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Synthetic access to optically active isoflavans by using allylic substitution

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ABSTRACT

A general approach to the (*S*)- and (*R*)-isoflavans was invented, and efficiency of the method was demonstrated by the synthesis of (*S*)-equol ((*S*)-**3**), (*R*)-sativan ((*R*)-**4**), and (*R*)-vestitol ((*R*)-**5**). The key step is the allylic substitution of (*S*)-**6a** (Ar^1=2,4-$(MeO)_2C_6H_3$) and (*R*)-**6b** (Ar^1=2,4-$(BnO)_2C_6H_3$) with copper reagents derived from CuBr·Me_2S and Ar^2-MgBr (**7a**, Ar^2=4-$MeOC_6H_4$; **7b**, 2,4-$(MeO)_2C_6H_3$; **7c**, 2-MOMO-4-$MeOC_6H_3$), furnishing *anti* S_N2' products (*R*)-**8a** and (*S*)-**8b**,**c** with 93–97% chirality transfer in 60–75% yields. The olefinic part of the products was oxidatively cleaved and the Me and Bn groups on the Ar^1 moieties was then removed. Finally, phenol bromide **9a** and phenol alcohols **9b**,**c** underwent cyclization with K_2CO_3 and the Mitsunobu reagent to afford (*S*)-**3** and (*R*)-**4** and -**5**, respectively.

1. Introduction

The isoflavonoids are secondary metabolites of daidzein (**1**) and formononetin (**2**) in the plants and act as phytoalexins in the defense against pathogens of the plants.[1] The isoflavans such as those shown in Figure 1 are a subclass of the isoflavonoids and distinctive by the chiral center at C3 of the pyran ring, which is created stereoselectively by the specific enzyme involved in the plants, thereby the (*R*)-isomers are produced in *Leguminosae* and *Papilionoideae*, whereas the (*S*)-isomers are found in certain woods such as *Machaerium* and *Dalbergia* species.[1,2] On the other hand, daidzein (**1**) ingested into our body by taking soy and foods thereof is transformed to (*S*)-equol ((*S*)-**3**) and other metabolites by intestinal bacteria such as gut microflora.[3,4] Among these metabolites, (*S*)-**3** stimulates an estrogenic response most effectively through binding to the estrogen receptor β (ERβ).[5] Interestingly, the binding affinity of (*S*)-**3** to ERβ is 13 times more potent than the unnatural (*R*)-isomer,[6] whereas the (*R*)-isomer is ERα selective. On the basis of these biological properties (*S*)-**3** is presently believed to be a dietary phytoestrogen. However, there is a controversy report that equol induces breast cancer cell proliferation at 100 nM levels.[7] To bring the discussion about propriety of (*S*)-**3** as a health benefit to a conclusion, further biological study using optically active equol, other isoflavans, and their derivatives is an urgent demand.

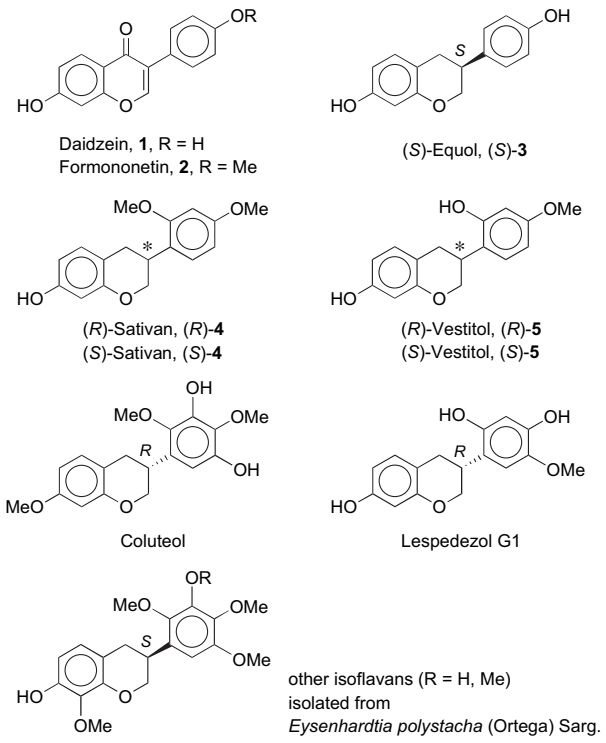

Figure 1. Daidzein, formononetin, and their isoflavan metabolites.

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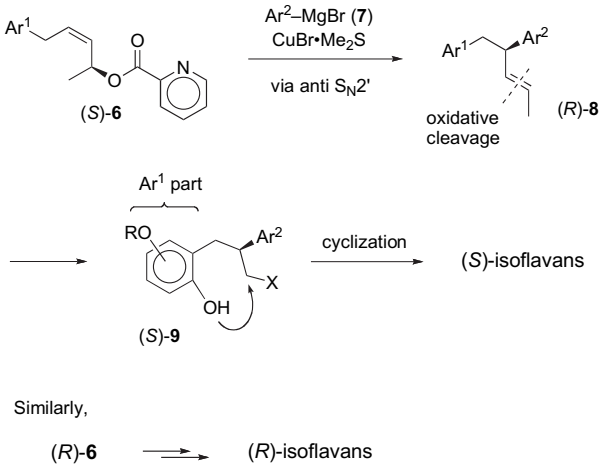
So far, several racemic syntheses of the isoflavans have been reported.[8] In contrast, asymmetric synthesis has been studied[9] only for (*S*)-equol ((*S*)-**3**) by using the Evans asymmetric alkylation.[10] However, the several steps involved in this method suffer from the moderate yields, and application of the method for synthesis of other isoflavans is not certain. Bacterial metabolism of daidzein[11] and separation of the enantiomers using chiral HPLC[6] have been studied as well, though these methods are limited to a small scale.

Recently, we reported the allylic substitution of allylic picolinates with copper reagents to furnish *anti* S_N2' products.[12] The prime merit of the method is compatibility with a wide variety of sp^2-C copper reagents such as aryl and alkenyl reagents, which are generally less reactive and less regioselective toward allylic esters other than picolinates. An easy preparation of the copper reagents from RMgBr and CuBr·Me_2S and a wide range of the RMgBr/CuBr·Me_2S ratios (1–4:1) for the successful reaction are other advantages of this reaction. With this allylic substitution in mind, we designed an approach to the isoflavans as outlined in Scheme 1, which involves (1) substitution of (*S*)-**6** with copper reagents derived from Ar^2-MgBr (**7**) and CuBr·Me_2S to afford *anti* S_N2' products (*R*)-**8**, which possess the chiral center of (*S*)-isoflavans; (2) oxidative conversion of (*R*)-**8** to phenol derivatives (*S*)-**9**; (3) cyclization of (*S*)-**9** to construct the pyran ring. Likewise, (*R*)-**6** would be transformed to (*R*)-isoflavans. We selected (*S*)-equol ((*S*)-**3**), (*R*)-sativan ((*R*)-**4**), and (*R*)-vestitol ((*R*)-**5**) as targets. In addition, we expected that the synthesis of the latter two would be a model study of more complicated isoflavans possessing an *ortho* substituent on the aromatic ring Ar^2. In practice, synthesis of (*S*)-equol was accomplished successfully as communicated recently.[13] Herein, we report a full account of the study, in which the equal access to the both enantiomers of the key substrates is secured.

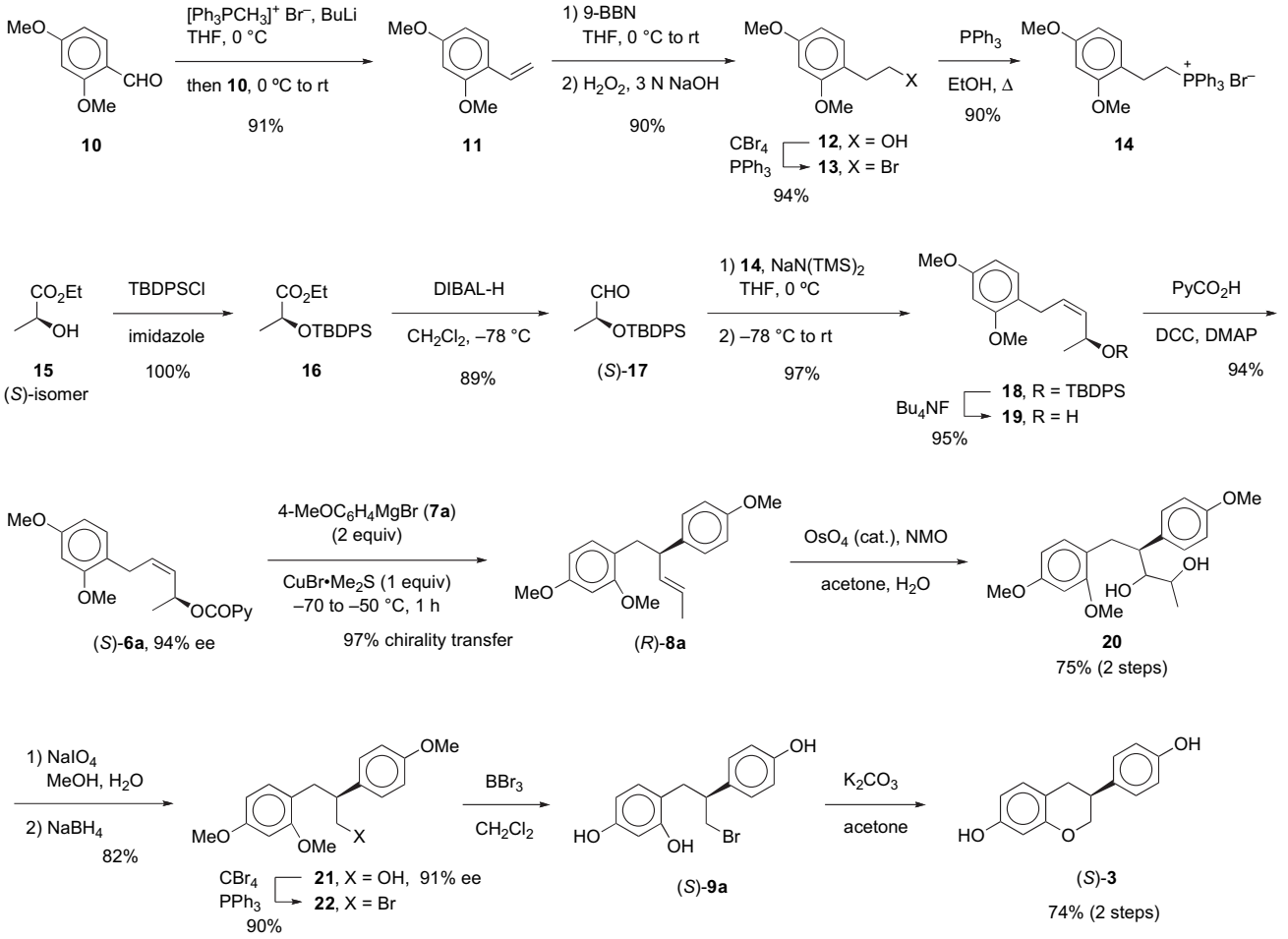


Scheme 1. Strategy to synthesize (*S*)- and (*R*)-isoflavans.

