 51.7, 66.3, 71.8, 76.8, 109.2; IR (neat) 510, 710, 780, 840, 870, 910, 940, 1000, 1110, 1220, 1250, 1380, 1470, 2860, 2890, 2930, 2990 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{14}H_{25}O_4Si$ [(M−Me)$^+$]: 285.1522, found 285.1508.

4.1.7. (1*S*,4*R*,5*R*,6*R*)-4-*tert*-Butyldimethylsiloxy-1-hydroxy-5,6-*O*-isopropylidenedioxy-2-cyclohexene (19). Sodium borohydride (663 mg, 18 mmol) was added in small portions to a stirred suspension of diphenyl diselenide (2.74 g, 8.8 mmol) in dry ethanol (30 ml) at 0 °C under argon. After 30 min, a solution of **18** (4.80 g, 16 mmol) in dry ethanol (30 ml) was added dropwise to the mixture at room temperature. The mixture was heated at reflux for 1 h. After cooling, the mixture was diluted with dry THF (24 ml). Hydrogen peroxide in water (30% solution, 19.5 ml, 0.17 mol) was added dropwise to the mixture at 0 °C. The resulting mixture was further stirred for 5 min at 0 °C and slowly heated at reflux for 1 h. After cooling, the mixture was diluted with ether (300 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2×150 ml) and brine (2×100 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/ethyl acetate, 3:1) to give **19** (3.74 g, 78%) as a colorless oil. $[\alpha]_D^{20}$ −42.4 (*c* 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (3H, s, Si-Me), 0.13 (3H, s, Si-Me), 0.90 (9H, s, Si-*t*-Bu), 1.34 (3H, s, C-Me), 1.40 (3H, s, C-Me), 2.90 (1H, d, *J*=8.3 Hz, OH), 4.12 (1H, m, C1–H), 4.21 (1H, t, *J*=3.7 Hz, C4–H), 4.29 (1H, dd, *J*=4.1, 7.5 Hz, C5–H), 4.33 (1H, dd, *J*=4.1, 7.5 Hz, C6–H), 5.95 (1H, dd, *J*=4.2, 9.8 Hz, C3–H), 6.07 (1H, dd, *J*=4.2, 9.8 Hz, C2–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.81, −4.75, 18.0, 24.6, 25.8 (3 carbons), 26.6, 67.9, 68.7, 78.8, 79.0, 108.7, 132.3, 132.3; IR (neat) 410, 480, 520, 640, 660, 690, 780, 840, 890, 940, 960, 990, 1010, 1060, 1120, 1160, 1210, 1250, 1380, 1460, 1640, 2860, 2900, 2930, 2960, 2990, 3050, 3450 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{14}H_{25}O_4Si$ [(M−Me)$^+$]: 285.1522, found 285.1534.

4.1.8. (4*R*,5*R*,6*S*)-4-*tert*-Butyldimethylsiloxy-5,6-*O*-isopropylidenedioxy-2-cyclohexen-1-one (10). Dess–Martin periodinane (14.5 g, 34 mmol) was added in small portions to a stirred solution of **19** (5.15 g, 17 mmol) in dry dichloromethane (200 ml) at room temperature. After 2 h, the mixture was diluted with ethyl acetate (500 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×200 ml), saturated aqueous sodium hydrogen carbonate (2×200 ml), and brine (2×200 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 7:1) to give **10** (4.86 g, 95%) as a white solid. Recrystallization from hexane/dichloromethane (5:1) afforded colorless prisms, mp 55–56 °C; $[\alpha]_D^{20}$ −84.7 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (3H, s, Si-Me), 0.17 (3H, s, Si-Me), 0.92 (9H, s, Si-*t*-Bu), 1.40 (3H, s, C-Me), 1.42 (3H, s, C-Me), 4.41 (1H, m, C5–H), 4.44 (1H, d, *J*=5.9 Hz, C6–H), 4.54 (1H, m, C4–H), 6.08 (1H, d, *J*=10.3 Hz, C2–H), 6.76 (1H, ddd, *J*=1.0, 3.8, 10.3 Hz, C3–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.74 (Si-Me), −4.73 (Si-Me), 18.1 (*C*-Me_3), 25.7 (3 carbons, C-*Me*$_3$), 25.9 (Me of *O*-isopropylidene), 27.4 (Me of *O*-isopropylidene), 67.1 (C4), 74.4 (C5), 79.6 (C6), 110.2 (*C*-Me_2 of *O*-isopropylidene), 127.9 (C2), 148.5 (C3), 194.5 (C1); IR (KBr) 470, 520, 630, 670, 730, 780, 840, 890, 940, 980, 1010, 1080, 1170, 1250, 1330, 1380, 1460, 1630, 1700, 2710, 2740, 2860, 2900, 2930, 2990, 3040, 3370, 3550 cm^{-1}; EIMS (*m*/*z*) 298 (M$^+$), 283 [(M−Me)$^+$], 241 [(M−*t*-Bu)$^+$]. Anal. Calcd for $C_{15}H_{26}O_4Si$: C, 60.37; H, 8.78. Found C, 60.03; H, 8.56.

4.1.9. (1*S*,5*R*,6*S*,1′*R*,2′*R*,3′*R*,4′*S*)-5,2′-Bis(*tert*-butyldimethylsiloxy)-1,6:3′,4′-bis(*O*-isopropylidenedioxy)bicyclohexyl-3-ene-2,5′-dione (20) and (4*R*,5*S*,6*S*)-6-benzoyl-4-*tert*-butyldimethylsiloxy-5,6-*O*-isopropylidenedioxy-2-cyclohexen-1-one (22). Lithium bis(trimethylsilyl)amide in THF (1.0 M solution, 1.7 ml, 1.7 mmol) was added dropwise to a stirred solution of **10** (50 mg, 0.17 mmol) and benzaldehyde (**8**) (82 μl, 0.77 mmol) in dry THF (4 ml) at −78 °C under argon, and the stirring was continued for 30 min at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (1 ml) at 0 °C, and the mixture was diluted with ether (50 ml). The organic layer was washed successively with saturated aqueous ammonium chloride (2×20 ml), saturated aqueous sodium hydrogen carbonate (2×20 ml), and brine (2×20 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethylacetate, 7:1) to give **20** (19 mg, 38%) as a white amorphous solid and **21** (7.4 mg, 12%) as colorless oil. Since compound **21** was unstable, this was immediately subjected to the following oxidation reaction.

Compound **21** (7.4 mg, 18 μmol) was treated with Dess–Martin periodinane (23.0 mg, 54 μmol) in dichloromethane (0.5 ml) at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate (30 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×10 ml), saturated aqueous sodium hydrogen carbonate (2×10 ml), and brine (2×10 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded

a residue, which was purified by column chromatography (hexane/ethyl acetate, 7:1) to give **22** (5.7 mg, 78%) as a colorless viscous oil.

Compound **20**. $[\alpha]_D^{20}$ −30.0 (*c* 1.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (3H, s, Si-Me of C6′–OTBS), 0.15 (3H, s, Si-Me of C5–OTBS), 0.17 (3H, s, Si-Me of C5–OTBS), 0.22 (3H, s, Si-Me of C6′–OTBS), 0.84 (9H, s, *t*-Bu of C6′–OTBS), 0.92 (9H, s, *t*-Bu of C5–OTBS), 1.27 (3H, s, Me of *O*-isopropylidene), 1.30 (3H, s, Me of *O*-isopropylidene), 1.35 (3H, s, Me of *O*-isopropylidene), 1.45 (3H, s, Me of *O*-isopropylidene), 2.58 (1H, dd, J=7.0, 16.8 Hz, C2′–H), 2.70 (1H, dd, J=10.5, 17.8 Hz, C2′–H), 2.98 (1H, dd, J=7.1, 10.3 Hz, C1′–H), 4.05 (1H, br s, C6′–H), 4.10 (1H, t, J=1.7 Hz, C6–H), 4.26 (2H, br, C4′–H, C5′–H), 4.61 (1H, dd, J=1.0, 4.3 Hz, C5–H), 6.01 (1H, d, J=10.2 Hz, C3–H) 6.58 (1H, br, C4–H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ −4.89, −4.80, −4.44, −4.30, 18.3, 18.4, 24.5, 25.9 (6 carbons), 26.5, 26.6, 27.1 (2 carbons), 30.1, 65.9, 78.2 (2 carbons), 79.3, 80.2, 83.5, 109.2, 111.9, 127.7, 143.5, 198.8, 204.5; IR (neat) 520, 670, 780, 810, 840, 940, 960, 980, 1010, 1040, 1070, 1100, 1130, 1180, 1210, 1230, 1260, 1380, 1470, 1700, 1730, 2860, 2930, 2950, 2990 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{29}H_{49}O_8Si_2$ [(M−Me)$^+$], 581.2966, found 581.2949.

Compound **22**. $[\alpha]_D^{20}$ −3.27 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (3H, s, Si-Me), 0.15 (3H, s, Si-Me), 0.92 (9H, s, *t*-Bu), 1.27 (3H, s, C-Me), 1.46 (3H, s, C-Me), 4.58 (1H, dt, J=1.6, 2.2 Hz, C4–H), 4.79 (1H, dd, J=1.2, 3.0 Hz, C5–H), 6.13 (1H, dd, J=1.6, 10.3 Hz, C2–H), 6.79 (1H, ddd, J=1.2, 3.4, 10.3 Hz, C3–H), 7.42 (2H, t, J=7.8 Hz, Ph-H), 7.55 (1H, d, J=7.8 Hz, Ph-H), 8.22 (2H, d, J=7.3 Hz, Ph-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.82, −4.72, 18.1, 25.7 (3 carbons), 26.3, 27.4, 68.1, 82.8, 89.7, 111.3, 127.1, 128.1 (2 carbons), 130.8 (2 carbons), 133.3, 134.9, 148.8, 192.8, 196.9; IR (neat) 690, 780, 840, 870, 900, 1050, 1100, 1180, 1260, 1380, 1450, 1460, 1580, 1600, 1680, 1700, 2860, 2890, 2930, 2960, 2990 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{22}H_{30}O_5Si$ (M^+): 402.1863, found 402.1835.

