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Graphical Abstract

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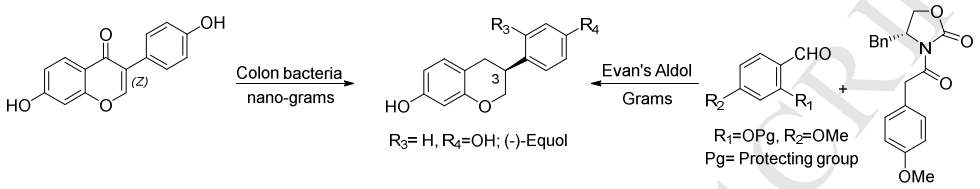

A Chiral Pool Approach for Asymmetric Syntheses of Both Antipodes of Equol and Sativan

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Abstract

For the first time, both antipodes of the isoflavans, equol and sativan were synthesized in >98 % *ee* with good overall yields starting from readily available starting materials. The chiral isoflavan, (–)-equol is produced from soy isoflavones, formonentin and daidzein by the action of intestinal bacteria in certain groups of population and other chiral isoflavans are reported from various phytochemical sources. To produce these chiral isoflavans in gram quantities, Evans' enantioselective aldol condensation was used as a chiral-inducing step to introduce the required chirality at the C-3 position. Addition of chiral boron-enolate to substituted benzaldehyde resulted in functionalized *syn*-aldol products with >90% yield and excellent diastereoselectivity. Functional group transformations followed by intramolecular Mitsunobu reaction and deprotection steps resulted the target compounds, *S*-(-)-equol and *S*-(+)-sativan, with high degree of enantiopurity. By simply switching the chiral auxiliary to (*S*)-4-benzyloxazolidin-2-one and following the same synthetic sequence the antipodes, *R*-(+)-equol and *R*-(-)-sativan were achieved. Both enantiomers are of interest from a clinical and pharmacological perspective and

are currently being developed as nutraceutical and pharmacological agents. This flexible synthetic process lends itself quite readily to the enantioselective syntheses of other biologically active C-3 chiral isoflavans.

Introduction

Isoflavanes are a subclass of isoflavonoids,[1] characterized by a chirality at the C-3 position of the pyran ring and are thought to be derived from the corresponding isoflavonids *via* reductive processes (Figure 1). In general, isoflavans of plant origin always have an oxygen at C2' and they almost never have oxygenation at C5.[2] There are a number of isoflavans with some reported to possess unique, promising biological activities. Examples include: sativan and vestitol isolated from the leaves of *Medicago sativa*[3,4] and in *Lotus corniculatus*;[5] colutelol, isolated from the roots of *Colutea arborescens*;[6] lespedezol G_1, isolated from the stems of *Lespedeza homoloba*;[7] and lespecyrtin D_1 isolated from the root extracts of *Lespedza cyrtobotrya*.[8]

Equol, the first isoflavan discovered, is widely considered as a dietary phytoestrogen. It was first isolated unexpectedly from equine urine, in an attempt to isolate estrogen[9,10] and later from the urine of other animals[11] and humans.[12] Its absolute configuration as a *S*-isomer[13] was assigned after the identification of naturally occurring isoflavans *S*-(+)-vestitol, *S*-(–)-duartin, *S*-(–)-mucronulatol from *Dalbergia variabilis* and several *Macherium* species.[13] The *S*-equol is reported to bind with several receptors[14,15] including estrogen receptors (ER)[16] with 13 times more selectivity to ER subtype β compared to subtype α.[16–18] In addition to estrogenic activity, several biological activities such as anti-fungal,[19] anti-cancer,[20] anti-osteoporotic, anti-androgen,[14] anti-inflammatory, anti-oxidant and anti-aging properties[21] are reported and claimed to promote brain mitochondrial function[22] and to inhibit prostate growth.[14]

The composition of colonic microbiota have been reported to influence the metabolic fate and biological effects of dietary intake of soy isoflavones. Indeed, the extent of at least some of the

potential health benefits of soy intake are thought to depend on one's capacity to convert isoflavones to key metabolites during digestion.[23,24] The gut bacteria *Adlercreutzia equolifaciens* is reported produce *S*-equol from daidzein (**2**) and genistein (**3**).[25] Studies measuring urinary equol excretion after soy consumption indicated that equol was produced by about 25%-30% of the adult population in Western countries compared to 50%-60% of adults living in Asian countries and Western adult vegetarians.[26,27] This high variability in equol production was presumably attributed to inter-individual differences in the composition of the intestinal microflora, such as *A. equolifaciens*.[28] Moreover, it was reported that the racemic equol may not show the same activities as that of pure enantiomers, as demonstrated in the pharmacokinetic studies on this compound.[26] Further studies of the biological and clinical properties of equol, including our own,[29,30] attest to the immense interest in this is an area of research. Given the desirable biological properties of isoflavans, it is important to have enantiopure, gram quantities of these isoflavans to enable further study of their biological, metabolic and pharmacokinetic properties.

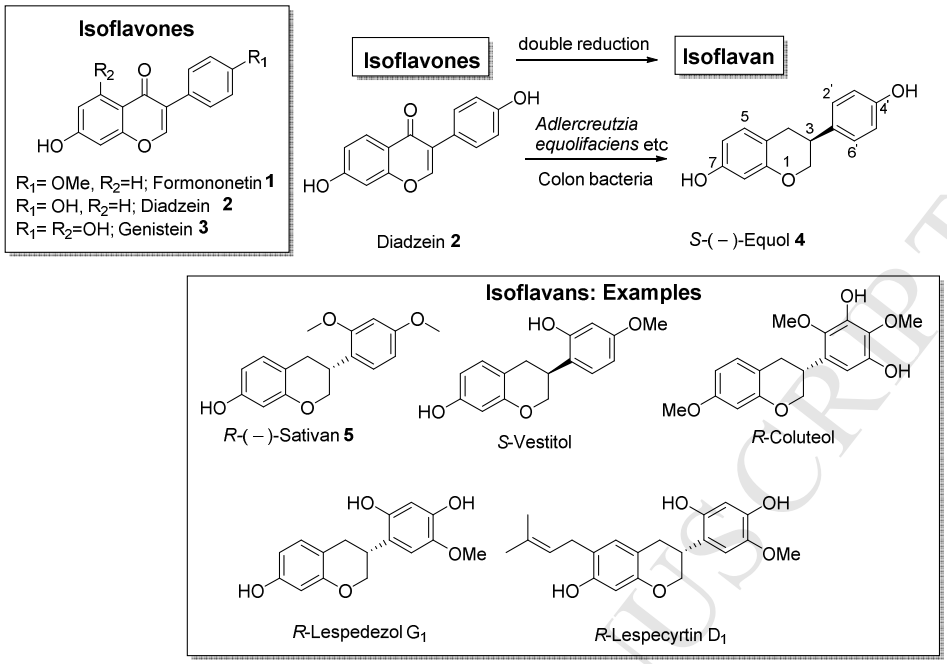


Figure 1. Soy isoflavonoids: Isoflavones (formonentin **1**, daidzein **2**, genistein **3**) and isoflavans including *S*-(–)-equol **4**.

The majority of reported syntheses were for the synthesis of a racemic form of isoflavans which are purified by chiral separation.[31-33] Examples of racemic synthesis include, catalytic hydrogenation of isoflavans using Pd catalysts at different solvent and pH conditions.[34-37] Multistep total syntheses of racemic mixtures of 5-*O*-methyllicoricidin,[38,39] halogen-substituted isoflavans and isoflavenes[40] were also reported.[41] Equol **4** was synthesized from formononetin **1** and daidzein **2** in racemic form using Pearlman's catalyst (20% $Pd(OH)_2$ on carbon),[17] by bacterial flora[42] and from resorcinol *via* an isoflavene intermediate.[43] Ferreira and co-workers have demonstrated the enantioselective synthesis of the dimethoxy analogue of *S*-equol *via* α-benzylation of *N*-acyl imidazolidinones.[44,45] In a similar approach for introduction of the required C–3 stereocenter, Heemstra *et al.* reported the enantioselective total synthesis of *S*-equol *via* Evans' alkylation followed by Buchwald intramolecular etherification.[46] However, the key transformations, such as Evans' alkylation of oxazolidinone with a regiomeric mixture of

bromobenzyl bromide and palladium-catalyzed Buchwald etherification, produced less than 50% conversion with an overall yield <10%. *S*-equol **4** and other chiral isoflavans, *R*-sativan **5** and *R*-vestitol **9**, were synthesized utilizing allylic substitution[47] as the chirality transfer step with the copper reagent derived from PhMgBr and CuBr·Me_2S. Yang *et al*, reported an enantioselective iridium-catalyzed hydrogenation[48] of α-arylcinnamic acids and applied the same methodology for the synthesis of *S*-equol **4** with an overall yield of 48%. Recently, Jingzhao Xia et al, reported the asymmetric hydrogenation of 2H□chromenes using Ir/In-BiphPHOX catalyst to produce to isoflavan derivatives, including *S*-equol in 82% yield with >95% ee.[49]

In continuation of our work on phytoestrogens for women's health, several grams of enantiomerically pure *S*-equol **4** and other chiral isoflavans were required. To address this need, we report herein a scalable enantioselective synthesis of four isoflavans: equol enantiomers, (–)-**4**, (+)-**4**, sativan isomers (+)-**5** and (–)-**5**, using Evans' aldol as common, chiral pool approach (**Figure 2**). Unlike in Evans' alkylation,[46] Evans' aldol addition is particularly powerful because it establishes two contiguous stereocenters simultaneously in high yield and with a high degree of selectivity and is reported to accommodate a wide range of substrates.