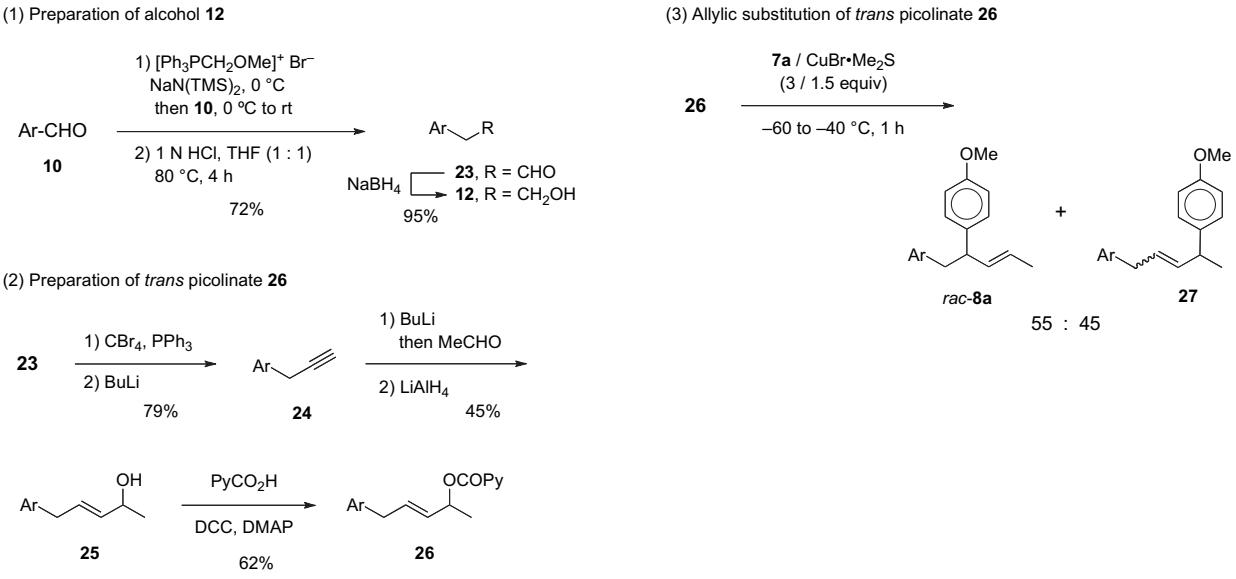
2. Results and discussion

2.1. Synthesis of (*S*)-equol

We envisioned Wittig reaction between phosphonium salt **14** and (*S*)-**17** (Scheme 2) for preparation of picolinate (S)-**6a**. To this end, Wittig reaction of aldehyde **10** with $Ph_3P{=}CH_2$ gave olefin **11**,



Scheme 2. Synthesis of (*S*)-equol ((*S*)-**3**).



Scheme 3. Related results to synthesis of (*S*)-equol. Ar=2,4-$(MeO)_2C_6H_3$–.

which upon hydroboration with 9-BBN produced alcohol **12** in 82% overall yield. Alcohol **12** was converted to the salt **14** by bromination followed by reaction with PPh_3 in EtOH.[14] We also examined another preparation of **12** consisting of Wittig reaction of **10** with Ph_3P=CHOMe, hydrolysis of the resulting enol ether (*E*:*Z*=6:4), and subsequent reduction of aldehyde **23** with $NaBH_4$ (Scheme 3). However, the overall yield of **12** by this method was 10% lower than that mentioned above (68% vs 82%). Wittig partner (*S*)-**17** was synthesized from ethyl (*S*)-lactate (**15**), the natural form, via aldehyde (*S*)-**17** according to the literature procedure[15] in good yield.

For the Wittig reaction, **14** was treated with $NaN(TMS)_2$ at 0 °C and the corresponding ylide was subjected to reaction with (*S*)-**17** initially at −78 °C and then at temperatures gradually raised to room temperature, producing *cis* olefin **18** ($J_{olefinic\text{-}H}$=11 Hz) in 97% yield. The TBDPS group of **18** was removed and the resulting alcohol **19** was esterified with $PyCO_2H$, DCC, and DMAP to furnish picolinate (*S*)-**6a** in 89% yield from **18**. Enantiomeric excess (ee) of (*S*)-**6a** was 94% by chiral HPLC and olefinic purity of (*S*)-**6a** over the *trans* isomer **26a** was 12–14:1 by ^1H NMR spectroscopy. An authentic sample of **26a** was synthesized stereoselectively from aldehyde **23** according to a sequence of reactions delineated in Scheme 3.

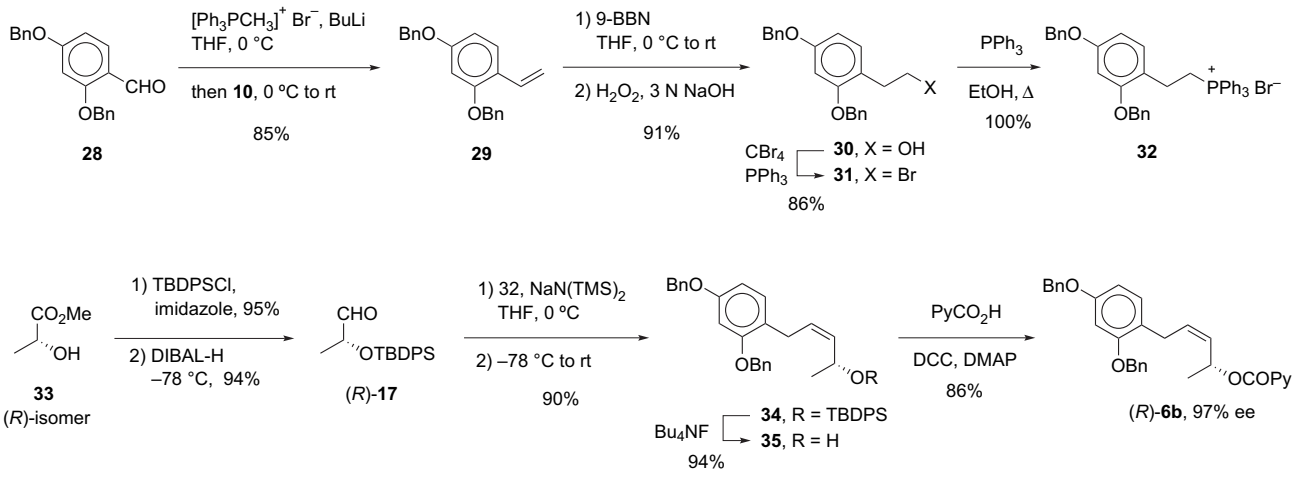
According to the procedure reported,[12] allylic substitution of (*S*)-**6a** with the copper reagent (1 equiv) derived from 4-$MeOC_6H_4MgBr$ (**7a**) and $CuBr\cdot Me_2S$ in a 2:1 ratio was carried out between −70 and −50 °C for 1 h (Scheme 2) to produce *anti* S_N2' product (*R*)-**8a** regioselectively by ^1H NMR spectroscopy. On the other hand, substitution of *trans* picolinate **26** (in racemic form) with the same copper reagent produced a mixture of the regioisomers *rac*-**8a** and **27** in a 55:45 ratio[16] (Scheme 3). Since complete separation of (*R*)-**8a** and the reagent-based byproducts by chromatography was unsuccessful due to the close mobility on silica gel, crude (*S*)-**8a** was subjected to OsO_4-catalyzed dihydroxylation and the resulting polar diol **20** (a diastereomeric mixture) was separated from the byproducts in 75% yield from (*S*)-**6a**. The diol moiety of **20** was cleaved with $NaIO_4$ and subsequent in situ reduction of the resulting aldehyde with $NaBH_4$ afforded alcohol **21** in 82% yield. The enantiomeric excess of **21** determined by chiral HPLC analysis was 91%, which indicates the allylic substitution of (*S*)-**6a** proceeded with 97% or more chirality transfer.[17]

An attempted demethylation and simultaneous bromination of **21** with BBr_3[18] was unsuccessful, giving unidentified products. After several unsuccessful trials, we found that demethylation of bromide **22** was successful to deliver bromophenol (*S*)-**9a**, which upon reaction with K_2CO_3 in acetone furnished (*S*)-equol ((*S*)-**2**) in 74% yield from bromide **22**. The ee was 91% by chiral HPLC, while the ^1H and ^{13}C NMR spectra and mp were consistent with those reported.[9,11] The structure was also supported by APT experiment (APT: Attached Proton Test).

2.2. Synthesis of (*R*)-sativan

To reproduce the phenol group at a later stage for construction of the pyran ring of (*R*)-sativan and -vestitol, a benzyl protective group was attached to 2,4-$(HO)_2C_6H_3CHO$ in 81% yield by benzylation with BnCl and K_2CO_3 (Scheme 4). Subsequently, **28** was transformed to a phosphonium salt **32** in 67% yield over four steps. The key aldehyde (*R*)-**17** for the (*R*)-isoflavans was synthesized from methyl (*R*)-lactate **33** (unnatural form) in good yield. A phosphorane generated from the salt **32** with $NaN(TMS)_2$ at 0 °C was subjected to Wittig reaction with (*R*)-**17** to produce *cis* olefin **34** in 90% yield. Deprotection of the TBDPS group was followed by esterification with $PyCO_2H$ to furnish picolinate (*R*)-**6b** in good yield. The enantiomeric purity of (*R*)-**6b** was 97% ee by ^1H NMR spectroscopy of the derived MTPA ester and a ratio of (*R*)-**6b** and the *trans* isomer (synthesized by a similar method to that for **26**) was 12:1 by ^1H NMR spectroscopy.

