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Synthetic Studies on Himbacine, a Potent Antagonist of the Muscarinic M_2 Subtype Receptor. Part 2: Synthesis and Muscarinic M_2 Subtype Antagonistic Activity of the Novel Himbacine Congeners Modified at the C-3 Position of Lactone Moiety†

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Abstract—With an aim to disclose the convergency and flexibility of our previously explored synthetic route to natural himbacine **1**, and moreover, to clarify some novel aspects of the structure–activity relationships of **1**, we prepared various structural types of novel himbacine congeners, 3-demethylhimbacine (3-norhimbacine) **2** and 4-*epi*-3-demethylhimbacine (4-*epi*-3-norhimbacine) 4-*epi*-**2** and their enantiomers (*ent*-**2** and *ent*-4-*epi*-**2**), 11-methylhimbacine **3**, and 3-epihimbacine **4** in optically pure forms by employing our methodology. All of the synthesized congeners correspond to the compounds modified at the C-3 position of γ-lactone moiety involved in **1**. Among these congeners, 3-demethylhimbacine (3-norhimbacine) **2** was found to exhibit more potent muscarinic M_2 receptor binding affinity than natural **1**.

Introduction

It is well known that acetylcholine (ACh) is an important transmitter that plays a key role in learning and memory,[2] and that senile dementia associated with Alzheimer's disease is directly correlated with the diminished levels of synaptic ACh in the cortical and hippocampal areas of the brain.[3] Several treatments for Alzheimer's disease are currently under investigation based on the cholinergic hypothesis of memory dysfunction.[4] It is anticipated that the synaptic ACh levels can be modulated by the feedback mechanism of muscarinic M_2 receptor, which acts as an autoreceptor.[5] Thus, selective antagonism of M_2 receptor has been shown to enhance the ACh levels in vivo.[6] Accordingly, the muscarinic M_2 antagonists that are more selective than other muscarinic receptor subtypes such as M_1, M_3, and M_4 receptors are expected to be novel drug candidates for the treatment of Alzheimer's disease.[7]

Himbacine **1**, a piperidine alkaloid isolated from the bark of *Galbulimima baccata* in the magnolia family, bears a characteristic structural feature in which the perhydronaphtho[2,3-*c*]furan ring system consisting of *cis*-fused γ-lactone and *trans*-fused decaline moieties is connected with *trans*-disubstituted piperidine via an (*E*)-double bond (Fig. 1).[8] It was reported that **1** is a potent antagonist of the muscarinic M_2 receptor with 10 to 20-fold selectivity toward the M_1 subtype.[9] Thus, it appears that **1** is an excellent candidate for the reasonable and attractive lead compound of a drug for the treatment of Alzheimer's disease.[6,10]

To disclose novel aspects of the structure–activity relationships of **1**, and, moreover, to explore the promising congeners of **1** which may show improved M_2 affinity and subtype selectivity, we achieved a novel total synthesis of **1** in 1999.[11] The characteristic feature of our explored synthetic route is a highly stereoselective intermolecular Diels–Alder reaction of the tetrahydroisobenzofuran with the chiral furan-2(5*H*)-one employed as a key step. Our explored synthetic route was more convergent and flexible for the synthesis of novel congeners of **1** than routes reported previously.[12]

†Part of this work has been the subject of a preliminary communication: see ref 1.

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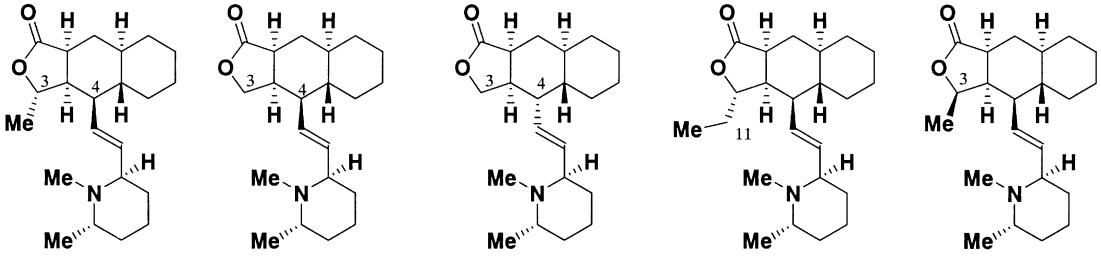


Figure 1. Structures of natural himbacine **1**, 3-demethylhimbacine **2**, 4-*epi*-3-demethylhimbacine 4-*epi*-**2**, 11-methylhimbacine **3**, and 3-epihimbacine **4**.

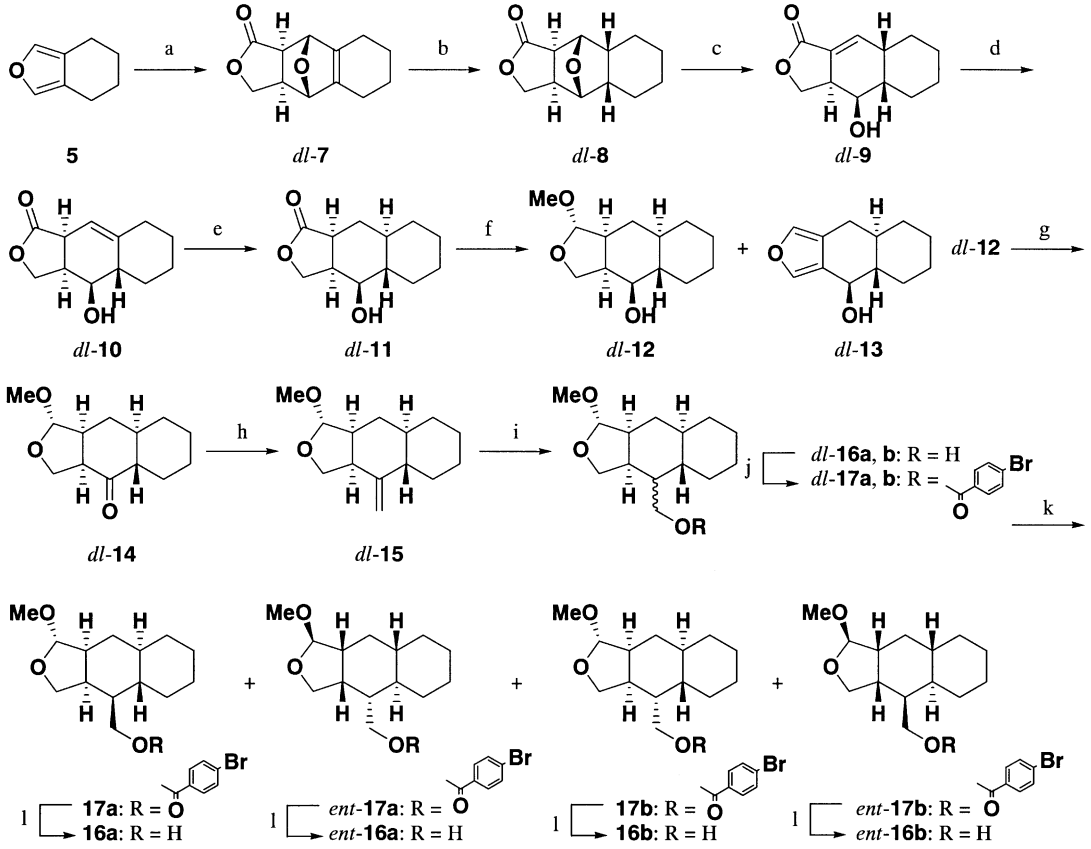
Since then, we have synthesized various structural types of novel congeners of **1** by employing our explored synthetic route,[11b, 13] and we have revealed interesting aspects of the structure–activity relationships of these congeners.

Prior to our studies, Kozikowski et al. reported the structure–activity relationships of the himbacine congeners, demonstrating that the tricyclic lactone framework and the *N*-methyl group in **1** are essential for the muscarinic M_2 subtype binding potency and selectivity.[9c,d] To our knowledge, little or no attention has been paid to the significance of the C-3 position of γ-lactone moiety of **1** for the muscarinic M_2 receptor binding activity in previous studies. Therefore, we focused our attention on the effect of the C-3 position of **1** (i.e., removal, carbon-chains extension, and stereo-inversion of the C-3 methyl group) on the muscarinic M_2 subtype antagonistic activity. As a result of these studies, we have succeeded in the first total synthesis of 3-demethylhimbacine (3-norhimbacine) **2** and 4-*epi*-3-demethylhimbacine (4-*epi*-3-norhimbacine) 4-*epi*-**2** and their enantiomers (*ent*-**2** and *ent*-4-*epi*-**2**),[1] 11-methylhimbacine **3**, and 3-epihimbacine **4** (Fig. 1). Among these novel congeners, 3-demethylhimbacine **2** bearing the same absolute configuration as that of natural **1** was found to show more potent muscarinic M_2 subtype receptor binding affinity than **1**. We report here full details of the synthesis of these novel congeners accomplished by featuring our previously explored synthetic route, some unique stereochemical features encountered in the congener's syntheses, and their muscarinic receptor binding affinity.

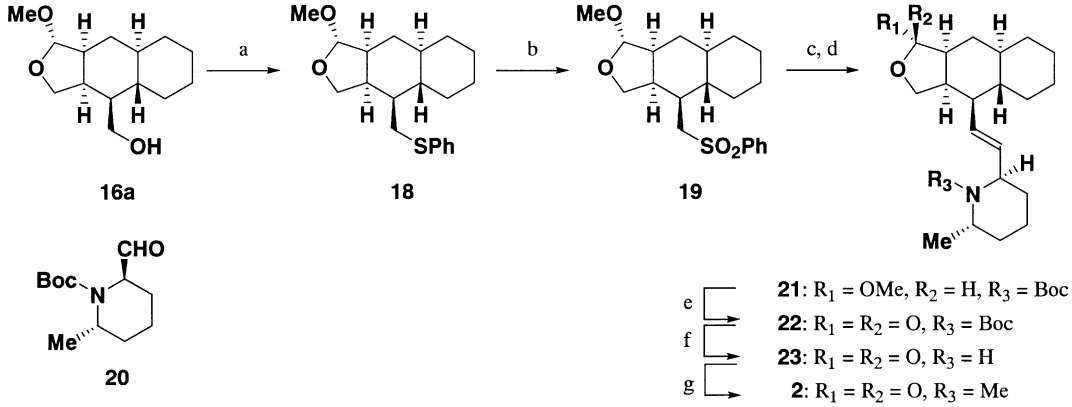
Results and Discussion

Removal of the C-3 methyl group: synthesis of 3-demethylhimbacine (3-norhimbacine) 2, 4-*epi*-3-demethylhimbacine (4-*epi*-3-norhimbacine) 4-*epi*-2, and their enantiomers (*ent*-2 and *ent*-4-*epi*-2) (Schemes 1 and 2). Due to the lack of a chiral center in furan-2(5*H*)-one that can be used as the starting material for our synthesis of 3-demethylhimbacines (**2**, *ent*-**2**, 4-*epi*-**2**, and *ent*-4-*epi*-**2**), we envisioned synthesizing these compounds by optical resolution and epimer separation at the stage of *dl*-4-carbinol *dl*-**16** obtainable as a mixture of the C_4-epimers. As we reported earlier,[11] racemic bicyclic lactone *dl*-**7**[14] was prepared in a 49% yield from tetrahydroisobenzofuran **5** and commercially available furan-2(5*H*)-one **6** by employing a highly stereoselective intermolecular Diels–Alder reaction. Hydrogenation of the double bond in *dl*-**7** was effected using 10% Pd/C as a catalyst, affording *dl*-**8** as a sole product in a 98% yield. Thus, much like the previous case,[11] the catalytic reduction took place highly stereoselectively from the less-hindered face. This was subjected to oxygen ring-opening reaction followed by thermodynamic double bond isomerization, providing *dl*-unsaturated alcohol *dl*-**10** by way of *dl*-**9**. The *dl*-unsaturated alcohol *dl*-**10** was found to be a slightly unstable compound under basic conditions. Catalytic hydrogenation of *dl*-**10** over PtO_2 in ethanol smoothly gave *dl*-saturated alcohol *dl*-**11** as a sole product in a 66% combined yield from *dl*-**8**. The lactone carbonyl group in *dl*-**11** was protected by sequential diisobutylaluminum hydride (DIBAL-H) reduction and acetalization, affording *dl*-acetal *dl*-**12** in a 62% combined yield along with a small amount of *dl*-furan derivative *dl*-**13**. Production of *dl*-**13** might be explained by acid-catalyzed dehydration of the hemiacetal moiety followed by air oxidation. The C-4 hydroxyl group of *dl*-**12** was transformed to an *exo*-methylene group by a two-step sequence involving tetrapropylammonium perruthenate (VII) (TPAP)[15] oxidation of the secondary hydroxyl group at the C-4 position and subsequent methylenation of the resulting carbonyl group, producing the *exo*-methylene compound *dl*-**15**. Next, *dl*-**15** was subjected to a sequential hydroboration-oxidation sequence using borane–tetrahydrofuran complex at ambient temperature, affording the *dl*-4-carbinol *dl*-**16a**,**b** as an inseparable mixture of 4β- and 4α-epimers in a ratio of 1:2 by ^{1}H NMR analysis. In our previous total synthesis of **1**, the stereoselectivity of the hydroboration-oxidation sequence for introducing the C-4 hydroxymethyl group was 8:1 (4β:4α).[11] This different stereoselectivity might be due to the steric effect of the C-3 methyl group involved in the γ-lactone moiety.

Without separation, *dl*-**16a**,**b** was directly converted to the corresponding 4-bromobenzoate *dl*-**17a**,**b** in a 99% yield by the reaction with 4-bromobenzoyl chloride in the presence of triethylamine. Then, *dl*-**17a**,**b**, which was a mixture of the *dl*-4β- and *dl*-4α-epimers, was subjected to simultaneous optical resolution and epimer separation by means of HPLC using a CHIRALCEL OD



Scheme 1. Synthesis of 3-demethylhimbacine (I). (a) 2(5*H*)-Furanone **6**, 5 M $LiClO_4$–Et_2O, 4,4′-thiobis(6-*tert*-butyl-*m*-cresol), rt, 48 h, 49%; (b) H_2, 10% Pd/C, EtOH, rt, 5 h, 98%; (c) $LiN(TMS)_2$, THF, −78 ∼−40 °C, 5 h, 99%; (d) DBU, toluene, 80 °C, 4 h, 70%; (e) H_2, PtO_2, EtOH, rt, 2 h, 95%; (f) (i) DIBAL-H, Et_2O, −70 °C, 1 h, 85%, (ii) BF_3–Et_2O, MeOH, −70 °C∼rt, 12 h, 62%; (g) TPAP, 4-methylmorpholine *N*-oxide, MS4A, CH_2Cl_2, rt, 1 h, 97%; (h) Ph_3PCH_3I, $NaN(TMS)_2$, Et_2O, −78 °C∼rt, 6 h, 54%; (i) BH_3–THF, THF, 0 °C∼rt, 7 h, (ii) 10% H_2O_2, 10% NaOH, 0 °C, 0.5 h, 82%; (j) 4-bromobenzoyl chloride, Et_3N, CH_2Cl_2, 0 °C∼rt, 18 h, 99%; (k) CHIRALCEL OD, **17a**: 19%, *ent*-**17a**: 18%, **17b**: 30%, *ent*-**17b**: 32%; (l) 10% NaOH, EtOH, rt, 0.5 h, **16a**: 100%, *ent*-**16a**: 100%, **16b**: 100%, *ent*-**16b**: 91%.



Scheme 2. Synthesis of 3-demethylhimbacine (II). (a) (Cyanomethyl)trimethylphosphonium iodide, thiophenol, *N*,*N*-diisopropylethylamine, MeCN, 80 °C, 2.5 h, 92%; (b) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 1.5 h, 82%; (c) (i) *n*BuLi, **20**, 1,2-dimethoxyethane, −78 ∼0 °C, 3 h, (ii) benzoyl chloride, −78 °C∼rt, 1 h, (iii) 3-(dimethylamino)propylamine, rt, 97% (a mixture of diastereomers); (d) 5% Na–Hg, Na_2HPO_4, MeOH, rt, 1 h, 63%; (e) Jones reagent, acetone, rt, 1.5 h, 58%; (f) trifluoroacetic acid, CH_2Cl_2, rt, 0.5 h, 87%; (g) 37% HCHO aq, $NaBH_3CN$, CH_3CN, rt, 1 h, 80%.

column, giving four stereoisomers **17a**, *ent*-**17a**, **17b**, and *ent*-**17b** with high optical purity, as follows: **17a**: 19%, 94% ee, t_R 23.5 min; *ent*-**17a**: 18%, 99% ee, t_R 22.7 min; **17b**: 30%, 99% ee, t_R 21.2 min; *ent*-**17b**: 32%, 98% ee, t_R 33.6 min. Optically pure samples of **17a**, *ent*-**17a**, **17b**, and *ent*-**17b** were prepared by subsequent recrystallizations. To determine their absolute configurations, we performed X-ray spectroscopic analysis of **17a** and **17b**, which were considered to be diastereomeric with respect to each other based on their ^1H NMR spectra, by employing the heavy atom method. Based on the results of X-ray analysis (Figs. 2 and 3), we definitely established that (i) **17a** and **17b** bear the same absolute configurations as that of natural **1** concerning the ring junctions and the C-1 methoxy group, (ii) **17a** and **17b** were the 4β- and 4α-epimer, respectively, and (iii) *ent*-

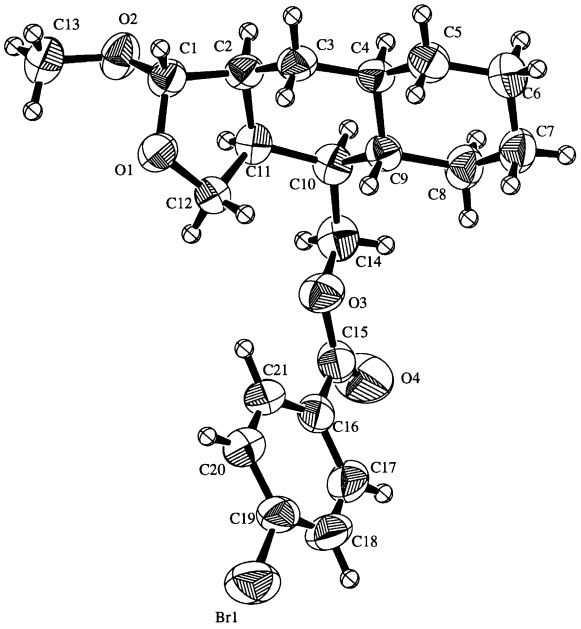


Figure 2. Ortep drawing of (+)-4β-carbinyl 4-bromobenzoate **17a**.

