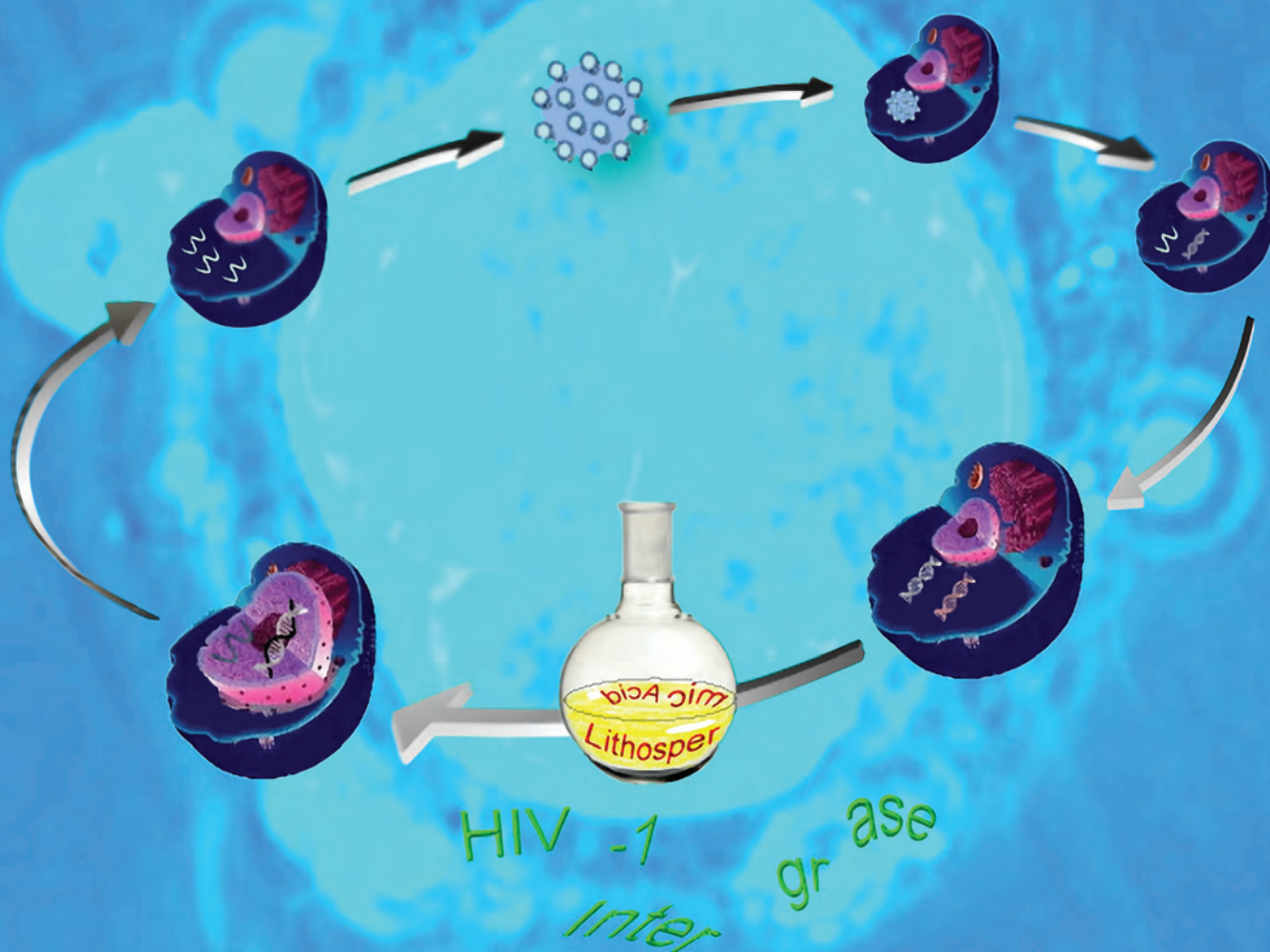


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PAPER

Synthesis of anti-HIV lithospermic acid by two diverse strategies†

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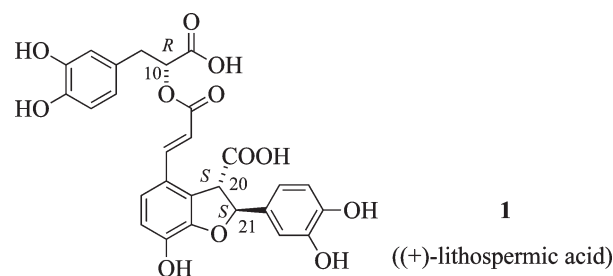
An efficient and convergent route for the synthesis of the natural product (+)-lithospermic acid, which possesses anti-HIV activity, was accomplished. The (±)-*trans*-dihydrobenzo[*b*]furan core therein was prepared by two different strategies. The first strategy involved the use of a palladium-catalyzed annulation to generate an appropriately substituted benzo[*b*]furan ester followed by a stereoselective reduction of a carbon–carbon double bond with Mg–HgCl₂–MeOH. The second strategy relied on an aldol condensation between a suitably substituted methyl arylacetate and 3,4-dimethoxybenzaldehyde, followed by cyclization. Finally, a total synthesis of (+)-lithospermic acid was completed *via* coupling of a *trans*-dihydrobenzo[*b*]furan cinnamic acid with an enantiomerically pure methyl lactate.

Introduction

In 1963, Johnson and co-workers¹ reported the first isolation of lithospermic acid (**1**) from the roots of *Lithospermum ruderales*. In 1975, Carmack and co-workers² isolated the same acid, **1**, from the *Lithospermum ruderales* Dougl. ex Lehm (*Boraginaceae*). They proposed a new structure through the possession of a *trans* relationship between the C(20)/C(21) substituents attached to the dihydrobenzo[*b*]furan moiety, on the basis of ¹H NMR coupling constants associated with similar compounds.² In the same year, Wagner and co-workers³ isolated the same compound from *Lithospermum officinale* and confirmed the structure of **1**. Moreover, they prepared its derivative (+)-heptamethylthiospermate. Though the structure of (+)-lithospermic acid (**1**) has been established independently by the groups of Carmack and Wagner, the absolute configuration remained unassigned.

In 2002, Huang and co-workers⁴ reported their isolation of (+)-lithospermic acid (**1**) from *Salvia miltiorrhiza* and its non-toxic HIV-1 integrase inhibitory activity. In addition, this caffeic acid trimer (**1**)⁵ was found to possess inhibition properties of adenylatecyclase by Kohda *et al.*⁶ and an antioxidizing low-density lipoprotein by Lin *et al.*⁷

Given these remarkable biological properties, the total synthesis of (+)-lithospermic acid (**1**) and its analogues has attracted much attention. In 1979, Jacobson and Rath⁸ completed the



synthesis of racemic heptamethylthiospermate. After two decades, Bergman, Ellman and co-workers⁹ accomplished the first asymmetric total synthesis of (+)-lithospermic acid (**1**) and established its absolute configuration as (+)-(10*R*,20*S*,21*S*)-**1**. Very recently, Wang and Yu¹⁰ have also reported a total synthesis of (+)-lithospermic acid. Meanwhile, Coster and co-workers¹¹ disclosed the formal total synthesis of (+)-lithospermic acid (**1**) by using a late stage separation of the diastereomeric mixture. In these published works, Bergman, Ellman and Yu utilized naturally-occurring (*R*)-rosmarinic acid to generate the C(10*R*) stereogenic center in the natural product **1**. To the best of our knowledge, no general synthetic route to establish the C(10*R*) chiral center from achiral starting material has been reported to date. Here, we report the first asymmetric synthesis of (+)-(10*R*)-methyl 3-(3,4-dimethoxyphenyl)-2-hydroxypropanoate (**3**) as well as the establishment of the C(10*R*) stereogenic center of **1** by a chemical method. In addition, we demonstrate two synthetic sequences leading to the *trans*-dihydrobenzo[*b*]furan core of the natural product **1** from different starting materials. Furthermore, our success on the synthesis of (+)-lithospermic acid (**1**) *via* the intermediate **2** is described.

A retrosynthetic plan for (+)-lithospermic acid (**1**) is depicted in Scheme 1. We decided to synthesize the enantiomerically-

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†Electronic supplementary information (ESI) available: Copies of ¹H and ¹³C NMR spectra as well as HPLC chromatograms for compounds **11**, (±)-**12**, (±)-**13**, (±)-**5**, **16**, **8**, (±)-**17**, (±)-**18**, (±)-**19**, **20**, and **21**. See DOI: 10.1039/c2ob25575h

enriched heptamethylthiospermate **2**, in which demethylation of all seven methyl groups to give lithospermic acid had already been reported.⁹ Esterification of cinnamic acid **5** with (+)-(*R*)-methyl lactate **3** would give the intermediate **2**. The (+)-lactate **3** could be synthesized from commercially available 3,4-dimethoxybenzaldehyde (**4**). Moreover, we planned to obtain the desired *trans*-dihydrobenzo[*b*]furan cinnamic acid **5** through two different strategies: namely palladium-catalyzed annulation and an aldol condensation.

