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First total synthesis of antihypertensive natural products S-(+)-XJP and R-(-)-XJP

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Abstract: The first asymmetric total synthesis of antihypertensive natural products S-(+)-XJP and R-(-)-XJP have been achieved in 8 steps starting from commercially available 6-bromo-2-hydroxy-3-methoxybenzaldehyde **6**. Key steps include intramolecular Heck reaction and oxidative ozonolysis reaction with the retention of stereochemistry. Latent functionality strategy was implemented to circumvent the racemisation in this endeavor. The protocol described here provided a fast and easy access synthetic method to obtain optically pure isochroman-4-one derivatives. Furthermore, the in vivo antihypertensive effects of (±)-XJP, S-(+)-XJP and R-(-)-XJP were investigated on spontaneously hypertensive rats (SHRs), the obtained results could provide the valuable information to identify a promising lead for further chemical modification research.

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Introduction

Medicinal plants and natural products continue to play significant roles in drug discovery and development. *Musa sapientum* L. are mainly grown in the tropical and subtropical countries and are widely used for its nutritional values all over the world. The fruits as well as the other parts of the plant have been widely used as a folk medicine for antihypertension, antiulceration, antibacterial and so on.[1]

In 2007, we firstly reported a novel and structurally unique isochromanone compound (±)-XJP (1, Fig. 1), isolated from the peel of *Musa sapientum* L.[2] In our previous investigation, the structure of (±)-XJP was determined by spectroscopic analysis and its total synthesis has been achieved.[3] It has been documented that (±)-XJP exerted a large variety of biological activities including antioxidative, antiinflammatory, antihypertension and cardioprotective.[4] Utilizing (±)-XJP as a lead, we have successfully designed and synthesized a series of derivatives to develop new antihypertensive agents.[5]

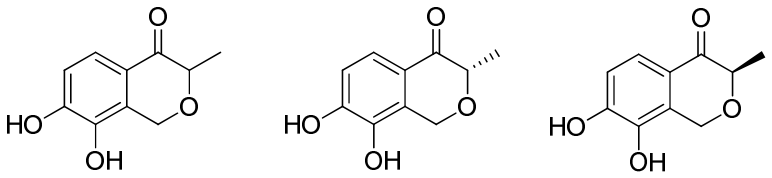
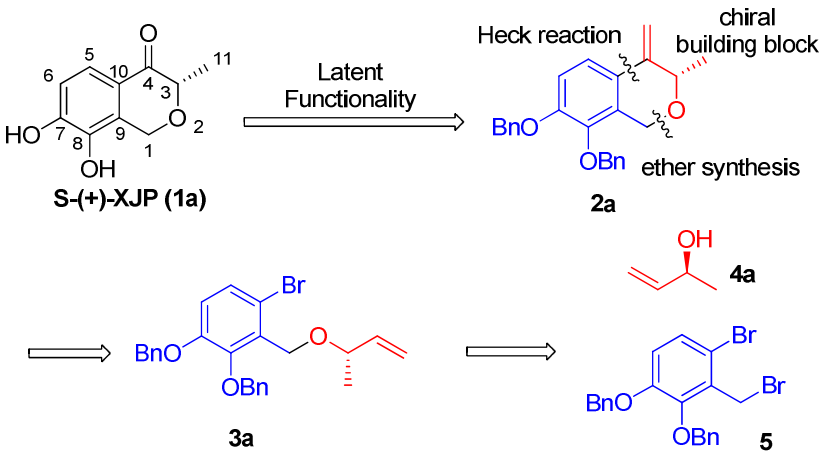


Fig. 1. Chemical structures of compounds **1**, **1a** and **1b**.

In the further research, the two enantiomers were obtained by Supercritical Fluid Chromatography and its absolute configuration was established by CD spectroscopy. Interestingly, evaluation of antihypertensive effects in vivo showed that the two enantiomers of (±)-XJP showed different profiles of antihypertensive activity, R-(-)-XJP (**1b**) exhibited somewhat potent antihypertensive activity than (±)-XJP and S-(+)-XJP (**1a**), which demonstrated that R-(-)-XJP played a more important role in the antihypertensive effect of (±)-XJP. In order to identify the promising lead for further structure optimization research, we focused on the asymmetric synthesis of the enantiomers. Initially, we attempted the asymmetric synthesis of single enantiomer of (±)-XJP via Parham cyclization reaction. Unfortunately, due to the racemisation in preparation process we got a disappointed result, The ee value of the final product was only 34%.[6] In continuation of our interest to find promising lead for drug

discovery, it was very desirable to find an efficient and general approach to prepare single enantiomer of (±)-XJP.