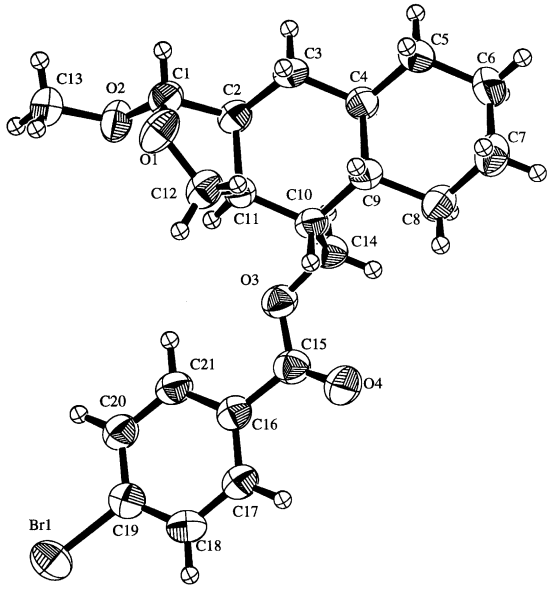


Figure 3. Ortep drawing of (+)-4α-carbinyl 4-bromobenzoate **17b**.

17a and *ent*-**17b** were the enantiomers of **17a** and **17b**, as shown in Scheme 1. Thus, in addition to **17a** bearing the same absolute configuration as that of natural **1** at the tricyclic moiety, we have its three stereoisomers *ent*-**17a**, **17b** (the C_4 epimer of **17a**), and *ent*-**17b**. These stereoisomeric 4-bromobenzoates were successfully utilized for synthesizing the novel himbacine congeners 3-demethylhimbacines (3-norhimbacines) (**2** and *ent*-**2**) and their C_4 epimers (4-*epi*-**2** and *ent*-4-*epi*-**2**).

First, in order to achieve 3-demethylhimbacine (3-norhimbacine) **2**, **17a** was transformed to sulfone **19**, the key intermediate, by the three-step sequence involving alkaline hydrolysis, benzenesulfenylation of 4β-carbinol **16a** using (cyanomethyl)trimethylphosphonium iodide,[16] and 3-chloroperoxybenzoic acid (*m*CPBA) oxidation of phenyl sulfide **18**. The Julia–Lythgoe coupling reaction of **19** with the piperidine-2-carboxyaldehyde **20** was effected at −78∼0 °C. Quenching the coupling reaction with excess benzoyl chloride followed by treatment of the resulting β-benzoxysulfone with 5% Na–Hg in methanol in the presence of Na_2HPO_4 gave rise to (*E*)-4β-olefin **21** in a 61% combined yield. In the case of 4α-sulfone 4-*epi*-**19**, however, the coupling reaction smoothly took place at −78 °C in a similar manner to that for the synthesis of natural **1**. Different reactivity observed for **19** and 4-*epi*-**19** might be explained by the stability of the lithium anions derived from them.

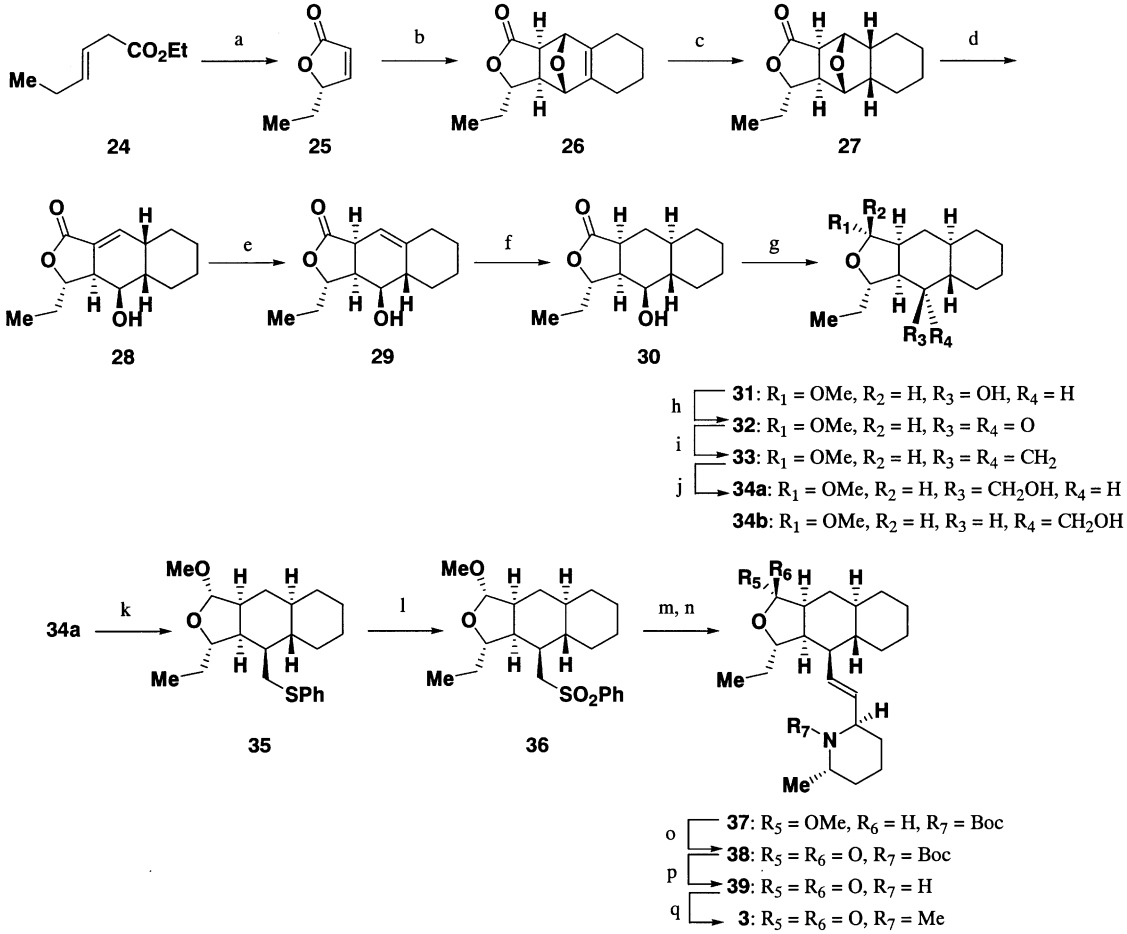
Resulting (*E*)-4β-olefin **21** was subjected to sequential oxidative deprotection of the hemiacetal moiety, deprotection of the *N*-Boc group, and reductive *N*-methylation, furnishing **2** in a 40% combined yield. By the same synthetic sequence, *ent*-**17a**, **17b**, and *ent*-**17b** were also successfully converted to *ent*-**2**, 4-*epi*-**2**, and *ent*-4-*epi*-**2** in good yield by way of *ent*-**19**, 4-*epi*-**19**, and *ent*-4-*epi*-**19**, respectively. To avoid confusion, the compounds carrying the configurations corresponding to that of natural **1** were only depicted in Scheme 2.

Carbon-chain extension of the C-3 methyl group: synthesis of 11-methylhimbacine 3 (Scheme 3)

In order to disclose the relationship between the carbon length at the C-3 position and the muscarinic M_2 antagonistic activity, we next examined the synthesis of 11-methylhimbacine **3** by employing tetrahydroisobenzofuran **5** and (*S*)-5-ethyl furan-2(5*H*)-one **25**[17] as the starting materials. According to the reported procedure, **25** was prepared from ethyl (*E*)-3-hexenoate **24** in ca. 75% ee optical purity. Following the same synthetic scheme as previously developed for the preparation of natural **1**, we have readily obtained phenyl sulfide **35** from **25** in 12 steps. At this stage, **35**, which was considered to be partially optically active, was subjected to purification by means of HPLC using a Chiralpak AD-H column, giving **35**, 99% ee, and *ent*-**35**, 90% ee, in 81 and 9% yields, respectively. Optically pure phenyl sulfide **35** thus obtained was transformed to sulfone **36**, the key intermediate, in a quantitative yield. The Julia–Lythgoe coupling reaction of **36** with **20** followed by sequential oxidation, deprotection, and *N*-methylation uneventfully afforded the desired **3** in a 22% combined yield.

Stereo-inversion of the C-3 methyl group: synthesis of 3-epihimbacine 4 (Scheme 4)

Finally, we explored the relationship between the stereochemistry at the C-3 methyl group and the muscarinic M_2 receptor binding activity. Our plan for synthesizing **4** was the stereo-inversion of the C-3 methyl group of the known lactone **40**,[11,12] the intermediate for the synthesis of natural **1**, by successive ring opening of γ-lactone moiety and ring-closure to epimeric γ-lactone with stereo-inversion. Thus, by following the Lansbury's and Blay's procedure,[18] **40** was subjected to sequential hydrolysis of the γ-lactone moiety using potassium hydroxide in 95% methanol, *O*-methanesulfonylation of the resulting hydroxycarboxylate, and lactone formation by the intramole-



Scheme 3. Synthesis of 11-methylhimbacine. (a) See ref 17, 92% (two steps); (b) **5**, 5M $LiClO_4$–Et_2O, 4,4′-thiobis(6-*tert*-butyl-*m*-cresol), rt, 72 h, 44%; (c) H_2, 10% Pd/C, EtOH, rt, 4 h, 74%; (d) $LiN(TMS)_2$, THF, −78 ∼ −40 °C, 5 h, 93%; (e) DBU, toluene, 80 °C, 3 h, 72%; (f) H_2, PtO_2, EtOH, rt, 4 h, 91%; (g) (i) DIBAL-H, Et_2O, −78 °C, 1 h, 87%, (ii) BF_3–Et_2O, MeOH, CH_2Cl_2, −78 °C∼rt, 16 h, 100%; (h) TPAP, 4-methylmorpholine *N*-oxide, MS4A, CH_2Cl_2, rt, 1.5 h, 70%; (i) Ph_3PCH_3I, $NaN(TMS)_2$, Et_2O, 0 °C∼rt, 14 h, 100%; (j) (i) BH_3–THF, THF, −78 °C∼rt, 10 h; (ii) 30% H_2O_2, 10% NaOH, 0 °C, 0.5 h, **34a**: 70%, **34b**: 8%; (k) (i) methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C, 2 h, 79%; (ii) thiophenol, *t*BuOK, DMSO, rt, 11 h, 71%, then HPLC separation, **35**: 81%, *ent*-**35**: 9%; (l) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 1 h, 100%; (m) (i) *n*BuLi, **20**, 1,2-dimethoxyethane, −78∼0 °C, 3.5 h; (ii) benzoyl chloride, −78 °C∼rt, 0.5 h, (iii) 3-(dimethylamino)propylamine, rt, 0.5 h, 60% (a mixture of diastereomers); (n) 5% Na–Hg, Na_2HPO_4, MeOH, rt, 1 h, 66%; (o) Jones reagent, acetone, rt, 1 h, 73%; (p) trifluoroacetic acid, CH_2Cl_2, rt, 1 h, 100%; (q) 37% HCHO aq, $NaBH_3CN$, CH_3CN, rt, 0.5 h, 81%.

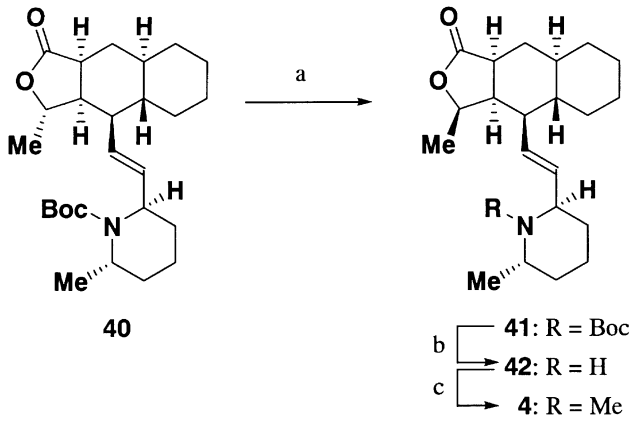
cular S_N2 type ring closure of the carboxylate anion, which afforded **41** possessing the 3β-methyl group in a 28% yield along with 21% recovery of **40**. These sequential operations were performed in a one-pot process. These epimers were separated by careful column chromatography, and **41** was successfully transformed to **4** in two steps in a 56% combined yield. Stereochemistry at the C-3 position of the desired **4** was confirmed by NOESY analysis of its ^1H NMR spectrum in comparison with that for **1** (Fig. 4).

Muscarinic M_2 receptor binding affinity of novel himbacine congeners

With completion of the synthesis of four 3-demethylhimbacine (3-norhimbacine) derivatives **2**, *ent*-**2**, 4-*epi*-**2**, and *ent*-4-*epi*-**2**, 11-methylhimbacine **3**, and 3-*epi*-himbacine **4**, they were subjected to receptor binding affinity assay against the muscarinic M_1 and M_2 subtype receptors. The results were summarized in Table 1. Surprisingly, we found that, despite lacking the 3α-methyl group, 3-demethylhimbacine (3-norhimbacinbe) **2** bearing the same absolute configuration as natural **1** showed superior M_2 receptor binding affinity and equal subtype selectivity to those of **1**, and that the other three stereoisomers *ent*-**2**, 4-*epi*-**2**, and *ent*-4-*epi*-**2** showed only weak M_2 receptor binding affinity compared to that of **1** and **2**. Additionally, it appeared that, similar to the case for **1** and its C_4-epimer,[11b] the stereochemistry at the C-4 position plays an important role for exhibiting muscarinic M_2 receptor binding affinity. Moreover, **3** and **4** were found to show less potent muscarinic M_2 subtype

Table 1. In vitro binding activity of novel himbacine congeners

Entry	Compd	$-\log K_i$	
		M_1 (cortex)	M_2 (brainstem)
1	**1**	7.1	7.9
2	**2**	7.4	8.1
3	*ent*-**2**	6.0	6.1
4	4-*epi*-**2**	6.2	6.4
5	*ent*-4-*epi*-**2**	6.3	6.4
6	**3**	6.4	6.7
7	**4**	6.8	7.4



Scheme 4. Synthesis of 3-epihimbacine. (a) (i) KOH, 95% MeOH, 70 °C, 2 h; (ii) methanesulfonyl chloride, Et_3N, THF, 0 °C∼rt, 1 h; (iii) NaOH, H_2O, 50 °C, 1 h, 36%; (b) trifluoroacetic acid, CH_2Cl_2, rt, 1 h, 93%; (c) 37% HCHO aq, $NaBH_3CN$, CH_3CN, rt, 0.5 h, 60%.

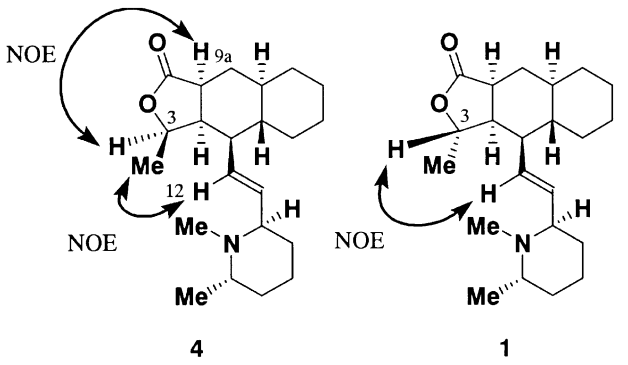


Figure 4. NOESY correlation of 3-epihimbacine **4** and natural himbacine **1**.

receptor binding affinity than **1** and **2**. Thus, it was clearly indicated that the C-3 methyl group on the γ-lactone ring moiety is not important for muscarinic M_2 receptor binding affinity and subtype selectivity, and that carbon-chain extension and stereo-inversion of the C-3 methyl group obviously decrease muscarinic M_2 receptor binding activity, probably due to their steric effects.

Conclusion

In conclusion, we have succeeded in synthesizing the novel himbacine congeners 3-demethylhimbacine (3-norhimbacine) **2** and 4-*epi*-3-demethylhimbacine (4-*epi*-3-norhimbacine) 4-*epi*-**2** and their enantiomers (*ent*-**2** and *ent*-4-*epi*-**2**), 11-methylhimbacine **3**, and 3-epihimbacine **4** in optically pure forms. All of these congeners were produced in order to study the effect of the C-3 methyl group of natural **1** on its activity. By testing their muscarinic M_2 subtype receptor binding activity, we found that 3-demethylhimbacine (3-norhimbacine) **2** exhibits a more potent binding affinity for muscarinic M_2 subtype receptor than does natural **1**. To the best of our knowledge, this is the first case in which muscarinic M_2 subtype receptor binding activity more potent than that of natural **1** has been exhibited by its close congener.[9,10] Further investigation of the pharmacological evaluation of **2** is in progress.