4.1.10. (1*R*,4*S*,4a*R*,5*R*,6*S*,7*S*,8a*S*)-5-*tert*-Butyldimethylsilyoxy-6,7-*O*-isopropylidenedioxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (27). Diethylaluminum chloride in hexane (1.0 M solution, 2.68 ml, 0.27 mmol) was added dropwise to a stirred solution of **10** (4.00 g, 13 mmol) and cyclopentadiene (11.1 ml, 0.13 mol) in dry dichloromethane (140 ml) at −78 °C under argon. The mixture was gradually warmed up to 0 °C over 1 h, and stirring was continued for 1 h at 0 °C. The mixture was diluted with ether (400 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2×200 ml) and brine (2×200 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 6:1) to give **27** (4.74 g, 97%) as a white solid. Recrystallization from hexane/dichloromethane (10:1) afforded colorless prisms, mp 92–93 °C; $[\alpha]_D^{20}$ +46.7 (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (3H, s, Si-Me), 0.09 (3H, s, Si-Me), 0.89 (9H, s, Si-*t*-Bu), 1.30 (3H, s, C-Me), 1.37 (1H, d, J=8.4 Hz, C9–H), 1.47 (3H, s, C-Me), 1.54 (1H, d, J=8.4 Hz, C9–H), 2.90 (1H, ddd, J=3.3, 5.6, 10.2 Hz, C4a–H), 3.08 (1H, s, C1–H), 3.11 (1H, s, C4–H), 3.18 (1H, dd, J=3.8, 10.2 Hz, C8a–H), 3.99 (1H, t, J=6.2 Hz, C5–H), 4.12 (1H, d, J=8.4 Hz, C7–H), 4.22 (1H, dd, J=7.0, 8.3 Hz, C6–H), 6.12 (1H, dd, J=3.0, 5.6 Hz, C2–H), 6.20 (1H, dd, J=3.0, 5.4 Hz, C3–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.93, −4.53, 18.0, 24.0, 25.8 (3 carbons), 26.5, 45.2, 45.7, 46.6, 49.6, 51.6, 71.6, 78.1, 79.7, 109.9, 133.1, 137.0, 208.7; IR (KBr) 560, 680, 730, 780, 840, 850, 900, 940, 970, 1010, 1040, 1080, 1110, 1160, 1210, 1260, 1380, 1460, 1720, 2860, 2900, 2930, 2960 cm^{-1}; EIMS (*m*/*z*) 349 [(M−Me)$^+$], 307 [(M−*t*-Bu)$^+$], 249 [(M−TBS)$^+$]; CIMS (*m*/*z*) 365 [(M+H)$^+$]; HREIMS (*m*/*z*) calcd for $C_{19}H_{29}O_4Si$ [(M−Me)$^+$]: 349.1835, found 349.1825.

4.1.11. (1*R*,4*S*,4a*R*,5*R*,6*S*,7*S*,8a*S*)-5-Trihydroxy-6,7-*O*-isopropylidenedioxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (28). Tetrabutylammonium fluoride in THF (1.0 M solution, 15.0 ml, 15 mmol) was added to a stirred solution of **27** (3.51 g, 9.6 mmol) in dry THF (100 ml) at 0 °C, and stirring was continued for 2 h at room temperature. The mixture was diluted with ether (400 ml). The organic layer was successively washed with saturated aqueous ammonium chloride (2×150 ml), saturated aqueous sodium hydrogen carbonate (2×150 ml), and brine (2×150 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 5:3) to give **24** (1.81 g, 75%) as a white solid. Recrystallization from hexane/dichloromethane (10:1) afforded colorless needles, mp 137–138 °C; $[\alpha]_D^{20}$ +112.9 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (3H, s, C-Me), 1.42 (1H, d, J=8.4 Hz, C9–H), 1.53 (3H, s, C-Me), 1.58 (1H, d, J=8.4 Hz, C9–H), 2.16 (1H, s, OH), 3.08–3.16 (3H, m, C1–H, C4–H, C5–H), 3.38 (1H, dd, J=3.3, 10.5 Hz, C8a–H), 4.15 (1H, t, J=4.1 Hz, C4a–H), 4.20 (1H, d, J=8.0 Hz, C7–H), 4.43 (1H, dd, J=5.9, 8.0 Hz, C6–H), 6.25 (1H, dd, J=2.6, 5.5 Hz, C3–H), 6.37 (1H, dd, J=3.0, 5.5 Hz, C2–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.9, 26.4, 44.6 (2 carbons), 45.3, 48.4, 51.7, 70.2, 78.1, 79.7, 111.0, 134.9, 137.4, 208.6; IR (KBr) 550, 740, 860, 890, 1040, 1060, 1160, 1210, 1260, 1380, 1630, 1710, 2940, 2980, 3440 cm^{-1}; EIMS (*m*/*z*) 250 (M^+), 235 [(M−Me)$^+$]. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.35, H, 7.24.

4.1.12. (1*S*,2*S*,3*S*,4*R*,4a*R*,5*R*,6*S*,7*S*,8a*R*)-2-Bromo-3,5-epoxy-6,7-(*O*-isopropylidenedioxy)perhydro-*endo*-1,4-methanonaphthalen-8-one (25). *N*-Bromosuccinimide (2.78 g, 16 mmol) was added in small portions to a stirred solution of **28** (3.02 g, 12 mmol) in dry dichloromethane (180 ml) at 0 °C, and stirring was continued for 1 h at room temperature. The mixture was diluted with ether (400 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×150 ml), saturated aqueous sodium hydrogen carbonate (2×150 ml), and brine (2×150 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **25** (3.41 g, 86%) as a white solid. Recrystallization from hexane/ether (5:1) afforded pale yellow prisms, mp 121–122 °C; $[\alpha]_D^{20}$ +65.9 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (3H, s, C-Me), 1.52 (3H, s, C-Me), 1.67 (1H, d, J=11.2 Hz, C9–H), 1.22 (1H, d, J=11.2 Hz,

C9–H), 2.82 (1H, br, C1–H), 2.97 (1H, br, C4–H), 3.00–3.10 (2H, m, C4a–H, C8a–H), 3.82 (1H, d, $J=1.2$ Hz, C2–H), 3.88 (1H, t, $J=1.9$ Hz, C5–H), 4.28 (1H, d, $J=6.3$ Hz, C7–H), 4.44 (1H, dd, $J=0.8$, 5.3 Hz, C3–H), 4.54 (1H, dd, $J=1.7$, 6.3 Hz, C6–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7, 26.6, 33.7, 41.4, 42.7, 46.1, 47.5, 55.0, 77.5, 77.7, 78.1, 87.3, 111.2, 207.0; IR (KBr) 540, 710, 750, 770, 810, 840, 860, 890, 940, 970, 1060, 1090, 1160, 1210, 1270, 1310, 1380, 1460, 1720, 1790, 2890, 2940, 2990 cm^{-1}; EIMS (*m/z*) 330 [$(M+2)^+$, ^{81}Br], 328 (M^+, ^{79}Br), 315 [$(M-Me+2)^+$, ^{81}Br], 313 [$(M-Me)^+$, ^{79}Br]. Anal. calcd for $C_{14}H_{17}BrO_4$: C, 51.08; H, 5.21; Br, 24.27. Found: C, 51.33; H, 5.23; Br, 24.50.

4.1.13. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-(*O*-isopropylidenedioxy)tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (29). Lithium bis(trimethylsilyl)amide in THF (1.0 M solution, 67 µl, 67 µmol) was added dropwise to a stirred solution of **25** (20 mg, 61 µmol) in dry THF (1.5 ml) at −78 °C under argon, and the stirring was continued for 30 min at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (1 ml) at −78 °C, and the mixture was diluted with ether (40 ml). The organic layer was washed successively with saturated aqueous ammonium chloride (2×15 ml), saturated aqueous sodium hydrogen carbonate (2×15 ml), and brine (2×15 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **29** (15 mg, 98%) as a white solid. Recrystallization from hexane/dichloromethane (10:1) afforded colorless prisms, mp 77–78 °C; $[\alpha]_D^{20}$ −61.6 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (3H, s, C-Me); 1.45 (3H, s, C-Me); 1.67 (1H, dd, $J=1.3$, 5.0 Hz, C10–H); 1.80 (1H, d, $J=11.4$ Hz, C11–H); 1.86 (1H, d, $J=11.4$ Hz, C11–H); 2.42 (1H, d, $J=4.3$ Hz, C1–H); 2.46 (1H, s, C8–H); 2.87 (1H, t, $J=2.4$ Hz, C7–H); 4.40–4.45 (3H, m, C4–H, C6–H, C9–H); 4.66 (1H, dd, $J=1.3$, 5.7 Hz, C5–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 25.0, 27.2, 30.4, 32.5, 34.3, 41.7, 44.7, 77.6, 77.9, 79.4, 82.5, 110.1, 201.7; IR (KBr) 520, 580, 630, 830, 860, 880, 920, 940, 960, 990, 1020, 1040, 1070, 1160, 1210, 1270, 1300, 1330, 1380, 1700, 2880, 2900, 2940, 2990 cm^{-1}; EIMS (*m/z*) 248 (M^+), 233 [$(M-Me)^+$], 190 [$(M-Me_2CO)^+$]. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.51; H, 6.57.

4.1.14. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4-[hydroxy(phenyl)methy]-4,5-(*O*-isopropylidenedioxy)-tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (23). Lithium bis(trimethylsilyl)amide in THF (1.0 M solution, 94 µl, 94 µmol) was added dropwise to a stirred solution of **29** (21.0 mg, 85 µmol) in dry THF (1.0 ml) at −78 °C under argon. After 30 min, a solution of benzaldehyde (**8**) (18 µl, 0.17 mmol) in dry THF (0.5 ml) was added slowly at −78 °C, and the stirring was continued for 1 h at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (1 ml) at 0 °C, and the mixture was diluted with ether (15 ml). The organic layer was washed successively with saturated aqueous ammonium chloride (2×7 ml), saturated aqueous sodium hydrogen carbonate (2×7 ml), and brine (2×7 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1→1:1) to give **23** (29.3 mg, 98%) as a hardly separable epimeric mixture (6:1 by 500 MHz ^{1}H NMR). In order to obtain analytical samples, a small amount of the epimeric mixture **23** was further subjected to column chromatography (hexane/ethyl acetate, 2:1→1:1) to provide pure samples of **23a** (major, more polar) and **23b** (minor, less polar).