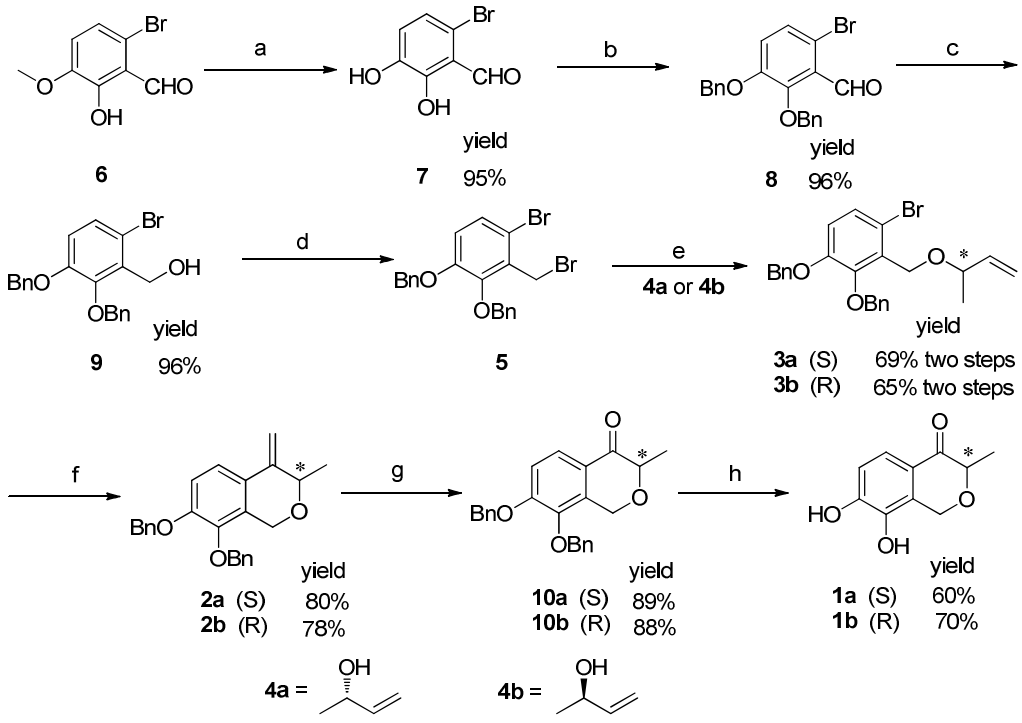
In this work, firstly, we explored the total synthesis of S-(+)-XJP, partly because the chiral building block was more economic, on the other hand, the total synthesis process of S-(+)-XJP could provide references for further synthesis of R-(-)-XJP. As a target for a total synthesis endeavor, S-(+)-XJP presents quite a significant challenge. Due to the keto-enol/enolate equilibria under the effect of a β-oxygen substituent in the isochroman-4-one system,[7] the chiral carbon at C3 position racemized easily during preparation process, especially under vigorous reaction conditions; In fact, in the process for extraction and separation of XJP, a great degree of racemisation occurred, indicating that this product is prone to racemisation. Meanwhile, in J. Stephen′s work, they also observed a gradual decline in the ee value of the similar products when reaction times were prolonged.[8] Therefore, it was conceivable that erosion of ee by racemisation resulted from isochroman-4-one system was an issue that cannot be easily avoided. In order to circumvent the difficulties, we recognized the importance of a flexible strategy through which the isochroman-4-one core be constructed with no racemisation occurred. Herein, we wish to report the first asymmetric total synthesis of S-(+)-XJP and R-(-)-XJP via intramolecular Heck reaction based on a latent functionality strategy.



Scheme 1. Retrosynthetic strategy for the syntheis of **S-(+)-XJP (1a)**.

Results and discussion

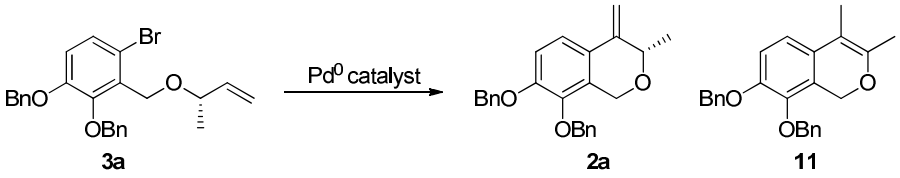
The retrosynthetic analysis is shown in Scheme 1. We envisioned that compound **2a** would be an advanced precursor of S-(+)-XJP **1a**. With an exocyclic double bond as the masked carbonyl equivalent of the carbonyl group, keto-enol tautomerism would not occur and the exocyclic double bond could stabilize the stereochemistry of the methyl group at C3 position in contrast to the carbonyl group. Then Intermediate **2a** would be accessed via intramolecular Heck reaction from ether **3a**, and the ether **3a** could be prepared from fragment **5** and (S)-but-3-en-2-ol **4a**. The requisite alcohol **4a** could be easily obtained from L-ethyl lactate via a routine synthesis.[9] In addition, we initially reviewed our previous experiments and found it would be a good choice to use benzyl group (Bn) as protecting group, as it could be removed under neutral condition avoiding the possible racemisation in the final step.