Experimental

All melting points were determined with a Yanaco MP-500D micro melting point apparatus and are uncorrected. Measurements of optical rotations were carried out using a P-1020 automatic digital polarimeter. Infrared (IR) spectra were recorded with a JASCO FT/IR-5300 spectrometer. ^1H NMR spectra were measured with a JEOL JNM-EX-400 (400 MHz) spectrometer. ^{13}C NMR spectra were taken with a JEOL JNM-EX-400 (100 MHz) spectrometer. The chemical shifts are expressed in parts per million (δ value) downfield from tetramethylsilane, using tetramethylsilane (δ = 0) and/or residual solvents such as chloroform (δ = 7.26) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Measurements of mass spectra were performed with a JMS-SX102A mass spectrometer. Data for elemental analysis are within ±0.3% of the theoretical values and were determined by a Yanaco CHN-corder MT-5. Analytical and preparative HPLC was carried out using a Hitachi L-4200 UV–vis detector, a Hitachi L-6200 intelligent pump, a Hitachi D-2500 chromato-integrator, and a GL Sciences Model 557 LC column oven. Conditions for separation were described for the respective experimental parts. Unless otherwise noted, all the experiments were carried out using anhydrous solvents under an atmosphere of dry argon. Throughout this work, Merck precoated TLC plates (Silica gel 60 F_{254}, 0.25 mm; Art. 5715) were used for thin layer chromatographic (TLC) analysis, and all the spots were visualized using ultraviolet (UV) light followed by coloring with phosphomolybdic acid. Wako Gel C-200, Wako Gel C-300, Silica gel 60 (0.040–0.063 mm, F_{254}; Art. 9385, Merck Co., Ltd.), or Chromatorex® NH-DM 1020 (100–200 mesh, Fuji Silysia Chemical, Ltd.) was used as an adsorbent for the flash column chromatography.

(3a*R,4*S**,9*R**,9a*R**)-4,9-Epoxy-3a,4,5,6,7,8,9,9a-octahydronaphtho[2,3-*c*]furan-1(3*H*)-one (*dl*-7).** To a solution of lithium perchlorate (3.18 g) and 4,4′-thiobis (6-*tert*-butyl-*m*-cresol) (0.96 g, 1.78 mmol) in diethyl ether (6 mL) were successively added **5** (6.54 g, 53.5 mmol) and **6** (3.00 g, 35.7 mmol), and the mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with diethyl ether (100 mL) and poured into water (100 mL). The upper organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were combined, dried over anhydrous magnesium sulfate ($MgSO_4$), filtered, and then concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate = 4:1, 2:1, then 1:1) of the residue gave *dl*-**7** (3.62 g, 49%) as a colorless powder. This crude material was immediately subjected to the next reaction without further purification by recrystallization. Mp 105–106 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.46–1.56 (m, 2H), 1.63–1.72 (m, 2H), 1.84–1.97 (m,

2H), 2.19–2.30 (m, 2H), 2.72 (td, $J=8.3$, 3.6 Hz, 1H), 2.81 (d, $J=7.8$ Hz, 1H), 4.21 (dd, $J=9.8$, 3.9 Hz, 1H), 4.51 (dd, $J=9.8$, 8.6 Hz, 1H), 4.71 (s, 1H), 5.04 (s, 1H). IR (KBr): 2950, 1750, 1190 cm^{-1}. MS (EI) (*m*/*z*): 206 (M^+), 122 (100). HRMS (EI) (*m*/*z*): calcd for $C_{12}H_{14}O_3$ (M^+): 206.0943. Found, 206.0970.

(3a*R,4*R**,4a*S**,8a*R**,9*S**,9a*R**)-4,9-Epoxy-decahydronaphtho[2,3-*c*]furan-1(3*H*)-one (*dl*-8).** A mixture of *dl*-**7** (17.0 g, 82.4 mmol) and 10% Pd/C (1.70 g, 10% w/w) in ethanol (300 mL) was stirred at room temperature for 5 h under H_2 atmosphere (1 atm). Insoluble materials were filtered and washed thoroughly with ethyl acetate (100 mL). The filtrates were combined and concentrated in vacuo to give *dl*-**8** (16.8 g, 98%) as a colorless powder. Mp 90–91 °C (hexane-ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04–1.21 (m, 2H), 1.30–1.57 (m, 4H), 1.68–1.78 (m, 2H), 2.01–2.17 (m, 2H), 3.00 (td, $J=8.3$, 3.9 Hz, 1H), 3.05 (d, $J=8.3$ Hz, 1H), 4.10 (dd, $J=9.3$, 4.0 Hz, 1H), 4.40 (d, $J=4.9$ Hz, 1H), 4.46 (t, $J=9.1$ Hz, 1H), 4.75 (d, $J=4.9$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 19.4, 19.5, 19.8, 37.8, 38.9, 39.6, 45.0, 72.4, 83.7, 86.2, 178.6. IR (KBr): 2940, 1760 cm^{-1}. MS (EI) (*m*/*z*): 208 (M^+), 190, 179, 95 (100). Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.97; H, 7.74.

(3a*R,4*R**,4a*S**,8a*S**) - 4 - Hydroxy - 3a,4,4a,5,6,7,8,8a - octahydronaphtho[2,3-*c*]furan-1(3*H*)-one (*dl*-9).** To a solution of *dl*-**8** (10.0 g, 48.0 mmol) in tetrahydrofuran (500 mL), lithium bis(trimethylsilyl)amide (1.05 M solution in tetrahydrofuran, 228.7 mL, 0.24 mol) was added dropwise at −70 °C. The resulting mixture was stirred at the same temperature for 5 h and then gradually warmed to −40 °C with stirring. After quenching the reaction by adding diluted aqueous citric acid solution (500 mL) at −40 °C, the mixture was stirred at room temperature for 5 min and concentrated in vacuo. The residual aqueous mixture was extracted with diethyl ether (150 mL×3). The organic extracts were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate = 1:1) of the residue gave *dl*-**9** (9.87 g, 99%) as a yellow oil. This material was directly used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98–1.74 (m, 4H), 1.81–1.89 (m, 2H), 1.95–2.10 (m, 2H), 2.14–2.21 (m, 1H), 2.31–2.38 (m, 1H), 2.77–2.84 (m, 1H), 3.16–3.23 (m, 1H), 4.03 (dd, $J=9.3$, 3.4 Hz, 1H), 4.31 (dd, $J=9.8$, 8.3 Hz, 1H), 4.45 (dd, $J=8.8$, 8.1 Hz, 1H), 6.75 (t, $J=2.8$ Hz, 1H). MS (EI) (*m*/*z*): 208 (M^+), 164, 149, 135, 121, 107, 91 (100). HRMS (EI) (*m*/*z*): calcd for $C_{12}H_{16}O_3$ (M^+): 208.1099. Found, 208.1086.

(3a*R,4*R**,4a*S**,9a*S**)-4-Hydroxy-3a,4,4a,5,6,7,8,9a-octahydronaphtho[2,3-*c*]furan-1(3*H*)-one (*dl*-10).** To a solution of *dl*-**9** (1.89 g, 9.08 mmol) in toluene (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (6.79 mL, 45.4 mmol), and the mixture was heated at 80 °C with stirring for 4 h. After cooling, the reaction mixture was concentrated in vacuo and diluted with diethyl ether (50 mL). The ethereal solution was washed with diluted aqueous citric acid solution (50 mL). The lower aqueous layer was extracted with diethyl ether (10 mL×3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate = 1:2) of the residue gave *dl*-**10** (1.33 g, 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (qd, $J=12.7$, 3.5 Hz, 1H), 1.19–1.33 (m, 1H), 1.38–1.49 (m, 1H), 1.73 (d, $J=3.9$ Hz, 1H), 1.79–1.90 (m, 2H), 1.96–2.10 (m, 2H), 2.14–2.22 (m, 1H), 2.31–2.38 (m, 1H), 3.02 (qd, $J=8.3$, 4.4 Hz, 1H), 3.21 (dq, $J=8.3$, 2.8 Hz, 1H), 3.83 (dt, $J=7.3$, 4.4 Hz, 1H), 4.24 (t, $J=8.8$ Hz, 1H), 4.45 (dd, $J=9.3$, 8.1 Hz, 1H), 5.34 (d, $J=3.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7, 27.1, 31.8, 34.8, 39.0, 41.3, 41.5, 68.6, 72.0, 111.9, 141.5, 177.0. IR (neat): 3450, 2930, 1770, 1010 cm^{-1}. MS (EI) (*m*/*z*): 208 (M^+), 164, 149, 135, 121, 107, 91 (100). HRMS (EI) (*m*/*z*): calcd for $C_{12}H_{16}O_3$ (M^+): 208.1099. Found, 208.1095.

(3a*R,4*R**,4a*S**,8a*R**,9a*S**)-4-Hydroxy-decahydronaphtho[2,3-*c*]furan-1(3*H*)-one (*dl*-11).** A mixture of *dl*-**10** (5.12 g, 24.6 mmol) and PtO_2 (0.50 g, 10% w/w) in ethanol (100 mL) was stirred at room temperature for 2 h under H_2 atmosphere (1 atm). Insoluble materials were filtered and washed thoroughly with ethyl acetate (100 mL). The filtrates were combined and concentrated in vacuo to give *dl*-**11** (4.93 g, 95%) as a colorless powder. Mp 149–150 °C (hexane–ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.93 (m, 1H), 0.98–1.32 (m, 6H), 1.69–1.86 (m, 4H), 1.96 (d, $J=3.9$ Hz, 1H), 2.05–2.12 (m, 1H), 2.62 (dt, $J=12.7$, 6.9 Hz, 1H), 3.01 (dq, $J=11.7$, 7.2 Hz, 1H), 3.66 (ddd, $J=10.3$, 6.4, 3.7 Hz, 1H), 4.31 (dd, $J=11.3$, 9.3 Hz, 1H), 4.43 (dd, $J=9.3$, 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6, 25.6, 28.9, 30.6, 32.9, 38.2, 39.6, 40.8, 43.6, 68.1, 73.0, 178.9. IR (KBr): 3440, 2920, 1750, 1190 cm^{-1}. MS (EI) (*m*/*z*): 210 (M^+), 192, 182, 164, 85 (100). Anal. calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.52; H, 8.81.

(1*S,3a*R**,4*R**,4a*S**,8a*R**,9a*S**) - Dodecahydro - 1 - methoxynaphtho[2,3-*c*]furan-4-ol (*dl*-12) and (4*R**,4a*S**,8a*R**)-4,4a,5,6,7,8,8a,9-octahydronaphtho[2,3-c]furan-4-ol (*dl*-13).** To a solution of *dl*-**11** (8.00 g, 38.0 mmol) in diethyl ether (500 mL), diisobutylaluminum hydride (0.93 M solution in hexane, 122.7 mL, 0.11 mol) was added dropwise at −70 °C, and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by adding methanol and water (each 10 mL) at −70 °C, and the mixture was stirred at room temperature for 1 h. The precipitates formed were removed by filtration through a pad of Celite, and the collected solid was washed with ethyl acetate/methanol (10:1) (300 mL). The filtrates were combined and concentrated in vacuo. The residue was diluted with brine (300 mL), and the aqueous mixture was extracted with a mixture of dichloromethane and ethanol (10:1) (50 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo, to give a crude anomeric mixture of the hemiacetals (6.88 g, 85%) as a colorless oil. This was directly subjected to the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–1.30 (m, 7H), 1.43–1.85 (m,

5H), 2.02–2.09 (m, 1H), 2.21 (dt, $J=12.2$, 6.2 Hz, 1H), 2.46 (d, $J=2.9$ Hz, 1H), 3.03–3.11 (m, 1H), 3.68 (ddd, $J=9.8$, 5.9, 3.7 Hz, 1H), 3.98 (dd, $J=10.3$, 8.8 Hz, 1H), 4.16 (apparent t, $J=8.8$ Hz, 1H), 5.15 (d, $J=3.0$ Hz, 1H). MS (CI) (m/z): 195 ($M^+ + H\text{-}H_2O$) (100). HRMS (CI) (m/z): calcd for $C_{12}H_{19}O_2$ ($M^+ + H\text{-}H_2O$): 195.1385. Found, 195.1364.

To a solution of the crude hemiacetals (6.88 g, 32.4 mmol) in CH_2Cl_2 (200 mL) and methanol (200 mL) was added boron trifluoride diethyl etherate (5.98 mL, 48.6 mmol) at −70 °C. The mixture was stirred at the same temperature for 12 h and then gradually warmed to room temperature with stirring. After the reaction was quenched by adding triethylamine (6.78 mL, 48.6 mmol) at 0 °C, the resulting mixture was further stirred at room temperature for 1 h and then concentrated in vacuo. The residue was diluted with diluted aqueous citric acid solution (300 mL), and the aqueous mixture was extracted with diethyl ether (100 mL×3). The organic extracts were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate = 2:1) of the residue gave *dl*-**12** (4.56 g, 62% from *dl*-**11**) as a colorless powder along with *dl*-**13** (236 mg, 4% from *dl*-**11**). *dl*-**12**: Mp 75-77 °C (hexane-ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81–1.05 (m, 4H), 1.11–1.30 (m, 3H), 1.45–1.51 (m, 1H), 1.63 (d, $J=3.9$ Hz, 1H), 1.63–1.84 (m, 3H), 2.02–2.09 (m, 1H), 2.17 (dt, $J=12.2$, 6.2 Hz, 1H), 2.93–3.01 (m, 1H), 3.32 (s, 3H), 3.65 (ddd, $J=10.3$, 6.4, 4.2 Hz, 1H), 3.97 (dd, $J=10.3$, 8.3 Hz, 1H), 4.06 (t, $J=9.1$ Hz, 1H), 4.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9, 25.9, 29.0, 32.0, 33.3, 38.4, 41.4, 43.3, 44.2, 54.4, 67.8, 74.5, 109.5. IR (KBr): 3350, 2920, 1040 cm^{-1}. MS (EI) (m/z): 193 (M^+-H_2OMe), 176, 148, 101, 86 (100). Anal. calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: 68.70; H, 9.66. *dl*-**13**: Mp 126–127 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97–1.30 (m, 6H), 1.33–1.46 (m, 1H), 1.72–1.89 (m, 3H), 2.09 (ddd, $J=16.1$, 11.7, 1.8 Hz, 1H), 2.30–2.37 (m, 1H), 2.63 (dd, $J=16.1$, 4.9 Hz, 1H), 4.28 (t, $J=7.6$ Hz, 1H), 7.11 (s, 1H), 7.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.8, 25.9, 27.4, 30.1, 34.1, 37.6, 48.0, 70.8, 120.9, 126.7, 136.8, 138.7. IR (KBr): 3240, 2920, 1030 cm^{-1}. MS (EI) (m/z): 192 (M^+) (100). Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.89; H, 8.46.

(1*S,3a*R**,4a*S**,8a*R**,9a*S**)-Decahydro-1-methoxynaphtho[2,3-*c*]furan-4(1*H*)-one (*dl*-14).** To a solution of *dl*-**12** (691 mg, 3.06 mmol), 4-methylmorpholine *N*-oxide (537 mg, 4.58 mmol), and molecular sieves (MS 4A, 1.50 g) in CH_2Cl_2 (6 mL) was added tetrapropylammonium perruthenate (VII) (TPAP) (53.7 mg, 0.15 mmol) at room temperature, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was filtered through a pad of Celite, and the collected solid was washed with diethyl ether (30 mL). The organic filtrates were combined, washed with 10% sodium thiosulfate solution (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flush column chromatography (hexane/ethyl acetate = 2:1) of the residue gave *dl*-**14** (667 mg, 97%) as a colorless powder. Mp 78-79 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08–1.33 (m, 5H), 1.39–1.49 (m, 1H), 1.68–1.86 (m, 4H), 1.95–2.04 (m, 2H), 2.56 (dt, $J=12.7$, 6.6 Hz, 1H), 3.21–3.31 (m, 1H), 3.31 (s, 3H), 3.95 (t, $J=9.1$ Hz, 1H), 4.17 (dd, $J=10.3$, 8.8 Hz, 1H), 4.77 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 25.4, 25.5, 32.5, 34.2, 40.9, 48.0, 50.0, 50.8, 54.4, 69.1, 109.4, 211.4. IR (KBr): 2940, 1700 cm^{-1}. MS (FAB) (m/z): 330 [(M^+ + diethanolamine) + H], 316, 298, 233 (100). Anal. calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.32; H, 9.07.

(1*S,3a*S**,4a*S**,8a*R**,9a*S**)-Dodecahydro-1-methoxy-4-methylenenaphtho[2,3-*c*]furan (*dl*-15).** To a suspension of methyltriphenylphosphonium iodide (13.2 g, 32.5 mmol) in diethyl ether (200 mL), sodium bis(trimethylsilyl)amide (1 M solution in toluene, 32.5 mL, 32.5 mmol) was added dropwise under ice cooling, and the mixture was stirred at room temperature for 0.5 h. The resulting mixture was added dropwise to a solution of *dl*-**14** (1.46 g, 6.51 mmol) in diethyl ether (30 mL) at −78 °C, and the mixture was stirred at the same temperature for 6 h and then gradually warmed to room temperature with stirring. After quenching the reaction by adding cold saturated aqueous ammonium chloride solution (30 mL), the mixture was filtered through a pad of Celite, and the collected solid was washed with diethyl ether (200 mL). The filtrates were combined and concentrated in vacuo. The residue was diluted with water (50 mL), and the aqueous mixture was extracted with diethyl ether (30 mL×3). The combined ethereal extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate = 10:1) of the residue gave *dl*-**15** (778 mg, 54%) as a yellow powder. Mp 53-55 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00–1.35 (m, 6H), 1.54–1.73 (m, 4H), 1.80–1.89 (m, 2H), 2.17–2.24 (m, 1H), 3.26–3.32 (m, 1H), 3.33 (s, 3H), 3.79 (dd, $J=10.3$, 8.1 Hz, 1H), 4.00 (dd, $J=9.3$, 8.3 Hz, 1H), 4.64 (s, 1H), 4.72 (t, $J=2.0$ Hz, 1H), 4.86 (t, $J=1.8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 26.3, 28.8, 32.9, 34.4, 41.4, 42.0, 45.1, 46.5, 54.5, 70.6, 109.3, 109.9, 148.5. IR (KBr): 2930, 1440, 1380, 1190, 1030 cm^{-1}. MS (EI) (m/z): 222 (M^+), 192 (100). HRMS (EI) (m/z): calcd for $C_{14}H_{22}O_2$ (M^+): 222.1620. Found, 222.1605.

