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2,3-Dimethoxy-2,3-dimethyl-1,4-dioxane as a useful precursor to 2,3-dimethylene-1,4-dioxane for [4+2] cycloaddition reaction†

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2,3-Dimethoxy-2,3-dimethyl-1,4-dioxane readily prepared from biacetyl serves as a stable precursor to 2,3-dimethylene-1,4-dioxane which undergoes a [4+2] cycloaddition reaction with dienophiles to give functionalized cyclohexene derivatives. The cycloaddition adducts obtained by the present procedure are transformed into potentially useful intermediates for biologically important materials.

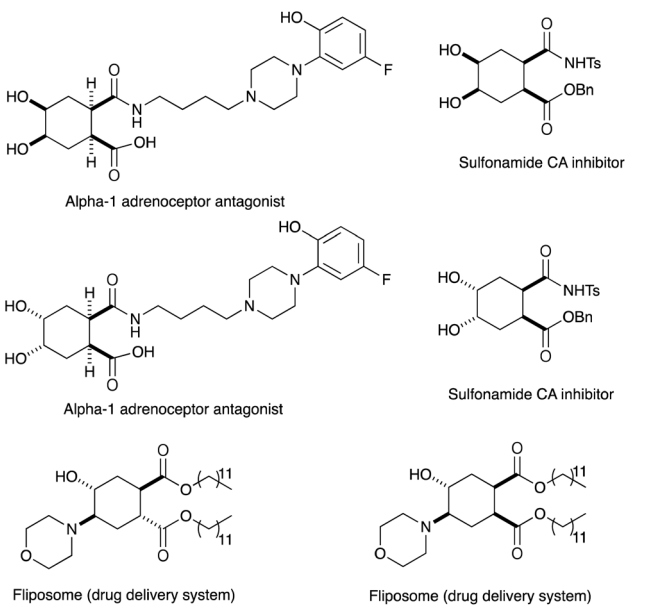
1 Introduction

In conjunction with the synthetic study of biologically important 1,2-dihydroxycyclohexanes and their 1,2-hydroxylamine analogues such as alpha-1 adrenoceptor antagonist,[1] sulfonamide CA inhibitor,[2] and fliposome (DDS)[3] (Scheme 1), we needed a simple and reliable method for the synthesis of these particular structures. Regarding the construction of six-membered carbocycles, the power of the Diels–Alder reaction means it has been recognized as one of the most reliable and straightforward approaches to these molecules, and several functionalized 1,3-dienes have been devised.[4] Among the dienes explored, 2,3-dialkoxy-1,3-butadienes[5] have received considerable attention since the cycloaddition products with dienophiles are latent 2-hydroxycyclohexanones which can be transformed into a variety of cyclohexanol derivatives. We have been interested in the synthesis and use of 2,3-dimethylene-1,4-dioxane for constructing thiophene derivatives,[6] which include 3,4-ethylenedioxythiophene (EDOT) commonly used as a starting material for poly(3,4-ethylenedioxythiophene) (PEDOT), one of the most useful electron-conducting polymers.[7] During these investigations, Diels–Alder cycloaddition using this particular diene intrigued us. A literature search into such diene has revealed that some derivatives are known, but many of them are unstable at room temperature.[8]

In an effort to find a stable precursor to this diene, we screened several compounds, and among the derivatives examined 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3** shows a reasonable stability and can work as a good precursor to 2,3-dimethylene-1,4-dioxane **2**. This paper describes [4+2] cycloaddition reactions using 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3** with dienophiles (Scheme 2, eqn (1)) and subsequent transformations of the cycloaddition products.

2 Results and discussion

An initial examination was carried out to find good precursors to the diene **2**. The investigation involves the use of readily available starting materials to synthesize a relatively large amount of the desired product. Among the derivatives



Scheme 1 Biologically important materials containing a cyclohexanol moiety.

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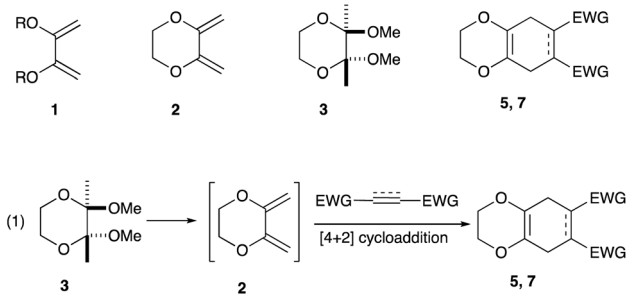
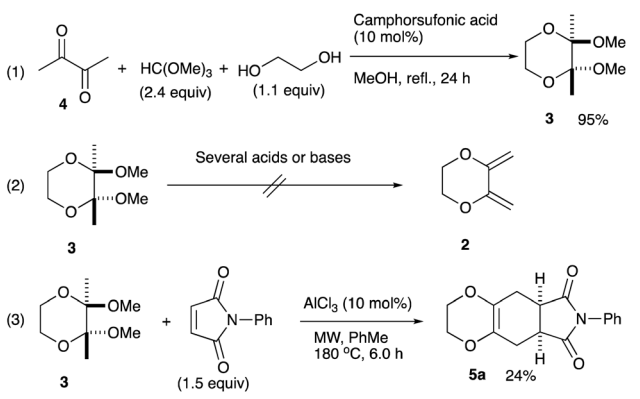


Scheme 2 Particular dienes, a precursor, and adducts.

examined 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3** show promising results (Scheme 3).

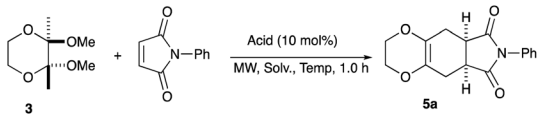
2,3-Dimethoxy-2,3-dimethyl-1,4-dioxane **3** was readily prepared from butane-2,4-dione **4** under camphorsulfonic acid-catalyzed acetalization conditions in 95% yield (Scheme 3, eqn (1)). Several attempts to convert 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3** into 2,3-dimethylene-1,4-dioxane **2** under either acidic or basic conditions met with disappointing results, where only a trace amount of the desired diene **2** was obtained (Scheme 3, eqn (2)). However, the treatment of 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3** with *N*-phenylmaleimide in the presence of a catalytic amount of aluminum chloride under microwave irradiation at 180 °C produced the [4+2] cycloaddition product **5a** in 24% yield (Scheme 3, eqn (3)), indicating that the *in situ* generation of the diene **2** could be used for the cycloaddition process. We next examined the best cycloaddition reaction conditions using *N*-phenylmaleimide as a dienophile, and Table 1 summarizes the results.