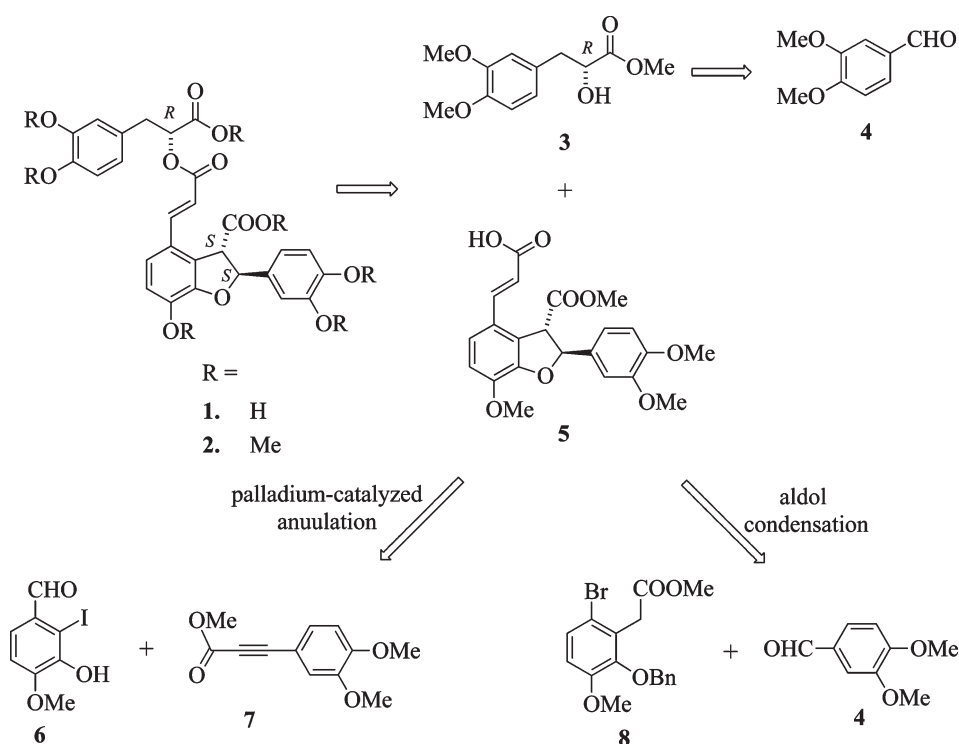
Results

At the outset, our approach towards obtaining the optically active lactate (*R*)-**3** was to reduce the enol ester **9** (see Scheme 2). It can be prepared from 3,4-dimethoxybenzaldehyde (**4**) and *N*-acetylglycine in three steps by the Dalla's procedure.¹² Although we were able to reduce **9** with NaBH₄ to give the racemic lactate **3**, use of chiral reducing agents including *NB*-Enantride, *K*-Glucoride and (*R,R*)-(-)-*trans*-4,5-bis[(diphenylphosphino)methyl]-2,2-di-methyl-1,3-dioxolane (*i.e.*, DIOP-Rh(I)) did not lead to (+)-**3** with a high % ee. Alternatively, we dehydroxylated the optically active diol **10**¹³ selectively at the benzylic position¹⁴ by Et₃SiH in the presence of CF₃COOH at 0 °C. The desired (+)-methyl lactate **3** was generated in a 75% yield with a >99% ee. These mild conditions did not cause epimerization of the hydroxyl group at the α position. Its enantiomeric excess was determined by HPLC analysis with a Chiralcel OD column. Bergman, Ellman and co-workers⁹ reported a method for generating this optically active lactate (*R*)-**3** by pentamethylation of commercially available rosmarinic acid followed by saponification. On the other hand, Eicher *et al.*¹⁵ obtained

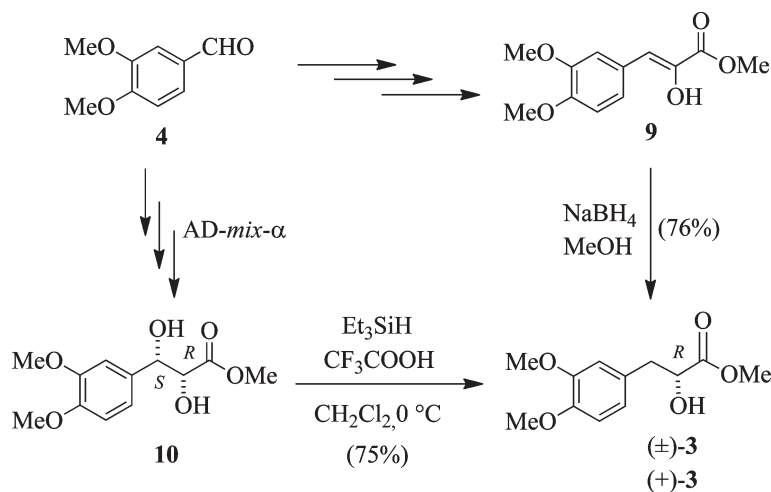
(+)-**3** from its racemates by kinetic resolution with the enzyme Lipase PS. In comparison with their results, we successfully developed a simple approach for the enantioselective synthesis of (+)-(*R*)-**3** and it can be regarded as a general route for the syntheses of other lactates.

Next, our goal was to synthesize the key intermediate *trans*-dihydrobenzo[*b*]furan cinnamic acid **5**. Recently, our group has utilized palladium-catalyzed annulation¹⁶ in the syntheses of functionalized benzo[*b*]furans and indoles for organic light-emitting diodes.¹⁷ We envisioned that similar chemistry could be applied to the synthesis of the dihydrobenzo[*b*]furan segment of (+)-lithospermic acid (**1**). Accordingly, we coupled 2-iodoisovanillin (**6**)¹⁸ with the activated alkyne **7** by using (PPh₃)₂PdCl₂ (0.060 equiv) with LiCl and NaHCO₃ in DMF at 110 °C to give the benzo[*b*]furan ester **11** as pale yellow needles (mp 166–167 °C, see Scheme 3). Subsequently, the chemo- and stereoselective reduction of **11** to the corresponding *trans*-dihydrobenzo[*b*]furan **13** was attempted. Application of the reduction conditions, including H₂/Pd-C¹⁹ and Et₃SiH/TFA,²⁰ led to the recovery of the starting material or undesired products.

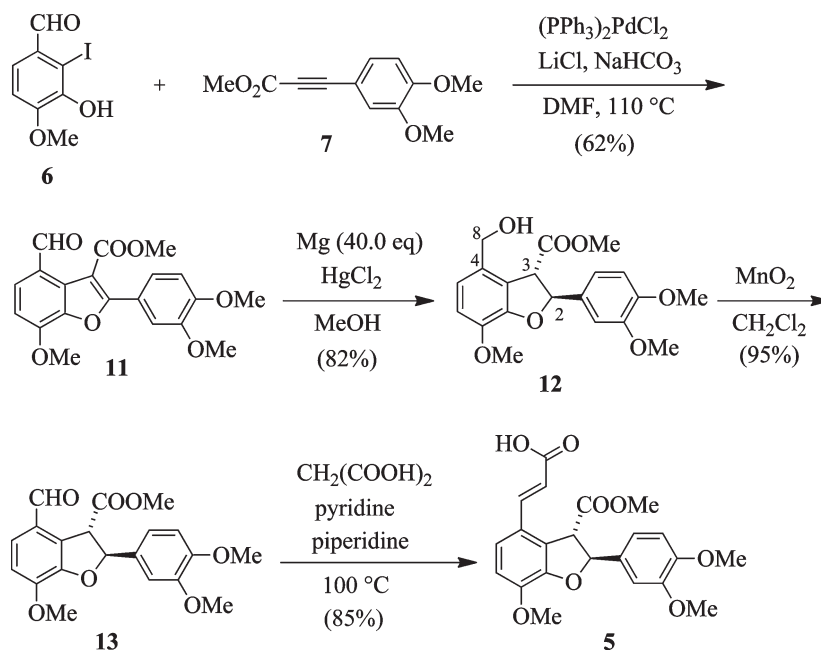
In order to circumvent this problem, we considered metallic Mg in methanol (Mg-MeOH)²¹ as an ideal reducing system, which has been used in the reduction of α,β -unsaturated esters.²¹ Accordingly, benzo[*b*]furan ester **11** was produced up to a 30% yield (see entry 1 of Table 1). Furthermore, we treated compound **11** with Mg (40.0 equiv) in the presence of a catalytic amount of HgCl₂ (0.10 equiv) by following the procedure reported by Lee *et al.* (entry 5 of Table 1).^{21a} (\pm)-*trans*-Dihydrobenzo[*b*]furan **12** was generated as a pale yellow liquid in a 82% yield. Separation of this racemate to give the desired compound **12** in its enantiomerically pure form met with failure when a reported procedure was used.²² This racemic compound exhibited four singlets



Scheme 1 Retrosynthetic analysis of (+)-lithospermic acid (**1**) via its heptamethyl derivative **2**.



