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ARTICLE

Lewis acid-catalyzed enantiospecific [3+2] annulations of γ-butyrolactone fused cyclopropanes with aromatic aldehydes: synthesis of chiral furanolignans

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An enantiospecific [3+2] annulation of γ-butyrolactone fused cyclopropanes with aromatic aldehydes was realized under Lewis acid catalysis. This method provides a facile access to a series of chiral furanolignan derivatives bearing multiple contiguous stereogenic centers in good-to-excellent yields, exclusive diastereoselectivities and excellent enantiopurities under mild reaction conditions. Elaboration work on the product of this reaction delivers stereoisomeric analogues of (+)-virgatusin and suggests a structural revision might be necessary for a previously reported isolated natural product.

Introduction

The furanolignans featuring a densely substituted chiral tetrahydrofuran skeleton belong to a family of natural products possessing a vast structural diversity with a range of biological activities such as antioxidant, antimicrobial, anti-inflammatory and anticancer activities (Figure 1).[1] The presence of multiple contiguous stereocenters is arguably one of the most challenging parts in constructing such a type of structures. While numerous synthetic methods have been developed for their construction,[2–4] enantioselective ones remain somewhat limited.[3–4] The use of a chiral auxiliary group such as the Evans' chiral oxazolidiones has been a common strategy in installing the requisite chirality in these molecules, which usually requires multi-step manipulations.[4]

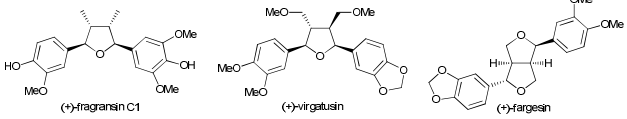

Figure 1. Representative natural chiral furanolignans.

On the other hand, the annulations of donor-acceptor (D–A) cyclopropanes with various dipolarophiles have evolved into a powerful strategy for fast construction of a range of functionalized cyclic structures.[5] In this field, very impressive advances have been achieved in the catalytic asymmetric annulations of racemic 2-monosubstituted 1,1-diester cyclopropanes *via* either kinetic resolution or dynamic kinetic asymmetric transformations (DyKATs), providing facile access to a variety of useful chiral cyclic compounds.[6] Racemic polysubstituted D–A cyclopropanes like 2,3-disubstituted 1,1-diester cyclopropanes, however, have rarely succumbed to direct catalytic asymmetric transformations, despite their great potential in the construction of structures bearing multiple contiguous stereocenters.

In this regard, the development of catalytic enantiospecific transformations of readily available enantioenriched 2,3-disubstituted D–A cyclopropanes has proved to be an efficient alternative strategy,[7] as exemplified by Johnson and co-workers in an elegant total synthesis of (+)-polyanthellin A.[7a] The same group have also first demonstrated the ingenious employment of a chiral 2,3-disubsituted-1,1-diester cyclopropane **10d**, which was synthesized following Wang's organocatalytic asymmetric Michael addition-intramolecular alkylation between an enal and bromomalonate,[8] in a five-step synthesis of (+)-virgatusin (Scheme 1).[7b] Notably, Zhang and co-workers have first disclosed a single example on the enantiospecific [3+2] annulation between benzaldehyde and a chiral γ-butyrolactone fused cyclopropane with a fairly good yield; the chiral fused cyclopropane was prepared by a Co(II)-catalyzed asymmetric intramolecular cyclopropanation of alkenes developed by the same group.[9] Our group have very recently revealed that γ-butyrolactone fused cyclopropanes could have higher reactivity in Lewis acid-promoted annulations with heterocumulenes, as compared to their parent 2,3-disubsituted-1,1-diester cyclopropanes.[10a] Inspired by these works, we then presumed that the use of chiral γ-butyrolactone fused cyclopropanes **1**, which could be prepared in two steps from the chiral cyclopropanes **10**, in the Lewis acid-catalyzed [3+2] annulations would provide access to a range of biologically interesting chiral furanolignans with

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†Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data for new compounds, x-ray data for **3ak** and **4dn** (CCDC 1824774 and 1824775), copies of ^{1}H, ^{13}C NMR spectra and HPLC traces (PDF). See DOI: 10.1039/x0xx00000x

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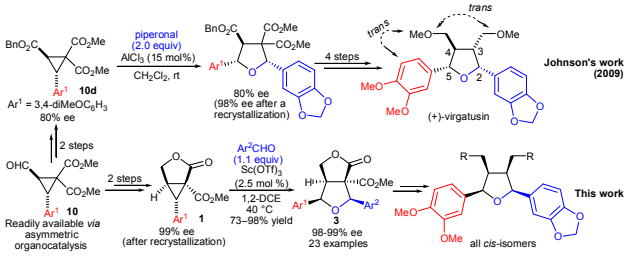
stereochemical features complementary to that obtained in Johnson's reaction system (Scheme 1). Herein, we report the details of this study.

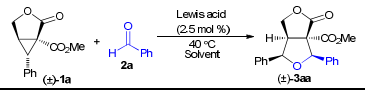


Scheme 1. Enantiospecific [3+2] annulations of 2,3-disubstituted D–A cyclopropanes with aromatic aldehydes

Results and discussion

Using the [3+2] annulation of racemic cyclopropane **1a** and benzaldehyde **2a** as model reaction, we first optimized several reaction parameters such as Lewis acid catalyst, solvent and reaction temperature (Table 1). While $Sc(OTf)_3$ proved to be the most efficient catalyst for the reaction in 1,2-dicholoroetheane (1,2-DCE) at 40 °C, the triflate salts of other metals including iron(III), tin(II) and aluminum(III) also provided excellent yields, albeit with longer reaction times (Table 1, entries 1–4). Surprisingly, the use of $Yb(OTf)_3$, $Mg(OTf)_2$ and $Zn(OTf)_2$ gave no formation of the desired product with most of the starting material cyclopropane **1a** being recovered (entries 6–8).