Due to the instability of the intermediary 2,3-dimethylene-1,4-dioxane **2**, excess amounts of 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3** were used throughout the present study and the yields were determined on the basis of the dienophile, *N*-phenylmaleimide. The use of 2 equivalents of 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3** in the presence of $AlCl_3$ increased the product yield up to 51% (entry 1). A better yield was obtained when the reaction was carried out at 200 °C, whereas the yield decreased at 220 °C (entries 2 and 3). We next examined the



Scheme 3 Preparation of 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3** and its reaction.

Table 1 Examination of the reaction conditions



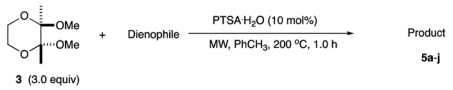
Entry	**3**: equiv.	Solv.	Acid	Temp. (°C)	Yield[a] (%)
1	2.0	$PhCH_3$	$AlCl_3$	180	51
2	2.0	$PhCH_3$	$AlCl_3$	200	68
3	2.0	$PhCH_3$	$AlCl_3$	220	44
4	3.0	$PhCH_3$	$AlCl_3$	200	73
5	5.0	$PhCH_3$	$AlCl_3$	200	59
6	3.0	$PhCH_3$	Et_2AlCl	200	75
7	3.0	$PhCH_3$	$ZrCl_4$	200	80
8	3.0	$PhCH_3$	$ZnCl_2$	200	32
9	3.0	$PhCH_3$	PTSA·H_2O[b]	200	89
10	3.0	$PhCH_3$	CSA[c]	200	82
11	3.0	$PhCH_3$	AcOH	200	0
12	3.0	*n*Hex	PTSA·H_2O	200	0
13	3.0	DCE[d]	PTSA·H_2O	200	73
14	3.0	EtCN	PTSA·H_2O	200	34
15	3.0	THF	PTSA·H_2O	200	19

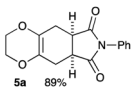
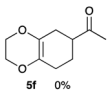
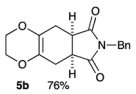
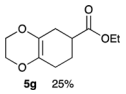
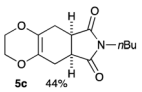
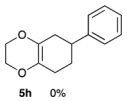
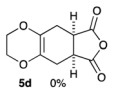
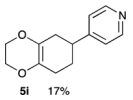
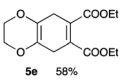
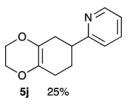
[a] Isolated yield. [b] *p*-Toluenesulfonic acid·H_2O. [c] Camphorsulfonic acid. [d] 1,2-Dichloroethane.

amount of 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3**. The use of 3.0 equivalents of **3** recorded a better yield of the desired product **5a**, although a large amount of **3** did not improve its formation (entries 4 and 5). Further examination into the use of other Lewis acids revealed that Et_2AlCl and $ZrCl_4$ could be used with comparable efficiency, although $ZnCl_2$ was less effective (entries 6–8). The use of Brønsted acids recorded better results. Among the Brønsted acids examined the presence of *p*-toluenesulfonic acid·H_2O recorded the best result, while camphorsulfonic acid could be used (entries 9 and 10). However, simple carboxylic acids (acetic acid) appear to be too weak to promote the 2,3-dimethylene-1,4-dioxane **2** formation (entry 11). The reactions in other solvents were also examined briefly. Although *n*hexane, EtCN, and THF were not suitable, DCE may be used with a small decrease in the product yield (entries 12–15). Thus, the optimized reaction conditions (entry 9) were found and used for further [4+2] cycloaddition reactions with 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3**. Table 2 summarizes [4+2] cycloaddition reactions using various dienophiles.

As shown in Table 2, among N-substituted maleimides examined the reaction using *N*-phenyl maleimide gave the addition product in the best yield of 89%, while its benzyl and *n*butyl analogues recorded decreased yields of 76 and 44%, respectively (entries 1–3). However, maleic anhydride could not be used as the dienophile for the present cycloaddition (entry 4). The use of diethyl acetylenedicarboxylate gave the addition product in 58% yield (entry 5). Regarding the mono-substituted olefins, although MVK did not give the addition product **5f**, ethyl acrylate afforded the cycloaddition the adduct **5g** in 25% yield (entries 6 and 7). While simple styrene did not give the

Table 2 [4+2] cycloaddition reaction using various dienophiles



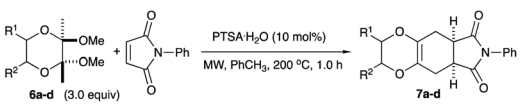
Entry	Dienophile	Product	Yield[a]	Entry	Dienophile	Product	Yield[a]
1		 5a 89%	89%	6		 5f 0%	0%
2		 5b 76%	76%	7		 5g 25%	25%
3		 5c 44%	44%	8		 5h 0%	0%
4		 5d 0%	0%	9		 5i 17%	17%
5		 5e 58%	56%	10		 5j 25%	25%

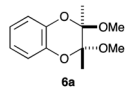
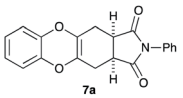
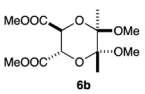
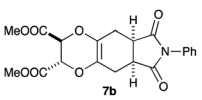
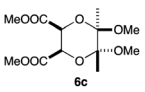
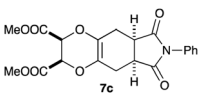
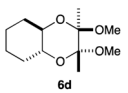
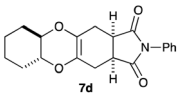
[a] Isolated yield.

cycloaddition product due to the polystyrene formation, 4- and 2-vinylpyridines gave the desired products in 17 and 25%, respectively (entries 8–10). These results indicate that the present procedure suffers from the side reaction of polymerization of the intermediate 2,3-dimethylene-1,4-dioxane **2** due to the high reaction temperature necessary for the formation of this particular diene **2** from the precursor **3**. Therefore, an excess amount of the diene precursor **3** is required for the optimum results and relatively stable dienophiles at high temperatures appear to be applicable. Regarding the reactivity and stability of 2,3-dimethylene-1,4-dioxane derivatives, several substituted derivatives were examined, and Table 3 summarizes the results.