Scheme 2 Syntheses of racemic and optically active (+)-(R)-methyl lactate **3**.



Scheme 3 A palladium-catalyzed annulation strategy in the synthesis of (±)-*trans*-dihydrobenzofuran cinnamic acid **5**.

Table 1 Reduction of benzo[*b*]furan ester **11** with Mg–HgCl₂–MeOH

Entry	Mg (equiv)	HgCl ₂ (equiv)	Temp (°C)	Time (h)	Yield (%)
1	40.0	—	25	48	30
2	40.0	—	65	12	0
3	5.0	0.10	25	3.0	35
4	40.0	0.10	25	3.0	60
5	40.0	0.10	25	20	82

between 3.69 and 3.84 ppm in its ¹H NMR spectrum for the 12 protons resulting from three unequivalent methoxy groups and one methyl ester. In addition, we observed two characteristic doublets with *J* = 6.0 Hz at 4.24 and 5.93 ppm for the C(3)- and

C(2)-protons of dihydrobenzo[*b*]furan moiety, respectively, as well as a doublet at 4.49 ppm with *J* = 12.4 Hz for the C(8)H₂ protons attached to a free hydroxyl group. Furthermore, in its ¹³C NMR spectrum, the resonance occurred at 55.94 and 87.08 ppm for the C(3)- and the C(2)-carbons, respectively, as well as at 62.66 ppm for the C(8) carbon. In its IR spectrum, one strong stretching absorption band appeared at 1736 cm⁻¹ for the O(C=O) group and at 3516 cm⁻¹ for the OH group. Moreover, its exact mass was detected as 374.1366, which agreed well with the theoretical value of 374.1360 for C₂₀H₂₂O₇. These spectroscopic data clearly confirm the structure of *trans*-dihydrobenzo[*b*]furan **12**.

We oxidized alcohol **12** to the corresponding aldehyde **13**,^{8,9} known to possess a *trans* configuration, by manganese

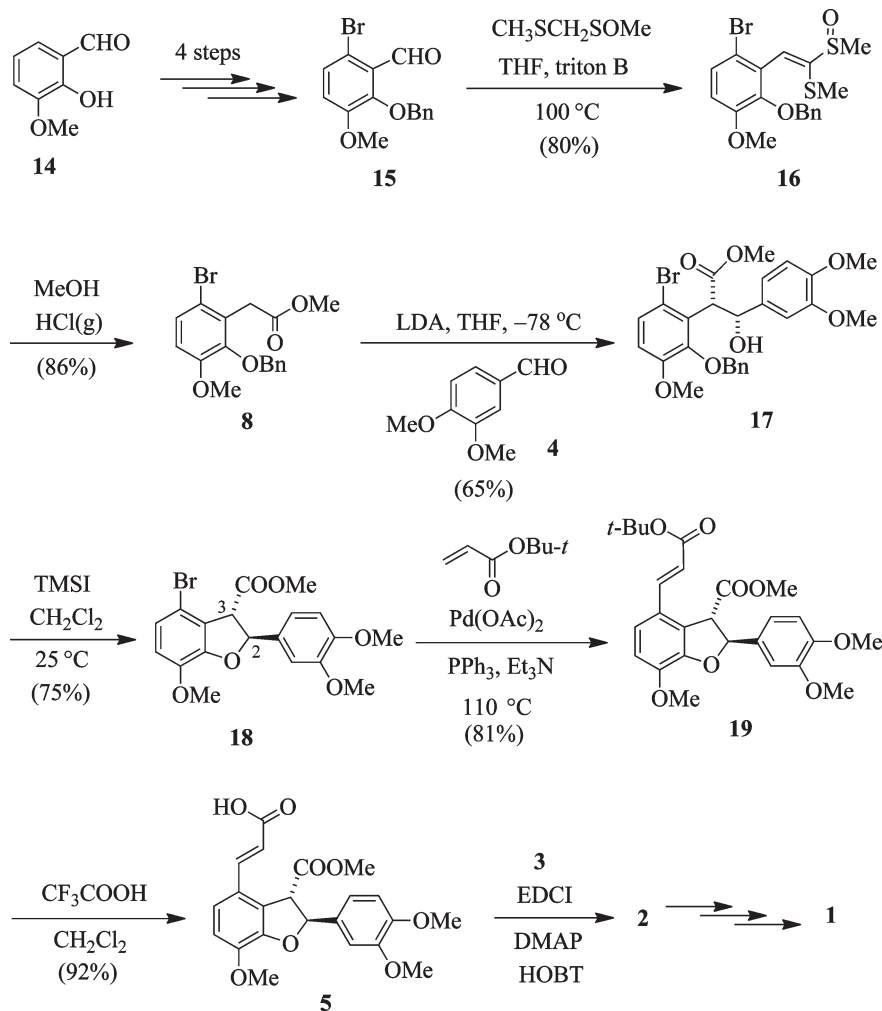
dioxide.²³ Finally, the Knoevenagel condensation of aldehyde (\pm)-**13** with malonic acid under basic conditions was performed by use of the Ellman's procedure to give the desired (\pm)-*trans*-dihydrobenzo[*b*]furan cinnamic acid **5**.^{8,9}

At this stage, we planned a completely different approach for the synthesis of dihydrobenzo[*b*]furan **5**, commencing with *o*-vanillin (**14**). This was converted to 2-benzyloxy-6-bromo-3-methoxybenzaldehyde (**15**) in four steps by the procedure reported by Nakanishi (Scheme 4).²⁴ Condensation of aldehyde **15** with $\text{CH}_3\text{SCH}_2\text{SOCH}_3$ ²⁵ in the presence of benzyltrimethylammonium hydroxide (Triton B) at 100 °C gave the ketene-thioacetal **16**. Upon acid-catalyzed hydrolysis in dry methanol, the desired methyl arylacetate **8** was formed in an 86% yield. We then performed an aldol condensation²⁶ between **8** and 3,4-dimethoxybenzaldehyde (**4**) in the presence of lithium diisopropylamide (LDA) at -78 °C to exclusively give a coupled (\pm)- β -hydroxy ester as white solids (mp 95–96 °C) in a 65% yield. At this time, the relative stereochemistry of the product was not important and was tentatively assigned as **17**. The hydroxyl group therein could be removed to form a carbocationic intermediate for cyclization, after which the required *trans* configuration of the dihydrofuran product must be ensured.²⁷

Subsequent cyclization of compound **17** with iodotrimethylsilane (2.2 equiv)²⁸ in dichloromethane led to the desired bromo-dihydrobenzo[*b*]furan **18** as a gummy oil in a 75% yield.

In the IR spectrum of the new dihydrobenzo[*b*]furan **18**, strong absorptions resulting from stretching vibrations appeared at 1736 cm^{-1} for the ester C=O group. Its ¹H NMR spectrum displayed two doublets at 5.82 and 4.30 ppm with $J = 7.2$ Hz for the H(2) and H(3) protons, respectively, and one singlet at 3.73 ppm for the CO_2CH_3 protons. Although the $J_{\text{H}(2)-\text{H}(3)}$ value is not diagnostic to distinguish the *cis* and *trans* isomers, the anisotropic effect of the C(2) aryl group causes a chemical shift of the H(3) proton upfield and the CO_2CH_3 protons downfield in the *trans* isomers than those of the corresponding *cis* isomers.¹¹ The *trans* compounds often display the H(3) protons around 4.3 ppm and the CO_2CH_3 protons around 3.8–3.9 ppm, yet the *cis* compounds display the H(3) protons around 4.9 ppm and the CO_2CH_3 protons around 3.3 ppm. Our experimental data clearly indicate the *trans* configuration of the dihydrobenzofuran moiety in compound **18**.