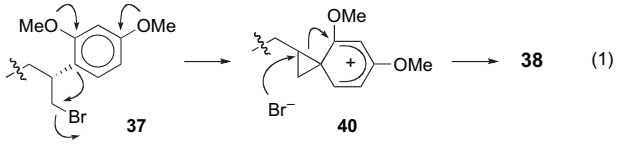
Arylation of (*R*)-**6b** with the copper reagent derived from 2,4-$(MeO)_2C_6H_3MgBr$ (**7b**) (2 equiv) and $CuBr\cdot Me_2S$ (1 equiv) at −60 °C to −50 °C was not significantly interfered with by the *ortho*-MeO group and completed within 1 h by TLC (Scheme 5). The ^1H NMR spectrum of crude (*S*)-**8b** disclosed no formation of the regioisomer. Without purification, (*S*)-**8b** was transformed to the diol (structure not shown), which upon oxidative cleavage followed by reduction of the resulting aldehyde with $NaBH_4$ produced alcohol **36** in 73% yield from (*R*)-**6b**. Ee of **36** was 94% by chiral HPLC, indicating 97% chirality transfer for the arylation. In contrast to the uneventful conversion up to **36**, bromination of alcohol **36** with CBr_4 and PPh_3 afforded a mixture of bromide **37** and unidentified byproducts. Without separation, the mixture was subjected to debenzylation using Pd/C under hydrogen followed by K_2CO_3-assisted cyclization to afford a mixture of (*R*)-**4** and furan **39** in a 1:1 ratio by ^1H NMR spectroscopy. The formation of the latter indicates that one of the byproducts produced with bromide **37** was the isomer **38**. The migration of the 2,4-$(MeO)_2C_6H_3$ group to the next carbon through

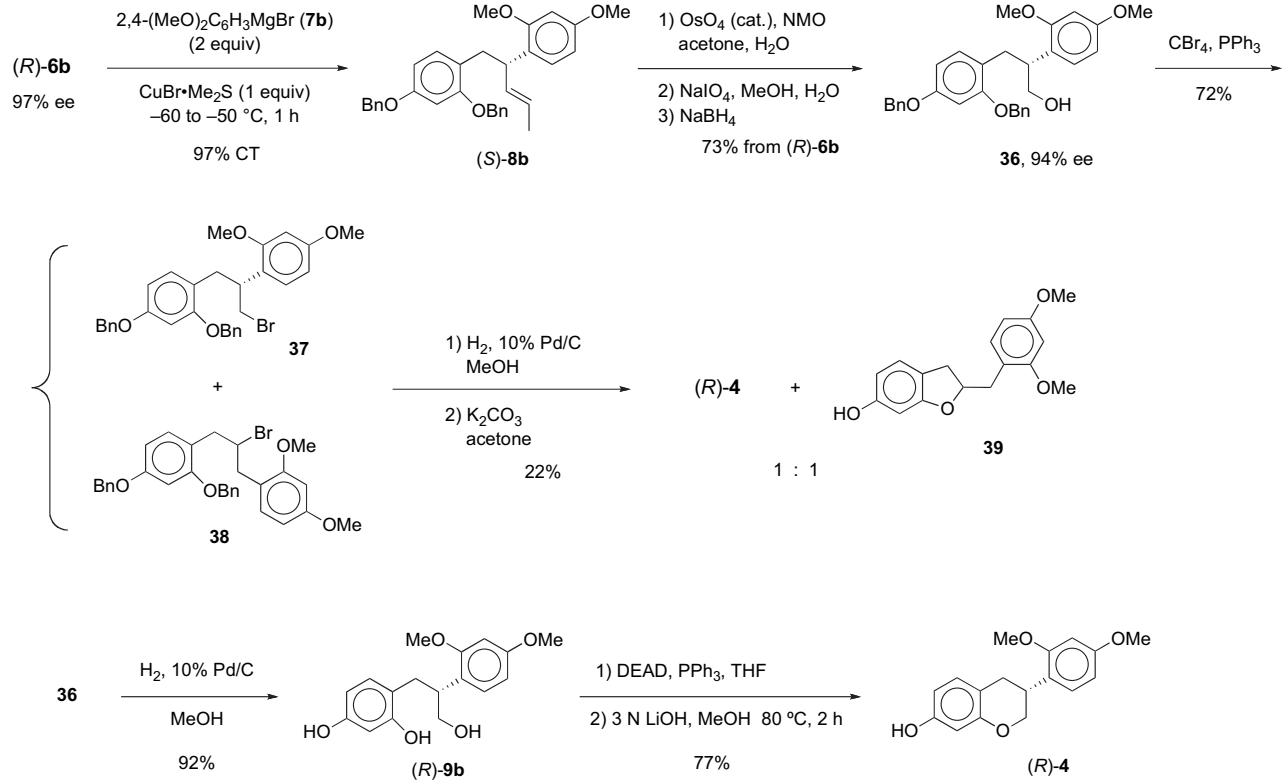


Scheme 4. Synthesis of the key picolinate (*R*)-**6b**.

benzenium cation **40** as drawn in Eq. 1 is a likely process, and must be driven by the two methoxy groups of the 2,4-$(MeO)_2C_6H_3$ group since such a migration was not observed with bromide **22**, which possesses the 4-$MeOC_6H_4$ group, instead.[19] In an attempt to elucidate another alcohol derivative suited for the cyclization, conversion of **36** to chloride, tosylate, and mesylate were examined, but the products were unfortunately unstable.

We then examined the cyclization using the Mitsunobu reagent, which has frequently been used for construction of the benzopyran ring of the flavans, the isoflavans, and other classes of compounds.[8a,10,19b,20] The benzyl group in **36** was removed to produce the phenol alcohol (*R*)-**9b** in 92% yield. Cyclization of (*R*)-**9b** with PPh_3 and DEAD proceeded cleanly to furnish a mixture of (*R*)-**4** and $(NHCO_2Et)_2$, which was hardly separated by chromatography. Finally, $(NHCO_2Et)_2$ in the mixture was removed by hydrolysis with 3 N LiOH in MeOH to allow easy chromatographic purification of (*R*)-**4**[21] in 77% yield. The ^1H NMR spectrum, $[\alpha]_D$, and mp were consistent with those reported.[21a,b] The structure was also supported by the APT spectrum.



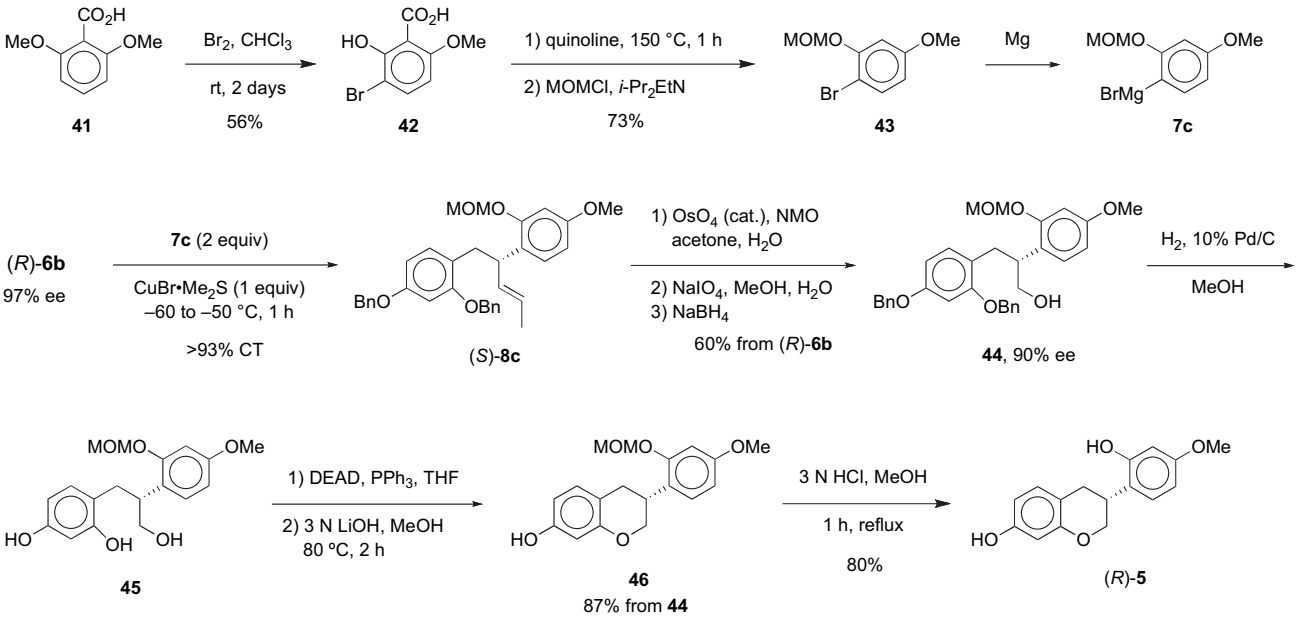


Scheme 5. Synthesis of (*R*)-sativan ((*R*)-**4**) from (*R*)-**6b**.

2.3. Synthesis of (*R*)-vestitol ((*R*)-5) from (*R*)-6b

Due to difficulty in obtaining bromide **43** from a commercial source, we synthesized it from **41**. Bromination of **41** with Br_2, according to the literature procedure,[22] took place regioselectively with concomitant demethylation to produce bromophenol **42** in 56% yield (Scheme 6). Decarboxylation of **42** was completed in quinoline under reflux and the OH group of the product was protected as the MOM ether to afford **43** in 73% yield, which was converted to the Grignard reagent **7c** as usual.

The copper reagent derived from **7c** and $CuBr \cdot Me_2S$ in a 2:1 ratio underwent substitution with (*R*)-**6b** (97% ee) at −60 °C to −50 °C to produce (*S*)-**8c** after 1 h. Absence of the regioisomer by ^1H NMR spectroscopy and the recorded reaction time for the completion (1 h) indicate that the *ortho*-MOM-oxy group did not interfere with the substitution as the MeO group did not. Without purification, (*S*)-**8c** was converted to alcohol **44** by dihydroxylation followed by oxidative cleavage of the resulting diol in 60% yield from (*R*)-**6b**. Chiral HPLC analysis revealed 90% ee of **44** and thus 93% chirality transfer for the substitution. Debenzylation of **44** gave phenol alcohol **45**, which under the Mitsunobu conditions afforded a mixture of benzophyran **46** and $(NHCO_2Et)_2$. The mixture was treated with LiOH in aqueous MeOH to remove the latter, allowing easy purification of **46** by chromatography in 87% yield from **44**. Finally, the MOM group was removed with 3 N HCl in MeOH to furnish (*R*)-**5** in 80% yield with 90% ee by HPLC. The spectral data (^1H and ^{13}C NMR spectra) and $[\alpha]_D$ were consistent with those reported.[23]



Scheme 6. Synthesis of (*R*)-vestitol ((*R*)-**5**) from (*R*)-**6b**.

3. Conclusion

We established a new access to optically active isoflavans, in which allylic substitution is used to construct the requisite chiral center with high chirality transfer. The copper reagents possessing a substitution at the *ortho* position did not interfere with the substitution. This compatibility would allow synthesis of more complicated isoflavans such as those listed in Figure 1. In addition, both enantiomers of the starting lactate are available easily at reasonable prices. We believe that biological researches of the isoflavans would be accelerated with the present method.

4. Experimental

4.1. General

Infrared (IR) spectra are reported in wave numbers (cm^{-1}). The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ (δ=0 ppm) and the center line of $CDCl_3$ triplet (δ=77.1 ppm) as internal standards, respectively. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (*J*) are given in Hertz (Hz). In some cases chemical shifts of carbons accompany plus (for C and CH_2) and minus (for CH and CH_3) signs of APT (Attached Proton Test) experiments. The following solvents were distilled before use: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2).