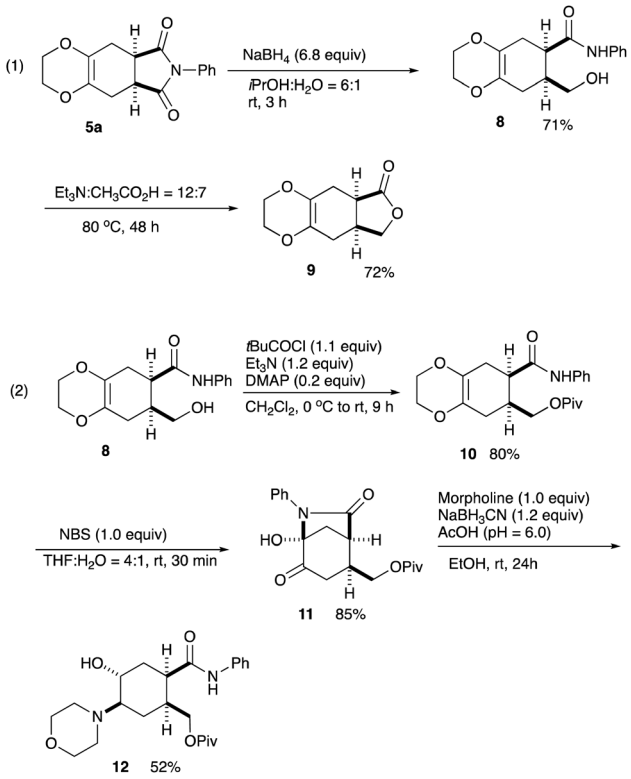
As can be seen from Table 3, the use of other substituted precursor **6a–d** did not record better results than that of 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3**. The benzo derivatives **6a** gave a small amount of the desired product (entry 1). 5,6-Dimethoxycarbonyl derivatives **6b**, **c** may be used, in which the *cis*-isomer **6c** was preferred (entries 2 and 3). Cyclohexane derivative **6d** could be used as a diene precursor for the present cycloadditions, giving the adduct **7d** in good yield (entry 4). In the cases of the low yields of the desired products, undesired polymerization of the intermediate diene was a major side reaction, and several attempts (addition of radical scavengers, reactions at lower temperatures, *etc.*) did not improve the product yields. Regarding the pathways of the present cycloaddition, there exist two representative mechanisms; non-polar and polar ones.[9] Considering the nature of the diene and dienophiles used in the present study, the present [4+2] cycloaddition reaction would proceed *via* a polar mechanism. We next examined the transformation of the Diels–Alder adduct **5a**

Table 3 [4+2] cycloaddition reaction using various diene precursors **6a–d**



Entry	Dienophile	Product	Yield[a] (%)
1	 6a	 7a	20
2	 6b	 7b	34
3	 6c	 7c	50
4	 6d	 7d	71

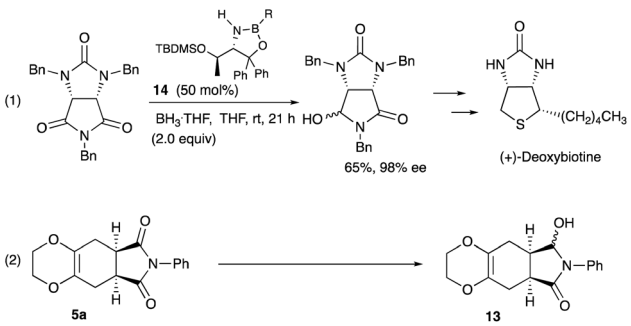
[a] Isolated yield.



Scheme 4 Useful transformations of the Diels–Alder adduct **5a**.

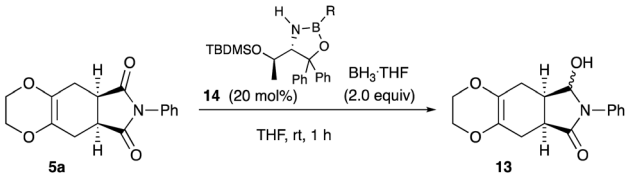
to useful intermediates to biologically important materials. Scheme 4 summarizes the results.

Regarding the imide moiety, $NaBH_4$ reduction readily opened up the five-membered ring to give the hydroxy amide **8** in 71% yield. The subsequent lactonization was conducted with Et_3N in AcOH at 80 °C to give the γ-lactone **9** in 72% yield (Scheme 4, eqn (1)).[10] Removal of the dioxane ring was next examined. Several oxidative transformations were attempted, in which the primary hydroxy group often participated in the oxidation to give many byproducts, and therefore, this hydroxy function was protected as the pivalate **10**. Treatment of the alcohol **8** with pivaloyl chloride in the presence of DMAP/Et_3N in CH_2Cl_2 at 0 °C to rt for 9 h gave the pivalate **10** in 80% yield. The pivalate **10** was then treated with NBS in THF–H_2O at rt for 30 min cleanly cleaved the dioxane ring to give the cyclized bicyclic product **11** in 85% yield. Toward the synthesis of important compounds for the drug delivery system (see, Scheme 1), a morpholino moiety was introduced *via* reductive amination. The lactam **11** was reduced with $NaBH_3CN$ in the presence of morpholine in EtOH to give the amino alcohol **12** in 52% yield.[11] This amino alcohol **12** is a potential intermediate for the synthesis of a series of fliposomes (DDS) (Scheme 4, eqn (2)). We next focussed on the symmetrical features of the Diels–Alder adduct **5a**.



Scheme 5 Desymmetrization reaction using the oxazaborolidine catalyst **14**.