Afterwards, we performed a Heck coupling²⁹ between furan **18** and *tert*-butyl ester, using $\text{Pd}(\text{OAc})_2$ (0.10 equiv) and PPh_3 (0.30 equiv) in Et_3N , to produce an α,β -unsaturated *tert*-butyl



Scheme 4 An alternative strategy to construct the dihydrobenzo[*b*]furan cinnamic acid **5** by use of an aldol condensation.

ester **19** in 81% yield. Finally, treatment of ester **19** with trifluoroacetic acid gave the desired (\pm)-*trans*-dihydrobenzo[*b*]furancinnamic acid **5** as a pale yellow solid in a 92% yield.^{8,9} The physical properties and spectroscopic characteristics obtained by us for compound **5** are consistent with the reported data.^{8,9}

Finally, to obtain heptamethylithospermate **2**, we esterified⁹ (\pm)-**5** with (+)-*R*-methyl lactate **3** in the presence of 4-dimethylaminopyridine (DMAP), 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (EDCI) and 1-hydroxybenzotriazole (HOBt, Scheme 4). A 1 : 1 mixture of (10*R*, 20*S*, 21*S*)-**2** and the corresponding diastereomeric counterpart (10*R*, 20*R*, 21*R*)-**2** was produced as a yellow foam in a 85% overall yield. Their physical properties and spectroscopic characteristics are consistent with those of the reported compounds.^{8,11} For example, a new characteristic peak at δ 5.26–5.35 ppm in the ¹H NMR spectrum for the proton in –O(C=O)CHCOO– indicates the formation of a new ester bond. Further conversion of (10*R*, 20*S*, 21*S*)-**2** to the final target (+)-**1** through multi-demethylation has been reported by Coster,¹¹ Bergman and Ellman.⁹

Discussion

Antus,¹⁹ Rupprecht,³⁰ and their co-workers reported that hydrogenation of 2,3-disubstituted benzo[*b*]furans with hydrogen gas in the presence of 10% palladium on carbon (Pd/C) affords the corresponding 2,3-dihydrobenzo[*b*]furans with a *cis* configuration. Isomerization of this *cis* isomer occurs under alkaline conditions at an elevated temperature to give the thermodynamically more stable *trans* diastereomer.³⁰ Using this method, we hydrogenated benzo[*b*]furan ester **11** in methanol¹⁹ for 3 h. 4-(Hydroxymethyl)benzo[*b*]furan **20** was obtained, in which the C(2)=C(3) double bond remained intact (see Scheme 5). Elongation of the hydrogenation time to 24 h produced 4-methylbenzo[*b*]furan **21** through deoxygenation of the benzyl alcohol moiety in **20**. Our results reveal that the formyl group in **11** was problematic and converted to an undesired methyl group before the conjugated C(2)=C(3) bond in the benzo[*b*]furan nucleus was hydrogenated.

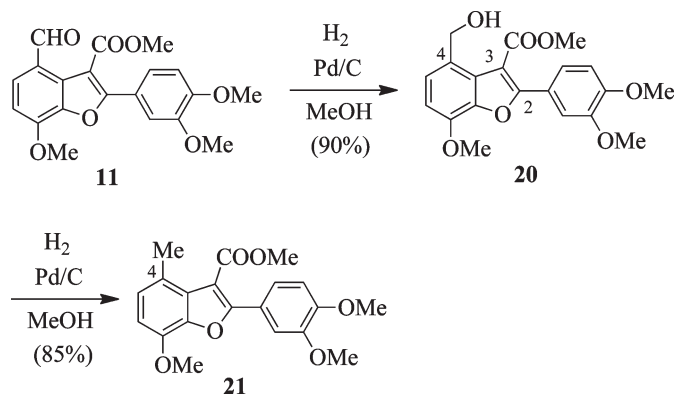
On the other hand, we endeavoured to circumvent the difficulty of the diastereoselective reduction of 2,3-disubstituted-benzo[*b*]furan by using metallic Mg in methanol.²¹ Accordingly,

the single electron transfer took place in benzo[*b*]furan ester **11** to chemo- and stereoselectively afford the hydroxymethyl *trans*-dihydrobenzo[*b*]furan **12** in a 30% yield (see Scheme 3 and entry 1 of Table 1). The yield was improved to 82% by the addition of a catalytic amount of HgCl₂. Lee^{21a} reported that the use of HgCl₂ can activate the Mg and thus accelerate the reduction. Moreover, generation of magnesium methoxide *in situ* was responsible for the base-promoted epimerization at the C(3) carbonyl ester to the *trans*-diastereomer **12**. In this regard, metallic Mg in a protic solvent acted not only as a single electron transfer reducing reagent but also the source of a base for epimerization.²¹

During the preparation of this manuscript, we noted that Coster and co-workers¹¹ obtained a similar key intermediate as (\pm)-*trans*-dihydrobenzo[*b*]furan **13** for the synthesis of lithospermic acid (**1**). It includes the Sonogashira coupling, protection of the C(4)-formyl group, Pd(II)-catalyzed carbonylative annulation, Mg-mediated reduction and finally deprotection. Through a different pathway, we were able to obtain the desired (\pm)-*trans*-**13** in three steps, including the palladium-catalyzed annulation,¹⁶ Mg/HgCl₂-mediated reduction, and oxidation with a 48% overall yield.

Conclusion

The first asymmetric syntheses of (+)-(*R*)-methyl lactate **3** (>99%ee) was completed in four steps with an overall yield of 75% from commercially available 3,4-dimethoxybenzaldehyde. Two different synthetic routes were also developed for the diastereoselective synthesis of the *trans*-dihydrobenzo[*b*]furan segment of lithospermic acid (**1**). The first strategy involved the chemo- and stereoselective reduction of benzo[*b*]furan ester **11** with metallic Mg and catalytic HgCl₂ in methanol. The second strategy involved an aldol condensation and subsequent intramolecular cyclization of β -hydroxy ester **17** to give the desired *trans*-dihydrobenzo[*b*]furan core of compound **1**. These two strategies demonstrate expedient and concise routes for the synthesis of heptamethylithospermate **2** from readily available starting materials in five and seven steps, respectively. Moreover, these two strategies were applied successfully in a total synthesis of (+)-lithospermic acid (**1**).



Scheme 5 Hydrogenation of benzo[*b*]furan ester **11** containing a formyl group.

Experimental section

General methods

All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen unless as indicated otherwise. Ethyl acetate and hexane from Mallinckrodt Chemical Co. were dried and distilled from CaH₂. Diethyl ether and THF from Mallinckrodt Chemicals Co. were dried by distillation from sodium and benzophenone under an atmosphere of nitrogen. Acetonitrile, acetone, dichloromethane and methanol were purchased from Mallinckrodt Chemical Co. Acetic anhydride, *tert*-butanol and pyridine were purchased from Echo Chemical Co. AD-*mix*- α , benzyltrimethylammonium hydroxide (Triton B), *tert*-butyl acrylate, bromine, *n*-butyllithium, carbon tetrabromide (CBr₄), 4-dimethylaminopyridine (DMAP), 2,2-dimethyl-1,3-propanediol, 3,4-dimethoxybenzaldehyde, *p*-dioxane, 1,2-ethanediol, 1-hydroxybenzotriazole (HOBt), iodine monochloride, iodo-trimethylsilane, isovanillin, magnesium, manganese dioxide, mercuric chloride, methanesulfonamide, palladium acetate, potassium bromide, potassium iodide, *p*-toluenesulfonic acid (PTSA), triethylsilane, trifluoroacetic acid, triphenylphosphine, and *o*-vanillin were purchased from Aldrich Chemical Co. Benzyl bromide (BnBr), bis(triphenylphosphine)palladium(II)-chloride, diisopropylamine, 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI), methyl chloroformate, methyl (methylthio)methyl sulfoxide (CH₃SCH₂SOCH₃) and 1,3-propanedithiol were purchased from Fluka Chemical Co. Methyl 2-oxo-3-(3,4-dimethoxyphenyl)propionate (**9**),¹² (2*R*,3*S*)-methyl 3-(3,4-dimethoxyphenyl)-2,3-dihydroxypropanoate (**10**),¹³ 4-formyl-2-hydroxy-3-iodoanisole (**6**),¹⁸ (3,4-dimethoxyphenyl)propynoic acid methyl ester (**7**)⁹ and 2-benzyloxy-6-bromo-3-methoxybenzaldehyde (**15**)²⁴ were prepared by literature methods.

Analytical thin layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), which were purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Silicycle ultra pure silica gel (particle size 40–63 μ m, 230–400 mesh). The enantiomeric excess was determined by an HPLC (Waters 515) with Chiralcel OD (250 \times 4.6 mm) column at 25 °C. The results were compared with racemic isomers with a flow rate of 1.0 mL min⁻¹ and with isopropyl alcohol in hexane as the mobile phase. Purity of all the products was >98.0%, as checked by an HPLC (Waters 515) with a Lichrosorb Si-100 (200 \times 4.6 mm, 5 μ m) column at 25 °C.