4.2. Synthesis of (*S*)-equol

*4.2.1. 2,4-Dimethoxy-1-vinylbenzene (**11**).* To an ice-cold mixture of $[Ph_3PCH_3]^+Br^-$ (216 mg, 0.605 mmol) in THF (1 mL) was added BuLi (0.220 mL, 2.64 M in THF, 0.581 mmol). The mixture was stirred at the same temperature for 1.5 h, and a solution of aldehyde **10** (53.3 mg, 0.321 mmol) in THF (1 mL) was added. The mixture was stirred at room temperature for 1 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with ether twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to leave an oil, which was purified by chromatography on silica gel with hexane/EtOAc (10:1) to afford olefin **11** (47.7 mg, 91%). The ^1H NMR spectrum of **11** was identical with that reported.[24]

*4.2.2. 2-(2,4-Dimethoxyphenyl)ethanol (**12**).* To an ice-cold solution of olefin **11** (2.09 g, 12.7 mmol) in THF (40 mL) was added 9-BBN (50.8 mL, 0.5 M in THF, 25 mmol). The reaction was conducted at ambient temperature for 18 h and quenched by addition of MeOH

(40 mL). After 30 min of stirring, 3 N NaOH (40 mL, 120 mmol) and 35% H_2O_2 (6.6 mL, 75 mmol) were added slowly. The resulting mixture was stirred at room temperature for 3 h and poured into H_2O. The product was extracted with ether twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford a residual oil, which was purified by chromatography on silica gel with hexane/EtOAc (from 5:1 to 1:2) to afford alcohol **12** (2.07 g, 90%) as colorless solids: IR (Nujol) 3331, 1212, 1126, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63 (t, J=6 Hz, 1H), 2.84 (t, J=6 Hz, 2H), 3.74–3.85 (m, 8H), 6.42–6.48 (m, 2H), 7.07 (d, J=8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.5 (+), 55.4 (−), 55.5 (−), 63.1 (+), 98.7 (−), 104.1 (−), 119.3 (+), 131.2 (−), 158.6 (+), 159.8 (+); HRMS (FAB) calcd for $C_{10}H_{14}O_3Na$ [(M+Na)$^+$] 205.0841, found 205.0846.

*4.2.3. 1-(2-Bromoethyl)-2,4-dimethoxybenzene (**13**).* To an ice-cold solution of alcohol **12** (202 mg, 1.11 mmol) and PPh_3 (349 mg, 1.33 mmol) in CH_2Cl_2 (2 mL) was added CBr_4 (406 mg, 1.22 mmol). The mixture was stirred at room temperature for 2 h and concentrated to afford a residual oil, which was purified by chromatography on silica gel with hexane/EtOAc (10:1) to afford bromide **13** (255 mg, 94%): IR (neat) 1613, 1507, 1209, 1143, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.10 (t, J=8 Hz, 2H), 3.53 (t, J=8 Hz, 2H), 3.798 (s, 3H), 3.803 (s, 3H), 6.40–6.47 (m, 2H), 7.05 (d, J=8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.7 (+), 34.1 (+), 55.3 (−), 55.4 (−), 98.6 (−), 103.9 (−), 119.6 (+), 131.0 (−), 158.5 (+), 160.1 (+).

*4.2.4. (2-(2,4-Dimethoxyphenyl)ethyl)triphenylphosphonium bromide (**14**).* A solution of bromide **13** (97.8 mg, 0.399 mmol) and PPh_3 (171 mg, 0.652 mmol) in EtOH (1 mL) was refluxed for 40 h and concentrated to afford a residual solid, which was recrystallized from ether/CH_2Cl_2 to afford phosphonium salt **14** (181 mg, 0.357 mmol, 90%) as white solids: IR (Nujol) 1507, 1292, 1108, 1022, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.90–3.03 (m, 2H), 3.68–3.86 (m, 8H), 6.35 (d, J=2 Hz, 1H), 6.41 (dd, J=8, 2 Hz, 1H), 7.26 (d, J=8 Hz, 1H), 7.67–7.94 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (d, J=14 Hz,) (+), 23.5 (d, J=29 Hz,) (+), 55.4 (−), 55.5 (−), 98.6 (−), 104.6 (−), 118.2 (d, J=14 Hz,) (+), 118.6 (d, J=85 Hz,) (+), 130.5 (d, J=13 Hz,) (−), 131.2 (−), 133.7 (d, J=10 Hz,) (−), 135.2 (d, J=3 Hz,) (−), 157.7 (+), 160.4 (+).

*4.2.5. (S)-2-(tert-Butyldiphenylsilyloxy)propanal ((S)-**17**).* A solution of ethyl lactate **15** (2.01 g, 17.0 mmol), TBDPSCl (6.51 mL, 25.4 mmol), and imidazole (2.32 g, 34.1 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 4.5 h and poured into saturated NH_4Cl. The product was extracted with CH_2Cl_2 twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford a residual oil, which was purified by chromatography on silica gel with hexane/EtOAc (from 1:0 to 100:1) to afford silyl ether **16** (6.05 g, 100%), which showed an identical ^1H NMR spectrum to that reported.[15]

To a solution of the above silyl ether **16** (1.51 g, 4.24 mmol) in CH_2Cl_2 (9 mL) was added DIBAL-H (4.63 mL, 1.0 M in THF, 4.63 mmol) at −78 °C. After 1 h at −78 °C, H_2O (0.80 mL, 44 mmol) and NaF (1.80 g, 42.9 mmol) were added carefully. The resulting mixture was stirred at room temperature for 30 min and filtered through a pad of Celite. The filtrate was concentrated, and the residue was subjected to chromatography on silica gel with hexane/EtOAc (from 1:0 to 10:1) to afford aldehyde (*S*)-**17** (1.18 g, 89%), which showed an identical ^1H NMR spectrum to that reported.[15]

*4.2.6. (S,Z)-1-(2,4-Dimethoxyphenyl)-4-(tert-butyldiphenyl-silyloxy)-pent-2-ene (**18**).* To an ice-cold solution of phosphonium salt **14** (4.88 g, 9.62 mmol) in THF (12 mL) was added $NaN(TMS)_2$ (9.60 mL, 1.0 M in THF, 9.60 mmol). After 0.5 h at ice-bath temperature, the mixture was cooled to −78 °C and a solution of aldehyde (*S*)-**17** (2.00 g, 6.40 mmol) in THF (20 mL) was added slowly. After the addition, the mixture was allowed to warm to ambient temperature, stirred for 19 h, and poured into saturated NH_4Cl. The product was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford a residual oil, which was subjected to chromatography on silica gel with hexane/EtOAc (20:1) to afford olefin **18** (2.99 g, 97%) as a yellow oil: IR (neat) 1613, 1506, 1209, 1112, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.17 (d, J=6 Hz, 3H), 2.86 (dd, J=16, 7 Hz, 1H), 2.98 (dd, J=16, 7 Hz, 1H), 3.68 (s, 3H), 3.76 (s, 3H), 4.68–4.82 (m, 1H), 5.35 (dt, J=11, 7 Hz, 1H), 5.59 (dd, J=11, 8 Hz, 1H), 6.31 (dd, J=8, 2 Hz, 1H), 6.37 (d, J=2 Hz, 1H), 6.76 (d, J=8 Hz, 1H), 7.24–7.44 (m, 6H), 7.65–7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (+), 24.7 (−), 27.0 (−), 27.3 (+), 55.2 (−), 55.4 (−), 66.1 (−), 98.4 (−), 103.9 (−), 121.4 (+), 126.7 (−), 127.5 (−), 127.6 (−), 129.4 (−), 129.5 (−), 129.6 (−), 134.5 (+), 134.8 (+), 135.1 (−), 135.9 (−), 136.0 (−), 158.0 (+), 159.2 (+); HRMS (FAB) calcd for $C_{29}H_{36}O_3SiNa$ [(M+Na)$^+$] 483.2331, found 483.2332.

*4.2.7. (S,Z)-5-(2,4-Dimethoxyphenyl)pent-3-en-2-ol (**19**).* To a solution of **18** (1.82 g, 3.79 mmol) in THF (20 mL) was added Bu_4NF (5.69 mL, 1.0 M in THF, 5.69 mmol). The solution was stirred at room temperature for 23 h and poured into H_2O. The product was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford a residual oil, which was chromatographed on silica gel with hexane/EtOAc (from 10:1 to 2:1) to afford alcohol **19** (0.799 g, 95%): IR (neat) 3389, 1507, 1209, 1156, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, J=6 Hz, 3H), 3.25 (dd, J=15, 6 Hz, 1H), 3.47 (dd, J=15, 7 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 4.82 (dq, J=7, 6 Hz, 1H), 5.45–5.58 (m, 2H), 6.43 (dd, J=8.5, 2 Hz, 1H), 6.45 (br s, 1H), 7.03 (d, J=8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (−), 28.0 (+), 55.41 (−), 55.46 (−), 63.6 (−), 98.7 (−), 104.2 (−), 120.9 (+), 129.9 (−), 134.0 (−), 158.0 (+), 159.5 (+); HRMS (FAB) calcd for $C_{13}H_{18}O_3Na$ [(M+Na)$^+$] 245.1154, found 245.1162.

*4.2.8. (S,Z)-5-(2,4-Dimethoxyphenyl)pent-3-en-2-yl picolinate ((S)-**6a**).* To an ice-cold solution of picolinic acid (141 mg, 1.15 mmol) and DMAP (111 mg, 0.909 mmol) in CH_2Cl_2 (4 mL) were added DCC (252 mg, 1.22 mmol) and, after 30 min, a solution of alcohol **19** (208 mg, 0.936 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at room temperature for 2.5 h, diluted with Et_2O, and filtered through a pad of Celite. The filtrate was concentrated, and the residual oil was purified by chromatography on silica gel with hexane/EtOAc (from 4:1 to 2:1) to afford the picolinate (*S*)-**6a** (286 mg, 94%): 94% ee by HPLC analysis (Chiralcel AD-H, hexane/*i*-PrOH=95/5, 1.0 mL/min, t_R/min=24.6 (*S*), 34.4 (*R*)); $[\alpha]_D^{27}$ +88 (*c* 0.22, $CHCl_3$); IR (neat) 1717, 1507, 1289, 1137, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, J=6.5 Hz, 3H), 3.42 (dd, J=15, 6 Hz, 1H), 3.54 (dd, J=15, 6 Hz, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 5.60–5.74 (m, 2H), 6.17 (dq, J=8, 7 Hz, 1H), 6.40 (dd, J=8, 3 Hz, 1H), 6.42 (d, J=3 Hz, 1H), 7.07 (d, J=8 Hz, 1H), 7.45 (ddd, J=8, 5, 1.5 Hz, 1H), 7.82 (td, J=8, 1.5 Hz, 1H), 8.12 (dt, J=8, 1 Hz, 1H), 8.77–8.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (−), 28.0 (+), 55.3 (−), 55.4 (−), 68.9 (−), 98.5 (−), 103.9 (−), 120.9 (+), 125.2 (−), 126.7 (−), 129.0 (−), 129.9 (−), 131.9 (−), 136.9 (−), 148.7 (+), 149.9 (−), 158.2 (+), 159.4 (+), 164.6 (+); HRMS (FAB) calcd for $C_{19}H_{21}NO_4Na$ [(M+Na)$^+$] 350.1368, found 350.1368.

