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Graphical Abstract

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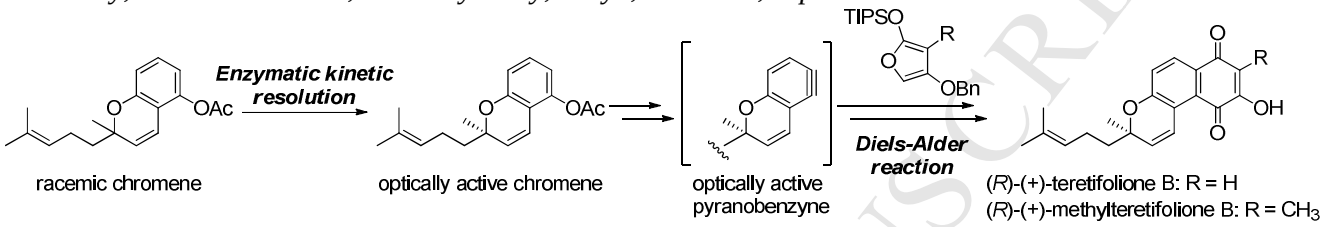

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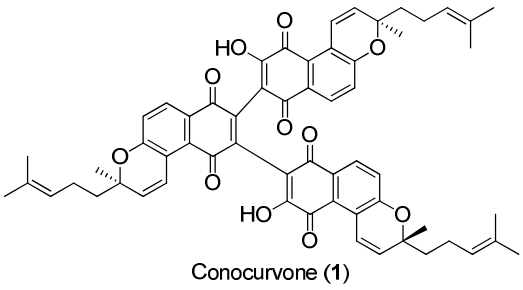
ABSTRACT

We report the asymmetric total syntheses of teretifolione B and methylteretifolione B, which are benzochromenes originally isolated from *Conospermum* plants. The synthesis involves enzymatic asymmetric transesterification of racemic acetoxychromene and construction of the basic framework via Diels-Alder reaction of optically active pyranobenzyne and substituted furans. The absolute configuration of the chiral chromene was unambiguously determined by asymmetric total synthesis of teretifolione B and its characterization. The first asymmetric total synthesis of methylteretifolione B was achieved in a similar manner and its absolute configuration, for which direct proof has not been reported, was established.

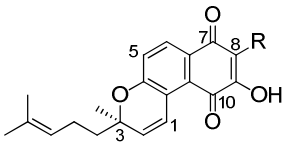
1. Introduction

Quinone natural products are widely distributed in plants and microorganisms, and they have diverse biological activities.[1] Angular benzochromenes are a small class of natural products isolated from *Conospermum* and *Pentas* plants. Conocurvone (**1**), a trimeric benzochromene isolated from *Conospermum* plants, has potent anti-HIV activity.[2,3] The structure of **1** was elucidated by spectroscopic analyses, derivatization, and semi-synthesis from the corresponding monomeric unit, teretifolione B (**2**).[2] Methylteretifolione B (**3**), a derivative with a methyl group at the 8-position,[4] was isolated from the same plant as an another monomeric benzochromene.[5] To date, total synthesis of **1** has not been achieved.[6] In contrast, several total syntheses of monomeric benzochromenes **2** and **3** have been reported. (±)-**2** was synthesized in the course of structure elucidation,[5] and total synthesis of (+)-**2** was achieved by Jacobsen *et al*. via kinetic resolution of a fully constructed racemic benzochromene by asymmetric epoxidation.[7] (±)-**3** was synthesized by Stagliano through regioselective ortho metalation.[8] For synthesizing an oligomeric structure like **1**, condensation of the monomeric unit, as in the semi-synthesis, would be a feasible method (Fig. 1).[2]

We have developed syntheses of quinone natural products, including the concise synthesis of substituted naphthoquinones and the total synthesis of a benzochromene, 9-hydroxy-3,3,8-~~trimethyl-~~3*H*-benzo[*f*]chromene-7,10-dione, via the Diels-Alder reaction (DAR) of benzynes and furan as a key step.[9,10] We expected that this strategy would be applicable to the asymmetric total syntheses of natural angular benzochromenes such as **1**–**3**. DAR of optically active pyranobenzyne and monomeric or suitably oligomerized furans can produce desired monomeric **2** and **3** or polymeric benzochromene **1**. In this paper, we describe



Conocurvone (**1**)



Teretifolione B (**2**): R = H
Methylteretifolione B (**3**): R = CH_3

Fig. 1. Structures of conocurvone (**1**), teretifolione B (**2**) and methylteretifolione B (**3**).

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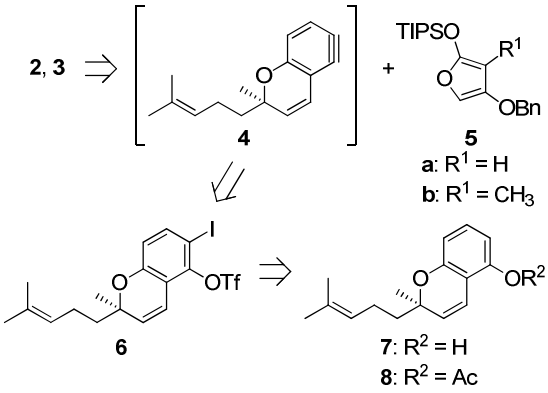
the asymmetric total synthesis of teretifolione B (**2**) and the first asymmetric total synthesis of methylteretifolione B (**3**) through preparing the optically active pyranobenzyne moiety via enzymatic kinetic resolution of racemic acetoxychromene and DAR with monomeric furans for constructing the basic framework.

2. Results and Discussion

2.1. Retrosynthetic analysis

Retrosynthetic analysis of **2** and **3** is shown in Scheme 1. Construction of the benzochromene framework was envisioned through DAR of pyranobenzyne **4** and monomeric furans **5**. The precursor of benzyne **4**, iodotriflate **6**, would be accessible from known chromene **7** via regioselective iodination. Optically active **7** would be obtained from catalytic asymmetric synthesis or enzymatic kinetic resolution[11] of acetate **8** in which a remote stereogenic center could be recognized.[12]

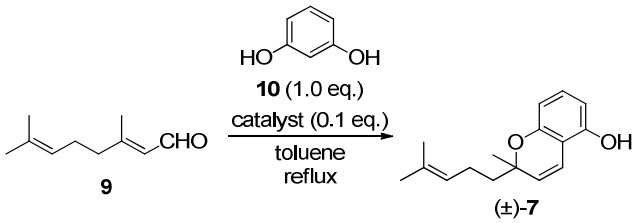


Scheme 1. Retrosynthetic analysis of **2** and **3**.

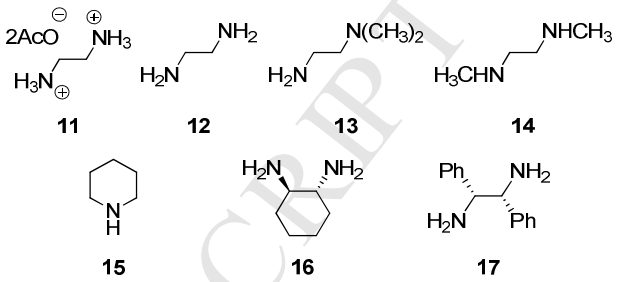
2.2. Establishing the synthetic route for racemic total synthesis of teretifolione B (2)

Lee *et al.* reported the concise one-step synthesis of racemic chromene **7** via cyclocondensation of citral (**9**) and resorcinol (**10**) catalyzed by ethylenediamine diacetate (**11**; EDDA) in xylene.[13] With this method, we obtained (±)-**7** in 23% yield using toluene as a solvent instead of xylene (Table 1, run 1). Because EDDA is highly hygroscopic and insoluble in low polar solvents, and the yield of **7** was low, we screened catalysts for better efficiency in this reaction. We found that ethylenediamine (**12**) catalyzed the reaction and gave **7** in slightly higher yield (40%) compared with **11** (run 2). *N*,*N*-Dimethylethylenediamine (**13**) showed similar results (run 3); however, a longer reaction time was required when *N*,*N*'-dimethyl derivative **14** was used (run 4). Piperidine (**15**) also catalyzed this reaction (run 5). On the other hand, tetramethylethylenediamine and triethylamine gave only trace amount of **7** (3~4%). Using chiral diamines, such as (1*R*,2*R*)-cyclohexanediamine (**16**) and (1*R*,2*R*)-diphenylethylenediamine (**17**), did not result in asymmetric induction and gave only racemic **7** (runs 6 and 7).

Table 1. Examination of catalyst for the synthesis of **7**.