Compound **23a**. Colorless prisms; mp 181–182 °C; $[\alpha]_D^{20}$ −68.9 (*c* 1.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, s, C-Me), 1.38 (3H, s, C-Me), 1.61 (1H, d, $J=5.2$ Hz, OH), 1.78 (1H, d, $J=11.5$ Hz, C11–H), 1.84 (1H, d, $J=11.5$ Hz, C11–H), 2.30 (1H, d, $J=5.2$ Hz), 2.45 (1H, s), 2.90 (1H, t, $J=2.3$ Hz), 3.13 (1H, d, $J=4.1$ Hz), 4.44 (1H, d, $J=3.0$ Hz), 4.51 (1H, t, $J=2.3$ Hz), 4.52 (1H, t, $J=2.8$ Hz), 5.05 (1H, d, $J=8.5$ Hz), 7.28–7.36 (3H, m, Ph), 7.42–7.46 (2H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 26.2, 28.0, 30.3, 30.4, 32.4, 41.1, 46.6, 76.4, 77.7, 79.6, 83.2, 88.1, 110.1, 127.8 (2 carbons), 128.4, 129.2 (2 carbons), 138.0, 205.6; IR (KBr) 510, 600, 700, 730, 830, 880, 920, 1020, 1060, 1110, 1170, 1250, 1290, 1380, 1450, 1720, 2940, 2990, 3380 cm^{-1}; EIMS (*m/z*) 337 [$(M-OH)^+$]; CIMS (*m/z*) 355 [$(M+H)^+$]. Anal. Calcd for $C_{21}H_{22}O_6$: C, 71.17; H, 6.26. Found: C, 71.24; H 6.35.

Compound **23b**. Colorless viscous oil. $[\alpha]_D^{20}$ −85.2 (*c* 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, s, C-Me), 1.38 (3H, s, C-Me), 1.78 (1H, d, $J=11.5$ Hz, C11–H), 1.84 (1H, d, $J=11.5$ Hz, C11–H), 1.92 (1H, dd, $J=1.5$, 5.1 Hz, OH), 2.41 (1H, d, $J=5.1$ Hz), 2.46 (1H, s), 2.89 (1H, t, $J=2.3$ Hz), 3.23 (1H, d, $J=8.6$ Hz), 4.51 (2H, m), 4.69 (1H, d, $J=2.7$ Hz), 5.06 (1H, d, $J=8.5$ Hz), 7.27–7.31 (1H, m, Ph), 7.34 (2H, t, $J=7.4$ Hz, Ph), 7.44 (2H, d, $J=7.2$ Hz, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 26.5, 28.5, 30.3, 33.3, 33.3, 41.0, 45.2, 75.3, 77.0, 78.6, 83.3, 86.9, 110.5, 127.8 (2 carbons), 128.1, 128.5 (2 carbons), 139.2, 204.2; IR (neat) 510, 590, 710, 730, 830, 880, 920, 1060, 1170, 1240, 1290, 1380, 1450, 1700, 2940, 2990, 3470 cm^{-1}; EIMS (*m/z*) 337 [$(M-OH)^+$], 248 [$(M-PhCHO)^+$] CIMS (*m/z*) 355 [$(M+H)^+$]; HREIMS (*m/z*) calcd for $C_{14}H_{16}O_4$ [$(M-PhCHO)^+$]: 248.1049, found 248.1057.

4.1.15. One-pot procedure for the preparation of 23 from 25. Lithium bis(trimethylsilyl)amide in THF (1.0 M solution, 1.43 ml, 1.4 mmol) was added dropwise to a stirred solution of **25** (213 mg, 0.65 mmol) in dry THF (8 ml) at −78 °C under argon. After 30 min, a solution of benzaldehyde (**8**) (0.20 ml, 2.0 mmol) in dry THF (1 ml) was added slowly to the mixture at −78 °C, and the stirring was continued for 1 h at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (2 ml) at 0 °C, and the mixture was diluted with ether (50 ml). The organic layer was washed successively with saturated aqueous ammonium chloride (2×20 ml), saturated aqueous sodium hydrogen carbonate (2×20 ml), and brine (2×20 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1→1:1) to give **23** (225 mg, 98%) as an epimeric mixture (6:1 by 500 MHz ^{1}H NMR). The IR, ^{1}H NMR, and mass spectra of this material were identical with those recorded for the preparation of **23** (see, Section 4.1.14).

4.1.16. [(1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-(*O*-isopropylidenedioxy)tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one-4-yl](phenyl)methyl *O*-phenyl carbonothioate (30). Phenyl thionochloroformate (0.18 ml, 1.3 mmol) was added to a stirred solution of **23** (6:1 epimeric mixture) (230 mg, 0.65 mmol) in dry acetonitrile (10 ml) containing 4-dimethylaminopyridine (DMAP) (316 mg, 2.6 mmol) at room temperature. After 12 h, the mixture was diluted with diethyl ether (100 ml). The organic layer was successively washed with 3% aqueous hydrochloric acid (2×50 ml), saturated aqueous sodium hydrogen carbonate (2×50 ml), and brine (2×50 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 5:2) to give **30** (292 mg, 92%) as a hardly separable epimeric mixture (6:1 by 500 MHz ^{1}H NMR), as a colorless oil. In order to obtain analytical samples, a small amount of the epimeric mixture **30** was further subjected to column chromatography (hexane/ethyl acetate, 4:1→3:1) to provide pure samples of **30a** (major, more polar) and **30b** (minor, less polar).

Compound **30a**. Colorless viscous oil. $[\alpha]_D^{20}$ −33.4 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (3H, s, C-Me), 1.44 (3H, s, C-Me), 1.68 (1H, br), 1.75 (1H, d, *J*=11.5 Hz), 1.83 (1H, d, *J*=11.5 Hz), 2.23 (1H, d, *J*=5.2 Hz), 2.44 (1H, s), 2.90 (1H, t, *J*=2.4 Hz), 4.50 (1H, br), 4.53 (1H, t, *J*=2.7 Hz), 4.60 (1H, br d, *J*=2.2 Hz), 6.70 (1H, s), 6.99–7.03 (2H, m), 7.22–7.27 (1H, m), 7.32–7.41 (5H, m), 7.51–7.55 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 26.2, 28.1, 30.1, 30.3, 32.2, 41.2, 46.9, 76.5, 80.0, 83.2, 86.2, 87.1, 110.8, 121.9 (2 carbons), 126.5, 128.0 (2 carbons), 129.2, 129.4 (2 carbons), 130.2 (2 carbons), 133.8, 153.5, 194.1, 202.2; IR (neat) 510, 690, 750, 850, 880, 940, 1030, 1070, 1120, 1200, 1270, 1380, 1460, 1490, 1590, 1710, 2940, 2990 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{28}H_{26}O_6S$ (M^+): 490.1450, found 490.1428.

Compound **30b**. Colorless viscous oil. $[\alpha]_D^{20}$ −64.7 (*c* 1.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, s, C-Me), 1.39 (3H, s, C-Me), 1.82 (1H, d, *J*=11.4 Hz), 1.88 (1H, d, *J*=11.4 Hz), 2.15 (1H, dd, *J*=1.8, 5.1 Hz), 2.46 (1H, d, *J*=5.0 Hz), 2.50 (1H, s), 2.94 (1H, t, *J*=2.4 Hz), 4.55 (1H, t, *J*=2.5 Hz), 4.58 (1H, t, *J*=2.3 Hz), 4.90 (1H, d, *J*=2.5 Hz), 6.55 (1H, s), 6.98–7.03 (2H, m, Ph), 7.22–7.27 (1H, m, Ph), 7.32–7.46 (5H, m, Ph), 7.49–7.55 (2H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 26.5, 28.7, 30.3, 33.5, 33.6, 41.3, 45.2, 77.2, 79.1, 83.1, 83.9, 85.8, 110.5, 121.9 (2 carbons), 126.6, 128.1 (2 carbons), 128.9, 129.3 (2 carbons), 129.5 (2 carbons), 134.2, 153.4, 192.9, 202.7; IR (neat) 690, 750, 880, 1020, 1070, 1200, 1270, 1380, 1460, 1490, 1590, 1700, 2940, 2990 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{28}H_{26}O_6S$ (M^+): 490.1450, found 490.1476.

4.1.17. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-4-Benzyl-6,9-epoxy-4,5-(*O*-isopropylidenedioxy)tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (31). Tri-*n*-butyltin hydride (0.35 ml, 1.3 mmol) and azobisisobutyronitrile (AIBN) (21 mg, 0.13 mmol) were added to a solution of **30** (6:1 epimeric mixture) (213 mg, 0.43 mmol) in dry toluene (7.5 ml). For the deaeration of the reaction mixture, it was frozen using liquid nitrogen, and the reaction vessel was evacuated in vacuo for 30 min and then filled with dry argon. The mixture was heated at reflux for 2 h. After cooling, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:0→3:1) to give **31** (116 mg, 79%) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless prisms, mp 107–108 °C; $[\alpha]_D^{20}$ −69.6 (*c* 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, s, C-Me), 1.36 (3H, s, C-Me), 1.67 (1H, dd, *J*=1.6, 5.1 Hz, C10–H), 1.80 (1H, d, *J*=11.4 Hz, C11–H), 1.85 (1H, d, *J*=11.4 Hz, C11–H), 2.33 (1H, d, *J*=4.9 Hz, C1–H), 2.46 (1H, s, C8–H), 2.90 (1H, t, *J*=2.3 Hz, C7–H), 2.99 (1H, d, *J*=13.7 Hz, CH_aH$_b$Ph), 3.22 (1H, d, *J*=13.7 Hz, CH$_a$$H_b$Ph), 4.39 (1H, d, *J*=3.0 Hz, C5–H), 4.54 (1H, t, *J*=2.8 Hz, C6–H), 4.57 (1H, t, *J*=2.3 Hz, C9–H), 7.22–7.34 (5H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 26.3, 28.1, 30.3, 31.9, 31.9, 41.2, 43.3, 46.1, 76.8, 78.5, 83.2, 85.7, 109.2, 127.0, 127.9 (2 carbons), 131.9 (2 carbons), 135.2, 207.5; IR (KBr) 510, 620, 700, 770, 830, 880, 920, 940, 990, 1030, 1060, 1080, 1100, 1120, 1140, 1170, 1240, 1300, 1330, 1380, 1450, 1490, 1710, 2870, 2930, 2990 cm^{-1}; EIMS (*m*/*z*) 338 (M^+), 280 [(M−Me_2CO)$^+$], 247 [(M−$PhCH_2$)$^+$]. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H 6.55. Found: C, 74.65; H, 6.61.