Reagents and conditions: (a) BBr_3, 0 °C, dry CH_2Cl_2, 3 h; (b) BnBr/K_2CO_3/KI, DMF, 80 °C, overnight; (c) $NaBH_4$, MeOH, rt, 30 min; (d) PPh_3/NBS, dry CH_2Cl_2, 1 h; (e) NaH/DMF, room temperature, 1.5 h; (f) $Pd(PPh_3)_4/Ag_2CO_3$/TEBA, DMF-H_2O, 4 h; (g) O_3, -78 °C,10-15 min, then PPh_3; (h) Pd-C/H_2, THF, rt, 4 h.

Scheme 2. The synthetic route toward **S-(+)-XJP** and **R-(-)-XJP.**

As shown in Scheme 2, commercially available benzaldehyde **6** was chosen as the starting material for the total synthesis of S-(+)-XJP. A known procedure was carried out with boron tribromide to give dihydroxybenzaldehyde **7** in excellent yield.[10] Protection of the both phenolic hydroxyl groups were realized by benzyl bromide under a modified protocol reported by Rastetter in 96% yield.[11] Bromobenzyl alcohol **9** was obtained by reducing benzyl-protected intermediate **8** with $NaBH_4$. Conversion of bromobenzyl alcohol **9** into bromobenzyl **5** using PPh_3/NBS in dry CH_2Cl_2, followed by ether synthesis with (S)-but-3-en-2-ol **4a** gave the compound **3a** in 69% yield over two steps.

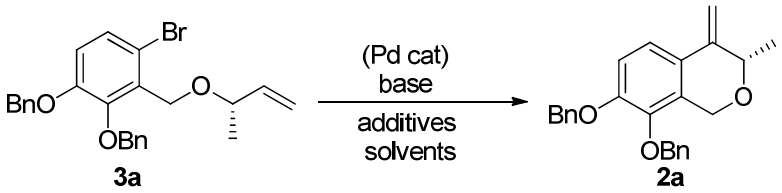


Scheme 3. Possible products **2a** and **11** of the Heck reaction

After obtained the compound **3a**, we turned our attention to the construction the skeleton of isochroman-4-one via intramolecular Heck reaction. There would be possibly two types of products from the intramolecular Heck reaction of **3a**, which was observed in many cases.[12] One was the desired methylene-isochroman **2a** but the other was isochromene **11**, which was more thermodynamically favored (Scheme 3). As a key step, it was reasonable to study the reaction in detail. So several reaction conditions were investigated and the selected results were summarized in Table 1. When using $Pd(OAc)_2$ as the catalyst, the solvent and the additive were both crucial for the cyclization (Table 1, entry 1, 2 and 3). It was interesting that the reaction was sensitive to some bases (Table 1, entry 3-5). Compound **2a** was formed in moderate yield when using 10 mol % $Pd(OAc)_2$ as the catalyst, K_2CO_3 as the base, and DMF as the solvent, while the other two bases, Cs_2CO_3 and Ag_2CO_3, suffered from incomplete conversion (50% yield at best) even with prolonged reaction time. To our surprise, under the catalysis of $Pd(PPh_3)_4$, using DMF as the solvent and K_2CO_3 as the base, the desired compound **2a** was not obtained in a detectable yield, only product **11** was detected (Table 1, entry 6). Fortunately, we found that H_2O could significantly promoted the reaction and reduce reaction time (Table 1, entry 7-10).[13] The best result was achieved when the reaction was performed with 10 mol % $Pd(PPh_3)_4$, Ag_2CO_3 (2

equiv), and TEBA (2 equiv) in DMF-H_2O (V:V= 3:1) under 80 ^oC for 4 h. Under this reaction condition, it could afford **2a** in 80% yield, with very small amount of byproduct **11** formed (entry 9, Table 1).

Table 1. Preparation of methyleneisochroman **2a** by intramolcular Heck reaction.



3a **2a**

Entry	Catalyst	Solvents[a]	Base	Additive[b]	PPh_3(eq)	T(℃)	T(h)	Yield(%)[c]
1	$Pd(OAc)_2$	DMF	K_2CO_3	-	0.2	80	>36	-[d]
2	$Pd(OAc)_2$	CH_3CN	K_2CO_3	TEBA	0.2	80	>36	-[d]
3	$Pd(OAc)_2$	DMF	K_2CO_3	TEBA	0.2	80	4	67
4	$Pd(OAc)_2$	DMF	Cs_2CO_3	TEBA	0.2	80	>36	-[d]
5	$Pd(OAc)_2$	DMF	Ag_2CO_3	TEBA	0.2	80	>36	-[d]
6	$Pd(PPh_3)_4$	DMF	K_2CO_3	TEBA	-	80	24	trace
7	$Pd(PPh_3)_4$	DMF-H_2O	K_2CO_3	TEBA	-	80	4	56
8	$Pd(PPh_3)_4$	DMF-H_2O	Cs_2CO_3	TEBA	-	80	4	60
9	$Pd(PPh_3)_4$	DMF-H_2O	Ag_2CO_3	TEBA	-	80	4	80
10	$Pd(PPh_3)_4$	DMF-H_2O	TEA	TEBA	-	80	6	38

[a] DMF-H_2O (V:V= 3:1); [b] TEBA: benzyltriethylammonium chloride; [c] isolated yield;

[d] the starting material cannot converse totally even with prolonged reaction time.