Table 1. Optimization of reaction conditions[a]

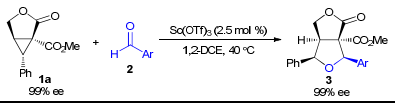


Entry	Lewis acid	Solvent	Time (h)	Yield (%)[b]
1	$Sc(OTf)_3$	1,2-DCE	4	97
2	$Fe(OTf)_3$	1,2-DCE	8	96
3	$Sn(OTf)_2$	1,2-DCE	22	91
4	$Al(OTf)_3$	1,2-DCE	30	93
5	$Cu(OTf)_2$	1,2-DCE	40	22
6	$Yb(OTf)_3$	1,2-DCE	40	-
7	$Mg(OTf)_2$	1,2-DCE	40	-
8	$Zn(OTf)_2$	1,2-DCE	40	-
9	$Sc(OTf)_3$	CH_2Cl_2	5	95
10	$Sc(OTf)_3$	$CHCl_3$	40	91
11	$Sc(OTf)_3$	CCl_4	40	89
12	$Sc(OTf)_3$	toluene	40	91
13[c]	$Sc(OTf)_3$	1,2-DCE	14	97
14[d]	$Sc(OTf)_3$	1,2-DCE	20	90
15[e]	$Sc(OTf)_3$	1,2-DCE	2.5	90
16[f]	$Sc(OTf)_3$	1,2-DCE	2.5	97

[a]Unless note otherwise, reactions were performed with (±)-**1a** (0.5 mmol) and **2a** (0.55 mmol) in 5.0 mL of solvent. [b]Isolated yield. [c]1 mol % of $Sc(OTf)_3$ was used. [d]Run at 20 °C. [e]Run at 60 °C. [f]Run in 2.0 mL of solvent.

The use of several other solvents led to inferior yields (entries 9–12). Reducing the catalyst loading from 2.5 mol % to 1 mol % led to a significantly prolonged reaction time while maintaining the excellent yield (entry 13). Performing the reaction at either a lower or higher reaction temperature is detrimental to the reaction yield (entries 14 and 15). The efficiency of the reaction could be further improved with an appropriately reduced amount of solvent (entry 16), which sets up the optimal reaction conditions as follows: 2.5 mol % of $Sc(OTf)_3$ as catalyst in 2.0 mL of 1,2-DCE at 40 °C. Notably, in all the cases examined above, the desired product **3aa** was obtained invariably as a single diastereomer. Moreover, the requirement of only a barely excess of benzaldehyde **2a** (1.1 eq) for obtaining an excellent yield highlights the high reactivity of this type of fused D–A cyclopropanes.

Table 2. Scope of aldehydes **2**[a]



Entry	**2** (Ar)	*t* (h)	**3** (yield %)[b]
1	**2a** (Ph)	2.5	**3aa** (97)
2	**2b** (4-MeC_6H_4)	4.0	**3ab** (98)
3	**2c** (4-$MeOC_6H_4$)	1.5	**3ac** (97)
4	**2d** (3-$MeOC_6H_4$)	2.0	**3ad** (98)
5	**2e** (2-$MeOC_6H_4$)	1.5	**3ae** (97)
6	**2f** (3,4-di$MeOC_6H_3$)	0.5	**3af** (95)
7	**2g** (4-FC_6H_4)	10.0	**3ag** (96)
8	**2h** (4-ClC_6H_4)	28.0	**3ah** (90)
9	**2i** (3-ClC_6H_4)	24.0	**3ai** (90)
10	**2j** (2-ClC_6H_4)	24.0	**3aj** (90)
11	**2k** (4-BrC_6H_4)	30.0	**3ak** (88, X-ray)
12	**2l** (4-$F_3CC_6H_4$)	10.0	**3al** (85)
13	**2m** (4-$O_2NC_6H_4$)	24.0	NR

[a]Reaction scale: 0.5 mmol, $[\mathbf{1a}]_0$ = 0.25 M. [b]Isolated yield.

Having established the optimum reaction conditions for the annulation with the racemic *γ*-butyrolactone fused cyclopropane **1a**, (+)-**1a** of 99% enantiomer excess (ee) was examined in the reaction (Table 2, entry 1). To our delight, the reaction proceeded efficiently to provide the enantiomerically enriched product **3aa** in excellent yield and with complete enantiospecificity (100% es). Then, a series of substituted benzaldehydes **2** were subjected to the reaction with (+)-**1a** to probe the reaction scope. In general, aldehydes bearing electron-donating groups on the benzene ring (entries 2–6) displayed appreciably higher reactivities in the reaction than those with electron-withdrawing ones (entries 7–12), which is similar to previous studies on related D–A cyclopropanes. The differentiated placement of the substituent showed no obvious influence on the reactivity of the aldehyde. However, the aldehyde **2m** bearing a strongly electron-withdrawing nitro group was inert to the reaction, with only the starting material being recovered (entry 13). It's worth mentioning that almost all the reactions examined have proceeded with 100% es to provide a series of chiral tetrahydrofurans containing four contiguous stereocenters including a quaternary carbon center in good to excellent yields and with exclusive diastereoselectivities.

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The absolute configuration of the product **3ak** was confirmed by single crystal X-ray crystallographic analysis. The absolute configurations of other products were assigned by analogy.

Subsequently, the reaction scope with respect to chiral *γ*-butyrolactone fused cyclopropanes **1** was examined (Figure 2). The presence of an electron-donating group (R) at the *para* position of the benzene ring in cyclopropanes **1** seems to be favorable in terms of reaction rate as demonstrated in the formation of the products **3ba**, **3ea** and **3fa**. Herein, the strongly electron-withdrawing substituent NO_2 is well tolerated, although a large excess of benzaldehyde, an increased catalyst loading and a prolonged reaction time were required to provide excellent yield. Placing a substituent at the *ortho* position somewhat slowed down the reaction (**3ca**), while the presence of two substituents at the 3,4-positions of the benzene ring was well tolerated (**3da**). Notably, a series of chiral tetrahydrofurans (**3bf**–**3dq**) containing multiple substituents on both benzene rings, which are widely present in biologically active furanolignans, were obtained in almost enantiopure forms as single diastereomers.

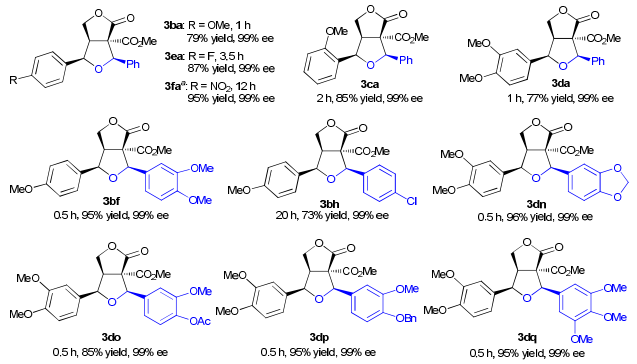
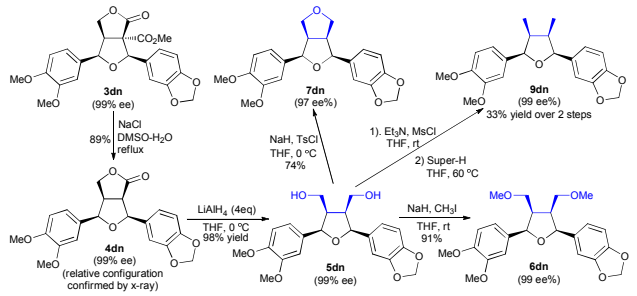


Figure 2. Scope of Cyclopropanes **1**. See Table 2 for general reaction conditions. [a]Run with 10.0 equiv of benzaldehyde **2a** in the presence of 10 mol % of $Sc(OTf)_3$.