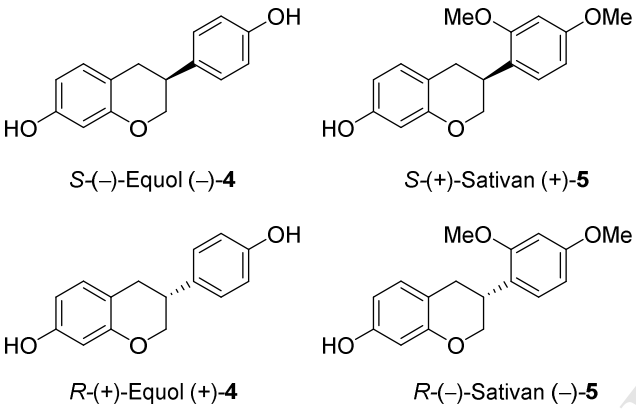
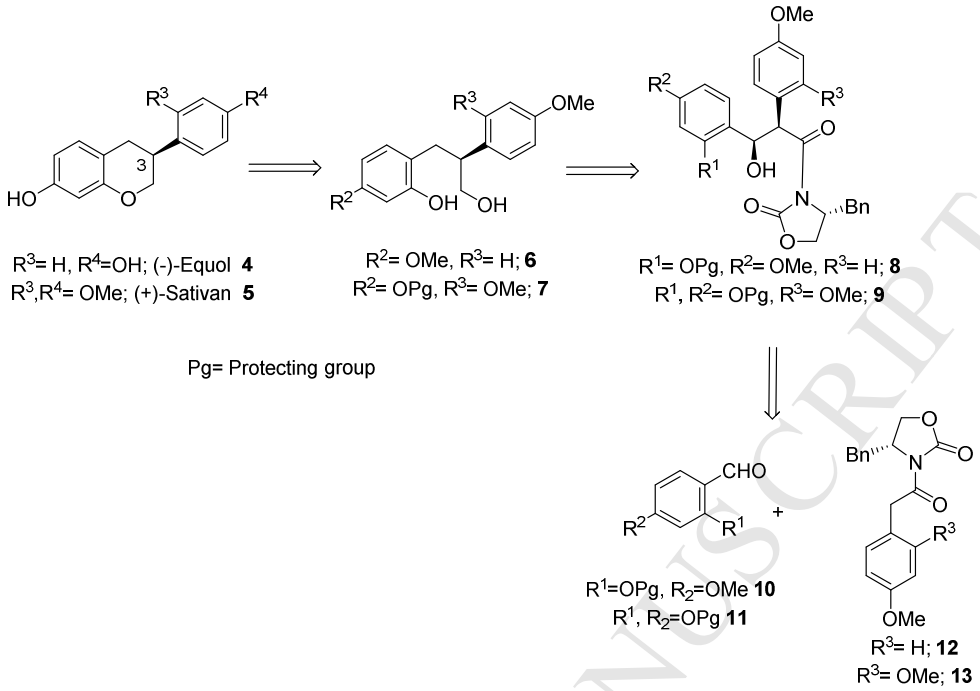


Figure 2. Structures of the synthesized chiral isoflavans.

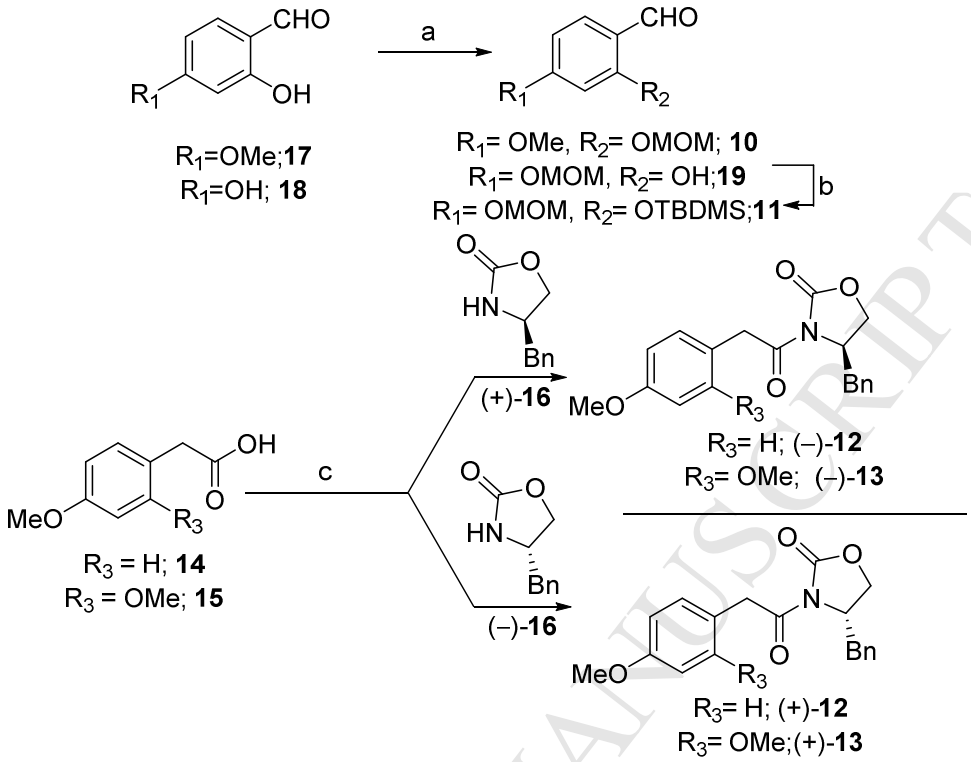
Results and Discussions

The retrosynthetic analysis of the chiral isoflavan scaffold is outlined in Scheme 1. The key intermediates, *syn*-aldol product **8** (key intermediate to produce *S*-equol) or **9** (intermediate to produce *S*-sativan), can be obtained *via* Evan's aldol reaction between aldehydes (**10** or **11**) and chiral-auxiliary substituted imides (**12** or **13**). Deoxygenation of the aldol product, followed by reduction, would furnish hydroxy phenols **6** (the intermediate to produce equols) and **7** (the intermediate to produce sativans). Cyclization under Mitsunobu conditions followed by deprotection would produce the isoflavans, equol **4** and sativan **5**.



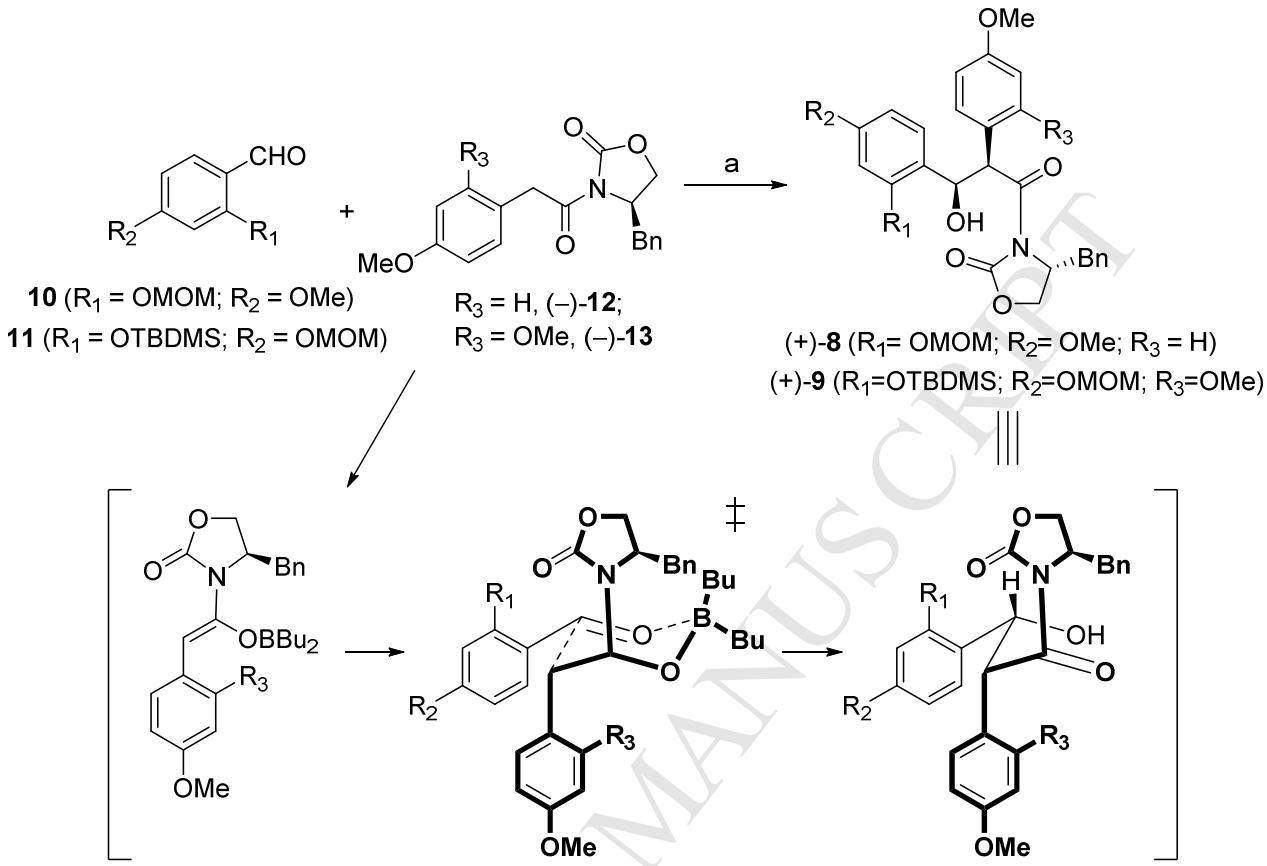
Scheme 1. Retrosynthesis of isoflavans, equol **4** and sativan **5** *via* Evans' aldol addition to introduce chirality at C-3.