Table 4 Desymmetrization catalyzed by the oxazaborolidine **14**

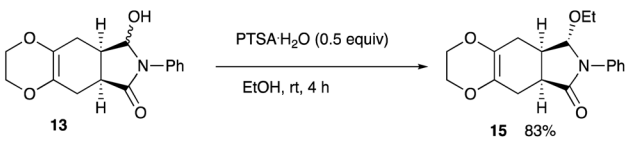


Entry	R	$BH_3 \cdot THF$ (equiv.)	Solvent	Yield[a] (%)	ee[b] (%)
1	H[c]	2.0	THF	58	98
2	H	2.0	THF	51	89
3	OMe	2.0	THF	61	98
4	OMe[d]	2.0	THF	11	77
5	OMe[e]	2.0	THF	55	93
6	OMe	1.0	THF	11	80
7	OMe	2.5	THF	62	91
8	OEt	2.5	THF	37	81
9	OMe	3.0	THF	45	99
10	OMe	2.0	$PhCH_3$	32	99
11	OMe	2.0	CH_2Cl_2	51	99
12	OMe	2.0	Et_2O	55	97
13	OMe	2.0	Dioxane	52	89
14	OMe	2.0	DME	55	99

[a] Isolated yield. [b] Determined by HPLC using a chiral stationary column (Daicel IB) after transformation into the ethoxy derivative **15** (Scheme 6). [c] Oxazaborolidine (50 mol%) was used. [d] Reaction was carried out at 0 °C. [e] Reaction was carried out for 0.5 h.

Desymmetrization[12] reaction of the Diels–Alder adducts **5a** was examined to obtain chiral molecules. Several years ago, we reported the synthesis of deoxybiotine using the reductive desymmetrization reaction of imides as a crucial step (Scheme 5, eqn (1)).[13] The same procedure was applied to the present Diels–Alder adducts (Scheme 5, eqn (2)), and Table 4 summarizes the results.

As shown in Table 4, the oxazaborolidine **14** (R = H, 50 mol%) used for the synthesis of (+)-deoxybiotine worked well to give the hydroxy lactone **13** with a high ee of 98% (entry 1)



Scheme 6 Transformation of the hydroxy lactam **13** into the ethoxy lactam **15**.

which was determined after the transformation into the ethoxy derivative **15** (Scheme 6).[14] However, decreasing the amount of the catalyst to 20 mol% decreased the ee value to 89% (entry 2). Introducing an alkoxy group onto the boron atom sometimes improves the discrimination ability. Actually, the use of the B-methoxy derivative **14** (R = OMe, 20 mol%) recorded an excellent ee of 98% (entry 3). Lowering the reaction temperature did not improve the result (entry 4). A decreased reaction time decreased both the yield and the ee (entry 5). The amount of the reducing reagent $BH_3 \cdot THF$ was next examined. As you can see, the best result was obtained when the reaction was carried out with 2 equivalents of $BH_3 \cdot THF$ (entries 3, 6, 7, and 9). The use of the B-ethoxy derivative **14** (R = OEt, 20 mol%) did not afford a satisfactory result (entry 8). Regarding the solvents, CH_2Cl_2, Et_2O, and DME may be used besides THF (entries 11, 12, and 14). Thus, the Diels–Alder adducts obtained from the present reaction served as good substrates for further functional group transformations.

3 Conclusions

In conclusion, 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3** readily prepared from biacetyl in good yield works as a convenient precursor to 2,3-dimethylene-1,4-dioxane **2** which can construct functionalized cyclohexene derivatives *via* a [4+2] cycloaddition reaction with dienophiles. The Diels–Alder adducts obtained by the present procedure are transformed into potentially useful intermediates for biologically important materials. As mentioned in the total synthesis of (+)-biotine and other examples,[12,13] the desymmetrization of the Diels–Alder adducts also serves as a straightforward method for the preparation of multi-functionalized chiral compounds in a single operation.

4 Experimental

4.1 General aspects

Reactions under microwave irradiation were carried out using a Biotage Initiator. *Analytical techniques*: melting points (mp) were determined using a YAMATO MP-21 instrument and are uncorrected. (Solid compounds were not recrystallized.) Infrared spectra were determined on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a JEOL ECX-400P, or a JEOL A-500 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL MS-700D spectrometer. High-performance liquid chromatography (HPLC) was carried out on a Hitachi L-4200 detector and a Hitachi L-6200 pump using a chiral stationary column (Daicel IB). *Materials*: toluene ($PhCH_3$), dichloroethane (DCE), dichloromethane (CH_2Cl_2), and *n*hexane were dried over CaH_2, distilled, and stored over molecular sieves 4 Å. Propionitrile (EtCN) was distilled from phosphorus pentaoxide and then from calcium hydride, and stored over Molecular Sieves 4A. 1,2-Dimethoxyethane (DME) and 1,4-dioxane were distilled from calcium hydride and then cupper(I) chloride, and stored over sodium. Methanol was distilled from Mg and stored over molecular sieves 3 Å. Ethanol was distilled from EtONa and stored over molecular sieves 4 Å. Isopropyl alcohol was distilled from iPrONa and stored over molecular sieves 4 Å. Triethylamine was distilled from CaH_2. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by the Glass Contour Organic Solvent Purification System of Nikko Hansen & Co., Ltd. Purification of products was performed by column chromatography on silica gel (Kanto Silica Gel 60N) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254 or Wako Gel B-5F). The staring materials **6a–d** were prepared as reported.[15]

4.2 Synthesis of 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane 3

To a solution of ethylene glycol (7.88 g, 127 mmol) in MeOH (63 mL) was added 2,3-butanedione (10.0 g, 116 mmol), trimethyl orthoformate (29.6 g, 279 mmol), and camphorsulfonic acid (2.93 g, 12.6 mmol) at room temperature under an argon atmosphere. The mixture was stirred at reflux for 24 h. Triethylamine (1.9 mL) was added to the reaction mixture to quench the reaction. The mixture was diluted with Et_2O and washed with water, sat. aqueous $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and filtered. The solvents were evaporated *in vacuo* and then the residue was purified by chromatography on silica gel (*n*Hex : ethyl acetate = 1 : 1, as an eluent) to give 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3** (19.4 g, 95%).