4.1.18. (1*S*,2*S*,3*S*,4*R*,4a*R*,5*R*,6*S*,7*S*,8a*R*)-7-Benzyl-3,5-epoxy-2-iodo-6,7-*O*-isopropylidenedioxy-1,2,3,4,4a,5,6,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (32). Iodotrimethylsilane (0.10 ml, 0.70 mmol) was added dropwise to a stirred solution of **31** (120 mg, 0.36 mmol) in carbon tetrachloride (4 ml) at −20 °C under argon, and stirring was continued for 3 h at −10 °C. The reaction was quenched with 20% aqueous sodium thiosulfate (2 ml) at −10 °C, and then the mixture was diluted with ether (40 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×20 ml), saturated aqueous sodium hydrogen carbonate (2×20 ml), and brine (2×20 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **32** (147 mg, 89%) as a colorless viscous oil. $[\alpha]_D^{20}$ +62.7 (*c* 0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, s, C-Me), 1.32 (3H, s, C-Me), 1.84 (1H, d, *J*=11.3 Hz, C9–H), 2.24 (1H, d, *J*=11.3 Hz, C9–H), 2.88–2.97 (4H, m, C1–H, C4–H, C4a–H, CH_aH$_b$Ph), 3.07 (1H, dd, *J*=4.9, 10.1 Hz, C8a–H), 3.35 (1H, d, *J*=14.1 Hz, CH$_a$$H_b$Ph), 3.61 (1H, d, *J*=2.4 Hz, C2–H), 4.25 (1H, t, *J*=3.7 Hz, C5–H), 4.36 (1H, d, *J*=4.3 Hz, C6–H), 4.80 (1H, d, *J*=5.4 Hz, C3–H), 7.22–7.32 (5H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 28.3, 33.0, 36.5, 38.7, 39.7, 47.0, 47.7, 48.2, 75.7, 76.1, 82.1, 89.4, 110.3, 126.8, 127.9 (2 carbons), 132.0 (2 carbons), 135.3, 210.6; IR (neat) 520, 610, 660, 700, 730, 770, 850, 890, 910, 940, 970, 1050, 1060, 1120, 1160, 1220, 1230, 1260, 1380, 1450, 1490, 1710, 2890, 2930, 2990 cm^{-1}; EIMS (*m*/*z*) 466 (M^+), 451 [(M−Me)$^+$], 408 [(M−Me_2CO)$^+$], 375 [(M−$PhCH_2$)$^+$]; HREIMS (*m*/*z*) calcd for $C_{21}H_{23}IO_4$ (M^+): 466.0641, found 466.0636.

4.1.19. (1*R*,4*S*,4a*R*,5*R*,6*S*,7*S*,8a*S*)-7-Benzyl-5-hydroxy-6,7-*O*-isopropylidenedioxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (33). Zinc powder (272 mg, 4.2 mmol) and acetic acid (0.24 ml, 4.2 mmol) were successively added to a stirred solution of **32** (130 mg, 0.28 mmol) in methanol (5 ml) at room temperature.

The mixture was gradually warmed to 60 °C and stirred for 1 h at the same temperature. After cooling, the mixture was diluted with ether (80 ml) and filtrated. The filtrate was washed with saturated aqueous sodium hydrogen carbonate (2×30 ml), and brine (2×30 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **33** (86 mg, 91%) as a white solid. Recrystallization from hexane/dichloromethane (10:1) afforded colorless prisms, mp 169–170 °C; $[\alpha]_D^{20}$ +161.0 (*c* 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (3H, s, C-Me), 1.41 (1H, d, J=8.4 Hz, C9–H), 1.47 (3H, s, C-Me), 1.54 (1H, d, J=8.4 Hz, C9–H), 1.58 (1H, d, J=3.2 Hz, OH), 2.73 (1H, d, J=14.4 Hz, CH_aH$_b$Ph), 2.99 (1H, s, C1–H), 3.21 (2H, m, C4–H, C8a–H), 3.41 (1H, d, J=14.4 Hz, CH$_a$$H_b$Ph), 3.46 (1H, dd, J=3.7, 11.6 Hz, C4a–H), 4.40 (1H, d, J=4.6 Hz, C6–H), 4.45 (1H, q, J=3.9 Hz, C5–H), 6.20 (1H, dd, J=2.9, 5.4 Hz, C2–H), 6.48 (1H, dd, J=3.1, 5.4 Hz, C3–H), 7.20 (1H, m, Ph), 7.28–7.26 (4H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 27.5, 38.8, 43.3, 43.5, 45.3, 47.2, 51.0, 68.1, 80.1, 83.2, 111.4, 126.3, 127.7 (2 carbons), 132.0 (2 carbons), 133.0, 136.6, 139.1, 207.6; IR (KBr) 540, 620, 660, 700, 730, 750, 820, 850, 910, 980, 1060, 1080, 1150, 1170, 1220, 1240, 1260, 1340, 1380, 1450, 1500, 1710, 2940, 2990, 3520 cm^{-1}; EIMS (*m*/*z*) 340 (M^+), 325 [$(M-Me)^+$], 282 [$(M-Me_2CO)^+$], 249 [$(M-PhCH_2)^+$]. Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09, H, 7.11. Found: C, 74.01, H, 7.17.

4.1.20. (4*R*,5*S*,6*S*)-6-Benzyl-4-hydroxy-5,6-*O*-isopropylidenedioxy-2-cyclohexen-1-one (34). A stirred solution of **33** (60 mg, 0.18 mmol) in diphenyl ether (4 ml) was heated at 230 °C for 4 h. After cooling, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:0→2:1) to give **34** (39.5 mg, 81%) as a colorless viscous oil. $[\alpha]_D^{20}$ −0.7 (*c* 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (3H, s, C-Me), 1.29 (3H, s, C-Me), 1.70 (1H, d, J=6.2 Hz, OH), 3.04 (1H, d, J=14.1 Hz, CH_aH$_b$Ph), 3.17 (1H, d, J=14.1 Hz, CH$_a$$H_b$Ph), 4.13 (1H, t, J=1.8 Hz, C5–H), 4.61 (1H, m, C4–H), 6.16 (1H, d, J=10.1 Hz, C2–H), 6.81 (1H, ddd, J=2.0, 4.9, 10.1 Hz, C3–H), 7.25–7.34 (5H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 27.4, 38.9, 64.6, 78.5, 81.8, 108.6, 127.1, 127.8 (2 carbons), 128.3, 131.5 (2 carbons), 134.7, 144.4, 199.6; IR (neat) 530, 590, 620, 670, 700, 730, 760, 800, 830, 860, 900, 920, 970, 1030, 1060, 1080, 1110, 1140, 1170, 1230, 1240, 1380, 1440, 1450, 1500, 1680, 2930, 2990, 3030, 3060, 3450 cm^{-1}; EIMS (*m*/*z*) 274 (M^+), 259 [$(M-Me)^+$]; HREIMS (*m*/*z*) calcd for $C_{15}H_{15}O_4$ [$(M-Me)^+$]: 259.0970, found 259.0992.

4.1.21. (1*R*,5*S*,6*S*)-5-Benzyl-5,6-*O*-isopropylidenedioxy-4-oxo-2-cyclohexenyl methanesulfonate (4). Methanesulfonyl chloride (0.17 ml, 2.1 mmol) was added to a stirred solution of **34** (58.8 mg, 0.21 mmol) in dichloromethane (5 ml) containing triethylamine (0.42 ml, 3.0 mmol) and 4-dimethylaminopyridine (DMAP) (24 mg, 0.21 mmol) at 0 °C, and stirring was continued for 3 h at room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (2 ml) at 0 °C, and the mixture was diluted with ether (80 ml). The organic layer was successively washed with 3% aqueous hydrochloric acid (2×30 ml), saturated aqueous sodium hydrogen carbonate (2×30 ml), and brine (2×30 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **4** (63 mg, 85%) as a colorless viscous oil. $[\alpha]_D^{20}$ −62.6 (*c* 1.19, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (3H, s, C-Me), 1.30 (3H, s, C-Me), 2.86 (1H, d, J=14.5 Hz, CH_aH$_b$Ph), 3.10 (3H, s, Ms), 3.27 (1H, d, J=14.5 Hz, CH$_a$$H_b$Ph), 4.14 (1H, t, J=1.7 Hz, C5–H), 5.45 (1H, dd, J=1.8, 4.8 Hz, C4–H), 6.30 (1H, d, J=10.1 Hz, C2–H), 6.85 (1H, ddd, J=1.8, 4.8, 10.1 Hz, C3–H), 7.25–7.34 (5H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.3, 27.4, 38.1, 38.8, 71.2, 76.3, 81.6, 109.7, 127.3, 128.1 (2 carbons), 130.8, 131.4 (2 carbons), 134.1, 138.9, 197.8; IR (KBr) 530, 620, 700, 760, 790, 850, 900, 950, 980, 1070, 1090, 1120, 1150, 1180, 1230, 1370, 1450, 1500, 1690, 1740, 2940, 2990, 3030 cm^{-1}; EIMS (*m*/*z*) 352 (M^+), 337 [$(M-Me)^+$], 294 [$(M-Me_2CO)^+$]; HREIMS (*m*/*z*) calcd for $C_{17}H_{20}O_6S$ (M^+): 352.0981, found 352.0982.

