Pergamon

Tetrahedron 58 (2002) 9903–9923

TETRAHEDRON

Synthetic studies of himbacine, a potent antagonist of the muscarinic M_2 subtype receptor 1. Stereoselective total synthesis and antagonistic activity of enantiomeric pairs of himbacine and (2′*S*,6′*R*)-diepihimbacine, 4-epihimbacine, and novel himbacine congeners

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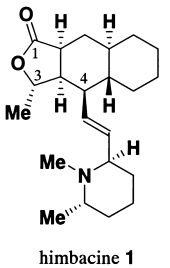
Received 25 September 2002; accepted 21 October 2002

Abstract—Total synthesis of an enantiomeric pair of himbacine **1** and *ent*-**1** was achieved in a highly stereoselective manner by employing an intermolecular Diels–Alder reaction of tetrahydroisobenzofuran **8** with chiral furan-2(5*H*)-one (*S*)-**9** and (*R*)-**9**, respectively, as a key step. An enantiomeric pair of (2′*S*,6′*R*)-diepihimbacine **24** and *ent*-**24**, 4-epihimbacine 4-*epi*-**1**, and novel himbacine congeners bearing the same tricyclic moiety as that of **1** were also successfully prepared by utilizing the key synthetic intermediates for **1**, establishing the convergency and flexibility of the explored synthetic route. All of the synthesized compounds used were subjected to muscarinic M_2 subtype receptor binding affinity assay, disclosing novel aspects of the structure–activity relationships for **1**.

1. Introduction

Himbacine **1**, isolated from the bark of *Galbulimima baccata*, is a potent antagonist of the muscarinic M_2 subtype receptor.[2] This alkaloid 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).



himbacine **1**

Figure 1. Structure of natural himbacine **1**.

It is well known that senile dementia associated with Alzheimer's disease is directly correlated with diminished levels of synaptic acetylcholine (ACh) in the cortical and hippocampal areas of the brain,[3] and current forms of therapy address this issue, relying on the cholinergic hypothesis[4] of memory dysfunction. Such therapies comprise the following four approaches to enhance synaptic ACh levels, namely, use of an ACh esterase inhibitor,[5] a choline acetyl transferase (ChAT) synthesis enhancer,[6] a choline re-uptake enhancer,[7] and a muscarinic receptor agent.[8] It has been reported that enhancement of synaptic ACh levels can be achieved by antagonizing presynaptic muscarinic M_2 receptors which regulate ACh release, the latter which acts as an autoreceptor.[9] Under these circumstances, the therapeutic agent requires the high M_2/M_1 selectivity because of the post-synaptic localization of the M_1 receptor. Himbacine **1** was reported to be a potent antagonist of the muscarinic M_2 subtype receptor with 10–20-fold selectivity toward the M_1 subtype. Therefore, much attention has been focused on **1** by medicinal and synthetic organic compound synthesis communities.[10] Two total syntheses of **1** have hitherto been achieved by Hart–Kozikowski[11] and Chackalamannil[12] by employing intramolecular Diels–Alder reaction as their key steps.

In order to disclose novel aspects of the structure–activity relationships of **1**, and moreover, to explore the promising congeners of **1** which may show more improved M_2 subtype selectivity, an efficient synthetic route to **1** was sought

Keywords: alkaloids; Diels–Alder reactions; natural products; asymmetric synthesis.

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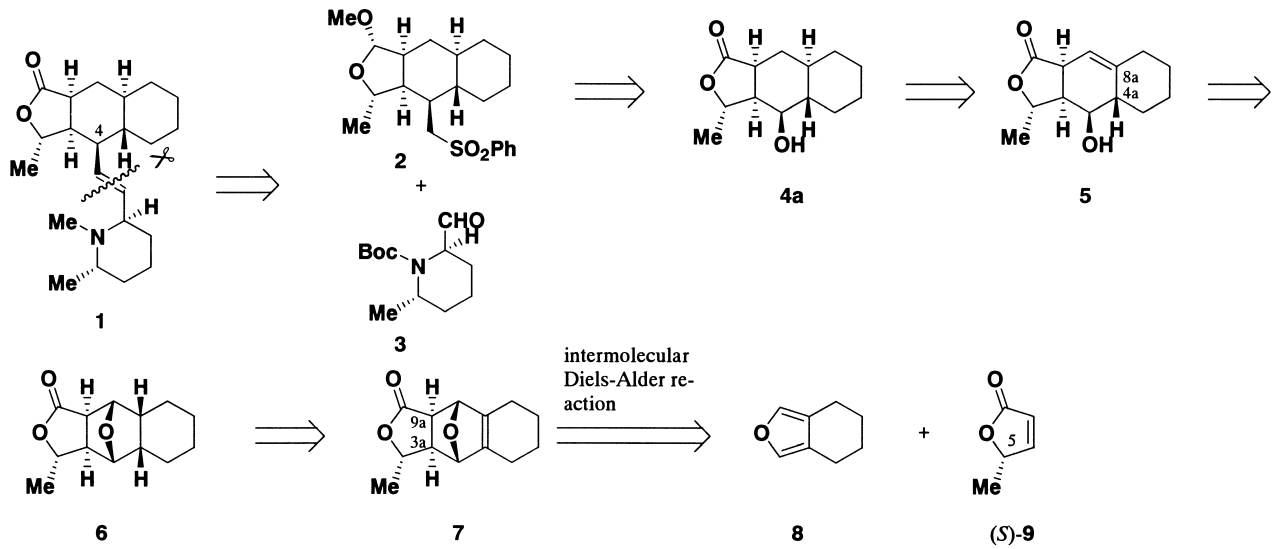
PII: S0040-4020(02)01358-3



Scheme 1. Novel synthetic design of himbacine **1** featuring intermolecular Diels–Alder reaction.

which would be more convergent and flexible than those that had been previously reported.[11,12] We wish to report here the novel total synthesis of an enantiomeric pair of himbacine **1** and *ent*-**1** accomplished by a method featuring a highly stereoselective intermolecular Diels–Alder reaction as a key step. This paper is also concerned with the synthesis of an enantiomeric pair of (2′*S*,6′*R*)-diepihimbacine **24** and *ent*-**24**, 4-epihimbacine 4-*epi*-**1**, and novel congeners of **1** prepared by employing the synthetic intermediates of **1** along with their M_2 antagonistic activity.[1] The latter studies were carried out in order to gain a more thorough understanding of the convergency and flexibility of the explored synthetic route and to disclose novel aspects of the structure–activity relationships of these molecules.

2. Results and discussion

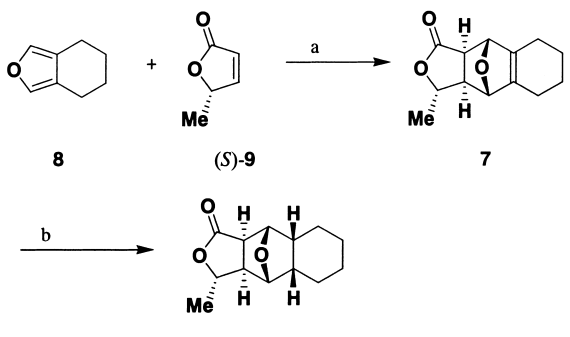
2.1. Synthetic strategy

Our synthetic strategy as regards **1** is outlined in Scheme 1. The key step of our synthesis was a highly stereoselective intermolecular Diels–Alder reaction between tetrahydroisobenzofuran **8** and chiral furan-2(5*H*)-one (*S*)-**9**. Thus, *exo*-selective construction of the cycloadduct **7** was envisioned, based on a previously reported result of the reaction of **8** with maleic anhydride.[13] It was expected that the four chiral centers of **7** could be introduced in a highly stereoselective manner due to the (*S*)-chirality of the methyl group at the C-5 position of (*S*)-**9**. All of the chiral centers of tricyclic alcohol **4a** bear the natural absolute configuration of **1**, and **4a** was readily derived from **7** by sequential hydrogenation to saturated tetracyclic compound **6** from a convex face, ring opening of **6**, followed by double bond isomerization to unsaturated alcohol **5**, and hydrogenation. Introduction of an arylsulfonylmethyl group into **4** gave tricyclic sulfone **2**, which was connected to the bottom half of **1**, the piperidinaldehyde **3**, according to Hart's procedure[11] featuring the Julia–Lythgoe olefination protocol, followed by subsequent deprotection and *N*-methylation of the piperidine moiety. It is generally accepted that intermolecular Diels–Alder reactions are more convergent and flexible than the corresponding intramolecular reactions, especially in the synthesis of complex natural products. Therefore, our approach was anticipated to be not only more advantageous for the total synthesis of **1** itself, but also more useful for the exploration of novel congeners of **1** by changing the starting tetrahydroisobenzofuran derivatives, the chiral furan-2(5*H*)-one derivatives, and/or the chiral piperidine units. Actually, the usefulness of the explored synthetic route was exemplified by successful syntheses of enantiomeric *ent*-**1** and some novel congeners of **1**. These studies were accomplished by employing (*R*)-**9** in place of (*S*)-**9** and by constructing novel structural features from the synthetic intermediates of **1**.

2.2. Synthesis of natural himbacine 1

The starting materials, tetrahydroisobenzofuran **8**[14] and furan-2(5*H*)-one (*S*)-**9**,[15] were synthesized in large quantities according to the reported procedure with some modifications. With **8** and (*S*)-**9** in hand, the intermolecular Diels–Alder reaction could then be examined (Scheme 2).

As shown in Table 1, heating of a mixture of **8** and (*S*)-**9** in the absence (entry 1) or the presence (entries 2–4) of Lewis acid[16,17] failed to afford **7**. The same unsuccessful results



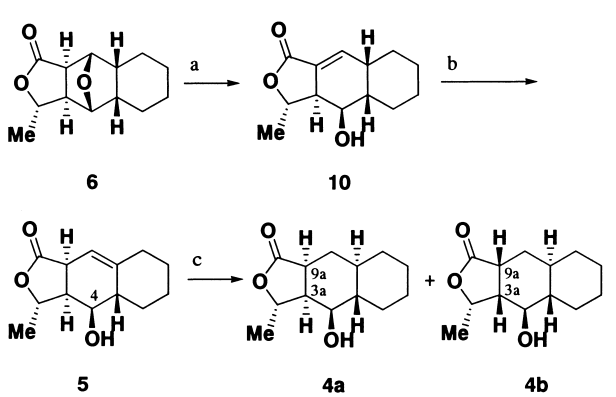
Scheme 2. Intermolecular Diels–Alder reaction of tetrahydroisobenzofuran **8** with (*S*)-furan-2(5*H*)-one (*S*)-**9**. (a) see Table 1; (b) H_2, 10% Pd–C, EtOH, rt, 12 h, 96%.

Table 1. Intermolecular Diels–Alder reaction of tetrahydroisobenzofuran **8** with furan-2(5*H*)-one (*S*)-**9**

Entry[a]	Catalyst (equiv.)	Solvent	Conditions	Result (yield of **7**, %)[b]
1	None	None	150°C, 65 h	Decomposition
2	SiO_2–Et_2AlCl	Toluene	rt–40°C, 19 h	Decomposition
3	SiO_2–$TiCl_4$	Toluene	rt, 9 h	Decomposition
4	Florisil	Toluene	rt, 48 h	No reaction
5	$ZnCl_2$ (2.0)	CH_2Cl_2	rt, 48 h	No reaction
6	$(Ph_3P)_3RhCl$ (0.1)	CF_3CH_2OH	rt, 168 h	16 (20)[c]
7	ZnI_2 (0.5)	CH_2Cl_2	rt, 120 h	59 (88)[c]
8	4 M $LiNTf_2$	Et_2O	rt, 48 h	No reaction
9	1 M $LiBF_4$	Benzene	rt, 24 h	Decomposition
10	5 M $LiClO_4$	Et_2O	rt, 168 h	58

[a] Tetrahydroisobenzofuran **8** was allowed to react with furan-2(5*H*)-one (*S*)-**9** (1–1.5 equiv.).
[b] The cycloadduct **7** was obtained as the sole product. No other reaction products were detected by ^1H NMR analysis of the crude reaction mixture.
[c] Corrected for the recovery of (*S*)-**9**.

were obtained by the reactions using $LiNTf_2$[18] and $LiBF_4$[19] (entries 8, 9). On the other hand, upon treatment with Wilkinson's catalyst[20] (entry 6), ZnI_2 (entry 7), or 5 M $LiClO_4$–Et_2O[21] (entry 10), the cycloaddition reaction took place successfully, giving rise to cycloadduct **7**. The reaction under Livinghouse's condition (entry 6) gave **7** with poor reproducibility. In the case of entry 7, the isolation of **7** was found to be troublesome due to the recovery of unreacted (*S*)-**9**. Among these conditions examined, use of 5 M $LiClO_4$–Et_2O afforded the best results, producing **7** as the sole product in a 58% yield. As expected, it appeared that this Diels–Alder reaction proceeded in a highly *exo*-selective manner, affording **7** as the sole product. Exclusive formation of **7** was determined by the ^1H NMR analysis of the crude reaction product. To the best of our knowledge, this is the first example of a Diels–Alder reaction of furan and furan-2(5*H*)-one derivative.[22] Since the structural determination of **7** by the spectral data proved difficult, and because **7** was also found to be fairly unstable, **7** was directly subjected to the next hydrogenation. Thus, hydrogenation of **7** under conventional conditions occurred from the sterically less hindered convex face to give the hydrogenated compound **6** as the sole product in a 96% yield. The stereochemistry of **6** included a *cis–anti–cis* ring system, and was confirmed by single-crystal X-ray diffraction analysis, as shown in Scheme 2.



Scheme 3. Stereoselective construction of the tricyclic part **4a** of **1**. (a) $LiN(TMS)_2$, THF, −78 to −40°C, 4 h, 92%; (b) DBU, toluene, 100°C, 5 h, 83%; (c) see Table 2.

Next, our synthetic efforts were focused on converting the stereochemistries of **6** to those of **1**, a *cis–trans* ring system (Scheme 3). Toward this end, we first examined a ring-opening reaction of the 7-oxabicyclo[2.2.1]heptane system in **6**. After conducting the experiments, it was found that this reaction proceeded under basic conditions,[23] giving rise to hydroxyenone **10** in a 92% yield. Treatment of **10** with 1,8-diazabicyclo[5.4.0]undec-7-ene efficiently underwent double-bond isomerization to afford deconjugated alcohol **5** as the sole product in an 83% yield. This highly selective formation of **5** may be explained by thermodynamic control. In order to obtain saturated alcohol **4a** bearing the desired *cis–trans* ring system, catalytic hydrogenation of **5** was next examined using the various catalytic systems shown in Table 2.

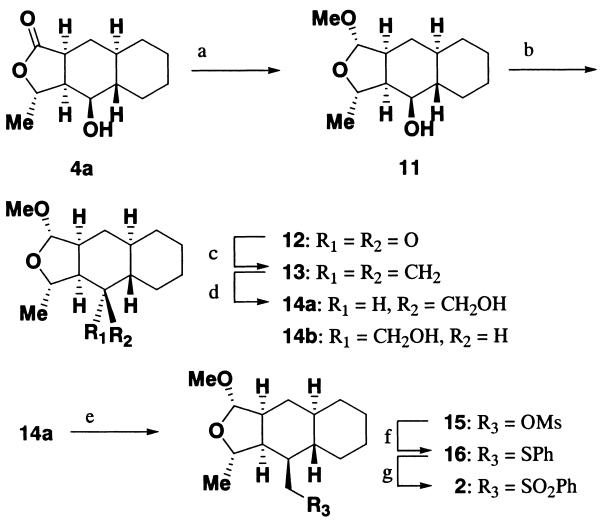
Among the catalytic systems tested, hydrogenation of **5** in the presence of PtO_2 was found to produce the saturated alcohol **4a** as the sole product in a 96% yield (entry 4). On the other hand, employing other catalytic systems for this hydrogenation regularly gave a mixture of **4a** and its isomer **4b** (C-3a, 9a position, the himbacine numbering). The structures of **4a** and **4b** were unambiguously determined by single-crystal X-ray diffraction analyses. The ratio of **4a** to **4b** definitely depended on the metal species of the catalytic systems. Formation of **4b** may be explained by the double-bond shift from C-8a, 9 to the C-3a, 9a position, followed by hydrogenation from the sterically less hindered direction opposite of the C-3 methyl group. However, the reason remains unclear why such an abnormal hydrogenation took place by catalytic systems not employing PtO_2. Thus, the stereoselective construction of the dodecahydronaphtho[2,3-*c*]furan ring system involved in **1** was readily accomplished in four steps from *exo*-cycloadduct **7**, produced by the intermolecular Diels–Alder reaction.

Prior to oxidation of the secondary hydroxy group at the C-4 position of **4a**, the lactone moiety was protected in a form of acetal by sequential reduction and acetalization, yielding α-methyl acetal **11**, the thermodynamically more stable compound, in a 74% yield from **4a** as almost the sole product (Scheme 4). The hydroxy group at the C-4 position of **11** was oxidized using the tetrapropylammonium perruthenate(VII)-4-methylmorpholine *N*-oxide (TPAP-NMO) system,[24] producing ketone **12** in a 95% yield. Methylenation of **12** by Wittig reaction provided *exo*-methylene compound **13** in an 86% yield. Sequential

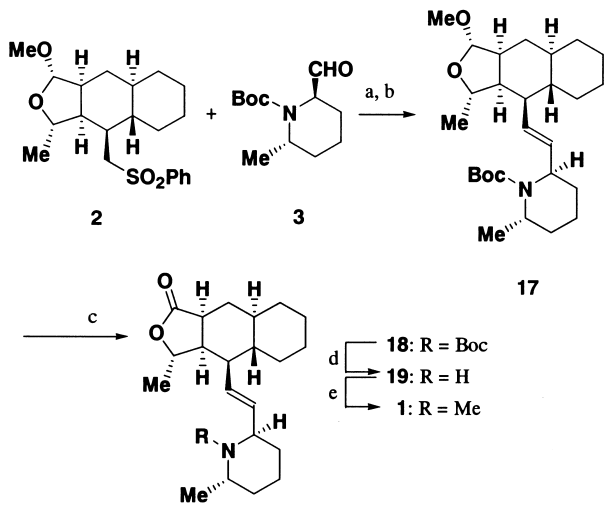
Table 2. Catalytic hydrogenation of deconjugated alcohol **5**

Entry[a]	Catalyst[b]	Ratio of **4a**/**4b** (yield, %)[c]
1	Rh–Al_2O_3	1:1 (92)
2	10% Pd–C	5:1 (65)
3	Raney Ni	10:1 (76)
4	PtO_2	1:0 (96)

[a] Hydrogenation was carried out at rt in EtOH.
[b] Amount of the catalyst corresponding to the 10% weight of **5** was used.
[c] The ratio of **4a**–**4b** was determined by the ^1H NMR spectrum of the crude reduction product.



Scheme 4. Synthesis of the sulfone **2**, the key intermediate of **1**. (a) (i) DIBAL-H, Et_2O, −78°C, 1 h, (ii) $BF_3{\cdot}Et_2O$, MeOH, CH_2Cl_2, −60–rt, 12 h, 74% (two steps); (b) TPAP, 4-methylmorpholine *N*-oxide, MS 4 Å, CH_2Cl_2, rt, 1.5 h, 95%; (c) Ph_3PCH_3I, $NaN(TMS)_2$, Et_2O, 0°C to rt, 2 h, 86%; (d) (i) $BH_3{\cdot}THF$, THF, −78°C to rt, 3 h, (ii) 30% H_2O_2, 10% NaOH, 0°C, 0.5 h, **14a**:**14b**=73:8%; (e) methanesulfonyl chloride, 4-(dimethylamino)pyridine, Et_3N, CH_2Cl_2, 0°C to rt, 3 h, 100%; (f) thiophenol, *t*BuOK, DMSO, rt, 3 h, 100%; (g) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 2 h, 82%.