The crucial starting materials required for Evans' aldol reaction are oxygenated benzaldehydes (**10** and **11**), and benzoxazolidinone-derived imides of phenyl acetic acids [(–)-, (+)-**12** and (–)-, (+)-**13**]. The oxygenated aldehydes **10** and **11** were prepared from the commercially available starting materials **17** and **18**, respectively (Scheme 2). The aldehyde **10** was produced by MOM protection of **17**, whereas, the aldehyde **11** was prepared via sequential protection of **18** initially with MOMCl at the *p*-hydroxy group to get **19** which was then subjected to further protection with TBSCl. The counterpart chiral auxiliary substituted imides (–)-, (+)-**12** and (–)-, (+)-**13**, were synthesized according to the literature procedure in two stages.[50] First, by activating the phenyl acetic acids as acid chlorides with thionyl chloride or as mixed anhydride with pivaloyl chloride; In the second stage, the resulting acid chloride/anhydride were then treated with the anions of the respective 4-benzyl oxazolidinones to produce the corresponding chiral imides.



Scheme 2. Synthesis of the starting materials for the Evans' aldol reaction. Reagents and Conditions: a) MOMCl, K_2CO_3, acetone, rt, 24 h, 94% (for **10**); MOMCl, DIPEA, DCM, rt, 20 h, 75% (for **19**); b) TBDMSCl, DIPEA/DCM, 0 °C, 1h; rt, 24 h, 97%. c) For **14**: $SOCl_2$, 2h; *n*-BuLi, –65 to –45 °C, (+)– or (–)-**16** in THF, 2 h to produce (+)- or (–)-**12**, 73%; For **15:** Pivaloyl chloride, DIPEA, THF, –78 °C; *n*-BuLi, (+)- or (–)-**16** in THF, –78 °C, 3 h, to produce (+)- or (–)-**13**, 90%.

The construction of the isoflavan scaffold began with a diastereoselective Evans' aldol addition reaction[51-53] of: benzaldehydes (**10** and **11**) with oxazolidinones (**12** and **13**, respectively), using Bu_2BOTf (Scheme 3). Typically, dialkyl boron enolates are known to produce the (*Z*)-boron enolates with little sensitivity towards the base used. However, the reactivity and stability of boron enolates resulting from **12** or **13** were found to be critical and sensitive to temperature. No aldol addition reaction was observed at temperatures below –25 °C, and decomposition of the aldol product was observed at reaction conditions above –10 °C.



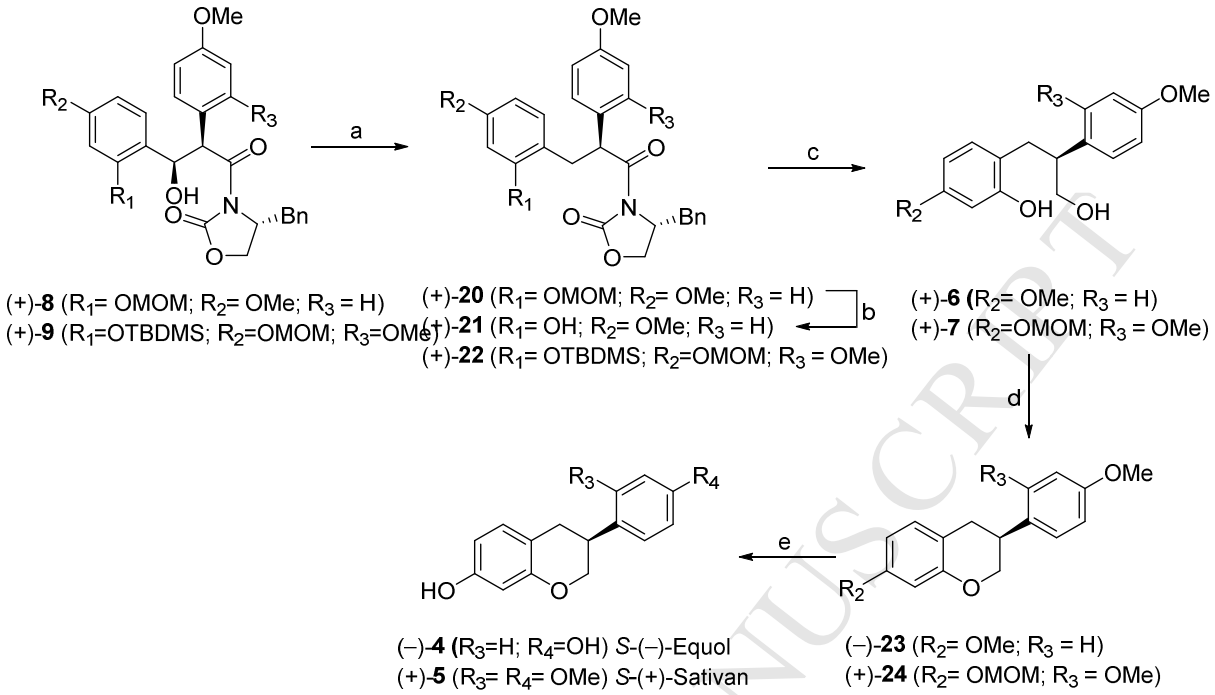
Scheme 3. Evans' aldol addition to generate *R*-*syn*-aldol products (+)-**8** and (+)-**9**. Reagents and conditions: a) add DIPEA to (–)-**12** or (–)-**13** in DCM at 0 °C; cool to –25 °C, 1 M BBu_2OTf in DCM (add dropwise); warm from –25 °C to –15 °C over 30 minutes, stir for 3 h; re-cool to –25 °C, add **10** or **11** in DCM (over 30 minutes); warm from –25 °C to –15 °C (over 20 minutes), stirr for 1.5 h, 82–90%.

The reaction of enolate from (–)-**12** with 4-methoxy-2-(methoxymethyl) benzaldehyde **10** furnished 2,3-*syn*-aldol product (+)-**8** at 90% yield with >95% diastereoselectivity, evidenced by the ^{1}H-NMR of crude product. The superior stereochemical outcome of the aldol reaction can be rationalized using a Zimmerman-Traxler six-membered chair-like transition state (Scheme 3). As anticipated, the facial selectivity of the aldehyde was directed by the chiral auxiliary of the enolate, resulting in *re*-face attack to produce Evans' *syn* aldol product. Similarly, the reaction of enolate from (–)-**13** with benzaldehyde **11** furnished 2,3-*syn*-aldol product (+)-**9** as a single

diastereomer in 90% yield after purification. Deoxygenation at the benzylic hydroxyl group of the resulting aldol product was found to be nontrivial. Several attempts to deoxygenate the aldol products (+)-**8** and (+)-**9** in the presence of Pd-C/H_2 in EtOAc, Pd-C/H_2 in MeOH, $Pd(OH)_2$-H_2 in MeOH, $HCOONH_4$, and Raney Ni/H_2 in MeOH were unsuccessful or produced complex mixtures with low quantities of the desired products. Conversion of the benzylic hydroxyl group of these compounds to their corresponding tosylates was also unsuccessful. This lack of reactivity may be due to the presence of an electron-rich aromatic system and possible chelation. However, deoxygenation of *syn*-aldol product using excess of triethylsilane in the presence of TFA, furnished the compounds in (+)-**20** and (+)-**22** in 81 and 75% yields, respectively. Next, the MOM group of (+)-**20** was selectively deprotected using HCl in MeOH to obtain (+)-**21** in 85% yield.

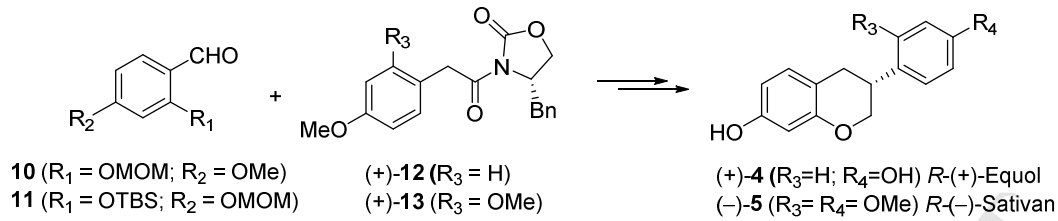
The chiral auxiliary of the deoxygenated compound (+)-**21** was removed by reduction with lithium aluminum hydride, producing the diol product (+)-**6** in 90% yield. Similarly, the chiral auxiliary of the deoxygenated compound (+)-**22** was reduced with LAH, and further, the TBS group was deprotected using TBAF in THF to produce the diol (+)-**7** in 89% yield. No loss of optical purity was observed with recovered chiral auxiliaries.

The diols (+)-**6** and (+)-**7** were then subjected to an intramolecular Mitsunobu reaction to produce cyclic products (–)-**23** and (+)-**24**, respectively in 86% yield. Alternatively, refluxing the diol with TsCl and K_2CO_3 in toluene also resulted the chromanes (–)-**23** and (+)-**24**, in good yields. The dimethoxy analogues of equol (–)-**23** and MOM-protected analogues of sativan (+)-**24** were then subjected to final deprotection to yield the desired chiral products (–)-**4** and (+)-**5** in >85% yields (Scheme 4).



Scheme 4. Enantioselective synthesis of *S*-equol (–)-**4** and *S*-sativan (+)-**5** starting from Evans' aldol products (+)-**8** and (+)-**9.** Reagents and conditions: a) TFA, Et_3SiH/DCM, 0 °C, 30 min (68–81%); b) 3N HCl in MeOH/reflux, 30 min, 85%; c) for (+)-**21**: $LiAlH_4$/THF, 0 °C to rt, 4 h, 90%; for (+)-**22**: $LiAlH_4$/THF,0 °C to rt, overnight, TBAF/THF, 89%; d) Mitsunobu reaction: DIAD, TPP/THF, rt, 6 h, 86% or TsCl, K_2CO_3, toluene, reflux, 5h, 78%; e) Deprotection: for (–)-**23**: Pyridinium.HCl/150 °C, overnight, 88%; for (+)-**24**: 3M HCl; rt, 0.5 to 0.75 h, 86%.