(1*S,3a*R**,4*R**,4a*S**,8a*R**,9a*S**)-Dodecahydro-1-methoxynaphtho[2,3-*c*]furan-4-methanol and Its (4*S**)-epimer (*dl*-16a and *dl*-16b).** To a solution of *dl*-**15** (141 mg, 0.63 mmol) in tetrahydrofuran (5 mL), borane-tetrahydrofuran complex (1 M solution in tetrahydrofuran, 952 μL, 0.95 mmol) was added dropwise at 0 °C, and the mixture was stirred at room temperature for 7 h. After adding water (5 mL) to the reaction mixture at 0 °C, 30% hydrogen peroxide (1.00 mL) and 10% sodium hydroxide solution (1.00 mL) were added to the aqueous mixture at the same temperature. After stirring for 0.5 h, the mixture was concentrated in vacuo. The residue was diluted with water (10 mL), and the aqueous mixture was extracted with diethyl ether (5 mL×3). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and then

concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate = 1:1) of the residue gave an inseparable mixture of *dl*-**16a** and its (4*S**)-epimer *dl*-**16b** (125 mg, 82%). MS (CI) (*m*/*z*): 241 ($M^+ + H$), 209 (100). This sample was directly subjected to the next step without separation.

[(1*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*) - Dodecahydro - 1 - methoxynaphtho[2,3-*c*]furan-4yl]methyl 4-bromobenzoate (17a), its (4*S*)-epimer (17b), and their enantiomers (*ent*-17a and *ent*-17b). To a solution of 4-bromobenzoic acid (226 mg, 1.12 mmol) in benzene (2 mL) was added thionyl chloride (0.50 mL), and the solution was stirred at 80 °C for 1 h. After concentration in vacuo, the residue was diluted with CH_2Cl_2 (2 mL), *dl*-**16a**, *dl*-**16b** (90.0 mg, 0.37 mmol) and triethylamine (261 μL, 1.87 mmol) were added at 0 °C. The mixture was stirred for 18 h with gradual warming to room temperature. After dilution with aqueous citric acid solution (10 mL), the reaction mixture was extracted with ethyl acetate (3 mL×3). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtrated, and then concentrated in vacuo. Flush column chromatography (hexane/ethyl acetate = 4:1) of the residue gave a mixture of **17a**, *ent*-**17a**, **17b**, and *ent*-**17b** (157 mg, 99%). MS (FAB) (*m*/*z*): 577 [(M^+ + 2,2′-dithiodiethanol) + H]. HRMS (FAB) (*m*/*z*): calcd for $C_{25}H_{38}BrO_6S_2$ [(M^+ + 2,2′-dithiodiethanol) + H]: 577.1293. Found, 577.1246.

A mixture of **17a**, *ent*-**17a**, **17b**, and *ent*-**17b** (1.00 g) was subjected to separation using HPLC [CHIRALCEL OD (Daicel Chemical Industries, Ltd.), 2×25 cm; mobile phase, hexane:2-propanol = 95:5 (v/v)], affording **17a** (186 mg, 19%), *ent*-**17a** (176 mg, 18%), **17b** (299 mg, 30%), and *ent*-**17b** (317 mg, 32%), respectively. The conditions for analytical HPLC were as follows: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), 1×25 cm; mobile phase, hexane:2-propanol = 10:1 (v/v); flow rate, 1.0 mL/min; temperature, 40 °C; monitoring, 254 nm. The retention times and ee values are as follows: **17b**, 21.2 min, 99% ee; *ent*-**17a**, 22.7 min, 99% ee**;** **17a**, 23.5 min, 94% ee; *ent*-**17b**, 33.6 min, 98% ee.

(a) **17a**: $[\alpha]_D^{23}$ +42° (*c* 0.16, $CHCl_3$). Mp 93–94 °C (pentane-ether). 99% ee by HPLC analysis. ^1H NMR (400 MHz, $CDCl_3$): δ 0.69–1.34 (m, 6H), 1.52–1.81 (m, 6H), 1.85–1.98 (m, 2H), 2.17 (dt, *J* = 11.7, 5.9 Hz, 1H), 2.82–2.89 (m, 1H), 3.32 (s, 3H), 3.94 (dd, *J* = 10.8, 8.3 Hz, 1H), 4.00 (apparent t, *J* = 8.3 Hz, 1H), 4.22 (dd, *J* = 11.7, 7.1 Hz, 1H), 4.36 (dd, *J* = 11.7, 3.7 Hz, 1H), 4.59 (s, 1H), 7.59 (dt, *J* = 8.8, 2.1 Hz, 2H), 7.87 (dt, *J* = 8.8, 2.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0, 26.4, 29.7, 30.1, 32.1, 34.0, 38.3, 38.4, 40.6, 44.7, 54.5, 66.3, 67.7, 109.1, 128.2, 129.0, 131.1, 131.1, 131.8, 131.8, 165.8. IR (KBr): 2920, 1720, 1590, 1270, 1100 cm^{-1}. MS (FAB) (*m*/*z*): 391 (M^+-HOMe), 362 (100). HRMS (FAB) (*m*/*z*): calcd for $C_{20}H_{24}BrO_3$ (M^+-HOMe): 391.0909. Found, 391.0949. Anal. calcd for $C_{21}H_{27}BrO_4$: C, 59.58; H, 6.43. Found: C, 59.68; H, 6.37.

(b) X-ray structural analysis of **17a**:[19] monoclinic space group $P2_1$, *a* = 12.243 (2) Å, *b* = 13.013 (3) Å, *c* = 6.254 (2) Å, β = 93.81 (2) °, *V* = 994.2 (4) $Å^3$, *Z* = 2, density ρ_{calcd} = 1.414 g/cm^3, μ(Cu-K_α) = 30.05 cm^{-1}, *T* = 298 K, size of crystal = 0.40 ~ 0.37 ~ 0.34 mm^{-1}. The structure was solved by direct methods and expanded using Fourier techniques. Final *R* and *Rw* were 0.040 and 0.053, respectively, for 3207 reflections.

(c) *ent*-**17a**: $[\alpha]_D^{22}$ −41° (*c* 0.63, $CHCl_3$). Mp 94–95 °C (pentane–ether). 99% ee by HPLC analysis. ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for **17a**. HRMS (FAB) (*m*/*z*): calcd for $C_{20}H_{24}BrO_3$ (M^+−HOMe): 391.0909. Found, 391.0949. Anal. calcd for $C_{21}H_{27}BrO_4$: C, 59.58; H, 6.43. Found: C, 59.47; H, 6.30.

(d) **17b**: $[\alpha]_D^{26}$ +5.7° (*c* 0.10, $CHCl_3$). Mp 107–108 °C (hexane). 99% ee by HPLC analysis. ^1H NMR (400 MHz, $CDCl_3$): δ 0.82–0.96 (m, 2H), 1.16–1.43 (m, 6H), 1.53–1.73 (m, 3H), 1.77–1.82 (m, 1H), 1.94–1.99 (m, 1H), 2.23 (dt, *J* = 12.7, 6.4 Hz, 1H), 2.83 (dt, *J* = 10.1, 5.9 Hz, 1H), 3.31 (s, 3H), 3.83 (dd, *J* = 11.3, 8.1 Hz, 1H), 4.07 (dd, *J* = 9.3, 7.8 Hz, 1H), 4.26 (dd, *J* = 11.3, 8.3 Hz, 1H), 4.50 (dd, *J* = 10.8, 4.2 Hz, 1H), 4.61 (s, 1H), 7.59 (dt, *J* = 8.8, 2.3 Hz, 2H), 7.89 (dt, *J* = 8.8, 2.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 27.1, 30.4, 32.8, 34.7, 34.8, 36.4, 37.7, 39.1, 41.1, 54.5, 66.4, 69.5, 110.2, 128.0, 129.2, 131.1, 131.1, 131.8, 131.8, 166.0. IR (KBr): 2940, 1710, 1590, 1270, 1110 cm^{-1}. MS (FAB) (*m*/*z*): 528 [(M^+ + diethanolamine) + H]. HRMS (FAB) (*m*/*z*): calcd for $C_{25}H_{39}BrNO_6$ [(M^+ + diethanolamine) + H]: 528.1961. Found, 528.1935. Anal. calcd for $C_{21}H_{27}BrO_4$: C, 59.58; H, 6.43. Found: C, 59.47; H, 6.32.

(e) X-ray structural analysis of **17b**:[19] monoclinic space group $P2_1$, *a* = 11.141 (2) Å, *b* = 8.876 (2) Å, *c* = 10.153 (2) Å, β = 93.53 (2) °, *V* = 1002.1 (3) $Å^3$, *Z* = 2, density ρ_{calcd} = 1.403 g/cm^3, μ(Cu-K_α) = 29.81 cm^{-1}, *T* = 298 K, size of crystal = 0.31×0.30×0.07 mm^{-1}. The structure was solved by direct methods and expanded using Fourier techniques. Final *R* and *Rw* were 0.041 and 0.054, respectively, for 3938 reflections.

(f) *ent*-**17b**: $[\alpha]_D^{26}$ −5.5° (*c* 0.10, $CHCl_3$). Mp 108–109 °C hexane). 99% ee by HPLC analysis. ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for **17b**. HRMS (FAB) (*m*/*z*): calcd for $C_{25}H_{39}BrNO_6$ [(M^+ + diethanolamine) + H]: 528.1961. Found, 528.1920. Anal. calcd for $C_{21}H_{27}BrO_4$: C, 59.58; H, 6.43. Found: 59.40; H, 6.26.

(1*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxynaphtho[2,3-*c*]furan-4-methanol and its enantiomer (16a and *ent*-16a). (a) Preparation of **16a**: To a solution of **17a** (186 mg, 0.44 mmol) in ethanol (3 mL), aq 10% sodium hydroxide solution (2 mL) was added, and the mixture was stirred at room temperature for 30 min. After concentration in vacuo, the mixture was diluted with water (10 mL). The aqueous mixture was extracted with diethyl ether (5 mL×3). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flush column chromatography (hexane/ethyl acetate = 1:1) of

the residue gave **16a** (196 mg, 100%) as a colorless oil. $[\alpha]_D^{24}$ +105° (*c* 0.98, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.82–1.09 (m, 5H), 1.16–1.29 (m, 2H), 1.37 (br, 1H), 1.48–1.52 (m, 1H), 1.59–1.88 (m, 5H), 2.12 (dt, *J* = 12.2, 6.2 Hz, 1H), 2.78–2.86 (m, 1H), 3.32 (s, 3H), 3.52 (dd, *J* = 10.8, 7.3 Hz, 1H), 3.74 (dd, *J* = 10.8, 3.4 Hz, 1H), 3.88 (dd, *J* = 11.3, 8.3 Hz, 1H), 4.04 (apparent t, *J* = 8.6 Hz, 1H), 4.57 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 26.5, 30.2, 32.2, 34.1, 37.9, 38.2, 40.6, 43.4, 44.8, 54.4, 66.8, 67.8, 109.1. IR (neat): 3450, 2920, 1450, 1100 cm^{-1}. MS (FAB) (*m*/*z*): 346 [(M^+ + diethanolamine) + H]. HRMS (FAB) (*m*/*z*): calcd for $C_{18}H_{36}NO_5$ [(M^+ + diethanolamine) + H]: 346.2593. Found, 346.2623.

(b) Preparation of *ent*-**16a**: the compound *ent*-**16a** (99.6 mg, 100%) was prepared as a colorless oil from *ent*-**17a** (176 mg, 0.42 mmol) in the same manner as described in a). $[\alpha]_D^{24}$ −106° (*c* 1.08, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for **16a**. HRMS (FAB) (*m*/*z*): calcd for $C_{18}H_{36}NO_5$ [(M^+ + diethanolamine) + H]: 346.2593. Found, 346.2571.

Preparation of (1*S*,3a*R*,4*S*,4a*S*,8a*R*,9a*S*)-dodecahydro-1-methoxynaphtho[2,3-*c*]furan-4-methanol and its enantiomer (16b and *ent*-16b). (a) Preparation of **16b**: the compound **16b** (107 mg, 100%) was prepared as a colorless powder from **17b** (188 mg, 0.44 mmol) in a manner similar to that described for the preparation of **16a**. $[\alpha]_D^{25}$ +30° (*c* 0.35, $CHCl_3$). Mp 65–66 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.79–0.92 (m, 2H), 1.13–1.35 (m, 5H), 1.41–1.70 (m, 6H), 1.75–1.80 (m, 1H), 2.18 (dt, *J* = 12.2, 6.2 Hz, 1H), 2.87 (dt, *J* = 10.1, 5.9 Hz, 1H), 3.32 (s, 3H), 3.59 (apparent t, *J* = 9.6 Hz, 1H), 3.80 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.85 (dd, *J* = 10.3, 3.9 Hz, 1H), 4.03 (dd, *J* = 9.3, 7.8 Hz, 1H), 4.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 27.2, 30.4, 32.8, 34.7, 34.8, 34.9, 36.8, 39.4, 39.5, 41.1, 54.4, 63.1, 69.6, 110.1. IR (KBr): 3260, 2920, 1450, 1100, 1030 cm^{-1}. MS (CI) (*m*/*z*): 241 (M^+ + H), 223, 209 (100). HRMS (CI) (*m*/*z*): calcd for $C_{14}H_{25}O_3$ (M^+ + H): 241.1804. Found, 241.1803.

(b) Preparation of *ent*-**16b**: the compound *ent*-**16b** (104 mg, 91%) was prepared as a colorless powder from *ent*-**17b** (201 mg, 0.47 mmol) similarly to the preparation of **16b**. $[\alpha]_D^{25}$ −28° (*c* 0.77, $CHCl_3$). Mp 65–66 °C. ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for **16b**. HRMS (CI) (*m*/*z*): calcd for $C_{14}H_{25}O_3$ (M^+ + H): 241.1804. Found, 241.1770.

(1*S*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-4-(phenylthio)methylnaphtho[2,3-*c*]furan and its enantiomer (18 and *ent*-18). (a) Preparation of **18**: to a solution of **16a** (117 mg, 0.49 mmol) in acetonitrile (10 mL) were added (cyanomethyl)trimethylphosphonium iodide (236 mg, 0.97 mmol), thiophenol (74.9 μL, 0.73 mmol), and *N*,*N*-diisopropylethylamine (212 μL, 1.21 mmol), all at room temperature, and the mixture was stirred at 80 °C for 2.5 h. The reaction mixture was concentrated in vacuo, and the residue was diluted with water (10 mL). The aqueous mixture was extracted with diethyl ether (5 mL×3). The ethereal extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flush column chromatography (hexane/ethyl acetate = 50:1, then 10:1) of the residue gave **18** (149 mg, 92%) as a colorless oil. $[\alpha]_D^{24}$ +171° (*c* 0.53, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.77–1.05 (m, 5H), 1.17–1.29 (m, 2H), 1.46–1.52 (m, 1H), 1.59–1.82 (m, 4H), 1.94–2.01 (m, 1H), 2.08 (dt, *J* = 12.2, 6.2 Hz, 1H), 2.43 (dd, *J* = 12.2, 11.1 Hz, 1H), 3.02–3.09 (m, 1H), 3.32 (s, 3H), 3.34 (dd, *J* = 14.2, 3.9 Hz, 1H), 3.80 (dd, *J* = 10.8, 8.1 Hz, 1H), 4.05 (apparent t, *J* = 8.3 Hz, 1H), 4.58 (s, 1H), 7.14–7.19 (m, 1H), 7.25–7.52 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0, 26.5, 30.1, 32.3, 34.0, 36.0, 37.8, 40.5, 40.6, 41.3, 44.4, 54.5, 67.2, 109.5, 125.8, 128.9, 128.9, 128.9, 137.0. IR (neat): 2920, 1580, 1480, 1440, 1100 cm^{-1}. MS (EI) (*m*/*z*): 332 (M^+), 300 (100). HRMS (EI) (*m*/*z*): calcd for $C_{20}H_{28}O_2S$ (M^+): 332.1810. Found, 332.1824.

(b) Preparation of *ent*-**18**: the compound *ent*-**18** (140 mg, 88%) was prepared as a brown oil from *ent*-**16a** (114 mg, 0.48 mmol) in the same manner as described for the preparation of **18**. $[\alpha]_D^{24}$ −177° (*c* 0.20, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for **18**. HRMS (EI) (*m*/*z*): calcd for $C_{20}H_{28}O_2S$ (M^+): 332.1810. Found, 332.1824.