Infrared (IR) spectra were measured on a Perkin–Elmer model spectrum one B spectrophotometer. Absorption intensities are recorded by the following abbreviations: s = strong; m = medium and w = weak. Proton NMR spectra were obtained on a Varian Mercury-400 (400 MHz) spectrometer, using chloroform-*d* (CDCl₃) and acetone-*d*₆ (CD₃COCD₃) as solvents. Proton NMR chemical shifts were referenced to residual protonated solvents (δ 7.24 and 2.05 ppm for chloroform and acetone, respectively). Carbon-13 NMR spectra were obtained on a Varian Mercury-400 (100 MHz) spectrometer using chloroform-*d* as the solvent. Carbon-13 chemical shifts are referenced to the center of the CDCl₃ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s = singlet; d = doublet; t = triplet;

q = quartet; m = multiplet; *J* = coupling constant (hertz). High-resolution mass spectra were obtained by means of a JEOL JMS-700 mass spectrometer. A Perkin–Elmer 241 polarimeter with a sodium lamp was used for the determination of specific rotations at room temperature. Melting points were obtained with a Fargo MP-2D melting point apparatus.

(+)-(R)-Methyl 3-(3,4-dimethoxyphenyl)-2-hydroxypropanoate ((+)-**3**)

To a solution containing (2*R*,3*S*)-methyl 3-(3,4-dimethoxyphenyl)-2,3-dihydroxypropanoate¹³ (**10**, 542.1 mg, 2.117 mmol, 1.0 equiv) and triethylsilane (270.4 mg, 2.326 mmol, 1.1 equiv) in CH₂Cl₂ (20 mL) at 0 °C, trifluoroacetic acid (3.671 g, 32.17 mmol, 15.0 equiv) was added *via* a syringe and stirring was continued for 30 min. The reaction was quenched with saturated aqueous NaHCO₃ (20 mL) and the resultant solution was extracted with CH₂Cl₂ (3 \times 15 mL). The combined organic layers were washed with a saturated aqueous NaCl solution (20 mL), dried over MgSO₄(s), filtered and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (40% EtOAc in hexane as the eluent) gave (+)-**3** (381.1 mg, 1.587 mmol) as a white solid in a 75% yield with >99%ee, as determined by HPLC with a Chiralcel OD column and isopropyl alcohol (10%) in hexane as the eluent. The major fraction showed up at *t*_r = 18.94 min and the minor fraction at *t*_r = 16.02 min by use of a UV detector with λ = 279 nm. For (+)-**3**: mp (recrystallized from toluene) 56–57 °C, lit.⁹ (53–54 °C); [α]_D²³ +9.9° (*c* = 0.77 in CH₂Cl₂), lit.⁹ +10.6° (*c* = 0.67 in CH₂Cl₂); TLC *R*_f: 0.56 (60% EtOAc in hexane as the eluent); ¹H NMR (CDCl₃; 400 MHz) δ 2.92 (dd, *J* = 14.0, 5.6 Hz, 1 H, ArCH), 3.07 (dd, *J* = 14.0, 5.6 Hz, 1 H, ArCH), 3.76 (s, 3 H, CO₂CH₃), 3.83 (s, 3 H, OCH₃), 3.84 (s, 3 H, OCH₃), 4.40–4.43 (m, 1 H, CHO), 6.71–6.79 (m, 3 H, 3 \times ArH); ¹³C NMR (CDCl₃; 100 MHz) δ 39.91, 52.18, 55.62, 55.65, 71.24, 111.00, 112.54, 121.31, 128.65, 147.81, 148.59, 174.35 (C=O). Its physical properties and spectroscopic characteristics are consistent with those previously reported.⁹ The corresponding racemate (\pm)-**3** was prepared through an established method¹² and its ¹H NMR and ¹³C NMR characteristics are consistent with those of (+)-**3**.

Methyl 2-(3,4-dimethoxyphenyl)-4-formyl-7-methoxybenzo[*b*]-furan-3-carboxylate (**11**)

To a solution containing 4-formyl-2-hydroxy-3-iodoanisole¹⁸ (**6**, 152.6 mg, 0.5488 mmol, 1.0 equiv), (Ph₃P)₂PdCl₂ (23.11 mg, 0.0329 mmol, 0.060 equiv), LiCl (23.26 mg, 0.5488 mmol, 1.0 equiv) and NaHCO₃ (230.5 mg, 2.744 mmol, 5.0 equiv) in DMF (20 mL) (3,4-dimethoxyphenyl)propynoic acid methyl ester⁹ (**7**, 145.0 mg, 0.6584 mmol, 1.2 equiv) was added. After the reaction mixture was stirred under nitrogen at 110 °C for 6 h, it was quenched with saturated aqueous NH₄Cl (50 mL) and extracted with Et₂O (3 \times 10 mL). The combined organic layers were washed with a saturated aqueous NaCl solution (10 mL), dried over MgSO₄(s), filtered and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (30%

EtOAc in hexane as the eluent) gave **11** (125.9 mg, 0.3402 mmol) as pale yellow crystalline solids in a 62% yield: mp (recrystallized from EtOAc) 166–167 °C; TLC R_f 0.36 (40% EtOAc in hexane as the eluent); ^1H NMR (CDCl_3 ; 400 MHz) δ 3.92 (s, 3 H, CO_2CH_3), 3.95 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.10 (s, 3 H, OCH_3), 6.92 (d, $J = 8.4$ Hz, 1 H, ArH), 6.94 (d, $J = 8.4$ Hz, 1 H, ArH), 7.49–7.54 (m, 2 H, $2 \times$ ArH), 7.75 (d, $J = 8.4$ Hz, 1 H, ArH), 10.03 (s, 1 H, CHO); ^{13}C NMR (CDCl_3 ; 100 MHz) δ 52.44, 55.85, 55.90, 56.26, 106.19, 110.10, 110.42, 111.00, 120.94, 121.40, 122.88, 126.79, 131.64, 142.85, 148.86, 149.61, 150.69, 157.10, 166.18 (C=O), 189.63 (C=O); IR (KBr) 3010 (w), 2031 (w), 1722 (s, C=O), 1677 (s), 1617 (m), 1575 (s), 1516 (s), 1499 (s), 1399 (m), 1300 (s), 803 cm^{-1} (m); MS (FAB) m/z 370 (M^+ , 75), 339 (100), 311 (9), 221 (15), 165 (8); HRMS (FAB) calcd for $\text{C}_{20}\text{H}_{18}\text{O}_7$: 370.1053, found 370.1050.

(±)-Methyl *trans*-2-(3,4-dimethoxyphenyl)-4-hydroxymethyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-3-carboxylate (12)

To a solution containing aldehyde **11** (150.1 mg, 0.4055 mmol, 1.0 equiv) and Mg (394.3 mg, 16.22 mmol, 40.0 equiv) in tetrahydrofuran (10 mL) and methanol (10 mL) HgCl_2 (11.01 mg, 0.0405 mmol, 0.10 equiv) was added. After the reaction mixture was stirred at room temperature for 48 h, it was quenched with $\text{HCl}_{(\text{aq})}$ (5.0 N, 20 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with a saturated aqueous NaCl solution (15 mL), dried over $\text{MgSO}_4(\text{s})$, filtered and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (35% EtOAc in hexane as the eluent) gave (±)-**12** (124.4 mg, 0.3325 mmol) as a pale yellow liquid in a 82% yield: TLC R_f 0.37 (40% EtOAc in hexane as the eluent); ^1H NMR (CDCl_3 ; 400 MHz) δ 3.74 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.84 (s, 3 H, CO_2CH_3), 4.24 (d, $J = 6.0$ Hz, 1 H, ArCHCO_2), 4.49 (d, $J = 12.4$ Hz, 2 H, CH_2O), 5.93 (d, $J = 6.0$ Hz, 1 H, ArOCHAr), 6.75–6.87 (m, 5 H, $5 \times$ ArH); ^{13}C NMR (CDCl_3 ; 100 MHz) δ 52.82, 55.71, 55.76, 55.77, 55.94, 62.66, 87.08, 108.72, 110.96, 112.54, 118.01, 121.48, 121.49, 123.10, 130.20, 132.47, 144.12, 148.26, 149.00, 172.58 (C=O); IR (neat) 3516 (br, OH), 2952 (m), 2834 (w), 1736 (s, C=O), 1593 (m), 1515 (s), 1438 (s), 1160 (s), 1024 (s), 808 (m) cm^{-1} ; MS (FAB) m/z 374 (M^+ , 9), 297 (37), 154 (55), 136 (70), 55 (100); HRMS (FAB) calcd for $\text{C}_{20}\text{H}_{22}\text{O}_7$: 374.1366, found 374.1360.