Catalyst

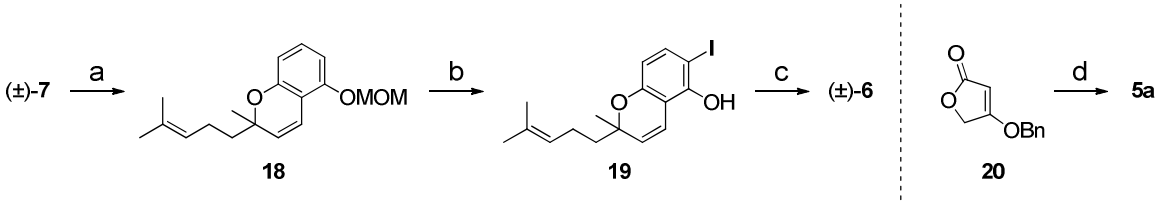


Run	Catalyst	Time (h)	Yield of **7** (%)
1	**11**	3.0	23
2	**12**	3.0	40
3	**13**	3.0	38
4	**14**	7.0	24
5[a]	**15**	18.0	33
6	**16**	3.0	39
7	**17**	22.0	25

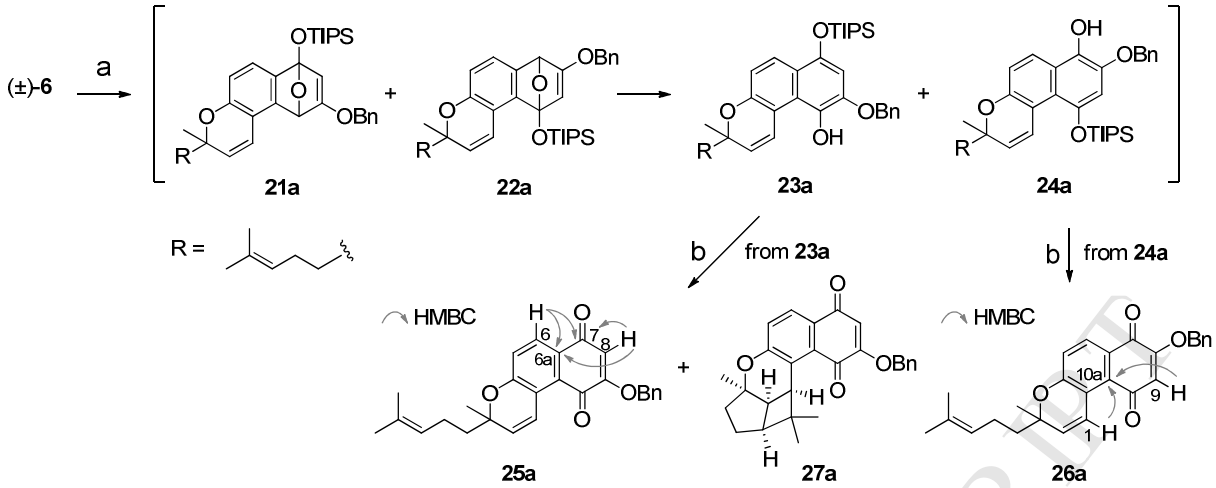
[a] 0.2 eq. of catalyst was used.

(±)-**7** was converted to MOM ether **18**. Regioselective iodination[14] of **18** and deprotection gave **19**, which was converted to iodotriflate **6** as a benzyne precursor. Substituted furan **5a** was prepared from benzyl tetronate (**20**) by our previously reported method (Scheme 2).[9]

DAR of furan **5a** with benzyne **4** generated from **6** and *n*-BuLi *in situ* produced a regioisomeric mixture of adducts **21a** and **22a** and these compounds isomerized to **23a** and **24a** spontaneously. Because of the anticipated instability of hydroquinones **23a** and **24a**, these compounds were separated by column chromatography and the isolated hydroquinones were immediately oxidized to the corresponding quinones **25a** and **26a**, respectively. When **25a** was purified by normal phase SiO_2 column chromatography, a trace amount of cyclized product **27a** was obtained. This class of compounds is generated under acidic,[15] basic,[16] and photoirradiation[17] conditions. We assumed that **27a** was produced during purification by the acidic nature of



Scheme 2. Preparation of benzyne precursor **6** and furan **5a**. Reagents and conditions: (a) MOMCl, NaH, THF, rt, 2 h, 71%; (b) 1) *t*-BuLi, Et_2O, -25 °C, 10 min to rt, 1 h then I_2, rt, 1 h; 2) cat. *p*-TsOH, EtOH, 50 °C, 24 h, 57% in two steps; (c) Tf_2O, Et_3N, CH_2Cl_2, -78 °C, 2.5 h, 97%; (d) TIPSOTf, Et_3N, CH_2Cl_2, 0 °C, 1 h, 75%.



Scheme 3. Construction of benzochromene core by Diels-Alder reaction. Reagents and conditions: (a) **5a**, *n*-BuLi, THF, -78 °C, 20 min; (b) 1M $FeCl_3$, MeOH – CH_2Cl_2, rt, 30 min, **25a**: 25%; **26a**: 35% from **6** respectively.

SiO_2 and light exposure. Therefore, crude **25a** was purified by ODS medium-pressure liquid chromatography (MPLC) shielded with aluminum foil from light and only **25a** was obtained without **27a**. **26a** was obtained in a similar way without cyclization.[18]

The structures of quinones **25a** and **26a** were confirmed by 2D-NMR analyses. In the HMBC spectra of **25a**, correlations between a carbonyl carbon (δ_C 184.3, C7) and aromatic hydrogens (δ_H 7.92, d, J = 8.2 Hz, C6-H, δ_H 6.11, s, C8-H), and correlations between a quaternary sp^2 carbon (δ_C 126.2, C6a) and aromatic hydrogens (δ_H 7.92 and 6.11) were observed. In contrast, in the HMBC spectra of **26a**, correlations between an aromatic carbon (δ_C 126.3, C10a), an sp^2 methine (δ_H 7.85, d, J = 10.5 Hz, C1-H), and the isolated aromatic hydrogen (δ_H 6.09, s, C9-H) were observed. These correlations were reasonable for the assignment of **25a** as benzylated **2** and **26a** as a regioisomer of **25a** (Scheme 3).

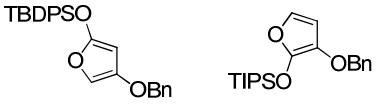
The regioselectivity of the reaction of benzyne **4** and furan **5a** was estimated as **21a**:**20a** = 1:1.7 based on isolated yields of **23a** and **24a**. Thus, we examined the effects of the reaction conditions, such as temperature, solvent, and substituents of furan **5a**, on the regioselectivity of DAR with benzyne **4**. The regioselectivity was evaluated by ^{1}H-NMR analysis of the crude product as a mixture of quinones **25a** and **26a** after the DAR followed by oxidation of the corresponding mixture of unstable hydroquinones **23a** and **24a**. The regioselectivity was independent of temperature (Table 2, runs 1–3). Next, we examined the solvent effect. DME gave a similar result to that of THF (run 4); however, the generation of undesired **26a** was increased in less polar solvents such as *n*-hexane and toluene (runs 5 and 6).[19] The furan substituents affected the regioselectivity. The ratio of **25a** was slightly improved when TBDPS-protected furan **28** was used (run 7). The amount of undesired **26a** increased when regioisomeric furan **29** was used (run 8).

We proposed transition state models for the DAR of **4** and **5a** based on our observations. The regioselectivity of the cycloaddition reaction with benzyne has been discussed in relation to the electrostatic effect and steric repulsion.[20] In our case, the electrostatic interaction between the high electron density 5-position in furan and the electrophilic 6-position in benzyne **4**[21] had the largest effect and resulted in the preferential formation of undesired isomer **22a**, despite the steric repulsion between the side chain in **4** and the bulky TIPS group in **5a** (Fig.

Table 2. Examination of regioselectivity in DAR.

Run	Furan	Solvent	Conditions	**25a**:**26a**
1	**5a**	THF	-78 °C/20 min	1:1.8[a]
2	**5a**	THF	-40 °C/20 min	1:1.8
3	**5a**	THF	0 °C/20 min	1:1.9
4	**5a**	DME	-78 °C/30 min	1:1.7
5	**5a**	*n*-Hexane	-78 °C/30 min	1:3.3
6	**5a**	Toluene	-78 °C/30 min	1:3.2
7	**28**	THF	-78 °C/20 min	1:1.4
8	**29**	THF	-78 °C/20 min	1:3.3

[a]60% yield from **6** as a mixture of **25a** and **26a** (1:1.7) after purification.



28 **29**

2, **TS1** > **TS2**). Greater formation of **22a** in less polar solvents was caused by conformational change in the side chain from closed to open, which decreased the steric repulsion between the side chain and the TIPS group (**TS3** > **TS1**). The sterically hindered TBDPS group in furan **28** increased the steric repulsion

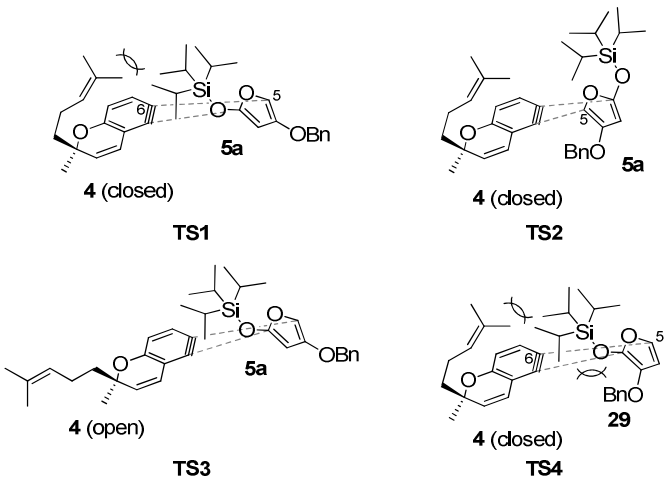
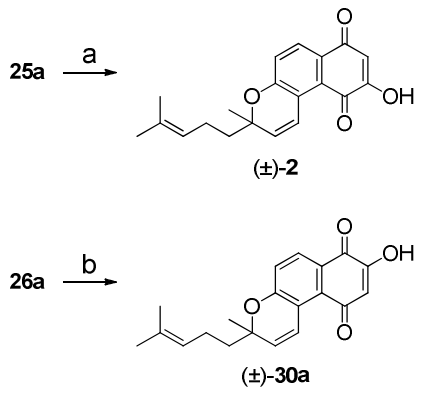


Fig. 2. Plausible transition state models for DAR of **4** and **5a**/**29**.

with the side chain in the closed conformation of **4** and the ratio of the desired isomer was slightly improved. For furan **29**,[22] steric repulsion of the TIPS group and side chain had a larger effect than the electrostatic effect, possibly because of the additional steric effect of the TIPS group that was affected by the adjacent benzyloxy group (**TS4**).