(1*S*,3a*S*,4*S*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-4-(phenylthio)methylnaphtho[2,3-*c*]furan and its enantiomer (4-*epi*-18 and *ent*-4-*epi*-18). (a) Preparation of 4-*epi*-**18**: The compound 4-*epi*-**18** (112 mg, 79%) was prepared as a colorless powder from **16b** (102 mg, 0.42 mmol) in a manner similar to that described for the preparation of **18**. $[\alpha]_D^{23}$ −33° (*c* 0.45, $CHCl_3$). Mp 104–105 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.79–0.96 (m, 2H), 1.13–1.43 (m, 6H), 1.53–1.82 (m, 5H), 2.16 (dt, *J* = 12.2, 6.2 Hz, 1H), 2.65 (dd, *J* = 12.7, 10.8 Hz, 1H), 3.07 (dt, *J* = 10.1, 6.9 Hz, 1H), 3.30 (dd, *J* = 12.7, 3.0 Hz, 1H), 3.32 (s, 3H), 3.74 (dd, *J* = 10.8, 8.3 Hz, 1H), 3.99 (dd, *J* = 9.3, 8.1 Hz, 1H), 4.58 (s, 1H), 7.14–7.19 (m, 1H), 7.24–7.35 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 26.9, 30.3, 33.1, 33.7, 34.6, 34.7, 36.8, 38.3, 40.2, 40.5, 54.5, 69.4, 110.1, 125.9, 128.9, 128.9, 129.2, 129.2, 136.9. IR (KBr): 2930, 1580, 1090 cm^{-1}. MS (EI) (*m*/*z*): 332 (M^+). HRMS (EI) (*m*/*z*): calcd for $C_{20}H_{28}O_2S$ (M^+): 332.1810. Found, 332.1835.

(b) Preparation of *ent*-4-*epi*-**18**: the compound *ent*-4-*epi*-**18** (137 mg, 76%) was prepared as a colorless powder from *ent*-**16b** (131 mg, 0.54 mmol) in a manner similar to that described for the preparation of **18**. $[\alpha]_D^{22}$ +34° (*c* 0.10, $CHCl_3$). Mp 105–106 °C. ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described in (a). HRMS (EI) (*m*/*z*): calcd for $C_{20}H_{28}O_2S$ (M^+): 332.1810. Found, 332.1827.

(1*S*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-4-(phenylsulfonyl)methylnaphtho[2,3-*c*]furan and its enantiomer (19 and *ent*-19). (a) Preparation of **19**: to a solution of **18** (149 mg, 0.45 mmol) in CH_2Cl_2 (10 mL) were added 3-chloroperoxybenzoic acid (65%, 358 mg, 1.35 mmol) and sodium bicarbonate (226 mg, 2.69 mmol) at

0 °C, and the mixture was stirred at room temperature for 1.5 h. After insoluble materials were filtered off through a pad of Celite, the collected solid was washed with CH_2Cl_2 (30 mL). The filtrates were combined and concentrated in vacuo. The residue was dissolved in diethyl ether (20 mL). The ethereal solution was washed with saturated aqueous sodium bicarbonate solution (5 mL×2) and brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate = 2:1) of the residue gave **19** (135 mg, 82%) as a colorless powder. $[\alpha]_D^{24}$ +160° (*c* 0.16, $CHCl_3$). Mp 159–160 °C (hexane–ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.62–74 (m, 1H), 0.83–1.02 (m, 4H), 1.08–1.27 (m, 2H), 1.45–1.52 (m, 1H), 1.57–1.77 (m, 5H), 2.05–2.14 (m, 1H), 2.69 (dd, *J* = 14.7, 10.3 Hz, 1H), 3.11–3.20 (m, 1H), 3.29 (s, 3H), 3.30 (dd, *J* = 14.2, 2.2 Hz, 1H), 3.71 (dd, *J* = 10.8, 7.3 Hz, 1H), 4.05 (dd, *J* = 8.8, 7.6 Hz, 1H), 4.58 (s, 1H), 7.55–7.61 (m, 2H), 7.64–7.69 (m, 1H), 7.90–7.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.8, 26.4, 29.9, 31.9, 34.1, 36.5, 37.9, 40.5, 40.6, 44.0, 54.3, 57.5, 67.2, 109.6, 127.8, 127.8, 129.3, 129.3, 133.6, 140.0. IR (KBr): 2930, 1450, 1300, 1160 cm^{-1}. MS (FAB) (*m*/*z*): 470 [(M^+ + diethanolamine) + H]. HRMS (FAB) (*m*/*z*): calcd for $C_{24}H_{40}NO_6S$ [(M^+ + diethanolamine) + H]: 470.2576. Found, 470.2572. Anal. calcd for $C_{20}H_{28}O_4S$: C, 65.90; H, 7.74. Found: C, 65.86; H, 7.73.

(b) Preparation of *ent*-**19**: the compound *ent*-**19** (152 mg, 99%) was prepared from *ent*-**18** (140 mg, 0.42 mmol) in the same manner as described for the preparation of **19**. $[\alpha]_D^{23}$ −159° (*c* 0.14, $CHCl_3$). Mp 160–161 °C (hexane–ethyl acetate). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for **19**. HRMS (FAB) (*m*/*z*): calcd for $C_{24}H_{40}NO_6S$ [(M^+ + diethanolamine) + H]: 470.2576. Found, 470.2578. Anal. calcd for $C_{20}H_{28}O_4S$: C, 65.90; H, 7.74. Found: C, 65.77; H, 7.85.

(1*S*,3a*S*,4*S*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-4-(phenylsulfonyl)methylnaphtho[2,3-*c*]furan and its enantiomer (4-*epi*-19 and *ent*-4-*epi*-19). (a) Preparation of 4-*epi*-**19**: the compound 4-*epi*-**19** (106 mg, 86%) was prepared as a colorless powder from 4-*epi*-**18** (112 mg, 0.34 mmol) in a manner similar to that described for the preparation of **19**. $[\alpha]_D^{22}$ +17° (*c* 0.30, $CHCl_3$). Mp 153–154 °C (hexane–ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75–1.35 (m, 7H), 1.51–1.74 (m, 5H), 2.09 (dt, *J* = 12.7, 6.4 Hz, 1H), 2.14–2.19 (m, 1H), 2.82–2.91 (m, 1H), 2.95 (dd, *J* = 14.2, 8.3 Hz, 1H), 3.26 (dd, *J* = 14.7, 2.0 Hz, 1H), 3.28 (s, 3H), 3.74 (dd, *J* = 10.3, 8.3 Hz, 1H), 4.00 (dd, *J* = 9.3, 8.3 Hz, 1H), 4.55 (s, 1H), 7.55–7.61 (m, 2H), 7.64–7.69 (m, 1H), 7.89–7.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0, 26.3, 29.7, 32.1, 32.6, 34.0, 34.2, 39.1, 40.6, 40.6, 54.3, 56.9, 68.8, 109.5, 128.1, 128.1, 129.3, 129.3, 133.7, 139.7. IR (KBr): 2920, 1450, 1310, 1140 cm^{-1}. MS (FAB) (*m*/*z*): 470 [(M^+ + diethanolamine) + H]. HRMS (FAB) (*m*/*z*): calcd for $C_{24}H_{40}NO_6S$ [(M^+ + diethanolamine) + H]: 470.2576. Found, 470.2567.

(b) Preparation of *ent*-4-*epi*-**19**: the compound *ent*-4-*epi*-**19** (123 mg, 82%) was prepared from *ent*-4-*epi*-**18** (137 mg, 0.41 mmol) in a manner similar to that described for the preparation of **19**. $[\alpha]_D^{22}$ −18° (*c* 0.22, $CHCl_3$). Mp 154–155 °C (hexane–ethyl acetate). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for 4-*epi*-**19**. HRMS (FAB) (*m*/*z*): calcd for $C_{24}H_{40}NO_6S$ [(M^+ + diethanolamine) + H]: 470.2576. Found, 470.2578.

(2*R*,6*S*)-*tert*-Butyl 2-[2-(*E*)-[(1*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-dodecahydro-1-methoxynaphtho[2,3-*c*]furan-4-yl]ethenyl]-6-methylpiperidine-1-carboxylate and its enantiomer (21 and *ent*-21). (a) Preparation of **21**: To a solution of **19** (50.0 mg, 0.14 mmol) in 1,2-dimethoxyethane (2 mL), *n*-butyllithium (1.5 M solution in hexane, 137 μL, 0.21 mmol) was added dropwise at −78 °C, and the mixture was stirred at the same temperature for 5 min. A solution of **20** (46.8 mg, 0.21 mmol) in 1,2-dimethoxyethane (1 mL) was added dropwise to the mixture at −78 °C, and the resulting mixture was stirred at the same temperature for 3 h and then gradually warmed to 0 °C with stirring. Benzoyl chloride (47.8 μL, 0.41 mmol) was added to the reaction mixture at −78 °C, and the reaction mixture was stirred at room temperature for 1 h. After quenching the reaction by adding 3-(dimethylamino)propylamine (51.8 μL, 0.41 mmol), the mixture was diluted with aqueous citric acid solution (10 mL). The aqueous mixture was extracted with diethyl ether (3 mL×3). The ethereal extracts were combined, washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate = 10:1, 4:1, then 1:1) of the residue gave the β-benzoxysulfone (possibly a mixture of the four diastereomers) (36.9 mg, 39%) as a yellow oil with recovery of a portion of the starting **19** (30.0 mg, 60%). The structure of this adduct was determined by its MS spectrum. MS (FAB) (*m*/*z*): 801 [(M^+ + diethanolamine) + H]. HRMS (FAB) (*m*/*z*): calcd for $C_{43}H_{65}N_2O_{10}S$ [(M^+ + diethanolamine) + H]: 801.4360. Found, 801.4335.

To a solution of the β-benzoxysulfone (36.9 mg) in methanol (10 mL), 5% sodium amalgam (0.50 g) and Na_2HPO_4 (1.00 g) were added, and the mixture was stirred at room temperature for 1 h. Insoluble materials were filtered and thoroughly washed with ethyl acetate (20 mL). The filtrates were combined and concentrated in vacuo. After adding water (10 mL), the aqueous mixture was extracted with diethyl ether (3 mL×3). The ethereal extracts were combined, washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate = 4:1) of the residue gave **21** (14.4 mg, 63%) as a colorless oil. In this case, formation of the (*Z*)-olefin was not observed by ^{1}H NMR analysis of the crude reaction product. $[\alpha]_D^{24}$ +108° (*c* 1.44, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65–0.77 (m, 1H), 0.85–1.02 (m, 4H), 1.12–1.29 (m, 3H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.41–1.78 (m, 8H), 1.45 (s, 9H), 1.85–2.00 (m, 2H), 2.03–2.13 (m, 2H), 2.61–2.69 (m, 1H), 3.30 (s, 3H), 3.83 (dd, *J* = 10.8, 8.3 Hz, 1H), 3.92 (apparent t, *J* = 8.6 Hz, 1H), 3.95–4.02 (m, 1H), 4.35–4.40 (m, 1H), 4.57 (s, 1H), 5.10 (ddd, *J* = 15.2, 9.3, 1.6 Hz, 1H), 5.48 (dd, *J* = 15.7, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ

13.4, 20.9, 25.3, 26.3, 26.4, 26.6, 28.5, 28.5, 28.5, 31.3, 32.1, 34.1, 40.2, 40.7, 41.2, 44.5, 45.8, 47.0, 52.2, 54.4, 67.9, 78.9, 109.5, 131.7, 133.3, 155.1. IR (neat): 2930, 1690, 1390, 1180, 1100 cm^{-1}. MS (FAB) (*m*/*z*): 434 ($M^+ + H$), 402, 376, 346 (100). HRMS (FAB) (*m*/*z*): calcd for $C_{26}H_{44}NO_4$ ($M^+ + H$): 434.3270. Found, 434.3278.

(b) Preparation of *ent*-**21**: the β-benzoxysulfone (51.9 mg, 34%) enantiomeric to that produced from **19** was prepared from *ent*-**19** (80.0 mg, 0.22 mmol) in the same manner as described for the preparation of the β-benzoxysulfone from **19** with recovery of starting *ent*-**19** (51.0 mg, 64%). HRMS (FAB) (*m*/*z*): calcd for $C_{43}H_{65}N_2O_{10}S$ [(M^+ + diethanolamine) + H]: 801.4360. Found, 801.4342.

The β-benzoxysulfone was subjected to elimination reaction in a manner similar to that described for the preparation of **21**, affording *ent*-**21** (17.9 mg, 55%) as a colorless oil. $[\alpha]_D^{23}$ −112° (*c* 1.19, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for **21**. HRMS (FAB) (*m*/*z*): calcd for $C_{26}H_{44}NO_4$ ($M^+ + H$): 434.3270. Found, 434.3275.

(2*R*,6*S*)-*tert*-Butyl 2-[2-(*E*)-[(1*S*,3a*R*,4*S*,4a*S*,8a*R*,9a*S*)-dodecahydro-1-methoxynaphtho[2,3-*c*]furan-4-yl]ethenyl]-6-methylpiperidine-1-carboxylate and its enantiomer (4-*epi*-21 and *ent*-4-*epi*-21). (a) Preparation of 4-*epi*-**21**: the reaction of 4-*epi*-**19** (50.0 mg, 0.14 mmol) and **20** (46.8 mg, 0.21 mmol) in a manner similar to that described for the preparation of **21** gave the corresponding β-benzoxysulfone (possibly a mixture of the four diastereomers) (40.0 mg, 42%) as a colorless oil with recovery of a portion of the starting 4-*epi*-**19** (29.0 mg, 58%), after flash column chromatography (hexane/ethyl acetate = 10:1, 4:1, then 1:1). Unlike the preparation of **21**, the addition reaction of the lithium anion derived from 4-*epi*-**19** was finished at −78 °C after 2.5 h without gradual warming to 0 °C. The structure of this adduct was determined by its MS spectrum. MS (FAB) (*m*/*z*): 801 [(M^+ + diethanolamine) + H]. HRMS (FAB) (*m*/*z*): calcd for $C_{43}H_{65}N_2O_{10}S$ [(M^+ + diethanolamine) + H]: 801.4360. Found, 801.4318.

Treatments of the β-benzoxysulfone (40.0 mg) in the same manner as described for the preparation of **21** from the corresponding β-benzoxysulfone gave 4-*epi*-**21** (19.2 mg, 77%) as a colorless oil after flash column chromatography (hexane/ethyl acetate = 4:1). In this case, formation of the (*Z*)-olefin was not observed by ^1H NMR analysis of the crude reaction product. $[\alpha]_D^{23}$ +50° (*c* 1.28, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.79–0.93 (m, 2H), 1.06–1.36 (m, 6H), 1.24 (d, *J* = 6.4 Hz, 3H), 1.46 (s, 9H), 1.42–1.82 (m, 8H), 1.88–2.00 (m, 2H), 2.15–2.22 (m, 2H), 2.47–2.56 (m, 1H), 3.34 (s, 3H), 3.79 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.98–4.05 (m, 2H), 4.39–4.44 (m, 1H), 4.58 (s, 1H), 5.44 (dd, *J* = 15.2, 3.9 Hz, 1H), 5.54 (ddd, *J* = 15.7, 9.8, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 20.8, 25.3, 26.3, 26.3, 26.8, 28.5, 28.5, 28.5, 31.2, 33.0, 34.2, 34.5, 39.9, 41.1, 41.2, 41.3, 47.0, 52.0, 54.4, 69.6, 78.9, 110.2, 130.0, 132.9, 155.2. IR (neat): 2930, 1690, 1390, 1180, 1100 cm^{-1}. MS (FAB) (*m*/*z*): 539 [(M^+ + diethanolamine) + H]. HRMS (FAB) (*m*/*z*): calcd for $C_{30}H_{55}N_2O_6$ [(M^+ + diethanolamine) + H]: 539.4060. Found, 539.4108.

(b) Preparation of *ent*-4-*epi*-**21**: the β-benzoxysulfone (37.0 mg, 39%) was prepared from *ent*-4-*epi*-**19** (50.0 mg, 0.14 mmol) as a colorless oil with recovery of starting *ent*-4-*epi*-**19** (30.0 mg, 60%) in a manner similar to that described for the preparation of the β-benzoxysulfone from **19**. HRMS (FAB) (*m*/*z*): calcd for $C_{43}H_{65}N_2O_{10}S$ [(M^+ + diethanolamine) + H]: 801.4360. Found, 801.4376.

The β-benzoxysulfone was subjected to elimination reaction in the same manner as that described for the preparation of **21** from the corresponding β-benzoxysulfone, affording *ent*-4-*epi*-**21** (14.0 mg, 61%) as a colorless oil. $[\alpha]_D^{23}$ −51° (*c* 1.20, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for 4-*epi*-**21**. HRMS (FAB) (*m*/*z*): calcd for $C_{30}H_{55}N_2O_6$ [(M^+ + diethanolamine) + H]: 539.4060. Found, 539.4108.