*4.2.9. (R,E)-2,4-Dimethoxy-1-(2-(4-methoxyphenyl)pent-3-enyl)-benzene ((R)-**8a**).* To an ice-cold suspension of $CuBr\cdot Me_2S$ (68 mg, 0.331 mmol) in THF (5 mL) was added 4-$MeOC_6H_4MgBr$ (0.64 mL, 0.95 M in THF, 0.608 mmol) dropwise. After 30 min of stirring, the mixture was cooled to −70 °C. A solution of picolinate (*S*)-**6a** (100 mg, 0.305 mmol, 94% ee) in THF (3 mL) was added to the mixture, which was stirred between −70 °C and −50 °C for 1 h. Saturated NH_4Cl and EtOAc were added to the mixture with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were

washed with brine, dried over $MgSO_4$, and concentrated to afford olefin (*R*)-**8a**, which was used for the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (dq, *J*=6, 1.5 Hz, 3H), 2.83 (dd, *J*=13, 7.5 Hz, 1H), 2.90 (dd, *J*=13, 7.5 Hz, 1H), 3.47 (dt, *J*=7.5, 7 Hz, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 5.29 (ddq, *J*=15, 1, 6 Hz, 1H), 5.62 (ddq, *J*=15, 7, 1.5 Hz, 1H), 6.31 (dd, *J*=8.5, 2.5 Hz, 1H), 6.39 (d, *J*=2.5 Hz, 1H), 6.74–6.84 (m, 3H), 7.01–7.11 (m, 2H).

*4.2.10. (4S)-5-(2,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)-pentane-2,3-diol (**20**).* To an ice-cold solution of crude olefin (*R*)-**8a** and NMO (53 mg, 0.45 mmol) in acetone and H_2O (2:1, 3 mL) was added OsO_4 (0.77 mL, 0.02 M in *t*-BuOH, 0.015 mmol). The mixture was stirred at room temperature for 5 h and poured into H_2O. The product was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford a residual oil, which was purified by chromatography on silica gel with hexane/EtOAc (from 10:1 to 1:1) to afford diol **20** (87 mg, 75% from (*S*)-**6a**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, *J*=6 Hz, 1.5H), 1.16 (d, *J*=6 Hz, 1.5H), 2.60–3.64 (m, 5H), 3.743 (s, 3H), 3.770 (s, 1.5H), 3.788 (s, 1.5H), 3.792 (s, 1.5H), 3.795 (s, 1.5H), 3.857 (s, 1.5H), 6.27 (dd, *J*=8, 2 Hz, 0.5H), 6.38–6.49 (m, 1.5H), 6.66 (d, *J*=8 Hz, 0.5H), 6.78 (d, *J*=9 Hz, 1H), 6.84 (d, *J*=9 Hz, 1H), 6.98 (d, *J*=8 Hz, 0.5H), 7.02 (d, *J*=9 Hz, 1.5H), 7.26 (d, *J*=9 Hz, 1.5H).

*4.2.11. (S)-3-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)propan-1-ol (**21**).* To an ice-cold solution of diol **20** (87 mg, 0.241 mmol) in MeOH and H_2O (2:3, 5 mL) was added $NaIO_4$ (80 mg, 0.374 mmol). After 0.5 h at 0 °C, $NaBH_4$ (55 mg, 1.47 mmol) was added. The mixture was stirred at 0 °C for 0.5 h and poured into saturated NH_4Cl. The product was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Chromatography of the crude product on silica gel with hexane/EtOAc (from 4:1 to 1:1) afforded alcohol **21** (59.7 mg, 82%) as solids: 91% ee by HPLC analysis (Chiralcel AD-H, hexane/*i*-PrOH=95/5, 1.0 mL/min, t_R/min=31.3 (*R*), 42.0 (*S*)); $[\alpha]_D^{23}$ +61 (*c* 0.29, $CHCl_3$); IR (Nujol) 3551, 1612, 1157, 1032, 839 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (t, *J*=6 Hz, 1H), 2.77 (dd, *J*=6, 3 Hz, 1H), 2.91–3.09 (m, 2H), 3.70 (t, *J*=6 Hz, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 6.35 (dd, *J*=8.5, 2.5 Hz, 1H), 6.43 (d, *J*=2.5 Hz, 1H), 6.82–6.89 (dm, *J*=9 Hz, 3H), 7.12–7.17 (dm, *J*=9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.4 (+), 48.0 (−), 55.3 (−), 55.4 (−), 55.5 (−), 66.2 (+), 98.5 (−), 104.1 (−), 113.9 (−), 120.6 (+), 129.1 (−), 131.2 (−), 134.9 (+), 158.31 (+), 158.35 (+), 159.4 (+); HRMS (FAB) calcd for $C_{18}H_{22}O_4$ [M^+] 302.1518, found 302.1512.

*4.2.12. (S)-1-(3-Bromo-2-(4-methoxyphenyl)propyl)-2,4-dimethoxybenzene (**22**).* To an ice-cold solution of alcohol **21** (103 mg, 0.341 mmol) and PPh_3 (135 mg, 0.515 mmol) in CH_2Cl_2 (1 mL) was added CBr_4 (123 mg, 0.371 mmol). The mixture was stirred at room temperature for 3 h and concentrated to afford a residual oil, which was purified by chromatography on silica gel with hexane/EtOAc (from 1:0 to 10:1) to afford bromide **22** (113 mg, 90%) as white solids: $[\alpha]_D^{26}$ +31 (*c* 0.21, $CHCl_3$); IR (Nujol) 1610, 1244, 1211, 1157, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (dd, *J*=13.5, 7 Hz, 1H), 3.02 (dd, *J*=13.5, 7.5 Hz, 1H), 3.20–3.31 (m, 1H), 3.54 (dd, *J*=10, 7.5 Hz, 1H), 3.60 (dd, *J*=10, 5.5 Hz, 1H), 3.76 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 6.34 (dd, *J*=8, 2.5 Hz, 1H), 6.41 (d, *J*=2.5 Hz, 1H), 6.80–6.90 (m, 3H), 7.08–7.12 (dm, *J*=8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.0 (+), 39.0 (+), 47.0 (−), 55.26 (−), 55.31 (−), 55.38 (−), 98.5 (−), 103.8 (−), 113.7 (−), 120.1 (+), 128.7 (−), 131.1 (−), 134.7 (+), 158.4 (+), 158.5 (+), 159.5 (+); HRMS (FAB) calcd for $C_{18}H_{21}BrO_3$ [M^+] 364.0674, found 364.0678.

*4.2.13. (S)-4-(3-Bromo-2-(4-hydroxyphenyl)propyl)benzene-1,3-diol ((S)-**9a**).* To a solution of bromide **22** (201 mg, 0.550 mmol) in CH_2Cl_2 (4 mL) was added BBr_3 (0.175 mL, 1.82 mmol) at −78 °C. The mixture was allowed to warm to ambient temperature, stirred for 19 h, and re-cooled to −50 °C. The reaction was quenched by addition of H_2O (1 mL) and most of the volatile materials were evaporated. The resulting mixture was diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc two times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford a residual solid mass, which was chromatographed on silica gel with hexane/EtOAc (1:1) to afford phenol (*S*)-**9a**, which was passed through a short column of silica gel for the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (dd, *J*=13.5, 7 Hz, 1H), 3.08 (dd, *J*=13.5, 7 Hz, 1H), 3.16–3.28 (m, 1H), 3.54–3.66 (m, 2H), 4.79–5.00 (m, 3H), 6.25–6.30 (m, 2H), 6.72–6.83 (m, 3H), 7.00–7.05 (m, 1H).

*4.2.14. (S)-Equol ((S)-**3**).* A mixture of the above phenol (*S*)-**9a** and K_2CO_3 (268 mg, 1.94 mmol) in acetone (6 mL) was stirred at 50 °C for 8 h, cooled to room temperature, and filtered through a pad of Celite. The filtrate was concentrated and the residual solid mass was purified by chromatography on silica gel with hexane/EtOAc (from 1:3) to afford (*S*)-**3** (110 mg, 74% from bromide **22**) as white solids: 91% ee by HPLC analysis (Chiralcel AD-H, hexane/*i*-PrOH=90/10, 1.0 mL/min, t_R/min=38.7 for (*R*)-isomer, 49.4 for (*S*)-**3**); mp 190–191 °C (lit.[9] 192–193 °C; lit.[11] 190.8 °C); $[\alpha]_D^{25}$ −13 (*c* 0.21, EtOH);[25] IR (Nujol) 3358, 1598, 1151, 1024, 829 cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 2.70–2.90 (m, 2H), 2.95–3.07 (m, 1H), 3.89 (t, *J*=10.5 Hz, 1H), 4.10–4.18 (dm, *J*=8 Hz, 1H), 6.19 (d, *J*=2.5 Hz, 1H), 6.28 (dd, *J*=8, 2.5 Hz, 1H), 6.72 (d, *J*=8.5 Hz, 2H), 6.86 (d, *J*=8 Hz, 1H), 7.10 (d, *J*=8.5 Hz, 2H), 9.16 (s, 1H), 9.28 (s, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 31.3 (+), 37.2 (−), 70.2 (+), 102.5 (−), 108.0 (−), 112.6 (+), 115.2 (−), 128.3 (−), 130.1 (−), 131.6 (+), 154.5 (+), 156.1 (+), 156.5 (+); HRMS (FAB) calcd for $C_{15}H_{14}O_3$ [M^+] 242.0943, found 242.0943. The ^{1}H and ^{13}C NMR spectra of (*S*)-**3** was identical with that reported.[9,11]

4.3. Synthesis of (*R*)-sativan

*4.3.1. 2,4-Bis(benzyloxy)benzaldehyde (**28**).* A mixture of 2,4-dihydroxybenzaldehyde (4.99 g, 36.1 mmol), BnCl (11.34 ml, 98.5 mmol), and K_2CO_3 (13.75 g, 99.5 mmol) in EtOH (50 mL) was stirred at 80 °C overnight, cooled to room temperature, and filtered through a pad of Celite. The filtrate was concentrated to afford a residual oil, which was diluted with brine. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford a residual solid, which was recrystallized from hexane/EtOAc to afford ether **28** (1.86 g 81%) as white solids, which showed the identical ^{1}H NMR spectrum to that reported.[26] Other data are: mp 85–86 °C (hexane/EtOAc); IR (Nujol) 1608, 1260, 1015 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (s, 2H), 5.14 (s, 2H), 6.60 (d, *J*=2 Hz, 1H), 6.64 (dd, *J*=8.5, 2 Hz, 1H), 7.32–7.46 (m, 10H), 7.84 (d, *J*=8.5 Hz, 1H), 10.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.3 (+), 70.4 (+), 100.0 (−), 107.0 (−), 119.4 (+), 127.3 (−), 127.5 (−), 128.3 (−), 128.4 (−), 128.7 (−), 130.4 (−), 135.86 (+), 135.90 (+), 162.7 (+), 165.1 (+), 188.2 (−).