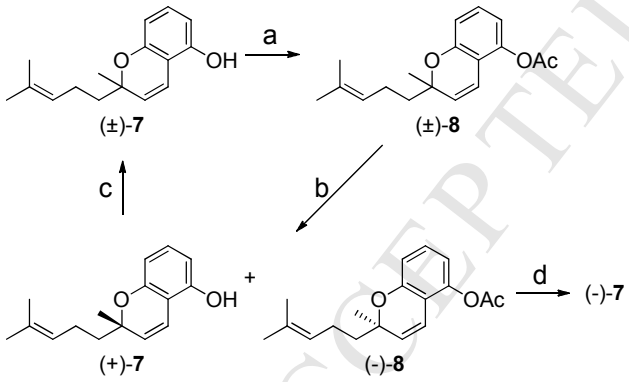
Finally, **25a** was debenzylated under hydrolytic conditions generally used for the demethylation of quinone methyl ether[23] to give (±)-**2**, and regioisomer **30a** was also obtained in a similar manner (Scheme 4).



Scheme 4. Racemic total syntheses of teretifolione B (**2**) and its regioisomer **30a**. Reagents and conditions: (a) 1M KOH, EtOH, rt, 25 min, 94%; (b) 1M KOH, EtOH, rt, 1 h, 97%.

2.3. Synthesis of optically active chromene and determination of absolute stereochemistry via asymmetric total synthesis of teretifolione B

Table 3. Asymmetric transesterification of (±)-**8**.



Reagents and conditions: (a) Ac_2O, pyridine, rt, 4 h, 79%; (b) Amano Lipase PS, alcohol, toluene, 35 °C (see table); (c) toluene, reflux, 9 d, 99%; (d) KOH, MeOH, rt, 1 h, quant.

Run	Alcohol	Time (h)	Ratio (**8**:**7**)[a]	% *ee* (**8**, **7**)[b]
1	Cyclopentanol	0.5	56:44	46, 57
2	^{t}BuOH	1	59:41	42, 63
3	^{t}BuOH	2	43:57	73, 55
4	^{t}BuOH	5.5	26:74	97, 23

[a]Ratio was estimated by the integration of ^{1}H-NMR of crude products.
[b]*ee* was estimated by chiral HPLC analysis of crude products.

Because catalytic asymmetric synthesis of **7** failed, we examined the synthesis of optically active chromenes by enzymatic kinetic resolution. (±)-**7** was acetylated to (±)-**8** and asymmetric hydrolysis[24] of (±)-**8** using Amano Lipase PS was examined; however, the optical purity of **7** and recovered **8** were up to 35% and 18% enantiomeric excess (*ee*), respectively. In contrast, asymmetric transesterification of (±)-**8** with the same enzyme in the presence of cyclopentanol[25] showed improved results, which afforded **7** and **8** in 57% and 46% *ee*, respectively (Table 3, run 1). Sterically hindered ^{t}BuOH gave a similar result (run 2). In further trials using ^{t}BuOH, the optical purity of **8** was improved to 73% *ee* after 2 h (run 3) and 97% *ee* after 5.5 h (run 4). Fortunately, (±)-**7** can be recovered after the complete racemization of (+)-**7** under thermal conditions.[26]

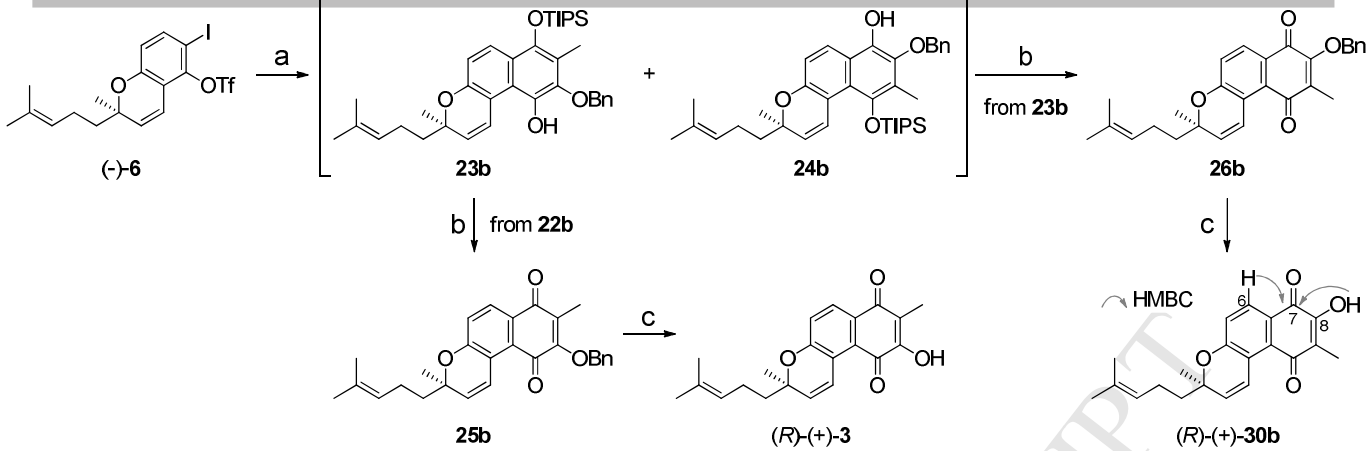
Next, (-)-**8** (95% *ee*) was prepared on a large scale and deacetylated to (-)-**7** for asymmetric synthesis of (+)-**2** through the above synthetic route. The spectroscopic data and specific rotation ($[\alpha]_D^{25}$ +73, *c* 0.1, CH_3OH) of synthesized (+)-**2** were in good agreement with those of natural **2** ($[\alpha]_D$ +66, *c* 0.1, CH_3OH).[2, 27] The absolute configuration of natural **2** was independently established by anomalous scattering in the X-ray analysis of the *p*-bromobenzoate derivative.[2] This result supported the assignment of the absolute configuration of acetoxy chromene (-)-**8** obtained by kinetic resolution as *R*.

2.4. Asymmetric total synthesis of methylteretifolione B

The synthetic route was used for the asymmetric total synthesis of methylteretifolione B (**3**). DAR of benzyne **4** generated from (-)-**6** and furan **5b** afforded a regioisomeric mixture of hydroquinones **23b** and **24b**. **23b** and **24b** isolated by SiO_2 column chromatography were oxidized to quinones **25b** and **26b**, respectively. Total synthesis of (*R*)-**3** and corresponding regioisomer **30b** was achieved by debenzylation of **25b** and **26b**. Lower yields in the final two steps (oxidation and debenzylation) were observed in the methylteretifolione B series than in the teretifolione B series. The reason for this result is not clear; it may be because of the *ortho*-quinone methide formation via tautomerism[28] of **25b** and **26b**. The spectroscopic data and specific rotation ($[\alpha]_D^{25}$ +35.0, *c* 0.35, $CHCl_3$) of synthetic (*R*)-**3** were in good agreement with those of natural **3** ($[\alpha]_D$ +29.7, *c* 0.33, $CHCl_3$).[29] The absolute configuration of natural **3** was assumed to be *R* from literature data;[30] however, the process was complicated and direct proof has not been reported. In this study, we achieved the asymmetric total synthesis of (+)-**3** from (*R*)-(-)-**8**, and the absolute configuration of (+)-**3** was determined as *R* directly. The structure of **30b** was deduced based on 2D-NMR analyses. HMBC showed that the hydroxy group (δ_H 7.28, 1H, br s) and aromatic hydrogen (δ_H 7.95, 1H, d, *J* = 8.2 Hz, C6-H) were correlated with a quinone carbonyl carbon (δ_C 188.0, C7), indicating that the hydroxy group was ortho to the carbonyl carbon and that the aromatic hydrogen was in the peri position to the same carbonyl group. Thus, **30b** has an 8-hydroxybenzo[*f*]chromene skeleton, assigned as the regioisomer of **3** (Scheme 5).