Scheme 5. Completion of the total synthesis of natural himbacine **1**. (a) *n*BuLi, −78°C, 1 h, 100% conversion (a mixture of the diastereomers); (b) 5% Na–Hg, Na_2HPO_4, MeOH, rt, 2.5 h, 66%; (c) Jones reagent, acetone, rt, 0.5 h, 100%; (d) trifluoroacetic acid, CH_2Cl_2, rt, 1.5 h, 100%; (e) 37% HCHO aq., $NaBH_3CN$, CH_3CN, rt, 0.5 h, 91%.

hydroboration and oxidation gave rise to 4β-carbinol **14a** in a 73% yield along with the undesired C-4 epimer **14b** in an 8% yield. When the hydroboration was carried out at 0°C instead of at −78°C, the ratio of **14a** to **14b** was reduced to 5:1. The structure of **14a** bearing all of the desired chiral centers in the tricyclic part of **1**, was rigorously confirmed, as shown by single-crystal X-ray diffraction analysis. Stereoselective formation of **14a** may reflect increased steric hindrance of the β-face of **13**.

With **14a** in hand, transformation of **14a** into the known sulfone **2**[11] was next examined. It was accomplished in an 82% combined yield by a three-step sequence involving *O*-mesylation of the hydroxy group of **14a**, replacement of the *O*-mesyl group in **15** with a phenylsulfide group, and oxidation of the resulting sulfide **16**. Spectral and physical data of **2** were identical to those that have previously been reported.[11]

The remaining task for the total synthesis was conversion of **2** to **1** according to the Hart–Kozikowski procedure[11] (Scheme 5). Thus, the coupling reaction[25,26] of **2** with aldehyde **3**, prepared according to the reported procedure,[27] and a subsequent elimination reaction of the intermediary β-hydroxy sulfone almost exclusively provided olefin **17** possessing (*E*)-stereochemistry in a 66% yield. Sequential oxidation of the acetal moiety in **17** and deprotection of the *N*-Boc group in **18** afforded the piperidine **19**. Finally, reductive *N*-methylation of **19** furnished natural himbacine **1** in a high yield over a three-step sequence. Physical and spectral properties of the synthetic sample of **1** were found to be identical to those previously reported.[11b] As described above, our efforts culminated in the successful development of a novel synthetic route to **1** in which the intermolecular Diels–Alder reaction of **8** with (*S*)-**9** is employed as the key stereoselective reaction.

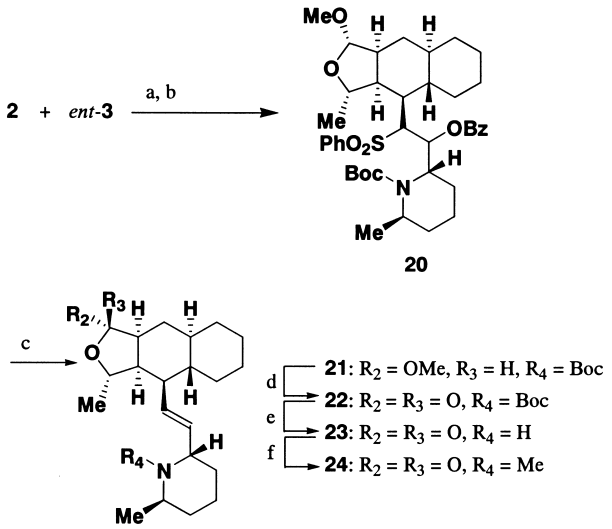
2.3. Synthesis of unnatural *ent*-himbacine *ent*-1

To clarify the relationship between the absolute configuration of **1** and muscarinic M_2 subtype antagonistic activity, as well as to explore the convergency and flexibility of the developed synthetic route to **1**, we next planned to synthesize the enantiomer of **1**, unnatural *ent*-himbacine *ent*-**1**, by using (*R*)-**9**[15] instead of (*S*)-**9** as a starting material. Synthesis of (*R*)-**9** was accomplished starting with (*R*)-methyl lactate. According to the synthetic scheme to **1** detailed above, we succeeded in obtaining *ent*-**1** from (*R*)-**9**, disclosing prominent aspects of the explored synthetic route. Spectral data of *ent*-**1** were superimposable on those of **1**. To avoid confusion, the compounds carrying natural configurations are the only compounds depicted in Scheme 2–5.

2.4. Synthesis of an enantiomeric pair of (2′*S*,6′*R*)-diepihimbacine

In order to elucidate the structure–activity relationships between the absolute configuration of the tricyclic moiety on **1** and the piperidine moiety, we next planned to synthesize an enantiomeric pair of (2′*S*,6′*R*)-diepihimbacine **24** and *ent*-**24**. It was expected that the synthesis of **24** could be accomplished by the use of our explored synthetic route, employing the sulfone **2** with a natural absolute configuration and the chiral piperidinaldehyde *ent*-**3** possessing an unnatural absolute configuration.

Thus, the Julia–Lythgoe coupling reaction of **2** and *ent*-**3** was examined to produce **24** (Scheme 6). However, in contrast to the cases for the synthesis of **1** and *ent*-**1**, the starting material **2** was fully recovered when the reaction was quenched by adding water. It seems likely that the retro-aldol type of reaction might have occurred when the materials were immersed in excess water, probably due to the decreased stability of the in situ formed lithium aldolate or an aldol-type product under protic conditions. After much



Scheme 6. Synthesis of (2′*S*,6′*R*)-diepihimbacine **24**. (a) *n*BuLi, DME, −78 to −20°C, 4 h; (b) (i) benzoyl chloride, −20°C to rt,1 h, (ii) 3-(dimethylamino)propylamine, rt, 1 h; (c) 5% Na–Hg, Na_2HPO_4, MeOH, rt, 1 h, 33% (four steps) (recovery of **2**: 51%); (d) Jones reagent, acetone, rt, 2 h, 68%; (e) trifluoroacetic acid, CH_2Cl_2, rt, 0.5 h, 91%; (f) 37% HCHO aq., $NaBH_3CN$, CH_3CN, rt, 3 h, 73%.

experimentation, it was finally found that quenching the reaction of **2** and *ent*-**3** by the addition of excess benzoyl chloride successfully gave the desired benzoate **20** as a diastereomeric mixture after removal of the excess benzoyl chloride with 3-(dimethylamino)propylamine. Without separation, the reaction mixture was directly subjected to reductive elimination, giving rise to (*E*)-olefin **21** in a 33% yield from **2**, along with a 51% recovery of **2**. In this case as well, formation of the (*Z*)-olefin was not observed by ^{1}H NMR analysis of the crude reaction product. According to the same synthetic procedure as that used for **1**, **21** was converted to the target compound **24** in a three-step sequence involving oxidation of the hemiacetal moiety, deprotection of the *N*-Boc group, and reductive *N*-methylation. The enantiomer of **24**, *ent*-**24**, was also synthesized employing *ent*-**2** and **3** in the same manner as that described for the synthesis of **24**.

2.5. Synthesis of 4-*epi*-1

Next, in order to disclose the relationships between muscarinic M_2 subtype antagonistic activity and C-4 stereochemistry in the tricyclic moiety of **1**, we examined the synthesis of 4-epihimbacine 4-*epi*-**1** by employing 4α-carbinol **14b** as a starting material. Thus, according to our methodology featuring the Julia–Lythgoe coupling reaction of the tricyclic sulfone and the chiral piperidinaldehyde that was established by the synthesis of **24** as well, we have readily succeeded in preparing 4-*epi*-**1** from **14b** in eight steps.

2.6. Muscarinic M_2 subtype binding activity of enantiomeric pairs of natural himbacine 1 and *ent*-1 and (2′*S*,6′*R*)-diepihimbacine, and 4-epihimbacine

With enantiomeric pairs of natural himbacine **1** and *ent*-**1** and (2′*S*,6′*R*)-diepihimbacine **24** and *ent*-**24**, and 4-epihimbacine 4-*epi*-**1** in hand, receptor binding affinity assays against the muscarinic M_1 and M_2 subtype receptors were performed. Results of these assays are shown in Table 3. In contrast to **1**, all of the tested compounds *ent*-**1**, **24**, *ent*-**24**, and 4-*epi*-**1** were found to show very weak comparable binding affinity against the muscarinic M_1 and M_2 subtype receptors. These results clearly indicated that the stereochemistry of both the tricyclic and the piperidine moieties of **1** play crucial roles in its strong muscarinic M_2 antagonistic activity.

Table 3. In vitro binding activity of **1**, *ent*-**1**, **24**, *ent*-**24**, and 4-*epi*-**1**

Entry	Compound	−log K_i	
		M_1 (cortex)	M_2 (brainstem)
1	**1**	7.1	7.9
2	**1**[a]	7.2	7.9
3	*ent*-**1**	5.9	6.3
4	**24**	6.5	6.7
5	*ent*-**24**	6.5	6.7
6	4-*epi*-**1**	6.1	5.7

[a] Authentic sample of **1**.[28]

2.7. Synthesis of some novel congeners of 1

With completion of the total synthesis of enantiomeric pairs of natural himbacine **1** and *ent*-**1**, (2′*S*,6′*R*)-diepihimbacine **24** and *ent*-**24**, and 4-epihimbacine 4-*epi*-**1**, we next examined the synthesis of some novel congeners of **1**. These studies were performed in order to further examine the convergency and flexibility of the explored synthetic scheme, and moreover, to disclose novel aspects of the structure–activity relationships. Studies of the synthesis and muscarinic M_2 subtype antagonistic activity of himbacine congeners have thus far been reported by Kozikowski et al.[10] and Chackalamannil et al.[12c] Our novel synthesis and activity evaluation of **1**, *ent*-**1**, **24**, *ent*-**24**, and 4-*epi*-**1** disclosed that the absolute configuration plays a pivotal role in muscarinic M_2 subtype antagonistic activity. Therefore, it appeared that novel congeners of himbacine should be synthesized in the natural configuration. Taking into account these points, we designed some novel congeners of **1**, shown in Fig. 2. It was anticipated that the chiral piperidine ring of **1** could be replaced with various substituted heterocycles such as pyridine, imidazole, morpholine, pyrrolidine, and piperidine derivative. Moreover, the (*E*)-olefin present in **1** was expected to be substituted by its bioisosteres such as ether, ester, carbamate, and amide bond species. Based on the above considerations, the compounds, **26**, **28**, **30**, **32**, **35**, **37**, **39**,

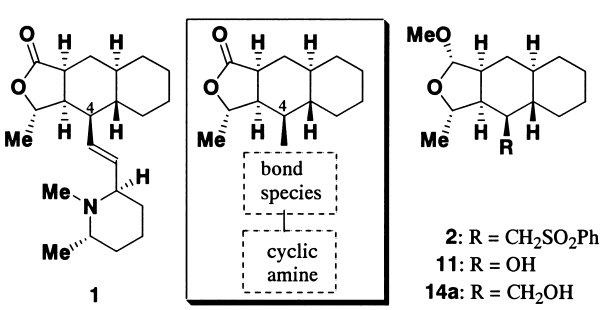
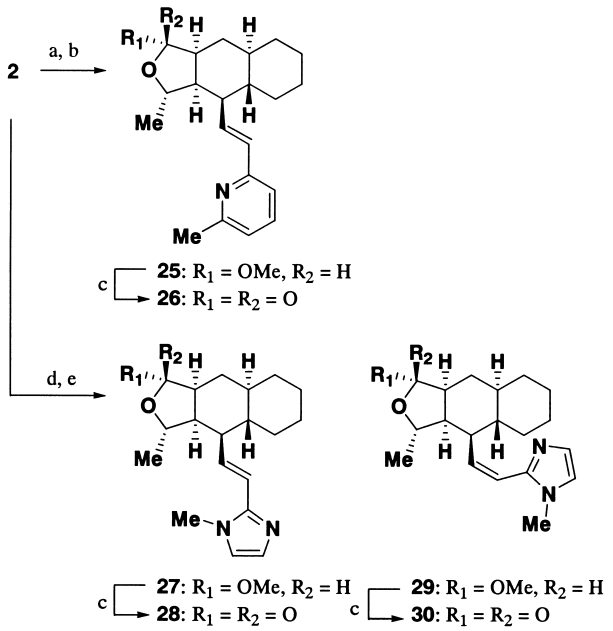


Figure 2. Novel himbacine congeners designed as synthetic targets.



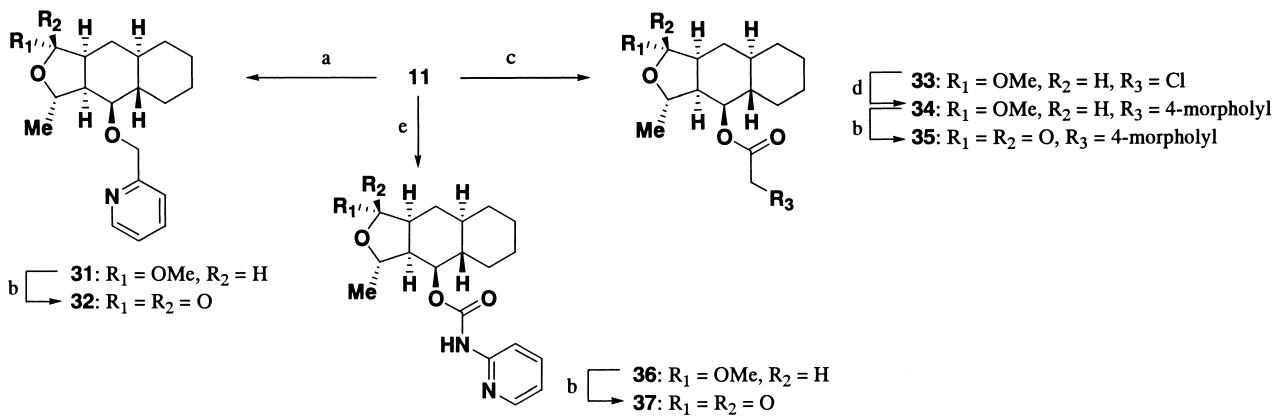
Scheme 7. Synthesis of himbacine congeners bearing the natural tricyclic moiety (I). (a) *n*BuLi, 6-methylpyridine-2-carboxaldehyde, DME, −78°C, 1 h, 100%; (b) 5% Na–Hg, Na_2HPO_4, MeOH, rt, 2 h, 19%; (c) Jones reagent, acetone, rt, 60% (for **26**), 13% (for **28**), 64% (for **30**); (d) *n*BuLi, 1-methylimidazole-2-carboxaldehyde, DME, −78°C, 1 h, 62%; (e) 5% Na–Hg, Na_2HPO_4, MeOH, rt, 4 h, 42% (for **27**), 20% (for **29**).

41, **44**, and **47** were designed as representative congeners of **1**, none of which had hitherto been prepared. These congeners were readily prepared from the functionalized intermediate for the synthesis of **1** such as **2**, **11**, and **14a**.

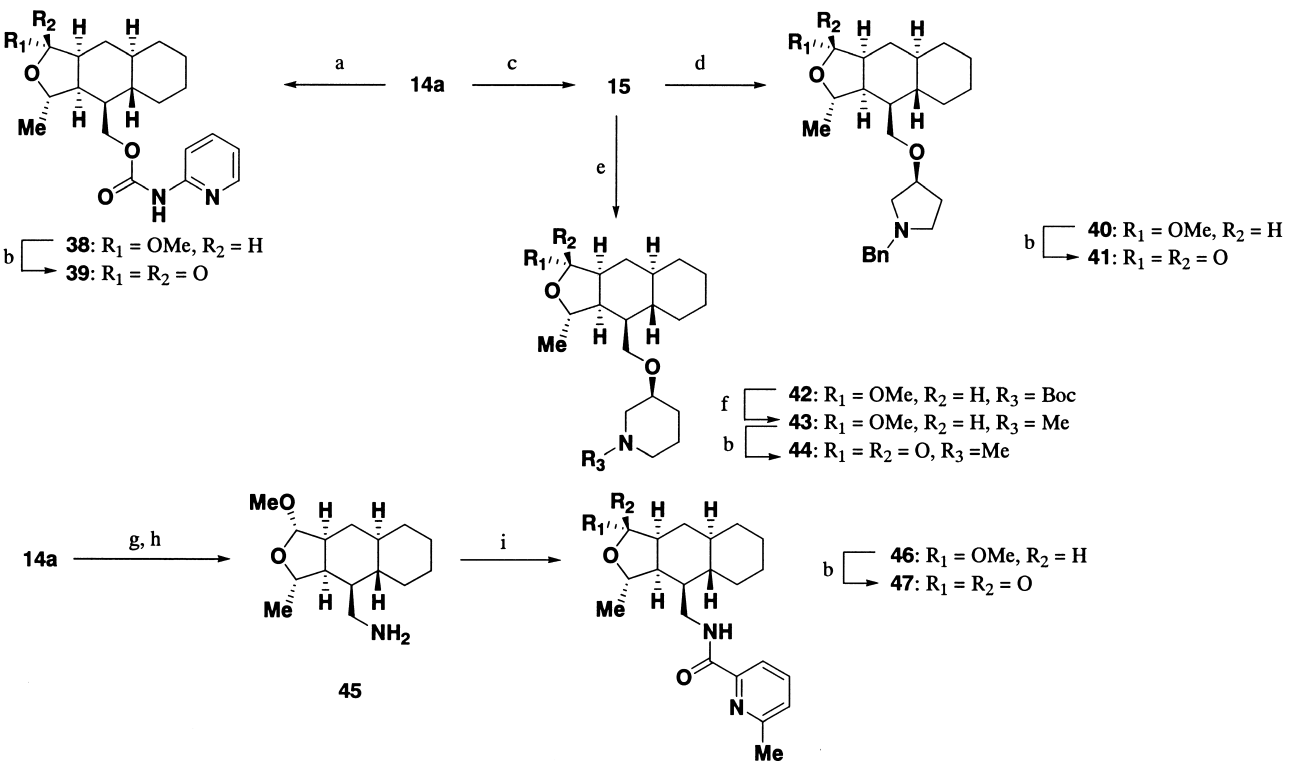
Thus, conversions of **2** to the 2-methylpyridine derivative **26** and 1-methylimidazole derivatives, **28** and **30** were readily obtained by employing a Julia–Lythgoe coupling reaction followed by elimination, and then a Jones oxidation, both in a similar manner to that described for the total synthesis of **1** (Scheme 7). Alkylation of **11** with commercially available 2-(chloromethyl)pyridine in the presence of NaH, and subsequent Jones oxidation clearly provided the 2-pyridylmethyl ether derivative **32** (Scheme 8). Similarly, acylation of **11** with chloroacetyl chloride followed by substitution with morpholine and Jones oxidation furnished the morpholin-4-yl acetate derivative **35** by way of 2-chloroacetate **33** and acetal **34**. The *N*-(pyridin-2-yl) carbamate derivative **37** was prepared by the reaction of **11** with 2-isocyanatopyridine in situ generated from 2-picolinic acid and subsequent oxidation with Jones reagent. In a similar fashion, 4β-carbinol **14a** was transformed to the homologous *N*-(pyridin-2-yl) carbamate derivative **39** (Scheme 9). The (*S*)-1-Benzylpyrrolidin-3-yl ether derivative **41** was synthesized using commercially available (*S*)-1-benzylpyrrolidin-3-ol by way of *O*-mesylate **15** derived from **14a**. The 1-methylpiperidin-3-yl ether derivative **44** was derived from **43** prepared by etherification of **15** with readily obtainable (*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-ol[29] followed by reduction of the *N*-Boc group to an *N*-Me group with lithium aluminum hydride. Furthermore, 4β-carbinamine **45** was prepared from **14a** by the Mitsunobu procedure[30] and subsequent removal of a phthalide moiety. This reaction was coupled with 6-methyl-2-picolinic acid by use of EDCI as a coupling reagent, affording the 2-methylpyridine-6-carboxamide **47** by way of acetal **46**.