4.1.22. (1*R*,5*S*,6*S*)-5-Benzyl-5,6-dihydroxy-4-oxo-2-cyclohexenyl methanesulfonate (35). A solution of **4** (60 mg, 0.17 mmol) in trifluoroacetic acid/water (6:1) (1 ml) was stirred at 0 °C for 30 min. The mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **35** (45 mg, 85%) as a colorless viscous oil. $[\alpha]_D^{20}$ −49.8 (*c* 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.99 (1H, d, J=3.6 Hz, C3–OH), 3.16 (3H, s, Ms), 3.18 (2H, s, CH_2Ph), 3.35 (1H, s, C6–OH), 4.14 (1H, dt, J=1.1, 3.7 Hz, C5–H), 5.47 (1H, dt, J=1.1, 3.9 Hz, C4–H), 6.24 (1H, dd, J=1.1, 10.2 Hz, C2–H), 6.85 (1H, ddd, J=1.1, 3.7, 10.2 Hz, C3–H), 7.14–7.19 (2H, m, Ph), 7.22–7.31 (3H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.6, 40.9, 73.3, 75.7, 78.1, 127.3, 128.4 (2 carbons), 129.0, 130.6 (2 carbons), 134.1, 141.7, 197.1; IR (neat) 530, 700, 730, 780, 850, 880, 940, 980, 1060, 1110, 1170, 1360, 1440, 1450, 1490, 1690, 2930, 3030, 3480 cm^{-1}; EIMS (*m*/*z*) 312 (M^+), 294 [$(M-H_2O)^+$]; HREIMS (*m*/*z*) calcd for $C_{14}H_{16}O_6S$ (M^+): 312.0668, found 312.0656.

4.1.23. (4*S*,5*S*,6*S*)-6-Benzyl-4,5-epoxy-6-hydroxy-2-cyclohexen-1-one (2). 0.2 M Sodium hydroxide (0.7 ml, 0.14 mmol) was added dropwise to a stirred solution of **35** (30 mg, 96 μmol) in ether (8 ml) at 0 °C. After 10 min, the mixture was extracted with ether (2×30 ml). The combined extracts were washed with brine (3×20 ml) and dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **2** (19 mg, 90%) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless prisms, mp 96–97 °C; $[\alpha]_D^{20}$ +45.6 (*c* 0.80, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.93 (1H, d, J=13.6 Hz, CH_aH$_b$Ph), 3.01 (1H, d, J=13.6 Hz, CH$_a$$H_b$Ph), 3.60 (1H, dt, J=1.6, 3.9 Hz, C4–H), 3.65 (1H, s, OH), 3.77 (1H, d, J=3.9 Hz, C5–H), 6.16 (1H, dd, J=1.5, 9.9 Hz, C2–H), 7.09–7.15 (3H, m, Ph, C3–H), 7.22–7.32 (3H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.4 (*C*H$_2$Ph), 47.9 (C4 or C5), 56.0 (C4 or C5), 77.7 (C6), 127.3 (Ph or C3), 128.4 (2 carbons, Ph), 130.2 (Ph or C3), 130.3 (2 carbons, Ph), 133.6 (Ph), 145.1 (C2), 197.5 (C1); IR (KBr) 500, 540, 580, 630, 670, 700, 750, 790, 840, 860, 900, 960, 1030, 1090,

1130, 1150, 1200, 1240, 1250, 1300, 1380, 1450, 1490, 1600, 1690, 2850, 2920, 3030, 3060, 3480 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{13}H_{12}O_3$ (M^+): 216.0786, found 216.0806. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 71.81; H, 5.58.

4.1.24. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-*O*-isopropylidenedioxy-4-[[(4*R*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]hydroxymethyl]tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (24). Lithium bis(trimethylsilyl)amide in THF (1.0 M solution, 5.30 ml, 5.3 mmol) was added dropwise to a stirred solution of **25** (800 mg, 2.4 mmol) in dry THF (40 ml) at −78 °C under argon. After 30 min, a solution of (*R*)-*N*-(*p*-toluenesulfonyl)-*N*,*O*-isopropylidene serinal (**9**) (1.72 g, 6.0 mmol) in dry THF (20 ml) was added slowly at −78 °C, and the resulting mixture was further stirred for 1 h at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (3 ml) at −78 °C, and the mixture was diluted with ether (300 ml). The organic layer was washed successively with saturated aqueous ammonium chloride (2×100 ml), saturated aqueous sodium hydrogen carbonate (2×100 ml), and brine (2×100 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1→1:1) to give **24** (1.27 g, 98%) (inseparable mixture, major/minor=9:1) as a colorless viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (3H, s, C-Me), 1.39 (3H, s, C-Me), 1.44 (3H, s, C-Me), 1.68 (3H, s, C-Me), 1.79 (1H, d, *J*=11.3 Hz, C11–H), 1.85 (1H, d, *J*=11.3 Hz, C11–H), 2.25 (1H, d, *J*=5.2 Hz, C1–H), 2.35 (1H, dd, *J*=1.8, 5.2 Hz, C2–H), 2.41 (3H, s, Me of Ts), 2.45 (1H, s, C8–H), 2.70 (1H, d, *J*=6.8 Hz, OH), 2.90 (1H, t, *J*=2.3 Hz, C7–H), 3.76 (1H, d, *J*=6.4, 9.8 Hz, C4′–H), 4.20 (1H, d, *J*=6.5 Hz, C5′–H), 4.39 (1H, d, *J*=7.0 Hz, CH-OH), 4.51 (1H, dd, *J*=1.3, 9.8 Hz, C5′–H), 4.55 (1H, t, *J*=2.3 Hz, C9–H), 4.59 (1H, t, *J*=2.8 Hz, C7–H), 5.05 (1H, d, *J*=3.1 Hz, C6–H), 7.30 (2H, d, *J*=8.2 Hz, Ar), 7.68 (2H, d, *J*=8.2 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 21.5, 24.4, 26.1, 27.8, 28.8, 29.2, 30.5, 32.6, 41.2, 47.2, 59.6, 64.7, 73.0, 76.2, 78.9, 83.2, 88.1, 96.9, 109.6, 127.8 (2 carbons), 129.7 (2 carbons), 137.8, 143.5, 206.7; IR (neat) 550, 590, 680, 730, 820, 830, 880, 940, 1030, 1100, 1150, 1230, 1250, 1340, 1370, 1380, 1460, 1710, 2880, 2940, 2990, 3440 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{27}H_{33}NO_8S$ (M^+): 531.1927, found 531.1903.

4.1.25. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-*O*-isopropylidenedioxy-4-[[(4*R*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl](methyldithiocarbonyloxy)-methyl]tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (36). Sodium bis(trimethylsilyl)amide in THF (1.0 M solution, 0.85 ml, 0.85 mmol) was added dropwise to a stirred solution of **24** (378 mg, 0.71 mmol) in dry THF (20 ml) at −78 °C under argon. After 30 min, carbon disulfide (0.43 ml, 7.1 mmol) was added slowly to the mixture at −78 °C, and stirring was continued for 1 h at the same temperature. The resulting mixture was gradually warmed to −50 °C over 1 h, and then iodomethane (0.54 ml, 7.1 mmol) was added slowly to the above mixture at −78 °C. After 1 h, the mixture was gradually warmed to −50 °C over 1 h. The reaction was quenched with saturated aqueous ammonium chloride (3 ml) at 0 °C, and then the mixture was diluted with ether (200 ml). The organic layer was washed successively with saturated aqueous sodium thiosulfate (2×80 ml), saturated aqueous sodium hydrogen carbonate (2×80 ml), and brine (2×80 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **36** (389 mg, 88%) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless prisms, mp 252–253 °C; $[\alpha]_D^{20}$ −2.0 (*c* 1.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (3H, s, C-Me), 1.41 (3H, s, C-Me), 1.47 (3H, s, C-Me), 1.51 (3H, s, C-Me), 1.79 (1H, d, *J*=11.4 Hz, C11–H), 1.84 (1H, d, *J*=11.4 Hz, C11–H), 2.25 (1H, d, *J*=5.2 Hz, C1–H), 2.42 (4H, s, Me of Ts, C8–H), 2.65 (3H, s, S-Me), 2.72 (1H, dd, *J*=1.9, 5.2 Hz, C10–H), 2.88 (1H, t, *J*=2.4 Hz, C7–H), 3.77 (1H, dd, *J*=7.0, 9.5 Hz, C4′–H), 4.46 (1H, dd, *J*=1.4, 9.6 Hz, C5′–H), 4.50 (1H, t, *J*=2.7 Hz, C6–H), 4.52 (1H, t, *J*=2.2 Hz, C9–H), 4.57 (1H, d, *J*=2.8 Hz, C5–H), 4.65 (1H, d, *J*=5.9 Hz, C5′–H), 6.88 (1H, s, C*H*–OCS$_2$Me), 7.31 (2H, d, *J*=8.2 Hz, Ar), 7.69 (2H, d, *J*=8.3 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 20.3, 21.5, 24.1, 25.8, 27.7, 28.7, 29.3, 30.5, 32.5, 41.4, 47.5, 58.6, 64.7, 75.6, 79.5, 80.9, 82.9, 87.4, 96.8, 109.4, 128.2 (2 carbons), 129.6 (2 carbons), 137.5, 143.4, 205.6, 214.0; IR (neat) 520, 550, 590, 650, 680, 730, 820, 880, 910, 940, 1060, 1100, 1150, 1180, 1210, 1250, 1350, 1370, 1460, 1710, 2880, 2940, 2990 cm^{-1}; EIMS (*m*/*z*) 621 (M^+), 606 [(M−Me)$^+$]. Anal. Calcd for $C_{29}H_{35}NO_8S_3$: C, 56.02; H, 5.67; N, 2.25; S, 15.47. Found: C, 55.85; H, 5.69; N, 2.29; S, 15.31.