3. Conclusion

We have achieved the asymmetric total syntheses of (+)-**2** and **3** with its regioisomers via enzymatic asymmetric transesterification and DAR of a benzyne and furan as key steps. The absolute configurations of (-)-**8** and (+)-**3** were unambiguously determined from asymmetric total synthesis of



Scheme 5. Asymmetric total syntheses of methylteretifolione B (**3**) and regioisomer **30b**. Reagents and conditions: (a) **5b**, *n*-BuLi, THF, -78 °C, 25 min; (b) 1M $FeCl_3$, MeOH – CH_2Cl_2, rt, 40 min, **25b**: 28%, **26b**: 17% from **6** respectively; (c) 1M KOH, EtOH, rt, **3**: 1 h, 46%, **30b**: 1.5 h, 14%.

(+)-**2**, the absolute configuration of which was determined. The regioselectivity in DAR of benzyne **4** and furans was examined to deduce the transition state models, and use of a bulky TBDPS group as the furan substituent resulted in only slight improvement in the desired selectivity. We propose this methodology as a novel synthetic route for optically active benzochromenes and expect that it will contribute to the evolution of the total synthesis of **1**. Studies of the regioselectivity in DAR of pyranobenzyne, and total synthesis of **1** and related benzochromene natural products are now underway in our laboratory.

4. Experimental

4.1. General

Commercially available reagents and anhydrous solvents were used without further purification. Anhydrous solvents (CH_2Cl_2 and THF) were purchased from Wako chemicals. Analytical thin layer chromatography was performed on silica gel 60 F_{254} plate from Merck KGaA. Flash chromatography was carried out with Silica gel 60N (40-50 μm) from Kanto Chemical Co. ODS MPLC was performed on Ultra Pack ODS-SM from Yamazen Co.

ODS HPLC was performed on Cosmosil 5C_{18}-AR-II 10 x 250 mm from Nacalai Tesque. IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer with Attenuated Total Reflectance Unit ATR PRO450-S. EI-MS was recorded on a JEOL GC-Mate II and DART-MS was recorded on a JEOL JMS-T100LP in positive ion mode. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra were recorded on a JEOL ECX 400 spectrometer with deuterated chloroform ($CDCl_3$) as a solvent and tetramethylsilane as an internal reference at room temperature. Chemical shifts were reported in ppm and *J* in Hz. Abbreviations were used for multiplicity: s = singlet, d = doublet, t = triplet, sept. = septet, m = multiplet.

4.2. Experimental procedures

4.2.1. *2-Methyl-2-(4-methylpent-3-en-1-yl)-2H-chromen-5-ol (**7**).* Resorcinol (220.8 mg, 2.01 mmol) was suspended in toluene (17 mL) and the mixture was refluxed for 5 min. After dissolution of resorcinol, ethylenediamine (13.5 μL, 0.202 mmol) was added and stirred at same temperature. After 10 min, citral (0.35 mL, 2.04 mmol) was added and the mixture was refluxed for further 3 h. The solvent was removed *in vacuo* and the residue was purified over SiO_2 column chromatography (AcOEt : *n*-hex. = 0 : 100 - 19 : 91) to afford (±)-**7** (a yellow oil, 196.8 mg, 40%). The spectral data, see (-)-**7**.

4.2.2. *5-Acetoxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-chromene (**8**).* To a stirred solution of (±)-**7** (12.4 g, 50.8 mmol) in pyridine (35.5 mL, 439 mmol), Ac_2O (33.5 mL, 354 mmol) was added and the mixture was stirred at rt for 4 h. The whole was diluted with AcOEt (600 mL), and sat. $NaHCO_3$ (360 mL) was added slowly. Organic layer was separated and washed with 5% HCl (1 x 240 mL), brine (1 x 75 mL) and the layer was dried over Na_2SO_4. The solvent was removed *in vacuo*, the residue was purified over SiO_2 column chromatography (AcOEt : *n*-hex. = 5 : 95) to afford (±)-**8** (a yellow oil, 11.6 g, 79%). The spectral data, see (-)-**8**.

4.2.3. *(R)-5-Acetoxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-chromene (**8**).* To a stirred solution of (±)-**8** (4.74 g, 16.9 mmol) in toluene (126 mL), ^{t}BuOH (4.8 mL, 50.2 mmol) and Amano Lipase PS from Burkholderiacepacia (Aldrich, 6.10 g) were added and the mixture was stirred at 35 °C for 5.5 h. The whole was filtered through Celite® pad, and the filtrate was concentrated *in vacuo*. The residue was purified over SiO_2 column chromatography (AcOEt : *n*-hex. = 5 : 95) to afford (-)-**8** (a yellow oil, 847 mg, 18%, 95% *ee*) and (+)-**7** (3.11 g, 75%). $[\alpha]_D^{23}$ = -66.2 (*c* 1.0, $CHCl_3$); IR ν_{max} 1769 cm^{-1}; ^{1}H-NMR δ_H 7.07 (1H, t, *J* = 8.1 Hz), 6.66 (1H, dt, *J* = 8.1, 0.9 Hz), 6.58 (1H, dd, *J* = 8.1, 0.9 Hz), 6.36 (1H, dd, *J* = 10.1, 0.9 Hz), 5.60 (1H, d, *J* = 10.1 Hz), 5.08 (1H, t sept., *J* = 7.1, 1.3 Hz), 2.32 (3H, s, Ac), 2.17 - 2.02 (2H, m), 1.74 (1H, ddd, *J* = 14.0, 10.5, 6.0 Hz), 1.65 (1H, ddd, *J* = 14.0, 10.5, 6.0 Hz), 1.66 (3H, d, *J* = 1.3 Hz), 1.57 (3H, s), 1.39 (3H, s); ^{13}C-NMR δ_C 169.1, 154.1, 146.3, 131.8, 130.3, 128.6, 123.9, 116.6, 114.1, 113.9, 78.5, 41.1, 26.3, 25.6, 22.7, 20.8, 17.6 (One sp^2 carbon is missing); LRMS (EI) *m/z* (%) 286 (M^+, 62), 271 (17), 229 (24), 203 (97), 161 (100); HRMS (EI) *m/z* 286.1568 (calcd. for $C_{18}H_{22}O_3$ 286.1569, Δ - 0.1 mmu).

4.2.4. *(R)-2-Methyl-2-(4-methylpent-3-en-1-yl)-2H-chromen-5-ol (**7**).* (-)-**8** (847 mg, 2.96 mmol) was dissolved in methanolic KOH

(285 mg (85%, 4.35 mmol) in 11.0 mL) and stirred at rt for 1 h. After the solvent was removed *in vacuo*, H_2O (9.0 mL) was added to the residue and pH was adjusted to 1 with 5% HCl (5.0 mL). The whole was extracted with AcOEt (3 x 45 mL). The combined organic layer was washed with half sat. $NaHCO_3$ (1 x 20 mL) and brine (1 x 15 mL). The layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude (-)-**7** (a yellow oil, 766 mg, quant.) was subjected to the next step without further purification. $[\alpha]_D^{25}$ = -86.4 (*c* 1.0, $CHCl_3$); IR ν_{max} 3385 cm^{-1}; ^{1}H-NMR δ_H 6.93 (1H, t, *J* = 8.0 Hz), 6.65 (1H, d, *J* = 10.1 Hz), 6.40 (1H, d, *J* = 8.0 Hz), 6.28 (1H, dd, *J* = 8.0, 0.9 Hz), 5.55 (1H, d, *J* = 10.1 Hz), 5.09 (1H, t sept., *J* = 7.3, 1.4 Hz), 4.74 (1H, s, -OH), 2.18 - 2.05 (2H, m), 1.74 (1H, ddd, *J* = 13.7, 10.3, 6.6 Hz), 1.65 (1H, ddd, *J* = 13.7, 10.3, 6.4 Hz), 1.66 (3H, s), 1.57 (3H, s), 1.39 (3H, s); ^{13}C-NMR δ_C 154.2, 151.3, 131.7, 128.9, 128.2, 124.1, 116.8, 109.4, 109.1, 107.5, 78.2, 41.0, 26.2, 25.6, 22.7, 17.6; LRMS (EI) *m/z* (%) 244 (M^+, 26), 229 (10), 161 (100); HRMS (EI) *m/z* 244.1481 (calcd. for $C_{16}H_{20}O_2$ 244.1463, Δ +1.8 mmu).