2.8. Muscarinic binding activity of some novel congeners of himbacine 1

Using the thus obtained congeners of **1**, receptor binding affinity assays against the muscarinic M_1 and M_2 subtype receptors were performed. Unfortunately, as shown in Table 4, all of the compounds tested exhibited poor M_2 receptor binding affinity and low selectivity compared to **1**. In the cases of (*E*)-olefin compounds (entry 2, 3), 2-methylpyridine and 1-methylimidazole rings were found to be unsuitable for binding muscarinic receptors, probably due to the aromaticity and planar structures of these rings. The (*Z*)-olefin **30** appeared to be unrewarding in a manner similar to that of the (*E*)-olefin **28**. The congeners bearing the bioisosteres of the (*E*)-olefin structure, e.g., ether (entries 5, 9, 10), ester (entry 6), carbamate (entries 7, 8), and amide (entry 11), also showed weak M_1 and M_2 receptor binding affinity. These observations clearly suggest that the conformations of these congeners might differ greatly from that of **1**.



Scheme 8. Synthesis of himbacine congeners bearing the natural tricyclic moiety (II). (a) 2-(chloromethyl)pyridine hydrochloride, NaH, DMF, rt, 14 h, 43%; (b) Jones reagent, acetone, rt, 37% (for **32**), 55% (for **35**), 13% (for **37**); (c) chloroacetyl chloride, NaH, DMF, rt, 6 h, 83%; (d) morpholine, 100°C, 5 h, 84%; (e) 2-picolinic acid, DPPA, Et_3N, toluene, 100°C, 6 h, 64%.



Scheme 9. Synthesis of himbacine congeners bearing the natural tricyclic moiety (III). (a) 2-picolinic acid, DPPA, Et_3N, toluene, 100°C, 7 h, 92%; (b) Jones reagent, acetone, rt, 56% (for **39**), 64% (for **41**), 21% (for **44**), 35% (for **47**); (c) methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0°C to rt, 2.5 h, 100%; (d) (*S*)-1-benzylpyrrolidin-3-ol, NaH, DMF, 80°C, 17 h, 8%; (e) (*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-ol, NaH, DMF, 80°C, 17 h, 38%; (f) lithium aluminum hydride, THF, rt, 1 h, then 80°C, 1 h, 100%; (g) phthalimide, diethyl azodicarboxylate, Ph_3P, THF, 0°C to rt, 7 h, 99%; (h) $H_2NNH_2{\cdot}H_2O$, EtOH, rt, 4 h, 52%; (i) 6-methyl-2-picolinic acid, EDCI, CH_2Cl_2, rt, 5 h, 80%.

3. Conclusion

In summary, we have succeeded in the highly stereoselective total synthesis of an enantiomeric pair of himbacine **1**, a potent antagonist of the muscarinic M_2 subtype receptor, by employing an intermolecular Diels–Alder reaction of **8** with (*S*)-**9** as a key step. Our explored synthetic route was successfully applied to the total synthesis of unnatural himbacine *ent*-**1**, an enantiomeric pair of (2′*S*,6′*R*)-diepihimbacine **24** and *ent*-**24**, and 4-epihimbacine 4-*epi*-**1**. Based on the observed muscarinic receptor binding affinity assay of these compounds, it appears that the absolute configuration of **1** plays a pivotal role in its activity. Based on the results obtained, selected novel congeners of **1** were further prepared by starting with the intermediates for the total synthesis of **1**, and these congeners were then subjected to receptor binding affinity assay. However, these latter congeners were unfortunately also found to exhibit very weak muscarinic M_2 subtype receptor binding affinity and low selectivity. Although no novel congener with a more prominent profile than **1** was found, the successful synthesis of various structural types of congeners clearly disclosed the convergency and flexibility of the explored synthetic route to **1**. Our goal to discover a novel drug candidate targeting muscarinic M_2 subtype receptors for the treatment of Alzheimer's disease still remains to be achieved, and studies along this line are ongoing in our laboratories.

Table 4. In vitro binding activity of some novel congeners of himbacine

Entry	Compound	$-\log K_i$	
		M_1 (cortex)	M_2 (brainstem)
1	**1**	7.1	7.9
2	**26**	5.2	≪6.1
3	**28**	5.2	≪6.1
4	**30**	<5.1	≪6.1
5	**32**	≪5.1	≪6.1
6	**35**	≪5.1	≪6.1
7	**37**	≪5.1	≪6.1
8	**39**	≪5.1	≪6.1
9	**41**	5.5	≪5.9
10	**44**	5.6	<5.4
11	**47**	≪5.1	≪6.1

4. Experimental

4.1. General

All melting points were determined with a Yamato MP-500 melting point apparatus, a Yamaco MP-3 micro melting point apparatus, or a Yanaco MP-500D micro melting point apparatus, and are uncorrected. Measurements of optical rotations were carried out using a Horiba SEPA-200 automatic digital polarimeter, a JASCO DIP-360 automatic digital polarimeter, or 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 or an Avance 500 (500 MHz) spectrometer. ^{13}C NMR spectra were taken with a JEOL JNM-EX-400 (100 MHz)

spectrometer or an Avance 500 (125 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 analyses are within ±0.3% of the theoretical values, and were determined by a Yanaco CHN-corder MT-5. Unless otherwise noted, all the experiments were carried out using anhydrous solvents under an atmosphere of dry argon. Throughout this study, 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 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.

4.1.1. 3,4,5,6-Tetrahydrobenzo[c]furan (8). 4,5,6,7-Tetrahydroisobenzofuran-5-ol was prepared as a colorless oil starting with furfuryl alcohol according to the reported procedure.[14a] Bp 103–105°C/3 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (d, J=4.9 Hz, 1H), 1.77–1.84 (m, 1H), 1.90–1.97 (m, 1H), 2.49–2.63 (m, 2H), 2.77 (dt, J=16.6, 6.0 Hz, 1H), 2.91 (dd, J=15.7, 4.9 Hz, 1H), 4.10–4.16 (m, 1H), 7.16–7.18 (m, 2H). IR (neat): 3360, 2930, 1640, 1440 cm^{-1}. MS (EI) m/z: 138 (M^+), 120, 94 (100). HRMS (EI) (m/z): calcd for $C_8H_{10}O_2$ (M^+): 138.0681. Found, 138.0686.

To a solution of 4,5,6,7-tetrahydroisobenzofuran-5-ol (34.1 g, 0.25 mol) and triethylamine (68.8 mL, 0.49 mol) in CH_2Cl_2 (400 mL), methanesulfonyl chloride (28.7 mL, 0.37 mol) was added dropwise at 0°C, and the resulting mixture was stirred at the same temperature for 1.5 h, then gradually warmed to rt. After concentration in vacuo, the residue was poured into water (500 mL), and the aqueous mixture was extracted with diethyl ether (100 mL×3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo, to give 4,5,6,7-tetrahydroisobenzofuran-5-yl methanesulfonate (53.3 g, 100%) as an oil. This material was immediately used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99–2.07 (m, 1H), 2.10–2.19 (m, 1H), 2.64–2.71 (m, 1H), 2.76–2.85 (m, 1H), 2.90 (dd, J=16.6, 6.4 Hz, 1H), 2.99–3.04 (m, 1H), 3.04 (s, 3H), 5.11–5.16 (m, 1H), 7.14–7.22 (m, 2H). IR (neat): 3650, 2940, 1350, 1170 cm^{-1}. MS (EI) m/z: 216 (M^+), 120 (100). HRMS (EI) (m/z): calcd for $C_8H_{12}O_2$ (M^+): 216.0456. Found, 216.0464.

To the methanesulfonate (53.3 g, 0.25 mol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (55.4 mL, 0.37 mol) was added, and the mixture was heated at 80°C for 2 h. After cooling, the reaction was quenched by adding cold water (500 mL), and the resulting aqueous solution was extracted with hexane (100 mL×3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo, to give 4,5-dihydroisobenzofuran (25.0 g, 84%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28–2.33 (m, 2H), 2.61–2.66 (m, 2H), 5.85 (dt, J=9.8, 4.4 Hz, 1H), 6.42–6.47 (m, 1H), 7.10–7.13 (m, 1H), 7.24 (s, 1H). IR (neat): 3040, 2940, 1550, 1440, 1030, 790 cm^{-1}. MS (EI) m/z: 120 (M^+), 91 (100). HRMS (EI) (m/z): calcd for C_8H_8O (M^+): 120.0575. Found, 120.0581.

A mixture of 4,5-dihydroisobenzofuran (25.0 g, 0.21 mol) and 10% Pd–C (3.00 g, 10% w/w) in ethanol (400 mL) was stirred at 0–10°C for 4 h under an atmosphere of H_2 (1 atm). Insoluble materials were filtered and thoroughly washed with ethyl acetate (300 mL). The combined filtrates were concentrated in vacuo to give **8** (12.0 g, 47%) as a pale yellow oil. Bp 35–40°C/3 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67–1.73 (m, 4H), 2.51–2.58 (m, 4H), 7.13 (s, 2H). IR (neat): 2930, 1670, 1440 cm^{-1}. MS (EI) m/z: 122 (M^+) (100). HRMS (EI) (m/z): calcd for $C_8H_{10}O$ (M^+): 122.0732. Found, 122.0730. These spectral data were identical to previously reported data.[13,14]

4.1.2. (*R*)- and (*S*)-5-Methylfuran-2(5*H*)-one [(*R*)- and (*S*)-9]. According to the reported procedure,[15] (*R*)-and (*S*)-5-methylfuran-2(5*H*)-one [(*R*)- and (*S*)-**9**] were prepared both as a volatile colorless oil from (*R*)-methyl lactate and (*S*)-ethyl lactate, respectively. (*R*)-**9**: bp 110–115°C/30 mmHg. $[\alpha]_D^{25}$=−100° (c 0.69, $CHCl_3$) (lit.,[15c] $[\alpha]_D$=−100° (c 0.13, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (d, J=6.8 Hz, 3H), 5.14 (qt, J=6.8, 2.0 Hz, 1H), 6.11 (dd, J=5.9, 2.0 Hz, 1H), 7.45 (dd, J=5.4, 1.5 Hz, 1H). IR (neat): 2990, 1760, 1170, 1110 cm^{-1}. MS (EI) m/z: 98 (M^+), 83, 69, 55 (100). HRMS (EI) (m/z): calcd for $C_5H_6O_2$ (M^+): 98.0368. Found, 98.0366. These spectra were identical to those reported previously.[15c] (*S*)-**9**: bp 105–110°C/30 mmHg. $[\alpha]_D^{21}$=+116° (c 0.61, $CHCl_3$) (lit.,[15c] $[\alpha]_D$=+111° (c 1.23, $CHCl_3$)). The ^{1}H NMR, IR, and MS spectra of this compound were superimposable on those described for (*R*)-**9**.

4.1.3. (3*S*,3a*R*,4*S*,9*R*,9a*R*)-3a,4,5,6,7,8,9,9a-Octahydro-3-methyl-4,9-epoxynaphtho[2,3-*c*]furan-1(3*H*)-one and its enantiomer (7 and *ent*-7). *(a) Preparation of 7.* To a solution of lithium perchlorate (1.06 g) in diethyl ether (2 mL) was added **8** (558 mg, 3.4 mmol) and (*S*)-**9** (224 mg, 2.3 mmol), and the mixture was stirred at rt for 168 h. The reaction mixture was poured into water (20 mL), and the resulting aqueous mixture was extracted with CH_2Cl_2 (10 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (CH_2Cl_2, then CH_2Cl_2–ethyl acetate=10:1) of the residue gave **7** (292 mg, 58%) as a colorless powder. This crude material was immediately subjected to the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (d, J=6.4 Hz, 3H), 1.48–1.55 (m, 2H), 1.63–1.71 (m, 2H), 1.84–1.96 (m, 2H), 2.18–2.30 (m, 2H), 2.28 (dd, J=7.6, 3.2 Hz, 1H), 2.87 (d, J=7.8 Hz, 1H), 4.48 (qd, J=6.4, 3.4 Hz, 1H), 4.72 (br, 1H), 5.03 (br, 1H). MS (CI) m/z: 211 (M^++H), 197, 123 (100). HRMS (CI) (m/z): calcd for $C_{13}H_{17}O_3$ (M^++H): 221.1178. Found, 221.1176.

*(b) Preparation of ent-**7***. The compound *ent*-**7** (2.20 g, 72%) was prepared from **8** (1.70 g, 14 mmol) and (*R*)-**9** (1.37 g, 14 mmol) in the same manner as that described in (a). ^{1}H NMR spectrum of this sample was identical to that of **7** described in (a). HRMS (CI) (*m/z*): calcd for $C_{13}H_{17}O_3$ (M^++H): 221.1178. Found, 221.1189.

4.1.4. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9*S*,9a*R*)-Decahydro-3-methyl-4,9-epoxynaphtho[2,3-*c*]furan-1(3*H*)-one and its enantiomer (6 and *ent*-6). *(a) Preparation of **6***. A mixture of **7** (79.4 mg, 0.36 mmol) and 10% Pd–C (8.0 mg, 10% w/w) in ethanol (5 mL) was stirred at rt for 12 h under an atmosphere of H_2 (1 atm). Insoluble materials were filtered and thoroughly washed with ethyl acetate (20 mL). The combined filtrates were concentrated in vacuo to give **6** (76.7 mg, 96%) as a colorless powder. $[\alpha]_D^{25}$=+44° (*c* 0.67, $CHCl_3$). Mp 150–151°C (colorless needles from hexane–ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02–1.18 (m, 2H), 1.32–1.56 (m, 4H), 1.40 (d, *J*=6.4 Hz, 3H), 1.69–1.75 (m, 2H), 2.00–2.15 (m, 2H), 2.50 (dd, *J*=8.3, 3.4 Hz, 1H), 3.12 (d, *J*=7.8 Hz, 1H), 4.39 (qd, *J*=6.4, 3.4 Hz, 1H), 4.40 (d, *J*=3.9 Hz, 1H), 4.75 (d, *J*=4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 19.5, 19.6, 19.9, 22.5, 38.9, 39.7, 45.9, 46.3, 81.2, 83.7, 85.6, 178.0. IR (KBr): 1750 cm^{-1}. MS (EI) *m/z*: 222 (M^+), 204, 193, 95 (100). HRMS (EI) (*m/z*): calcd for $C_{13}H_{18}O_3$ (M^+): 222.1256. Found, 222.1239. Anal. calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.97; H, 8.40.

*(b) X-Ray structural analysis of **6***.[31]: Orthorhombic space group $P2_12_12_1$, a=8.066(1) Å, b=20.038(4) Å, c=7.196(1) Å, α=90.00(0)°, β=90.00(0)°, γ=90.00(0)°, V=1163.1(4) Å^3, Z=4, density ρ_{calcd}=1.27 g/cm^3, Cu Kα (λ=1.54178 Å), T=298 K, size of crystal=0.10×0.10×0.02 mm^{-1}. The structure was solved by direct methods and expanded using Fourier techniques. Final *R* and *Rw* were 0.0425 and 0.0487, respectively, for 1225 reflections.

*(c) Preparation of ent-**6***. The compound *ent*-**6** (1.36 g, 61%) was prepared from *ent*-**7** (2.20 g, 9.99 mmol) in a manner similar to that described in (a). $[\alpha]_D^{25}$=−43° (*c* 0.52, $CHCl_3$). Mp 148–149°C (colorless plates from hexane–ethyl acetate). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical with those described in (a). Anal. calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.13; H, 8.04.

4.1.5. (3*S*,3a*S*,4*R*,4a*S*,8a*S*)-3a,4,4a,5,6,7,8,8a-Octahydro-4-hydroxy-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one and its enantiomer (10 and *ent*-10). *(a) Preparation of **10***. To a solution of **6** (110 mg, 0.50 mmol) in tetrahydrofuran (20 mL), lithium bis(trimethylsilyl)amide (1 M solution in tetrahydrofuran, 2.50 mL, 2.50 mmol) was added dropwise at −78°C. The resulting mixture was stirred at the same temperature for 4 h, and then gradually warmed to −40°C with stirring. After quenching the reaction by adding saturated aqueous ammonium chloride solution (2 mL) at −40°C, the mixture was stirred at rt for 5 min, then concentrated in vacuo. Water (10 mL) was added to the residue, and the mixture was extracted with diethyl ether (5 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate =2:1) of the residue gave **10** (101 mg, 92%) as a colorless powder. This crude material was directly used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94–1.29 (m, 4H), 1.41 (d, *J*=5.4 Hz, 1H), 1.52 (d, *J*=6.4 Hz, 3H), 1.56–1.77 (m, 3H), 1.94–2.04 (m, 2H), 2.58–2.64 (m, 1H), 2.74–2.81 (m, 1H), 4.01–4.04 (m, 1H), 4.61 (dq, *J*=9.1, 5.9 Hz, 1H), 6.69 (t, *J*=2.5 Hz, 1H). MS (CI) *m/z*: 223 (M^++H). HRMS (CI) (*m/z*): calcd for $C_{13}H_{19}O_3$ (M^++H): 223.1334. Found, 223.1303.

*(b) Preparation of ent-**10***. The compound *ent*-**10** (1.35 g, 100%) was prepared from *ent*-**6** (1.35 g, 6.1 mmol) in a manner similar to the preparation of **10**, described in a). ^{1}H NMR, and MS spectra of this sample were identical to those described in a). HRMS (FAB) (*m/z*): calcd for $C_{13}H_{19}O_3$ (M^++H): 223.1334. Found, 223.1315.

4.1.6. (3*S*,3a*S*,4*R*,4a*S*,9a*S*)-3a,4,4a,5,6,7,8,9a-Octahydro-4-hydroxy-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one and its enantiomer (5 and *ent*-5). *(a) Preparation of **5***. To a solution of **10** (61.8 mg, 0.28 mmol) in toluene (2 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (208 μL, 1.4 mmol) was added, and the mixture was heated at 100°C for 5 h with stirring. After cooling, the reaction was quenched by adding diluted aqueous hydrochloric acid solution, and the mixture was concentrated in vacuo. The residue was extracted with CH_2Cl_2 (5 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate =1:1) of the residue gave **5** (51.2 mg, 83%) as a colorless powder. $[\alpha]_D^{20}$=+148° (*c* 0.29, $CHCl_3$). Mp 159–160°C (colorless plates from hexane–ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 (qd, *J*=12.7, 3.5 Hz, 1H), 1.17–1.32 (m, 1H), 1.36–1.48 (m, 1H), 1.52 (d, *J*=6.2 Hz, 3H), 1.69 (d, *J*=4.2 Hz, 1H), 1.77–1.90 (m, 2H), 1.95–2.08 (m, 2H), 2.17–2.25 (m, 1H), 2.33 (dt, *J*=14.2, 1.9 Hz, 1H), 2.56 (dt, *J*=8.4, 4.7 Hz, 1H), 3.29 (dq, *J*=8.6, 3.0 Hz, 1H), 3.82 (dt, *J*=8.5, 4.4 Hz, 1H), 4.60 (dq, *J*=8.6, 6.2 Hz, 1H), 5.31 (d, *J*=2.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.9, 25.6, 26.9, 31.8, 34.6, 41.0, 43.9, 46.8, 72.4, 77.5, 112.8, 141.1, 176.0. IR (KBr): 1730 cm^{-1}. MS (EI) *m/z*: 222 (M^+), 204, 178, 168, 149 (100). Anal. calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.29; H, 8.31.

*(b) Preparation of ent-**5***. The compound *ent*-**5** (1.05 g, 78%) was prepared from *ent*-**10** (1.35 g, 6.1 mmol) in the same manner as that described in (a). $[\alpha]_D^{23}$=−148° (*c* 0.30, $CHCl_3$). Mp 156–157°C (colorless prisms from hexane–ethyl acetate). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described in (a). Anal. calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.02; H, 8.26.