Yield 95% (19.4 g); a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (dd, J = 12.2, 19.5 Hz, 2H), 3.43 (dd, J = 12.2, 19.5 Hz, 2H), 3.31 (s, 6H), 1.29 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.5, 58.9, 48.1, 17.8; IR (neat) 2954, 2831, 1449, 1373, 1308, 1264, 1269, 1141, 1084, 1037, 941, 918, 871, 829 cm^{-1}; HRMS (EI) calcd for $C_8H_{16}O_4$ $(M)^+$ 176.1049, found 176.1050.

4.3 Synthesis of (5*aR**,8*aS**)-7-phenyl-2,3,5,5*a*,8*a*,9-hexahydro-6*H*-[1,4]dioxino[2,3-*f*]isoindole-6,8(7*H*)-dione 5*a* (general procedure for the [4+2] cycloaddition)

To a microwave vial were added *N*-phenylmaleimide (17.3 mg, 0.1 mmol), 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **3** (52.9 mg, 0.3 mmol), *p*-toluenesulfonic acid·H_2O (1.9 mg, 0.01 mmol), and toluene (1 mL). The vial was sealed with a cap, placed in the microwave cavity, and heated under the following conditions. Absorption level: low, temperature: 200 °C, vial type: 0.5–2.0 mL, pre-stirring: 30 s, reaction time: 1 h, initial power: 0, dynamic deflector optimization: off. After the reaction, a solution of sat. aqueous $NaHCO_3$ was added to the mixture, which was extracted with EtOAc (10 mL × 3). The combined extracts were washed with sat. aqueous NaCl and dried over Na_2SO_4. After filtration and concentration, the mixture was purified by silica gel column chromatography (*n*hexane : ethyl acetate = 2 : 1) to give (5*aR**,8*aS**)-7-phenyl-2,3,5,5*a*,8*a*,9-hexahydro-6*H*-[1,4]dioxino[2,3-*f*]isoindole-6,8(7*H*)-dione **5a**.

Yield 89% (25.3 mg); orange solid; mp = 120–124 °C; R_f = 0.40 (*n*hexane : ethyl acetate = 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.57–2.71 (m, 4H), 3.23–3.30 (m, 2H), 3.99–4.09 (m, 4H), 7.26–7.29 (m, 2H), 7.36–7.41 (m, 1H), 7.44–7.49 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.8, 39.5, 64.9, 126.2, 127.7, 128.5, 129.1, 131.9, 178.3; IR (neat): 2926, 1711, 1598, 1500, 1386, 1229, 1195, 1039, 917, 732, 693 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{15}NO_4$ $(M)^+$ 285.1001, found 285.1001.

4.4 (5*aR**,8*aS**)-7-benzyl-2,3,5,5*a*,8*a*,9-hexahydro-6*H*-[1,4]dioxino[2,3-*f*]isoindole-6,8(7*H*)-dione 5b

Yield 76% (22.8 mg); orange oil; R_f = 0.50 (*n*hexane : ethyl acetate = 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47–2.59 (m, 4H), 3.07–3.12 (m, 2H), 3.75–3.80 (m, 2H), 3.91–3.97 (m, 2H), 4.66 (s, 2H), 7.22–7.35 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.9, 39.6, 42.6, 64.8, 127.6, 127.8, 128.4, 128.6, 135.9, 179.0; IR (neat): 2928, 2872, 1700, 1431, 1399, 1346, 1277, 1227, 1173, 1033, 951, 734, 702 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{10}NO_4$ (M − C_7H_7)$^+$ 208.0610, found 208.0610.

4.5 (5*aR**,8*aS**)-7-Butyl-2,3,5,5*a*,8*a*,9-hexahydro-6*H*-[1,4]dioxino[2,3-*f*]isoindole-6,8(7*H*)-dione 5c

Yield 44% (11.6 mg); orange oil; R_f = 0.50 (*n*hexane : ethyl acetate = 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H), 1.25–1.32 (m, 2H), 1.51–1.57 (m, 2H), 2.50–2.59 (m, 4H), 3.07–3.08 (m, 2H), 3.52 (t, J = 7.0 Hz, 2H), 3.95–4.05 (m, 4H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.6, 19.9, 25.8, 25.9, 29.7, 38.8, 64.9, 127.7, 179.4; IR (neat): 2933, 2873, 1775, 1700, 1439, 1402, 1356, 1227, 1197, 1113, 1042, 946, 890 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{10}NO_4$ (M − C_4H_9)$^+$ 208.0610, found 208.0611.

4.6 Diethyl 2,3,5,8-tetrahydrobenzo[*b*][1,4]dioxine-6,7-dicarboxylate 5e

Yield 58% (16.4 mg); yellow oil; R_f = 0.60 (*n*hexane : ethyl acetate = 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, J = 7.1 Hz, 6H), 3.13 (s, 4H), 4.10 (s, 4H), 4.23 (q, J = 7.2 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.0, 29.9, 61.3, 65.9, 125.7, 131.7, 167.0; IR (neat): 2979, 2360, 1720, 1459, 1262, 1214, 1133, 1060, 917, 889, 763 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}O_6$ (M)$^+$ 282.1103, found 282.1101.

4.7 Ethyl 2,3,5,6,7,8-hexahydrobenzo[*b*][1,4]dioxine-6-carboxylate 5g

Yield 24% (5.0 mg); colorless oil; R_f = 0.30 (*n*hexane : ethyl acetate = 15 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.1 Hz, 3H), 1.73–1.80 (m, 1H), 1.98–2.03 (m, 1H), 2.14–2.15 (m, 2H), 2.27–2.39 (m, 1H), 2.36–2.45 (m, 1H), 4.01–4.35 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.8, 22.7, 25.6, 30.1, 38.3, 40.0, 64.6, 64.7, 128.1, 128.4, 176.0; IR (neat): 3448, 2977, 2933, 2873, 1731, 1456, 1381, 1348, 1313, 1277, 1131, 1042, 891, 876 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{16}O_4^+$ 212.1049, found 212.1055.