4.2.5. *(R)-5-(Methoxymethoxy)-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-chromene (**18**).* To an ice-cooled stirred solution of (-)-**7** (766 mg, 3.14 mmol) in CH_2Cl_2 (8.0 mL), ^{i}Pr_2NEt (0.88 mL, 5.05 mmol) and MOMCl (0.33 mL, 4.35 mmol) were added. The reaction mixture was warmed to rt and stirred for 4.5 h. The mixture was poured into ice water (7.5 mL), and the whole was extracted with AcOEt (2 x 40 mL, 1 x 20 mL). The combined organic layer was washed with brine (7.5 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified over SiO_2 column chromatography (AcOEt : *n*-hex. = 5 : 95 - 15 : 85) to afford (-)-**18** (a yellow oil, 639 mg, 71%, 82% brsm) and (-)-**7** (107 mg, 14%). $[\alpha]_D^{25}$ = -66.0 (*c* 1.0, $CHCl_3$); IR no characteristic absorption; ^{1}H-NMR δ_H 7.01 (1H, t, *J* = 8.2 Hz), 6.71 (1H, d, *J* = 10.1 Hz), 6.59 (1H, dd, *J* = 8.2, 0.9 Hz), 6.47 (1H, d, *J* = 8.2 Hz), 5.54 (1H, d, *J* = 10.1 Hz), 5.18 (2H, s), 5.09 (1H, t sept., *J* = 7.3, 1.4 Hz), 3.49 (3H, s), 2.18 - 2.03 (2H, m), 1.73 (1H, ddd, *J* = 14.1, 10.2, 6.4 Hz), 1.65 (1H, ddd, *J* = 14.1, 10.5, 6.2 Hz), 1.66 (3H, d, *J* = 0.9 Hz), 1.57 (3H, s), 1.39 (3H, s); ^{13}C-NMR δ_C 154.0, 152.8, 131.6, 128.9, 128.3, 124.1, 117.2, 111.4, 110.2, 106.4, 94.7, 78.0, 56.1, 41.1, 26.3, 25.6, 22.7, 17.6; LRMS (EI) *m/z* (%) 288 (M^+, 31), 273 (16), 205 (100), 175 (49), 161 (52); HRMS (EI) *m/z* 288.1722 (calcd. for $C_{18}H_{24}O_3$ 286.1726, Δ -0.4 mmu).

4.2.6. *(R)-6-Iodo-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-chromen-5-ol (**19**).* (-)-**18** (146 mg, 0.505 mmol) was dissolved in THF (3.0 mL) and cooled to -78 °C. After 10 min, *n*-BuLi (1.55 M in *n*-hex., 0.46 mL, 0.713 mmol) was added. After 10 min, the reaction mixture was warmed to rt and stirred for 40 min. After the mixture was cooled to -78 °C for 10 min, a solution of I_2 (154 mg, 0.606 mmol) in THF (1.1 mL) was added. The mixture was stirred at -78 °C for 10 min, then it was warmed to rt and stirred for 1 h. Sat. NH_4Cl (1.5 mL) was added to the mixture and the whole was extracted with AcOEt (1 x 10 mL, 2 x 3.0 mL). The combined organic layer was washed with 5%$Na_2S_2O_3$ (1 x 5.0 mL), brine (1 x 1.5 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was subjected to next reaction without further purification.

The residue described above was dissolved in ethanolic solution of *p*-TsOH monohydrate (35.9 mg (0.185 mmol) in 3.3 mL) and warmed to 50 °C. After the reaction mixture was stirred for 2 h, solvent was removed *in vacuo*. The residue was dissolved in AcOEt (8 mL) and washed with H_2O (1 x 2 mL). After the aqueous layer was extracted with AcOEt (2 x 4.0 mL), the combined organic layer was washed with brine (1 x 2.0 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified over SiO_2 column chromatography (AcOEt : *n*-hex. = 5 : 95) to afford (-)-**19** (a yellow oil, 87.8 mg, 47% from (-)-**18**). $[\alpha]_D^{25}$ = -41.6 (*c* 1.0, $CHCl_3$); IR ν_{max} 3385 cm^{-1}; ^{1}H-NMR δ_H 7.31 (1H, t, *J* = 8.7 Hz), 6.69 (1H, d, *J* = 10.1 Hz), 6.24 (1H, dd, *J* = 8.7, 0.9 Hz), 5.55 (1H, d, *J* = 10.1 Hz), 5.21 (1H, s, -OH), 5.08 (1H, t sept., *J* = 7.1, 1.4 Hz), 2.16 - 2.02 (2H, m), 1.73 (1H, ddd, *J* = 14.0, 10.1, 6.6 Hz), 1.64 (1H, ddd, *J* = 14.0, 10.1, 6.4 Hz), 1.66 (3H, d, *J* = 1.4 Hz), 1.57 (3H, s), 1.38 (3H, s); ^{13}C-NMR δ_C 154.9, 150.1, 136.5, 131.8, 128.7, 123.9, 117.6, 111.4, 109.5, 78.6, 74.7, 41.1, 26.3, 25.7, 22.7, 17.6; LRMS (EI) *m/z* (%) 370 (M^+, 12), 287 (100), 160 (17); HRMS (EI) *m/z* 370.0442 (calcd. for $C_{16}H_{19}IO_2$ 370.0430, Δ +1.2 mmu).

4.2.7. *(R)-6-Iodo-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-chromen-5-yl trifluoromethanesulfonate (**6**).* To a solution of (-)-**19** (75.6 mg, 0.204 mmol) in CH_2Cl_2 (0.5 mL) was added Et_3N (0.06 mL, 0.430 mmol), and the mixture was cooled to -78 °C. Tf_2O (0.04 mL, 0.238 mmol) was added and stirred for 20 min. After quenched with H_2O (0.3 mL), the mixture was warmed to rt. Additional H_2O (0.3 mL) was added, and the whole was extracted with Et_2O (1 x 5.0 mL, 2 x 2.5 mL). The combined organic layer was washed with brine (1 x 0.6 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was combined with another crude product, which was obtained from 87.8 mg (0.237 mmol) of (-)-**19**, and was purified over SiO_2 column chromatography ($CHCl_3$: *n*-hex. = 1 : 9) to afford (-)-**6** (a colorless oil, 180 mg, 81%). $[\alpha]_D^{26}$ = -39.7 (*c* 1.0, $CHCl_3$); IR no characteristic absorption; ^{1}H-NMR δ_H 7.56 (1H, d, *J* = 8.5 Hz), 6.60 (1H, d, *J* = 8.5 Hz), 6.59 (1H, d, *J* = 10.3 Hz), 5.73 (1H, d, *J* = 10.3 Hz), 5.07 (1H, t sept., *J* = 7.1, 1.4 Hz), 2.15 - 1.99 (2H, m), 1.77 (1H, ddd, *J* = 13.9, 10.3, 6.4 Hz), 1.66 (1H, ddd, *J* = 13.9, 10.8, 6.2 Hz), 1.66 (3H, d, *J* = 0.9 Hz), 1.56 (3H, s), 1.41 (3H, s); ^{13}C-NMR δ_C 155.0, 145.2, 139.4, 132.2, 132.1, 123.5, 118.5 (q, *J* = 319 Hz), 118.2, 117.3, 116.8, 79.2, 77.2, 40.9, 26.2, 25.7, 22.6, 17.6; LRMS (EI) *m/z* (%) 502 (M^+, 14), 487 (4), 419 (82), 286 (100); HRMS (EI) *m/z* 501.9924 (calcd. for $C_{17}F_3H_{18}IO_4S$ 501.9923, Δ + 0.1 mmu).

4.2.8. *4-Benzyloxy-2-triisopropylsiloxyfuran (**5a**).* To a solution of 4-benzyloxy-5*H*-furan-2-one (100 mg, 0.526 mmol) and Et_3N (0.10 mL, 0.717 mmol) in CH_2Cl_2 (0.5 mL), TIPSOTf (0.15 mL, 0.558 mmol) was added at 0 °C and the whole was stirred at 0 °C for 1 h. The mixture was diluted with hexane (anhydrous, 2.5 mL), washed with ice-cooled half sat. $NaHCO_3$ (2 x 1 mL) and ice-cooled brine (1 x 1 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was suspended in hexane (anhydrous, 1.5 mL) then filtered. The filtrate was concentrated *in vacuo* to give a mixture of **5a** and TIPSOH in 1 : 0.25 (a colorless oil, 154 mg, 89% w/w purity, 75% yield as **5a**). IR ν_{max} 1621 cm^{-1}; ^{1}H-NMR δ_H 7.42 - 7.30 (5H, m), 6.53 (1H, d, *J* = 1.4 Hz), 5.10 (1H, d, *J* = 1.4 Hz), 4.82 (2H, s), 1.29 - 1.20 (3H, m), 1.09 (18H, d, *J* = 7.1 Hz); ^{13}C-NMR δ_C 155.1, 149.3, 136.7, 128.5, 128.1, 127.7, 113.0, 79.3, 71.9, 17.5, 12.1; HRMS (DART+) *m/z* 347.2038 (M+H, calcd. for $C_{20}H_{31}O_3Si$ 347.2043, Δ -0.5 mmu).

4.2.9. *(R)-9-(Benzyloxy)-3-methyl-3-(4-methylpent-3-en-1-yl)-7-((triisopropylsilyl)oxy)-3H-benzo[f]chromen-10-ol (**23a**) and (R)-8-(benzyloxy)-3-methyl-3-(4-methylpent-3-en-1-yl)-10-((triisopropylsilyl)oxy)-3H-benzo[f]chromen-7-ol (**24a**).* To a solution of **5a** (159 mg, 90% w/w purity, 0.412 mmol) in THF (1.0 mL) was added a solution of (-)-**6** (172 mg, 0.343 mmol,

94% *ee*) in THF (3.5 mL) and cooled to -78 °C. *n*-BuLi (1.42 M in *n*-hex., 0.48 mL, 0.682 mmol) was added and the mixture was stirred for 20 min. After quenched with H_2O (3.5 mL), the mixture was warmed to rt. The whole was extracted with AcOEt (2 x 10 mL, 1 x 5 mL) and the combined organic layer was washed with H_2O and brine (1 x 1.5 mL each) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified over SiO_2 column chromatography (CH_2Cl_2 : *n*-hex. = 2 : 8 - 5 : 5) to afford **23a** (a pale red oil, 50.2 mg, 26%) and **24a** (a yellowish brown oil, 89.1 mg, 45%), respectively. The obtained hydroquinones were oxidized immediately.