(2*R*,6*S*)-*tert*-Butyl 2-[2-(*E*)-[(3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-decahydronaphtho[2,3-*c*]furan-1(3*H*)-on-4-yl]ethenyl]-6-methylpiperidine-1-carboxylate and its enantiomer (22 and *ent*-22). (a) Preparation of **22**: to a solution of **21** (14.4 mg, 33.2 μmol) in acetone (2 mL), Jones reagent (0.20 mL) was added at room temperature, and the mixture was stirred at the same temperature for 1.5 h. After 2-propanol (1 mL) was added, the reaction mixture was concentrated in vacuo. The residue was diluted with water (10 mL), and the aqueous mixture was extracted with diethyl ether (3 mL×3). The ethereal extracts were combined, washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flush column chromatography (hexane/ethyl acetate = 2:1) of the residue gave **22** (8.00 mg, 58%) as a colorless oil. $[\alpha]_D^{24}$ +83° (*c* 0.48, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.68–0.80 (m, 1H), 0.93–1.29 (m, 6H), 1.23 (d, *J* = 6.4 Hz, 3H), 1.38–2.13 (m, 12H), 1.45 (s, 9H), 2.55 (dt, *J* = 12.7, 6.4 Hz, 1H), 2.66–2.75 (m, 1H), 3.98–4.05 (m, 1H), 4.19 (dd, *J* = 11.7, 9.1 Hz, 1H), 4.27 (apparent t, *J* = 8.6 Hz, 1H), 4.36–4.41 (m, 1H), 5.11 (ddd, *J* = 15.2, 9.8, 1.5 Hz, 1H), 5.56 (dd, *J* = 15.2, 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 20.9, 25.3, 26.2, 26.2, 26.4, 28.5, 28.5, 28.5, 30.7, 31.2, 33.6, 39.7, 39.8, 41.0, 44.8, 47.1, 52.1, 68.1, 79.1, 129.1, 134.9, 155.0, 179.3. IR (neat): 2920, 1780, 1680, 1390 cm^{-1}. MS (FAB) (*m*/*z*): 418 ($M^+ + H$), 318 (100). HRMS (FAB) (*m*/*z*): calcd for $C_{25}H_{40}NO_4$ ($M^+ + H$): 418.2957. Found, 418.2990.

(b) Preparation of *ent*-**22**: this compound *ent*-**22** (5.10 mg, 62%) was prepared from *ent*-**21** (8.50 mg, 19.6 μmol) in the same manner as that described for the preparation of **22**. $[\alpha]_D^{24}$ −85° (*c* 0.34, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for **22**. HRMS (FAB) (*m*/*z*): calcd for $C_{25}H_{40}NO_4$ ($M^+ + H$): 418.2957. Found, 418.2984.

(2*R*,6*S*)-*tert*-Butyl 2-[2-(*E*)-[(3a*R*,4*S*,4a*S*,8a*R*,9a*S*)-decahydronaphtho[2,3-*c*]furan-1(3*H*)-on-4-yl]ethenyl]-6-

methylpiperidine-1-carboxylate and its enantiomer (4-*epi*-22 and *ent*-4-*epi*-22). (a) Preparation of 4-*epi*-22: The compound 4-*epi*-22 (12.0 mg, 60%) was prepared as a colorless powder from 4-*epi*-21 (20.6 mg, 47.5 μmol) in a similar manner to that described for the preparation of 22. $[\alpha]_D^{24}$ +14° (*c* 0.59, $CHCl_3$). Mp 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85–0.97 (m, 1H), 1.06–1.30 (m, 6H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.35–1.79 (m, 8H), 1.46 (s, 9H), 1.82–2.02 (m, 3H), 2.17–2.22 (m, 1H), 2.56–2.66 (m, 2H), 4.00–4.07 (m, 1H), 4.21 (dd, *J* = 11.3, 8.8 Hz, 1H), 4.31 (apparent t, *J* = 8.3 Hz, 1H), 4.40–4.44 (m, 1H), 5.45–5.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 20.8, 25.5, 26.1, 26.3, 26.6, 28.5, 28.5, 28.5, 30.9, 31.3, 33.7, 34.0, 37.3, 40.2, 40.9, 41.6, 47.1, 52.0, 69.0, 79.0, 128.5, 134.1, 155.1, 179.4. IR (KBr): 2930, 1770, 1690, 1400, 1370, 1180 cm^{-1}. MS (FAB) (*m*/*z*): 418 (M^+ + H), 362 (100). HRMS (FAB) (*m*/*z*): calcd for $C_{25}H_{40}NO_4$ (M^+ + H): 418.2957. Found, 418.2953.

(b) Preparation of *ent*-4-*epi*-22: The compound *ent*-4-*epi*-22 (9.40 mg, 70%) was prepared from *ent*-4-*epi*-21 (14.0 mg, 32.3 μmol) in a manner similar to that described for the preparation of 22. $[\alpha]_D^{24}$ −13° (*c* 0.54, $CHCl_3$). Mp 112–114 °C. ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were superimposable on those described in (a). HRMS (FAB) (*m*/*z*): calcd for $C_{25}H_{40}NO_4$ (M^+ + H): 418.2957. Found, 418.2952.

(3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-4-[2-(*E*)-[(2*R*,6*S*)-6-methylpiperidin-2-yl]ethenyl]naphtho[2,3-*c*]furan-1(3*H*)-one and its enantiomer (23 and *ent*-23). (a) Preparation of 23: To a solution of 22 (8.00 mg, 19.2 μmol) in CH_2Cl_2 (1 mL), trifluoroacetic acid (0.10 mL) was added at room temperature, and the mixture was stirred at the same temperature for 0.5 h. After the reaction mixture was made alkaline by adding cold diluted aqueous sodium hydroxide solution, the mixture was extracted with diethyl ether (5 mL×3). The ethereal extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo, giving 23 (5.30 mg, 87%) as a colorless oil. $[\alpha]_D^{23}$ +38° (*c* 0.30, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68–1.33 (m, 10H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.43–1.88 (m, 9H), 2.06–2.14 (m, 1H), 2.56 (dt, *J* = 12.7, 6.4 Hz, 1H), 2.66–2.75 (m, 1H), 3.06–3.14 (m, 1H), 3.53–3.59 (m, 1H), 4.21 (dd, *J* = 11.7, 8.8 Hz, 1H), 4.27 (apparent t, *J* = 8.6 Hz, 1H), 5.20 (ddd, *J* = 15.7, 9.8, 1.3 Hz, 1H), 5.72 (dd, *J* = 15.7, 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 21.1, 26.2, 26.4, 30.7, 30.8, 31.2, 32.5, 33.6, 39.7, 39.8, 40.8, 41.0, 45.1, 46.4, 52.7, 68.1, 129.9, 135.7, 179.2. IR (neat): 2920, 1780, 1180, 1100 cm^{-1}. MS (FAB) (*m*/*z*): 318 (M^+ + H). HRMS (FAB) (*m*/*z*): calcd for $C_{20}H_{32}NO_2$ (M^+ + H): 318.2433. Found, 318.2453.

(b) Preparation of *ent*-23: the compound *ent*-23 (7.30 mg, 94%) was prepared as a colorless oil from *ent*-22 (10.2 mg, 24.4 μmol) in the same manner as that described for the preparation of 23. $[\alpha]_D^{23}$ −38° (*c* 0.28, $CHCl_3$). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described in (a). HRMS (FAB) (*m*/*z*): calcd for $C_{20}H_{32}NO_2$ (M^+ + H): 318.2433. Found, 318.2435.

(3a*R*,4*S*,4a*S*,8a*R*,9a*S*)-Decahydro-4-[2-(*E*)-[(2*R*,6*S*)-6-methylpiperidin-2-yl]ethenyl]naphtho[2,3-*c*]furan-1(3*H*)-one and its enantiomer (4-*epi*-23 and *ent*-4-*epi*-23). (a) Preparation of 4-*epi*-23: The compound 4-*epi*-23 (6.20 mg, 93%) was prepared as a colorless powder from 4-*epi*-22 (8.80 mg, 21.1 μmol) in a manner similar to that described for the preparation of 23. $[\alpha]_D^{21}$ −28° (*c* 0.41, $CHCl_3$). Mp 103–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80–0.98 (m, 2H), 1.04–1.42 (m, 8H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.46–1.79 (m, 8H), 1.87–1.95 (m, 1H), 2.17 (dd, *J* = 8.8, 2.7 Hz, 1H), 2.59–2.70 (m, 2H), 3.06–3.14 (m, 1H), 3.59 (dd, *J* = 10.3, 5.2 Hz, 1H), 4.21 (dd, *J* = 11.3, 8.8 Hz, 1H), 4.32 (apparent t, *J* = 8.3 Hz, 1H), 5.59 (dd, *J* = 15.7, 8.8 Hz, 1H), 5.66 (dd, *J* = 15.2, 5.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 21.3, 26.2, 26.6, 30.9, 31.1, 31.4, 32.7, 33.7, 34.1, 37.2, 40.1, 41.2, 41.5, 46.3, 53.0, 69.0, 130.0, 134.2, 179.4. IR (KBr): 2920, 1760, 1210, 1190 cm^{-1}. MS (FAB) (*m*/*z*): 318 (M^+ + H) (100). HRMS (FAB) (*m*/*z*): calcd for $C_{20}H_{32}NO_2$ (M^+ + H): 318.2433. Found, 318.2435.

(b) Preparation of *ent*-4-*epi*-23: the compound *ent*-4-*epi*-23 (7.10 mg, 99%) was prepared from *ent*-4-*epi*-22 (9.40 mg, 22.5 μmol) in the same manner as that described for the preparation of 23. $[\alpha]_D^{22}$ +30° (*c* 0.33, $CHCl_3$). Mp 105–107 °C. ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were superimposable on those described in (a). HRMS (FAB) (*m*/*z*): calcd for $C_{20}H_{32}NO_2$ (M^+ + H): 318.2433. Found, 318.2437.

(3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-4-[2-(*E*)-[(2*R*,6*S*)-1,6-dimethylpiperidin-2-yl]ethenyl]naphtho[2,3-*c*]furan-1(3*H*)-one [3-demethylhimbacine (3-norhimbacine)] and its enantiomer [*ent*-3-demethylhimbacine (*ent*-3-norhimbacine)] (2 and *ent*-2). (a) Preparation of 2: To a solution of 23 (5.30 mg, 16.7 μmol) in acetonitrile (1 mL) were added formaldehyde (37 wt.% solution in water, 0.10 mL) and sodium cyanoborohydride (2.31 mg, 36.7 μmol), and the mixture was stirred at room temperature for 1 h. The mixture was adjusted to pH 7.0 by adding acetic acid, and it was further stirred at room temperature for 1 h. After the addition of cold diluted aqueous sodium hydroxide solution, the mixture was concentrated in vacuo, and the residue was extracted with diethyl ether (3 mL ×3). The ethereal extracts were combined, washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flash column chromatography (Chromatorex, hexane/ethyl acetate = 2:1) of the residue gave 2 (4.40 mg, 80%) as a colorless oil. $[\alpha]_D^{24}$ +69° (*c* 0.44, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70–1.30 (m, 9H), 1.00 (d, *J* = 6.4 Hz, 3H), 1.38–1.88 (m, 9H), 2.05–2.20 (m, 1H), 2.22 (s, 3H), 2.56 (dt, *J* = 12.7, 6.4 Hz, 1H), 2.66–2.74 (m, 1H), 2.79–2.86 (m, 1H), 2.98–3.04 (m, 1H), 4.20 (dd, *J* = 11.7, 8.8 Hz, 1H), 4.24 (apparent t, *J* = 8.3 Hz, 1H), 5.20 (dd, *J* = 15.2, 9.3 Hz, 1H), 5.65 (dd, *J* = 15.7, 9.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 19.0, 26.2, 26.4, 30.7, 31.3, 33.1, 33.3, 33.6, 39.7, 39.8, 40.9, 41.1, 41.1, 45.2, 53.4, 61.2, 68.1, 131.3, 134.5, 179.2. IR (neat): 2930, 1770, 1450, 1370, 1170 cm^{-1}. MS (FAB) (*m*/*z*): 332 (M^+ + H). HRMS (FAB) (*m*/*z*): calcd for $C_{21}H_{34}NO_2$ (M^+ + H): 332.2590. Found, 332.2609.

(b) Preparation of *ent*-**2**: the compound *ent*-**2** (4.50 mg, 59%) was prepared from *ent*-**23** (7.30 mg, 23.0 μmol) in a manner similar to that described for the preparation of **2**. $[\alpha]_D^{24}$ −72° (*c* 0.30, $CHCl_3$). ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for **2**. HRMS (FAB) (*m*/*z*): calcd for $C_{21}H_{34}NO_2$ ($M^+ + H$): 332.2590. Found, 332.2579.

(3a*R*,4*S*,4a*S*,8a*R*,9a*S*)-Decahydro-4-[2-(*E*)-[(2*R*,6*S*)-1,6-dimethylpiperidin - 2 - yl]ethenyl]naphtho[2,3 - *c*]furan - 1(3*H*)-one [4-*epi*-3-demethylhimbacine (4-*epi*-3-norhimbacine)] and its enantiomer [*ent*-4-*epi*-3-demethylhimbacine (*ent*-4-*epi*-3-norhimbacine)] (4-*epi*-2 and *ent*-4-*epi*-2). (a) Preparation of 4-*epi*-**2**: the compound 4-*epi*-**2** (6.30 mg, 78%) was prepared as a colorless powder from 4-*epi*-**23** (7.70 mg, 24.3 μmol) in a manner similar to that described for the preparation of **2**. $[\alpha]_D^{24}$ −9.1° (*c* 0.42, $CHCl_3$). Mp 86-88 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.81–0.97 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.06–1.32 (m, 8H), 1.37–1.79 (m, 8H), 1.87–1.95 (m, 1H), 2.21 (ddd, *J* = 19.8, 7.8, 2.7 Hz, 1H), 2.22 (s, 3H), 2.60–2.70 (m, 2H), 2.76–2.85 (m, 1H), 3.03–3.09 (m, 1H), 4.22 (dd, *J* = 11.3, 8.8 Hz, 1H), 4.34 (apparent t, *J* = 8.3 Hz, 1H), 5.55 (dd, *J* = 15.9, 8.3 Hz, 1H), 5.62 (dd, *J* = 15.2, 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 19.1, 26.2, 26.6, 31.0, 31.4, 33.0, 33.4, 33.7, 34.1, 37.3, 40.2, 40.8, 40.9, 41.7, 53.3, 61.3, 69.0, 131.3, 132.7, 179.4. IR (KBr): 2930, 1760, 1450, 1370, 1210, 1180 cm^{-1}. MS (FAB) (*m*/*z*): 332 ($M^+ + H$) (100). HRMS (FAB) (*m*/*z*): calcd for $C_{21}H_{34}NO_2$ ($M^+ + H$): 332.2590. Found, 332.2573.

(b) Preparation of *ent*-4-*epi*-**2**: the compound *ent*-4-*epi*-**2** (4.70 mg, 63%) was prepared from *ent*-4-*epi*-**23** (7.10 mg, 22.4 μmol) as a colorless powder in the same manner as that described for the preparation of **2**. $[\alpha]_D^{24}$ +9.7° (*c* 0.47, $CHCl_3$). Mp 85–87 °C. ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for 4-*epi*-**2**. HRMS (FAB) (*m*/*z*): calcd for $C_{21}H_{34}NO_2$ ($M^+ + H$): 332.2590. Found, 332.2569.

(*S*)-5-Ethylfuran-2(5*H*)-one (25). Compound **25** was prepared as a volatile colorless oil from ethyl (*E*)-3-hexenoate **24** following the reported procedure.[17] $[\alpha]_D^{21}$ +71° (*c* 0.54, $CHCl_3$) [lit.,[17d] $[\alpha]_D$ +95° (*c* 3.61, $CHCl_3$)]. Optical purity of this sample was calculated to be ca. 75% ee based on its $[\alpha]_D$ value. ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, *J* = 7.3 Hz, 3H), 1.69–1.90 (m, 2H), 4.99–5.30 (m, 1H), 6.13 (dd, *J* = 5.4, 2.0 Hz, 1H), 7.45 (dd, *J* = 5.9, 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.03, 26.3, 84.4, 121.8, 156.0, 173.2. IR (neat): 2970, 1750, 1360, 1170 cm^{-1}. MS (EI) (*m*/*z*): 112 (M^+), 83 (100). HRMS (EI) (*m*/*z*): calcd for $C_6H_8O_2$ (M^+): 112.0524. Found, 112.0514. These spectra were identical to those reported.[17d]

(3*S*,3a*R*,4*S*,9*R*,9a*R*)-4,9-Epoxy-3-ethyl-3a,4,5,6,7,8,9,9a - octahydronaphtho[2,3 - *c*]furan - 1(3*H*) - one (26). Diels–Alder reaction of **5** (3.92 g, 32.1 mmol) and **25** (3.00 g, 26.8 mmol) in a manner similar to that described for the preparation of *dl*-**7** from **5** and **6** gave **26** (0.91 g, 15%) as a yellow oil with recovery of a portion of the starting **25** (2.00 g, 67%) after flash column chromatography (hexane/ethyl acetate = 2:1, then 1:1). This crude product was immediately subjected to the next reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, *J* = 7.3 Hz, 3H), 1.49–1.78 (m, 6H), 1.89–1.94 (m, 2H), 2.18–2.26 (m, 2H), 2.31 (dd, *J* = 7.8, 3.4 Hz, 1H), 2.82 (d, *J* = 7.8 Hz, 1H), 4.29 (td, *J* = 6.4, 3.4 Hz, 1H), 4.69 (br, 1H), 5.03 (br, 1H). MS (FAB) (*m*/*z*): 235 ($M^+ + H$). HRMS (FAB) (*m*/*z*): calcd for $C_{14}H_{19}O_3$ ($M^+ + H$): 235.1334. Found, 235.1326.

(3*S*,3a*R*,4*R*,4a*S*,8a*R*,9*S*,9a*R*)-4,9-Epoxy-3-ethyl-decahydronaphtho[2,3-*c*]furan-1(3*H*)-one (27). Hydrogenation of **26** (2.56 g, 10.9 mmol) in a manner similar to that described for the preparation of *dl*-**8** from *dl*-**7** gave **27** (1.90 g, 74%) as a colorless powder. $[\alpha]_D^{22}$ +29° (*c* 0.26, $CHCl_3$). Mp 92–94 °C (hexane–ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, *J* = 7.3 Hz, 3H), 1.07–1.20 (m, 2H), 1.30–1.76 (m, 8H), 2.00–2.15 (m, 2H), 2.55 (dd, *J* = 8.8, 3.7 Hz, 1H), 3.08 (d, *J* = 8.3 Hz, 1H), 4.20 (td, *J* = 6.4, 3.9 Hz, 1H), 4.38 (d, *J* = 4.9 Hz, 1H), 4.75 (d, *J* = 4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.13, 19.4, 19.5, 19.6, 19.9, 29.3, 38.9, 39.7, 43.8, 46.1, 83.6, 85.8, 86.1, 178.2. IR (KBr): 2940, 1740, 1220 cm^{-1}. MS (EI) (*m*/*z*): 236 (M^+). Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.13; H, 8.52.