4.8 4-(2,3,5,6,7,8-Hexahydrobenzo[*b*][1,4]dioxin-6-yl) pyridine 5i

Yield 17% (3.6 mg); dark orange oil; R_f = 0.20 (*n*hexane : ethyl acetate = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74–1.97 (m, 2H), 2.13–2.37 (m, 4H), 2.88–2.93 (m, 1H), 4.04–4.13 (m, 4H), 7.16–7.17 (m, 2H), 8.52–8.53 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.7, 29.0, 32.7, 39.5, 64.6, 64.7, 122.3, 128.9, 129.9, 149.9, 154.2, 162.1; IR (neat): 2921, 2871, 1718, 1598, 1415, 1201, 1125, 1002, 908, 870 cm^{-1}; HRMS (EI) calcd for $C_8H_{11}O_2$ (M − C_5H_4N)$^+$ 139.0759, found 139.0761.

4.9 2-(2,3,5,6,7,8-Hexahydrobenzo[*b*][1,4]dioxin-6-yl) pyridine 5j

Yield 25% (5.5 mg); dark orange oil; R_f = 0.20 (*n*hexane : ethyl acetate = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85–2.51 (m, 6H), 3.04–3.10 (m, 1H), 3.98–4.21 (m, 4H), 7.12–7.14 (m, 1H), 7.19–7.21 (m, 1H), 7.61–7.64 (m, 1H), 8.55–8.56 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 26.0, 28.7, 32.0, 42.4, 64.6, 64.7, 121.2, 121.4, 129.3, 129.8, 136.4, 149.2, 164.2; IR (neat): 2923, 2364, 1712, 1590, 1472, 1434, 1275, 1200, 1126, 1028, 885, 868 cm^{-1}; HRMS (EI) calcd for $C_8H_{11}O_2$ (M − C_5H_4N)$^+$ 139.0759, found 139.0761.

4.10 (3*aR**,11*aS**)-2-Phenyl-3*a*,4,11,11*a*-tetrahydro-1*H*-benzo[5,6][1,4]dioxino[2,3-*f*]isoindole-1,3(2*H*)-dione 7a

Yield 20% (6.5 mg); orange solid; mp = 172–177 °C; R_f = 0.20 (*n*hexane : ethyl acetate = 5 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63–2.72 (m, 4H), 3.33–3.35 (m, 2H), 6.64–6.67 (m, 2H), 6.80–6.86 (m, 2H), 7.30–7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 38.7, 116.1, 124.0, 126.3, 127.6, 128.7, 129.2, 131.8, 142.6, 177.7; IR (neat): 2914, 1705, 1598, 1493, 1384, 1262, 1194, 1169, 925, 850, 747 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{10}NO_4$ (M − C_6H_5)$^+$ 256.0610, found 256.0597.

4.11 Dimethyl (2*S*,3*S**,5*aR*,8*aS**)-6,8-dioxo-7-phenyl-2,3,5*a*,6,7,8,8*a*,9-octahydro-5*H*-[1,4]dioxino[2,3-*f*]isoindole-2,3-dicarboxylate 7b

Yield 34% (13.7 mg); orange oil; R_f = 0.10 (*n*hexane : ethyl acetate = 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65–2.81 (m, 4H), 3.26–3.32 (m, 2H), 3.66 (s, 3H), 3.81 (s, 3H), 5.01 (s, 1H), 5.03 (s, 1H), 7.36–7.38 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.2, 25.7, 52.8, 52.9, 72.7, 72.8, 126.5, 127.5, 128.5, 128.9, 132.1, 167.4, 167.9, 177.9, 178.1; IR (neat): 2957, 2856, 1761, 1712, 1498, 1435, 1388, 1217, 1083, 911, 731, 695 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{19}NO_8$ (M)$^+$ 401.1111, found 401.1117.

4.12 Dimethyl (2*R**,3*S**,5*aR**,8*aS**)-6,8-dioxo-7-phenyl-2,3,5*a*,6,7,8,8*a*,9-octahydro-5*H*-[1,4]dioxino[2,3-*f*]isoindole-2,3-dicarboxylate 7c

Yield 50% (19.9 mg); orange oil; R_f = 0.10 (*n*hexane : ethyl acetate = 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71–2.88 (m, 4H), 3.31–3.33 (m, 2H), 3.80 (s, 6H), 4.83 (s, 2H), 7.26–7.48 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.2, 39.1, 52.8, 73.2, 125.9, 126.1, 126.7, 127.8, 128.6, 129.1, 166.7, 171.0, 172.2; IR (neat): 2956, 1761, 1710, 1500, 1440, 1388, 1187, 1048, 913, 726 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{16}NO_6$ (M − $C_2H_3O_2$)$^+$ 342.0978, found 342.0988.

4.13 (3*aR**,5*aR**,9*aR**,11*aS**)-2-Phenyl-3*a*,4,5*a*,6,7,8,9,9*a*,11,11*a*-decahydro-1*H*-benzo[5,6][1,4]dioxino[2,3-*f*]isoindole-1,3(2*H*)-dione 7d

Yield 71% (24.0 mg); orange oil; R_f = 0.20 (*n*hexane : ethyl acetate = 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30–1.36 (m, 4H), 1.76 (brs, 2H), 2.08 (brs, 2H), 2.54–2.76 (m, 4H), 3.23–3.30 (m, 2H), 3.41–3.53 (m, 2H), 7.26–7.48 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 23.8, 23.9, 25.4, 26.1, 29.9, 39.4, 39.6, 60.2, 77.0, 126.2,

127.3, 128.5, 129.1, 132.0, 178.3, 178.4; IR (neat): 2939, 2863, 1704, 1500, 1392, 1228, 1196, 1037, 925, 769 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{21}NO_4$ $(M)^+$ 339.1471, found 339.1488.

4.14 Synthesis of (6*R**,7*S**)-7-(hydroxymethyl)-*N*-phenyl-2,3,5,6,7,8-hexahydrobenzo[*b*][1,4]dioxine-6-carboxamide 8

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed $NaBH_4$ (25.7 mg, 0.68 mmol). To it was added a solution of (5*aR**,8*aS**)-7-phenyl-2,3,5,5*a*,8*a*,9-hexahydro-6*H*-[1,4]dioxino[2,3-*f*]isoindole-6,8(7*H*)-dione **5a** (28.5 mg 0.10 mmol) in iso-PrOH (1.8 mL)–H_2O (0.3 mL) at rt, and the mixture was stirred at rt for 3 h. The reaction was quenched with sat. aqueous $NaHCO_3$, and the whole mixture was extracted with CH_2Cl_2 (30 mL × 3). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (dichloromethane : isopropyl alcohol = 20 : 1) to give the title compound.