By implementing the same synthetic approach (Schemes 3 and 4), the stereoselective synthesis of the *R*-isomers of equol (+)-**4** and sativan (–)-**5** (Scheme 5) were achieved from their respective starting materials, (+)-**12** and (+)-**13**, *via* aldol intermediates (–)-**8** and (–)-**9**, which were subjected to the same deoxygenation, deprotection, cyclization, and deprotection steps. The overall yield starting from their respective phenyl acetic acids and benzaldehydes were: 32% for *S*-(–) and *R*-(+)-equol (+)-**4**, 28% for (+)-**5** and 23% for sativan (–)-**5**.



Scheme 5. Synthesis of (+)-equol **4** and (–)-sativan **5**.

In conclusion, chiral isoflavans were successfully synthesized starting from phenyl acetic acid precursors, with the aid of an Evans aldol reaction as a key transformation. The ready availability of both antipodes of 4-benzyl-2-oxazolidinone allowed us to develop practical synthetic sequence to access the isoflavans with high enantiopurity. Reaction of boron enolates with oxygenated aldehydes produced in *syn* aldol products with excellent diastereoselectivities. This was followed by deprotection, removal of chiral auxiliaries, cyclization and deprotection to produce the chiral isoflavans in >30% overall yields. Furthermore, this flexible synthetic approach allowed the synthesis of their antipodes by simply switching the chiral auxiliary. This synthetic sequence delineates the advantage of the aldol addition reaction over the alkylation for the efficient construction of isoflavan scaffolds with the required chirality at C3 position.

Experimental Section:

General information

All reactions were performed under an atmosphere of argon with oven-dried glassware and standard syringe/septa techniques. All reaction mixtures were magnetically stirred with Teflon stir bars, and temperatures were measured externally. Solvents were distilled under an argon atmosphere prior to use. The solvents tetrahydrofuran (THF) and Et_2O were distilled from sodium benzophenone, while CH_2Cl_2 was dried over P_2O_5. Triethylamine and was distilled from CaH_2. Ethanol and methanol used were reagent-grade solvents. All reagents obtained commercially were used without further purification. The reaction progress was monitored on

precoated silica gel thin-layer chromatography (TLC) plates. Spots were visualized under 254 nm UV light and/or by dipping the TLC plate into a staining solution (prepared by mixing 2 mL of anisaldehyde, 10 mL of glacial acetic acid, and 5 mL of H_2SO_4 in 340 mL of EtOH), followed by heating with a heat gun. Column chromatography was performed with silica gel (230−400 mesh). All the solvents were purchased as reagent grade solvents for column chromatography. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ or MeOH-d_4 on 400 MHz (100 MHz) or 500 MHz (125 MHz) machines. Chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane (δ) as the internal standard, and coupling constants are in hertz (Hz). Assignment of proton resonances were confirmed by correlated spectroscopy. IR spectra were recorded by use of a universal attenuated total reflection sampling accessory (diamond ATR) on an Agilent Cary 630 FT-IR spectrometer. High-resolution mass spectra were recorded on an Agilent electrospray ionization quadrupole time-of-flight (ESI-QTOF) instrument. Optical rotations were recorded using Autopol IV (A7040-12) polarimeter.

Synthesis of the aldehydes, 10 and 11

Synthesis of the aldehyde **10**

N,*N*-diisopropylethylamine (DIPEA) (17.0 mL, 98 mmol) was added dropwise into an ice-cold solution of 2-hydroxy-4-methoxybenzaldehyde **17** (10g, 65.8 mmol) in dichloromethane (DCM) (200 mL), and stirred. After 30 minutes, neat MOMCl (7.5 mL, 99 mmol) was added dropwise and stirred further for 20 h. The reaction mixture was quenched with water (50 mL) and layers were separated. The aqueous layer was further extracted with (2 x 50 mL) DCM and the combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to produce MOM protected aldehyde **10** (12.1 g, 61.8 mmol, 94%) as a pale yellow

crystalline solid and used as the starting material for Evans aldol reaction without further purification.

4-Methoxy-2-(methoxymethoxy)benzaldehyde **10**:

MP: 58 °C; lit 59–60 °C;[54] **IR** (cm^{-1}): 2941, 2844, 1678, 1600, 1259, 1154, 1078, 987, 925 and 815; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.32 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 6.70 (d, *J* = 2.3 Hz, 1H), 6.60 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.28 (s, 2H), 3.85 (s, 3H), 3.51 (d, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.3, 166.0, 161.5, 130.3, 119.5, 107.7, 100.6, 94.7, 56.5, 55.6; **ESI-HRMS**: calcd. for $C_{10}H_{13}O_4$ 197.0808 $[M+H]^+$; found 197.0800.

Synthesis of the *2-((tert-Butyldimethylsilyl)oxy)-4-(methoxymethoxy)benzaldehyde* **11**

The aldehyde **11** was synthesized starting from **18** in two steps by following a reported procedure.[55] The first step is the synthesis of MOM protected benzaldehyde **19** and the second step is the synthesis of **11** from **19** by TBS protection.

2-Hydroxy-4-(methoxymethoxy)benzaldehyde **19**

To a suspension of dihydroxybenzaldehyde **18** (10.0g, 72.5 mmol) and anhydrous potassium carbonate (15.0 g, 109 mmol) in acetone (150 mL) at 0 °C, MOMCl (5.5 mL, 72.4 mmol) was added dropwise, allowed to warm to room temperature and stirred for 28 h. The reaction mixture was filtered to remove potassium carbonate, concentrated and purified using column chromatography to obtain MOM-protected *o*-hydroxy benzaldehyde **19** as brick colored crystals (9.90 g, 54.4 mmol, 75%).

2-Hydroxy-4-(methoxymethoxy)benzaldehyde **19**:

MP: 55 °C (observed); lit[56] 54.9 °C. **IR** (cm^{-1}): 2961, 2848, 1628, 1503, 1290, 1225, 1156,

1078, 992, 959 and 804; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.34 (s, 1H), 9.71 (s, 1H), 7.42 (d, *J* = 8.6 Hz, 1H), 6.63 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 1H), 5.20 (s, 2H), 3.46 (s, 3H); **ESI-HRMS**: calcd. for $C_9H_{11}O_4$ 183.0652 $[M+H]^+$; found 183.0666.

2-((tert-Butyldimethylsilyl)oxy)-4-(methoxymethoxy)benzaldehyde **11**

To a solution of 2-hydroxy-4-(methoxymethoxy)benzaldehyde **19** (5.62 g, 31 mmol) and TBDMSCl (9.31 g, 61.8 mmol) dissolved in anhydrous DCM (250 mL), DIPEA (16 mL, 92 mmol) was added and stirred at room temperature for 30 h. The reaction was then quenched with water, extracted with DCM (2x40 mL) and the combined organic layer was dried over anhydrous $MgSO_4$, filtered and dried to obtain brick red colored crystals **11** (8.86 g, 30 mmol, 97%).

2-((tert-Butyldimethylsilyl)oxy)-4-(methoxymethoxy)benzaldehyde **11**:

MP: 53.6 °C **; IR** (cm^{-1}): 2961, 2848, 1628, 1577, 1501, 1290, 1223, 1154, 1078, 989, and 806; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 6.68 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 5.17 (s, 2H), 3.46 (s, 3H), 1.06 – 0.91 (s, 9H), 0.27 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.7, 163.4, 160.6, 129.9, 121.9, 109.8, 107.1, 94.1, 56.2, 25.7 (3C), 18.3, –4.4 (2C); **ESI-HRMS**: calcd. for $C_{15}H_{24}NaO_4Si$ 319.1342 $[M+Na]^+$; found: 319.1289.

Synthesis of chiral imides (+)-**12** and (–)-**12**

(+)-**12** and (–)-**12** were prepared from the corresponding 4-benzyloxazolidin-2-ones (+)-**16** and (–)-**16** by following the reported procedure.[46]

(*R*)-4-Benzyl-3-(2-(4-methoxyphenyl)acetyl)oxazolidin-2-one (–)-**12**:

Yellow needles; $[\alpha]_D^{25}$ = –73.3 (c = 1.20, $CHCl_3$); **MP**: 88 °C; **IR** (cm^{-1}): 3028, 2924, 1778, 1700, 1514, 1357, 1248, 1181, 1033, and 706; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H),

7.17–7.09 (m, 2H), 6.92–6.85 (m, 2H), 4.72–4.61 (m, 1H), 4.33–4.11 (m, 4H), 3.80 (s, 3H), 3.26 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.75 (dd, *J* = 13.4, 9.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.7, 159.0, 153.5, 135.3, 131.0 (2C), 129.6 (2C), 129.1 (2C), 127.5, 125.6, 114.2 (2C), 66.3, 55.5, 55.4, 40.8, 37.9; **ESI-HRMS**: calcd. for $C_{19}H_{20}NO_4$ 326.1387 $[M+H]^+$; found: 326.1339.

(S)-4-Benzyl-3-(2-(4-methoxyphenyl)acetyl)oxazolidin-2-one (+)**-12**:

$[\alpha]_D^{25}$ = +70.377 (c = 1.06, $CHCl_3$); **IR** (cm^{-1}): 1780, 1700, 1514, 1359, 1249, 1181, and 1033; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H), 7.16–7.11 (m, 2H), 6.92–6.84 (m, 2H), 4.70–4.61 (m, 1H), 4.31–4.11 (m, 4H), 3.80 (s, 3H), 3.25 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.75 (dd, *J* = 13.4, 9.4 Hz, 1H).; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.7, 158.9, 153.5, 135.3, 130.9 (2C), 129.5 (2C), 129.0 (2C), 127.4, 125.6, 114.2 (2C), 66.2, 55.4, 55.4, 40.8, 37.9; **ESI-HRMS**: calcd. for $C_{19}H_{20}NO_4$ 326.1387 $[M+H]^+$; found 326.1395.