Scheme 2. Product transformations

To illustrate the utility of the [3+2] annulation products, the transformations of **3dn** to several chiral furanolignan analogues were studied (Scheme 2). Selective Krapcho decarboxylation of the pendant methyl carboxylate group provided an 89% yield of **4dn**, which could be converted into the diol **5dn** in an almost quantitative yield after reduction with $LiAlH_4$. The relative configuration of the compound **4dn** has been confirmed by a single crystallographic analysis of its racemic sample. The diol **5dn** could be transformed to **6dn**, a stereoisomer of (+)-virgatusin, *via* a single-step treatment with NaH and CH_3I; to **7dn**, an analogue of fargesin, *via* a single-step treatment with NaH and TsCl; and to **9dn**, an analogue of fragransin C1, *via* a tandem mesylation-reduction sequence. The stereochemical purity of the starting materials could be maintained during almost all of these manipulations. Moreover, both the relative and absolute configurations of these products are highly complementary to that obtained with the corresponding non-fused chiral D–A cyclopropane in Johnson's work despite the same chirality source (all from (2*S*, 3*R*)-**10d**), highlighting the great influence of the fused lactone moiety on the reactivity of the cyclopropane. Notably, the structure of **9dn** has previously been assigned to a natural product with insect growth inhibitive activity firstly isolated from *Machilus japonica*; however, the spectroscopic data and specific rotation value reported in the literature[11a] differ significantly from those of ours, which suggests a revision of the original structure assigned to the isolated natural product may be necessary.

Conclusions

In summary, we have developed a stereoselective way to a range of chiral furanolignans bearing multiple adjacent stereogenic centers in almost optically pure forms. The high yields, simple manipulations and mild conditions render this method a good complement to previous ones in the construction of structurally diverse chiral furanolignans with biological relevance.

Experimental

General remarks

All the [3+2] annulation reactions were carried out with flame-dried Schlenk-type glassware using a Schlenk line. All reagents were purchased from commercial suppliers and purified by standard techniques unless specified otherwise. Flash column chromatography was performed using silica gel (200–400 mesh). For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded in $CDCl_3$. All chemical shifts (δ) are given in ppm relative to TMS (δ = 0 ppm) as internal standard. Data are reported as follows: chemical shift, multiplicity, coupling constants and integration. Melting points were uncorrected. High resolution mass spectral (HRMS) data were obtained with an ionization mode of ESI and a TOF analyzer.

Typical procedure for the enantiospecific [3+2] annulation

To a solution of *γ*-butyrolactone fused cyclopropanes **1** (0.5 mmol) and aromatic aldehydes **2** (0.55 mmol) in 2.0 mL of dry 1,2-dichloroethane was added $Sc(OTf)_3$ (0.0125 mmol). The reaction mixture was stirred at 40 °C and monitored by TLC. Upon completion, the reaction mixture was cooled down to room temperature followed by the addition of 10.0 mL of