Yield 71% (20.5 mg); yellow solid; mp = 258–262 °C; R_f = 0.30 (*n*hexane : ethyl acetate = 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05–2.33 (m, 5H), 2.82–2.86 (m, 1H), 3.27–3.44 (m, 2H), 3.92–4.04 (m, 4H), 4.53 (t, J = 5.2 Hz, 1H), 7.00–7.03 (m, 1H), 7.27–7.30 (m, 2H), 7.58–7.59 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.3, 27.2, 38.2, 41.7, 59.4, 64.0, 119.1, 123.0, 127.5, 127.7, 128.6, 139.3, 171.6; IR (neat): 3308, 2963, 2933, 1718, 1652, 1598, 1525, 1442, 1331, 1204, 1047, 983, 856 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}NO_4$ $(M)^+$ 289.1314, found 289. 1312.

4.15 Synthesis of (5*aR**,8*aS**)-2,3,5,8,8*a*,9-hexahydro-[1,4]dioxino[2,3-*f*]isobenzofuran-6(5*aH*)-one 9

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed (6*R**,7*S**)-7-(hydroxymethyl)-*N*-phenyl-2,3,5,6,7,8-hexahydrobenzo[*b*][1,4]dioxine-6-carboxamide **8** (42.2 mg, 0.15 mmol). To it was added triethylamine (2.4 mL) and acetic acid (1.4 mL) at rt, and the mixture was stirred at 80 °C for 48 h. The reaction was cooled to 0 °C and quenched with sat. aqueous $NaHCO_3$. The whole mixture was extracted with CH_2Cl_2 (30 mL × 3). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (*n*hexane : ethyl acetate = 1 : 1) to give the title compound.

Yield 72% (20.6 mg); colorless oil; R_f = 0.70 (*n*hexane : ethyl acetate = 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09–2.83 (m, 6H), 4.00–4.09 (m, 5H), 4.26–4.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 26.8, 33.1, 38.1, 64.6, 72.0, 127.1, 127.6, 177.8; IR (neat): 2975, 2915, 2878, 1773, 1716, 1451, 1375, 1276, 1208, 1043, 971, 890 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{12}O_4$ $(M)^+$ 196.0736, found 196. 0743.

4.16 Synthesis of ((6*S**,7*R**)-7-(phenylcarbamoyl)-2,3,5,6,7,8-hexahydrobenzo[*b*][1,4]dioxin-6-yl)methyl pivalate 10

In a 100 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed (6*R**,7*S**)-7-(hydroxymethyl)-*N*-phenyl-2,3,5,6,7,8-hexahydrobenzo[*b*][1,4]dioxine-6-carboxamide **8** (867.9 mg, 3.0 mmol). To it was added triethylamine (0.50 mL, 3.6 mmol), DMAP (73.3 mg, 0.60 mmol), and dichloromethane (20 mL) at rt. The mixture was cooled to 0 °C and to it was slowly added pivaloyl chloride (0.40 mL, 3.3 mmol). The mixture was allowed to stand at rt for 9 h. The reaction was quenched with HCl (2 M, 20 mL). The whole mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (*n*hexane : ethyl acetate = 2 : 1) to give the title compound.

Yield 80% (901.3 mg); yellow solid; mp = 154–162 °C; R_f = 0.40 (*n*hexane : ethyl acetate = 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 1H), 2.17–2.23 (m, 1H), 2.31–2.36 (m, 1H), 2.41–2.54 (m, 3H), 2.84–2.89 (m, 1H), 4.08–4.13 (m, 5H), 4.26–4.31 (m, 1H), 7.00–7.13 (m, 1H), 7.30–7.34 (m, 2H), 7.50–7.57 (m, 2H), 7.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 27.1, 27.6, 34.9, 38.8, 42.8, 64.6, 64.7, 64.7, 120.0, 124.3, 127.9, 128.4, 128.9, 137.8, 137.8, 170.2, 178.7; IR (neat): 3319, 2972, 2928, 2873, 1720, 1664, 1600, 1540, 1442, 1283, 1199, 1160, 1041, 982, 887 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{27}NO_5$ $(M)^+$ 373.1889, found 373.1876.

4.17 Synthesis of [(1*R**,2*S**,5*R**)-5-hydroxy-4,7-dioxo-6-phenyl-6-azabicyclo[3.2.1]octan-2-yl]methyl pivalate 11

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed [(6*S**,7*R**)-7-(phenylcarbamoyl)-2,3,5,6,7,8-hexahydrobenzo[*b*][1,4]dioxin-6-yl]methyl pivalate (75.0 mg, 0.20 mmol). To it was added THF (8.0 mL), NBS (35.6 mg, 0.20 mmol), and H_2O (2.0 mL) successively at rt. The mixture was stirred at rt for 30 min. The reaction was quenched with sat. aqueous $NaHSO_3$. The whole mixture was extracted with Et_2O (10 mL × 3). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 1 : 1) to give the title compound.

Yield 85% (58.6 mg); yellow powder; mp = 62–64 °C; R_f = 0.70 (*n*hexane : ethyl acetate = 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (s, 9H), 2.04–2.12 (m, 1H), 2.48–2.55 (m, 1H), 2.59–2.68 (m, 1H), 2.77–2.81 (m, 1H), 2.88–2.94 (m, 1H), 3.03–3.04 (m, 1H), 4.09–4.17 (m, 1H), 4.25–4.29 (m, 1H), 4.41 (s, 1H), 7.08–7.14 (m, 2H), 7.24–7.28 (m, 1H) 7.35–7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.1, 37.1, 38.6, 38.8, 40.7, 42.5, 64.8, 90.5, 124.9, 127.2, 127.2, 129.1, 129.1, 133.5, 171.3, 178.0, 204.8; IR (neat): 3404, 2973, 2908, 2875, 1719, 1598, 1542, 1501, 1367, 1285, 1159, 1035 cm^{-1};. HRMS (EI) calcd for $C_{19}H_{23}O_5$ $(M)^+$ 345.1576, found 345.1572.