(R)-4-Benzyl-3-(2-(2,4-dimethoxyphenyl)acetyl)oxazolidin-2-one (–)**-13**:

The chiral amides (–)**-13** and (+)**-13** were prepared by following the reported procedure by Liu et al[50] with slight modifications. For example, to a solution of 2-(2,4-dimethoxyphenyl)acetic acid **15** (3.9 g, 20 mmol) and DIPEA (3.77 mL, 21.6 mmol) in anhydrous THF (50 mL) at –78 °C, trimethylacetyl chloride (pivaloyl chloride) (3.17 mL, 25.7 mmol) was added dropwise under argon atmosphere. The resulting mixture was stirred for 15 min at –78 °C, 1 h at 0 °C, and then re-cooled to –78 °C to produce mixed anhydride. Meanwhile, in a separate flask to a solution of (*R*)-4-benzyl-oxazolidin-2-one [(+)**16**] (4.3 g, 24.3 mmol) in anhydrous THF at –78 °C under

atmosphere of argon, *n*-BuLi (25 mmol; 10 mL of 2.5 M in hexanes) was added dropwise and the mixture was stirred for 40 min at –78 °C. This solution was then transferred with a cannula to the preformed mixed anhydride mixture. After stirring the reaction mixture for 15 min, it was allowed to warm to room temperature over 2 h, then quenched with saturated aqueous NH_4Cl (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to obtain a viscous liquid **13** (6.40 g, 18 mmol, 91%).

(R)-4-Benzyl-3-(2-(2,4-dimethoxyphenyl)acetyl)oxazolidin-2-one (–)**-13**:

Viscous liquid $[\alpha]_D^{25}$ = –76.1 (c = 1.0, $CHCl_3$); **MP:** 78.9 °C; **IR** (cm^{-1}): 2941, 1778, 1706, 1616, 1512, 1212, 1158 and 1037; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.16 (m, 5H), 7.07 (dd, *J* = 7.9, 2.3 Hz, 1H), 6.54–6.42 (m, 2H), 4.68 (bt, 1H), 4.31–4.04 (m, 4H), 3.81 (s, 6H), 3.28 (dd, *J* = 13.2, 2.5 Hz, 1H), 2.81 (dd, *J* = 13.2, 9.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.6, 160.5, 158.6, 153.8, 135.5, 131.6, 129.6 (2C), 129.0 (2C), 127.4, 115.1, 104.3, 98.8, 66.3, 55.6, 55.5 (2C), 37.9, 36.9; **ESI-HRMS**: calcd. for $C_{20}H_{22}NO_5$ 356.1492 $[M+H]^+$; found 356.1493.

By following above procedure, the reaction between **15** and (–)-**16** produced (+)-**13**.

(S)-4-Benzyl-3-(2-(2,4-dimethoxyphenyl)acetyl)oxazolidin-2-one (+)-**13**:

$[\alpha]_D^{25}$ = +78.8 (c = 1.0, $CHCl_3$), reported +113.7 (c = 1.36, CH_2Cl_2);[57] **MP**: 78.9 °C ; **IR** (cm^{-1}): 2939, 1178, 1708, 1616, 1592, 1512, 1393, 1367, 1212 and 1037; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 7.28–7.23 (m, 1H), 7.20 (d, *J* = 7.5 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.53–

6.44 (m, 2H), 4.68 (ddtd, *J* = 9.4, 6.3, 3.2, 1.1 Hz, 1H), 4.29–4.07 (m, 4H), 3.80 (m, 6H), 3.29 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.80 (dd, *J* = 13.2, 9.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.7, 160.6, 158.7, 153.8, 149.2, 135.6, 131.6, 129.6 (2C), 129.1 (2C), 127.4, 115.3, 104.5, 99.0, 66.4, 55.6, 55.5, 38.0, 36.9; **ESI-HRMS**: calcd. for $C_{20}H_{22}NO$ 356.1492 $[M+H]^+$; found 356.1483.

General procedure for Evans' aldol reaction

In a 0.5 L round bottom flask, to a pre-cooled solution of chiral 4-benzyl-(acetyl)oxazolidin-2-one (1 equiv.) in anhydrous DCM (200 mL) at 0 °C, DIPEA (1 equiv.) was added drop wise and cooled to –25 °C. To this resulting mixture, a solution of dibutyl(((trifluoromethyl)-sulfonyl)oxy)borane in DCM (1.0 M, 1.1 equiv.) was added drop wise to produce orange colored solution which was warmed, over 30 min, to –15 °C and then stirred for 3h at –15 °C. The solution was re-cooled to –25 °C and a solution of benzaldehyde (1 equiv.) in DCM (50 mL) was added drop wise and stirred at –25 °C for 20 minutes. The temperature of the mixture was raised to –15 °C over a period of 30 min and stirred further for additional 1 h. The mixture was quenched with methanol (25 mL) and phosphate buffer (15 mL, pH 7.4). To this, a solution of hydrogen peroxide (15 mL, 30%) in MeOH (35 mL) was added dropwise, warmed to room temperature and stirred for additional 1h. The whole mixture was concentrated under reduced pressure and the residue was diluted with water (150 mL) and extracted with diethyl ether (3 x 150 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, concentrated. The resulting residue was purified using column chromatography by eluting with

10–25% ethyl acetate in hexanes to isolate the aldol product.

Reaction between oxazolidine-2-one (–)-**12** and aldehyde **10** produced (+)-**8** as a viscous liquid in 90% yield.

(R)-4-Benzyl-3-((2*R*,3*R)*-3-hydroxy-3-(4-methoxy-2-(methoxymethoxy)phenyl)-2-(4-methoxyphenyl)propanoyl)oxazolidin-2-one (+)-**8**:

$[\alpha]_D^{25}$ = +97 (c = 0.12, $CHCl_3$); **IR** (cm^{-1}): 3529, 2956, 2935, 1777, 1611, 1510, 1156, 1000, 998, 732 and 704; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 7.22–7.18 (m, 3H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.99–6.95 (m, 2H), 6.88–6.84 (m, 2H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.42 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.54 (s, 2H), 5.25–5.19 (dd, *J* = 16.0Hz, 2H), 4.60 (ddt, *J* = 9.1, 7.1, 3.5 Hz, 1H), 4.06–3.97 (m, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.54 (s, 3H), 3.09 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.55 (dd, *J* = 13.5, 9.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.7, 160.1, 159.1, 155.2, 152.5, 134.8, 131.1 (2C), 129.4 (2C), 129.1, 128.8 (2C), 127.2, 126.3, 121.8, 113.7 (2C), 106.0, 101.1, 94.7, 70.8, 65.7, 56.3, 55.3, 55.2, 54.7, 53.1, 37.2; **ESI-HRMS**: calcd. for $C_{29}H_{30}NO_7$ $[M+H-H_20]^+$ 504.2017; found 504.2030.

Reaction between oxazolidine-2-one (+)-**12** and aldehyde **10** produced (–)-**8**.

(S)-4-Benzyl-3-((2*S*,3*S)*-3-hydroxy-3-(4-methoxy-2-(methoxymethoxy)phenyl)-2-(4-methoxyphenyl)propanoyl)oxazolidin-2-one (–)-**8**:

Yield 89%; $[\alpha]_D^{25}$ = –111.3 (c = 0.39, $CHCl_3$); **IR** (cm^{-1}): 3528, 2957, 2838, 1777, 1611, 1510, 1156, and 1000; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 7.23–7.17 (m, 3H), 7.03 (d, *J* = 8.5 Hz, 1H), 7.00–6.94 (m, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.42 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.54 (s, 2H), 5.30–5.21 (m, 2H), 4.60 (ddt, *J* = 8.9, 7.2, 3.6 Hz,

1H), 4.06–3.97 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.54 (s, 3H), 3.08 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.56 (dd, *J* = 13.5, 9.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.7, 160.1, 159.1, 155.2, 152.5, 134.8, 131.1 (2C), 129.4 (2C), 129.1, 128.8 (2C), 127.2, 126.3, 121.9, 113.7 (2C), 106.0, 101.1, 94.7, 70.8, 65.7, 56.3, 55.3, 55.2, 54.7, 53.1, 37.2; **ESI-HRMS**: calcd. for $C_{29}H_{30}NO_7$ 504.2017 $[M+H-H_20]^+$; found 504.1997.

Similarly, the reaction between oxazolidine-2-one (–)**-13** and aldehyde **11** produced (+)-**9** as amorphous solid in 82% yield**.**

(*R*)-4-Benzyl-3-((2*R*,3*R*)-3-(2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)phenyl)-2-(2,4-dimethoxyphenyl)-3-hydroxypropanoyl)oxazolidin-2-one (+)**-9**:

MP: 72.9 °C; $[\alpha]_D^{25}$ = +203.5 (c = 1.0, $CHCl_3$); **IR** (cm^{-1}): 3542, 2931, 2857, 1791, 1674, 1613, 1588, 1508, 1389, 1212, and 1160; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 3H), 7.20–7.10 (m, 2H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.56–6.51 (m, 1H), 6.48–6.41 (m, 2H), 6.35–6.30 (m, 1H), 5.63 (d, *J* = 3.6 Hz, 1H), 5.47 (d, *J* = 4.1 Hz, 1H), 5.09 (s, 2H), 4.72–4.62 (m, 1H), 4.01 (d, *J* = 5.5 Hz, 2H), 3.79 (s, 3H), 3.71 (s, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 3.35 (dd, *J* = 13.3, 3.5 Hz, 1H), 2.53 (dd, *J* = 13.3, 10.0 Hz, 1H), 1.00 (s, 9H), 0.34 (s, 3H), 0.32 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.1, 160.3, 159.3, 157.1, 153.2, 152.0, 135.5, 131.1, 129.5 (2C), 129.1 (2C), 128.4, 127.4, 125.4, 114.5, 108.1, 106.2, 103.8, 98.6, 94.7, 69.0, 66.0, 55.9, 55.4, 55.2 (2C), 48.2, 37.8, 25.9 (3C), 18.4, –3.9, –4.1; **ESI-HRMS**: calcd. for $C_{35}H_{44}NO_8Si$ 634.2831$[M+H-H_2O]^+$; found 634.2827.