In the next step, the exocyclic double bond, strategically introduced as a latent carbonyl group, had to be exposed. We chose ozonolysis reaction to cleave the double bond. This method was generally carried out under -78 ^oC without any base or acid. The neutral condition and ultra low temperature were both favored to the retention of stereochemistry at C3 position. As expected, the reaction was performed smoothly in 89% yield. Finally, removal of the benzyl group using H_2 and Pd/C furnished **1a** with excellent enantiopurity [14] (ee, 96.5%, by chiral HPLC) in 60% yield. The spectral data (^{1}H-NMR and ^{13}C-NMR) and specific rotation of **1a** were in full agreement with the reported values.[3] It should be noted that the ee value (96.5%, by chiral HPLC) of the final product **1a** was in accordance with the chiral building block (S)-but-3-en-2-ol (**4a**) (ee, 96.6%, by chiral HPLC) indicating that we have successfully avoided racemisation in the synthetic process and our strategy worked to excellent in this endeavor. Following the synthetic sequence outlined in Scheme 2 for the synthesis of S-(+)-XJP (**1a**), (R)-but-3-en-2-ol was elaborated to R-(-)-XJP (**1b**) (ee, 96.5%, by chiral HPLC).[15]

Furthermore, in vivo antihypertensive effects of the synthetic two enantiomers and (±)-XJP were studied on spontaneously hypertensive rats (SHRs). As shown in Table 2, S-(+)-XJP exhibited a slight decrease in the systolic arterial blood pressure (SAP) of SHRs, while the SAP of SHRs treated with (±)-XJP and R-(-)-XJP was reduced significantly throughout the observation period, especially the maximum reduction rate of blood pressure by R-(-)-XJP was nearly 30% at 6 h. Moreover, the antihypertensive activity of R-(-)-XJP was more potent than that of (±)-XJP (22.3% at 6 h). It is demonstrated that R-(-)-XJP displayed more effective than (±)-XJP and S-(+)-XJP, which was consistent with previous results.[6] The obtained results could aid in selecting an optimal lead for further research.

Table 2. Antihypertensive effects of (±)-XJP and its enantiomers on SAP in SHRs.

	SAP (mm Hg) [a]				Change rate (%)[b]			
T (h)	control	(±)-XJP	(+)-XJP	(-)-XJP	control	(±)-XJP	(+)-XJP	(-)-XJP
0	179.50±9.16	180.2 ± 11.4	185.2 ± 15.4	187.3±17.2	–	–	–	–
1	180.20±14.22	170.9 ± 17.2	179.5 ± 10.3	174.2±18.9	-0.4	5.2	3.3	7.0
2	175.40±19.55	165.4 ± 20.8	175.8 ±13.5	166.6±25.1*	2.2	8.2	5.1	11.1
4	174.87±13.44	151.5 ± 21.3*	162.9± 15.7*	157.2±19.4*	2.6	15.9	12.0	16.1
6	175.43±16.01	140.1 ± 24.5**	155.1 ± 11.3*	132.1±20.7**	2.3	22.3	16.3	29.5
8	173.89±14.35	150.6 ± 23.6*	162.6± 19.2*	151.8±29.5**	3.1	16.4	12.2	19.0

[a] values are expressed in mean ± SD, n = 10. *p < 0.05, **p < 0.01 as compared with the respective control, dosage of XJP was taken as 80 mg·Kg^{-1}.

[b] Change rate (%)=SAP (at 0 h) – SAP (at 1-8h) / SAP (at 0 h) x 100.

Conclusions

In summary, starting from commercially available material, the first total synthesis of S-(+)-XJP (**1a**) and R-(-)-XJP (**1b**) were achieved efficiently in 8 steps with about 25% overall yield under mild conditions and the ee values were up to 96.5%. The key step in this approach was H_2O-promoted intramolecular Heck reaction. A functional group equivalency concept has been garnered to ensure the kept stereochemistry at C3 position. The protocol described here provided a practical synthetic method for optically pure isochroman-4-one derivatives. The bioactivity evaluation verified that R-(-)-XJP is more potent than (±)-XJP and S-(+)-XJP on antihypertensive activity. Therefore, R-(-)-XJP will be selected as an optimal lead for further chemical modification to find potential antihypertensive candidates. Moreover, the

investigation involving target identification, target validation and the mechanism with R-(-)-XJP are currently in progress and will be reported in due course.