(3*S*,3a*S*,4*R*,4a*S*,8a*S*) - 3 - Ethyl - 4 - hydroxy - 3a,4,4a,5,6,7,8,8a-octahydronaphtho[2,3-*c*]furan-1(3*H*)-one (28). Reaction of **27** (1.90 g, 8.04 mmol) in the same manner as described for the preparation of *dl*-**9** from *dl*-**8** gave **28** (1.77 g, 93%) as a pale yellow oil after flash column chromatography (hexane/ethyl acetate = 1:1). This crude product was directly used for the next reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 0.96–2.08 (m, 10H), 1.10 (t, *J* = 7.3 Hz, 3H), 2.15–2.36 (m, 2H), 2.63–2.70 (m, 1H), 2.74–2.80 (m, 1H), 4.01 (dd, *J* = 9.3, 3.9 Hz, 1H), 4.40–4.47 (m, 1H), 6.69 (t, *J* = 2.5 Hz, 1H). MS (EI) (*m*/*z*): 236 (M^+), 218, 149 (100). HRMS (EI) (*m*/*z*): calcd for $C_{14}H_{20}O_3$ (M^+): 236.1412. Found, 236.1445.

(3*S*,3a*S*,4*R*,4a*S*,9aS) - 3 - Ethyl - 4 - hydroxy - 3a,4,4a,5,6,7,8,9a - octahydronaphtho[2,3 - *c*]furan - 1(3*H*) - one (29). Treatment of **28** (1.77 g, 7.49 mmol) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5.60 mL, 37.5 mmol) in a manner similar to that described for the preparation of *dl*-**10** from *dl*-**9** gave **29** (1.27 g, 72%) as a pale yellow oil after flash column chromatography (hexane/ethyl acetate = 2:1). $[\alpha]_D^{24}$ +80° (*c* 0.33, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.90–1.12 (m, 1H), 1.05 (t, *J* = 7.3 Hz, 3H), 1.20–1.32 (m, 1H), 1.37–1.48 (m, 1H), 1.52–1.70 (m, 2H), 1.69 (d, *J* = 4.4 Hz, 1H), 1.78–2.09 (m, 4H), 2.14–2.22 (m, 1H), 2.30–2.37 (m, 1H), 2.61 (td, *J* = 8.3, 4.9 Hz, 1H), 3.27 (dq, *J* = 8.3, 2.4 Hz, 1H), 3.80 (dt, *J* = 7.8, 4.4 Hz, 1H), 4.42 (td, *J* = 8.3, 2.9 Hz, 1H), 5.33 (d, *J* = 2.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.2, 25.6, 27.1, 29.2, 31.8, 34.7, 41.3, 43.3, 43.9, 72.3, 82.7, 112.7, 141.3, 176.3. IR (neat): 3460, 2930, 1750, 1210 cm^{-1}. MS (EI) (*m*/*z*): 236 (M^+), 218, 149 (100). HRMS (EI) (*m*/*z*): calcd for $C_{14}H_{20}O_3$ (M^+): 236.1412. Found, 236.1420.

(3*S*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-4-hydroxy-3-ethylnaphtho[2,3-*c*]furan-1(3*H*)-one (30). Hydrogenation of **29** (400 mg, 1.69 mmol) over PtO_2 (40.0 mg, 10% w/w) in a manner similar to that described for the preparation of *dl*-**11** from *dl*-**10** gave **30** (382 mg, 95%) as a colorless powder after flash column chromatography (hexane/ethyl acetate = 1:1). $[\alpha]_D^{23}$ +32° (*c* 0.33, $CHCl_3$). Mp 183–184 °C (hexane–ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 0.81–1.33 (m, 7H), 1.06 (t, *J* = 7.3 Hz, 3H), 1.54–1.88 (m, 6H), 2.05–2.13 (m, 1H), 2.16 (dqd, *J* = 15.2, 7.8, 2.5 Hz, 1H), 2.58 (dt, *J* = 9.8, 5.9 Hz, 1H), 2.61–2.69 (m, 1H), 3.64 (ddd, *J* = 9.8, 5.9, 3.4 Hz, 1H), 4.55 (td, *J* = 10.8, 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4, 25.7, 25.7, 28.8, 29.3, 31.7, 32.9, 38.5, 41.7, 44.2, 45.4, 73.4, 82.4, 178.1. IR (KBr): 3480, 2920, 1740, 1250, 1210 cm^{-1}. MS (EI) (*m*/*z*): 238 (M^+), 220 (100). Anal. calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.32; H, 9.36.

(1*S*,3*S*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-3-Ethyl-dodecahydro-1-methoxynaphtho[2,3-*c*]furan-4-ol (31). Reduction of **30** (1.00 g, 4.20 mmol) followed by *O*-methylation in the same manner as described for the preparation of *dl*-**12** from *dl*-**11** gave **31** (924 mg, 87% from **30**) as a colorless powder after flash column chromatography (hexane/ethyl acetate = 4:1) by way of a crude mixture of the hemiacetals (873 mg, 87%). The anomeric mixture of the hemiacetals: ^1H NMR (400 MHz, $CDCl_3$): δ 0.81–1.08 (m, 4H), 1.04 (t, *J* = 7.3 Hz, 3H), 1.13–1.30 (m, 3H), 1.43–1.84 (m, 6H), 1.89–1.99 (m, 1H), 2.05–2.11 (m, 1H), 2.24 (dt, *J* = 12.2, 6.2 Hz, 1H), 2.33 (d, *J* = 2.5 Hz, 1H), 2.61 (dt, *J* = 9.3, 5.9 Hz, 1H), 3.66 (ddd, *J* = 10.3, 5.9, 4.3 Hz, 1H), 4.12 (td, *J* = 9.3, 2.5 Hz, 1H), 5.07 (d, *J* = 2.5 Hz, 1H). MS (EI) (*m*/*z*): 222 ($M^+ - H_2O$). HRMS (EI) (*m*/*z*): calcd for $C_{14}H_{22}O_2$ ($M^+ - H_2O$): 222.1620. Found, 222.1608. **31**: $[\alpha]_D^{26}$ +47° (*c* 0.27, $CHCl_3$). Mp 105–106 °C (hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 0.80–1.07 (m, 4H), 1.05 (t, *J* = 7.3 Hz, 3H), 1.12–1.31 (m, 3H), 1.54 (d, *J* = 4.4 Hz, 1H), 1.41–1.91 (m, 6H), 2.03–2.11 (m, 1H), 2.21 (dt, *J* = 12.2, 6.2 Hz, 1H), 2.52 (dt, *J* = 8.8, 6.0 Hz, 1H), 3.32 (s, 3H), 3.63 (ddd, *J* = 10.3, 5.9, 4.2 Hz, 1H), 4.09 (td, *J* = 9.3, 2.5 Hz, 1H), 4.55 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.2, 25.9, 26.0, 29.0, 32.2, 32.7, 33.3, 38.5, 43.9, 45.6, 46.4, 54.0, 74.6, 81.6, 108.4. IR (KBr): 3420, 2920, 1450 cm^{-1}. MS (EI) (*m*/*z*): 222 (M^+-HOMe), 204, 176 (100). Anal. calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.54; H, 10.38.

(1*S*,3*S*,3a*R*,4a*S*,8a*R*,9a*S*)-3-Ethyl-decahydro-1-methoxynaphtho[2,3-*c*]furan-4(1*H*)-one (32). Oxidation of **31** (289 mg, 1.14 mmol) in a manner similar to that described for the preparation of *dl*-**14** from *dl*-**12** gave **32** (254 mg, 89%) as a colorless powder after flash column chromatography (hexane/ethyl acetate = 4:1). $[\alpha]_D^{27}$ +102° (*c* 1.10, $CHCl_3$). Mp 55-56 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.6 Hz, 3H), 1.11–1.49 (m, 6H), 1.52–1.84 (m, 6H), 1.94–2.06 (m, 2H), 2.58 (dt, *J* = 12.7, 6.4 Hz, 1H), 2.86 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.31 (s, 3H), 4.12 (td, *J* = 7.8, 5.1 Hz, 1H), 4.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4, 25.1, 25.5, 25.5, 30.5, 32.6, 34.2, 41.3, 49.4, 51.3, 54.1, 56.4, 83.6, 108.9, 211.3. IR (KBr): 2920, 1690, 1450, 1110 cm^{-1}. MS (EI) (*m*/*z*): 252 (M^+), 234, 221, 207, 192 (100). HRMS (EI) (*m*/*z*): calcd for $C_{15}H_{24}O_3$ (M^+): 252.1725. Found, 252.1732.

(1*S*,3*S*,3a*S*,4a*S*,8a*R*,9a*S*)-3-Ethyl-dodecahydro-1-methoxy-4-methylenenaphtho[2,3-*c*]furan (33). Methylenation of **32** (648 mg, 2.57 mmol) in a manner similar to that described for the preparation of *dl*-**15** from *dl*-**14** gave **33** (645 mg, 100%) as a yellow oil after flash column chromatography (hexane/ethyl acetate = 10:1). $[\alpha]_D^{28}$ +43° (*c* 0.33, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.6 Hz, 3H), 1.04–1.33 (m, 7H), 1.38–1.49 (m, 1H), 1.59–1.73 (m, 4H), 1.80–1.90 (m, 2H), 2.24 (dt, *J* = 12.2, 6.2 Hz, 1H), 2.81 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.33 (s, 3H), 3.92 (td, *J* = 8.8, 3.4 Hz, 1H), 4.59 (s, 1H), 4.71 (t, *J* = 2.0 Hz, 1H), 4.81 (t, *J* = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8, 26.1, 26.4, 28.8, 28.9, 33.3, 34.5, 41.6, 42.7, 47.7, 51.2, 54.1, 83.3, 108.9, 109.4, 149.1. IR (neat): 2920, 1640, 1450 cm^{-1}. MS (CI) (*m*/*z*): 251 ($M^+ + H$), 219 (100). HRMS (CI) (*m*/*z*): calcd for $C_{16}H_{27}O_2$ ($M^+ + H$): 251.2011. Found, 251.2029.

(1*S*,3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-3-Ethyl-dodecahydro-1-methoxynaphtho[2,3-*c*]furan-4-methanol and its (4*S*)-epimer (34a and 34b). Sequential hydroboration-oxidation of **33** (200 mg, 0.80 mmol) in the same manner as described for the preparation of *dl*-**16** from *dl*-**15** gave **34a** (149 mg, 70%) as a pale yellow oil and **34b** (15.5 mg, 7%) as a colorless oil, respectively, after flash column chromatography (hexane/ethyl acetate = 5:1). **34a**: $[\alpha]_D^{25}$ +38° (*c* 0.40, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.84–1.08 (m, 6H), 1.06 (t, *J* = 7.3 Hz, 3H), 1.09–1.28 (m, 2H), 1.37–1.89 (m, 8H), 2.16 (dt, *J* = 11.7, 5.9 Hz, 1H), 2.44 (dt, *J* = 9.8, 4.9 Hz, 1H), 3.33 (s, 3H), 3.58–3.64 (m, 1H), 3.73–3.78 (m, 1H), 4.03 (td, *J* = 9.3, 2.4 Hz, 1H), 4.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.4, 26.0, 26.5, 30.1, 31.2, 33.4, 34.1, 38.6, 40.7, 42.9, 43.9, 46.4, 54.0, 62.8, 80.9, 108.0. IR (neat): 3450, 2920, 1450, 1300 cm^{-1}. MS (EI) (*m*/*z*): 237 (M^+–OMe), 207 (100). HRMS (EI) (*m*/*z*): calcd for $C_{15}H_{25}O_2$ (M^+–OMe): 237.1855. Found, 237.1853. **34b**: $[\alpha]_D^{27}$ −4.6° (*c* 1.03, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.81–0.96 (m, 2H), 1.04 (t, *J* = 7.6 Hz, 3H), 1.13–1.80 (m, 14H), 2.21 (dt, *J* = 12.7, 6.4 Hz, 1H), 2.39 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.32 (s, 3H), 3.52–3.60 (m, 1H), 3.80–3.87 (m, 1H), 3.94 (ddd, *J* = 9.8, 7.8, 3.4 Hz, 1H), 4.54 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8, 26.3, 27.2, 29.4, 30.5, 33.3, 34.9, 34.9, 39.9, 40.2, 42.3, 42.4, 54.0, 63.1, 82.3, 109.1. IR (neat): 3430, 2920, 1450, 1100 cm^{-1}. MS (EI) (*m*/*z*): 239 ($M^+ - C_2H_5$) (100). HRMS (EI) (*m*/*z*): calcd for $C_{14}H_{23}O_3$ ($M^+ - C_2H_5$): 239.1647. Found, 239.1646.

(1*S*,3*S*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-3-Ethyl-dodecahydro-1-methoxy-4-[(phenylthio)methyl]naphtho[2,3-*c*]furan (35). To a solution of **34a** (149 mg, 0.56 mmol) in CH_2Cl_2 (5 mL) were added triethylamine (388 μL, 2.78 mmol) and methanesulfonyl chloride (129 μL, 1.67 mmol) at 0 °C. The mixture was stirred at the same temperature for 4 h and gradually warmed to room temperature. It was then poured into water (5 mL) and extracted with diethyl ether (5 mL×3). The ethereal extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate = 2:1) of the residue gave

the crude *O*-mesylate of **34a** (180 mg, 93%) as a colorless oil. This material was immediately used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86–1.28 (m, 6H), 1.07 (d, J = 7.3 Hz, 3H), 1.37–1.49 (m, 1H), 1.52–1.90 (m, 8H), 2.16–2.22 (m, 1H), 2.45 (dt, J = 10.3, 5.2 Hz, 1H), 3.01 (s, 3H), 3.32 (s, 3H), 3.99 (dt, J = 8.8, 2 Hz, 1H), 4.15 (dd, J = 9.8, 7.8 Hz, 1H), 4.32 (dd, J = 9.8, 3.4 Hz, 1H), 4.50 (s, 1H). MS (FAB) (*m*/*z*): 452 [(M^+ + diethanolamine) + H]. HRMS (FAB) (*m*/*z*): calcd for $C_{21}H_{42}NO_7S$ [(M^+ + diethanolamine) + H]: 452.2682. Found, 452.2662.

To a solution of potassium *t*-butoxide (225 mg, 2.01 mmol) in methyl sulfoxide (5 mL), thiophenol (206 μL, 2.01 mmol) was added at room temperature, and the mixture was stirred at the same temperature for 10 min. The resulting mixture was added to a solution of the crude *O*-mesylate of **34a** (465 mg, 1.34 mmol) in methyl sulfoxide (5 mL), and the mixture was stirred at room temperature for 14 h. The mixture was poured into cold water (50 mL) and extracted with diethyl ether (10 mL×3). The ethereal extracts were combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flush column chromatography (hexane/ethyl acetate = 50:1, then 10:1) of the residue gave **35** (346 mg, 71%) as a yellow oil. This material was found to be ca. 75% ee based on the HPLC analysis. The analytical conditions for HPLC were as follows: CHIRALPAK AD-H (Daicel Chemical Industries, Ltd.), 0.46×25 cm; mobile phase, hexane:2-propanol = 95:5 (v/v); flow rate, 0.3 mL/min; temperature, 40 °C; monitoring, 254 nm. Accordingly, this sample (317 mg) was subjected to separation using HPLC [CHIRALPAK AD-H (Daicel Chemical Industries, Ltd.), 2×25 cm; mobile phase, hexane/2-propanol = 98:2 (v/v); flow rate, 5.0 mL/min; temperature, 40 °C; monitoring, 254 nm], affording major enantiomer **35** (279 mg, 81%) with the natural absolute configuration as a colorless powder and minor enantiomer *ent*-**35** (31.9 mg, 9%) with the unnatural absolute configuration as a colorless powder. The retention times and ee were as follows: **35**: 15.0 min, 99% ee, and *ent*-**35**: 16.8 min, 90% ee. **35**: $[\alpha]_D^{22}$ +157° (*c* 0.10, $CHCl_3$). Mp 65–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77–1.11 (m, 5H), 1.08 (t, J = 7.3 Hz, 3H), 1.16–1.30 (m, 2H), 1.43–1.83 (m, 7H), 1.97–2.04 (m, 1H), 3.33 (s, 3H), 3.97 (td, J = 9.3, 2.3 Hz, 1H), 4.49 (s, 1H), 7.14–7.19 (m, 1H), 7.25–7.31 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.4, 26.0, 26.6, 30.2, 32.0, 33.5, 34.1, 35.3, 40.8, 41.2, 41.7, 42.4, 46.2, 54.0, 80.8, 108.2, 125.6, 128.6, 128.6, 128.9, 128.9, 137.4. IR (KBr): 2920, 1580, 1480, 1440, 1100 cm^{-1}. MS (FAB) (*m*/*z*): 360 (M^+ + H), 329 (100). HRMS (FAB) (*m*/*z*): calcd for $C_{22}H_{32}O_2S$ (M^+ + H): 360.2123. Found, 360.2170. *ent*-**35**: $[\alpha]_D^{24}$ −139° (*c* 0.14, $CHCl_3$). Mp 63–64 °C. ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described for **35**. HRMS (FAB) (*m*/*z*): calcd for $C_{22}H_{32}O_2S$ (M^+ + H): 360.2123. Found, 360.2104.