4.1.7. (3*S*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-4-hydroxy-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one and its enantiomer (4a and *ent*-4a). *(a) Preparation of **4a***. A suspension of **5** (375 mg, 1.7 mmol) and PtO_2 (40 mg, 10% w/w) in ethanol (5 mL) was stirred at rt for 16 h under an atmosphere of H_2 (1 atm). Insoluble materials were filtered and thoroughly washed with ethyl acetate (20 mL). The combined filtrates were concentrated in vacuo. Flash column chromatography (CH_2Cl_2–ethyl acetate =4:1) of the residue gave **4a** (364 mg, 96%) as a colorless powder. $[\alpha]_D^{25}$=+69° (*c* 0.41, $CHCl_3$). Mp 185–186°C (colorless

plates from hexane–ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81–0.92 (m, 1H), 0.98–1.30 (m, 6H), 1.54 (d, J=6.0 Hz, 3H), 1.69–1.77 (m, 2H), 1.74 (d, J=4.0 Hz, 1H), 1.80–1.87 (m, 2H), 2.04–2.10 (m, 1H), 2.51 (dt, J=10.1, 6.7 Hz, 1H), 2.67 (dt, J=12.3, 6.6 Hz, 1H), 3.65 (ddd, J=10.2, 6.1, 4.0 Hz, 1H), 4.73 (dq, J=11.9, 6.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.1, 25.7, 25.7, 28.9, 31.7, 33.0, 38.6, 41.9, 44.3, 48.2, 73.4, 77.4, 177.8. IR (KBr): 3460, 1740 cm^{-1}. MS (EI) m/z: 224 (M^+), 206 (100). Anal. calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.72; H, 8.93.

(b) X-Ray structural analysis of ***4a***.[31] Orthorhombic space group $P2_12_1$, a=8.859(2) Å, b=16.565(4) Å, c=8.175(2) Å, α=90.00(0)°, β=90.00(0)°, γ=90.00(0)°, V=1199.7(4) Å^3, Z=4, density ρ_{calcd}=1.24 g/cm^3, Cu Kα (λ=1.54178 Å), T=298 K, size of crystal=0.30×0.05×0.03 mm^{-1}. The structure was solved by direct methods and expanded using Fourier techniques. Final R and Rw were 0.0382 and 0.0402, respectively, for 1240 reflections.

*(c) Preparation of ent-****4a***. The compound *ent*-**4a** (0.98 g, 93%) was prepared from *ent*-**5** (1.04 g, 4.7 mmol) in a similar manner to that described in (a). $[\alpha]_D^{22}$=−69° (c 0.33, $CHCl_3$). Mp 185–186°C (colorless plates from hexane–ethyl acetate). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described in (a). Anal. calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.31; H, 9.09.

4.1.8. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*R*)-Decahydro-4-hydroxy-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one (4b). *(a) Preparation of* ***4b***. A mixture of **5** (199 mg, 0.89 mmol) and Rh–Al_2O_3 (20 mg, 10% w/w) in ethanol (10 mL) was stirred at rt for 2.5 h under an atmosphere of H_2 (1 atm). Insoluble materials were filtered and thoroughly washed with ethyl acetate (20 mL). The combined filtrates were concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=2:1) of the residue gave **4a** (100 mg, 50%) and **4b** (85 mg, 42%), both as colorless powders. **4b**: $[\alpha]_D^{22}$=−28° (c 0.18, $CHCl_3$). Mp 218°C (colorless needles from hexane–ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78–1.04 (m, 4H), 1.15–1.29 (m, 3H), 1.53 (d, J=6.9 Hz, 3H), 1.68 (d, J=5.4 Hz, 1H), 1.66–1.83 (m, 3H), 2.03–2.11 (m, 2H), 2.28 (ddd, J=9.8, 7.3, 4.4 Hz, 1H), 2.87 (td, J=7.3, 1.5 Hz, 1H), 3.23 (dt, J=9.3, 5.0 Hz, 1H), 4.55 (dq, J=6.8, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 25.5, 25.7, 28.7, 29.8, 33.2, 35.7, 41.7, 47.1, 47.3, 71.0, 77.9, 177.8. IR (KBr): 3360, 2920, 1780, 1180 cm^{-1}. MS (EI) m/z: 224 (M^+), 206 (100). Anal. calcd for $C_{13}H_{20}O_3\cdot 0.1H_2O$: C, 69.06; H, 9.00. Found: C, 69.27; H, 9.19.

(b) X-Ray structural analysis of ***4b***.[31] Monoclinic space group $P2_1$, a=11.32(1) Å, b=5.118(5) Å, c=11.09(1) Å, α=90.00(0)°, β=110.63(7)°, γ=90.00(0)°, V=601(1) Å^3, Z=2, density ρ_{calcd}=1.24 g/cm^3, Cu Kα (λ=1.54178 Å), T=298 K, size of crystal=0.30×0.20×0.12 mm^{-1}. The structure was solved by direct methods and expanded using Fourier techniques. Final R and Rw were 0.0600 and 0.0754, respectively, for 1219 reflections.

4.1.9. (1*S*,3*S*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-3-methylnaphtho[2,3-*c*]furan-4-ol and its enantiomer (11 and *ent*-11). *(a) Preparation of* ***11***. To a solution of **4a** (1.88 g, 8.4 mmol) in diethyl ether (200 mL), diisobutylaluminum hydride (0.94 M solution in hexane, 26.7 mL, 25 mmol) was added dropwise at −78°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 −78°C, and the mixture was stirred at rt for 1 h. The resulting precipitates were removed by filtration through a pad of celite, and the collected residue was washed with ethyl acetate (50 mL). The combined filtrates were concentrated in vacuo. The residue was diluted with brine, and the aqueous mixture was extracted with CH_2Cl_2 (5 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo, to give an anomeric mixture of the hemiacetal (1.89 g, 100%) as a colorless oil. This material was directly subjected to the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82–1.05 (m, 4H), 1.11–1.32 (m, 3H), 1.45 (d, J=6.4 Hz, 3H), 1.47–1.84 (m, 5H), 2.05–2.11 (m, 1H), 2.26 (dt, J=12.2, 6.2 Hz, 1H), 2.38 (d, J=2.9 Hz, 1H), 2.56 (dt, J=9.3, 5.9 Hz, 1H), 3.67 (ddd, J=10.3, 5.9, 4.4 Hz, 1H), 4.32 (dq, J=9.3, 6.1 Hz, 1H), 5.06 (d, J=2.5 Hz, 1H). IR (KBr): 3290, 2910, 1450 cm^{-1}. MS (EI) m/z: 355 [[M+(TMS)$_2$]$^+$−CH_3]. HRMS (EI) (m/z): calcd for $C_{18}H_{35}O_3Si_2$ [[M+(TMS)$_2$]$^+$−CH_3]: 355.2125. Found, 355.2156.

To a solution of the crude hemiacetal in CH_2Cl_2 (50 mL) and methanol (50 mL) was added boron trifluoride diethyl etherate (1.55 mL, 12.6 mmol) at −60°C, and the mixture was stirred at the same temperature for 12 h, then gradually warmed to rt with stirring. After the reaction was quenched by adding triethylamine (1.75 mL, 13 mmol) at 0°C, the resulting mixture was further stirred at rt for 1 h, then concentrated in vacuo. The residue was diluted with diluted aqueous sodium bicarbonate solution, and the aqueous mixture was extracted with CH_2Cl_2 (5 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate =2:1) of the residue gave **11** (1.50 g, 74% from **4a**) as a colorless powder. $[\alpha]_D^{20}$=+90° (c 0.21, $CHCl_3$). Mp 117–118°C (colorless needles from hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81–1.04 (m, 4H), 1.13–1.30 (m, 3H), 1.39 (d, J=6.0 Hz, 3H), 1.45–1.53 (m, 2H), 1.60–1.74 (m, 2H), 1.77–1.84 (m, 1H), 2.04–2.11 (m, 1H), 2.20 (dt, J=12.3, 6.0 Hz, 1H), 2.47 (dt, J=9.1, 6.0 Hz, 1H), 3.32 (s, 3H), 3.64 (ddd, J=9.6, 5.7, 3.5 Hz, 1H), 4.30 (dq, J=9.1, 6.0 Hz, 1H), 4.53 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.0, 26.0, 26.0, 29.1, 32.7, 33.4, 38.6, 44.1, 46.0, 48.6, 54.0, 74.6, 76.4, 108.5. IR (KBr): 3410, 2980, 1450, 1440, 1360 cm^{-1}. MS (EI) m/z: 208 (M^+−HOMe), 190, 162 (100). Anal. calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.72; H, 9.82.

*(b) Preparation of ent-****11***. The compound *ent*-**11** (0.89 g, 85%) was prepared from *ent*-**4a** (0.98 g, 4.4 mmol) in a manner similar to the preparation of **11**. *Ent*-hemiacetal: HRMS (EI) (m/z): calcd for $C_{18}H_{35}O_3Si_2$ [[M+(TMS)$_2$]$^+$−CH_3]: 355.2125. Found, 355.2151. *Ent*-**11**: $[\alpha]_D^{21}$=−95° (c 0.34, $CHCl_3$). Mp 118–119°C (colorless needles from hexane). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described in (a). Anal. calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.73; H, 10.31.

4.1.10. (1*S*,3*S*,3a*R*,4a*S*,8a*R*,9a*S*)-Decahydro-1-methoxy-3-methylnaphtho[2,3-*c*]furan-4(1*H*)-one and its enantiomer (12 and *ent*-12). *(a) Preparation of **12***. To a solution of **11** (1.05 g, 4.4 mmol), 4-methylmorpholine *N*-oxide (0.77 g, 6.56 mmol), and molecular sieves (MS 4 Å, 2.50 g) in CH_2Cl_2 (10 mL), tetrapropylammonium perruthenate (VII) (TPAP) (76.8 mg, 0.22 mmol) was added at rt, and the mixture was stirred at the same temperature for 1.5 h. The reaction mixture was filtered through a pad of celite, and the collected residue was washed with diethyl ether (100 mL). The combined filtrates were washed with 10% aqueous sodium thiosulfate solution (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo to give **12** (0.99 g, 95%) as a colorless powder. $[\alpha]_D^{20}=+165°$ (*c* 0.16, $CHCl_3$). Mp 86–87°C (colorless powder from hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10–1.50 (m, 6H), 1.33 (d, *J*=6.1 Hz, 3H), 1.68–1.86 (m, 4H), 1.96–2.03 (m, 2H), 2.59 (dt, *J*=12.7, 6.3 Hz, 1H), 2.80 (dd, *J*=9.1, 6.9 Hz, 1H), 3.32 (s, 3H), 4.33 (dq, *J*=9.2, 6.1 Hz, 1H), 4.71 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.8, 25.1, 25.5, 25.6, 32.5, 34.3, 41.3, 49.5, 51.4, 54.1, 58.1, 78.4, 109.1, 210.8. IR (KBr): 2930, 1700, 1450 cm^{-1}. MS (FAB) *m*/*z*: 344 [(M$^+$+diethanolamine)+H]. Anal. calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.26; H, 9.29.

*(b) Preparation of ent-**12***. The compound *ent*-**12** (786 mg, 92%) was prepared from *ent*-**11** (866 mg, 3.6 mmol) in the same manner as that described in (a). $[\alpha]_D^{21}=-165°$ (*c* 0.41, $CHCl_3$). Mp 86–87°C (colorless plates from hexane). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described in (a). Anal. calcd for $C_{14}H_{22}O_3\cdot 0.1H_2O$: C, 70.03; H, 9.32. Found: C, 70.24; H, 9.58.

4.1.11. (1*S*,3*S*,3a*S*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-3-methyl-4-methylenenaphtho[2,3-*c*]furan and its enantiomer (13 and *ent*-13). *(a) Preparation of **13***. To a suspension of methyltriphenylphosphonium iodide (9.96 g, 25 mmol) in diethyl ether (400 mL), sodium bis(trimethylsilyl)amide (0.60 M solution in toluene, 41.1 mL, 25 mmol) was added under conditions of cooling with ice, and the mixture was stirred at rt for 1 h. The resulting mixture was added dropwise to a solution of **12** (1.17 g, 4.9 mmol) in diethyl ether (30 mL) at 0°C, and the mixture was stirred at rt for 2 h. After quenching the reaction by adding cold saturated aqueous ammonium chloride solution, the mixture was concentrated in vacuo. The residue was diluted with brine (100 mL), and the mixture was extracted with diethyl ether (50 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=10:1) of the residue gave **13** (1.01 g, 86%) as a yellow oil. $[\alpha]_D^{20}=+56°$ (*c* 0.53, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99–1.33 (m, 6H), 1.26 (d, *J*=5.8 Hz, 3H), 1.59–1.73 (m, 4H), 1.80–1.91 (m, 2H), 2.25 (dt, *J*=12.2, 6.2 Hz, 1H), 2.73 (dd, *J*=9.4, 6.5 Hz, 1H), 3.33 (s, 3H), 4.20 (dq, *J*=9.8, 6.0 Hz, 1H), 4.58 (s, 1H), 4.71 (s, 1H), 4.82 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4, 26.1, 26.4, 28.9, 33.3, 34.5, 41.6, 42.8, 47.9, 53.4, 54.1, 78.2, 109.2, 109.3, 148.8. IR (neat): 2920, 1640, 1450, 1380 cm^{-1}. MS (CI) *m*/*z*: 237 (M$^+$+H), 205 (100). HRMS (CI) (*m*/*z*): calcd for $C_{15}H_{25}O_2$ (M$^+$+H): 237.1855. Found, 237.1832.

*(b) Preparation of ent-**13***: The compound *ent*-**13** (684 mg, 88%) was prepared from *ent*-**12** (786 mg, 3.3 mmol) in a similar manner to that described in (a). $[\alpha]_D^{23}=-58°$ (*c* 0.29, $CHCl_3$). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described in (a). HRMS (CI) (*m*/*z*): calcd for $C_{15}H_{25}O_2$ (M$^+$+H): 237.1855. Found, 237.1880.

4.1.12. (1*S*,3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-3-methylnaphtho[2,3-*c*]furan-4-methanol, (1*S*,3*S*,3a*R*,4*S*,4a*S*,8a*R*,9a*S*)-dodecahydro-1-methoxy-3-methylnaphtho[2,3-*c*]furan-4-methanol, and their enantiomers (14a, 14b, *ent*-14a, and *ent*-14b). *(a) Preparation of **14a** and **14b***. To a solution of **13** (293 mg, 1.2 mmol) in tetrahydrofuran (20 mL) was added borane–tetrahydrofuran complex (1 M solution in tetrahydrofuran, 1.86 mL, 1.9 mmol) at −78°C. The mixture was stirred at the same temperature for 3 h, and gradually warmed to rt. After adding water (2 mL) to the reaction mixture at 0°C, 30% hydrogen peroxide (3.0 mL) and 10% aqueous sodium hydroxide solution (3.0 mL) was 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 brine (20 mL), and the resulting mixture was extracted with CH_2Cl_2 (10 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate =4:1, then 1:1) of the residue gave **14a** (229 mg, 73%) and **14b** (25.8 mg, 8%), respectively. **14a**: $[\alpha]_D^{25}=+84°$ (*c* 0.43, $CHCl_3$). Mp 92–93°C (colorless prisms from hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84–1.13 (m, 6H), 1.18–1.29 (m, 2H), 1.39 (d, *J*=6.0 Hz, 3H), 1.49–1.81 (m, 5H), 1.83–1.89 (m, 1H), 2.17 (dt, *J*=12.4, 6.0 Hz, 1H), 2.40 (dt, *J*=9.1, 5.0 Hz, 1H), 3.33 (s, 3H), 3.58–3.65 (m, 1H), 3.74–3.79 (m, 1H), 4.23 (dq, *J*=9.3, 6.0 Hz, 1H), 4.48 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2, 26.1, 26.5, 30.2, 33.3, 34.1, 38.7, 40.7, 43.9, 45.2, 46.8, 53.9, 62.9, 75.5, 108.1. IR (KBr): 3450, 2930, 1450, 1400 cm^{-1}. MS (FAB) *m*/*z*: 360 [(M$^+$+diethanolamine)+H]. Anal. calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.31. Found: C, 70.90; H, 10.49. **14b**: A colorless oil. $[\alpha]_D^{20}=+11°$ (*c* 0.46, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82–0.94 (m, 2H), 1.14–1.33 (m, 6H), 1.30 (d, *J*=6.0 Hz, 3H), 1.41–1.81 (m, 6H), 2.22 (dt, *J*=13.1, 6.3 Hz, 1H), 2.31 (dd, *J*=9.8, 6.3 Hz, 1H), 3.33 (s, 3H), 3.56 (dd, *J*=10.6, 8.6 Hz, 1H), 3.84 (1H, dd, *J*=10.6, 4.3 Hz, 1H), 4.15 (dq, *J*=9.9, 6.0 Hz, 1H), 4.53 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 26.4, 27.2, 30.5, 33.2, 34.9, 35.0, 39.9, 40.0, 42.6, 44.8, 54.1, 63.1, 77.1, 109.3. IR (KBr): 3420, 2920, 1450, 1375 cm^{-1}. MS (CI) *m*/*z*: 255 (M$^+$+H), 237, 223 (100). HRMS (CI) (*m*/*z*): calcd for $C_{15}H_{27}O_3$ (M$^+$+H): 255.1960. Found, 255.1942.

*(b) X-Ray structural analysis of **14a***.[31] Monoclinic space group $P2_1$, a=9.494(2) Å, b=8.489(2) Å, c=9.276(2) Å, α=90.00(0)°, β=105.28(1)°, γ=90.00(0)°, V=721.2(2) Å^3, Z=2, density ρ_{calcd}=1.17 g/cm^3, Cu Kα (λ=1.54178 Å), T=298 K, size of crystal=0.41×0.20×0.18 mm^{-1}. The structure was solved by direct methods and expanded using Fourier techniques. Final *R* and *Rw* were 0.0336 and 0.0437, respectively, for 1425 reflections.

*(c) Preparation of ent-**14a** and ent-**14b***. These compounds,

ent-**14a** (538 mg, 75%) and *ent*-**14b** (55.2 mg, 8%), were prepared from *ent*-**13** (664 mg, 2.8 mmol) in a manner similar to the preparation of **14a** and **14b**, described in (a). *Ent*-**14a**: $[\alpha]_D^{22}=-84°$ (*c* 0.53, $CHCl_3$). Mp 93–94°C (colorless needles from hexane). Anal. calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.31. Found: C, 70.59; H, 10.08. *Ent*-**14b**: A yellow oil. $[\alpha]_D^{22}=-10°$ (*c* 0.42, $CHCl_3$). HRMS (CI) (*m/z*): calcd for $C_{15}H_{27}O_3$ (M^++H): 255.1960. Found, 255.1985. ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of these samples were identical to those described in (a).

4.1.13. (1*S*,3*S*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-3-methyl-4-[(phenylsulfonyl)methyl]-naphtho[2,3-*c*]furan and its enantiomer (2 and *ent*-2). *(a) Preparation of 2*. To a solution of **14a** (461 mg, 1.8 mmol) in CH_2Cl_2 (20 mL) 4-(dimethylamino)pyridine (20.3 mg, 0.18 mmol), triethylamine (1.26 mL, 9.1 mmol), and methanesulfonyl chloride (420 μL, 5.4 mmol) were added at 0°C. The mixture was stirred at the same temperature for 3 h, and gradually warmed to rt. The mixture was poured into water (20 mL), and extracted with CH_2Cl_2 (3 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=2:1) of the residue gave mesylate **15** (602 mg, 100%) as a viscous 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, 8H), 1.37 (d, *J*= 5.9 Hz, 3H), 1.50–1.92 (m, 5H), 2.17–2.23 (m, 1H), 2.42 (dt, *J*=10.3, 4.9 Hz, 1H), 3.01 (s, 3H), 3.33 (s, 3H), 4.10–4.15 (m, 2H), 4.20 (dq, *J*=9.3, 6.1 Hz, 1H), 4.35 (dd, *J*=9.8, 3.4 Hz, 1H), 4.49 (s, 1H). MS (FAB) *m/z*: 438 [(M^++diethanolamine)+H]. HRMS (FAB) (*m/z*): calcd for $C_{20}H_{40}NO_7S$ [(M^++diethanolamine)+H]: 438.2525. Found, 438.2548.