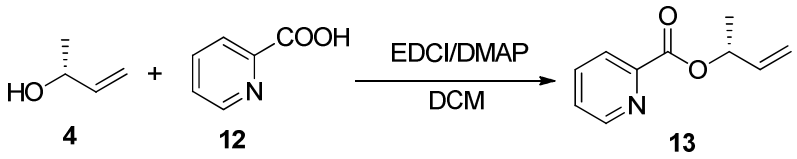
Experimental

General

All commercially available starting materials and solvents were reagent grade and used without further purification unless otherwise noted. Anhydrous CH_3CN and DMF were obtained by distillation over CaH_2. ^{1}H-NMR and ^{13}C NMR spectra were recorded on Bruker-300 spectrometers, and were referenced to the residual peaks of $CHCl_3$ at 7.26 ppm or DMSO-d_6 at 2.50 ppm (^{1}H-NMR) and $CDCl_3$ at 77.23 ppm or DMSO-d_6 at 39.52 ppm (^{13}C-NMR). Chemical shifts (δ) were reported relative to residual protic solvent signals. HRMS was performed on an Agilent 6530 Q-TOF mass spectrometer, and ESI-MS was carried out on an Agilent 6120 mass spectrometer. TLC was performed on Huanghai HSGF 254 silica gel plates (China). Silica gel 60 H (200-300 mesh), manufactured by Qingdao Haiyang Chemical Group Co., Ltd (China) was used for general chromatography.

(S)-but-3-en-2-ol (4a)

(S)-but-3-en-2-ol was prepared from L-ethyl lactate according to a standard procedure. [9] Enantiomeric excess (ee) was determined by chiral HPLC base on the ester **13**.



4 **12** **13**

To a solution of (S)-but-3-en-2-ol **4a** (0.032 g, 0.44 mmol) and picolinic acid (0.05 g, 0.4 mmol) in CH_2Cl_2 (2 mL) was added EDCI (0.15 g, 0.8 mmol), DMAP (trace). The reaction mixture was stirred overnight at room temperature. Then the mixture was concentrated *in vacuo*, and the residue was purified by a silica gel column chromatography (petrol ether/ethyl acetate (V/V) = 4/1) to give a colorless oil (0.042 g, 60% yield). $[\alpha]_D^{20}$ +24.00 (c, 0.2, CH_2Cl_2); MS-ESI: (ESI, pos.ion) m/z: 200.1 $[M + Na]^+$; HRMS (ESI) calcd for $C_{10}H_{11}NNaO_2$ $[M + Na]^+$ 200.0682, found 200.0685; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.72 (m, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.79

(td, J = 7.8 Hz, 1.8 Hz, 1H), 7.42 (m, 1H), 6.01-5.89 (m, 1H), 5.62 (m, 1H), 5.34-5.13 (m, 2H), 1.45 (d, J = 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 164.1, 149.4, 147.9, 137.7, 137.1, 127.0, 125.3, 116.8, 73.2, 19.9. Enantiomeric excess (ee), 96.6%. CHIRALCEL OD-H (4.6 × 250 mm, 5 μm), hexane: isopropanol = 95: 5, flow rate 1.2 mL/min, retention time 6.79 (1.70%), 7.31 (98.30%).

6-bromo-2, 3-dihydroxybenzaldehyde (7)[10]

To a solution of 6-bromo-2-hydroxy-3-methoxybenzaldehyde **6** (4.6 g, 20 mmol) in anhydrous CH_2Cl_2 (60 mL) under N_2 atmosphere was added BBr_3 (50 mL 1.0 M in CH_2Cl_2, 50 mmol) dropwise at 0 ^oC. The reaction mixture was gradually warmed to room temperature and stirred for 3 h. Then the reaction was quenched with H_2O (100 mL) at 0 ^oC. CH_2Cl_2 was evaporated *in vacuo* and the residue was filtered, washed with water, then the filter cake was dried *in vacuo* to give a yellow solid (4.1 g, 95% yield). The product was used directly in the next step without further purification. MS-ESI: (ESI, neg.ion) m/z: 214.8 $[M - H]^-$; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.76 (br s, 2H), 10.20 (s, 1H), 7.07 (d, J=8.4 Hz, 1H), 7.01 (d, J=8.4 Hz, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 196.8, 152.1, 146.1, 123.8, 122.3, 117.8, 113.3.