(±)-Methyl *trans*-2-(3,4-dimethoxyphenyl)-4-formyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-3-carboxylate (13)

To a solution containing alcohol (±)-**12** (112.6 mg, 0.3009 mmol, 1.0 equiv) in dichloromethane (10 mL) manganese dioxide (130.7 mg, 1.504 mmol, 5.0 equiv) was added. After stirring at room temperature for 48 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (30% EtOAc in hexane as the eluent) gave (±)-**13** (106.3 mg, 0.2856 mmol) as pale yellow crystals in a 95% yield: mp (recrystallized from EtOAc)

48–49 °C; TLC R_f 0.47 (40% EtOAc in hexane as the eluent); ^1H NMR (CDCl_3 ; 400 MHz) δ 3.75 (s, 3 H, OCH_3), 3.83 (s, 6 H, $2 \times \text{OCH}_3$), 3.96 (s, 3 H, CO_2CH_3), 4.69 (d, $J = 7.0$ Hz, 1 H, ArCHCO_2), 5.85 (d, $J = 7.0$ Hz, 1 H, ArOCHAr), 6.82 (d, $J = 8.0$ Hz, 1 H, ArH), 6.90–6.97 (m, 3 H, $3 \times$ ArH), 7.40 (d, $J = 8.4$ Hz, 1 H, ArH), 9.81 (s, 1 H, CHO); ^{13}C NMR (CDCl_3 ; 100 MHz) δ 52.57, 55.85, 55.86, 56.16, 56.52, 88.73, 108.71, 110.96, 111.60, 118.17, 124.49, 126.50, 128.52, 132.01, 149.13, 149.23, 149.47, 149.54, 171.82 (C=O), 190.56 (C=O); MS (EI) m/z (relative intensity) 372 (M^+ , 100), 313 (68), 272 (11), 155 (13), HRMS (EI) calcd for $\text{C}_{20}\text{H}_{20}\text{O}_7$: 372.1209, found 372.1176. Its spectroscopic characteristics are consistent with those previously reported.⁸

(±)-(2*E*)-3-[2-(3,4-Dimethoxyphenyl)-7-methoxy-3-methoxycarbonyl-2,3-dihydro benzo[*b*]furan-4-yl]prop-2-enoic acid (5): method 1

To a solution containing aldehyde (±)-**13** (51.20 mg, 0.1375 mmol, 1.0 equiv) and malonic acid (43.21 mg, 0.4152 mmol, 3.0 equiv) in pyridine (10 mL) piperidine (68.79 mg, 0.6875 mmol, 5.0 equiv) was added. After the reaction mixture was stirred under nitrogen at 100 °C for 8 h, it was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with $\text{HCl}_{(\text{aq})}$ (1.0 N, 30 mL), dried over $\text{MgSO}_4(\text{s})$, filtered and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (85% EtOAc in hexane as the eluent) gave (±)-**5** (48.20 mg, 0.1169 mmol) as a light yellow solid in a 85% yield: mp (recrystallized from EtOAc) 65–66 °C; TLC R_f 0.47 (40% EtOAc in hexane as the eluent); ^1H NMR (CDCl_3 ; 400 MHz) δ 3.81 (s, 3 H, OCH_3), 3.87 (s, 6 H, $2 \times \text{OCH}_3$), 3.93 (s, 3 H, CO_2CH_3), 4.52 (d, $J = 5.6$ Hz, 1 H, ArCHCO_2), 6.07 (d, $J = 5.6$ Hz, 1 H, ArOCHAr), 6.31 (d, $J = 15.8$ Hz, 1 H, Ph-C=CH-CO_2), 6.85–6.92 (m, 4 H, $4 \times$ ArH), 7.26 (d, $J = 8.8$ Hz, 1 H, ArH), 7.84 (d, $J = 15.8$ Hz, 1 H, Ph-CH=C-CO_2); ^{13}C NMR (CDCl_3 ; 100 MHz) δ 52.80, 55.81, 55.82, 55.83, 56.07, 87.36, 108.69, 111.09, 112.91, 116.61, 117.96, 120.77, 124.04, 125.14, 132.15, 143.12, 146.44, 148.36, 149.15, 149.21, 171.68 (C=O), 172.20 (C=O). Its spectroscopic characteristics are consistent with those previously reported.^{9,11}

(±)-(2*E*)-3-[2-(3,4-Dimethoxyphenyl)-7-methoxy-3-methoxycarbonyl-2,3-dihydro benzo[*b*]furan-4-yl]prop-2-enoic Acid (5): method 2

To a solution containing *tert*-butyl ester(±)-**19** (21.20 mg, 0.045 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) trifluoroacetic acid (5.41 mg, 0.4509 mmol, 10.0 equiv) was added *via* a syringe at 0 °C. After stirring at room temperature for 2 h, it was quenched with saturated aqueous NaHCO_3 (5.0 mL) and the resultant solution was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with a saturated aqueous NaCl solution (10 mL), dried over $\text{MgSO}_4(\text{s})$, filtered and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (90% EtOAc in hexane as the eluent) gave (±)-**5** (17.14 mg,

0.0416 mmol) as a pale yellow solid in a 92% yield. Its spectroscopic characteristics are consistent with those previously reported.⁹

(10*R*,20*S*,21*S*)-Methyl 2-(3,4-dimethoxyphenyl)-4-([3-(3,4-dimethoxyphenyl)-1-methoxy-1-oxopropan-2-yloxy]-3-oxoprop-1-enyl)-7-methoxy-2,3-dihydrobenzo[*b*]furan-3-carboxylate (2) and its (10*R*,20*R*,21*R*)-diastereomer (2)

To a solution containing cinnamic acid (\pm)-**5** (55.21 mg, 0.1333 mmol, 1.0 equiv), EDCI (28.11 mg, 0.1466 mmol, 1.1 equiv), DMAP (17.92 mg, 0.1466 mmol, 1.1 equiv) and HOBT (19.80 mg, 0.1466 mmol, 1.1 equiv) in CHCl_3 (10 mL) (+)-methyl lactate (**3**, 38.40 mg, 0.1596 mmol, 1.2 equiv) was added at 0 °C. After the reaction mixture was stirred under nitrogen at room temperature for 48 h, it was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 \times 15 mL). The combined organic layers were washed with a saturated aqueous NaCl solution (15 mL), dried over $\text{MgSO}_4(\text{s})$, filtered and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with silica gel column (40% EtOAc in hexane as the eluent) gave a 1:1 mixture of the title compound (10*R*,20*S*,21*S*)-**2** and the corresponding diastereomeric counterpart (10*R*,20*R*,21*R*)-**2** (72.19 mg, 0.1135 mmol) as a yellow foam in a 85% overall yield: TLC R_f 0.43 (40% EtOAc in hexane as the eluent); ^1H NMR (CDCl_3 ; 400 MHz) δ 3.15–3.16 (m, 2 H, ArCH_2), 3.70 (s, 6 H, $2 \times \text{CO}_2\text{CH}_3$), 3.71 (s, 3 H, OCH_3), 3.80 (s, 6 H, $2 \times \text{OCH}_3$), 3.81 (s, 3 H, OCH_3), 3.82 (s, 6 H, $2 \times \text{OCH}_3$), 3.91 (s, 3 H, OCH_3), 4.40 (d, $J = 5.6$ Hz, 1 H, ArCHCO_2), 5.26–5.35 (m, 1 H, OCHCOO), 5.99–6.00 (m, 1 H, ArOCHAr), 6.30 (dd, diastereomers, $J = 16.0$, 4.2 Hz, 1 H), 6.73–6.87 (m, 7 H, $7 \times \text{ArH}$), 7.19 (m, 1 H, ArH), 7.73 (dd, diastereomers, $J = 16.0$, 4.2 Hz, 1 H); ^{13}C NMR (CDCl_3 ; 100 MHz) δ 37.09, 37.12, 52.27, 52.78, 52.74, 55.78, 55.81, 55.82, 55.90, 55.92, 56.07, 56.14, 73.07, 87.41, 108.77, 108.79, 110.55, 111.13, 111.16, 112.44, 112.48, 112.93, 112.96, 116.37, 116.42, 117.98, 118.01, 120.54, 120.81, 121.40, 121.45, 124.25, 124.34, 124.95, 125.14, 128.30, 132.27, 132.30, 135.26, 142.28, 142.41, 146.35, 148.04, 148.06, 148.40, 148.45, 148.78, 149.23, 149.30, 166.03, 170.23, 171.62, 171.70. The spectral data are consistent with those previously reported.^{8,11}

2-Benzylloxy-6-bromo-3-methoxy-2-[2-(methylsulfinyl)-2-(methylthio)vinyl] benzene (16)