To a solution of potassium *t*-butoxide (305 mg, 2.7 mmol) in methyl sulfoxide (10 mL), thiophenol (279 μL, 2.7 mmol) was added at rt, and the mixture was stirred at the same temperature for 10 min. The resulting mixture was added to a solution of crude **15** (602 mg, 1.8 mmol) in methyl sulfoxide (10 mL), and the mixture was stirred at rt for 3 h. The mixture was poured into diluted aqueous sodium bicarbonate solution (20 mL), and extracted with diethyl ether (10 mL×3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=50:1, then 10:1) of the residue gave phenylsulfide **16** (627 mg, 100%) as a colorless powder. $[\alpha]_D^{25}=+142°$ (*c* 0.12, $CHCl_3$) (lit.[11b] $[\alpha]_D^{20}=+138.5°$ (*c* 0.73, $CHCl_3$)). Mp 42–43°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81–1.07 (m, 4H), 1.18–1.29 (m, 3H), 1.41 (d, *J*=6.4 Hz, 3H), 1.49–1.83 (m, 5H), 1.97–2.05 (m, 1H), 2.12–2.18 (m, 1H), 2.55–2.62 (m, 1H), 2.67–2.72 (m, 1H), 3.31–3.35 (m, 1H), 3.33 (s, 3H), 4.18 (dq, *J*=8.8, 6.2 Hz, 1H), 4.48 (s, 1H), 7.13–7.52 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 26.0, 26.6, 30.2, 33.3, 34.1, 35.2, 40.8, 41.4, 41.5, 44.5, 46.5, 54.0, 75.4, 108.3, 125.6, 128.6, 128.6, 128.9, 128.9, 137.3. IR (KBr): 2920, 1580, 1480, 1380 cm^{-1}. MS (EI) *m/z*: 346 (M^+), 314 (100). HRMS (EI) (*m/z*): calcd for $C_{21}H_{30}O_2S$ (M^+): 346.1967. Found, 346.1936.

To a solution of **16** (627 mg, 1.8 mmol) in CH_2Cl_2 (50 mL), 3-chloroperoxybenzoic acid (80%, 976 mg, 4.5 mmol) and sodium bicarbonate (760 mg, 9.1 mmol) were added at 0°C, and the mixture was stirred at rt for 2 h. After the insoluble materials were filtered off through a pad of celite, the collected residue was washed with CH_2Cl_2 (20 mL). The combined filtrates were concentrated in vacuo, and the residue was dissolved in diethyl ether (50 mL). The ethereal solution was washed with saturated aqueous sodium bicarbonate solution (10 mL×3) and brine (10 mL). The organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=2:1) of the residue gave **2** (564 mg, 82%) as a colorless powder. $[\alpha]_D^{20}=+104°$ (*c* 0.35, $CHCl_3$) (lit.[11b] $[\alpha]_D^{20}=+100°$ (*c* 0.35, $CHCl_3$)). Mp 127–128°C (colorless powder from hexane–ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.63 (qd, *J*=12.2, 3.0 Hz, 1H), 0.85–1.03 (m, 4H), 1.09–1.24 (m, 2H), 1.45 (d, *J*=6.1 Hz, 3H), 1.48–1.77 (m, 5H), 2.06–2.13 (m, 1H), 2.19 (dt, *J*=12.4, 6.0 Hz, 1H), 2.77 (dt, *J*=8.8, 5.5 Hz, 1H), 2.99 (dd, *J*=14.7, 9.5 Hz, 1H), 3.27 (dd, *J*=14.7, 1.7 Hz, 1H), 3.30 (s, 3H), 4.09 (dq, *J*=8.9, 6.1 Hz, 1H), 4.46 (s, 1H), 7.55–7.61 (m, 2H), 7.64–7.69 (m, 1H), 7.89–7.93 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.7, 25.8, 26.5, 29.9, 33.0, 34.1, 36.7, 40.8, 41.0, 45.0, 46.2, 53.9, 55.7, 75.3, 108.3, 127.9, 127.9, 129.3, 129.3, 133.7, 139.9. IR (KBr): 2920, 1450, 1380, 1310, 1140 cm^{-1}. MS (FAB) *m/z*: 484 [(M^++diethanolamine)+H]. Anal. calcd for $C_{21}H_{30}O_4S$: C, 66.63; H, 7.99. Found: C, 66.33; H, 8.15.

(b) Preparation of ent-2. The compound *ent*-**2** (311 mg, 40% from *ent*-**15**) was prepared from *ent*-**14a** (532 mg, 2.1 mmol) by way of *ent*-**15** (988 mg, 99%) and *ent*-**16** in the same manner similar as that described in (a). *Ent*-**15**: HRMS (FAB) (*m/z*): calcd for $C_{20}H_{40}NO_7S$ [(M^++diethanolamine)+H]: 438.2525. Found, 438.2519. *Ent*-**16**: $[\alpha]_D^{25}=-140°$ (*c* 0.15, $CHCl_3$), HRMS (EI) (*m/z*): calcd for $C_{21}H_{30}O_2S$ (M^+): 346.1967. Found, 346.1965. *Ent*-**2**: $[\alpha]_D^{22}=-104°$ (*c* 0.35, $CHCl_3$). Mp 129–130°C (colorless powder from hexane–ethyl acetate). Anal. calcd for $C_{21}H_{30}O_4S$: C, 66.63; H, 7.99. Found: C, 66.35; H, 8.01. ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of these samples were identical to those described in (a).

4.1.14. (2*R*,6*S*)-*tert*-Butyl 2-formyl-6-methylpiperidine-1-carboxylate and its enantiomer (3 and *ent*-3). These compounds **3** and *ent*-**3** were both prepared as unstable colorless oils from commercially available *dl*-2-methylpiperidine by sequential optical resolution with (2*R*, 3*R*)-(+)-tartaric acid [for *ent*-**3**: (2*S*,3*S*)-(−)-tartaric acid], protection with a *tert*-butoxycarbonyl group, and formylation according to the reported procedures.[27] **3**: $[\alpha]_D^{26}=+120°$ (*c* 1.03, $CHCl_3$) (lit.[11b] $[\alpha]_D^{20}=+122°$ (*c* 0.96, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, *J*=6.9 Hz, 3H), 1.46 (s, 9H), 1.36–1.77 (m, 6H), 3.63 (dt, *J*=11.3, 3.9 Hz, 1H), 4.27 (br, 1H), 9.30 (d, *J*=3.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 16.5, 25.5, 28.3, 28.3, 29.4, 47.4, 59.3, 81.4, 196.4. One carbon was not observed. IR (neat): 2940, 1730, 1690, 1360 cm^{-1}. MS (FAB) *m/z*: 228 (M^++H), 198, 172 (100). HRMS (FAB) (*m/z*): calcd for $C_{12}H_{22}NO_3$ (M^++H): 228.1600. Found, 228.1610. *Ent*-**3**: $[\alpha]_D^{22}=-128°$ (*c* 0.82, $CHCl_3$). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those of **3**.

HRMS (FAB) (*m*/*z*): calcd for $C_{12}H_{22}NO_3$ (M^++H): 228.1600. Found, 228.1602.

4.1.15. (2*R*,6*S*)-*tert*-Butyl 2-[2-(*E*)-[(1*S*,3*S*,3a*R*,4*R*,4a-*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-3-methylnaphtho[2,3-*c*]furan-4-yl]ethenyl]-6-methylpiperidine-1-carboxylate and its enantiomer (17 and *ent*-17). *(a) Preparation of 17*. To a solution of **2** (201 mg, 0.53 mmol) in 1,2-dimethoxyethane (10 mL) was added dropwise *n*-butyllithium (1.54 M solution in hexane, 690 μL, 1.1 mmol) at −78°C, and the mixture was stirred at the same temperature for 10 min. A solution of **3** (241 mg, 1.1 mmol) in 1,2-dimethoxyethane (2 mL) was added dropwise to the mixture at −78°C, and the resulting solution was stirred at the same temperature for 1 h. After quenching the reaction by adding water (10 mL), the mixture was diluted with brine (20 mL), and extracted with diethyl ether (10 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=9:1, then 1:1) of the residue gave the β-hydroxy sulfone as a diastereomeric mixture (145 mg, 45%) along with the recovery of **2** (111 mg, 55%). The structure of this adduct was determined by its characteristic ^{1}H NMR (400 MHz, $CDCl_3$) signals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 9H, *N*-Boc), 3.34 (s, 3H, OMe), 7.52–7.68 (m, 3H, Ph-H), 7.90–8.04 (m, 2H, Ph-H).

To a solution of the above adduct (334 mg, 0.55 mmol) in methanol (14 mL) was added 5% sodium amalgam (5.96 g) and Na_2HPO_4 (1.08 g), and the mixture was stirred at rt for 2.5 h. After quenching the reaction by adding water (10 mL), the mixture was concentrated in vacuo. The residue was diluted with brine (20 mL), and the aqueous mixture was extracted with diethyl ether (10 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=5:1) of the residue gave **17** (162 mg, 66%) as a colorless powder. In this case, formation of the (*Z*)-olefin was not observed by ^{1}H NMR analysis of the crude reaction product. $[\alpha]_D^{25}$=+93° (*c* 1.09, $CHCl_3$) (lit.[11b] $[\alpha]_D^{20}$=+90.5° (*c* 0.38, $CHCl_3$)). Mp 91–93°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63–0.74 (m, 1H), 0.87–1.01 (m, 4H), 1.16–1.34 (m, 3H), 1.23 (d, *J*=6.9 Hz, 3H), 1.29 (d, *J*=5.9 Hz, 3H), 1.44 (s, 9H), 1.46–1.79 (m, 8H), 1.87–2.08 (m, 3H), 2.14–2.22 (m, 2H), 3.31 (s, 3H), 3.95–4.02 (m, 1H), 4.18 (dq, *J*=8.3, 6.4 Hz, 1H), 4.41 (br, 1H), 4.48 (s, 1H), 5.21 (dd, *J*=15.2, 10.3 Hz, 1H), 5.47 (dd, *J*=15.2, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 20.9, 24.8, 25.8, 26.4, 26.4, 26.6, 28.5, 28.5, 28.5, 31.4, 33.1, 34.1, 40.3, 41.3, 46.4, 46.6, 47.0, 48.7, 52.4, 53.9, 75.6, 78.9, 108.4, 133.0, 133.0, 155.1. IR (neat): 2930, 1690, 1390 cm^{-1}. MS (EI) *m*/*z*: 447 (M^+), 415, 359, 315 (100). HRMS (EI) (*m*/*z*): calcd for $C_{27}H_{45}NO_4$ (M^+): 447.3349. Found, 447.3342.

(b) Preparation of ent-17. The compound *ent*-**17** (110 mg, 64%) was prepared from *ent*-**2** (283 mg, 0.75 mmol) and *ent*-**3** (340 mg, 1.5 mmol) in a manner similar to the preparation of **17**, described in a). $[\alpha]_D^{23}$=−88° (*c* 0.35, $CHCl_3$). Mp 90–92°C (colorless powder). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described in (a). HRMS (EI) (*m*/*z*): calcd for $C_{27}H_{45}NO_4$ (M^+): 447.3349. Found, 447.3350.

4.1.16. (2*R*,6*S*)-*tert*-Butyl 2-[2-(*E*)-[(3*S*,3a*R*,4*R*,4a-*S*,8a*R*,9a*S*)-Dodecahydro-3-methyl-1-oxonaphtho[2,3-*c*]furan-4-yl]ethenyl]-6-methylpiperidine-1-carboxylate and its enantiomer (18 and *ent*-18). *(a) Preparation of 18*. To a solution of **17** (155 mg, 0.35 mmol) in acetone (6 mL), Jones reagent (0.90 mL, 3.1 mmol) was added at rt, and the mixture was stirred at the same temperature for 0.5 h. After adding water (10 mL), the mixture was concentrated in vacuo. The residue was diluted with brine (10 mL), and the aqueous mixture was extracted with diethyl ether (5 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo to give **18** (149 mg, 100%) as a colorless oil. $[\alpha]_D^{25}$=+68° (*c* 0.14, $CHCl_3$) (lit.[11b] $[\alpha]_D^{20}$=+60.8° (*c* 0.55, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.64–0.75 (m, 1H), 0.93–1.06 (m, 3H), 1.12–1.28 (m, 3H), 1.24 (d, *J*=6.9 Hz, 3H), 1.42 (d, *J*=5.9 Hz, 3H), 1.44 (s, 9H), 1.50–2.12 (m, 12H), 2.24 (dt, *J*=10.3, 6.4 Hz, 1H), 2.61 (dt, *J*=13.2, 6.6 Hz, 1H), 3.96–4.03 (m, 1H), 4.40–4.46 (m, 1H), 4.64 (dq, *J*=11.7, 5.6 Hz, 1H), 5.23 (ddd, *J*=15.2, 10.3, 1.5 Hz, 1H), 5.53 (dd, *J*=15.2, 5.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 20.9, 22.2, 25.6, 26.1, 26.3, 26.4, 28.5, 28.5, 28.5, 31.2, 32.0, 33.7, 40.1, 41.6, 42.3, 45.7, 47.0, 48.8, 52.2, 77.0, 79.1, 131.3, 134.2, 155.0, 178.4. IR (neat): 2930, 1770, 1680 cm^{-1}. MS (FAB) *m*/*z*: 432 (M^++H), 375, 332 (100). HRMS (FAB) (*m*/*z*): calcd for $C_{26}H_{42}NO_4$ (M^++H): 432.3114. Found, 432.3126.

(b) Preparation of ent-18. The compound *ent*-**18** (147 mg, 98%) was prepared from *ent*-**17** (156 mg, 0.35 mmol) in the same manner as that described in (a). $[\alpha]_D^{25}$=−63° (*c* 0.50, $CHCl_3$). ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical with those described in a). HRMS (FAB) (*m*/*z*): calcd for $C_{26}H_{42}NO_4$ (M^++H): 432.3114. Found, 432.3111.

4.1.17. (3*S*,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 and its enantiomer (19 and *ent*-19). *(a) Preparation of 19*. To a solution of **18** (149 mg, 0.35 mmol) in CH_2Cl_2 (2 mL), trifluoroacetic acid (1.00 mL) was added at rt, and the mixture was stirred at the same temperature for 1.5 h. After the reaction mixture was made alkaline by adding cold diluted aqueous sodium hydroxide solution, the mixture was concentrated in vacuo. The residue was extracted with diethyl ether (5 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo to give **19** (115 mg, 100%) as a colorless oil. $[\alpha]_D^{21}$=+17° (*c* 0.27, $CHCl_3$) (lit.[11b] $[\alpha]_D^{20}$=+17.1° (*c* 0.56, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68–0.77 (m, 1H), 0.92–1.07 (m, 3H), 1.10 (d, *J*=6.4 Hz, 3H), 1.08–1.36 (m, 4H), 1.41 (d, *J*=5.9 Hz, 3H), 1.40–1.77 (m, 10H), 1.81–1.89 (m, 1H), 2.05–2.13 (m, 1H), 2.24 (dt, *J*=10.3, 6.4 Hz, 1H), 2.62 (dt, *J*=13.2, 6.7 Hz, 1H), 3.07–3.15 (m, 1H), 3.54 (q, *J*=5.4 Hz, 1H), 4.64 (dq, *J*=10.3, 6.2 Hz, 1H), 5.25 (ddd, *J*=15.2, 9.8, 1.0 Hz, 1H), 5.70 (dd, *J*=15.2, 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 21.3, 22.3, 26.1, 26.4, 31.0, 31.3, 32.0, 32.6, 33.6, 40.0, 41.5, 42.3, 45.6, 46.4, 49.0, 53.1, 76.8, 131.5, 135.1, 178.3. IR (neat): 2930, 1770, 1450,

1200, 1060 cm^{-1}. MS (EI) (*m/z*): 331 (M^+), 316 (100). HRMS (EI) (*m/z*): calcd for $C_{21}H_{33}NO_2$ (M^+): 331.2511. Found, 331.2496.

*(b) Preparation of ent-**19***. The compound *ent*-**19** (113 mg, 98%) was prepared from *ent*-**18** (147 mg, 0.34 mmol) in a manner similar to that described in a). $[\alpha]_D^{22}=-15°$ (*c* 0.44, $CHCl_3$). ^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 $C_{21}H_{33}NO_2$ (M^+): 331.2511. Found, 331.2518.

4.1.18. (3*S*,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 [(+)-himbacine] and its enantiomer (1 and *ent*-1). *(a) Preparation of **1***. To a solution of **19** (115 mg, 0.35 mmol) in acetonitrile (6 mL), formaldehyde (37 wt% solution in water, 0.30 mL) and sodium cyanoborohydride (47.8 mg, 0.76 mmol) were added, and the mixture was stirred at rt for 0.5 h. The mixture was rendered pH 7.0 by adding acetic acid, and was further stirred at rt for 1 h. After adding cold diluted aqueous sodium hydroxide solution, the mixture was concentrated in vacuo. The residue was extracted with diethyl ether (10 mL×3), and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (Chromatorex, hexane–ethyl acetate=5:1) of the residue gave **1** (109 mg, 91%) as a colorless powder. $[\alpha]_D^{24}=+55°$ (*c* 0.21, $CHCl_3$) [authentic sample:[28] $[\alpha]_D^{24}=+56°$ (*c* 0.21, $CHCl_3$), (lit.:[11b,12b] $[\alpha]_D^{20}=+51.4°$ (*c* 1.01, $CHCl_3$)). Mp 127–128°C (colorless powder from hexane) (authentic sample:[28] Mp 128–129°C (recrystallized from hexane), lit.:[11b,12b] mp 129–130°C). ^1H NMR (400 MHz, $CDCl_3$): δ 0.70–0.75 (m, 1H), 0.93–1.06 (m, 3H), 1.00 (d, *J*=6.4 Hz, 3H), 1.12–1.28 (m, 3H), 1.38–1.47 (m, 2H), 1.40 (d, *J*=6.4 Hz, 3H), 1.50–1.61 (m, 2H), 1.64–1.80 (m, 6H), 1.87 (ddd, *J*=13.2, 5.9, 2.4 Hz, 1H), 2.07–2.14 (m, 1H), 2.22 (s, 3H), 2.22–2.27 (m, 1H), 2.63 (dt, *J*=13.2, 6.7 Hz, 1H), 2.80–2.87 (m, 1H), 2.99–3.06 (m, 1H), 4.63 (dq, *J*=11.0, 5.9 Hz, 1H), 5.26 (dd, *J*=15.2, 9.8 Hz, 1H), 5.58 (dd, *J*=15.0, 9.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.0, 22.2, 26.1, 26.5, 31.5, 32.1, 32.6, 33.3, 33.6, 39.9, 41.2, 41.6, 42.3, 45.8, 49.2, 53.4, 61.4, 76.8, 133.4, 133.6, 178.3. IR (KBr): 2930, 2850, 1790, 1450 cm^{-1}. MS (EI) *m/z*: 345 (M^+), 330 (100). HRMS (EI) (*m/z*): calcd for $C_{22}H_{35}NO_2$ (M^+): 345.2668. Found, 345.2696.

*(b) Preparation of ent-**1***. The compound *ent*-**1** (101 mg, 86%) was prepared from *ent*-**19** (113 mg, 0.34 mmol), in a manner similar to the preparation of **1**. $[\alpha]_D^{23}=-59°$ (*c* 0.29, $CHCl_3$). Mp 128–130°C (colorless powder from hexane). ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were superimposable on those described in (a). HRMS (EI) (*m/z*): calcd for $C_{22}H_{35}NO_2$ (M^+): 345.2668. Found, 345.2674.