2, 3-bis (benzyloxy)-6-bromobenzaldehyde (8)[11]

To a solution of 6-bromo-2, 3-dihydroxybenzaldehyde **7** (0.87 g, 4.0 mmol) in anhydrous DMF (20 mL) was added benzyl bromide (1.5 g, 8.8 mmol), potassium carbonate (1.21 g, 8.8 mmol) and KI (0.33 g, 2.0 mmol) at room temperature under N_2 atmosphere. The reaction mixture was warmed to 80 ^oC and stirred overnight. After it was cooled to room temperature, ethyl acetate (40 mL) and water (20 mL) were added to the reaction mixture. The organic layer was separated and the aqueous phase was additionally extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with water (40 mL), brine (20 mL) and dried over Na_2SO_4. Then the mixture was concentrated *in vacuo*, and the residue was purified by a short silica gel column chromatography (petrol ether/ethyl acetate (V/V) = 10/1) to give a yellow solid (1.48 g, 93% yield). MS-ESI: (ESI, pos.ion) m/z: 397.1 $[M + H]^+$; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.42-7.31 (m, 11H), 7.02 (d, J = 9.0 Hz, 1H), 5.15 (s, 2H), 5.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.4, 151.9, 151.3, 136.3, 135.9, 129.6, 129.3, 128.9, 128.8, 128.6, 128.4, 127.6, 119.4, 113.1, 76.6, 71.4.

(2, 3-bis(benzyloxy)-6 -bromophenyl)methanol (9)

To a suspension of 2, 3-bis (benzyloxy)-6-bromobenzaldehyde **8** (5.92 g, 14.9 mmol) in anhydrous MeOH (25 mL) was added $NaBH_4$ (0.28 g, 7.45 mmol) in portions over 30 min under stirring at room temperature. Upon complete conversion, the reaction mixture was filtered, washed with water, then the filter cake was dried *in vacuo* to give a white solid (5.7 g, 96% yield). The product was used directly in the next step without further purification. MS-ESI: (ESI, pos.ion) m/z: 421.0 $[M + Na]^+$; HRMS (ESI) calcd for $C_{21}H_{19}BrNaO_3$ $[M + Na]^+$ 421.0410, found 421.0414; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.49-7.35 (m, 10H), 7.28 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 5.15 (s, 2H), 5.12 (s, 2H), 4.77 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 151.4, 147.9, 136.9, 136.4, 134.5, 129.5, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 127.5, 115.5, 115.3, 76.0, 71.2, 60.5.

(S)- (((4-bromo-3-((but-3-en-2-yloxy) methyl)-1,2-phenylene)bis(oxy)) bis(methylene)) dibenzene (3a)

To a suspension of (2, 3-bis (benzyloxy)-6-bromophenyl) methanol **9** (1.0 g, 2.5 mmol) and PPh_3 (1.31 g, 5.0 mmol) in anhydrous CH_2Cl_2 (50 mL) was added NBS (0.89 g, 5.0 mmol) in portions over 15 min at room temperature under N_2 atmosphere. Upon complete conversion, the reaction mixture was filtered through a 3-5cm silicon pad, washed with the mixture of petrol ether/ethyl acetate (V/V = 10/1). The operation was repeated twice and the filtrate was concentrated *in vacuo* to give **5** as a white solid, which was used directly in the next step without further purification.

To a solution of (((4-bromo-3-(bromomethyl)-1, 2-phenylene)bis(oxy)) bis-(methylene)) dibenzene **5** obtained above and (S)-but-3-en-2-ol (0.2 g, 2.75 mmol) in anhydrous DMF (20 mL) under N_2 atmosphere was added NaH (0.3 g, 7.5 mmol) at room temperature. Then the reaction mixture was warmed to 50 ^{o}C. After 30 min, the reaction was quenched with H_2O (20 mL) carefully at 0 ^{o}C. Ethyl acetate (40 mL) was added to the reaction mixture. The organic layer was separated and the aqueous phase was additionally extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with water (40 mL), brine (20 mL), and dried over Na_2SO_4. Then the organic layers were concentrated *in vacuo*, and the residue was purified by a silica gel column chromatography (petrol ether/ethyl acetate (V/V) = 50/1) to give a white

solid (0.78 g, 69% yield in two steps). $[\alpha]_D^{25}$ +4.00 (c, 0.1, CH_2Cl_2); MS-ESI: (ESI, pos.ion) m/z: 475.1 $[M + Na]^+$; HRMS (ESI) calcd for $C_{25}H_{25}BrNaO_3$ $[M + Na]^+$ 475.0879, found 475.0884; ^{1}H- NMR (300 MHz, $CDCl_3$): δ 7.46-7.25 (m, 11H), 6.84 (d, *J* = 9.0 Hz, 1H), 5.81 (m, 1H), 5.24 (d, *J* = 17.1 Hz, 1H), 5.12 (d, *J* = 17.1 Hz, 1H), 5.10 (s, 2H), 5.05 (s, 2H), 4.68 (d, *J* = 9.0 Hz, 1H), 4.46 (d, *J* = 9.0 Hz, 1H), 3.95 (m, 1H), 1.27 (d, *J* = 6.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): 151.7, 149.0, 140.5, 137.8, 136.7, 128.8, 128.5, 128.3, 128.2, 127.7, 117.1, 116.2, 115.5, 77.5, 76.3, 71.1, 65.3, 21.7.