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saturated sodium bicarbonate aqueous solution. Then the mixture was extracted with dichloromethane (10.0 mL × 3), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude products were purified by flash chromatography to give the pure products.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 4-oxo-1,3-diphenylhexahydrofuro [3,4-c]furan-3a-carboxylate (3aa). Purified by column chromatography (petroleum ether/ethyl acetate = 6/1) to afford a colorless oil in 97% yield (164 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (95/5 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 16.4 (major), 19.0 (minor) min). $[\alpha]^{20}_D$ = +24.7 (c = 0.59, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.53 (d, J = 7.3 Hz, 2H), 7.48–7.31 (m, 8H), 5.77 (s, 1H), 5.34 (d, J = 4.8 Hz, 1H), 4.13 (t, J = 9.2 Hz, 1H), 4.03–3.92 (m, 2H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.1, 168.9, 135.9, 135.5, 128.9, 128.8, 128.5, 128.2, 126.4, 125.6, 85.2, 81.1, 66.7, 66.3, 53.7, 51.1. HRMS (ESI-TOF) calcd for $C_{20}H_{19}O_5$ ($[M + H]^+$) 339.1232, found 339.1239.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 4-oxo-1-phenyl-3-(*p*-tolyl)hexahy drofuro[3,4-c]furan-3a-carboxylate (3ab). Purified by column chromatography (petroleum ether/ethyl acetate = 4/1) to afford a white solid in 98% yield (173 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (9/1 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 210 nm; t_R = 29.0 (major), 21.6 (minor) min). $[\alpha]^{20}_D$ = −78.9 (c = 0.59, $CHCl_3$). Mp: 160–161 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50–7.38 (m, 6H), 7.38–7.32 (m, 1H), 7.20 (d, J = 7.9 Hz, 2H), 5.73 (s, 1H), 5.32 (d, J = 4.8 Hz, 1H), 4.13 (t, J = 9.2 Hz, 1H), 4.01–3.91 (m, 2H), 3.89 (s, 3H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.3, 169.0, 138.6, 135.9, 132.5, 129.2, 128.9, 128.2, 126.4, 125.6, 85.3, 81.1, 66.7, 66.4, 53.6, 51.1, 21.3. HRMS (ESI-TOF) calcd for $C_{21}H_{21}O_5$ ($[M + H]^+$) 353.1389, found 353.1379.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 3-(4-anisyl)-4-oxo-1-phenylhexa hydrofuro[3,4-c]furan-3a-carboxylate (3ac). Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 97% yield (179 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (4/1 hexane/i-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 24.3 (major), 16.3 (minor) min). $[\alpha]^{20}_D$ = −71.3 (c = 0.50, $CHCl_3$). Mp: 156–157 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54–7.39 (m, 6H), 7.38–7.32 (m, 1H), 6.93 (d, J = 8.7 Hz, 2H), 5.71 (s, 1H), 5.31 (d, J = 4.8 Hz, 1H), 4.13 (t, J = 9.1 Hz, 1H), 4.01–3.92 (m, 2H), 3.89 (s, 3H), 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.3, 169.0, 159.9, 136.0, 128.9, 128.2, 127.8, 127.5, 125.6, 113.9, 85.2, 81.0, 66.7, 66.3, 55.2, 53.6, 51.0. HRMS (ESI-TOF) calcd for $C_{21}H_{21}O_6$ ($[M + H]^+$) 369.1338, found 369.1334.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 3-(3-anisyl)-4-oxo-1-phenylhexahy drofuro[3,4-c]furan-3a-carboxylate (3ad). Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 98% yield (181 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (95/5 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 23.2 (major), 29.6 (minor) min). $[\alpha]^{20}_D$ = +56.0 (c = 0.12, $CHCl_3$). Mp: 126–127 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46–7.39 (m, 4H), 7.38–7.29 (m, 2H), 7.12 (d, J = 7.7 Hz, 1H), 7.08 (s, 1H), 6.88 (dd, J = 8.2, 2.2 Hz, 1H), 5.74 (s, 1H), 5.32 (d, J = 4.7 Hz, 1H), 4.12 (t, J = 9.0 Hz, 1H), 4.01–3.91 (m, 2H), 3.90 (s, 3H), 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.1, 168.9, 159.5, 137.1, 135.8, 129.5, 128.9, 128.2, 125.6, 118.8, 113.6, 112.6, 85.0, 81.0, 66.4, 66.3, 55.2, 53.7, 51.2. HRMS (ESI-TOF) calcd for $C_{21}H_{21}O_6$ ($[M + H]^+$) 369.1338, found 369.1330.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 3-(2-anisyl)-4-oxo-1-phenylhexahydro furo[3,4-c]furan-3a-carboxylate (3ae). Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 97% yield (179 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AS-H column (4/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 14.4 (major), 10.9 (minor) min). $[\alpha]^{20}_D$ = −59.7 (c = 0.52, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): Mp: 139–140 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 (d, J = 7.3 Hz, 1H), 7.50–7.38 (m, 4H), 7.38–7.28 (m, 2H), 7.00 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 5.95 (s, 1H), 5.45 (d, J = 4.9 Hz, 1H), 3.99 (t, J = 9.5 Hz, 1H), 3.91 (s, 3H) , 3.86 (dd, J = 9.5, 6.8 Hz, 1H), 3.81 (s, 3H). 3.79–3.71 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.7, 169.8, 156.8, 136.0, 129.7, 128.8, 128.1, 126.0, 125.6, 124.4, 120.6, 110.3, 82.8, 81.1, 65.7, 64.1, 55.3, 53.3, 52.6. HRMS (ESI-TOF) calcd for $C_{21}H_{21}O_6$ ($[M + H]^+$) 369.1338, found 369.1331.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 3-(3,4-dimethoxyphenyl)-4-oxo-1-phenylhexahydrofuro[3,4-c]furan-3a-carboxylate (3af). Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 95% yield (189 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (4/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 17.3 (major), 20.4 (minor) min). $[\alpha]^{20}_D$ = −28.7 (c = 0.59, $CHCl_3$). Mp: 109–110 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48–7.39 (m, 4H), 7.39–7.31 (m, 1H), 7.09 (dd, J = 8.3, 1.8 Hz, 1H), 7.01 (d, J = 1.8 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 5.71 (s, 1H), 5.31 (d, J = 4.7 Hz, 1H), 4.14 (t, J = 9.1 Hz, 1H), 4.01–3.92 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.2, 169.0, 149.3, 148.9, 135.9, 128.9, 128.2, 127.9, 125.6, 118.9, 111.0, 109.9, 85.2, 81.0, 66.7, 66.2, 55.9, 55.8, 53.7, 51.1. HRMS (ESI-TOF) calcd for $C_{22}H_{23}O_7$ ($[M + H]^+$) 399.1444, found 399.1443.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 3-(4-fluorophenyl)-4-oxo-1-phenylhexa hydrofuro[3,4-c]furan-3a-carboxylate (3ag). Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 96% yield (171 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AS-H column (4/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 14.6 (major), 9.9 (minor) min). $[\alpha]^{20}_D$ = +67.7 (c = 0.66, $CHCl_3$). Mp: 151–152 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55–7.48 (m, 2H), 7.47–7.33 (m, 5H), 7.14–7.03 (m, 2H), 5.74 (s, 1H), 5.33 (d, J = 4.8 Hz, 1H), 4.14 (t, J = 8.9 Hz, 1H), 4.00–3.91 (m, 2H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.1, 168.8, 162.9 (d, $^1J_{C–F}$ = 247.0 Hz), 135.7, 131.3, 128.9, 128.3, 128.2, 125.6, 115.5 (d, $^2J_{C–F}$ = 21.7 Hz), 84.6, 81.3, 66.8, 66.2, 53.7, 51.0. HRMS (ESI-TOF) calcd for $C_{20}H_{18}FO_5$ ($[M + H]^+$) 357.1138, found 357.1137.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 3-(4-chlorophenyl)-4-oxo-1-phenylhexa hydrofuro[3,4-c]furan-3a-carboxylate (3ah). Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 90% yield (168 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (4/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 21.1 (major), 13.9 (minor) min). $[\alpha]^{20}_D$ = +94.1 (c = 0.59, $CHCl_3$). Mp: 165–166 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52–

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7.33 (m, 9H), 5.73 (s, 1H), 5.33 (d, *J* = 4.7 Hz, 1H), 4.14 (t, *J* = 8.7 Hz, 1H), 3.98–3.91 (m, 2H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.0, 168.8, 135.7, 134.6, 134.0, 128.9, 128.7, 128.3, 127.9, 125.6, 84.5, 81.3, 66.8, 66.2, 53.8, 51.0. HRMS (ESI-TOF) calcd for $C_{20}H_{18}ClO_5$ ([M + H]$^+$) 373.0843, found 373.0840.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 3-(3-chlorophenyl)-4-oxo-1-phenylhexa hydrofuro[3,4-c]furan-3a-carboxylate (3ai). Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 90% yield (168 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (4/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 7.2 (major), 8.2 (minor) min). $[\alpha]^{20}_D$ = +104.3 (c = 0.33, $CHCl_3$). Mp: 135–136 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.51 (s, 1H), 7.49–7.29 (m, 8H), 5.73 (s, 1H), 5.33 (d, *J* = 4.9 Hz, 1H), 4.14 (t, *J* = 9.1 Hz, 1H), 4.01–3.87 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 170.9, 168.7, 137.5, 135.5, 134.4, 129.7, 128.9, 128.3, 126.5, 125.6, 124.8, 84.2, 81.3, 66.8, 66.2, 53.8, 51.0. HRMS (ESI-TOF) calcd for $C_{20}H_{18}ClO_5$ ([M + H]$^+$) 373.0843, found 373.0835.