The reaction between oxazolidine-2-one (+)**-13** and aldehyde **11** produced (–)**-9** in 85% yield.

(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-(2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)phenyl)-2-(2,4-dimethoxyphenyl)-3-hydroxypropanoyl)oxazolidin-2-one (–)-**9**:

Colorless amorphous solid; $[\alpha]_D^{25}$ = –201.4 (c = 1.0, $CHCl_3$); **MP**:74.6 °C; **IR** (cm^{-1}): 3540, 2931, 1790, 1672, 1611, 1508, 1366, 1292, 1212 and 1158; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.19 (m, 3H), 7.20–7.11 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.53 (d, *J* = 2.2 Hz, 1H), 6.48–6.39 (m, 2H), 6.32 (d, *J* = 2.2 Hz, 1H), 5.63 (bt, 1H), 5.47 (d, *J* = 3.6 Hz, 1H), 5.09 (s, 2H), 4.72–4.61 (m, 1H), 4.01 (d, *J* = 5.4 Hz, 2H), 3.78 (s, 3H), 3.71 (d, *J* = 3.0 Hz, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 3.34 (dd, *J* = 13.2, 2.8 Hz, 1H), 2.53 (dd, *J* = 13.2, 10.2 Hz, 1H), 1.00 (s, 9H), 0.34 (s, 3H), 0.32 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.1, 160.3, 159.3, 157.1, 153.2, 152.0, 135.5, 131.1, 129.5 (2C), 129.0 (2C), 128.3, 127.4, 125.4, 114.5, 108.1, 106.2, 103.8, 98.6, 94.7, 69.0, 66.0, 55.9, 55.4, 55.2 (2C), 48.2, 37.8, 25.9 (3C), 18.4, –3.9, –4.1; **ESI-HRMS**: calcd. for $C_{35}H_{44}NO_8Si$ 634.2831 $[M+H-H_20]^+$; found 634.2817.

Deoxygenation of the aldol products

To a solution of the aldol adduct (*R*)-4-benzyl-3-((*2R,3R*)-3-hydroxy-3-(4-methoxy-2-(methoxymethoxy)phenyl)-2-(4-methoxyphenyl)propanoyl)oxazolidin-2-one (+)-**8** (1.04 g, 2 mmol) in dichloromethane (10 mL) cooled at 0 °C, triethyl silane (10 mL, 62.6 mmol) was added dropwise and stirred for 10 min. To this mixture, trifluoroacetic acid (1 mL, 13 mmol) was added drop-wise in two installments, allowed to warm to room temperature, and the reaction was monitored using TLC. After 30 min, the reaction was cooled to 0 °C and quenched using $NaHCO_3$ (10 mL) and extracted with dichloromethane (2 x 15mL). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated and purified using column chromatography to

obtain a colorless viscous liquid (+)**-20** (0.81 g, 1.60 mmol, 81%).

(R)-4-Benzyl-3-((*S*)-3-(4-methoxy-2-(methoxymethoxy)phenyl)-2-(4-methoxyphenyl)propanoyl)oxazolidin-2-one (+)**-20**:

$[\alpha]_D^{25}$ = +24.0 (c = 0.15, $CHCl_3$); **IR** (cm^{-1}): 2933, 2836, 1778, 1695, 1613, 1510, 1218, 1156, and 1007; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.22–7.15 (m, 3H), 7.02–6.92 (m, 3H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 2.5 Hz, 1H), 6.39 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.41 (dd, *J* = 8.8, 6.2 Hz, 1H), 5.18 (s, 2H), 4.63 (tt, *J* = 7.6, 3.5 Hz, 1H), 4.07–3.95 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.52 (s, 3H), 3.35 (dd, *J* = 13.6, 8.8 Hz, 1H), 3.13–2.98 (m, 2H), 2.56 (dd, *J* = 13.6, 8.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 159.4, 158.8, 156.4, 152.7, 135.1, 131.3 , 130.8, 129.8 (2C), 129.4 (2C), 128.8(2C), 127.1, 120.2, 113.9 (2C), 105.8, 101.0, 94.6, 65.6, 56.1, 55.3, 55.2, 54.9, 47.9, 37.4, 34.4; **ESI-HRMS**: calcd. for $C_{29}H_{32}NO_7$ 506.2173 $[M+H]^+$; found 506.2176.

The deoxygenation of (–)**-8** produced (–)**-20** as a viscous liquid in 75% yield.

(S)-4-Benzyl-3-((*R*)-3-(4-methoxy-2-(methoxymethoxy)phenyl)-2-(4-methoxyphenyl)propanoyl)oxazolidin-2-one (–)**-20**:

$[\alpha]_D^{25}$ = -26.4 (c = 0.33, $CHCl_3$); **IR** (cm^{-1}): 2933, 1178, 1695, 1510, 1218, 1156 and 1007; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 2H), 7.24–7.16 (m, 3H), 7.00–6.93 (m, 3H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.39 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.41 (dd, *J* = 8.8, 6.2 Hz, 1H), 5.19 (s, 2H), 4.63 (ddt, *J* = 8.9, 7.7, 3.3 Hz, 1H), 4.06–3.98 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.51 (s, 3H), 3.34 (dd, *J* = 13.4, 8.9 Hz, 1H), 3.09–3.01 (m, 2H), 2.56 (dd, *J* = 13.5, 9.0 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.0, 159.6, 158.9, 156.5, 152.9, 135.2, 131.5, 130.9,

129.9 (2C), 129.6 (2C), 128.9 (2C), 127.3, 120.3, 114.1 (2C), 105.9, 101.1, 94.6, 65.7, 56.3, 55.4, 55.4, 55.0, 48.1, 37.5, 34.6; **ESI-HRMS**: calcd. for $C_{29}H_{32}NO_7$ 506.2173 $[M+H]^+$; found 506.2151.

Deoxygenation of (+)-**9** produced (+)-**22** as a crystalline solid in 73% yield.

(*R*)-4-Benzyl-3-((*S*)-3-(2-((*tert*-butyldimethylsilyl)oxy-4-(methoxymethoxy)phenyl)-2-(2,4-dimethoxyphenyl)propanoyl)oxazolidin-2-one (+)-**22**:

MP: 107.5 °C; $[\alpha]_D^{25}$ = +11.6 (c = 1.0, $CHCl_3$); **IR** (cm^{-1}): 2931, 1784, 1696, 1611, 1506, 1292, 1210 and 1156; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.21 (m, 4H), 7.19–7.11 (m, 2H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 6.50–6.46 (m, 2H), 6.42 (d, *J* = 2.4 Hz, 1H), 5.54 (t, *J* = 7.6 Hz, 1H), 5.15–5.01 (m, 2H), 4.60 (ddt, *J* = 10.7, 7.4, 3.2 Hz, 1H), 3.98–3.90 (m, 2H), 3.80 (s, 3H), 3.68 (s, 3H), 3.44 (s, 3H), 3.34–3.24 (m, 2H), 3.03 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.55 (dd, *J* = 13.2, 10.0 Hz, 1H), 1.01 (s, 9H), 0.30 (s, 3H), 0.29 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.9, 159.9, 158.3, 156.5, 154.7, 152.4, 135.7, 131.0, 129.5, 129.3 (2C), 128.9 (2C), 127.2, 123.1, 120.1, 108.1, 107.1, 104.1, 98.6, 94.6, 65.7, 55.8, 55.6, 55.4, 55.3, 42.7, 37.7, 32.5, 25.9 (3C), 18.3, –4.1, –4.2; **ESI-HRMS**: calcd. for $C_{35}H_{46}NO_8Si$ 636.2987 $[M+H]^+$; found 636.2995.

Deoxygenation of (–)-**9** produced (–)-**22** as a crystalline solid in 68% yield.

(*S*)-4-Benzyl-3-((*R*)-3-(2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)phenyl)-2-(2,4-dimethoxyphenyl)propanoyl)oxazolidin-2-one (–)-**22**:

MP: 106.9 °C; $[\alpha]_D^{25}$ = –10.7 (c = 1.0, $CHCl_3$); **IR** (cm^{-1}): 2957, 2935, 1788, 1698, 1613, 1508, 1292, 1212, 1158 and 1018; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.23 (m, 4H), 7.21–7.13 (m,

2H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.48 (dd, *J* = 8.4, 2.4 Hz, 2H), 6.42 (d, *J* = 2.4 Hz, 1H), 5.53 (t, *J* = 7.7 Hz, 1H), 5.17–5.01 (m, 2H), 4.60 (ddt, *J* = 10.6, 6.7, 3.1 Hz, 1H), 3.98-3.90 (m, 2H), 3.81 (s, 3H), 3.68 (s, 3H), 3.45 (s, 3H), 3.34–3.23 (m, 2H), 3.02 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.55 (dd, *J* = 13.3, 10.0 Hz, 1H), 1.01 (s, 9H), 0.29 (s, 3H), 0.28 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.9, 159.9, 158.3, 156.5, 154.8, 152.4, 135.8, 131.0, 129.5, 129.3 (2C), 128.9 (2C), 127.2, 123.2, 120.1, 108.1, 107.1, 104.1, 98.6, 94.6, 65.7, 55.8, 55.6, 55.4, 55.3, 42.7, 37.7, 32.5, 25.9 (3C), 18.3, –4.1, –4.2; **ESI-HRMS**: calcd. for $C_{35}H_{46}NO_8Si$ 636.2987 $[M+H]^+$; found 636.2979.