4.1.19. (2*S*,6*R*)-*tert*-Butyl 2-[2-Benzenesulfonyl-1-benzoyl-2-[(1*S*,3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-dodecahydro-1-methoxy-3-methylnaphtho[2,3-*c*]furan-4-yl]ethyl]-6-methylpiperidine-1-carboxylate and its enantiomer (20 and *ent*-20). *(a) Preparation of **20***. To a solution of **2** (100 mg, 0.26 mmol) in 1,2-dimethoxyethane (2 mL) was added dropwise *n*-butyllithium (1.5 M solution in hexane, 264 μL, 0.40 mmol) at −78°C, and the mixture was stirred at the same temperature for 5 min. A solution of *ent*-**3** (90.1 mg, 0.40 mmol) in 1,2-dimethoxyethane (1 mL) was added dropwise to the mixture at −78°C, and the resulting solution was stirred at the same temperature for 4 h. Benzoyl chloride (92.0 μL, 0.79 mmol) was added to the reaction mixture at −20°C, and the reaction mixture was stirred at rt for 1 h. After quenching the reaction by adding 3-(dimethylamino)propylamine (99.7 μL, 0.79 mmol), the mixture was diluted with diethyl ether (10 mL), and washed with diluted aqueous citric acid solution (5 mL) and brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=2:1) of the residue gave a mixture of β-benzoyloxy sulfone **20** as a yellow oil and **2** (159 mg), a starting material. The structure of **20**, possibly consisting of a mixture of four diastereomers, was determined by its characteristic ^1H NMR (400 MHz, $CDCl_3$) signals. ^1H NMR (400 MHz, $CDCl_3$): δ 3.30 (s, 3H, OMe), 7.20–7.33 (m, 5H), 7.51–7.60 (m, 2H, Ph-H), 7.63–7.68 (m, 1H, Ph-H), 7.90–7.95 (m, 2H). MS (FAB) *m/z*: 710 (M^++H), 578, 474, 358, 314, 154, 142 (100). HRMS (FAB) (*m/z*): calcd for $C_{40}H_{56}NO_8S$ (M^++H): 710.3727. Found, 710.3776.

*(b) Preparation of ent-**20***. A mixture of *ent*-**20** and *ent*-**2** (99.4 mg), a starting material, was prepared from *ent*-**2** (60 mg, 0.16 mmol) as a yellow oil in a manner similar to the preparation of **20**, described in (a). ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were almost identical with those described in (a). HRMS (FAB) (*m/z*): calcd for $C_{40}H_{56}NO_8S$ (M^++H): 710.3727. Found, 710.3768.

4.1.20. (2*S*,6*R*)-*tert*-Butyl 2-[2-(*E*)-[(1*S*,3*S*,3a*R*,4*R*,4a-*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-3-methylnaphtho[2,3-*c*]furan-4-yl]ethenyl]-6-methylpiperidine-1-carboxylate and its enantiomer (21 and *ent*-21). *(a) Preparation of **21***. Treatment of the mixture of **20** and **2** (159 mg), using the same methods described for the preparation of **17**, gave **21** (38.9 mg, 68% from **2**) as a colorless oil, along with the recovery of **2** (51.3 mg, 51%) after flash column chromatography (hexane–ethyl acetate=8:1, then 1:2). In this case, formation of the (*Z*)-olefin was not observed by ^1H NMR analysis of the crude reaction product. $[\alpha]_D^{22}=+16°$ (*c* 0.58, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.64–0.75 (m, 1H), 0.86–0.99 (m, 4H), 1.11–1.29 (m, 3H), 1.23 (d, *J*=6.9 Hz, 3H), 1.28 (d, *J*=5.9 Hz, 3H), 1.44 (s, 9H), 1.41–1.80 (m, 8H), 1.86–1.97 (m, 2H), 2.03–2.09 (m, 1H), 2.14–2.23 (m, 2H), 3.31 (s, 3H), 3.90–3.96 (m, 1H), 4.17 (dq, *J*=8.8, 6.1 Hz, 1H), 4.45–4.51 (m, 1H), 4.47 (s, 1H), 5.21 (ddd, *J*=15.7, 9.8, 1.8 Hz, 1H), 5.49 (dd, *J*=15.7, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 20.7, 24.7, 25.3, 26.4, 26.5, 26.7, 28.5, 28.5, 28.5, 31.4, 33.1, 34.1, 40.4, 41.3, 46.4, 46.6, 47.2, 48.6, 51.4, 54.0, 75.7, 79.0, 108.4, 132.4, 133.5, 155.2. IR (neat): 2930, 1690, 1390, 1180, 1100 cm^{-1}. MS (EI) *m/z*: 447 (M^+), 415, 359, 315 (100). HRMS (EI) (*m/z*): calcd for $C_{27}H_{45}NO_4$ (M^+): 447.3349. Found, 447.3342.

*(b) Preparation of ent-**21***: The compound *ent*-**21** (34.3 mg, 75% from *ent*-**2**) was prepared from the mixture of *ent*-**20** and *ent*-**2** (99.4 mg) similar to the preparation of **21**, described in (a). In this case, recovery of *ent*-**2** was 21.3 mg

(36%). $[\alpha]_D^{22}=-17°$ (*c* 0.47, $CHCl_3$). ^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 $C_{27}H_{45}NO_4$ (M^+): 447.3349. Found, 447.3309.

4.1.21. (2*S*,6*R*)-*tert*-Butyl 2-[2-(*E*)-[(3*S*,3a*R*,4*R*,4a-*S*,8a*R*,9a*S*)-Dodecahydro-3-methyl-1-oxonaphtho[2,3-*c*]furan-4-yl]ethenyl]-6-methylpiperidine-1-carboxylate and its enantiomer (22 and *ent*-22). *(a) Preparation of 22*. Treatment of **21** (33.1 mg, 73.9 μmol), using the same methods as those described for the preparation of **18**, gave **22** (21.7 mg, 68%) as a colorless oil after flush column chromatography (hexane–ethyl acetate=2:1). $[\alpha]_D^{24}=-16°$ (*c* 1.45, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.66–0.76 (m, 1H), 0.93–1.06 (m, 3H), 1.12–1.28 (m, 3H), 1.23 (d, *J*=6.8 Hz, 3H), 1.42 (d, *J*=5.9 Hz, 3H), 1.44 (s, 9H), 1.46–1.99 (m, 11H), 2.06–2.12 (m, 1H), 2.25 (dt, *J*=10.3, 6.4 Hz, 1H), 2.61 (dt, *J*=13.2, 6.6 Hz, 1H), 3.91–4.00 (m, 1H), 4.44–4.49 (m, 1H), 4.64 (dq, *J*=9.8, 6.2 Hz, 1H), 5.24 (ddd, *J*=15.2, 9.8, 1.8 Hz, 1H), 5.57 (dd, *J*=15.7, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 20.6, 22.1, 25.3, 26.1, 26.4, 26.6, 28.5, 28.5, 28.5, 31.3, 32.0, 33.6, 40.1, 41.6, 42.4, 45.6, 47.3, 48.8, 51.4, 77.0, 79.1, 130.9, 134.7, 155.2, 178.4. IR (neat): 2930, 1780, 1680 cm^{-1}. MS (FAB) *m/z*: 432 (M^++H), 375, 332 (100). HRMS (FAB) (*m/z*): calcd for $C_{26}H_{42}NO_4$ (M^++H): 432.3114. Found, 432.3116.

(b) Preparation of ent-22: The compound *ent*-**22** (10.5 mg, 73%) was prepared from *ent*-**21** (15.0 mg, 33.5 μmol) in the same manner as that described in a). ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical with those described in (a). $[\alpha]_D^{24}=+14°$ (*c* 1.05, $CHCl_3$). HRMS (FAB) (*m/z*): calcd for $C_{26}H_{42}NO_4$ (M^++H): 432.3114. Found, 432.3118.

4.1.22. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[2-(*E*)-[(2*S*,6*R*)-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*. Using the same methods as those employed for the preparation of **19**, **22** (21.7 mg, 50.3 μmol) was treated, giving **23** (15.2 mg, 91%) as a colorless oil. $[\alpha]_D^{21}=+15°$ (*c* 1.01, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.65–0.77 (m, 1H), 0.93–1.29 (m, 7H), 1.08 (d, *J*=6.4 Hz, 3H), 1.41 (d, *J*=5.9 Hz, 3H), 1.47–1.80 (m, 10H), 1.84–1.91 (m, 1H), 2.10 (dt, *J*=10.3, 5.9 Hz, 1H), 2.25 (dt, *J*=10.3, 6.4 Hz, 1H), 2.62 (dt, *J*=13.2, 6.6 Hz, 1H), 3.01–3.09 (m, 1H), 3.57 (q, *J*=5.2 Hz, 1H), 4.65 (dq, *J*=9.8, 6.2 Hz, 1H), 5.24 (ddd, *J*=15.7, 9.8, 1.5 Hz, 1H), 5.69 (dd, *J*=15.7, 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 21.5, 22.2, 26.1, 26.4, 30.6, 31.3, 32.0, 32.9, 33.6, 40.0, 41.5, 42.3, 45.6, 46.4, 49.0, 52.9, 76.8, 131.5, 135.1, 178.3. 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, 332.2587.

(b) Preparation of ent-23. The compound *ent*-**23** (6.70 mg, 83%) was prepared from *ent*-**22** (10.5 mg, 24.3 μmol) in a similar manner to that described in (a). ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were identical to those described in (a). $[\alpha]_D^{21}=-14°$ (*c* 0.67, $CHCl_3$). HRMS (FAB) (*m/z*): calcd for $C_{21}H_{34}NO_2$ (M^++H): 332.2590. Found, 332.2601.

4.1.23. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-4-[2-(*E*)-[(2*S*,6*R*)-1,6-dimethylpiperidin-2-yl]ethenyl]-3-methyl-naphtho[2,3-*c*]furan-1(3*H*)-one and its enantiomer (24 and *ent*-24). *(a) Preparation of 24*. Using the same methods as those employed for the preparation of **1**, **23** (10.2 mg, 30.8 μmol) was treated, giving **24** (7.80 mg, 73%) as a colorless powder after flash column chromatography (Chromatorex, hexane–ethyl acetate =2:1). $[\alpha]_D^{24}=+6.6°$ (*c* 0.10, $CHCl_3$). Mp 136–138°C (colorless powder from hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 0.66–0.76 (m, 1H), 0.92–1.07 (m, 3H), 1.00 (d, *J*=6.9 Hz, 3H), 1.11–1.30 (m, 3H), 1.38–1.59 (m, 4H), 1.43 (d, *J*=6.4 Hz, 3H), 1.63–1.80 (m, 6H), 1.84–1.89 (m, 1H), 2.11 (dt, *J*=10.6, 5.9 Hz, 1H), 2.21–2.29 (m, 1H), 2.22 (s, 3H), 2.63 (dt, *J*=13.2, 6.7 Hz, 1H), 2.83–2.88 (m, 1H), 3.02–3.07 (m, 1H), 4.65 (dq, *J*=9.8, 6.1 Hz, 1H), 5.25 (dd, *J*=15.2, 10.3 Hz, 1H), 5.59 (dd, *J*=15.2, 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.0, 22.2, 26.1, 26.4, 29.7, 31.2, 32.0, 33.2, 33.7, 40.0, 41.1, 41.4, 42.3, 45.8, 49.0, 53.4, 61.2, 76.7, 132.6, 133.7, 178.3. IR (KBr): 2930, 1780, 1440, 1200 cm^{-1}. MS (EI) *m/z*: 345 (M^+), 330 (100). HRMS (EI) (*m/z*): calcd for $C_{22}H_{35}NO_2$ (M^+): 345.2668. Found, 345.2675.

(b) Preparation of ent-24: The compound *ent*-**24** (12.6 mg, 76%) was prepared from *ent*-**23** (16.0 mg, 48.3 μmol) in a manner similar to the preparation of **24**. $[\alpha]_D^{21}=-7.0°$ (*c* 0.40, $CHCl_3$). Mp 135–137 °C (colorless powder from hexane). ^1H NMR, ^{13}C NMR, IR, and MS spectra of this sample were superimposable on those described in (a). HRMS (EI) (*m/z*): calcd for $C_{22}H_{35}NO_2$ (M^+): 345.2668. Found, 345.2704.

4.1.24. (1*S*,3*S*,3a*R*,4*S*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-4-(methanesulfonyloxy)methyl-3-methyl-naphtho[2,3-*c*]furan (4-*epi*-15). The compound 4-*epi*-**15** (76.9 mg, 82%) was prepared from **14b** (71.8 mg, 0.28 mmol) as a yellow oil in the same manner as that described for the preparation of **15**. ^1H NMR (400 MHz, $CDCl_3$): δ 0.83–0.95 (m, 2H), 1.13–1.40 (m, 5H), 1.30 (d, *J*=6.4 Hz, 3H), 1.51–1.62 (m, 2H), 1.63–1.72 (m, 2H), 1.77–1.81 (m, 1H), 1.82–1.88 (m, 1H), 2.18–2.28 (m, 2H), 3.02 (s, 3H), 3.32 (s, 3H), 4.13 (dq, *J*=9.3, 5.9 Hz, 1H), 4.16 (dd, *J*=9.8, 8.3 Hz, 1H), 4.41 (dd, *J*=9.8, 4.4 Hz, 1H), 4.54 (s, 1H). MS (FAB) *m/z*: 438 [(M^++diethanolamine)+H]. HRMS (FAB) (*m/z*): calcd for $C_{20}H_{40}NO_7S$ [(M^++diethanolamine)+H]: 438.2525. Found, 438.2506.

4.1.25. (1*S*,3*S*,3a*S*,4*S*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-3-methyl-4-(phenylsulfonyl)methylnaphtho-[2,3-*c*]furan (4-*epi*-16). The compound 4-*epi*-**16** (61.8 mg, 77%) was prepared from 4-*epi*-**15** (76.9 mg, 0.23 mmol) as a colorless powder in a manner similar to the preparation of **16**. $[\alpha]_D^{25}=-18°$ (*c* 0.10, $CHCl_3$). Mp 70–71°C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.82–0.94 (m, 2H), 1.12–1.43 (m, 5H), 1.22 (d, *J*=5.9 Hz, 3H), 1.54–1.82 (m, 6H), 2.19 (dt, *J*=12.7, 6.4 Hz, 1H), 2.54 (dd, *J*=9.8, 5.9 Hz, 1H), 2.60 (dd, *J*=12.7, 10.8 Hz, 1H), 3.30 (dd, *J*=13.2, 2.9 Hz, 1H), 3.32 (s, 3H), 4.06 (dq, *J*=9.3, 6.2 Hz, 1H), 4.52 (s, 1H), 7.14–7.19 (m, 1H), 7.24–7.30 (m, 2H), 7.32–7.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 26.3, 26.9, 30.3, 33.4, 33.9, 34.7, 34.7, 36.9, 40.8, 41.9, 46.0, 54.1, 76.9, 109.3, 126.0, 128.8, 128.8, 129.7, 129.7, 136.6. IR (KBr): 2930,

1580, 1480, 1090, 1050 cm^{-1}. MS (FAB) *m/z*: 452 [(M^++ diethanolamine)+H]. HRMS (FAB) (*m/z*): calcd for $C_{25}H_{42}NO_4S$ [(M^++diethanolamine)+H]: 452.2835. Found, 452.2806.

4.1.26. (1*S*,3*S*,3a*S*,4*S*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-3-methyl-4-(phenylsulfonyl)methylnaphtho-[2,3-*c*]furan (4-*epi*-2). The compound 4-*epi*-**2** (51.4 mg, 76%) was prepared as a colorless powder from 4-*epi*-**16** (58.8 mg, 0.17 mmol) in a manner similar to the preparation of **2**. $[\alpha]_D^{26}$ =+11° (*c* 0.39, $CHCl_3$). Mp 159–160°C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.79–1.33 (m, 6H), 1.21 (d, *J*=6.4 Hz, 3H), 1.51–1.75 (m, 6H), 2.02–2.07 (m, 1H), 2.12 (dt, *J*=12.4, 6.0 Hz, 1H), 2.77 (dt, *J*=8.8, 5.5 Hz, 1H), 2.99 (dd, *J*=14.7, 9.5 Hz, 1H), 3.27 (dd, *J*=12.7, 6.4 Hz, 1H), 2.25–2.31 (m, 1H), 2.94 (dd, *J*=14.7, 8.3 Hz, 1H), 3.28 (s, 3H), 3.28–3.32 (m, 1H), 4.07 (dq, *J*=9.8, 6.1 Hz, 1H), 4.49 (s, 1H), 7.55–7.62 (m, 2H), 7.64–7.69 (m, 1H), 7.89–7.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 26.0, 26.3, 29.7, 32.4, 32.9, 34.1, 34.2, 39.8, 42.0, 48.4, 54.0, 56.7, 76.5, 108.8, 128.2, 128.2, 129.3, 129.3, 133.7, 139.5. IR (KBr): 2920, 1450, 1370, 1310, 1150, 1090 cm^{-1}. MS (FAB) *m/z*: 484 [(M^++diethanolamine)+H]. HRMS (FAB) (*m/z*): calcd for $C_{25}H_{42}NO_6S$ [(M^++ diethanolamine)+H]: 484.2733. Found, 484.2697.

4.1.27. (2*R*,6*S*)-*tert*-Butyl 2-[2-(*E*)-[(1*S*,3*S*,3a*R*,4*S*,4a-*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-3-methylnaphtho-[2,3-*c*]furan-4-yl]ethenyl]-6-methylpiperidine-1-carboxylate (4-*epi*-17). The compound 4-*epi*-**17** (2.60 mg, 33%) was prepared from 4-*epi*-**2** (34.8 mg, 91.9 μmol) as a colorless oil by way of β-benzoyloxy sulfone (12.6 mg, 19%) in the same manner as that described for the preparation of **17**. In this case, 4-*epi*-**2** (27.5 mg, 79%) was recovered by flash column chromatography at the stage of β-benzoyloxy sulfone production. β-Benzoyloxy sulfone: HRMS (FAB) (*m/z*): calcd for $C_{44}H_{67}N_2O_{10}S$ [(M^++ diethanolamine)+H]: 815.4516. Found, 815.4505. 4-*epi*-**17**: $[\alpha]_D^{22}$=+34° (*c* 0.17, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.80–0.94 (m, 4H), 1.07–1.83 (m, 12H), 1.24 (d, *J*=6.9 Hz, 3H), 1.28 (d, *J*=5.9 Hz, 3H), 1.46 (s, 9H), 1.88–2.01 (m, 3H), 2.06–2.14 (m, 1H), 2.24 (dt, *J*=12.7, 6.4 Hz, 1H), 3.30 (s, 3H), 3.98–4.05 (m, 1H), 4.13 (dq, *J*=10.3, 6.1 Hz, 1H), 4.38–4.44 (m, 1H), 4.51 (s, 1H), 5.44 (dd, *J*=15.7, 4.2 Hz, 1H), 5.54 (ddd, *J*=15.7, 9.3, 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 20.8, 22.0, 25.2, 26.3, 26.8, 28.6, 28.6, 28.6, 31.2, 33.3, 34.4, 34.5, 40.5, 41.7, 42.6, 47.1, 49.1, 52.1, 54.0, 77.2, 78.9, 109.3, 130.1, 132.8, 155.2. One carbon was not observed. IR (neat): 2930, 1690, 1450, 1390, 1180 cm^{-1}. MS (FAB) *m/z*: 553 [(M^++ diethanolamine)+H]. HRMS (FAB) (*m/z*): calcd for $C_{31}H_{57}N_2O_6$ [(M^++diethanolamine)+H]: 553.4217. Found, 553.4251.