(1*R*,3*S*,3a*R*,6a*R*)-Methyl 3-(2-chlorophenyl)-4-oxo-1-phenylhexa hydrofuro[3,4-c]furan-3a-carboxylate (3aj). Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 90% yield (168 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (9/1 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 210 nm; t_R = 41.3 (major), 33.0 (minor) min). $[\alpha]^{20}_D$ = –124.7 (c = 0.80, $CHCl_3$). Mp: 220–221 °C (petroleum ether/ethyl acetate).^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.63 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.49–7.27 (m, 8H), 6.13 (s, 1H), 5.50 (d, *J* = 4.8 Hz, 1H), 4.07 (t, *J* = 9.5 Hz, 1H), 3.98–3.88 (m, 4H), 3.86–3.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 170.6, 169.3, 135.5, 134.0, 132.9, 129.9, 129.6, 128.9, 128.2, 127.4, 127.1, 125.5, 83.3, 81.2, 66.0, 64.8, 53.8, 52.6. HRMS (ESI-TOF) calcd for $C_{20}H_{18}ClO_5$ ([M + H]$^+$) 373.0843, found 373.0843.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 3-(4-bromophenyl)-4-oxo-1-phenylhexa hydrofuro[3,4-c]furan-3a-carboxylate (3ak). Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 88% yield (184 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (4/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 8.8 (major), 10.7 (minor) min). $[\alpha]^{20}_D$ = –58.6 (c = 0.59, $CHCl_3$). Mp: 186–187 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.52 (d, *J* = 8.5 Hz, 2H), 7.49–7.32 (m, 7H), 5.71 (s, 1H), 5.33 (d, *J* = 4.7 Hz, 1H), 4.14 (t, *J* = 8.6 Hz, 1H), 4.00–3.91 (m, 2H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.1, 168.7, 135.6, 134.5, 131.6, 128.9, 128.3, 128.1, 125.5, 122.8, 84.4, 81.3, 66.8, 66.2, 53.8, 50.9. HRMS (ESI-TOF) calcd for $C_{20}H_{18}BrO_5$ ([M + H]$^+$) 417.0338, found 417.0336.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 4-oxo-1-phenyl-3-(4-(trifluoromethyl) phenyl)hexahydrofuro[3,4-c]furan-3a-carboxylate (3al). Purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to afford a white solid in 85% yield (173 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (9/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 20.8 (major), 13.4 (minor) min). $[\alpha]^{20}_D$ = +29.1 (c = 0.50, $CHCl_3$). Mp: 128–129 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.74–7.62 (m, 4H), 7.52–7.34 (m, 5H), 5.80 (s, 1H), 5.36 (d, *J* = 4.9 Hz, 1H), 4.16 (t, *J* = 8.8 Hz, 1H), 4.02–3.92 (m, 2H), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 170.9, 168.7, 139.5, 135.5, 130.8 (q, $^2J_{C-F}$ = 32.4 Hz), 129.0, 128.4, 126.9, 125.6, 125.4, 124.1 (q, $^1J_{C-F}$ = 272.3 Hz), 84.3, 81.5, 66.8, 66.3, 53.8, 51.0. HRMS (ESI-TOF) calcd for $C_{21}H_{18}F_3O_5$ ([M + H]$^+$) 407.1106, found 407.1100.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 1-(4-anisyl)-4-oxo-3-phenylhexahydro furo[3,4-c]furan-3a-carboxylate (3ba). Purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a white solid in 79% yield (145 mg) and 99% ee. The ee was determined by HPLC analysis using a CHIRALPAK IC column (4/1 *i*-PrOH/hexane; flow rate 1.0 mL/min; λ = 254 nm; t_R = 21.3 (major), 19.1 (minor) min). $[\alpha]^{20}_D$ = –14.7 (c = 0.59, $CHCl_3$). Mp: 158–159 °C (petroleum ether/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.51 (d, *J* = 7.3 Hz, 2H), 7.44–7.31 (m, 5H), 6.95 (d, *J* = 8.7 Hz, 2H), 5.75 (s, 1H), 5.29 (d, *J* = 5.0 Hz, 1H), 4.13 (t, *J* = 9.4 Hz, 1H), 4.00 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.90 (s, 3H), 3.89–3.84 (m, 1H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.2, 169.0, 159.4, 135.6, 128.8, 128.5, 127.8, 126.8, 126.5, 114.3, 85.1, 81.0, 66.6, 66.4, 55.4, 53.6, 51.3. (ESI-TOF) calcd for $C_{21}H_{21}O_6$ ([M + H]$^+$) 369.1338, found 369.1334.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl (4-anisyl)-3-(3,4-dimethoxyphenyl)-1-4-oxohexahydrofuro[3,4-c]furan-3a-carboxylate (3bf). Purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to afford a colorless oil in 95% yield (204 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (2/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 14.9 (major), 24.7 (minor) min). $[\alpha]^{20}_D$ = +109.7 (c = 0.34, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.32 (d, *J* = 8.6 Hz, 2H), 7.08 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.69 (s, 1H), 5.26 (d, *J* = 5.0 Hz, 1H), 4.14 (t, *J* = 9.4 Hz, 1H), 3.99 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.96–3.78 (m, 13H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.3, 169.0, 159.4, 149.3, 148.8, 127.94, 127.87, 126.8, 118.9, 114.3, 111.0, 109.9, 85.1, 80.8, 66.7, 66.2, 55.9, 55.8, 55.3, 53.6, 51.2. HRMS (ESI-TOF) calcd for $C_{23}H_{25}O_8$ ([M + H]$^+$) 429.1549, found 429.1550.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 1-(4-anisyl)-3-(4-chlorophenyl)-4-oxo hexahydrofuro[3,4-c]furan-3a-carboxylate (3bh). Purified by column chromatography (petroleum ether/ethyl acetate = 6/1) to afford a white solid in 73% yield (147 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (9/1 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 210 nm; t_R = 25.6 (major), 27.6 (minor) min). $[\alpha]^{20}_D$ = –170.7 (c = 0.20, $CHCl_3$). Mp: 167–168 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.45 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 5.71 (s, 1H), 5.28 (d, *J* = 4.8 Hz, 1H), 4.14 (t, *J* = 9.4 Hz, 1H), 3.97 (dd, *J* = 9.1, 6.5 Hz, 1H), 3.89 (s, 3H), 3.88–3.78 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.1, 168.8, 159.5, 134.6, 134.1, 128.7, 127.9, 127.6, 126.8, 114.3, 84.4, 81.2, 66.8, 66.2, 55.4, 53.7, 51.1. HRMS (ESI-TOF) calcd for ([M + NH_4]$^+$) 420.1214, found 420.1205.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 1-(2-anisyl)-4-oxo-3-phenylhexahydro furo[3,4-c]furan-3a-carboxylate (3ca). Purified by column chromatography (petroleum ether/ethyl acetate = 7/1) to afford a white solid in 85% yield (156 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AS-H column (4/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 11.4 (major), 9.9 (minor) min). $[\alpha]^{20}_D$ = –29.7 (c = 0.60, $CHCl_3$). Mp: 125–126 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.69 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.75 (s, 1H), 5.37 (d, *J* = 5.1 Hz, 1H), 4.10 (t, *J* = 9.1 Hz, 1H), 4.07–4.00 (m, 1H), 3.96–3.88 (m, 4H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.7, 169.3, 155.2, 135.7, 129.2, 128.7, 128.4, 127.0, 126.6, 124.4, 120.9, 110.0, 84.4, 78.1, 67.0, 66.3, 55.4, 53.6, 49.7. HRMS (ESI-TOF) calcd for $C_{21}H_{21}O_6$ ([M + H]$^+$) 369.1338, found 369.1331.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 1-(3,4-dimethoxyphenyl)-4-oxo-3-phenylhexahydrofuro[3,4-c]furan-3a-carboxylate (3da). Purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to