4.2.10. *(R)-9-(Benzyloxy)-3-methyl-3-(4-methylpent-3-en-1-yl)-3H-benzo[f]chromene-7,10-dione (**25a**).* To a solution of **23a** (50.2 mg, 0.0876 mmol) in MeOH (1.8 mL) - CH_2Cl_2 (0.4 mL) was added aq. 1M $FeCl_3$ (0.18 mL, 0.18 mmol) and the mixture was stirred for 30 min at rt. H_2O (3.0 mL) was added and the whole was extracted with CH_2Cl_2 (2 x 10 mL, 1 x 5 mL). The combined organic layer was washed with H_2O and brine (1 x 2 mL each), and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by ODS MPLC (CH_3CN : H_2O = 9 : 1) to afford **25a** (an orange oil, 34.0 mg, 24% from (-)-**6**). $[\alpha]_D^{25}$ = +49.6 (*c* 0.61, $CHCl_3$); IR ν_{max} 1676, 1644, 1615 cm^{-1}; ^{1}H-NMR δ_H 7.92 (1H, d, *J* = 8.4 Hz, C6-H), 7.80 (1H, d, *J* = 10.5 Hz, C1-H), 7.45 - 7.33 (5H, m, Ar-H), 7.06 (1H, dd, *J* = 8.4, 0.7 Hz, C5-H), 6.11 (1H, s, C8-H), 5.90 (1H, d, *J* = 10.5 Hz, C2-H), 5.09 (2H, s, -OC*H*$_2$Ar), 5.07 (1H, t sept., *J* = 7.2, 1.5 Hz, C3'-H), 2.13 - 2.07 (2H, m, C2'-H_2), 1.78 (1H, ddd, *J* = 14.0, 9.4, 7.0 Hz, C1'-H), 1.68 (1H, ddd, *J* = 14.0, 10.1, 6.5 Hz, C1'-H), 1.65 (3H, d, *J* = 0.9 Hz, C4'-CH_3), 1.55 (3H, s, C4'-CH_3), 1.43 (3H, s, C3-CH_3); ^{13}C-NMR δ_C 184.2 (C7), 182.3 (C10), 159.4 (C9), 158.6 (C4a), 134.4 (C2), 134.3 (Ar), 132.1 (C4'), 128.8 (Ar), 128.6 (Ar), 128.1 (C6), 127.5 (Ar), 126.1 (C6a), 125.5 (C10a), 123.5 (C3'), 121.4 (C5), 121.2 (C10b), 120.2 (C1), 109.6 (C8), 79.2 (C3), 71.0 (-O*C*H_2Ph), 41.2 (C1'), 26.5 (C3-*C*H_3), 25.6 (C4'-*C*H_3), 22.6 (C2'), 17.6 (C4'-*C*H_3); HRMS (DART+) *m/z* 415.1891 (M+H, calcd. for $C_{27}H_{27}O_4$ 415.1909, Δ -1.8 mmu).

4.2.11. *9-(Benzyloxy)-1,1,3a-trimethyl-1a,2,3,3a-tetrahydro-1H-4-oxacyclobuta[3,4]indeno[5,6-a]naphthalene-7,10(1a^{1}H,10cH)-dione (**27a**).* (±)-**23a** (43.3 mg, 0.0756 mmol) which was obtained from **5a** (161 mg, 89% w/w purity, 0.414 mmol) and (±)-**6** (174 mg, 0.346 mmol), was treated with 1M $FeCl_3$ (0.15 mL, 0.15 mmol) in MeOH (1.5 mL) - CH_2Cl_2 (0.3 mL). The crude product was obtained in similar manner described at **25a** and was purified over SiO_2 column chromatography (AcOEt : *n*-hex. = 15 : 85) to afford **25a** containing trace amount of **27a**. A portion of the mixture (4.0 mg) was purified by ODS HPLC (CH_3CN : H_2O = 8 : 2) to afford **25a** (2.0 mg, estimated yield 41%) and **27a** (yellow solids, 0.1 mg, estimated yield 2%). IR ν_{max} 1684, 1647, 1618 cm^{-1}; ^{1}H-NMR δ_H 7.95 (1H, d, *J* = 8.2 Hz, C6-H), 7.44-7.33 (5H, m, Ar-H), 7.18 (1H, d, *J* = 8.2 Hz, C5-H), 6.09 (1H, s, C8-H), 5.14 (1H, d, *J* = 12.3 Hz, -OC*H*$_2$Ph), 5.09 (1H, d, *J* = 12.3 Hz, -OC*H*$_2$Ph), 4.20 (1H, d, *J* = 9.4 Hz, C10c-H), 2.63 (1H, t, *J* = 9.2 Hz, C1a^1-H), 2.50 (1H, dt, *J* = 3.9, 8.2 Hz, C1a-H), 1.99 (1H, dt, *J* = 6.0, 12.1 Hz, C3-H), 1.82-1.65 (3H, m, C2-H_2, C3-H), 1.63 (3H, s, C1-CH_3), 1.32 (3H, s, C3a-CH_3), 0.52 (3H, s, C1-CH_3); ^{13}C-NMR δ_C 184.7 (C7), 181.8 (C10), 159.54 (C4a*), 159.49 (C9*), 134.4 (Ar), 129.9 (C10a), 128.9 (Ar), 128.7 (Ar), 128.4 (C10b), 127.5 (Ar), 127.1 (C6a), 126.4 (C6), 124.2 (C5), 109.5 (C8), 84.9 (C3a), 71.1 (-*C*H_2Ph), 47.2 (C1a), 41.8 (C1), 40.6 (C3), 39.8 (C1a^1), 37.9 (C10c), 34.4 (C1-CH_3), 25.6 (C3a-CH_3), 25.2 (C2), 19.0 (C1-CH_3) *interchangeable; HRMS (DART+) *m/z* 415.1929 (M+H, calcd. for $C_{27}H_{27}O_4$ 415.1909, Δ +2.0 mmu).

4.2.12. *(R)-8-(Benzyloxy)-3-methyl-3-(4-methylpent-3-en-1-yl)-3H-benzo[f]chromene-7,10-dione (**26a**).* **26a** was prepared from **24a** (89.1 mg, 0.156 mmol) in similar conditions described at compound **25a**. The crude material was purified by ODS MPLC (CH_3CN : H_2O = 9 : 1) to afford **26a** (a yellow oil, 53.2 mg, 37% from (-)-**6**). $[\alpha]_D^{25}$ = +43.1 (*c* 0.62, $CHCl_3$); IR ν_{max} 1669, 1644, 1613 cm^{-1}; ^{1}H-NMR δ_H 8.00 (1H, d, *J* = 8.5 Hz, C6-H), 7.85 (1H, d, *J* = 10.5 Hz, C1-H), 7.44 - 7.32 (5H, m, Ar-H), 7.02 (1H, dd, *J* = 8.5, 0.7 Hz, C5-H), 6.09 (1H, s, C9-H), 5.87 (1H, d, *J* = 10.5 Hz, C2-H), 5.10 (2H, s, -OC*H*$_2$Ph), 5.07 (1H, t sept., *J* = 7.2, 1.4 Hz, C3'-H), 2.09 (2H, m, C2'-H_2), 1.78 (1H, ddd, *J* = 14.0, 9.2, 7.2 Hz, C1'-H), 1.69 (1H, ddd, *J* = 14.0, 9.9, 6.6 Hz, C1'-H), 1.65 (3H, d, *J* = 1.1 Hz, C4'-CH_3), 1.55 (3H, s, C4'-CH_3), 1.43 (3H, s, C3-CH_3); ^{13}C-NMR δ_C 187.8 (C10), 179.2 (C7), 159.8 (C4a), 158.2 (C8), 134.3 (Ar), 133.7 (C2), 132.1 (C4'), 129.2 (C6), 128.8 (Ar), 128.6 (Ar), 127.5 (Ar), 126.3 (C10a), 125.4 (C6a), 123.5 (C3'), 120.5 (C10b), 120.4 (C5*), 120.3 (C1*), 112.5 (C9), 79.5 (C3), 70.9 (-O*C*H_2Ph), 41.3 (C1'), 26.7 (C3-*C*H_3), 25.6 (C4'-*C*H_3), 22.6 (C2'), 17.6 (C4'-*C*H_3) *interchangeable; HRMS (DART+) *m/z* 415.1892 (M+H, calcd. for $C_{27}H_{27}O_4$ 415.1909, Δ -1.7 mmu).