(S)-7, 8-bis (benzyloxy)-3-methyl-4-methyleneisochroman (2a)

To a degassed solution of (S)-(((4-bromo-3-((but-3-en-2-yloxy) methyl)-1,2-phenylene)bis(oxy)) bis(methylene)) dibenzene **3** (0.045 g, 0.1 mmol), Ag_2CO_3 (0.034 g, 0.2 mmol), TEBAC (0.027 g, 0.12 mmol) in the mixture of DMF (3 mL) and H_2O (1 mL) was added $Pd(PPh_3)_4$ (0.012 g, 0.01 mmol) under N_2 atmosphere. The reaction mixture was stirred at 80 ^oC for 4 h. Then the reaction mixture was passed through a short column of diatomite (eluent: ethyl acetate) to remove the catalyst and inorganic salts. The organic layer was separated and the aqueous phase was additionally extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), and dried over Na_2SO_4. Then the mixture was concentrated *in vacuo*, and the residue was purified by a silica gel column chromatography (petrol ether/ethyl acetate (V/V) = 50/1) to give a white solid (0.03 g, 80% yield). $[\alpha]_D^{25}$ +45.00 (c, 0.1, CH_2Cl_2); MS-ESI: (ESI, pos.ion) m/z: 373.2 $[M + H]^+$; HRMS (ESI) calcd for $C_{25}H_{25}O_3$ $[M + H]^+$ 373.1798, found 373.1804; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.36-7.13 (m, 11H), 6.82 (d, *J* = 8.7 Hz, 1H), 5.39 (s, 1H), 5.05 (s, 2H), 4.95 (dd, *J* = 11.0 Hz, 2H), 4.83 (d, *J* = 16.0 Hz, 2H), 4.55 (d, *J* = 16.0 Hz, 1H), 4.14 (q, *J* = 6.3 Hz, 1H), 1.34 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 150.3, 142.8, 142.1, 137.0, 136.3, 128.7, 128.1, 127.9, 127.6, 127.5, 127.0, 125.4, 119.3, 112.6, 104.4, 74.1, 72.4, 70.5, 63.1, 18.1.

7, 8-bis (benzyloxy)-3,4-dimethyl-1H-isochromene (11)

MS-ESI: (ESI, pos.ion) m/z: 373.2 $[M + H]^+$; HRMS (ESI) calcd for $C_{25}H_{25}O_3$ $[M + H]^+$ 373.1798, found 373.1804. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.37-7.21 (m, 10H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.03 (s, 2H), 4.94 (s, 2H),

4.81 (s, 2H), 1.82 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 150.1, 148.3, 137.5, 137.1, 128.6, 128.5, 128.3, 128.1, 128.0, 127.6, 123.0, 115.9, 113.4, 105.3, 75.2, 71.2, 62.9, 16.5, 12.6.

(S)-7, 8-bis (benzyloxy)-3-methylisochroman-4-one (10a)

(S)-7, 8-bis (benzyloxy)-3-methyl-4-methyleneisochroman **2** (0.20 g, 0.54 mmol) was dissolved in CH_2Cl_2 (10 mL) and the solution was cooled down to -78 ^{o}C. O_3 was directed into the solution and TLC was used to indicate the conversion of the substrate every two min. After about 10-15 min, upon complete conversion, the resulting solution was then bubbled with nitrogen immediately to remove excess O_3. Triphenylphosphine (0.2 g, 0.75 mmol) was added and the solution was allowed to warm up to room temperature and stirred for another 3 h. The resulting solution was concentrated *in vacuo* and the crude product was purified by column chromatography on silica gel (petrol ether/ethyl acetate (V/V) = 12/1) to give the pure product **10** as a white solid (0.18 g, 89% yield). $[\alpha]_D^{25}$ +34.00 (c, 0.1, CH_2Cl_2); MS-ESI: (ESI, pos.ion) m/z: 397.1 $[M + Na]^+$; HRMS (ESI) calcd for $C_{24}H_{22}NaO_4$ $[M + Na]^+$ 397.1410, found 397.1415. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.7 Hz, 1H), 7.47-7.32 (m, 10H), 7.03 (d, *J* = 8.7 Hz, 1H), 5.23 (s, 2H), 5.09-4.98 (m, 3H), 4.54 (d, *J* = 15.9 Hz, 1H), 4.10 (q, *J* = 6.9 Hz, 1H), 1.45 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 194.9, 155.9, 142.2, 137.0, 136.6, 135.9, 128.8, 128.6, 128.5, 128.4, 127.5, 124.0, 123.4, 77.7, 74.9, 70.8, 63.1, 15.6.