4.1.28. (2*R*,6*S*)-*tert*-Butyl 2-[2-(*E*)-[(3*S*,3a*R*,4*S*,4a-*S*,8a*R*,9a*S*)-Dodecahydro-3-methyl-1-oxonaphtho[2,3-*c*]furan-4-yl]ethenyl]-6-methylpiperidine-1-carboxylate (4-*epi*-18). The compound 4-*epi*-**18** (2.00 mg, 80%) was prepared as a colorless oil from 4-*epi*-**17** (2.60 mg, 5.81 μmol) in a manner similar to the preparation of **18**. $[\alpha]_D^{22}$=−4.5° (*c* 0.27, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.82–0.96 (m, 2H), 1.06–1.27 (m, 5H), 1.24 (d, *J*=6.9 Hz, 3H), 1.29–1.79 (m, 8H), 1.41 (d, *J*=5.9 Hz, 3H), 1.46 (s, 9H), 1.82–2.06 (m, 4H), 2.17–2.21 (m, 1H), 2.68 (dt, *J*=13.2, 6.7 Hz, 1H), 3.99–4.07 (m, 1H), 4.40–4.44 (m, 1H), 4.58 (dq, *J*=10.8, 6.2 Hz, 1H), 5.45–5.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 19.1, 20.8, 25.5, 26.1, 26.3, 26.5, 28.6, 28.6, 28.6, 31.0, 31.9, 33.8, 34.1, 39.0, 40.6, 40.7, 47.1, 49.8, 52.0, 77.2, 79.0, 128.6, 134.0, 155.1, 178.6. IR (neat): 2930, 1770, 1680, 1460 cm^{-1}. MS (FAB) *m/z*: 432 (M^++H). HRMS (FAB) (*m/z*): calcd for $C_{26}H_{42}NO_4$ (M^++H): 432.3114. Found, 432.3109.

4.1.29. (3*S*,3a*R*,4*S*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[2-(*E*)-[(2*R*,6*S*)-6-methylpiperidine-2-yl]ethenyl]-naphtho[2,3-*c*]furan-1(3*H*)-one (4-*epi*-19). The compound 4-*epi*-**19** (3.60 mg, 100%) was prepared as a yellow oil from 4-*epi*-**18** (4.70 mg, 10.9 μmol) in a manner similar to the preparation of **19**. $[\alpha]_D^{22}$=−35° (*c* 0.36, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.81–0.98 (m, 2H), 1.06–1.38 (m, 7H), 1.13 (d, *J*=6.9 Hz, 3H), 1.41 (d, *J*=5.9 Hz, 3H), 1.48–1.79 (m, 8H), 1.91 (ddd, *J*=13.7, 6.9, 2.7 Hz, 1H), 2.03 (br, 1H), 2.05–2.11 (m, 1H), 2.14–2.20 (m, 1H), 2.70 (dt, *J*=13.2, 6.7 Hz, 1H), 3.08–3.16 (m, 1H), 3.56–3.62 (m, 1H), 4.58 (dq, *J*=9.8, 6.4 Hz, 1H), 5.58 (dd, *J*=15.2, 8.8 Hz, 1H), 5.64 (dd, *J*=15.2, 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 19.5, 21.1, 26.2, 26.6, 30.8, 31.1, 32.0, 32.5, 33.8, 34.1, 38.9, 40.5, 40.9, 46.4, 49.6, 52.9, 77.2, 130.4, 133.8, 178.6. IR (neat): 2920, 1770, 1450, 1200 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, 332.2617.

4.1.30. (3*S*,3a*R*,4*S*,4a*S*,8a*R*,9a*S*)-Decahydro-4-[2-(*E*)-[(2*R*,6*S*)-1,6-dimethylpiperidine-2-yl]ethenyl]-3-methyl-naphtho[2,3-*c*]furan-1(3*H*)-one (4-*epi*-1). The compound 4-*epi*-**1** (2.40 mg, 64%) was prepared as a colorless oil from 4-*epi*-**19** (3.60 mg, 10.9 μmol) in the same manner as that described for the preparation of **1**. $[\alpha]_D^{22}$=−7.7° (*c* 0.12, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.80–0.93 (m, 4H), 1.03 (d, *J*=6.4 Hz, 3H), 1.11–1.32 (m, 4H), 1.33–1.72 (m, 10H), 1.42 (d, *J*=5.9 Hz, 3H), 1.88–1.94 (m, 1H), 2.02–2.11 (m, 1H), 2.17–2.27 (m, 1H), 2.23 (s, 3H), 2.70 (dt, *J*=13.2, 6.6 Hz, 1H), 2.81–2.90 (m, 1H), 3.03–3.10 (m, 1H), 4.58 (dq, *J*=10.8, 5.9 Hz, 1H), 5.55 (dd, *J*=14.7, 8.3 Hz, 1H), 5.62 (dd, *J*=15.7, 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.1, 22.7, 26.2, 26.6, 29.4, 30.0, 30.3, 31.0, 31.9, 33.8, 34.1, 39.0, 40.5, 40.7, 49.9, 55.9, 67.8, 77.2, 125.5, 125.5, 178.3. IR (neat): 2930, 1770, 1450, 1200 cm^{-1}. MS (FAB) *m/z*: 346 (M^++H). HRMS (FAB) (*m/z*): calcd for $C_{22}H_{36}NO_2$ (M^++H): 346.2746. Found, 346.2720.

4.1.31. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[2-(*E*)-[6-methylpyridin-2-yl]ethenyl]naphtho[2,3-*c*]furan-1(3*H*)-one (25). Treatment of **2** (50.0 mg, 0.13 mmol) and 6-methylpyridine-2-carboxaldehyde (40.0 mg, 0.33 mmol), using the same methods as those described for the preparation of **17**, gave the corresponding β-hydroxy sulfone (66.0 mg, 100%) as a yellow oil after flash column chromatography (hexane–ethyl acetate=1:1). ^1H NMR (400 MHz, $CDCl_3$): δ 3.36, 3.37 (two s, 6H, Me×2), 6.97 (m, 8H, aromatic protons). MS (CI) *m/z*: 500 (M^++H) (100). HRMS (CI) (*m/z*): calcd for $C_{28}H_{38}NO_5S$ (M^++H): 500.2471. Found, 500.2452.

The β-hydroxy sulfone (96.0 mg, 0.19 mmol) prepared in a

separate experiment was treated in a manner similar to that described for the preparation of **17** to afford (*E*)-olefin **25** (12.3 mg, 19%) as a yellow oil. In this case, formation of the (*Z*)-olefin was not observed by TLC and ^{1}H NMR analysis of the crude reaction product. $[\alpha]_D^{24}=+65°$ (*c* 0.42, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.73–1.34 (m, 6H), 1.28 (d, *J*=6.4 Hz, 3H), 1.54–1.81 (m, 6H), 2.22–2.34 (m, 3H), 2.53 (s, 3H), 3.31 (s, 3H), 4.30 (dq, *J*=9.3, 6.4 Hz, 1H), 4.52 (s, 1H), 6.35 (dd, *J*=16.1, 9.3 Hz, 1H), 6.46 (d, *J*=15.6 Hz, 1H), 6.96 (d, *J*=7.3 Hz, 1H), 7.10 (d, *J*=7.8 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H). IR (neat): 3420, 2920, 1590, 1450 cm^{-1}. MS (EI) *m/z*: 341 (M^+), 326, 282, 266, 252, 120, 107 (100). HRMS (EI) (*m/z*): calcd for $C_{22}H_{31}NO_2$ (M^+): 341.2355. Found, 341.2402.

Oxidation of **25** (12.3 mg, 36.0 μmol) with Jones reagent (0.50 mL), using a method similar to that used for the preparation of **18**, gave **26** (7.00 mg, 60%) as a colorless oil after flash column chromatography (hexane–ethyl acetate=2:1). $[\alpha]_D^{25}=-39°$ (*c* 0.70, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.73–1.32 (m, 6H), 1.42 (d, *J*=5.9 Hz, 3H), 1.54–1.86 (m, 5H), 1.91 (ddd, *J*=13.2, 6.4, 2.1 Hz, 1H), 2.30–2.37 (m, 2H), 2.54 (s, 3H), 2.69 (dt, *J*=12.7, 6.4 Hz, 1H), 4.75 (dq, *J*=7.8, 5.9 Hz, 1H), 6.41 (dd, *J*=15.7, 9.3 Hz, 1H), 6.49 (d, *J*=15.7 Hz, 1H), 6.99 (d, *J*=7.3 Hz, 1H), 7.07 (d, *J*=7.8 Hz, 1H), 7.51 (t, *J*=7.6 Hz, 1H). IR (neat): 2930, 1770, 1450, 1200 cm^{-1}. MS (EI) *m/z*: 325 (M^+), 281, 120 (100). HRMS (EI) (*m/z*): calcd for $C_{21}H_{27}NO_2$ (M^+): 325.2042. Found, 325.2044.

4.1.32. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[2-(*E*)-(1-methylimidazol-2-yl)]ethenyl]naphtho[2,3-*c*]furan-1(3*H*)-one (28) and its (*Z*)-isomer (30). Treatment of **2** (100 mg, 0.26 mmol) and 1-methylimidazole-2-carboxaldehyde (72.7 mg, 0.66 mmol), using the same methods as those described for the preparation of **17**, gave the corresponding β-hydroxy sulfone (80.0 mg, 62%) as a yellow oil after flash column chromatography (hexane–ethyl acetate=1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78, 4.03 (two s, 6H, Me×2). MS (CI) *m/z*: 489 (M^++H), 457, 347 (100). HRMS (CI) (*m/z*): calcd for $C_{26}H_{37}N_2O_5S$ (M^++H): 489.2423. Found, 489.2404. This compound was treated in a similar manner to that described for the preparation of **17**. This case differed from the preparation of **17** in that a mixture of (*E*)- and (*Z*)-olefin **27** and **29** was produced. These compounds were separated by flash column chromatography (hexane–ethyl acetate=1:1, then 1:4) to give **27** (22.8 mg, 42%) as a colorless powder and **29** (10.7 mg, 20%) as a colorless oil. **27**: $[\alpha]_D^{24}=+48°$ (*c* 0.15, $CHCl_3$). Mp 176–178°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70–1.31 (m, 6H), 1.30 (d, *J*=6.4 Hz, 3H), 1.47–1.83 (m, 6H), 2.18–2.31 (m, 3H), 3.31 (s, 3H), 3.61 (s, 3H), 4.29 (dq, *J*=8.3, 6.1 Hz, 1H), 4.51 (s, 1H), 6.23 (d, *J*=15.7 Hz, 1H), 6.44 (dd, *J*=15.7, 9.8 Hz, 1H), 6.80 (d, *J*=1.0 Hz, 1H), 6.99 (d, *J*=1.0 Hz, 1H). IR (KBr): 2920, 1440, 1280, 1100 cm^{-1}. MS (EI) *m/z*: 330 (M^+), 315, 299, 270, 255, 109 (100). HRMS (EI) (*m/z*): calcd for $C_{20}H_{30}N_2O_2$ (M^+): 330.2307. Found, 330.2340. **29**: $[\alpha]_D^{24}=+98°$ (*c* 0.71, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81–1.30 (m, 6H), 1.29 (d, *J*=5.9 Hz, 3H), 1.51–1.74 (m, 6H), 2.32 (dt, *J*=12.7, 6.2 Hz, 1H), 2.47 (dt, *J*=9.3, 5.9 Hz, 1H), 3.29 (s, 3H), 3.59 (s, 3H), 3.67 (td, *J*=10.8, 5.6 Hz, 1H), 4.24 (dq, *J*=8.3, 6.1 Hz, 1H), 4.49 (s, 1H), 5.55 (dd, *J*=11.7, 10.8 Hz, 1H), 6.20 (d, *J*=11.7 Hz, 1H), 6.80 (d, *J*=1.0 Hz, 1H), 7.06 (d, *J*=1.0 Hz, 1H). IR (neat): 2920, 1450, 1280, 1050 cm^{-1}. MS (EI) *m/z*: 330 (M^+), 315, 298, 269 (100). HRMS (EI) (*m/z*): calcd for $C_{20}H_{30}N_2O_2$ (M^+): 330.2307. Found, 330.2322.

Oxidation of **27** (31.2 mg, 94.4 μmol) and **29** (13.9 mg, 42.1 μmol) using a method similar to that used for the preparation of **18**, afforded **28** (4.00 mg, 13%) as a colorless powder and **30** (8.50 mg, 64%) as a colorless oil, respectively, after flash column chromatography (**28**: ethyl acetate, **30**: hexane–ethyl acetate=1:4). **28**: $[\alpha]_D^{27}$ −26° (*c* 0.40, $CHCl_3$). Mp 171–172°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71–0.81 (m, 1H), 1.00–1.28 (m, 5H), 1.45 (d, *J*=5.9 Hz, 3H), 1.60–1.75 (m, 4H), 1.76–1.85 (m, 1H), 1.99 (ddd, *J*=13.7, 6.4, 2.0 Hz, 1H), 2.26–2.35 (m, 2H), 2.66 (dt, *J*=12.7, 6.4 Hz, 1H), 3.64 (s, 3H), 4.73 (dq, *J*=9.8, 6.1 Hz, 1H), 6.28 (d, *J*=15.7 Hz, 1H), 6.45 (dd, *J*=15.5, 10.1 Hz, 1H), 6.83 (d, *J*=1.5 Hz, 1H), 7.01 (d, *J*=1.0 Hz, 1H). IR (KBr): 2920, 1770, 1450, 1200 cm^{-1}. MS (EI) *m/z*: 314 (M^+) (100). HRMS (EI) (*m/z*): calcd for $C_{19}H_{26}N_2O_2$ (M^+): 314.1994. Found, 314.1991. **30**: $[\alpha]_D^{27}=+100°$ (*c* 0.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77–0.87 (m, 1H), 0.94–1.28 (m, 5H), 1.41 (d, *J*=5.9 Hz, 3H), 1.60–1.78 (m, 5H), 1.86–1.93 (m, 1H), 2.75–2.82 (m, 2H), 3.63 (s, 3H), 3.67 (td, *J*=11.8, 4.9 Hz, 1H), 4.70 (dq, *J*=10.3, 5.9 Hz, 1H), 5.57 (dd, *J*=11.7, 10.3 Hz, 1H), 6.28 (d, *J*=11.7 Hz, 1H), 6.84 (d, *J*=1.0 Hz, 1H), 7.07 (d, *J*=1.0 Hz, 1H). IR (neat): 2920, 1770, 1200, 1060 cm^{-1}. MS (EI) *m/z*: 314 (M^+) (100). HRMS (EI) (*m/z*): calcd for $C_{19}H_{26}N_2O_2$ (M^+): 314.1994. Found, 314.1992.

4.1.33. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[(2-pyridylmethyl)oxy]naphtho[2,3-*c*]furan-1(3*H*)-one (32). To a solution of **11** (29.0 mg, 0.12 mmol) in *N*,*N*-dimethylformamide (3 mL), sodium hydride (60% dispersion in mineral oil, 12.1 mg, 0.30 mmol) was added at rt, and the mixture was stirred at the same temperature for 30 min. 2-(Chloromethyl)pyridine hydrochloride (19.8 mg, 0.12 mmol) was added to the resulting solution at rt, and the mixture was stirred at rt for 14 h. After quenching the reaction by adding cold water (10 mL), the mixture was extracted with diethyl ether (3 mL×3). The combined organic extracts were washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=2:1) of the residue gave ether **31** (17.2 mg, 43%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75–1.06 (m, 4H), 1.12–1.41 (m, 3H), 1.35 (d, *J*=6.4 Hz, 3H), 1.59–1.81 (m, 4H), 2.16–2.27 (m, 2H), 2.76 (dt, *J*=9.3, 5.9 Hz, 1H), 3.33 (s, 3H), 3.41 (dd, *J* =10.8, 5.4 Hz, 1H), 4.35 (dq, *J*=9.3, 6.4 Hz, 1H), 4.50 (d, *J*=13.2 Hz, 1H), 4.54 (s, 1H), 4.82 (d, *J*=12.7 Hz, 1H), 7.18 (dd, *J*=7.3, 5.7 Hz, 1H), 7.46 (d, *J*=7.8 Hz, 1H), 7.69 (td, *J*=7.8, 2.0 Hz, 1H), 8.54 (d, *J*=3.9 Hz, 1H). MS (FAB) *m/z*: 332 (M^++H), 300 (100). HRMS (FAB) (*m/z*): calcd for $C_{20}H_{30}NO_3$ (M^++H): 332.2226. Found, 332.2206.

Oxidation of **31** (17.2 mg, 52 μmol) in the same manner as that described for the preparation of **18**, gave **32** (6.00 mg, 37%) as a colorless oil. $[\alpha]_D^{20}=+52°$ (*c* 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74–1.46 (m, 7H), 1.48 (d, *J*=5.9 Hz, 3H), 1.61–1.87 (m, 4H), 2.16–2.24 (m, 1H),

2.67 (dt, *J*=12.2, 6.9 Hz, 1H), 2.73 (dt, *J*=10.3, 6.8 Hz, 1H), 3.44 (dd, *J*=10.3, 5.7 Hz, 1H), 4.54 (d, *J*=12.7 Hz, 1H), 4.76 (dq, *J*=9.8, 5.9 Hz, 1H), 4.79 (d, *J*=12.7 Hz, 1H), 7.21 (dd, *J*=7.8, 4.9 Hz, 1H), 7.45 (d, *J*=7.8 Hz, 1H), 7.69–7.74 (m, 1H), 8.55 (d, *J*=4.4 Hz, 1H). IR (neat): 2920, 1770, 1200, 1080 cm^{-1}. MS (EI) *m/z*: 315 (M^+), 286, 272, 208, 108 (100). HRMS (EI) (*m/z*): calcd for $C_{19}H_{25}NO_3$ (M^+): 315.1834. Found, 315.1834.

4.1.34. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[2-(4-morpholyl)acetoxy]naphtho[2,3-*c*]furan-1(3*H*)-one (35). To a solution of **11** (100 mg, 0.42 mmol) in *N*,*N*-dimethylformamide (3 mL), sodium hydride (60% dispersion in mineral oil, 99.9 mg, 2.5 mmol) was added at rt, and the mixture was stirred at the same temperature for 30 min. Chloroacetyl chloride (99.4 μL, 1.25 mmol) was added to the resulting solution at rt, and the mixture was stirred at the same temperature for 6 h. After quenching the reaction by adding cold water (5 mL), the mixture was extracted with diethyl ether (3 mL×3). The combined organic extracts were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=10:1) of the residue gave chloroacetate **33** (110.0 mg, 83%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–1.41 (m, 5H), 1.29 (d, *J*=5.9 Hz, 3H), 1.51–1.54 (m, 1H), 1.66–1.82 (m, 4H), 2.31 (dt, *J*=12.2, 6.2 Hz, 1H), 2.59 (dt, *J*=8.8, 5.9 Hz, 1H), 3.30 (s, 3H), 4.05 (dd, *J*=15.7, 12.2 Hz, 1H), 4.29–4.37 (m, 1H), 5.02 (dd, *J*=10.8, 6.2 Hz, 1H). MS (EI) *m/z*: 285 (M^+−OMe), 162 (100). HRMS (EI) (*m/z*): calcd for $C_{15}H_{22}ClO_3$ (M^+−OMe): 285.1257. Found, 285.1257.

A solution of **33** (17.8 mg, 49 μmol) in morpholine (43.0 μL, 0.49 mmol) was stirred at 100°C for 5 h. After concentration in vacuo, flash column chromatography (hexane–ethyl acetate=2:1, then 1:2) of the residue gave 2-(4-morpholyl)acetate **34** (15.2 mg, 84%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81–1.34 (m, 6H), 1.28 (d, *J*=6.4 Hz, 3H), 1.50–1.55 (m, 1H), 1.63–1.78 (m, 5H), 2.29 (dt, *J*=12.7, 5.9 Hz, 1H), 2.49–2.61 (m, 5H), 3.14 (d, *J*=16.6 Hz, 1H), 3.22 (d, *J*=16.6 Hz, 1H), 3.30 (s, 3H), 3.75 (t, *J*=4.7 Hz, 4H), 4.32 (dq, *J*=9.3, 5.9 Hz, 1H), 4.53 (s, 1H), 5.00 (dd, *J*=10.8, 5.9 Hz, 1H). MS (EI) *m/z*: 367 (M^+), 352, 335, 100 (100). HRMS (EI) (*m/z*): calcd for $C_{20}H_{33}NO_5$ (M^+): 367.2359. Found, 367.2338.