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afford a white solid in 77% yield (153 mg) and 99% ee. The ee was determined by HPLC analysis using a CHIRALPAK IC column (4/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 48.9 (major), 39.5 (minor) min). $[\alpha]^{20}_D$ = +87.7 (c = 0.51, $CHCl_3$). Mp: 187–188 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.51 (d, *J* = 7.3 Hz, 2H), 7.45–7.32 (m, 3H), 7.02–6.88 (m, 3H), 5.75 (s, 1H), 5.29 (d, *J* = 5.0 Hz, 1H), 4.16 (t, *J* = 9.4 Hz, 1H), 4.02 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.97–3.84 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.2, 168.9, 149.4, 148.9, 135.5, 128.8, 128.5, 128.3, 126.5, 117.8, 111.4, 108.9, 85.2, 81.0, 66.7, 66.3, 56.1, 56.0, 53.6, 51.2. HRMS (ESI-TOF) calcd for $C_{22}H_{23}O_7$ ([M + H]$^+$) 399.1444, found 399.1443.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 3-(benzo[d][1,3]dioxol-5-yl)-1-(3,4-dimethoxyphenyl)-4-oxohexahydrofuro[3,4-c]furan-3a-carboxylate (3dn). Purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to afford a colorless oil in 96% yield (212 mg) and 99% ee. The ee was determined by HPLC analysis using a CHIRALPAK IC column (2/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 40.0 (major), 33.4 (minor) min). $[\alpha]^{20}_D$ = –35.0 (c = 1.20, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.05–6.86 (m, 5H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 2H), 5.65 (s, 1H), 5.25 (d, *J* = 4.9 Hz, 1H), 4.16 (t, *J* = 9.4 Hz, 1H), 3.99 (dd, *J* = 9.7, 6.3 Hz, 1H), 3.96–3.83 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.3, 168.9, 149.3, 148.8, 147.9, 147.7, 129.2, 128.2, 120.2, 117.8, 111.3, 108.7, 108.4, 106.9, 101.2, 85.1, 80.9, 66.7, 66.2, 56.04, 55.98, 53.7, 51.1. HRMS (ESI-TOF) calcd for $C_{23}H_{26}NO_9$ ([M + NH_4]$^+$) 460.1608, found 460.1605.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 3-(4-acetoxy-3-methoxyphenyl)-1-(3,4-dimethoxyphenyl)-4-oxohexahydrofuro[3,4-c]furan-3a-carboxyl ate (3do). Purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to afford a colorless oil in 85% yield (207 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AS-H column (2/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 23.7 (major), 15.0 (minor) min). $[\alpha]^{20}_D$ = –24.9 (c = 0.59, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.15–7.09 (m, 2H), 7.08–7.02 (m, 1H), 6.97–6.86 (m, 3H), 5.71 (s, 1H), 5.27 (d, *J* = 5.0 Hz, 1H), 4.17 (t, *J* = 9.4 Hz, 1H), 3.99 (dd, *J* = 9.6, 6.2 Hz, 1H), 3.96–3.86 (m, 10H), 3.84 (s, 3H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.0, 168.9, 151.0, 149.4, 148.9, 140.0, 134.4, 128.3, 122.8, 118.8, 117.8, 111.5, 111.0, 108.8, 84.7, 81.0, 66.7, 66.2, 56.0. 55.9, 53.7, 51.2, 20.7. HRMS (ESI-TOF) calcd for $C_{25}H_{30}NO_{10}$ ([M + NH_4]$^+$) 504.1870, found 504.1872.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 3-(4-(benzyloxy)-3-methoxyphenyl)-1-(3,4-dimethoxyphenyl)-4-oxohexahydrofuro[3,4-c]furan-3a-carbo xylate (3dp). Purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to afford a colorless oil in 95% yield (254 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (1/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 12.3 (major), 7.3 (minor) min). $[\alpha]^{20}_D$ = –2.7 (c = 0.59, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.43 (d, *J* = 7.3 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.08–6.99 (m, 2H), 6.97–6.86 (m, 4H), 5.67 (s, 1H), 5.25 (d, *J* = 5.0 Hz, 1H), 5.15 (s, 2H), 4.16 (t, *J* = 9.4 Hz, 1H), 4.00 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.97–3.82 (m, 13H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.2, 169.0, 149.5, 149.3, 148.8, 148.6, 137.2, 128.6, 128.42, 128.39, 127.8, 127.3, 118.9, 117.8, 113.6, 111.4, 110.5, 108.8, 85.1, 80.8, 71.0, 66.7, 66.2, 56.0, 53.6, 51.2. HRMS (ESI-TOF) calcd for $C_{30}H_{34}NO_9$ ([M + NH_4]$^+$) 552.2234, found 552.2243.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 1-(3,4-dimethoxyphenyl)-4-oxo-3-(3,4,5-trimethoxyphenyl)hexahydrofuro[3,4-c]furan-3a-carboxylate (3dq). Purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to afford a colorless oil in 95% yield (232 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (1/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 10.3 (major), 23.6 (minor) min). $[\alpha]^{20}_D$ = +20.0 (c = 0.33, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 6.98–6.87 (m, 3H), 6.73 (s, 2H), 5.68 (s, 1H), 5.27 (d, *J* = 5.0 Hz, 1H), 4.18 (t, *J* = 9.4 Hz, 1H), 4.00 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.97–3.80 (m, 19H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.1, 169.0, 153.2, 149.4, 148.9, 138.3, 131.0, 128.3, 117.7, 111.4, 108.8, 103.8, 85.2, 80.8, 66.7, 66.2, 60.9, 56.1, 56.00, 55.95, 53.7, 51.2. HRMS (ESI-TOF) calcd for $C_{25}H_{29}O_{10}$ ([M + H]$^+$) 489.1761, found 489.1757.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 1-(4-fluorophenyl)-4-oxo-3-phenylhexa hydrofuro[3,4-c]furan-3a-carboxylate (3ea). Purified by column chromatography (petroleum ether/ethyl acetate = 7/1) to afford a white solid in 87% yield (155 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AS-H column (4/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 14.9 (major), 10.0 (minor) min). $[\alpha]^{20}_D$ = +24.9 (*c* = 0.69, $CHCl_3$). Mp: 178–179 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.51 (d, *J* = 7.2 Hz, 2H), 7.46–7.32 (m, 5H), 7.17–7.08 (m, 2H), 5.76 (s, 1H), 5.30 (d, *J* = 4.8 Hz, 1H), 4.14 (t, *J* = 9.0 Hz, 1H), 3.99–3.86 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 171.0, 168.8, 162.4 (d, $^1J_{FC}$ = 247.3 Hz), 135.3, 131.6, 128.9, 128.5, 127.3 (d, $^3J_{FC}$ = 8.1 Hz), 126.4, 115.9 (d, $^2J_{FC}$ = 21.7 Hz), 85.2, 80.6, 66.5, 66.3, 53.7, 51.1. HRMS (ESI-TOF) calcd for $C_{20}H_{18}FO_5$ ([M + H]$^+$) 357.1138, found 357.1137.