To a solution containing aldehyde²⁴ **15** (2.125 g, 6.617 mmol, 1.0 equiv) and Triton B (4.0 mL) in THF (10 mL) $\text{CH}_3\text{SCH}_2\text{SOCH}_3$ (986.2 mg, 7.939 mmol, 1.2 equiv) was added *via* a syringe at 0 °C. After the reaction mixture was refluxed at 100 °C for 12 h, it was quenched with saturated aqueous NH_4Cl (20 mL) and the resultant solution was extracted with CH_2Cl_2 (3 \times 50 mL). The combined organic layers were washed with a saturated aqueous NaCl solution (50 mL), dried over $\text{MgSO}_4(\text{s})$, filtered and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (20% EtOAc in hexane as the eluent) gave **16** (2.260 g, 5.305 mmol) as a yellow gum in a 80% yield: TLC R_f

0.51 (25% EtOAc in hexane as the eluent); ^1H NMR (CDCl_3 ; 400 MHz) δ 2.11 (s, 3 H, SMe), 2.60 (s, 3 H, SOMe), 3.85 (s, 3 H, OCH_3), 4.95 (dd, $J = 11.2$, 10.8 Hz, 2 H, PhCH_2), 6.82 (d, $J = 8.8$ Hz, 1 H, ArH), 7.24–7.35 (m, 6 H, $6 \times \text{ArH}$), 7.44 (s, 1 H, $\text{C}=\text{C}-\text{H}$); ^{13}C NMR (CDCl_3 ; 100 MHz) δ 16.75, 40.14, 55.63, 74.77, 113.01, 113.04, 127.32, 127.73, 127.74, 127.75, 127.82, 128.00, 129.95, 132.11, 136.66, 145.70, 146.66, 151.87; IR (neat) 3391 (w), 3003 (m), 2838 (m), 1567 (s), 1528 (s), 1436 (s), 1350 (s), 1293 (s), 1063 (s), 979 (s), 883 (m), 802 (s), 733 (s), 698 (s) cm^{-1} ; MS (FAB) m/z 427 ($\text{M}^+ + 2$, 9), 425 (M^+ , 9), 347 (16), 287 (40), 147 (55), 91 (100); HRMS (FAB) calcd for $\text{C}_{18}\text{H}_{19}\text{BrO}_3\text{S}_2$: 425.9959, found 425.9956.

Methyl 2-(2-benzylloxy-6-bromo-3-methoxyphenyl)ethanoate (8)

To a solution containing ketenethioacetal **16** (1.256 g, 2.948 mmol, 1.0 equiv) in dry MeOH (25 mL) HCl (g) was added at room temperature for 2 h. After the reaction mixture was stirred for 2 h, the solvent therein was evaporated under reduced pressure and the resultant solution was extracted with EtOAc (3 \times 20 mL). The combined organic layers were washed with a saturated aqueous NaCl solution (20 mL), dried over $\text{MgSO}_4(\text{s})$, filtered and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (20% EtOAc in hexane as the eluent) gave **8** (927.1 mg, 2.546 mmol) as a yellow liquid in a 86% yield: TLC R_f 0.38 (30% EtOAc in hexane as the eluent); ^1H NMR (CDCl_3 ; 400 MHz) δ 3.62 (s, 3 H, OCH_3), 3.82 (s, 2 H, CH_2CO_2), 3.85 (s, 3 H, CO_2CH_3), 5.01 (s, 2 H, PhCH_2) 6.78 (d, $J = 9.2$ Hz, 1 H, ArH), 7.26–7.42 (m, 6 H, $6 \times \text{ArH}$); ^{13}C NMR (CDCl_3 ; 100 MHz) δ 35.85, 51.92, 55.88, 74.89, 112.69, 112.70, 115.89, 127.55, 127.98, 128.09, 123.33, 128.35, 129.14, 137.28, 147.37, 152.09, 171.05 ($\text{C}=\text{O}$); IR (neat) 2074 (w), 1736 (m, $\text{C}=\text{O}$), 1635 (s), 1470 (m), 1273 (m), 1078 (m), 1004 (w), 747 (s) cm^{-1} ; MS (EI) m/z (relative intensity) 366 ($\text{M}^+ + 2$, 65), 364 (M^+ , 65), 242 (4), 213 (20), 91 (100), 65 (10); HRMS (EI) calcd for $\text{C}_{17}\text{H}_{17}\text{BrO}_4$: 364.0310, found 364.0307.

(\pm)-Methyl 2-[(2-benzylloxy-6-bromo-3-methoxyphenyl)]-3-hydroxy-3-(3,4-dimethoxy-phenyl)propanoate (17)

To a solution containing diisopropylamine (649.6 mg, 6.416 mmol, 1.1 equiv) in tetrahydrofuran (50 mL) *n*-butyllithium (397.9 mg, 6.416 mmol, 1.1 equiv) was added at 0 °C. After stirring for 30 min, the resultant mixture was cooled to –78 °C. Methyl phenyl acetate **8** (2.125 g, 5.837 mmol, 1.0 equiv) was then added to the reaction mixture, which was stirred at the same temperature for an additional 30 min. Finally, 3,4-dimethoxybenzaldehyde (**4**, 969.6 mg, 5.835 mmol, 1.0 equiv) was added to the reaction mixture and stirring was continued for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 \times 50 mL). The combined organic layers were washed with a saturated aqueous NaCl solution (30 mL), dried over $\text{MgSO}_4(\text{s})$, filtered and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (30% EtOAc in hexane as the eluent) gave (\pm)-**17** (2.010 g, 3.792 mmol) as a white solid in a 65% yield: mp (recrystallized

from EtOAc) 95–96 °C; TLC R_f 0.56 (30% EtOAc in hexane as the eluent); ^1H NMR ($(\text{CD}_3)_2\text{CO}$; 400 MHz) δ 3.56 (s, 3 H, OCH_3), 3.66 (s, 6 H, $2 \times \text{OCH}_3$), 3.92 (s, 3 H, CO_2CH_3), 4.56 (br, 1 H), 4.72 (s, 2 H, PhCH_2), 5.59 (d, 1 H, CHO), 6.20–6.69 (m, 3 H, $3 \times \text{ArH}$), 6.75 (s, 1 H, ArH), 6.86 (d, $J = 8.4$ Hz, 1 H, ArH), 7.15 (d, $J = 8.4$ Hz, 1 H, ArH), 7.37–7.44 (m, 3 H, $3 \times \text{ArH}$), 7.53–7.55 (d, $J = 7.2$ Hz, 1 H, ArH); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$; 100 MHz) δ 52.45, 55.56, 55.78, 56.27, 56.28, 73.01, 74.31, 111.31, 111.42, 114.08, 119.88, 128.53, 128.54, 128.55, 128.58, 129.05, 129.06, 129.07, 132.02, 134.57, 134.58, 138.68, 149.18, 149.30, 151.95, 174.42 ($\text{C}=\text{O}$); IR (neat) 3478 (br, OH), 2934 (s), 2829 (w), 1718 (s, $\text{C}=\text{O}$), 1514 (m), 1465 (s), 1432 (m), 1027 (m), 805 (m) cm^{-1} ; MS (FAB) m/z 532 ($\text{M}^+ + 2$, 9), 364 (20), 285 (35), 273 (25), 136 (30), 91 (100); HRMS (FAB) calcd for $\text{C}_{26}\text{H}_{27}\text{BrO}_7$: 530.0940, found 530.0947.

(\pm)-Methyl *trans*-2-(3,4-dimethoxyphenyl)-4-bromo-7-methoxy-2,3-dihydrobenzo[*b*]-furan-3-carboxylate (18**)**

To a solution containing (\pm)-**17** (915.6 mg, 1.727 mmol, 1.0 equiv) in dry dichloromethane (30 mL) iodotrimethylsilane (760.3 mg, 3.799 mmol, 2.2 equiv) was added *via* a syringe at 0 °C. After stirring at room temperature for 1 h, it was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with a saturated aqueous NaCl solution (15 mL), dried over $\text{MgSO}_4(\text{s})$, filtered and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with silica gel column (25% EtOAc in hexane as the eluent) gave (\pm)-**18** (546.8 mg, 1.295 mmol) as a yellow gummy oil in a 75% yield: TLC R_f 0.64 (20% EtOAc in hexane as the eluent); ^1H NMR (CDCl_3 ; 400 MHz) δ 3.73 (s, 3 H, OCH_3), 3.81 (s, 9 H, $\text{CO}_2\text{CH}_3 + 2 \times \text{OCH}_3$), 4.30 (d, $J = 7.2$ Hz, 1 H, ArCHCO_2), 5.82 (d, $J = 7.2$ Hz, 1 H, ArOCHAr), 6.70 (d, $J = 8.8$ Hz, 1 H, ArH), 6.79 (d, $J = 8.0$ Hz, 1 H, ArH), 6.86–6.92 (m, 2 H, $2 \times \text{ArH}$), 6.95 (d, $J = 8.8$ Hz, 1 H, ArH); ^{13}C NMR (CDCl_3 ; 100 MHz) δ 52.74, 55.93, 55.95, 56.31, 58.09, 87.89, 108.90, 109.70, 111.18, 114.38, 118.29, 118.30, 124.49, 126.21, 131.78, 144.10, 149.29, 149.44, 171.43 ($\text{C}=\text{O}$); IR (neat) 2069 (w), 1736 (m, $\text{C}=\text{O}$), 1637 (s), 1517 (m), 1485 (m), 1263 (m), 1025 (s), 762 (w) cm^{-1} ; MS (EI) m/z (relative intensity) 424 ($\text{M}^+ + 2$, 74), 422 (M^+ , 73), 392 (100), 390 (99), 343 (34), 311 (33), 284 (30), 84 (55); HRMS (EI) calcd for $\text{C}_{19}\text{H}_{19}\text{BrO}_6$: 422.0365, found 422.0362.