4.1.26. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-*O*-isopropylidenedioxy-4-[[(4*R*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl]tetracyclo[6.2.1.0^{2,7}.0^{2,10}]-undecan-3-one (37). Tri-*n*-butyltin hydride (0.33 ml, 1.2 mmol) and triethylborane in hexane (1.0 M solution, 0.63 ml, 0.63 mmol) were added successively to a stirred solution of **36** (384 mg, 0.62 mmol) in dry toluene (24 ml) at room temperature. After 1 h, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:0→2:1) to give **37** (303 mg, 95%) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless prisms, mp 207–208 °C; $[\alpha]_D^{20}$ +49.1 (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (3H, s, C2′-Me), 1.37 (3H, s, C-Me), 1.40 (3H, s, C-Me), 1.67 (3H, s, C2′-Me), 1.79 (1H, d, *J*=11.4 Hz, C11–H), 1.84 (1H, d, *J*=11.4 Hz, C11–H), 2.20 (1H, dd, *J*=10.9, 14.7 Hz, C4–CH_aH$_b$–C4′), 2.29 (1H, d, *J*=5.3 Hz, C1–H), 2.41 (3H, s, Me of Ts), 2.46 (1H, s, C8–H), 2.51 (1H, dd, *J*=1.8, 5.2 Hz, C10–H), 2.57 (1H, d, *J*=14.6 Hz, C4–CH$_a$H$_b$–C4′), 2.89 (1H, t, *J*=2.3 Hz, C7–H), 3.67 (1H, m, C5′–H), 4.12–4.18 (2H, m, C4′–H, C5′–H), 4.34 (1H, d, *J*=2.9 Hz, C5–H), 4.57 (2H, d, *J*=2.6 Hz, C6–H, C9–H), 7.28 (2H, d, *J*=8.1 Hz, Ar), 7.65 (2H, d, *J*=8.3 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0, 21.5, 24.0, 26.8, 27.8, 30.3, 30.5, 31.7, 41.4, 44.5, 47.0, 55.7, 69.2, 76.30, 77.2, 83.5, 84.9, 84.9, 96.6, 109.7, 127.5 (2 carbons), 129.6 (2 carbons), 138.0, 143.2, 207.2; IR (neat) 520, 550, 600, 650, 680, 710, 840, 880, 920, 940, 1030, 1060, 1240, 1300, 1340, 1370, 1450, 1710, 2880, 2940, 2990 cm^{-1}; EIMS (*m*/*z*) 500 [(M−Me)$^+$]; CIMS (*m*/*z*) 516 [(M+H)$^+$]. Anal. Calcd for $C_{27}H_{33}NO_7S$: C, 62.89; H, 6.45; N, 2.72; S, 6.22. Found: C, 62.59; H, 6.49; N, 2.74; S, 6.25.

4.1.27. (1*S*,2*S*,3*S*,4*R*,4a*R*,5*R*,6*S*,7*S*,8a*R*)-3,5-Epoxy-2-iodo-6,7-*O*-isopropylidenedioxy-7-[(2*S*)-2-*p*-toluenesulfonylamino-3-hydroxypropyl]-1,2,3,4,4a,5,6,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (38). Iodotrimethylsilane (82 μl, 0.46 mmol) was added dropwise to a stirred solution of **37** (98 mg, 0.15 mmol) in carbon tetrachloride (10 ml) at −20 °C under argon, and stirring was continued at −10 °C for 3 h. The reaction mixture was quenched with saturated aqueous sodium thiosulfate (2 ml) at 0 °C, and then the mixture was diluted with chloroform (80 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×30 ml), saturated aqueous sodium hydrogen carbonate (2×30 ml), and brine (2×30 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **38** (104 mg, 91%) as a white amorphous solid. $[\alpha]_D^{20}$ +44.3 (*c* 1.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (6H, s, C-Me), 1.74 (1H, d, *J*=11.2 Hz, C9–H), 1.86 (1H, dd, *J*=3.5, 15.5 Hz, C1′–H), 2.20–2.32 (3H, m, C9–H, C1′–H, OH), 2.42 (3H, s, Me of Ts), 2.61 (1H, dd, *J*=4.8, 10.5 Hz, C8a–H), 2.75 (1H, br, C1–H), 2.87 (1H, br, C4–H), 2.91 (1H, dt, *J*=3.8, 10.5 Hz, C4a–H), 3.43 (1H, m, C2′–H), 3.67 (2H, t, *J*=4.7 Hz, C3′H_2OH), 3.75 (1H, d, *J*=1.9 Hz, C2–H), 3.80 (1H, t, *J*=2.6 Hz, C5–H), 4.17 (1H, d, *J*=2.4 Hz, C6–H), 4.60 (1H, d, *J*=11.2 Hz, C3–H), 5.84 (1H, d, *J*=4.6 Hz, N–H), 7.27 (2H, d, *J*=8.0 Hz, Ar), 7.70 (2H, d, *J*=8.2 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 28.2, 28.5, 32.4, 35.8, 36.5, 42.0, 44.3, 46.6, 48.1, 51.4, 66.3, 77.0, 82.8, 85.5, 88.2, 112.8, 127.6 (2 carbons), 129.3 (2 carbons), 137.42, 143.0, 210.6; IR (neat) 550, 670, 730, 810, 850, 920, 940, 1050, 1090, 1130, 1160, 1220, 1230, 1330, 1380, 1420, 1600, 1710, 2890, 2930, 2980, 3280, 3510 cm^{-1}; HREIMS *m*/*z* for $C_{23}H_{27}INO_6S$ [(M−CH_2OH)$^+$]: 572.0604, found 572.0604.

4.1.28. (1*S*,2*S*,3*S*,4*R*,4a*R*,5*R*,6*S*,7*S*,8a*R*)-3,5-Epoxy-2-iodo-6,7-*O*-isopropylidenedioxy-7-[(4*S*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-1,2,3,4,4a,5,6,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (39). *p*-Toluenesulfonic acid (6 mg, 34 μmol) was added to a stirred solution of **38** (100 mg, 0.17 mmol) in benzene (6 ml) containing 2,2-dimethoxypropane (0.20 ml, 1.7 mmol) at room temperature. The mixture was gradually warmed to 60 °C and stirred for 1 h at the same temperature. After cooling, the mixture was diluted with ether (80 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2×30 ml) and brine (2×30 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **39** (88 mg, 83%) as a colorless viscous oil. $[\alpha]_D^{20}$ +138.4 (*c* 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (3H, s, C-Me), 1.43 (3H, s, C-Me), 1.44 (3H, s, C-Me), 1.70 (3H, s, C-Me), 1.83 (1H, d, *J*=11.2 Hz, C9–H), 2.13 (1H, dd, *J*=10.7,14.8 Hz, C7–CH_2–C4′), 2.27 (1H, d, *J*=11.2 Hz, C9–H), 2.43 (3H, s, Me of Ts), 2.48 (1H, d, *J*=4.6 Hz, C7–CH_2–C4′), 2.89–2.98 (3H, m, C1–H, C4–H, C4a–H), 3.02 (1H, dd, *J*=4.9, 10.2 Hz, C8a–H), 3.67 (1H, dd, *J*=5.5, 8.1 Hz, C5′–H), 3.93 (1H, d, *J*=2.1 Hz, C2–H), 4.16–4.22 (2H, m, C5–H, C5′–H), 4.40–4.46 (2H, m, C4′–H, C6–H), 4.80 (1H, d, *J*=5.1 Hz, C3–H), 7.32 (2H, d, *J*=8.0 Hz, Ar), 7.83 (2H, d, *J*=8.3 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 24.2, 27.3, 28.2, 30.5, 33.0, 36.8, 40.2, 41.0, 46.6, 47.7, 48.3, 55.6, 68.7, 75.9, 81.4, 81.9, 89.2, 96.9, 111.3, 127.8 (2 carbons), 129.5 (2 carbons), 138.0, 143.2, 209.9; IR (neat) 510, 550, 590, 650, 680, 710, 730, 820, 840, 920, 940, 1100, 1160, 1230, 1340, 1370, 1460, 1600, 1710, 1890, 2930, 2990 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{26}H_{31}INO_7S$ [(M−Me)$^+$]: 628.0866, found 628.0853.

4.1.29. (1*R*,4*S*,4a*R*,5*R*,6*S*,7*S*,8a*S*)-5-Hydroxy-6,7-*O*-isopropylidenedioxy-7-[(4*S*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (40). Zinc powder (123 mg, 1.9 mmol) and acetic acid (0.11 ml, 1.9 mmol) were successively added to a stirred solution of **39** (81 mg, 0.13 mmol) in methanol (6 ml) at room temperature. The mixture was gradually warmed to 60 °C and stirred for 1 h at the same temperature. After cooling, the mixture was diluted with ether (50 ml) and filtrated. The filtrate was washed with saturated aqueous sodium hydrogen carbonate (2×20 ml), and brine (2×20 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **40** (64 mg, 98%) as a colorless viscous oil. $[\alpha]_D^{20}$ +127.1 (*c* 1.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (1H, m, C9–H), 1.45 (3H, s, C-Me), 1.47 (3H, s, C-Me), 1.53 (4H, s, C-Me, C9–H), 1.67 (3H, s, C-Me), 1.81 (1H, d, *J*=2.3 Hz, OH), 2.17 (1H, dd, *J*=10.5, 14.0 Hz, C7–C$H_a$$H_b$–C4′), 2.25 (1H, dd, *J*=1.8, 14.4 Hz, C7–C$H_a$$H_b$–C4′), 2.41 (3H, s, Me of Ts), 2.98 (1H, s, C4–H), 3.13 (1H, s, C1–H), 3.21 (1H, dt, *J*=3.4, 11.7 Hz, C4a–H), 3.43 (1H, dd, *J*=3.6, 11.7 Hz, C8a–H), 3.60 (1H, dd, *J*=5.5, 9.0 Hz, C5′–H), 4.12 (1H, dd, *J*=1.8, 9.0 Hz, C5′–H), 4.37 (1H, br, C5–H), 4.43 (1H, d, *J*=4.3 Hz, C6–H), 4.45 (1H, m, C4′–H), 6.19 (1H, dd, *J*=3.0, 5.5 Hz, C3–H), 6.50 (1H, dd, *J*=3.1, 5.6 Hz, C2–H), 7.27 (2H, d, *J*=8.2 Hz, Ar), 7.85 (2H, d, *J*=8.3 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 24.4, 26.5, 27.3, 30.1, 41.8, 43.1, 43.6, 45.5, 46.4, 51.2, 56.4, 68.1, 68.7, 83.0, 85.2, 96.9, 112.2, 127.7 (2 carbons), 129.4 (2 carbons), 132.7, 138.5, 140.0, 142.9, 207.6; IR (neat) 550, 600, 650, 680, 710, 730, 780, 830, 920, 1050, 1100, 1160, 1210, 1240, 1340, 1380, 1450, 1600, 1720, 1880, 2940, 2990, 3530 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{26}H_{32}NO_7S$ [(M−Me)$^+$]: 502.1900, found 502.1869.