Oxidation of **34** (15.2 mg, 41 μmol) in a manner similar to that described for the preparation of **18**, gave **35** (8.00 mg, 55%) as a colorless oil after flash column chromatography (hexane–ethyl acetate=1:1, then 1:2). $[\alpha]_D^{25}$=+41° (*c* 0.76, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82–1.40 (m, 7H), 1.42 (d, *J*=5.9 Hz, 3H), 1.57–1.81 (m, 4H), 1.89 (dd, *J*=10.8, 6.4 Hz, 1H), 2.53–2.62 (m, 5H), 2.72–2.78 (m, 1H), 3.16 (d, *J*=16.6 Hz, 1H), 3.25 (d, *J*=16.6 Hz, 1H), 3.76 (t, *J*=4.7 Hz, 4H), 4.74 (dq, *J*=12.2, 5.9 Hz, 1H), 4.97 (dd, *J*=11.3, 5.9 Hz, 1H). IR (neat): 2930, 1780, 1750, 1200 cm^{-1}. MS (EI) *m/z*: 351 (M^+), 100 (100). HRMS (EI) (*m/z*): calcd for $C_{19}H_{29}NO_5$ (M^+): 351.2046. Found, 351.2045.

4.1.35. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[(2-pyridylcarbamoyl)oxy]naphtho[2,3-*c*]furan-1(3*H*)-one (37). A solution of **11** (100 mg, 0.42 mmol), 2-picolinic acid (256 mg, 2.1 mmol), diphenylphosphoryl azide (448 μL, 2.1 mmol), and triethylamine (580 μL, 4.2 mmol) in toluene (3 mL) was heated at 100°C for 6 h with stirring, and then concentrated in vacuo. After quenching the reaction by adding water (5 mL), the resulting insoluble materials were filtered off, and the filtrate was extracted with diethyl ether (3 mL×3). The combined organic extracts were washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=2:1) of the residue gave carbamate **36** (95.5 mg, 64%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91–1.79 (m, 6H), 1.30 (d, *J*=5.9 Hz, 3H), 1.85–1.92 (m, 1H), 2.32 (dt, *J*=12.2, 6.2 Hz, 1H), 2.69 (dt, *J*=8.3, 6.4 Hz, 1H), 3.30 (s, 3H), 4.34 (dq, *J*=9.8, 6.4 Hz, 1H), 4.55 (s, 1H), 4.91 (dd, *J*=11.3, 5.9 Hz, 1H), 6.99 (dd, *J*=7.3, 4.7 Hz, 1H), 7.67–7.71 (m, 1H), 7.97 (d, *J*=8.3 Hz, 1H), 8.23–8.25 (m, 1H). MS (FAB) *m/z*: 361 (M^++H), 327, 276 (100). HRMS (FAB) (*m/z*): calcd for $C_{20}H_{29}N_2O_4$ (M^++H): 361.2127. Found, 361.2126.

Treatments of **36** (95.5 mg, 0.26 mmol) in a manner similar to the preparation of **18**, gave **37** (11.9 mg, 13%) as a colorless oil after flash column chromatography (hexane–ethyl acetate=2:1). $[\alpha]_D^{25}$=+36° (*c* 0.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77–1.31 (m, 6H), 1.35–1.44 (m, 1H), 1.39 (d, *J*=5.9 Hz, 3H), 1.64–1.98 (m, 5H), 2.71–2.81 (m, 2H), 4.73 (dq, *J*=10.3, 6.1 Hz, 1H), 4.89 (dd, *J*=11.2, 5.9 Hz, 1H), 6.98–7.06 (m, 1H), 7.70–7.76 (m, 1H), 8.00 (d, *J*=8.3 Hz, 1H), 8.26–8.28 (m, 1H), 8.74 (br, 1H). IR (neat): 2930, 1780, 1730, 1590, 1540, 1440, 1220 cm^{-1}. MS (EI) *m/z*: 344 (M^+), 326, 276, 206, 120 (100). HRMS (EI) (*m/z*): calcd for $C_{19}H_{24}N_2O_4$ (M^+): 344.1736. Found, 344.1745.

4.1.36. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[(2-pyridylcarbamoyl)oxymethyl]naphtho[2,3-*c*]furan-1(3*H*)-one (39). Preparation of **38** (40.6 mg, 92%) as a yellow oil from **14a** (30.0 mg, 0.12 mmol) was carried out in the same manner as that described for the preparation of **36**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–1.33 (m, 7H), 1.32 (d, *J*=5.9 Hz, 3H), 1.52–1.90 (m, 6H), 2.19 (dt, *J*=12.2, 6.2 Hz, 1H), 2.43 (dt, *J*=9.3, 4.7 Hz, 1H), 3.33 (s, 3H), 4.02 (dd, *J*=11.3, 8.6 Hz, 1H), 4.21 (dq, *J*=9.3, 6.2 Hz, 1H), 4.34 (dd, *J*=10.8, 3.7 Hz, 1H), 4.49 (s, 1H), 6.98–7.01 (m, 1H), 7.35 (br, 1H), 7.66–7.71 (m, 1H), 7.95 (d, *J*=8.3 Hz, 1H), 8.24–8.25 (m, 1H). MS (FAB) *m/z*: 375 (M^++H), 363, 343, 327, 154 (100). HRMS (FAB) (*m/z*): calcd for $C_{21}H_{31}N_2O_4$ (M^++H): 375.2284. Found, 375.2273.

Oxidation of **38** (40.6 mg, 0.11 mmol) in a manner similar to the preparation of **18**, gave **39** (21.8 mg, 56%) as a colorless oil. $[\alpha]_D^{24}$=+22° (*c* 0.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–1.31 (m, 7H), 1.44 (d, *J*=5.9 Hz, 3H), 1.63–1.94 (m, 6H), 2.42–2.47 (m, 1H), 2.64 (dt, *J*=13.2, 6.7 Hz, 1H), 4.09–4.15 (m, 1H), 4.33 (dd, *J*=11.2, 3.9 Hz, 1H), 4.67 (dq, *J*=9.8, 6.1 Hz, 1H), 7.00–7.04 (m, 1H), 7.61 (br, 1H), 7.69–7.73 (m, 1H), 7.94 (d, *J*=8.3 Hz, 1H), 8.25–8.27 (m, 1H). IR (neat): 2930, 1770, 1730, 1540, 1310 cm^{-1}. MS (EI) *m/z*: 358 (M^+), 210, 163, 135, 120 (100). HRMS (EI) (*m/z*): calcd for $C_{20}H_{26}N_2O_4$ (M^+): 358.1893. Found, 358.1870.

4.1.37. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[(3*S*)-1-benzylpyrrolidin-2-yl]oxymethylnaphtho[2,3-*c*]furan-1(3*H*)-one (41). To a solution of (*S*)-1-benzylpyrrolidin-3-ol (104 mg, 0.59 mmol) in *N*,*N*-dimethylformamide (2 mL), sodium hydride (60% dispersion in mineral oil, 39.1 mg, 0.98 mmol) was added at rt, and the mixture was stirred at the same temperature for 20 min. *O*-Mesylate **15** (65.0 mg, 0.20 mmol) was added to the resulting solution at rt, and the mixture was stirred at 80°C for 17 h. After quenching the reaction by adding cold water (10 mL), the mixture was extracted with diethyl ether (3 mL×3). The combined ethereal extracts were washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, and then were concentrated in vacuo. Flash column chromatography (ethyl acetate) of the residue gave **40** (12.4 mg, 8%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77–1.09 (m, 5H), 1.17–1.30 (m, 2H), 1.29 (d, *J*=6.4 Hz, 3H), 1.47–1.83 (m, 7H), 1.97–2.06 (m, 1H), 2.14 (dt, *J*=11.7, 5.9 Hz, 1H), 2.36 (dt, *J*=10.8, 5.4 Hz, 1H), 2.43 (dd, *J*=9.8, 4.2 Hz, 1H), 2.52–2.62 (m, 2H), 2.86 (dd, *J*=9.8, 6.4 Hz, 1H), 3.25–3.35 (m, 1H), 3.32 (s, 3H), 3.59 (d, *J*=12.7 Hz, 1H), 3.64 (d, *J*=13.2 Hz, 1H), 3.88–3.93 (m, 1H), 4.19 (dq, *J*=9.3, 5.9 Hz, 1H), 4.45 (s, 1H), 7.22–7.34 (m, 5H). MS (CI) *m*/*z*: 414 (M^++H). HRMS (CI) (*m*/*z*): calcd for $C_{26}H_{40}NO_3$ (M^++H): 414.3008. Found, 414.2999.

Oxidation of **40** (12.4 mg, 30 μmol) in a manner similar to the preparation of **18**, gave **41** (7.60 mg, 64%) as a colorless oil after flash column chromatography (ethyl acetate–methanol=10:1). $[\alpha]_D^{24}$=+36° (*c* 0.76, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79–1.29 (m, 8H), 1.42 (d, *J*=5.9 Hz, 3H), 1.62–1.88 (m, 6H), 2.01–2.10 (m, 1H), 2.40 (dt, *J*=10.8, 5.4 Hz, 1H), 2.47 (dd, *J*=10.3, 3.9 Hz, 1H), 2.53–2.65 (m, 3H), 2.79 (dd, *J*=10.3, 6.4 Hz, 1H), 3.26–3.38 (m, 2H), 3.62 (q, *J*=12.7 Hz, 2H), 3.88–3.93 (m, 1H), 4.66 (dq, *J*=10.3, 5.9 Hz, 1H), 7.23–7.35 (m, 5H). IR (neat): 2920, 1770, 1450, 1200 cm^{-1}. MS (EI) *m*/*z*: 397 (M^+), 368, 320, 306, 159, 133, 120, 91 (100). HRMS (EI) (*m*/*z*): calcd for $C_{25}H_{35}NO_3$ (M^+): 397.2617. Found, 397.2623.

4.1.38. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[(3*S*)-1-methylpiperidin-3-yloxymethylnaphtho[2,3-*c*]furan-1(3*H*)-one (44). The compound **42** (25.1 mg, 38%), a colorless oil, was prepared from **15** (50.0 mg, 0.15 mmol) and (*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-ol (90.8 mg, 0.45 mmol) in the same manner as that described for the preparation of **40**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79–1.28 (m, 10H), 1.31 (d, *J*=5.9 Hz, 3H), 1.38–1.91 (m, 8H), 1.56 (s, 9H), 2.11–2.18 (m, 1H), 2.31–2.39 (m, 1H), 2.96–3.22 (m, 3H), 3.32 (s, 3H), 3.39–3.64 (m, 3H), 4.16–4.25 (m, 1H), 4.46 (s, 1H). MS (FAB) *m*/*z*: 543 [(M^++diethanolamine)+H]. HRMS (FAB) (*m*/*z*): calcd for $C_{29}H_{55}N_2O_7$ [(M^++diethanolamine)+H]: 543.4009. Found, 543.3998.

To a solution of **42** (14.3 mg, 33 μmol) in tetrahydrofuran (5 mL), lithium aluminum hydride (3.7 mg, 98 μmol) was added at rt, and the mixture was stirred at the same temperature for 1 h, then heated at reflux for 1 h. After quenching the reaction by adding water (5 mL), the insoluble materials were filtered off. The filtrate was concentrated in vacuo, and the residue was extracted with diethyl ether (3 mL×3). The combined organic extracts were washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo, to afford the *N*-methyl derivative **43** (11.5 mg, 100%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80–1.35 (m, 10H), 1.31 (d, *J*=5.9 Hz, 3H), 1.47–1.99 (m, 9H), 2.11–2.17 (m, 1H), 2.27 (s, 3H), 2.37 (dt, *J*=10.3, 5.2 Hz, 1H), 2.62–2.68 (m, 1H), 2.89–2.95 (m, 1H), 3.26–3.34 (m, 1H), 3.32 (s, 3H), 3.39 (dd, *J*=9.3, 7.8 Hz, 1H), 3.49 (dd, *J*=8.8, 3.7 Hz, 1H), 4.20 (dq, *J*=9.3, 6.1 Hz, 1H), 4.45 (s, 1H). MS (CI) *m*/*z*: 352 (M^++H) (100). HRMS (CI) (*m*/*z*): calcd for $C_{21}H_{38}NO_3$ (M^++H): 352.2852. Found, 352.2891.

Oxidation of **43** (11.5 mg, 33.0 μmol) in a manner similar to the preparation of **18**, gave **44** (2.3 mg, 21%) as a yellow oil. $[\alpha]_D^{24}$=+13° (*c* 0.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–1.35 (m, 10H), 1.45 (d, *J*=5.9 Hz, 3H), 1.56–2.04 (m, 9H), 2.29 (s, 3H), 2.38–2.43 (m, 1H), 2.57 (dt, *J*=12.7, 6.4 Hz, 1H), 2.63–2.71 (m, 1H), 2.87–2.96 (m, 1H), 3.30–3.35 (m, 1H), 3.45 (apparent t, *J*=8.6 Hz, 1H), 3.52 (dd, *J*=9.3, 3.2 Hz, 1H), 4.68 (dq, *J*=10.3, 6.4 Hz, 1H). IR (neat): 2930, 1770, 1450, 1200, 1070 cm^{-1}. MS (EI) *m*/*z*: 335 (M^+), 320, 167, 149, 114, 99 (100). HRMS (EI) (*m*/*z*): calcd for $C_{20}H_{33}NO_3$ (M^+): 335.2460. Found, 335.2492.

4.1.39. (1*S*,3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Dodecahydro-4-aminomethyl-1-methoxy-3-methylnaphtho[2,3-*c*]furan (45). To a solution of **14a** (100 mg, 0.39 mmol), phthalimide (63.6 mg, 0.43 mmol), and triphenylphosphine (113 mg, 0.43 mmol) in tetrahydrofuran (3 mL), diethyl azodicarboxylate (92.9 μL, 0.59 mmol) was added at 0°C, and the mixture was stirred at rt for 7 h, then concentrated in vacuo. Diluted aqueous citric acid solution (5 mL) was added to the residue and extracted with diethyl ether (3 mL×3). The combined organic extracts were washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=4:1) of the residue gave the phthalimide derivative (150 mg, 99%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80–1.26 (m, 6H), 1.40 (d, *J*=5.9 Hz, 3H), 1.51–1.73 (m, 5H), 1.83–1.90 (m, 1H), 2.21–2.26 (m, 1H), 2.34–2.43 (m, 2H), 3.31 (s, 3H), 3.49 (dd, *J*=13.7, 5.9 Hz, 1H), 3.78 (dd, *J*=13.7, 6.9 Hz, 1H), 4.23 (dq, *J*=8.3, 5.9 Hz, 1H), 4.46 (s, 1H), 7.71 (dd, *J*=5.4, 2.9 Hz, 2H), 7.83 (dd, *J*=5.4, 3.0 Hz, 2H). MS (FAB) *m*/*z*: 489 [(M^++diethanolamine)+H]. HRMS (FAB) (*m*/*z*): calcd for $C_{27}H_{41}N_2O_6$ [(M^++diethanolamine)+H]: 489.2965. Found, 489.2939.

To a solution of the phthalimide derivative (150 mg, 0.39 mmol) in ethanol (5 mL) was added hydrazine hydrate (0.20 mL), and the mixture was stirred at rt for 4 h, then concentrated in vacuo. The residue was diluted with water (10 mL) and extracted with diethyl ether (3 mL×3). The combined organic extracts were washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo, to give 4β-carbinamine **45** (51.2 mg, 52%) as a yellow oil. $[\alpha]_D^{25}$=+85° (*c* 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79–1.04 (m, 6H), 1.15–1.90 (m, 9H), 1.39 (d, *J*=6.4 Hz, 3H), 2.11–2.20 (m, 1H), 2.39–2.48 (m, 2H), 2.97 (dd, *J*=13.2, 3.9 Hz, 1H), 3.33 (s, 3H), 4.16 (dq, *J*=9.3, 6.1 Hz, 1H), 4.48 (s, 1H). IR (neat): 3390, 2920, 1450 cm^{-1}. MS (FAB) *m*/*z*: 254 (M^++H), 222, 154 (100).

HRMS (FAB) (*m*/*z*): calcd for $C_{15}H_{28}NO_2$ (M^++H): 254.2120. Found, 254.2104.

4.1.40. (3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-(6-methylpyridine-2-carboxamido)methylnaphtho[2,3-*c*]furan-1(3*H*)-one (47). A solution of **45** (46.2 mg, 0.18 mmol), 6-methyl-2-picolinic acid (75.0 mg, 0.55 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (105 mg, 0.55 mmol) in CH_2Cl_2 (3 mL) was stirred at rt for 5 h, then concentrated in vacuo. Diluted aqueous sodium hydroxide solution (5 mL) was added to the residue, and the mixture was extracted with diethyl ether (3 mL×3). The combined organic extracts were washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Flash column chromatography (hexane–ethyl acetate=2:1) of the residue gave acetal **46** (54.1 mg, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91–1.10 (m, 5H), 1.17–1.30 (m, 3H), 1.40 (d, *J*=5.9 Hz, 3H), 1.53–1.73 (m, 2H), 1.76–1.87 (m, 2H), 1.98–2.05 (m, 1H), 2.19 (dt, *J*=12.2, 6.2 Hz, 1H), 2.46 (dt, *J*=9.8, 4.9 Hz, 1H), 2.58 (s, 3H), 3.09 (ddd, *J*=13.7, 9.8, 5.7 Hz, 1H), 3.32 (s, 3H), 3.86 (ddd, *J*=13.7, 5.9, 4.4 Hz, 1H), 4.24 (dq, *J*=9.3, 6.1 Hz, 1H), 4.49 (s, 1H), 7.27 (d, *J*=8.8 Hz, 1H), 7.72 (t, *J*=7.8 Hz, 1H), 7.97 (d, *J*=7.8 Hz, 1H), 8.20 (br, 1H). MS (EI) *m*/*z*: 372 (M^+), 252, 220, 192, 176, 149. HRMS (EI) (*m*/*z*): calcd for $C_{22}H_{32}N_2O_3$ (M^+): 372.2413. Found, 372.2452.

Oxidation of **46** (54.1 mg, 0.15 mmol) in the same manner as that described for the preparation of **18**, gave **47** (18.0 mg, 35%) as a colorless powder after flash column chromatography (hexane–ethyl acetate=1:1). $[\alpha]_D^{24}$=+30° (*c* 0.13, $CHCl_3$). Mp 137–139°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97–1.33 (m, 7H), 1.55 (d, *J*=5.9 Hz, 3H), 1.67–1.96 (m, 5H), 1.99–2.06 (m, 1H), 2.47–2.52 (m, 1H), 2.58 (s, 3H), 2.64 (dt, *J*=12.7, 6.4 Hz, 1H), 3.12 (ddd, *J*=14.2, 10.3, 5.9 Hz, 1H), 3.90 (dt, *J*=12.7, 5.6 Hz, 1H), 4.72 (dq, *J*=10.3, 5.9 Hz, 1H), 7.30 (d, *J*=7.3 Hz, 1H), 7.74 (t, *J*=7.6 Hz, 1H), 7.98 (d, *J*=8.7 Hz, 1H), 8.24 (br, 1H). IR (KBr): 3400, 2930, 1770, 1680, 1530, 1460, 1210 cm^{-1}. MS (EI) *m*/*z*: 356 (M^+), 338, 328, 236 (100). HRMS (EI) (*m*/*z*): calcd for $C_{21}H_{28}N_2O_3$ (M^+): 356.2100. Found, 356.2079.

4.2. Binding assay

The 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 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. The 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, respectively, of the radioligands. The K_d values were determined by Scatchard analysis.

Acknowledgements

We are grateful to Dr H. Ohkubo and Dr T. Ishizaki, Kyorin Pharmaceutical Co. Ltd, for their numerous valuable suggestions and for their encouragement. We would also like to thank Dr Y. Fukuda, Kyorin Pharmaceutical Co. Ltd, for his discussions with us and for his helpful suggestions. The in vitro binding activity assay was performed by Dr T. Kawai, Kyorin Pharmaceutical Co. Ltd, to whom our thanks are also due. We also thank Mr Y. Ijuin, Sagami Chemical Research Center, for the single-crystal X-ray crystallographic analysis.

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