(1*R*,3*R*,3a*R*,6a*R*)-Methyl 1-(4-nitrophenyl)-4-oxo-3-phenylhexa hydrofuro[3,4-c]furan-3a-carboxylate (3fa). Purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to afford a white solid in 95% yield (182 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (2/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 210 nm; t_R = 9.6 (major), 11.2 (minor) min). $[\alpha]^{20}_D$ = –77.7 (c = 0.79, $CHCl_3$). Mp: 181–182 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 8.31 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.47–7.33 (m, 3H), 5.79 (s, 1H), 5.40 (d, *J* = 4.9 Hz, 1H), 4.16 (t, *J* = 9.4 Hz, 1H), 4.05–3.99 (m, 1H), 3.91 (s, 3H), 3.85 (dd, *J* = 9.5, 6.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 170.5, 168.5, 147.9, 143.1, 134.9, 129.1, 128.6, 126.7, 126.4, 124.2, 85.6, 80.4, 66.22, 66.20, 53.9, 50.8. HRMS (ESI-TOF) calcd for $C_{20}H_{18}NO_7$ ([M + H]$^+$) 384.1083, found 384.1076.

(3a*R*,4*R*,6*S*,6a*R*)-6-(Benzo[d][1,3]dioxol-5-yl)-4-(3,4-dimethoxy phenyl)tetrahydrofuro[3,4-c]furan-1(3H)-one (4dn). A mixture of compound **3dn** (141 mg, 0.32 mmol) and NaCl (150 mg, 2.57 mmol) in DMSO (10 mL) and water (1 mL) was heated at 100 °C under an argon atmosphere. After completion of the reaction, the mixture was cooled to room temp, diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, and the residue was purified by column chromatography (petroleum ether/CH_2Cl_2 = 2/1) to afford a white solid in 89% yield (109 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (2/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 26.8 (major), 19.1 (minor) min). $[\alpha]^{20}_D$ = –175.3 (*c* = 0.21, $CHCl_3$). Mp: 164–165 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 6.98–6.87 (m, 5H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.02–5.95 (m, 2H), 5.22 (d, *J* = 8.6 Hz, 1H), 5.19 (d, *J* = 5.0 Hz, 1H), 4.09 (t, *J* = 9.5 Hz, 1H), 3.96 (dd, *J* = 9.8, 6.7 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.68–3.57 (m, 1H), 3.51 (t, *J* = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 175.1, 149.2, 148.7, 147.9, 147.7, 130.0, 129.1, 120.0, 117.8, 111.3, 108.9, 108.4, 106.7, 101.2, 82.7, 81.6, 67.9, 56.1, 56.0, 50.9, 45.3. HRMS (ESI-TOF) calcd for $C_{21}H_{24}NO_7$ ([M + NH_4]$^+$) 402.1553, found 402.1551.

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((2*S*,3*S*,4*R*,5*R*)-2-(Benzo[d][1,3]dioxol-5-yl)-5-(3,4-dimethoxy phenyl)tetrahydrofuran-3,4-diyl)dimethanol (5dn). $LiAlH_4$ (74 mg, 1.95 mmol) was added slowly to a solution of compound **4dn** (189 mg, 0.49 mmol) in THF (10 mL) at 0 °C under an argon atmosphere. After completion of the reaction, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 1/1) to afford a colorless oil in 98% yield (187 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel IA column (2/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 33.0 (major), 27.5 (minor) min). $[\alpha]^{20}_D$ = –88.7 (c = 0.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 6.97 (d, *J* = 8.2 Hz, 1H), 6.96–6.84 (m, 4H), 6.81 (d, *J* = 8.0 Hz, 1H), 5.98 (s, 2H), 5.13 (t, *J* = 6.2 Hz, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.54–3.46 (m, 2H), 3.46–3.36 (m, 2H), 3.02–2.87 (m, 2H), 2.63–2.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 149.0, 148.4, 147.8, 146.9, 132.8, 131.3, 119.3, 118.2, 111.2, 109.4, 108.3, 106.6, 101.1, 81.0, 61.0, 56.0, 48.20, 48.17, 48.05, 48.01. HRMS (ESI-TOF) calcd for $C_{21}H_{25}O_7$ ([M + H – H_2O]$^+$) 371.1495, found 371.1488.