*4.3.2. 2,4-Bis(benzyloxy)-1-vinylbenzene (**29**).* To an ice-cold mixture of $[Ph_3PCH_3]^+Br^-$ (5.08 g, 14.2 mmol) in THF (40 mL) was added BuLi (8.10 mL, 1.6 M in THF, 13.0 mmol). After 1 h at the ice-bath temperature, a solution of aldehyde **28** (3.44 g, 10.8 mmol) in THF (40 mL) was added. The reaction mixture was stirred at room temperature overnight and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc and the product was purified by chromatography to afford olefin **29** (2.90 g, 85%): IR (neat) 1604, 1501, 1173, 1119, 1026 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 2H), 5.04 (s, 2H), 5.14 (dd, *J*=11.5, 1.5 Hz, 1H), 5.65 (dd, *J*=17.5, 1.5 Hz, 1H), 6.54–6.61 (m, 2H), 7.03 (dd, *J*=17.5, 11.5 Hz, 1H), 7.28–7.49 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.2 (+), 70.3 (+),

100.7 (−), 106.3 (−), 112.4 (+), 120.5 (+), 127.3 (−), 127.4 (−), 127.6 (−), 128.0 (−), 128.1 (−), 128.6 (−), 128.7 (−), 131.2 (−), 136.9 (+), 137.0 (+), 157.0 (+), 159.7 (+); HRMS (FAB) calcd for $C_{22}H_{20}O_2$ [M^+] 316.1463, found 316.1459.

*4.3.3. 2-(2,4-Bis(benzyloxy)phenyl)ethanol (**30**).* To an ice-cold solution of olefin **29** (2.00 g, 6.32 mmol) in THF (20 mL) was added 9-BBN (25.2 mL, 0.5 M in THF, 12.6 mmol). The solution was stirred at ambient temperature for 14 h and diluted with MeOH (20 mL). After 1 h of stirring, 3 N NaOH (21 mL, 63 mmol), and 35% H_2O_2 (3.3 mL, 38 mmol) were added slowly. The resulting mixture was stirred at room temperature for 3 h, diluted with H_2O, and extracted with EtOAc. The product was purified by chromatography to afford alcohol **30** (1.91 g, 91%) as white solids: IR (Nujol) 3388, 1612, 1505, 1168, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61(br s, 1H) 2.88 (t, J=6.5 Hz, 2H), 3.80 (t, J=6.5 Hz, 2H), 5.02 (s, 2H), 5.03 (s, 2H), 6.53 (dd, J=8, 2 Hz, 1H), 6.61 (d, J=2 Hz, 1H), 7.08 (d, J=8 Hz, 1H), 7.27–7.48 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.6 (+), 63.0 (+), 70.1 (+), 70.2 (+), 100.8 (−), 105.6 (−), 119.9 (+), 127.3 (−), 127.6 (−), 128.0 (−), 128.1 (−), 128.68 (−), 128.70 (−), 131.3 (−), 136.9 (+), 137.0 (+), 157.7 (+), 158.9 (+); HRMS (FAB) calcd for $C_{22}H_{22}O_3$ [M^+] 334.1569, found 334.1559.

*4.3.4. (1,3-Bis(benzyloxy)-4-(2-bromoethyl))benzene (**31**).* A solution of alcohol **30** (3.90 g, 11.7 mmol), CBr_4 (4.73 g, 14.3 mmol), and PPh_3 (4.07 g, 15.5 mmol) in CH_2Cl_2 (23 mL) was stirred at room temperature for 2 h and the product was purified by chromatography to afford bromide **31** (3.96 g, 86%): ^1H NMR (300 MHz, $CDCl_3$) δ 3.16 (t, J=7.5 Hz, 2H), 3.57 (t, J=7.5 Hz, 2H), 5.02 (s, 2H), 5.04 (s, 2H), 6.52 (dd, J=8, 2 Hz, 1H), 6.59 (d, J=2 Hz, 1H), 7.07 (d, J=8 Hz, 1H), 7.28–7.45 (m, 10H).

*4.3.5. (2-(2,4-Bis(benzyloxy)phenyl)ethyl)triphenylphosphonium bromide (**32**).* A solution of bromide **31** (0.53 g, 1.33 mmol) and PPh_3 (0.54 g, 2.06 mmol) in EtOH (3.5 mL) was refluxed for 40 h and concentrated. The residual solid was recrystallized from Et_2O to afford phosphonium salt **32** (0.89 g, 100%) as white solids: ^1H NMR (300 MHz, $CDCl_3$) δ 2.96 (dt, J=10, 6 Hz, 2H), 3.74−3.87 (m, 2H), 4.94 (s, 2H), 5.02 (s, 2H), 6.52–6.57 (m, 2H), 7.30–7.45 (m, 13H), 7.52–7.61 (m, 5H), 7.64–7.79 (m, 8H).

*4.3.6. (R)-2-(tert-Butyldiphenylsilyloxy)propanal ((R)-**17**).* A solution of methyl lactate **33** (1.99 g, 19.1 mmol), TBDPSCl (7.40 mL, 26.9 mmol), and imidazole (2.64 g, 38.8 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature overnight and the crude product was purified by chromatography to afford the silyl ether of **33** (6.25 g, 95%), which showed the identical ^1H NMR spectrum to that reported.[15a,27]

To a solution of the above silyl ether (6.25 g, 18.2 mmol) in CH_2Cl_2 (35 mL) was added DIBAL-H (19.5 mL, 1.03 M in THF, 20.1 mmol) at −78 °C. After 1 h at −78 °C, H_2O (3.30 mL, 183 mmol) and NaF (7.60 g, 181 mmol) were added carefully. The resulting mixture was stirred at room temperature for 30 min and filtered through a pad of Celite. The product was purified by chromatography to afford aldehyde (*R*)-**17** (5.38 g, 94%), which showed the identical ^1H NMR spectrum to that reported.[15a]

*4.3.7. (R,Z)-5-(2,4-Bis(benzyloxy)phenyl)-2-(tert-butyldiphenylsilyloxy)-3-pentene (**34**).* To an ice-cold solution of phosphonium salt **32** (3.22 g, 4.88 mmol) in THF (6 mL) was added $NaN(TMS)_2$ (4.80 mL, 1.0 M in THF, 4.80 mmol). The mixture was stirred at 0 °C for 0.5 h and cooled to −78 °C. A solution of aldehyde (*R*)-**17** (1.00 g, 3.20 mmol) in THF (10 mL) was added to the mixture. The mixture was allowed to warm to ambient temperature slowly, stirred overnight, and diluted with saturated NH_4Cl. The mixture was extracted with EtOAc and the product was purified by chromatography to afford olefin **34** (1.77 g, 90%): $[\alpha]_D^{23}$ −8.8 (*c* 0.92, $CHCl_3$); IR (neat) 1611, 1588, 1505, 1111, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.13 (d, J=6.5 Hz, 3H), 2.89 (dd, J=16, 7 Hz, 1H), 3.10 (dd, J=16, 8 Hz, 1H), 4.63–4.74 (m, 1H), 4.95 (s, 2H), 4.98 (s, 2H), 5.38 (dt, J=11, 7 Hz, 1H), 5.59 (dd, J=11, 8 Hz, 1H), 6.39 (dd, J=8, 2.5 Hz, 1H), 6.52 (d, J=2.5 Hz, 1H), 6.75 (d, J=8 Hz, 1H), 7.25–7.44 (m, 16H), 7.62–7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (+), 24.7 (−), 27.0 (−), 27.3 (+), 66.0 (−), 69.9 (+), 70.2 (+), 100.5 (−), 105.3 (−), 122.0 (+), 126.6 (−), 127.2 (−), 127.5 (−), 127.56 (−), 127.60 (−), 127.9 (−), 128.0 (−), 128.6 (−), 128.7 (−), 129.45 (−), 129.53 (−), 129.6 (−), 134.4 (+), 134.7 (+), 135.2 (−), 135.9 (−), 136.0 (−), 137.1 (+), 157.0 (+), 158.3 (+); HRMS (FAB) calcd for $C_{41}H_{44}O_3SiNa$ [$(M+Na)^+$] 635.2957, found 635.2953.

*4.3.8. (R,Z)-5-(2,4-Bis(benzyloxy)phenyl)-3-penten-2-ol (**35**).* To a solution of **34** (1.77 g, 2.89 mmol) in THF (15 mL) was added Bu_4NF (4.40 mL, 1.0 M in THF, 4.40 mmol). The solution was stirred at room temperature for 25 h and diluted with H_2O. The resulting mixture was extracted with EtOAc and the product was purified by chromatography to afford alcohol **35** (1.02 g, 94%) as white solids: $[\alpha]_D^{23}$ +21 (*c* 0.56, $CHCl_3$); IR (Nujol) 3340, 1610, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J=6 Hz, 3H), 1.47 (br s, 1H), 3.38 (dd, J=15.5, 7 Hz, 1H), 3.46 (dd, J=15.5, 7 Hz, 1H), 4.72 (dq, J=6, 6 Hz, 1H), 5.00 (s, 2H), 5.02 (s, 2H), 5.42–5.61 (m, 2H), 6.52 (dd, J=8.5, 2 Hz, 1H), 6.59 (d, J=2 Hz, 1H), 7.04 (d, J=8.5 Hz, 1H), 7.28–7.47 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4 (−), 28.0 (+), 63.7 (−), 70.1 (+), 70.2 (+), 100.7 (−), 105.6 (−), 121.7 (+), 127.4 (−), 127.6 (−), 128.0 (−), 128.1 (−), 128.6 (−), 129.4 (−), 129.8 (−), 134.2 (−), 136.9 (+), 137.0 (+), 157.2 (+), 158.5 (+); HRMS (FAB) calcd for $C_{25}H_{26}O_3$ [M^+] 374.1882, found 374.1887.

*4.3.9. ((R,Z)-4-(2,4-Bis(benzyloxy)phenyl)-1-methyl-2-butene)picolinate ((R)-**6b**).* To an ice-cold mixture of picolinic acid (392 mg, 3.18 mmol), DMAP (155 mg, 1.27 mmol), and DCC (704 mg, 3.41 mmol) in CH_2Cl_2 (7 mL) was added a solution of alcohol **35** (940 mg, 2.51 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature overnight, diluted with Et_2O, and filtered through a pad of Celite. The product was purified by chromatography to afford the picolinate (*R*)-**6b** (1.04 g, 86%): 97% ee by ^1H NMR spectroscopy of the derived MTPA ester; $[\alpha]_D^{27}$ −61 (*c* 0.48, $CHCl_3$); IR (Nujol) 1714, 1505, 1135, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.42 (d, J=6.5 Hz, 3H), 3.48 (dd, J=15, 7.5 Hz, 1H), 3.62 (dd, J=15, 7.5 Hz, 1H), 5.00 (s, 2H), 5.04 (s, 2H), 5.64 (dd, J=10.5, 8.5 Hz, 1H), 5.73 (dt, J=10.5, 7.5 Hz, 1H), 6.11 (dq, J=8.5, 6.5 Hz, 1H), 6.50 (dd, J=8.5, 3 Hz, 1H), 6.58 (d, J=3 Hz, 1H), 7.09 (d, J=8.5 Hz, 1H), 7.27–7.43 (m, 10H), 7.45 (dd, J=7.5, 4.5 Hz, 1H), 7.81 (dd, J=7.5, 7.5 Hz, 1H), 8.11 (dm, J=7.5 Hz, 1H), 8.77 (dm, J=4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9 (−), 28.1 (+), 68.9 (−), 70.0 (+), 70.2 (+), 100.6 (−), 105.5 (−), 121.5 (+), 125.1 (−), 126.7 (−), 127.2 (−), 127.6 (−), 127.8 (−), 128.0 (−), 128.59 (−), 128.62 (−), 129.1 (−), 130.1 (−), 132.0 (−), 136.9 (−), 137.1 (+), 148.6 (+), 149.9 (−), 157.2 (+), 158.5 (+), 164.5 (+); HRMS (FAB) calcd for $C_{31}H_{30}NO_4$ [$(M+H)^+$] 480.2175, found 480.2188.