(S)-7, 8-dihydroxy-3-methylisochroman-4-one S-(+)-XJP (1a)

To a solution of (S)-7, 8-bis (benzyloxy)-3-methylisochroman-4-one **10** (0.05 g, 0.13 mmol) in THF (5 mL), was added Pd-C (0.01 g, 10%) and the mixture was stirred under H_2 atmosphere for 4 h at room temperature. Then the reaction solution was passed through a short diatomite pad and washed with THF. The combined organic phase was concentrated *in vacuo*, and the residue was purified by a short silica gel column chromatography (dichloromethane/methanol (V/V) = 15/1) to give a white solid (0.015 g, 60% yield). $[\alpha]_D^{20}$ +78.00 (c, 0.1, MeOH); MS-ESI: (ESI, neg.ion) m/z: 193.0 $[M - H]^-$; HRMS (ESI) calcd for $C_{10}H_9O_4$ $[M - H]^-$ 193.0506, found 193.0501; ^{1}H-NMR (300 MHz, DMSO-*d*$_6$): δ 10.47 (s, 1H), 8.96 (s, 1H), 7.32 (d, *J* = 8.4, 1H), 6.84 (d, *J* = 8.4, 1H), 4.92 (d, *J* = 15.6, 1H), 4.69 (d, *J* = 15.6, 1H), 4.21 (q, *J* = 6.6, 1H), 1.31 (d, *J* = 6.6, 3H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$): δ 194.5, 150.5,

139.4, 129.9, 121.3, 118.6, 114.3, 76.4, 62.3, 15.5. Enantiomeric excess (ee), 96.5%. CHIRALCEL AD-H (4.6 × 250 mm, 5 μm), hexane: EtOH: TFA = 85: 15:0.1, flow rate 1.0 mL/min, retention time 7.45 (98.23%), 8.63 (1.77%).

(R)- (((4-bromo-3-((but-3-en-2-yloxy) methyl)-1,2-phenylene)bis(oxy)) bis(methyl -ene)) dibenzene (3b)

A procedure analogous to the preparation of **3a** was used to give **3b** as a white solid. $[\alpha]_D^{25}$ - 6.00 (c, 0.1, CH_2Cl_2); Other data are the same as those for **3a**.

(R)-7, 8-bis (benzyloxy)-3-methyl-4-methyleneisochroman (2b)

A procedure analogous to the preparation of **2a** was used to give **2b** as a white solid. $[\alpha]_D^{25}$ - 45.00 (c, 0.1, CH_2Cl_2); Other data are the same as those for **2a**.

(R)-7, 8-bis (benzyloxy)-3-methylisochroman-4-one (10b)

A procedure analogous to the preparation of **10a** was used to give **10b** as a white solid. $[\alpha]_D^{25}$ -30.00 (c, 0.1, CH_2Cl_2); Other data are the same as those for **10a**.

(R)-7, 8-dihydroxy-3-methylisochroman-4-one R-(-)-XJP (1b)

A procedure analogous to the preparation of **1a** was used to give **1b** as a white solid. $[\alpha]_D^{20}$ -80.00 (c, 0.1, MeOH); Enantiomeric excess (ee), 96.5%. CHIRALCEL AD-H (4.6 × 250 mm, 5 μm), hexane: EtOH: TFA = 85: 15:0.1, flow rate 1.0 mL/min, retention time 8.17 (1.77%), 9.98 (98.23%). Other data are the same as those for **1a**.

Antihypertensive effects in the spontaneously hypertensive rats (SHRs)

The in vivo antihypertensive activity study of the title compound was evaluation on its effects on systolic arterial blood pressure (SAP) of spontaneous hypertension rats (SHRs) by tail-cuff method with a blood pressure monitor (BP-2000, Visitech Systems, Inc., US). The male rats (10-weeks-old, 180–200 g body weight) were purchased from Vital River Laboratory Animal Technology Co. Ltd, (Beijing, China). In each group, ten rats were taken. After one week of acclimation, 40 SHRs were randomly divided into four groups, namely the control, S-(+)-XJP group, R-(-)-XJP group and (±)-XJP group. After oral administration with saline water, S-(+)-XJP (80 mg/kg), R-(-)-XJP (80 mg/kg) and (±)-XJP (80 mg/kg) to SHRs respectively, the SAP were recorded from 0 to 8 h. Results of the study were expressed as mean ± SD. A

probability level of less than 0.05 was considered significant. Percent decrease in blood pressure (BP) was calculated by the following formula: % Reduction in BP = (BP of SHR before treatment – BP of SHR after treatment) / (BP of SHR before treatment) x 100.[16]

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14. Enantiomeric excess (ee) of (S)-(+)-XJP (**1)** was determined by chiral HPLC. CHIRALCEL AD-H (4.6 × 250 mm, 5 μm), hexane: EtOH: TFA = 85:15:0.1, flow rate 1.0 mL/min, retention time 7.45 (98.23%), 8.63 (1.77%).
15. (R)-but-3-en-2-ol was prepared from D-methyl lactate instead of D-ethyl lactate due to the cost that D-ethyl lactate is nearly hundreds of times more than D-methyl lactate.
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