4.18 Synthesis of [(1*S**,2*R**,4*R**,5*R**)-4-hydroxy-5-morpholino-2-(phenylcarbamoyl)cyclohexyl]methyl pivalate 12

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed [(1*R**,2*S**,5*R**)-5-hydroxy-4,7-dioxo-6-phenyl-6-azabicyclo[3.2.1]octan-2-yl]methyl pivalate **11** (34.5 mg, 0.10

mmol). To it was added EtOH (4.0 mL), morpholine (8.7 μL, 0.10 mmol), and $NaBH_3CN$ (7.5 mg, 0.12 mmol) successively at rt. To the mixture was added AcOH to reach pH 6.0, and it was stirred at rt for 24 h. The reaction was quenched with sat. aqueous $NaHCO_3$. The whole mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (dichloromethane : methanol = 10 : 1) to give the title compound.

Yield 52% (21.7 mg); colorless oil; R_f = 0.30 (dichloromethane : methanol = 10 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09, (s, 9H)1.53–1.57 (m, 1H), 1.74–1.84 (m, 1H), 2.01–2.04 (m, 1H), 2.22–2.25 (m, 1H), 2.31–2.35 (m, 1H), 2.46–2.47 (m, 1H) 2.52–2.54 (m, 1H), 2.57–2.74 (m, 4H), 3.71–3.74 (m, 4H), 3.75–3.76 (m, 1H) 4.05 (s, 1H) 4.29–4.34 (m, 1H), 4.43–4.48 (m, 1H), 7.07–7.10 (m, 1H), 7.28–7.32 (m, 2H), 7.57–7.59 (m, 2H), 7.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 27.0, 31.7, 34.1, 38.6, 45.6, 50.2, 64.5, 64.5, 67.2, 119.8, 124.2, 128.9, 138.0, 171.0, 179.1; IR (neat): 3310, 2961, 1722, 1600, 1544, 1500, 1442, 1286, 1161, 1119, 755, 517, 504 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{34}N_2O_5$ $(M)^+$ 418.2468, found 418.2477.

4.19 Synthesis of (5*aS*,8*aR*)-8-hydroxy-7-phenyl-2,3,5,5*a*,7,8,8*a*,9-octahydro-6*H*-[1,4]dioxino[2,3-*f*]isoindol-6-one 13

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed (2*S*,3*R*)-2-amino-3-(*tert*-butyldimethylsilyloxy)-1,1-diphenylbutan-1-ol[16] (7.4 mg, 0.02 mmol). To it was added THF (1.0 mL) and trimethyl borate (1.0 M, 0.02 mL, 0.02 mmol), and the mixture was stirred at rt for 1 h. To the mixture were slowly added solutions of (5*aR**,8*aS**)-7-phenyl-2,3,5,5*a*,8*a*,9-hexahydro-6*H*-[1,4]dioxino[2,3-*f*]isoindole-6,8(7*H*)-dione **5a** (28.5 mg 0.1 mmol) in THF (2 mL) and BH_3·THF (1.0 M, 0.20 mL, 0.20 mmol). After stirring at rt for 1 h, the reaction was quenched with sat. aqueous $NaHCO_3$. The whole mixture was extracted with AcOEt (10 mL × 3). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 2 : 1) to give the title compound.

Yield 61% (17.5 mg); colorless oil; R_f = 0.10 (*n*hexane : ethyl acetate = 1 : 1); $[\alpha]_D^{14}$ −42.3 (*c* 0.012, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30–2.65 (m, 4H), 2.76–2.90 (m, 3H), 4.02–4.14 (m, 4H), 5.55–5.57 (m, 1H), 7.20–7.54 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 26.1, 37.9, 38.6, 64.6, 64.7, 88.5, 122.5, 126.0, 126.6, 128.3, 129.2, 137.7, 174.8; IR (neat): 3425, 2920, 1682, 1497, 1404, 1278, 1207, 1128, 1039, 890, 758 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{16}NO_3^+$ $(M - HO)^+$ 270.1130, found 270.1142.

4.20 Determination of the enantiomeric purity of the reduction product *via* the ethoxy derivative 15

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed (5*aS*,8*aR*)-8-hydroxy-7-phenyl-2,3,5,5*a*,7,8,8*a*,9-octahydro-6*H*-[1,4]dioxino[2,3-*f*]isoindol-6-one **13** (8.1 mg, 0.028 mmol). To it was added PTSA·H_2O (2.7 mg, 0.014 mmol) and EtOH (4.0 mL), and the mixture was stirred at rt for 4 h. The reaction was quenched with sat. aqueous $NaHCO_3$. The whole mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 1 : 1) to give (5*aS*,8*S*,8*aR*)-8-ethoxy-7-phenyl-2,3,5,5*a*,7,8,8*a*,9-octahydro-6*H*-[1,4]dioxino [2,3-*f*]isoindol-6-one **15**.

Yield 83% (7.4 mg); colorless oil; R_f = 0.50 (*n*hexane : ethyl acetate = 1 : 1); $[\alpha]_D^{25}$ −46.8 (*c* 0.089, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (dd, *J* = 6.7, 7.3 Hz, 3H), 1.95–2.05 (m, 1H), 2.28–2.45 (m, 2H), 2.65–2.76 (m, 2H), 3.19–3.22 (m, 1H), 3.49–3.53 (m, 2H), 3.95–4.12 (m, 5H), 4.88 (s, 1H), 7.16–7.19 (m, 1H), 7.33–7.36 (m, 2H), 7.47–7.49 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 15.3, 22.8, 26.2, 35.9, 38.0, 63.9, 64.6, 94.6, 122.6, 125.7, 126.5, 128.5, 128.9, 138.7, 174.8; IR (neat): 2974, 2911, 1714, 1598, 1497, 1395, 1280, 1200, 1071, 920, 890, 859 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{16}NO_4$ $(M - C_2H_5)^+$ 286.1079, found 286.1071.

The enantiomeric purity of the above ethoxide **15** was determined by HPLC using a chiral stationary column (Daicel IB). Flow rate 1.0 mL min^{-1}, *n*hexane : iPrOH = 9 : 1, detection at 254 nm, set temperature 35 °C.

Conflicts of interest

There are no conflicts to declare.

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