4.1.30. (4*R*,5*S*,6*S*)-4-Hydroxy-5,6-*O*-isopropylidenedioxy-7-[(4*S*)-2,2-dimethyl-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-2-cyclohexen-1-one (41). A stirred solution of **40** (23.0 mg, 44 μmol) in diphenyl ether (5 ml) was heated at 230 °C for 2 h. After cooling, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:0→1:1) to give **41** (5.0 mg, 25%) as a colorless viscous oil. $[\alpha]_D^{20}$ +58.1 (*c* 0.46, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, s, C-Me), 1.39 (6H, s, C-Me, C-Me), 1.68 (3H, s, C-Me), 2.13 (1H, dd, *J*=10.8, 14.5 Hz, C6–C$H_a$$H_b$–C4′), 2.42 (3H, s, Me of Ts), 2.43 (1H, d, *J*=14.5 Hz, C6–C$H_a$$H_b$–C4′), 2.52 (1H, br, OH), 3.74 (1H, ddd, *J*=1.3, 5.4, 9.2 Hz, C5′–H), 4.07 (1H, dd, *J*=5.3, 10.7 Hz, C4′–H), 4.09 (1H, d, *J*=9.0 Hz, C5′–H), 4.16 (1H, t, *J*=1.7 Hz, C5–H), 4.66 (1H, br, C4–H), 6.17 (1H, d, *J*=10.2 Hz, C2–H), 6.84 (1H, ddd, *J*=2.0, 4.6, 10.1 Hz,

C3–H), 7.29 (2H, d, $J=8.0$ Hz, Ar), 7.69 (2H, d, $J=8.3$ Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 24.1, 26.7, 27.2, 30.3, 39.5, 55.3, 64.7, 69.2, 80.7, 83.8, 97.0, 109.5, 127.6 (2 carbons), 128.2, 129.6 (2 carbons), 137.7, 143.4, 143.6, 198.8; IR (neat) 550, 590, 650, 680, 710, 750, 830, 880, 910, 1040, 1100, 1160, 1230, 1340, 1370, 1460, 1490, 1600, 1680, 2880, 2940, 2990, 3470 cm^{-1}; HREIMS (*m/z*) calcd for $C_{21}H_{26}NO_7S$ [$(M-Me)^+$]: 436.1430, found 436.1403.

4.1.31. (1*R*,2*S*,4*S*,5*S*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,9-Epoxy-4,5-*O*-isopropylidenedioxy-4-[[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl]tetracyclo[6.2.1.0^{2,7}.0^{2,10}]undecan-3-one (43). 1.0 M Hydrochloric acid (1.36 ml, 1.4 mmol) was added to a stirred solution of **37** (320 mg, 0.62 mmol) in THF (15 ml) at room temperature, and the mixture was heated at 55 °C for 6 h. After cooling, the mixture was neutralized with saturated aqueous sodium hydrogen carbonate (ca. 20 ml), and the resulting mixture was extracted with ether (3×50 ml). The combined extracts were washed with brine (2×50 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give an equilibrium mixture (290 mg) of **42a** and **42b** (1:1 by 500 MHz ^{1}H NMR) as a colorless viscous oil. This equilibrium mixture was directly used for the following reaction without separation.

Trichloromethyl chloroformate (1.23 ml, 6.2 mmol) was added dropwise to a stirred solution of the above equilibrium mixture of **42a** and **42b** (290 mg, 0.61 mmol) in dry THF (30 ml) containing pyridine (1.96 ml, 24 mmol) at 0 °C, and the mixture was gradually warmed to room temperature. After 2 h, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (5 ml) at 0 °C, and the mixture was diluted with ether (200 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid (2×80 ml), saturated aqueous sodium hydrogen carbonate (2×80 ml), and brine (2×80 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 3:2) to give **43** (209 mg, 67% in two steps) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless needles, mp 174–175 °C; $[\alpha]_D^{20}$ +27.5 (*c* 1.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (3H, s, C-Me), 1.39 (3H, s, C-Me), 1.82 (1H, d, $J=11.6$ Hz, C11–H), 1.87 (1H, d, $J=11.6$ Hz, C11–H), 2.02–2.09 (1H, m, C4–CH_aH$_b$–C4′), 2.25 (1H, dd, $J=1.8$, 5.2 Hz, C10–H), 2.34 (1H, d, $J=5.1$ Hz, C1–H), 2.45 (3H, s, Me of Ts), 2.50 (1H, s, C8–H), 2.90 (1H, t, $J=2.2$ Hz, C7–H), 2.92 (1H, d, $J=14.6$ Hz, C4–CH$_a$H$_b$–C4′), 4.33 (1H, d, $J=3.0$ Hz, C5–H), 4.37–4.44 (2H, m, C4′=H, C5′=H), 4.57 (1H, d, $J=5.4$ Hz, C5′=H), 4.60 (1H, t, $J=2.8$ Hz, C6–H), 4.62 (1H, t, $J=2.2$ Hz, C9–H), 7.33 (2H, d, $J=8.4$ Hz, Ar), 7.86 (2H, d, $J=8.4$ Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 21.7, 26.8, 27.8, 30.3, 30.5, 32.1, 41.3, 43.3, 46.6, 54.6, 68.6, 76.2, 83.3, 83.9, 84.1, 110.3, 128.5 (2 carbons), 129.8 (2 carbons), 134.7, 145.7, 152.3, 205.8; IR (KBr) 540, 580, 620, 670, 750, 810, 840, 880, 920, 940, 990, 1030, 1070, 1090, 1140, 1170, 1220, 1250, 1300, 1370, 1600, 1710, 1790, 2880, 2940, 2990 cm^{-1}; EIMS (*m/z*) 501 (M^+), 486 [$(M-Me)^+$]; HREIMS (*m/z*) calcd for $C_{25}H_{27}NO_8S$ (M^+): 501.1457, found 501.1481.

4.1.32. (1*S*,2*S*,3*S*,4*R*,4a*R*,5*R*,6*S*,7*S*,8a*R*)-3,5-Epoxy-2-iodo-6,7-*O*-isopropylidenedioxy-7-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-1,2,3,4,4a,5,6,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (44). Iodotrimethylsilane (68 μl, 0.48 mmol) was added dropwise to a stirred solution of **43** (210 mg, 0.42 mmol) in carbon tetrachloride (20 ml) at −20 °C under argon. After 1 h, the reaction was quenched with saturated aqueous sodium thiosulfate (2 ml) at −20 °C, and then the mixture was diluted with ether (150 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate (2×80 ml), saturated aqueous sodium hydrogen carbonate (2×80 ml), and brine (2×80 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 3:2) to give **44** (195 mg, 74%) as a white solid. Recrystallization from hexane/ether (5:1) afforded colorless needles, mp 233–234 °C; $[\alpha]_D^{20}$ +152.8 (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (3H, s, C-Me), 1.41 (3H, s, C-Me), 1.85 (1H, d, $J=11.3$ Hz, C9–H$_a$), 2.05 (1H, dd, $J=10.7$, 14.6 Hz, C7–CH_aH$_b$–C4′), 2.29 (1H, d, $J=11.1$ Hz, C9–H$_b$), 2.45 (3H, s, Me of Ts), 2.89–2.95 (3H, m, C1–H, C4a-H, C7–CH$_a$H$_b$–C4′), 2.97–3.04 (2H, m, C4–H, C8a-H), 3.80 (1H, d, $J=2.4$ Hz, C2–H), 4.29 (1H, t, $J=3.7$ Hz, C5–H), 4.42 (1H, t, $J=9.0$ Hz, C5′–H), 4.45 (1H, d, $J=4.1$ Hz, C6–H), 4.56 (1H, dd, $J=4.4$, 9.3 Hz, C5′–H), 4.80 (1H, m, C4′–H), 4.85 (1H, d, $J=5.3$ Hz, C3–H), 7.37 (2H, d, $J=8.3$ Hz, Ar), 7.96 (2H, d, $J=8.3$ Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 27.1, 28.0, 32.2, 36.7, 39.9, 40.7, 46.9, 47.9, 48.3, 54.5, 68.8, 75.6, 80.8, 81.0, 89.3, 111.5, 128.5 (2 carbons), 129.8 (2 carbons), 134.8, 145.5, 152.5, 210.3; IR (KBr) 540, 570, 610, 670, 760, 820, 920, 1050, 1090, 1130, 1170, 1310, 1370, 1450, 1600, 1700, 1790, 2990 cm^{-1}; EIMS (*m/z*) 629 (M^+), 614 [$(M-Me)^+$]; HRCIMS (*m/z*) calcd for $C_{25}H_{29}INO_8S$ [$(M+H)^+$]: 630.0659, found 630.0693. Anal. Calcd for $C_{25}H_{28}INO_8S$: C, 47.70; H, 4.48; N, 2.23; S, 5.09. Found: C, 47.78; H, 4.47; N, 2.30; S, 4.82.

4.1.33. (1*R*,4*S*,4a*S*,5*R*,6*S*,7*S*,8a*S*)-5-Hydroxy-6,7-*O*-isopropylidenedioxy-7-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-methanonaphthalen-8-one (45). Zinc powder (300 mg, 4.6 mmol) and acetic acid (0.26 ml, 4.6 mmol) were successively added to a stirred solution of **44** (194 mg, 0.31 mmol) in THF/methanol (1:1) (20 ml) at room temperature. The mixture was gradually warmed to 60 °C and stirred for 1 h at the same temperature. After cooling, the mixture was diluted with ether (150 ml) and filtrated. The filtrate was washed with saturated aqueous sodium hydrogen carbonate (2×70 ml), and brine (2×70 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 3:2) to give **45** (148 mg, 95%) as a colorless viscous oil. $[\alpha]_D^{20}$ +155.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (1H, d, $J=8.4$ Hz, C9–H), 1.50 (3H, s, C-Me), 1.53 (3H, s, C-Me), 1.56 (1H, d, $J=8.4$ Hz, C9–H), 1.94 (1H, s, OH), 2.30 (1H, dd, $J=10.5$, 14.2 Hz, C7–CH_aH$_b$–C4′), 2.44 (3H, s, Me of Ts), 2.72 (1H, dd, $J=2.1$, 14.1 Hz, C7–CH$_a$H$_b$–C4′), 3.01 (1H, s, C4–H), 3.14 (1H, s, C1–H), 3.25 (1H, dt, $J=3.2$, 11.6 Hz, C4a–H), 3.44 (1H, dd, $J=3.6$, 11.6 Hz, C8a–H), 4.17 (1H, t, $J=8.5$ Hz, C5′–H), 4.36 (1H, dd, $J=5.1$,

9.3 Hz, C5′–H), 4.44 (1H, s, C5–H), 4.59 (1H, d, J=4.3 Hz, C6–H), 4.92 (1H, m, C4′–H), 6.20 (1H, dd, J=3.0, 5.3 Hz, C3–H), 6.49 (1H, dd, J=3.1, 5.5 Hz, C2–H), 7.34 (2H, d, J=8.3 Hz, Ar), 7.95 (2H, d, J=8.3 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 26.3, 27.2, 41.1, 43.1, 43.7, 45.5, 46.1, 51.2, 54.8, 67.9, 69.2, 82.9, 84.0, 112.5, 128.5 (2 carbons), 129.8 (2 carbons), 132.9, 134.9, 139.6, 145.5, 152.8, 207.7; IR (neat) 540, 580, 610, 670, 700, 760, 820, 850, 920, 1050, 1090, 1120, 1170, 1210, 1250, 1310, 1380, 1450, 1600, 1720, 1780, 2940, 2990, 3540 cm^{-1}; HREIMS (m/z) calcd for $C_{25}H_{29}NO_8S$ (M^+): 503.1614, found 503.1595.