*4.3.10. (S,E)-1,3-Bis(benzyloxy)-4-(2-(2,4-dimethoxyphenyl)pent-3-enyl)benzene ((S)-**8b**).* To an ice-cold suspension of $CuBr\cdot Me_2S$ (21.7 mg, 0.106 mmol) in THF (1.5 mL) was added 2,4-$(MeO)_2C_6H_3MgBr$ (0.20 mL, 1.00 M in THF, 0.200 mmol) dropwise. After 30 min of stirring, the resulting mixture was cooled to −60 °C. A solution of picolinate (*R*)-**6b** (49.9 mg, 0.104 mmol, 96.7% ee) in THF (1 mL) was added dropwise to the reaction mixture. The reaction mixture was allowed to warm to −50 °C over 1 h and diluted with saturated NH_4Cl. The mixture was extracted with EtOAc and the product was passed through a short column of silica gel to afford olefin (*S*)-**8b**, which was used for the next step: $[\alpha]_D^{23}$ −4.2 (*c* 0.87, $CHCl_3$); IR (neat) 1610, 1586, 1507, 1288, 1157 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 1.58 (dm, J=6.5 Hz, 3H), 2.87 (dd, J=13.5, 7 Hz, 1H), 3.00 (dd, J=13.5, 8 Hz, 1H), 3.59 (s, 3H), 3.77 (s, 3H), 3.92–4.05 (m, 1H), 4.98 (s, 2H), 5.02 (s, 2H), 5.29 (ddm, J=15, 6.5 Hz, 1H), 5.68 (ddm, J=15, 8 Hz, 1H), 6.34–6.47 (m, 3H), 6.54 (d, J=2.5 Hz, 1H), 6.85 (d, J=8.5 Hz, 1H), 7.06 (d, J=8.5 Hz, 1H), 7.26–7.52 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (−), 35.7 (+), 41.5 (−), 55.3 (−) 55.4 (−), 69.8 (+), 70.1 (+), 98.7 (−), 100.2 (−), 104.1 (−), 104.9 (−), 122.4 (+), 124.4 (−), 126.1 (+), 127.1 (−), 127.7 (−), 128.0 (−), 128.50 (−), 128.53 (−), 128.60 (−), 131.3 (−), 134.4 (+), 137.2 (+), 137.6 (+) 157.6 (+), 157.9 (+), 158.0 (+), 158.8 (+); HRMS (FAB) calcd for $C_{33}H_{34}O_4Na$ [(M+Na)$^+$] 517.2355, found 517.2363.

4.3.11. (4R)-5-(2,4-Bis(benzyloxy)phenyl)-4-(2,4-dimethoxyphenyl)pentane-2,3-diol. To an ice-cold solution of the above olefin and NMO (17.8 mg, 0.152 mmol) in acetone and H_2O (4:1, 1 mL) was added OsO_4 (0.50 mL, 0.02 M in *t*-BuOH, 0.010 mmol). The mixture was stirred at room temperature overnight and diluted with H_2O. The resulting mixture was extracted with EtOAc and the product was chromatographed to afford a diastereomeric mixture of the corresponding diol (45.0 mg, 85% over two steps) as brown amorphous solids.

*4.3.12. (R)-3-(2,4-Bis(benzyloxy)phenyl)-2-(2,4-dimethoxyphenyl)-propan-1-ol (**36**).* To an ice-cold solution of the above diol (45.0 mg, 0.085 mmol) in MeOH and H_2O (4:1, 1 mL) was added $NaIO_4$ (31.0 mg, 0.142 mmol). After 2 h at room temperature, $NaBH_4$ (22.7 mg, 0.600 mmol) was added to the mixture, which was stirred at room temperature for further 0.5 h. The mixture was diluted with saturated NH_4Cl and extracted with EtOAc twice. Chromatography of the crude product afforded alcohol **36** (36.5 mg, 86%) as brown amorphous solids: 94.0% ee by HPLC analysis (Chiralcel AD-H, hexane/*i*-PrOH=91/9, 0.5 mL/min, 25 °C; t_R (min)=91.9 (*S*), 99.0 (*R*)); $[\alpha]_D^{27}$ −12.9 (*c* 0.59, $CHCl_3$); IR (neat) 3418, 1505, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (br s, 1H), 2.85 (dd, J=13.5, 6.5 Hz, 1H), 3.03 (dd, J=13.5, 8.5 Hz, 1H), 3.45–3.56 (m, 1H), 3.66–3.84 (m, 2H), 3.68 (s, 3H), 3.78 (s, 3H), 5.00 (s, 2H), 5.03 (s, 2H), 6.39–6.46 (m, 2H), 6.47 (d, J=2 Hz, 1H), 6.58 (d, J=2 Hz, 1H), 6.93 (d, J=9 Hz, 1H), 7.07 (d, J=9 Hz, 1H), 7.28–7.50 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.0 (+), 41.3 (−), 55.4 (−), 65.1 (+), 70.2 (+), 98.7 (−), 100.5 (−), 104.1 (−), 105.5 (−), 121.9 (+), 123.4 (+), 127.4 (−), 127.6 (−), 127.97 (−), 128.03 (−), 128.6 (−), 128.8 (−), 131.3 (−), 137.0 (+), 137.1 (+), 157.5 (+), 158.3 (+), 158.4 (+), 159.3 (+); HRMS (FAB) calcd for $C_{31}H_{32}O_5$ [M$^+$] 484.2250, found 484.2272.

*4.3.13. (R)-4-(2-(2,4-Dimethoxyphenyl)-3-hydroxypropyl)benzene-1,3-diol ((R)-**9b**).* A solution of alcohol **36** (35.6 mg, 0.073 mmol) and 10% Pd/C (7.4 mg) in MeOH (1 mL) was stirred at room temperature for 3 h under hydrogen, diluted with EtOAc, and filtered through a pad of Celite. The product was purified by chromatography on silica gel with hexane/EtOAc (2:1) to afford phenol (*R*)-**9b** (20.6 mg, 92%) as white solids: mp 140–141 °C (hexane/EtOAc); $[\alpha]_D^{27}$ −43.9 (*c* 1.21, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 2.66 (dd, J=14, 7 Hz, 1H), 2.93 (dd, J=14, 7 Hz, 1H), 3.43 (tt, J=7, 7 Hz, 1H), 3.60–3.75 (m, 2H), 3.73 (s, 3H), 3.74 (s, 3H), 6.09 (dd, J=8, 2 Hz, 1H), 6.23 (d, J=2 Hz, 1H), 6.41 (dd, J=8, 2 Hz, 1H), 6.45 (d, J=2 Hz, 1H), 6.62 (dd, J=8 Hz, 1H), 7.04 (d, J=8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.7 (+), 43.2 (−), 56.5 (−), 56.7 (−), 66.5 (+), 100.2 (−), 104.1 (−), 106.1 (−), 108.1 (−), 120.2 (+), 125.5 (+), 130.7 (−), 133.2 (−), 157.9 (+), 158.1 (+), 160.7 (+), 161.4 (+); HRMS (FAB) calcd for $C_{17}H_{20}O_5K$ [(M+Na)$^+$] 343.0948, found 343.0948.

*4.3.14. (R)-Sativan ((R)-**4**).* To an ice-cold solution of (*R*)-**9b** (20.6 mg, 0.068 mmol) and PPh_3 (183 mg, 0.698 mmol) in THF (1.4 mL) was added DEAD (0.123 ml, 40% in toluene, 0.270 mmol). After 2 h of stirring at room temperature, the resulting mixture was concentrated to afford a residual solid, which was diluted with MeOH (0.7 mL) and 3 N LiOH (0.7 mL, 2.1 mmol). The mixture was heated to 80 °C for 2 h and diluted with H_2O. The mixture was extracted with EtOAc and the product was purified by chromatography to afford sativan (*R*)-**4** (15.0 mg, 77%) as yellow solids: 93.8% ee by HPLC analysis (Chiralcel OD-H, hexane/*i*-PrOH=94/6, 0.5 mL/min, 25 °C; t_R (min)=41.4 (*S*), 55.3 (*R*)); $[\alpha]_D^{24}$ −8 (*c* 0.28, MeOH); mp 129–130 °C (hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (dd, J=15.5, 5.5 Hz, 1H), 2.96 (dd, J=15.5, 10.5 Hz, 1H), 3.50–3.62 (m, 1H), 3.80 (s, 6H), 3.99 (dd, J=10, 10 Hz, 1H), 4.29 (dm, J=10 Hz, 1H), 5.16 (br s, 1H), 6.34–6.53 (m, 4H), 6.93 (d, J=8 Hz, 1H), 7.01 (d, J=8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.4 (+), 31.6 (−), 55.39 (−), 55.44 (+), 70.2 (−), 98.7 (−), 103.2 (−), 104.2 (−), 108.0 (−), 114.9 (+), 121.9 (+), 127.6 (−), 130.5 (−), 154.9 (+), 155.1 (+), 158.3 (+), 159.7 (+); HRMS (EI) calcd for $C_{17}H_{18}O_4$ [M$^+$] 286.1205, found 286.1209. The ^{1}H NMR spectrum, $[\alpha]_D$, and mp were consistent with those reported: ^{1}H NMR spectrum ($CDCl_3$),[21a,b] $[\alpha]_D^{24}$ −9.9 (*c* 0.33, MeOH);[21b] mp 128–129 °C.[21a]

4.4. Synthesis of (*R*)-vestitol

*4.4.1. 3-Bromo-2-hydroxy-6-methoxybenzoic acid (**42**)[22].* To an ice-cold solution of acid **41** (10.0 g, 54.9 mmol) in $CHCl_3$ (120 mL) was added Br_2 (2.8 mL, 54.6 mmol) in $CHCl_3$ (100 mL). The mixture was stirred at room temperature for two days and concentrated to afford a residual solid, which was recrystallized from MeOH to afford bromide **42** (7.61 g, 56%) as white solids: mp 144–145 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (s, 3H), 6.47 (d, J=9 Hz, 1H), 7.68 (d, J=9 Hz, 1H), 11.36 (br s, 1H), 12.93 (s, 1H).