Deprotection of MOM group

A solution of deoxygenated aldol product (+)-**20** (1 g, 1.98 mmol) dissolved in 3 M HCl in methanol (10 mL) was refluxed and the reaction was monitored by TLC. After 30 min, the reaction was cooled to 0 °C, quenched with saturated $NaHCO_3$ (10 mL), methanol and was evaporated. The reaction mixture was extracted using ethyl acetate (2 x 20 mL) and the combined organic layer was dried over anhydrous $MgSO_4$, concentrated and purified using column chromatography to obtain phenol (+)-**21** as a colorless viscous (0.78 g, 1.7 mmol, 85%).

(R)-4-Benzyl-3-((*S*)-3-(2-hydroxy-4-methoxyphenyl)-2-(4-ethoxyphenyl)propanoyl)oxazolidin-2-one (+)-**21**:

$[\alpha]_D^{25}$ = +37.1 (c = 0.21, $CHCl_3$); **IR** (cm^{-1}): 3388, 2928, 1777, 1695, 1620, 1510, 1164, 1181, and 1033; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.7 Hz, 2H), 7.25–7.15 (m, 4H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.99–6.88 (m, 4H), 6.48 (d, *J* = 2.5 Hz, 1H), 6.45 (dd, *J* = 8.3, 2.6 Hz, 1H), 5.21 (dd, *J* = 11.0, 4.3 Hz, 1H), 4.68 (tt, *J* = 8.5, 3.3 Hz, 1H), 4.09 (t, *J* = 8.5 Hz, 1H), 4.02 (dd, *J* =

9.1, 3.1 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.45 (dd, *J* = 14.3, 11.1 Hz, 1H), 3.07 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.76 (dd, *J* = 14.4, 4.3 Hz, 1H), 2.56 (dd, *J* = 13.5, 8.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.8, 159.7, 159.1, 155.1, 152.3, 134.6, 131.9, 130.2, 129.6 (2C), 129.4 (2C), 128.9 (2C), 127.3, 117.8, 114.3 (2C), 107.0, 102.8, 65.7, 55.3, 55.2, 54.8, 50.8, 37.1, 33.9; **ESI-HRMS**: calcd. for $C_{27}H_{28}NO_6$ 462.1911 $[M+H]^+$; found 462.1917.

MOM group deprotection of (–)-**20** produced (–)-**21** as viscous liquid in 87% yield.

(S)-4-benzyl-3-((*R*)-3-(2-hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)propanoyl)oxazolidin-2-one (–)-**21**:

$[\alpha]_D^{25}$ = –34.7 (c = 0.15, $CHCl_3$); **IR** (cm^{-1}): 3388, 2928, 1777, 1695, 1620, 1510, 1181 and 1033; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.6 Hz, 2H), 7.26–7.13 (m, 4H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.97–6.93 (m, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.48 (d, *J* = 2.5 Hz, 1H), 6.45 (dd, *J* = 8.3, 2.6 Hz, 1H), 5.21 (dd, *J* = 11.0, 4.3 Hz, 1H), 4.68 (tt, *J* = 8.5, 3.3 Hz, 1H), 4.09 (t, *J* = 8.5 Hz, 1H), 4.02 (dd, *J* = 9.1, 3.1 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.45 (dd, *J* = 14.3, 11.0 Hz, 1H), 3.07 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.77 (dd, *J* = 14.4, 4.3 Hz, 1H), 2.56 (dd, *J* = 13.5, 8.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.9, 159.9, 159.2, 155.3, 152.5, 134.8, 132.0, 130.3 (2C), 129.8 (2C), 129.5 (2C), 129.0 (2C), 127.4, 118.0, 114.4 (2C), 107.1, 102.9, 65.9, 55.4, 55.4, 55.0, 50.9, 37.3, 34.1. **ESI-HRMS**: calcd. for $C_{27}H_{28}NO_6$ 462.1911 $[M+H]^+$; found 462.1891.

Reduction

(*S*)-2-(3-Hydroxy-2-(4-methoxyphenyl)propyl)-5-methoxyphenol (+)-**6**

To a suspension of $LiAlH_4$ (4 g, 105 mmol) in THF (25 mL) at 0 °C, solution of the compound

(+)-**21** (24 g, 52 mmol) in THF (150 mL) was added dropwise and stirred for 4 hours at room temperature. Then the reaction was cooled to 0 °C and carefully quenched with a dropwise addition of saturated NaOH (50 mL). THF was evaporated and the resulting solution was extracted with ethyl acetate (3 x 50 mL) and separated, dried over anhydrous $MgSO_4$ and isolated using flash chromatography to produce colorless liquid (+)-**6** (13.5 g, 47 mmol, 90%), which was solidified on standing.

(*S)*-2-(3-Hydroxy-2-(4-methoxyphenyl)propyl)-5-methoxyphenol (+)-**6**:

$[\alpha]_D^{25}$ = +31.6 (c = 0.185, $CHCl_3$); **IR** (cm^{-1}): 3342, 2930, 2836, 1614, 1510, 1441, 1285, 1242, 1178, 1031, 958, and 828; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.44 (d, *J* = 2.5 Hz, 1H), 6.39 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.80 (s, 3H), 3.74 (bs, 5H), 3.08 (dd, *J* = 13.5, 8.4 Hz, 1H), 2.98 (dq, *J* = 9.9, 4.8 Hz, 1H), 2.82 (dd, *J* = 13.5, 5.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 158.4, 155.5, 134.6, 131.9, 128.8 (2C), 118.0, 114.0 (2C), 106.3, 102.1, 65.1, 55.3, 55.3, 47.5, 31.5; **ESI-HRMS**: calcd. for $C_{17}H_{21}O_4$ 289.1434 $[M+H]^+$; found 289.1433.

Reduction of (–)-**21** with LAH produced (–)-**6** as a viscous liquid and solidified on standing.

(*R)*-2-(3-Hydroxy-2-(4-methoxyphenyl) propyl)-5-methoxyphenol (–)-**6**:

$[\alpha]_D^{25}$ = –33.3 (c = 0.19, $CHCl_3$); **IR** (cm^{-1}): 3351, 2931, 2836, 1737, 1615, 1511, 1441, 1285, 1243, 1159, 1108, 1032, 958, and 829; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.44 (d, *J* = 2.5 Hz, 1H), 6.39 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.74 (t, 2H), 3.08 (dd, *J* = 13.6, 8.5 Hz, 1H), 2.98 (dq, *J* = 9.9, 5.0 Hz, 1H), 2.82 (dd, *J* = 13.6, 5.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 158.4, 155.6, 134.6, 131.9, 128.8 (2C), 117.9, 114.0 (2C), 106.3, 102.1, 65.1, 55.3, 55.2, 47.4, 31.4;

ESI-HRMS: calcd. for $C_{17}H_{21}O_4$ 289.1434 $[M+H]^+$; found 289.1441.

(*S*)-2-(2-(2,4-Dimethoxyphenyl)-3-hydroxypropyl)-5-(methoxymethoxy)phenol (+)-**7**

To a suspension of $LiAlH_4$ (0.2 g, 5.13 mmol) in 15 mL THF (15 mL) at 0 °C, solution of (*R*)-4-benzyl-3-((S)-3-(2-((tert-butyldimethylsilyl)oxy-4-(methoxy-methoxy)phenyl)-2-(2,4-dimethoxyphenyl)propanoyl)oxazolidin-2-one (+)**-22** (1.18 g, 1.86 mmol) in THF (50 mL) was added dropwise and stirred overnight at room temperature. Then the reaction was cooled to 0 °C, and quenched with the careful addition of saturated NaOH (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$. TLC indicated a mixture of the expected alcohol along with monosilylated alcohol as the major product. Without further purification, the mixture was subjected to desilylation using TBAF in THF. After workup, the crude mixture was purified using flash chromatography to produce diol (+)**-7** (0.58 g, 1.65 mmol, 89%) as a colorless, viscous liquid.

(*S*)-2-(2-(2,4-Dimethoxyphenyl)-3-hydroxypropyl)-5-(methoxymethoxy)phenol (+)-**7**:

Yield 89%; Colorless viscous liquid, $[\alpha]_D^{25}$ = +26.9 (c = 1.0, $CHCl_3$); **IR** (cm^{-1}): 3362, 2954, 1615, 1588, 1508, 1467, 1292, 1210 and 1156; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 6.55–6.41 (m, 3H), 5.12 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.80–3.66 (m, 3H), 3.47 (s, 3H), 3.32 (dt, *J* = 9.6, 4.6 Hz, 1H), 3.04 (dd, *J* = 14.0, 9.6 Hz, 1H), 2.74 (dd, *J* = 14.0, 4.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 157.7, 156.9, 155.8, 131.7, 128.5, 123.4, 119.8, 108.3, 104.5, 104.2, 98.9, 94.4, 63.5, 55.9, 55.5, 55.4, 41.3, 30.5; **ESI-HRMS:** calcd. for $C_{19}H_{25}O_6$ 349.1646 $[M+H]^+$; found 349.1655.

Similarly, the reduction of (–)-**22** with LAH produced diol, (–)-**7** in 74% yield.

(*R*)-2-(2-(2,4-Dimethoxyphenyl)-3-hydroxypropyl)-5-(methoxymethoxy)phenol (–)-**7**: $[\alpha]_D^{25}$ = –24.4 (c = 1.0, $CHCl_3$) ; **IR** (cm^{-1}): 3391, 2939, 1615, 1588, 1506, 1290, 1210, 1154, and 1015; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.3 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 6.57–6.42 (m, 3H), 5.13 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.79–3.70 (m, 2H), 3.47 (s, 3H), 3.29 (dq, *J* = 9.3, 4.6 Hz, 1H), 3.04 (dd, *J* = 14.1, 9..3 Hz, 1H), 2.73 (dd, *J* = 14.1, 4.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.7, 157.8, 157.1, 156.0, 131.8, 128.6, 123.5, 119.8, 108.5, 104.8, 104.3, 99.1, 94.6, 63.6, 56.1, 55.6, 55.5, 41.7, 30.7; **ESI-HRMS**: calcd. for $C_{19}H_{25}O_6$ 349.1646 $[M+H]^+$; found 349.1645.