5-((2*S*,3*S*,4*R*,5*R*)-5-(3,4-Dimethoxyphenyl)-3,4-bis(methoxy methyl)tetrahydrofuran-2-yl)benzo[d][1,3]dioxole (6dn). Under an argon atmosphere, to an ice-cooled solution of diol **5dn** (430 mg, 1.11 mmol) in THF (10 mL) was added NaH (440 mg, 60% dispersion in mineral oil, 11 mmol). The resultant suspension was stirred for 30 min before the addition of CH_3I (0.68 mL, 11 mmol). The resulting reaction solution was stirred at room temperature for 2.5 h before the addition of H_2O. After concentration of the reaction mixture, the residue was dissolved in 20 mL of CH_2Cl_2 and 20 mL of H_2O and the queous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine solution (30 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to afford a colorless oil in 91% yield (421 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (3/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 26.3 (major), 19.2 (minor) min). $[\alpha]^{20}_D$ = +91.4 (c = 0.65, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.10–6.99 (m, 3H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 2H), 5.22–5.11 (m, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.30–3.20 (m, 2H), 3.12–2.94 (m, 8H), 2.92–2.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 148.4, 148.0, 147.3, 146.5, 133.2, 131.7, 119.8, 118.7, 110.6, 110.1, 107.8, 107.3, 100.8, 81.43, 81.39, 70.1, 70.0, 58.3, 55.82, 55.79, 46.44, 46.39. HRMS (ESI-TOF) calcd for $C_{23}H_{29}O_7$ ([M + H]$^+$) 417.1913, found 417.1899.

5-((1*S*,3*R*,3a*R*,6a*S*)-3-(3,4-Dimethoxyphenyl)hexahydrofuro[3,4-c]furan-1-yl)benzo[d][1,3]dioxole (7dn). Under an argon atmosphere, to an ice-cooled solution of diol **5dn** (430 mg, 1.11 mmol) in THF (10 mL) was added NaH (92 mg, 60% dispersion in mineral oil, 2.3 mmol). The resultant suspension was stirred for 30 min before the addition of *p*-TsCl (438 mg, 2.3 mmol). Then the reaction mixture was stirred at room temperature for 2.5 h before being quenched by the addition of H_2O. The residue was dissolved in 20 mL of CH_2Cl_2 and 20 mL of H_2O and the queous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine solution (30 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 6/1) to afford a white solid in 74% yield (304 mg) and 97% ee. The ee was determined by HPLC analysis using a CHIRALPAK IA column (1/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 25.4 (major), 28.6 (minor) min). $[\alpha]^{20}_D$ = +28.6 (c = 0.52, $CHCl_3$). Mp: 175–176 °C (petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 6.96 (s, 3H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 2H), 5.11–5.00 (m, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.53–3.44 (m, 2H), 3.44–3.35 (m, 2H), 3.26–3.14 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 148.9, 148.2, 147.7, 146.7, 132.7, 131.3, 119.2, 118.3, 111.1, 109.5, 108.2, 106.9, 101.0, 82.0, 81.9, 70.3, 70.2, 56.00, 55.96, 49.89, 49.87. HRMS (ESI-TOF) calcd for $C_{21}H_{26}NO_6$ ([M + NH_4]$^+$) 388.1760, found 388.1762.

((2*S*,3*S*,4*R*,5*R*)-2-(Benzo[d][1,3]dioxol-5-yl)-5-(3,4-dimethoxy phenyl)tetrahydrofuran-3,4-diyl)bis(methylene) dimethanesulfonate (8dn). Under an argon atmosphere, to an ice-cooled solution of diol **5dn** (430 mg, 1.11 mmol) and Et_3N (0.32 mL, 2.3 mmol) in CH_2Cl_2 (10 mL) was added MsCl (0.18 mL, 2.3 mmol). The reaction mixture was stirred at room temperature for 30 min before the addition of H_2O (20 mL) and CH_2Cl_2 (20 mL). The organic phase was separated, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 3/1) to afford a red oil in 98% yield (592 mg) and 98% ee. The ee was determined by HPLC analysis using a Chiralcel IC column (2/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 11.6 (major), 8.7 (minor) min). $[\alpha]^{20}_D$ = –93.3 (c = 0.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.00 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.95 (d, *J* = 1.1 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 5.98 (s, 2H), 5.24–5.14 (m, 2H), 4.13–3.97 (m, 4H), 3.91 (s, 3H), 3.89 (s, 3H), 3.22–3.10 (m, 2H), 2.82 (s, 3H), 2.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 149.0, 148.7, 147.9, 147.3, 130.8, 129.3, 119.6, 118.5, 111.2, 109.6, 108.4, 106.7, 101.2, 80.4, 80.3, 66.9, 66.7, 56.0, 55.9, 44.9, 37.0, 36.8. HRMS (ESI-TOF) calcd for $C_{23}H_{32}NO_{11}S_2$ ([M + NH_4]$^+$) 562.1417, found 562.1419.

5-((2*S*,3*R*,4*S*,5*R*)-5-(3,4-Dimethoxyphenyl)-3,4-dimethyltetrahyd rofuran-2-yl)benzo[d][1,3]dioxole (9dn). Under an argon atmosphere, to an ice-cooled solution of the mesylate **8dn** (272 mg, 0.5 mmoL) in THF (50 mL) was added Super-hydride (12.5 mL, 1.0 M in THF, 12.5 mmol). The resulting reaction mixture was stirred at room temperature for 2.5 h before the addition of saturated NH_4Cl solution (15 mL). After evaporation of the volatile organic solvent, the residue was dissolved in 20 mL of CH_2Cl_2 and 20 mL of H_2O and the queous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 20/1) to afford a colorless oil in 34% yield (62 mg) and 99% ee. The ee was determined by HPLC analysis using a Chiralcel AD-H column (3/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 254 nm; t_R = 32.7 (major), 20.5 (minor) min). $[\alpha]^{20}_D$ = –103.5 (c = 0.09, MeOH). ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.01–6.92 (m, 3H), 6.91–6.83 (m, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.96 (s, 2H), 5.10 (d, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 6.6 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.71–2.58 (m, 2H), 0.60 (d, *J* = 7.3 Hz, 3H), 0.59 (d, *J* = 7.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 148.6, 147.8, 147.4, 146.3, 134.5, 133.0, 119.5, 118.5, 110.8, 109.8, 107.9, 107.0, 100.9, 82.8, 82.7, 55.9, 41.52, 41.46, 11.8. HRMS (ESI-TOF) calcd for $C_{21}H_{25}O_5$ ([M + H]$^+$) 357.1702, found 357.1705.

Conflicts of interest

There are no conflicts to declare.

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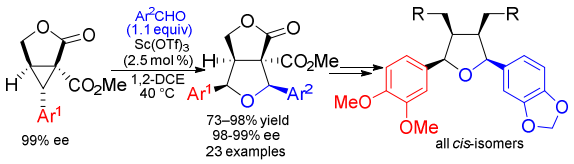

An enantiospecific [3+2] annulation of γ-butyrolactone fused cyclopropanes with aromatic aldehydes was realized to construct chiral furanolignans.