4.2.13. *General procedure for the examination of regioselectivity in DAR of **4** and furans.* To a solution of (±)-**6** (50 mg, 0.10 mmol) in solvent (0.3 mL) was added a solution of furan (0.12 mmol) in solvent (1.0 mL) and cooled. *n*-BuLi (1.5 M in *n*-hex., 0.13 mL, 0.20 mmol) was added and the mixture was stirred for 30 min. After the reaction was quenched with H_2O (1.0 mL), the mixture was warmed to rt. The whole was extracted with AcOEt (3 x 5 mL) and the combined organic layer was washed with H_2O and brine (1 x 1 mL each) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was dissolved in MeOH (1.4 mL) - CH_2Cl_2 (0.3 mL). Aqueous 1M $FeCl_3$ (0.14 mL, 0.14 mmol) was added to the solution, and the mixture was stirred for 30 min. H_2O (3.0 mL) was added and the whole was extracted with CH_2Cl_2 (2 x 10 mL, 1 x 5 mL). The combined organic layer was washed with H_2O and brine (1 x 2 mL each), and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was analyzed by ^{1}H-NMR.

4.2.14. *2-tert-Butyldiphenylsiloxy-4-benzyloxyfuran (**28**).* **28** (a brown oil, 234.7 mg, quant.) was prepared from 4-benzyloxy-5*H*-furan-2-one (100 mg, 0.527 mmol) in similar conditions described at compound **5a**. IR ν_{max} 1616 cm^{-1}; ^{1}H-NMR δ_H 7.71 - 7.68 (4H, m), 7.47 - 7.29 (11H, m), 6.50 (1H, d, *J* = 1.3 Hz), 4.76 (1H, d, *J* = 1.3 Hz), 4.73 (2H, s), 1.11 (9H, s); ^{13}C-NMR δ_C 154.4, 149.0, 135.4, 131.6, 130.2, 128.5, 128.0, 127.8, 127.7, 113.4, 80.2, 71.9, 26.4, 19.3; HRMS (DART+) *m/z* 429.1892 (M+H, calcd. for $C_{27}H_{29}O_3Si$ 429.1886, Δ +0.6 mmu).

4.2.15. *(3R,4R)-3,4-Dihydroxytetrahydrofuran-2-one.* Title compound was synthesized from D-araboascorbic acid along with a report of Pavlik *et al* (see reference 20a). The obtained residue was extracted with hot AcOEt repeatedly, and the combined extract was concentrated. The crude material was recrystallized from AcOEt to give title compound. Mp 102 - 103 °C.

4.2.16. *3-(Benzyloxy)furan-2(5H)-one.* To a mixture of (3*R*,4*R*)-3,4-dihydroxytetrahydrofuran-2-one (592 mg, 5.02 mmol) and

Ag_2O (5.22 g, 22.5 mmol) in DMF (7.5 mL) was added BnBr (2.0 mL, 16.8 mmol) and was stirred at 70 °C for 16 h. The whole was filtered through Celite® pad, and the filtrate was concentrated *in vacuo*. The residue was purified over SiO_2 column chromatography (AcOEt : *n*-hex. = 30 : 70 - 50 : 50) to afford title compound (brown amorphous solids, 348 mg, 36%). Mp 80 - 82 °C; IR ν_{max} 1763, 1653 cm^{-1}; ^{1}H-NMR δ_H 7.41 - 7.32 (5H, m), 6.14 (1H, t, *J* = 2.1 Hz), 5.04 (2H, s), 4.75 (2H, d, *J* = 2.1 Hz); ^{13}C-NMR δ_C 168.1, 145.6, 134.8, 128.7, 128.6, 127.6, 114.2, 72.8, 67.5; HRMS (DART+) *m/z* 191.0701 (M+H, calcd. for $C_{11}H_{11}O_3$ 191.0708, Δ -0.7 mmu).

4.2.17. *2-Triisopropylsilyloxy-3-benzyloxyfuran (**29**).* A mixture of **29** and TIPSOH in 1 : 0.23 (a yellow oil, 169.2 mg, 90% w/w purity, 84% yield as **29**) was prepared from 3-(benzyloxy)furan-2(5*H*)-one (99.6 mg, 0.524 mmol) in similar conditions described at compound **5a**. IR ν_{max} 1665 cm^{-1}; ^{1}H-NMR δ_H 7.40 - 7.27 (5H, m), 6.59 (1H, d, *J* = 2.5 Hz), 6.15 (1H, d, *J* = 2.5 Hz), 4.91 (2H, s), 1.29 - 1.20 (3H, m), 1.09 (18H, d, *J* = 7.3 Hz); ^{13}C-NMR δ_C 144.6, 137.7, 128.6, 128.3, 127.8, 121.7, 107.0, 74.5, 17.5, 12.3 (one sp^2 carbon is missing); HRMS (DART+) *m/z* 347.2028 (M+H, calcd. for $C_{20}H_{31}O_3Si$ 347.2043, Δ -1.5 mmu).

4.2.18. *(R)-(+)-Teretifolione B (**2**).* To a solution of **25a** (12.2 mg, 0.0294 mmol) in EtOH (1.0 mL) was added 1M KOH (0.20 mL, 0.200 mmol) and the mixture was stirred at rt for 30 min. 5% HCl (1.0 mL) was added and the whole was extracted with AcOEt (1 x 10 mL, 2 x 5 mL). The combined organic layer was washed with brine (1 x 2 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was dissolved in CH_3CN : H_2O = 1 : 1 (5.0 mL) and the solvent was removed *in vacuo*. This operation was repeated four times for azeotropic removal of BnOH with H_2O. The residue was purified over SiO_2 column chromatography (MeOH : $CHCl_3$ = 0 : 100 - 1 : 99) to afford **2** (an orange oil, 7.5 mg, 79%, 93% *ee*). $[\alpha]_D^{25}$ = +73.4 (*c* 0.10, MeOH); IR ν_{max} 3357, 1652 cm^{-1}; ^{1}H-NMR δ_H 7.97 (1H, d, *J* = 8.4 Hz), 7.83 (1H, d, *J* = 10.5 Hz), 7.50 (1H, br s), 7.10 (1H, d, *J* = 8.4 Hz), 6.26 (1H, s), 5.96 (1H, d, *J* = 10.5 Hz), 5.08 (1H, t sept., *J* = 7.1, 1.3 Hz), 2.18 - 2.02 (2H, m), 1.80 (1H, ddd, *J* = 14.0, 9.6, 6.8 Hz), 1.71 (1H, ddd, *J* = 14.0, 10.2, 6.4 Hz), 1.66 (3H, s), 1.56 (3H, s), 1.48 (3H, s); ^{13}C-NMR δ_C 184.4, 184.0, 158.2, 156.3, 135.5, 132.2, 128.7, 127.0, 123.4, 123.3, 122.2, 121.6, 120.0, 109.0, 79.4, 41.2, 26.6, 25.6, 22.6, 17.6; HRMS (DART+) *m/z* 325.1424 (M+H, calcd. for $C_{20}H_{21}O_4$ 325.1440, Δ -1.6 mmu).

4.2.19. *(R)-8-Hydroxy-3-methyl-3-(4-methylpent-3-en-1-yl)-3H-benzo[f]chromene-7,10-dione (**30a**).* **30a** was prepared from **26a** (11.7 mg, 0.0282 mmol) in similar conditions described at compound **2**. The crude material was purified over SiO_2 column chromatography (MeOH : $CHCl_3$ = 0 : 100 - 1 : 99) to afford **30a** (an orange oil, 9.1 mg, 99%, 94% *ee*). $[\alpha]_D^{25}$ = +57.1 (*c* 0.10, MeOH); IR ν_{max} 3330, 1647 cm^{-1}; ^{1}H-NMR δ_H 7.98 (1H, d, *J* = 8.5 Hz, C6-H), 7.90 (1H, dd, *J* = 10.5, 0.7 Hz, C1-H), 7.02 (1H, dd, *J* = 8.5, 0.7 Hz, C5-H), 6.22 (1H, s, C9-H), 5.90 (1H, d, *J* = 10.5 Hz, C2-H), 5.07 (1H, t sept., *J* = 7.1, 1.4 Hz, C3'-H), 2.14 - 2.05 (2H, m, C2'-H), 1.80 (1H, ddd, *J* = 14.0, 8.8, 7.6 Hz, C1'-H), 1.69 (1H, ddd, *J* = 14.0, 9.6, 6.9 Hz, C1'-H), 1.65 (3H, d, *J* = 1.1 Hz, C4'-C*H*$_3$), 1.56 (3H, s, C4'-C*H*$_3$), 1.45 (3H, s, C3'-C*H*$_3$); ^{13}C-NMR δ_C 188.1 (C10), 180.7 (C7), 161.0 (C4a), 155.3 (C8), 134.0 (C2), 132.2 (C4'), 129.2 (C6), 127.2 (C10a), 123.44 (C3'), 123.36 (C6a), 121.3 (C10b), 120.3 (C1), 120.1 (C5), 111.6 (C9), 79.8 (C3), 41.4 (C1'), 26.8 (C3-*C*H$_3$), 25.6 (C4'-*C*H$_3$), 22.6 (C2'), 17.6 (C4'-*C*H$_3$); HRMS (DART+) *m/z* 325.1424 (M+H, calcd. for $C_{20}H_{21}O_4$ 325.1440, Δ -1.6 mmu).