4.1.34. (4*R*,5*S*,6*S*)-4-Hydroxy-5,6-*O*-isopropylidenedioxy-6-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-2-cyclohexen-1-one (46). A stirred solution of **45** (148 mg, 0.29 mmol) in diphenyl ether (15 ml) was heated at 230 °C for 2 h. After cooling, the mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:0→1:1) to give **46** (75.9 mg, 59%) as a colorless viscous oil. $[\alpha]_D^{20}$ +80.9 (c 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (3H, s, C-Me), 1.40 (3H, s, C-Me), 2.09 (1H, dd, J=11.0, 14.5 Hz, C6–CH_aH$_b$–C4′), 2.20 (1H, d, J=5.3 Hz, OH), 2.44 (3H, s, Me of Ts), 2.92 (1H, dd, J=2.2, 14.4 Hz, C6–CH$_a$$H_b$–C4′), 4.19 (1H, t, J=1.7 Hz, C5–H), 4.45 (2H, d, J=6.2 Hz, C5′–H$_2$), 4.59 (1H, m, C4′–H), 4.72 (1H, t, J=4.7 Hz, C4–H), 6.19 (1H, d, J=10.2 Hz, C2–H), 6.90 (1H, ddd, J=1.9, 4.8, 10.1 Hz, C3–H), 7.34 (2H, d, J=8.2 Hz, Ar), 7.87 (2H, d, J=8.2 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 26.6, 27.2, 39.0, 54.3, 64.1, 69.2, 80.0, 83.2, 109.9, 128.0, 128.4 (2 carbons), 129.9 (2 carbons), 134.5, 144.7, 145.8, 152.5, 198.0; IR (neat) 540, 570, 600, 670, 760, 820, 910, 1040, 1090, 1130, 1170, 1230, 1380, 1490, 1600, 1680, 1790, 2930, 3480 cm^{-1}; CIMS (m/z) 438 [(M+H)$^+$]; HREIMS (m/z) calcd for $C_{19}H_{20}NO_8S$ [(M−Me)$^+$]: 422.0910, found 422.0926.

4.1.35. (1*R*,5*S*,6*S*)-5,6-*O*-Isopropylidenedioxy-4-oxo-5-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-2-cyclohexenyl methanesulfonate (5). Methanesulfonyl chloride (73 μl, 0.93 mmol) was added to a stirred solution of **46** (68.3 mg, 0.16 mmol) in dichloromethane (7 ml) containing triethylamine (0.17 ml, 1.2 mmol) and 4-dimethylaminopyridine (38.0 mg, 0.31 mmol) at 0 °C, and stirring was continued for 4 h at room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (1 ml) at 0 °C, and the mixture was diluted with ether (70 ml). The organic layer was successively washed with 3% aqueous hydrochloric acid (2×30 ml), saturated aqueous sodium hydrogen carbonate (2×30 ml), and brine (2×30 ml), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **5** (66.8 mg, 83%) as a colorless viscous oil. $[\alpha]_D^{20}$ +47.3 (c 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, s, C-Me), 1.42 (3H, s, C-Me), 2.10 (1H, dd, J=10.8, 14.3 Hz, C6–CH_aH$_b$–C4′), 2.45 (3H, s, Me of Ts), 2.91 (1H, dd, J=2.2, 14.3 Hz, C6–CH$_a$$H_b$–C4′), 3.19 (3H, s, Me of Ms), 4.34 (1H, t, J=1.8 Hz, C5–H), 4.43 (1H, dd, J=4.8, 9.4 Hz, C5′–H), 4.46 (1H, t, J=9.3 Hz, C5′–H), 4.58 (1H, m, C4′–H), 5.58 (1H, dd, J=1.7 Hz, C4–H), 6.34 (1H, d, J=10.1 Hz, C2–H), 6.89 (1H, ddd, J=1.9, 5.0, 10.2 Hz, C3–H), 7.36 (2H, d, J=8.2 Hz, Ar), 7.88 (2H, d, J=8.3 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 26.8, 27.1, 38.5, 39.1, 54.0, 69.0, 69.7, 79.8, 80.9, 111.0, 128.4 (2 carbons), 129.9 (2 carbons), 130.9, 134.4, 138.9, 145.8, 152.2, 196.5; IR (neat) 540, 570, 600, 620, 670, 730, 760, 820, 860, 950, 990, 1060, 1090, 1130, 1170, 1230, 1370, 1600, 1690, 1790, 2930, 2990 cm^{-1}; CIMS (m/z) 516 [(M+H)$^+$]; HREIMS (m/z) calcd for $C_{20}H_{22}NO_{10}S_2$ [(M−Me)$^+$]: 500.0685, found 500.0696.

4.1.36. (1*R*,5*S*,6*S*)-5,6-Dihydroxy-4-oxo-5-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methyl-2-cyclohexenyl methanesulfonate (47). A solution of **5** (59.2 mg, 0.11 mmol) in trifluoroacetic acid/water (6:1) (3 ml) was stirred at 0 °C for 30 min. The mixture was concentrated in vacuo to give **47** (54.6 mg, quant.) as a colorless viscous oil. $[\alpha]_D^{20}$ +25.9 (c 1.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (1H, dd, J=10.0, 14.7 Hz, C6–CH_aH$_b$–C4′), 2.30–2.40 (1H, br, OH), 2.45 (3H, s, Me of Ts), 2.50–2.90 (1H, br, OH), 2.98 (1H, d, J=14.6 Hz, C6–CH$_a$$H_b$–C4′), 3.18 (3H, s, Me of Ms), 4.20–4.27 (2H, m, C5–H, C4′–H), 4.30 (1H, dd, J=4.4, 9.3 Hz, C5′–H), 4.45 (1H, t, J=8.8 Hz, C5′–H), 5.47 (1H, t, J=3.5 Hz, C4–H), 6.38 (1H, d, J=10.2 Hz, C2–H), 6.89 (1H, ddd, J=1.3, 4.1, 10.2 Hz, C3–H), 7.37 (2H, d, J=8.2 Hz, Ar), 7.87 (2H, d, J=8.3 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 38.8, 40.2, 53.6, 70.4, 74.8, 75.0, 77.0, 128.5 (2 carbons), 129.3, 130.0 (2 carbons), 134.2, 140.6, 146.1, 152.4, 198.0; IR (neat) 540, 570, 670, 730, 760, 820, 850, 940, 1090, 1170, 1360, 1600, 1700, 1780, 2360, 2930, 3480 cm^{-1}; HRCIMS (m/z) calcd for $C_{18}H_{22}NO_{10}S_2$ [(M+H)$^+$]: 476.0685, found 476.0658.

4.1.37. (4*S*,5*S*,6*S*)-4,5-Epoxy-6-hydroxy-6-[(4*S*)-2-oxo-3-(*p*-toluenesulfonyl)oxazolidin-4-yl]methy-2-cyclohexen-1-one (3b). 0.2 M Sodium hydroxide (1.5 ml, 0.30 mmol) was added dropwise to a stirred solution of **47** (54.5 mg, 0.11 mmol) in ether (5 ml) at 0 °C. After 20 min, the mixture was extracted with ether (3×30 ml). The combined extracts were washed with brine (3×30 ml) and dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **3b** (32.3 mg, 75%) as a white solid. Recrystallization from hexane/dichloromethane (3:1) afforded colorless prisms, mp 224–225 °C; $[\alpha]_D^{20}$ +153.3 (c 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.34 (1H, dd, J=10.5, 14.2 Hz, C6–CH_aH$_b$–C4′), 2.45 (3H, s, Me of Ts), 2.51 (1H, dd, J=1.1, 14.2 Hz, C6–CH$_a$$H_b$–C4′), 3.49 (1H, br, OH), 3.67 (2H, m, C4–H, C5–H), 4.16 (1H, m, C4′–H), 4.34 (1H, dd, J=4.6, 9.4 Hz, C5′–H), 4.44 (1H, t, J=9.1 Hz, C5′–H), 6.35 (1H, m, C2–H), 7.27 (1H, m, C3–H), 7.38 (2H, m, Ar), 7.80 (2H, m, Ar); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 21.9 (Me of Ts), 40.7 (C6–CH$_2$–C4′), 48.6 (C4′), 53.7 (C4), 56.5 (C5), 70.5 (C5′), 77.3 (C6), 128.7 (2 carbons, Ar), 130.3 (3 carbons, Ar, C2), 134.7 (C3), 145.9 (Ar), 146.6 (Ar), 152.4 (C2′), 197.9 (C1); IR (KBr) 540, 570, 600, 670, 760, 840, 990, 1090, 1170, 1370, 1690, 1780, 2360, 2930, 3460 cm^{-1}; HRCIMS (m/z) calcd for $C_{17}H_{17}NO_7S$ [(M+H)$^+$]: 380.0804, found 380.0786.

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35. Crystal data for compound **3b** had been filed with Cambridge Structural Database after publication of the preliminary communication (Ref. 20b).