4.4.2. 2-Bromo-5-methoxyphenol. A solution of bromide **42** (1.97 g, 7.97 mmol) in quinoline (80 mL) was stirred at 150 °C for 1 h and diluted with EtOAc. The resulting mixture was extracted with 3 N HCl three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford a residual oil, which was chromatographed on silica gel with hexane/EtOAc (30:1) to afford bromide 2-bromo-5-methoxyphenol (1.24 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 5.51 (s, 1H), 6.41 (dd, J=9, 3 Hz, 1H), 6.60 (d, J=3 Hz, 1H), 7.31 (d, J=9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6 (−), 100.9 (+), 101.7 (−), 108.4 (−), 132.0 (−), 153.0 (+), 160.6 (+). The ^{1}H NMR spectrum of the product was identical with that reported.[28]

*4.4.3. 1-Bromo-4-methoxy-2-(methoxymethoxy)benzene (**43**).* A solution of the above bromide (1.42 g, 6.99 mmol), MOMCl (1.58 mL, 21.0 mmol), and *i*-Pr_2EtN (3.65 mL, 21.0 mmol) in CH_2Cl_2 (14 mL) was stirred at room temperature overnight and diluted with H_2O. The resulting mixture was extracted with CH_2Cl_2 twice. The combined organic layers were washed with 1 N HCl, saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residual oil was purified by chromatography on silica gel with hexane/EtOAc (from 20:1 to 10:1) to afford the MOM ether **43** (1.65 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 3H), 3.78 (s, 3H), 5.23 (s, 2H), 6.47 (dd, J=9, 3 Hz, 1H), 6.76 (d, J=3 Hz, 1H), 7.41 (d, J=9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5 (−), 56.3 (−), 95.1 (+), 103.2 (−), 103.4 (+), 108.1 (−), 133.1 (−), 154.4 (+), 160.0 (+). The ^{1}H NMR spectrum of the product was identical with that reported.[29]

*4.4.4. (S,E)-1,3-Bis(benzyloxy)-4-(2-(4-methoxy-2-methoxymethoxyphenyl)pent-3-enyl)benzene ((S)-**8c**).* To an ice-cold suspension of $CuBr\cdot Me_2S$ (43.2 mg, 0.210 mmol) in THF (3 mL) was added 2-MOMO-4-$MeOC_6H_3MgBr$ (0.35 mL, 1.18 M in THF, 0.413 mmol) dropwise. After 30 min of stirring, the resulting mixture was cooled to −60 °C. A solution of picolinate (*R*)-**6b** (101 mg, 0.210 mmol, 96.7% ee) in THF (2 mL) was added to the reaction mixture dropwise. The mixture was allowed to warm to −50 °C over 1 h and diluted with saturated NH_4Cl with vigorous stirring. The mixture

was extracted with EtOAc and the product was purified by chromatography to afford olefin (*S*)-**8c**, which was passed through a short column of silica gel for the next step: ^{1}H NMR (300 MHz, $CDCl_3$) characteristic signals δ 1.59 (d, *J*=6 Hz, 3H), 2.87 (dd, *J*=14, 7.5 Hz, 1H), 3.04 (dd, *J*=14, 7.5 Hz, 1H), 3.32 (s, 3H), 3.76 (s, 3H), 4.01 (dt, *J*=7.5, 7.5 Hz, 1H), 5.31 (dq, *J*=15, 6 Hz, 1H), 5.67 (dd, *J*=15, 7.5, 2 Hz, 1H).

4.4.5. (4R)-5-(2,4-Bis(benzyloxy)phenyl)-4-(4-methoxy-2-(methoxymethoxy)phenyl)pentane-2,3-diol. To an ice-cold solution of the above olefin (*S*)-**8c** and NMO (35.3 mg, 0.301 mmol) in acetone and H_2O (4:1, 2 mL) was added OsO_4 (0.50 mL, 0.02 M in *t*-BuOH, 0.010 mmol). The mixture was stirred at room temperature overnight and diluted with H_2O. The resulting mixture was extracted with EtOAc and the product was purified by chromatography to afford the title diol (83.4 mg, 72% form (*R*)-**6b**) as brown amorphous solids.

*4.4.6. (R)-3-(2,4-Bis(benzyloxy)phenyl)-2-(4-methoxy-2-(methoxymethoxy)phenyl)propan-1-ol (**44**).* To an ice-cold solution of the above diol (83.4 mg, 0.149 mmol) in MeOH and H_2O (4:1, 1.8 mL) was added $NaIO_4$ (58.9 mg, 0.269 mmol). After 3.5 h at room temperature, $NaBH_4$ (37 mg, 0.98 mmol) was added to the mixture, which was stirred at room temperature further for 0.5 h. The mixture was diluted with saturated NH_4Cl and extracted with EtOAc and the product was chromatographed to afford alcohol **44** (64.0 mg, 83%) as brown amorphous solids: 90.2% ee by HPLC analysis (Chiralcel AD-H, hexane/*i*-PrOH=90/10, 0.5 mL/min, 25 °C; t_R (min)=69.5 (*S*), 76.5 (*R*)); $[\alpha]_D^{23}$ −26.6 (*c* 0.26, $CHCl_3$); IR (neat) 3421, 1610, 1507, 1156 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (br s, 1H), 2.84 (dd, *J*=13.5, 6 Hz, 1H), 3.06 (dd, *J*=13.5, 8 Hz, 1H), 3.36 (s, 3H), 3.49–3.58 (m, 1H), 3.68–3.76 (m, 1H), 3.77 (s, 3H), 4.98–5.07 (m, 6H), 6.45 (dd, *J*=8.5, 3 Hz, 1H), 6.45 (dd, *J*=8.5, 3 Hz, 1H), 6.50 (dd, *J*=8.5, 3 Hz, 1H), 6.58 (d, *J*=3 Hz, 1H), 6.66 (d, *J*=3 Hz, 1H), 6.90 (d, *J*=8.5 Hz, 1H), 7.09 (d, *J*=8.5 Hz, 1H), 7.29–7.49 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.2 (+), 41.3 (−), 55.4 (−), 56.0 (−), 65.3 (+), 70.2 (+), 94.6 (+), 100.5 (−), 101.5 (−), 105.5 (−), 106.3 (−), 121.7 (+), 123.8 (+), 127.4 (−), 127.6 (−), 128.1 (−), 128.67 (−), 128.69 (−), 128.8 (−), 131.3 (−), 137.0 (+), 137.1 (+), 156.1 (+), 157.5 (+), 158.4 (+), 159.1 (+); HRMS (FAB) calcd for $C_{32}H_{34}O_6$ [M^+] 514.2355, found 514.2369.

*4.4.7. (R)-4-(3-Hydroxy-2-(4-methoxy-2-(methoxymethoxy)phenyl)propyl)benzene-1,3-diol (**45**).* A mixture of alcohol **44** (56.3 mg, 0.109 mmol) and 10% Pd/C (11.3 mg) in MeOH (1 mL) was stirred at room temperature for 3 h under hydrogen, diluted with EtOAc, and filtered through a pad of Celite. The product was purified by chromatography to afford phenol **45** (37.5 mg) as white solids: ^{1}H NMR (300 MHz, CD_3OD) δ 2.64 (dd, *J*=13.5, 8 Hz, 1H), 2.97 (dd, *J*=13.5, 7 Hz, 1H), 3.41 (s, 3H), 3.46–3.56 (m, 1H), 3.67–3.72 (m, 1H), 3.73 (s, 3H), 5.01 (d, *J*=7 Hz, 1H), 5.09 (d, *J*=7 Hz, 1H), 6.07 (dd, *J*=8.5, 2.5 Hz, 1H), 6.22 (d, *J*=2.5 Hz, 1H), 6.51 (dd, *J*=8.5, 2.5 Hz, 1H), 6.60 (d, *J*=8.5 Hz, 1H), 6.62 (dd, *J*=2.5 Hz, 1H), 7.11 (dd, *J*=8.5 Hz, 1H).

*4.4.8. (R)-3-(4-Methoxy-2-(methoxymethoxy)phenyl)chroman-7-ol (**46**).* To an ice-cold solution of the above phenol **45** and PPh_3 (109 mg, 0.416 mmol) in THF (2.2 mL) was added DEAD (0.20 mL, 40 % in toluene, 0.439 mmol). After 2 h of stirring at room temperature, the mixture was concentrated. The mixture was dissolved in MeOH (0.5 mL) and 3 N LiOH (0.5 mL, 1.5 mmol) and heated to 80 °C for 2 h. The product was purified by chromatography to afford phenol **46** (30.2 mg, 87% from **44**) as yellow solids: $[\alpha]_D^{23}$ −4.7 (*c* 0.29, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (dd, *J*=16, 5 Hz, 1H), 2.98 (dd, *J*=16, 10.5 Hz, 1H), 3.48 (s, 3H), 3.53–3.66 (m, 1H), 3.79 (s, 3H), 4.00 (t, *J*=10 Hz, 1H), 4.31 (dm, *J*=10 Hz, 1H), 5.20 (s, 2H), 6.34–6.43 (m, 2H), 6.54 (d, *J*=8.5, 2 Hz, 1H), 6.74 (d, *J*=2 Hz, 1H), 6.94 (d, *J*=8.5 Hz, 1H), 7.04 (d, *J*=8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6 (+), 31.7 (−), 55.5 (−), 56.2 (−), 70.3 (+), 94.5 (+), 101.5 (−), 103.3 (−), 106.4 (−), 108.0 (−), 114.8 (+), 122.3 (+), 127.7 (−), 130.5 (−), 155.0 (+), 155.2 (+), 156.0 (+), 159.6 (+); HRMS (FAB) calcd for $C_{18}H_{20}O_5$ [M^+] 316.1311, found 316.1308.

*4.4.9. (R)-Vestitol ((R)-**5**).* A solution of phenol **46** (14 mg, 0.044 mmol) and 3 N HCl (two drops) in MeOH (1 mL) was stirred at 80 °C for 1 h and diluted with H_2O. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to afford a residual oil, which was subjected to chromatography on silica gel with hexane/EtOAc (10:1) to afford (*R*)-**5** (9.6 mg, 80%) as yellow solids: 89.9% ee by HPLC analysis (Chiralcel OD-H, hexane/*i*-PrOH=92/8, 0.7 mL/min, 25 °C; t_R (min)=39.0 (*S*), 69.3 (*R*)); $[\alpha]_D^{23}$ −16.5 (*c* 0.22, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (dd, *J*=15.5, 5 Hz, 1H), 2.99 (dd, *J*=15.5, 10 Hz, 1H), 3.44–3.55 (m, 1H), 3.77 (s, 6H), 4.04 (dd, *J*=10, 10 Hz, 1H), 4.33 (dm, *J*=10 Hz, 1H), 4.67 (br s, 1H), 4.95 (br s, 1H), 6.33–6.42 (m, 3H), 6.48 (dd, *J*=8.5, 2.5 Hz, 1H), 6.94 (d, *J*=8.5 Hz, 1H), 7.01 (d, *J*=8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.4, 31.8, 55.4, 70.0, 102.2, 103.3, 106.1, 108.0, 114.8, 119.9, 128.3, 130.5, 154.3, 154.9, 155.2, 159.4; HRMS (EI) calcd for $C_{16}H_{16}O_4$ [M^+] 272.1049, found 272.1046. The ^{1}H and ^{13}C NMR spectra and $[\alpha]_D$ were consistent with those reported: ^{1}H and ^{13}C NMR spectra ($CDCl_3$),[23c] $[\alpha]_D^{22}$ −18.9 (*c* 0.50, MeOH).[23b]

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