(1*S*,3*S*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-3-Ethyl-dodecahydro-1-methoxy-4-[(phenylsulfonyl)methyl]naphtho[2,3-*c*]furan (36). Oxidation of **35** (192 mg, 0.53 mmol) in a manner similar to that described for the preparation of **19** from **18** gave **36** (209 mg, 100%) as a colorless powder after flash column chromatography (hexane/ethyl acetate = 2:1). $[\alpha]_D^{24}$ +85° (*c* 0.14, $CHCl_3$). Mp 129–130 °C (hexane–ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.53–0.63 (m, 1H), 0.85–1.00 (m, 4H), 1.06–1.23 (m, 2H), 1.08 (t, J = 7.3 Hz, 3H), 1.48–1.84 (m, 7H), 2.01–2.10 (m, 1H), 2.14–2.21 (m, 1H), 2.78 (dt, J = 8.8, 5.4 Hz, 1H), 3.00 (dd, J = 15.2, 9.1 Hz, 1H), 3.27 (dd, J = 14.7, 1.8 Hz, 1H), 3.30 (s, 3H), 3.86 (td, J = 9.3, 1.8 Hz, 1H), 4.47 (s, 1H), 7.55–7.61 (m, 2H), 7.64–7.69 (m, 1H), 7.89–7.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3, 25.8, 26.5, 29.9, 32.6, 33.1, 34.1, 36.9, 40.7, 41.0, 42.9, 45.8, 54.0, 55.6, 80.7, 108.3, 127.9, 127.9, 129.3, 129.3, 133.7, 139.8. IR (KBr): 2920, 1450, 1300, 1150 cm^{-1}. MS (FAB) (*m*/*z*): 498 [(M^+ + diethanolamine) + H]. HRMS (FAB) (*m*/*z*): calcd for $C_{26}H_{44}NO_6S$ [(M^+ + diethanolamine) + H]: 498.2889. Found, 498.2893.

(2*R*,6*S*)-*tert*-Butyl 2-[2-(*E*)-[(1*S*,3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-3-ethyl-dodecahydro-1-methoxynaphtho[2,3-*c*]furan-4-yl]ethenyl]-6-methylpiperidine-1-carboxylate (37). Reaction of **36** (110 mg, 0.28 mmol) and **20** (95.5 mg, 0.42 mmol) in a manner similar to that described for the preparation of **21** from **19** gave the β-benzoxysulfone (possibly a mixture of the four diastereomers) (52.9 mg, 26%) with recovery of a portion of the starting **36** (62.5 mg, 57%). Subsequent reduction of the β-benzoxysulfone (52.9 mg) similarly to the preparation of **21** from **19** afforded **37** (22.1 mg, 66%) as a colorless oil after flash column chromatography (hexane/ethyl acetate = 8:1). In this case, formation of the (*Z*)-olefin was not observed by ^{1}H NMR analysis of the crude reaction product. The β-benzoxysulfone: MS (FAB) (*m*/*z*): 829 [(M^+ + diethanolamine) + H]. HRMS (FAB) (*m*/*z*): calcd for $C_{45}H_{69}N_2O_{10}S$ [(M^+ + diethanolamine) + H]: 829.4673. Found, 829.4689. **37**: $[\alpha]_D^{21}$ +42° (*c* 0.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.62–0.76 (m, 1H), 0.84–1.02 (m, 6H), 1.00 (t, J = 7.3 Hz, 3H), 1.14–1.78 (m, 11H), 1.23 (d, J = 6.4 Hz, 3H), 1.44 (s, 9H), 1.86–2.08 (m, 3H), 2.12–2.19 (m, 1H), 2.20–2.28 (m, 1H), 3.31 (s, 3H), 3.94–4.02 (m, 2H), 4.37–4.43 (m, 1H), 4.49 (s, 1H), 5.22 (ddd, J = 15.2, 9.8, 1 Hz, 1H), 5.47 (dd, J = 15.2, 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0, 13.4, 20.9, 25.8, 26.4, 26.5, 26.6, 28.5, 28.5, 28.5, 28.6, 31.3, 31.4, 33.1, 34.1, 40.4, 41.2, 46.2, 46.3, 46.5, 47.0, 54.0, 78.9, 80.9, 108.3, 132.9, 133.2, 155.1. IR (neat): 2920, 1690, 1460, 1390 cm^{-1}. MS (FAB) (*m*/*z*): 462 (M^+ + H), 374 (100). HRMS (FAB) (*m*/*z*): calcd for $C_{28}H_{48}NO_4$ (M^+ + H): 462.3583. Found, 462.3584.

(2*R*,6*S*)-*tert*-Butyl 2-[2-(*E*)-[(3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-3-ethyl-decahydronaphtho[2,3-*c*]furan-1(3*H*)-on-4-yl]ethenyl]-6-methylpiperidine-1-carboxylate (38). Oxidation of **37** (8.10 mg, 17.5 μmol) in the same manner as described for the preparation of **22** from **21** gave **38** (5.70 mg, 73%) as a colorless oil after flush column chromatography (hexane/ethyl acetate = 5:1). $[\alpha]_D^{24}$ +49° (*c* 0.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63–0.75 (m, 1H), 0.80–1.07 (m, 4H), 1.00 (t, J = 7.1 Hz, 3H), 1.13–1.34 (m, 5H), 1.24 (d, J = 6.4 Hz, 3H), 1.40–2.10 (m, 11H), 1.45 (s, 9H), 2.33 (dt, J = 10.3, 6.4 Hz, 1H), 2.60 (dt, J = 13.2, 6.7 Hz, 1H), 3.95–4.02 (m, 1H), 4.39–4.44 (m, 1H), 4.48 (ddd, J = 10.3, 8.3, 2.0 Hz, 1H), 5.25 (dd,

J = 15.2, 9.8 Hz, 1H), 5.53 (dd, J = 15.2, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.99, 13.4, 20.9, 25.6, 26.2, 26.4, 26.4, 28.5, 28.5, 28.5, 28.7, 31.3, 32.1, 33.7, 40.1, 41.5, 42.2, 45.4, 45.8, 47.1, 52.3, 79.1, 81.8, 131.6, 134.0, 155.1, 178.6. IR (neat): 2930, 1770, 1690, 1390, 1180 cm^{-1}. MS (FAB) (m/z): 446 ($M^+ + H$), 346 (100). HRMS (FAB) (m/z): calcd for $C_{27}H_{44}NO_4$ ($M^+ + H$): 446.3270. Found, 446.3262.

(3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-3-Ethyl-decahydro-4-[2-(*E*)-[(2*R*,6*S*) - 6 - methylpiperidin - 2 - yl]ethenyl]naphtho[2,3 - *c*]furan-1(3*H*)-one (39). Removal of the *tert*-butoxycarbonyl group of **38** (5.70 mg, 12.8 μmol) in a manner similar to that described for the preparation of **23** from **22** gave **39** (4.40 mg, 100%) as a colorless oil. $[\alpha]_D^{25}$ +12° (*c* 0.44, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65–0.76 (m, 1H), 0.77–1.07 (m, 4H), 1.00 (t, J = 7.3 Hz, 3H), 1.11 (d, J = 6.4 Hz, 3H), 1.17–1.33 (m, 5H), 1.39–1.79 (m, 8H), 1.85–1.97 (m, 2H), 2.04 (br, 1H), 2.05–2.13 (m, 1H), 2.34 (dt, J = 10.8, 6.7 Hz, 1H), 2.61 (dt, J = 13.2, 6.6 Hz, 1H), 3.08–3.15 (m, 1H), 3.52–3.59 (m, 1H), 4.49 (ddd, J = 10.3, 7.8, 2.2 Hz, 1H), 5.27 (dd, J = 15.2, 9.8 Hz, 1H), 5.70 (dd, J = 15.7, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.78, 19.5, 21.2, 26.1, 26.4, 28.7, 30.8, 31.3, 32.1, 32.4, 33.6, 40.0, 41.4, 42.1, 45.4, 45.7, 46.4, 53.1, 81.6, 131.8, 134.6, 178.5. IR (neat): 2930, 1770, 1450, 1200, 1060 cm^{-1}. MS (FAB) (m/z): 346 ($M^+ + H$) (100). HRMS (FAB) (m/z): calcd for $C_{22}H_{36}NO_2$ ($M^+ + H$): 346.2746. Found, 346.2749.

(3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-3-Ethyl-decahydro-4-[2-(*E*)-[(2*R*,6*S*)-1,6-dimethylpiperidin-2-yl]ethenyl]naphtho[2,3-*c*]furan-1(3*H*)-one (11-methylhimbacine) (3). Reductive *N*-methylation of **39** (4.40 mg, 12.7 μmol) in a manner similar to that described for the preparation of **2** from **23** gave **3** (3.70 mg, 81%) as a colorless oil after flash column chromatography (Chromatorex, hexane/ethyl acetate = 2:1). $[\alpha]_D^{24}$ +35° (*c* 0.37, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68–1.07 (m, 5H), 1.00 (t, J = 7.3 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H), 1.13–1.33 (m, 5H), 1.38–1.80 (m, 8H), 1.85–1.96 (m, 2H), 2.05–2.14 (m, 1H), 2.22 (s, 3H), 2.35 (dt, J = 10.8, 6.4 Hz, 1H), 2.62 (dt, J = 13.2, 6.7 Hz, 1H), 2.81–2.89 (m, 1H), 2.99–3.06 (m, 1H), 4.49 (ddd, J = 10.3, 7.8, 2.5 Hz, 1H), 5.27 (dd, J = 15.2, 10.1 Hz, 1H), 5.58 (dd, J = 15.2, 9.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.69, 14.1, 19.0, 26.1, 26.5, 28.6, 31.5, 32.1, 32.6, 33.3, 33.6, 40.0, 41.2, 41.5, 42.2, 45.5, 45.9, 53.4, 61.4, 81.6, 133.3, 133.3, 178.5. IR (neat): 2930, 1770, 1450, 1180, 1040 cm^{-1}. MS (FAB) (m/z): 360 ($M^+ + H$) (100). HRMS (FAB) (m/z): calcd for $C_{23}H_{38}NO_2$ ($M^+ + H$): 360.2903. Found, 360.2899.

(2*R*,6*S*)-*tert*-Butyl 2-[2-(*E*)-[(3*R*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-decahydro-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-on-4-yl]-ethenyl]-6-methylpiperidine-1-carboxylate (41). To a solution of **40**[11,13] (46.5 mg, 0.11 mmol) in 95% methanol (1 mL), powdered potassium hydroxide (7.26 mg, 0.13 mmol) was added at room temperature, and the resulting mixture was heated at reflux for 2 h and concentrated in vacuo. The residual potassium salt was suspended in tetrahydrofuran (1 mL), and the suspension was cooled at 0 °C. Triethylamine (150 μL, 1.08 mmol) and methanesulfonyl chloride (83.5 μL, 1.08 mmol) were added, and the mixture was stirred at room temperature for 1 h. Sodium hydroxide (21.6 mg, 0.54 mmol) and water (0.50 mL) were added, and the mixture was warmed at 50 °C for 1 h. After acidification with diluted citric acid solution, the mixture was concentrated in vacuo. The residue was diluted with water (10 mL) and extracted with diethyl ether (3 mL ×3). The ethereal extracts were combined, washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. Flush column chromatography (hexane/ethyl acetate = 2:1) of the residue gave **41** (13.2 mg, 28%) as a colorless oil with recovery of a portion of the starting **40** (9.60 mg, 21%). $[\alpha]_D^{23}$ +88° (*c* 0.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.62–0.73 (m, 1H), 0.83–1.30 (m, 6H), 1.24 (d, J = 6.4 Hz, 3H), 1.43–2.05 (m, 11H), 1.45 (s, 9H), 1.50 (d, J = 6.9 Hz, 3H), 2.16–2.23 (m, 1H), 2.57 (dq, J = 7.8, 6.5 Hz, 1H), 2.83 (dd, J = 15.2, 8.3 Hz, 1H), 3.99–4.06 (m, 1H), 4.38–4.44 (m, 1H), 4.71 (dq, J = 8.3, 6.9 Hz, 1H), 5.41 (ddd, J = 15.7, 9.3, 1.5 Hz, 1H), 5.59 (dd, J = 15.7, 4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 20.9, 21.9, 25.3, 26.2, 26.3, 26.4, 28.5, 28.5, 28.5, 31.8, 33.0, 33.8, 39.8, 40.9, 41.8, 42.8, 45.3, 47.1, 52.1, 79.0, 79.2, 128.9, 135.4, 155.0, 179.1. IR (neat): 2930, 1770, 1690, 1390, 1180 cm^{-1}. MS (FAB) (m/z): 432 ($M^+ + H$), 375, 358, 332(100). HRMS (FAB) (m/z): calcd for $C_{26}H_{42}NO_4$ ($M^+ + H$): 432.3114. Found, 432.3121.

(3*R*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[2-(*E*)-[(2*R*,6*S*) - 6 - methylpiperidin - 2 - yl]ethenyl]naphtho[2,3 - *c*]furan-1(3*H*)-one (42). Removal of the *tert*-butoxycarbonyl group of **41** (13.2 mg, 30.6 μmol) in the same manner as described for the preparation of **23** from **22** gave **42** (9.40 mg, 93%). $[\alpha]_D^{23}$ +46° (*c* 0.63, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63–0.75 (m, 1H), 0.82–0.91 (m, 1H), 0.99–1.33 (m, 7H), 1.11 (d, J = 6.4 Hz, 3H), 1.43–1.87 (m, 7H), 1.52 (d, J = 6.9 Hz, 3H), 1.97 (ddd, J = 13.7, 6.9, 1.9 Hz, 1H), 2.16–2.23 (m, 1H), 2.58 (dq, J = 7.8, 6.6 Hz, 1H), 2.84 (dd, J = 15.2, 7.8 Hz, 1H), 3.05–3.13 (m, 1H), 3.54–3.61 (m, 1H), 4.72 (dq, J = 8.3, 6.9 Hz, 1H), 5.48 (ddd, J = 15.7, 8.8, 1.1 Hz, 1H), 5.77 (ddd, J = 15.7, 6.4, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 21.3, 21.8, 26.2, 26.4, 30.9, 31.9, 32.6, 33.0, 33.8, 39.8, 40.9, 41.7, 42.7, 45.4, 46.4, 52.9, 79.2, 129.7, 136.3, 179.1. IR (neat): 2930, 1770, 1450, 1200 cm^{-1}. MS (FAB) (m/z): 332 ($M^+ + H$) (100). HRMS (FAB) (m/z): calcd for $C_{21}H_{34}NO_2$ ($M^+ + H$): 332.2590. Found, 332.2617.

(3*R*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-4-[2-(*E*)-[(2*R*,6*S*)-1,6-dimethylpiperidin-2-yl]ethenyl]-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one (3-epihimbacine) (4). Reductive *N*-methylation of **42** (9.40 mg, 28.4 μmol) in a manner similar to that described for the preparation of **2** gave **4** (5.90 mg, 60%) as a colorless oil. $[\alpha]_D^{22}$ +77° (*c* 0.59, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65–0.78 (m, 1H), 1.00–1.33 (m, 6H), 1.00 (d, J = 6.4 Hz, 3H), 1.38–1.61 (m, 4H), 1.52 (d, J = 6.8 Hz, 3H), 1.65–1.89 (m, 6H), 1.95–2.00 (m, 1H), 2.17–2.27 (m, 1H), 2.23 (s, 3H), 2.58 (dq, J = 8.3, 6.7 Hz, 1H), 2.80–2.85 (m, 2H), 3.02–3.07 (m, 1H), 4.69 (dq, J = 8.3, 6.9 Hz, 1H), 5.49 (dd, J = 15.2, 9.3 Hz, 1H), 5.68 (dd, J = 15.2, 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 19.0, 21.9, 26.2,

26.5, 32.0, 33.0, 33.1, 33.3, 33.8, 39.8, 40.9, 41.1, 41.8, 42.9, 45.6, 53.4, 61.3, 79.2, 131.4, 134.9, 179.1. IR (neat): 2930, 1770, 1450, 1180, 1040 cm^{-1}. MS (FAB) (m/z): 346 ($M^+ + H$) (100). HRMS (FAB) (m/z): calcd for $C_{22}H_{36}NO_2$ ($M^+ + H$): 346.2746. Found, 346.2738.

Binding assay

Receptor binding analyses for the muscarinic M_1 and M_2 subtype receptors were performed using homogenates of the cerebral cortex and brainstem of a rat, respectively. The radioligands used were [^{3}H]-pirenzepine for the cerebral cortex and [^{3}H]-quinuclidinyl benzilate (QNB) for the brainstem. The homogenates were incubated in a 50 mM Tris-buffer (pH 7.4) at 25 °C for 90 min, and then rapidly filtrated on Whatman GF-B filters. Radioactivity was counted using a liquid scintillation counter. Non-specific binding was defined in the presence of 2 μM atropine. The test compounds were dissolved in DMSO and diluted with buffer to the final concentrations. Competitive binding experiments were performed in the presence of less than 0.1% DMSO, which did not affect the specific binding. The equilibrium dissociation constants (K_i) were calculated using the Cheng–Prusoff equation, $K_i = IC_{50}/(1 + L/K_d)$, where L and K_d were the concentration and the dissociation constants of the radioligands, respectively. The K_d values were determined by Scatchard analysis.

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19. The crystallographic data (excluding structure factors) for compounds **17a** and **17b** have been deposited in the Cambridge Crystallographic Data Centre under supplementary publication numbers CCDC 183427 and 183426, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).