4.2.20. *(R)-9-(Benzyloxy)-3,8-dimethyl-3-(4-methylpent-3-en-1-yl)-7-((triisopropylsilyl)oxy)-3H-benzo[f]chromen-10-ol (**23b**) and (R)-8-(benzyloxy)-3,9-dimethyl-3-(4-methylpent-3-en-1-yl)-10-((triisopropylsilyl)oxy)-3H-benzo[f]chromen-7-ol (**24b**).* Hydroquinones **23b** and **24b** were prepared by Diels-Alder reaction of furan **5b** (459 mg, 89% w/w purity, 1.13 mmol) and benzyne derived from (-)-**6** (472 mg, 0.940 mmol) in similar conditions described at compound **23a** and **24a**. The crude material was purified over SiO_2 column chromatography ($CHCl_3$: *n*-hex. = 2 : 8 - 5 : 5) to afford **23b** (a red oil, 166 mg, 30%) and **24b** (a yellow oil, 245 mg, 44%). The obtained hydroquinones were oxidized immediately.

4.2.21. *(R)-9-(Benzyloxy)-3,8-dimethyl-3-(4-methylpent-3-en-1-yl)-3H-benzo[f]chromene-7,10-dione (**25b**).* **25b** was prepared from **23b** (166 mg, 0.284 mmol) in similar conditions described at compound **25a**. The crude material was purified by ODS MPLC (CH_3CN : H_2O = 9 : 1) to afford **25b** (an orange oil, 151 mg, 28% from **6**). $[\alpha]_D^{25}$ = +48.0 (*c* 0.99, $CHCl_3$); IR ν_{max} 1646 cm^{-1}; ^{1}H-NMR δ_H 7.91 (1H, d, *J* = 8.5 Hz), 7.77 (1H, d, *J* = 10.4 Hz), 7.44 - 7.31 (5H, m), 7.02 (1H, d, *J* = 8.5 Hz), 5.90 (1H, d, *J* = 10.4 Hz), 5.30 (2H, s), 5.08 (1H, tt, *J* = 7.2, 1.3 Hz), 2.16 - 2.06 (2H, m), 1.99 (3H, s), 1.82 - 1.68 (2H, m), 1.66 (3H, s), 1.57 (3H, s), 1.42 (3H, s); ^{13}C-NMR δ_C 185.0, 183.7, 158.6, 157.3, 136.8, 134.0, 132.1, 131.6, 128.6, 128.4, 128.3, 126.3, 126.0, 123.6, 120.9, 120.7, 120.3, 79.2, 74.8, 41.2, 26.5, 25.6, 22.6, 17.6, 9.4 (one sp^2 carbon is missing); LRMS (EI) *m/z* (%) 428 (M^+, 6), 359 (15), 346 (17), 345 (67), 255 (100), 227 (36), 105 (26); HRMS (EI) *m/z* 428.1993 (calcd. for $C_{28}H_{28}O_4$ 428.1988, Δ -0.5 mmu).

4.2.22. *(R)-8-(Benzyloxy)-3,9-dimethyl-3-(4-methylpent-3-en-1-yl)-3H-benzo[f]chromene-7,10-dione (**26b**).* **26b** was prepared from **24b** (245 mg, 0.417 mmol) in similar conditions described at compound **25a**. The crude material was purified over ODS MPLC (CH_3CN : H_2O = 9 : 1) to afford **26b** (an orange oil, 68.4 mg, 84%, 17% from **6**). $[\alpha]_D^{26}$ = +49.5 (*c* 0.98, $CHCl_3$); IR ν_{max} 1656 cm^{-1}; ^{1}H-NMR δ_H 7.93 (1H, d, *J* = 8.5 Hz), 7.81 (1H, d, *J* = 10.5 Hz), 7.45 - 7.41 (2H, m), 7.39 - 7.31 (3H, m), 7.01 (1H, dd, *J* = 8.5, 0.7 Hz), 5.87 (1H, d, *J* = 10.5 Hz), 5.40 (2H, s), 5.07 (1H, t sept., *J* = 7.1, 1.4 Hz), 2.09 (2H, m), 1.98 (3H, s), 1.78 (1H, ddd, *J* = 13.9, 9.3, 7.2 Hz), 1.68 (1H, ddd, *J* = 13.9, 10.1, 6.4 Hz), 1.65 (3H, d, *J* = 0.9 Hz), 1.56 (3H, s), 1.43 (3H, s); ^{13}C-NMR δ_C 188.4, 180.6, 159.3, 155.7, 136.9, 133.8, 133.6, 132.1, 128.54, 128.50, 128.3, 126.6, 125.7, 123.6, 120.5, 120.4, 79.3, 74.8, 41.2, 26.6, 25.6, 22.6, 17.6, 9.8 (two sp^2 carbons are missing); LRMS (EI) *m/z* (%) 428 (M^+, 6), 345 (100), 269 (16), 255 (30), 226 (25), 91 (83); HRMS (EI) *m/z* 428.1990 (calcd. for $C_{28}H_{28}O_4$ 428.1988, Δ +0.2 mmu).

4.2.23. *(R)-(+)-Methylteretifolione B (**3**).* **3** was prepared from **25b** (18.6 mg, 0.0434 mmol) in similar conditions described at compound **2**. The crude material was purified over SiO_2 column chromatography (AcOEt : *n*-hex. = 1 : 9) to afford **3** (an orange oil, 6.8 mg, 46%, 95% *ee*). $[\alpha]_D^{25}$ = +35.0 (*c* 0.35, $CHCl_3$); IR ν_{max} 3359, 1654, 1625 cm^{-1}; ^{1}H-NMR δ_H 7.98 (1H, d, *J* = 8.2 Hz), 7.84 (1H, d, *J* = 10.8 Hz), 7.44 (1H, s, -OH), 7.06 (1H, dd, *J* = 8.2, 0.9 Hz), 5.94 (1H, d, *J* = 10.8 Hz), 5.08 (1H, t sept., *J* = 7.1, 1.4 Hz), 2.14 - 2.07 (2H, m), 2.07 (3H, s), 1.79 (1H, ddd, *J* = 13.9, 9.4, 6.9 Hz), 1.69 (1H, ddd, *J* = 13.9, 10.2, 6.6 Hz), 1.65 (3H, d, *J* = 1.4 Hz), 1.56 (3H, s), 1.44 (3H, s); ^{13}C-NMR δ_C

184.5, 183.3, 158.0, 153.3, 135.1, 132.2, 128.8, 127.0, 123.5, 123.3, 121.7, 121.3, 120.1, 118.6, 79.3, 41.3, 26.6, 25.6, 22.6, 17.6, 8.6; LRMS (EI) *m/z* (%) 338 (M^+, 22), 323 (6), 255 (100), 227 (36); HRMS (EI) *m/z* 338.1517 (calcd. for $C_{21}H_{22}O_4$ 338.1518, Δ -0.1 mmu).

4.2. 24. *(R)-8-Hydroxy-3,9-dimethyl-3-(4-methylpent-3-en-1-yl)-3H-benzo[f]chromene-7,10-dione (**30b**).* **30b** was prepared from **26b** (19.5 mg, 0.0455 mmol) in similar conditions described at compound **2**. The crude material was purified over SiO_2 column chromatography (AcOEt : *n*-hex. = 8 : 92) to afford **30b** (an orange oil, 2.2 mg, 14%, 97% *ee*). $[\alpha]_D^{25}$ = +74.7 (*c* 0.24, $CHCl_3$); IR (ATR) ν_{max} 3342, 1645 cm^{-1}; ^{1}H-NMR δ_H 7.95 (1H, d, *J* = 8.2 Hz, C6-H), 7.90 (1H, dd, *J* = 10.5, 0.9 Hz, C1-H), 7.28, (1H, br s, -OH), 6.99 (1H, dd, *J* = 8.2, 0.9 Hz, C5-H), 5.89 (1H, d, *J* = 10.5 Hz, C2-H), 5.07 (1H, t sept., *J* = 7.1, 1.4 Hz, C3'-H), 2.09 (2H, m, C2'-H_2), 2.05 (3H, s, C9-CH_3), 1.79 (1H, ddd, *J* = 14.2, 9.4, 7.1 Hz, C1'-H), 1.69 (1H, ddd, *J* = 14.2, 10.1, 6.9 Hz, C1'-H), 1.65 (3H, d, *J* = 0.9 Hz, C4'-CH_3), 1.56 (3H, s, C4'-CH_3), 1.44 (3H, s, C3-CH_3); ^{13}C-NMR δ_C 188.0 (C10), 180.1 (C7), 160.6 (C4a), 152.2 (C8), 133.8 (C2), 132.2 (C4'), 128.7 (C6), 127.4 (C10a), 123.5 (C3'), 123.4 (C6a), 121.4 (C10b), 120.8 (C9), 120.6 (C1), 119.9 (C5), 79.6 (C3), 41.3 (C1'), 26.7 (C3-CH_3), 25.7 (C4'-CH_3), 22.6 (C2'), 17.6 (C4'-CH_3), 8.9 (C9-CH_3); LRMS (EI) *m/z* (%) 338 (M^+, 11), 279 (15), 255 (100), 227 (22), 167 (35); HRMS (EI) *m/z* 338.1517 (calcd. for $C_{21}H_{22}O_4$ 338.1518, Δ -0.1 mmu).

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Supplementary material

Supplementary data (Experimental procedures for synthesis of (±)-**2**, experimental data of S1, ^{1}H and ^{13}C NMR spectra and chiral HPLC chromatograms) associated with this article can be found in the online version, at

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