Intramolecular Mitsunobu cyclization

To the alcohol, (*S)*-2-(3-hydroxy-2-(4-methoxyphenyl)propyl)-5-methoxyphenol (+)-**6** (10.0 g, 34.7 mmol) dissolved in THF (125 mL) at room temperature, triphenyl phosphine (30 g, 114 mmol) was added, followed by diisopropyl azodicarboxylate (23 g, 114 mmol), dropwise, and stirred for 6 h. Then the solvent was removed and purified using flash chromatography with 7% ether in hexanes to obtain (–)-**23** as a pale pink solid (8.1 g, 30 mmol, 86 %).

Alternatively, a solution of the alcohol (+)-**6** (1.0 g, 3.47 mmol) in anhydrous toluene (25 mL) was added to suspension of tosyl chloride (1.46 g, 7.66 mmol) and potassium carbonate (2.4 g, 17.4 mmol) in anhydrous toluene (50 mL). The resulting solution was heated to reflux and the reaction was monitored by TLC. After 5h, the mixture was cooled to room temperature, filtered over celite and washed with toluene (2 x 15 mL). The combined layers were concentrated and purified by flash purification with 7% ether in hexanes to yield (–)-**23** as a pale pink solid (0.73g,

2.70 mmol, 78%).

(*S*)-7-methoxy-3-(4-methoxyphenyl)chromane (–)**-23**:

$[\alpha]_D^{25}$ = –12.2 (c = 0.66, $CHCl_3$); **IR** (cm^{-1}): 2961, 2039, 1886, 1613, 1584, 1505, 1460, 1441, 1330, 1302, 1248, 1201, 1158, and 1026; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.49 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.44 (d, *J* = 2.6 Hz, 1H), 4.31 (dd, *J* = 10.6, 2.9 Hz, 1H), 3.98 (t, *J* = 10.6 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.18 (tdd, *J* = 10.5, 7.1, 3.5 Hz, 1H), 2.99–2.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 158.6, 155.0, 133.4, 130.2, 128.3 (2C), 114.2 (3C), 107.3, 101.4, 71.1, 55.3, 55.3, 37.9, 31.9; **ESI-HRMS**: calcd. for $C_{17}H_{19}O_3$ 271.1329 $[M+H]^+$; found 271.1339.

Similarly, (+)-**23** was prepared from (–)**-6** using TsCl and potassium carbonate and subsequently demethylated with pyridinium hydrocholride resulting in (+)-equol (+)**-4** with data identical to the reported data.[17]

Similarly, the intramolecular Mitsunobu cyclization of (+)**-7** produced compound (+)**-24** in 86% yield.

(*S*)-3-(2,4-Dimethoxyphenyl)-7-(methoxymethoxy)chromane (+)**-24**:

$[\alpha]_D^{25}$ = +9.2 (c = 1.0, $CHCl_3$); **IR** (cm^{-1}): 2933, 1616, 1506, 1467, 1261, 1208 and 1154; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.3 Hz, 1H), 7.00 (d, *J* = 9.1 Hz, 1H), 6.64–6.54 (m, 2H), 6.54–6.42 (m, 2H), 5.15 (s, 2H), 4.32 (ddd, *J* = 10.4, 3.4, 2.0 Hz, 1H), 4.01 (t, *J* = 10.3 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.65–3.49 (m, 1H), 3.49 (s, 3H), 3.00 (dd, *J* = 15.8, 10.8 Hz, 1H), 2.89 (dd, *J* = 15.7, 3.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.7, 158.3, 156.6, 155.1,

130.2, 127.6, 121.8, 116.1, 108.8, 104.4, 104.1, 98.7, 94.6, 70.2, 55.9, 55.4 (2C), 31.6, 30.5. **ESI-HRMS**: calcd. for $C_{19}H_{23}O_5$ 331.1540 $[M+H]^+$; found 331.1543.

Similarly, (–)-**24** was prepared from (–)**-7** in 83% yield.

(*R*)-3-(2,4-Dimethoxyphenyl)-7-(methoxymethoxy)chromane (–)**-24**:

$[\alpha]_D^{25}$ = -10.6 (c = 1.0, $CHCl_3$); **IR** (cm^{-1}): 2933, 1618, 1587, 1506, 1467, 1261, 1154, 1127, and 1033; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 9.1 Hz, 1H), 6.62–6.55 (m, 2H), 6.52–6.42 (m, 2H), 5.14 (s, 2H), 4.31 (ddd, *J* = 10.2, 3.5, 2.0 Hz, 1H), 4.00 (t, *J* = 10.2 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.63–3.49 (m, 1H), 3.48 (s, 3H), 2.99 (dd, *J* = 15.7, 10.6 Hz, 1H), 2.88 (dd, *J* = 15.7, 4.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.8, 158.4, 156.7, 155.2, 130.3, 127.7, 122.0, 116.2, 109.0, 104.5, 104.3, 98.9, 94.7, 70.3, 56.1, 55.5, 55.5, 31.7, 30.6; **ESI-HRMS**: calcd. for $C_{19}H_{23}O_5$ 331.1540 $[M+H]^+$; found 331.1532.

Demethylation

The dimethoxy chromane (–)**-23** (18 g, 66.7 mmol) was dissolved in pyridine hydrochloride (192 g, 148 mL, 1.67 mol), heated overnight at 150 °C and cooled to room temperature. After neutralizing with excessive $NaHCO_3$ (aqueous), the mixture was extracted with dichloromethane (3 x 100mL). The crude product was further purified by column chromatography using diethyl ether in hexanes to yield white solid in 88% yield. (14.2 g, 58.7 mmol).

(S)-3-(4-Hydroxyphenyl)chroman-7-ol. (*S*)-(–)-Equol (–)**-4**:

$[\alpha]_D^{25}$ = –19.5 (c = 1.05, MeOH), lit[46] $[\alpha]_D^{25}$ = –13 (c = 0.21, EtOH); **^{1}H NMR** (400 MHz, CD_3OD) δ 7.09 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 2H), 6.33 (dd, *J*

= 8.2, 2.5 Hz, 1H), 6.25 (d, *J* = 2.5 Hz, 1H), 4.20 (ddd, *J* = 10.5, 3.6, 1.8 Hz, 1H), 3.91 (t, *J* = 10.5 Hz, 1H), 3.05 (tdd, *J* = 10.2, 6.0, 3.6 Hz, 1H), 2.93–2.77 (m, 2H).**^{13}C NMR** (100 MHz, CD_3OD) δ 157.6, 157.3, 156.3, 133.8, 131.2, 129.3 (2C), 116.4 (2C), 114.6, 109.1, 103.8, 72.2, 39.4, 33.0.

MOM group deprotection

The chromane (+)-**24** (0.034 g, 0.1 mmol) was dissolved in freshly prepared 3 M HCl in methanol (2 mL). After stirring for 30 min, the initial suspension turned into clear solution which was stirred for additional 15 min at room temperature. The reaction was cooled to 0 °C, carefully quenched with saturated $NaHCO_3$ solution. The whole mixture was concentrated under reduced pressure and the resulting mixture was purified by flash chromatography with 10-15% ethyl acetate in hexanes to obtain brown-red crystalline solid (+)-**5** (25 mg, 0.087 mmol, 86%).

(*S*)-3-(2,4-Dimethoxyphenyl)chroman-7-ol (*S*)-Sativan (+)-**5**:

$[\alpha]_D^{25}$ = +8.5 (c = 1.0, $CHCl_3$); **MP**: 125 °C; **IR** (cm^{-1}): 3363, 2928, 2840, 1616,1508, 1300, 1210, 1158, 1117, 1033, and 799; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.55–6.43 (m, 2H), 6.43–6.30 (m, 2H), 5.18 (bs, 1H), 4.30 (ddd, *J* = 10.2, 3.2, 1.9 Hz, 1H), 4.00 (t, *J* = 10.1 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.57 (tt, *J* = 9.8, 5.1 Hz, 1H), 2.97 (dd, *J* = 15.6, 10.7 Hz, 1H), 2.86 (dd, *J* = 15.6, 5.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.6, 158.3, 155.1, 154.9, 130.4, 127.5, 121.8, 114.8, 107.9, 104.1, 103.2, 98.7, 70.1, 55.4, 55.3, 31.5, 30.3; **ESI-HRMS**: calcd. for $C_{17}H_{19}O_4$ 287.1278 $[M+H]^+$; found 287.1290.

Similarly, (–)-**5** was prepared from (–)**-24** in 88% yield.

(*S*)-3-(2,4-Dimethoxyphenyl)chroman-7-ol, (*R*)-Sativan (–)-**5**:

$[\alpha]_D^{25}$ = –9.5 (c = 1.0, $CHCl_3$) lit –8 (c 0.28, MeOH),[47] –9.9 (c 0.33, MeOH);[4] **MP**: 127 °C; lit[4] 128–129 °C, 129–130 °C;[47] **IR** (cm^{-1}): 3404, 2935, 1616, 1508, 1460, 1158, 1117 and 1033; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.53–6.43 (m, 2H), 6.43–6.33 (m, 2H), 5.06 (bs, 1H), 4.30 (dd, *J* = 10.3, 1.4 Hz, 1H), 4.00 (t, *J* = 10.1 Hz, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.56 (tt, *J* = 9.8, 4.5 Hz, 1H), 2.97 (dd, *J* = 15.7, 10.5 Hz, 1H), 2.86 (dd, *J* = 15.6, 4.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.8, 158.4, 155.3, 155.0, 130.5, 127.7, 122.0, 114.9, 108.0, 104.3, 103.3, 98.8, 70.2, 55.5, 55.5, 31.7, 30.5; **ESI-HRMS**: calcd. for $C_{17}H_{19}O_4$ 287.1278 $[M+H]^+$; found 287.1290.

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