(\pm)-*tert*-Butyl (2*E*)-3-[2-(3,4-Dimethoxyphenyl)-7-methoxy-3-methoxycarbonyl-2,3-dihydrobenzo[*b*]-furan-4-yl]propenoate (19**)**

To a solution containing (\pm)-**18** (151.2 mg, 0.3582 mmol, 1.0 equiv), $\text{Pd}(\text{OAc})_2$ (8.043 mg, 0.0358 mmol, 0.10 equiv) and PPh_3 (28.17 mg, 0.1074 mmol, 0.30 equiv) in Et_3N (362.1 mg, 3.582 mmol, 10.0 equiv) *tert*-butyl acrylate (229.5 mg, 1.791 mmol, 5.0 equiv) was added. After the reaction mixture was stirred under nitrogen at 110 °C for 16 h, it was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (3×30 mL). The combined organic layers were washed with a

saturated aqueous NaCl solution (20 mL), dried over $\text{MgSO}_4(\text{s})$, filtered and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (20% EtOAc in hexane as the eluent) gave (\pm)-**19** (136.4 mg, 0.2901 mmol) as a yellow foam in a 81% yield: mp (recrystallized from EtOAc) 101–102 °C; TLC R_f 0.50 (30% EtOAc in hexane as the eluent); ^1H NMR (CDCl_3 ; 400 MHz) δ 1.53 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 3.84 (s, 3 H, OCH_3), 3.89 (s, 6 H, $2 \times \text{OCH}_3$), 3.97 (s, 3 H, CO_2CH_3), 4.52 (d, $J = 5.8$ Hz, 1 H, ArCHCO_2), 6.05 (d, $J = 5.8$ Hz, 1 H, ArOCHAr), 6.27 (d, $J = 16.0$ Hz, 1 H, $\text{Ph}-\text{C}=\text{CH}-\text{CO}_2$), 6.86–6.96 (m, 4 H, $4 \times \text{ArH}$), 7.24 (d, $J = 8.4$ Hz, 1 H, ArH), 7.66 (d, $J = 16.0$ Hz, 1 H, $\text{Ph}-\text{CH}=\text{C}-\text{CO}_2$); ^{13}C NMR (CDCl_3 ; 100 MHz) δ 28.07, 28.08, 28.09, 52.70, 55.83, 55.84, 56.01, 56.02, 80.25, 87.44, 108.69, 111.04, 112.84, 117.98, 119.78, 120.24, 124.68, 124.75, 132.27, 139.59, 145.77, 148.26, 149.12, 149.18, 166.11 ($\text{C}=\text{O}$), 171.84 ($\text{C}=\text{O}$); IR (neat) 2972 (w), 2936 (w), 1702 (s, $\text{C}=\text{O}$), 1627 (m, $\text{C}=\text{O}$), 1589 (s), 1483 (s), 1276 (s), 1146 (s), 1084 (m), 971 (m), 805 (s) cm^{-1} ; MS (EI) m/z (relative intensity) 470 (M^+ , 64), 440 (8), 414 (52), 382 (32), 337 (100), 309 (23), 239 (16), 231 (23); HRMS (EI) calcd for $\text{C}_{26}\text{H}_{30}\text{O}_8$: 470.1941, found 470.1944.

Methyl 4-hydroxymethyl-7-methoxy-2-(3,4-dimethoxyphenyl)-benzo[*b*]-furan-3-carboxylate (20**)**

To a solution containing aldehyde **11** (51.20 mg, 0.1383 mmol, 1.0 equiv) in dry methanol (10 mL) 10% Pd/C (14.72 mg, 0.1383 mmol, 1.0 equiv) was added. The flask was evacuated and back-filled with a H_2 balloon three times and allowed to stir under a $\text{H}_2(\text{g})$ atmosphere at room temperature for 3 h. Afterwards, the reaction mixture was filtered through Celite (rinsing several times with methanol) and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (40% EtOAc in hexane as the eluent) gave **20** (46.12 mg, 0.1239 mmol) as white solids in a 90% yield: mp (recrystallized from CH_2Cl_2) 98–99 °C; TLC R_f 0.37 (35% EtOAc in hexane as the eluent); ^1H NMR (CDCl_3 ; 400 MHz) δ 3.82 (s, 3 H, OCH_3), 3.90 (s, 6 H, $2 \times \text{OCH}_3$), 3.95 (s, 3 H, CO_2CH_3), 4.72 (s, 2 H, CH_2O), 6.74 (d, $J = 8.0$ Hz, 1 H, ArH), 6.90 (d, $J = 8.4$ Hz, 1 H, ArH), 7.11 (d, $J = 8.0$ Hz, 1 H, ArH), 7.28–7.32 (m, 2 H, $2 \times \text{ArH}$); ^{13}C NMR (CDCl_3 ; 100 MHz) δ 52.18, 55.84, 55.85, 55.92, 63.43, 106.51, 108.90, 110.62, 111.50, 121.98, 122.15, 125.58, 126.18, 126.62, 143.50, 144.94, 148.50, 150.48, 158.70, 166.74 ($\text{C}=\text{O}$); IR (neat) 3435 (br, OH), 2849 (w), 2056 (w), 1728 (s, $\text{C}=\text{O}$), 1630 (s), 1507 (m), 1464 (m), 1265 (m), 1096 (w), 1052 (w), 738 (s) cm^{-1} ; MS (EI) m/z (relative intensity) 372 (M^+ , 77) 356 (100), 339 (43), 309 (31), 85 (29), 57 (66); HRMS (EI) calcd for $\text{C}_{20}\text{H}_{20}\text{O}_7$: 372.1209, found 372.1208.

Methyl 4-methyl-7-methoxy-2-(3,4-dimethoxyphenyl)benzo[*b*]-furan-3-carboxylate (21**)**

To a solution containing aldehyde **11** (65.28 mg, 0.1763 mmol, 1.0 equiv) in dry methanol (10 mL) 10% Pd/C (18.73 mg, 0.1760 mmol, 1.0 equiv) was added. The flask was evacuated and back-filled with a H_2 balloon three times and allowed to stir

under a H₂(g) atmosphere at room temperature for 24 h. Afterwards, the reaction mixture was filtered through Celite (rinsing several times with methanol) and concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column (40% EtOAc in hexane as the eluent) gave **21** (53.36 mg, 0.1498 mmol) as a yellow foam in a 85% yield: mp (recrystallized from EtOAc) 88–89 °C; TLC *R_f* 0.46 (20% EtOAc in hexane as the eluent); ¹H NMR (CDCl₃; 400 MHz) δ 2.47 (s, 3 H, CH₃), 3.88 (s, 3 H, OCH₃), 3.91 (s, 3 H, OCH₃), 3.93 (s, 3 H, OCH₃), 3.97 (s, 3 H, CO₂CH₃), 6.72 (d, *J* = 8.0 Hz, 1 H, ArH), 6.90–6.94 (m, 2 H, 2 × ArH), 7.39–7.42 (m, 2 H, 2 × ArH); ¹³C NMR (CDCl₃; 100 MHz) δ 18.94, 52.10, 55.89, 55.96, 56.08, 106.94, 109.57, 110.80, 110.86, 121.13, 122.25, 123.13, 125.25, 127.28, 142.97, 143.41, 148.72, 150.28, 155.91, 166.40 (C=O); IR (neat) 2917 (m), 2848 (w), 1723 (s, C=O), 1629 (s), 1509 (s), 1463 (s), 1364 (w), 1262 (s), 1229 (s), 1123 (m), 1043 (m), 800 (m), 736 (m) cm⁻¹; MS (EI) *m/z* (relative intensity) 356 (M⁺, 100), 325 (13), 97 (11), 85 (38), 71 (55), 57 (93); HRMS (EI) calcd for C₂₀H₂₀O₆: 356.1260, found 356.1261.

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