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Chromatography-free "two-pots" asymmetric total synthesis of (+)-sesamin and (+)-aschantin

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ABSTRACT

A gram-scale chromatography-free asymmetric total synthesis of both homo- and heterobiaryl furofuran lignans containing at least one methylenedioxy phenyl unit such as (+)-sesamin and (+)-aschantin is accomplished in "two-pots" from easily accessible enantiopure lactone involving four steps in high overall yields. Steps- and pot economy are the key advantages of the protocol. Additionally, the bromo-functionality of the intermediates is useful for late stage functionalization.

1. Introduction

In 21st century, the modern science and industry are emphasizing on two principal issues – "green" and "efficiency" (practicability) for the synthesis of a target compound. These are characterized in terms of different economic factors such as atom economy, redox economy, step economy and pot economy. The minimization of number of reaction steps to a target compound (step economy) reduces the length, cost, effort, separation methods, development- and execution time. Similarly, the carrying out several reactions in one-pot or reactor omitting work up procedure and/or without isolating or purifying the intermediate compounds (pot economy) reduces the amount of solvent, waste, time, labor and the cost. Thus, both the step- and pot-economy are very important issues in synthesizing a target molecule in terms of 'greenness' and practicability [1].

Furofuran lignans are important and the largest subclass of non-butyrolactone lignans isolated from various vascular plants. These lignans are known to exhibit a broad range of biological properties. The variation of aryl units and their stereochemical orientation led to the structural as well as biological diversity [2]. Among all the oxyarenes, 3,4-methylenedioxy arene is more abundant than others and is also known to have strong impact in bioactivities, for example, (+)-sesamin **1** and (+)-aschantin **2** (Scheme 1). (+)-Sesamin **1** is a symmetrical furofuran lignan having two 3,4-methylenedioxy arene units and a major constituent of sesame seeds. It exhibits anticancer, anti-inflammatory, antihypertensive, antioxidant and estrogen receptor modulator properties [3]. On the other hand, (+)-aschantin **2**, an unsymmetrical furofuran lignan having two different arene units, exhibits various bioactivities like inhibition of inducible NO synthetase, antiplasmodial activity, Ca2+-antagonistic activity, platelet activating factor-antagonistic activity, chemo-preventative or therapeutic activity mediated via inhibition of mTOR kinase etc. [4] Thus because of widespread biological properties, several efforts are made for the racemic as well as non-racemic synthesis of both symmetrical and unsymmetrical furofuran lignans such as (+)-sesamin **1** and (+)-aschantin **2**, respectively [5,6]. But in terms of step- and pot-economy all the reported protocols are inefficient and reveal a lack of greenness. Herein, we report gram-scale unified asymmetric total synthesis of (+)-sesamin **1** and (+)-aschantin **2** accomplished in two-pots and free from any chromatography in whole process.

Both (+)-sesamin **1** and (+)-aschantin **2** are *exo-exo* furofuran lignans having the same stereochemistry and a common 3,4-methylenedioxy arene unit. So we realized that both could be

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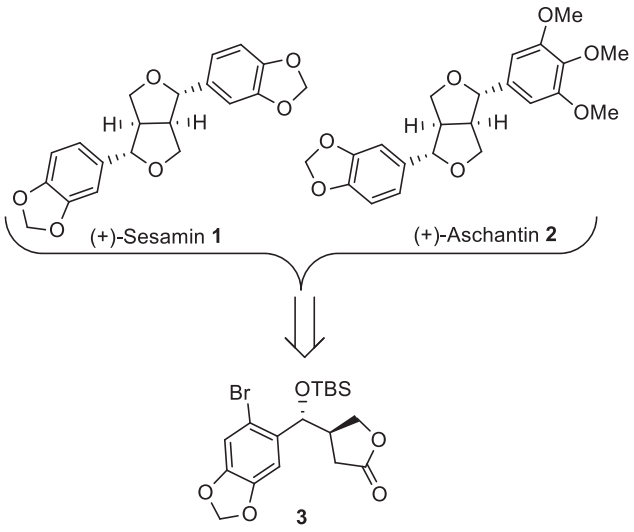


Scheme 1. Important bioactive furofuran lignans and their proposed synthetic precursor.

synthesized from the enantiopure lactone **3** using a same sequence of reactions such as aldol reaction varying aldehyde, reduction and cyclization (Scheme 1). Recently, we have developed an organocatalytic one-pot protocol for highly diastereo- and enantioselective synthesis of the lactone **3**, where electronic and steric factor of *ortho*-bromo-group played an important role in the reactivity and selectivity and it was further utilized in building the complex lignan [7]. Here, we presumed that the bromo-functionality may help in solidification/precipitation of intermediate compounds and would be useful for the late stage functionalization too.

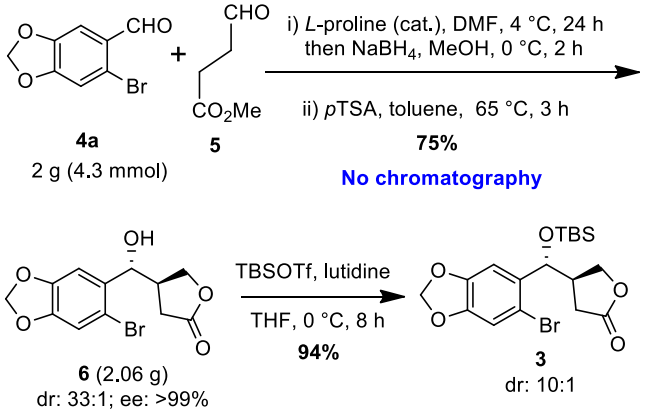
2. Results and discussion

We commenced the synthesis of (+)-sesamin **1** from the enantiopure lactone **3**, which was obtained in gram scale with high diastereoselectivity (dr 10:1) and excellent enantioselectivity (>99%) in two steps by following our developed protocol from 6-bromopiperonal **4a** and methyl 4-oxobutanoate **5** (Scheme 2) [7c]. We planned to execute the one-pot base mediated aldol reaction of lactone **3** with 6-bromopiperonal **4a**, reduction followed by deprotection-cyclization using same solvent. For this purpose, we initially validated each step using THF as solvent and carried forward the crude product for the subsequent steps without purification (Scheme 3). LiHMDS mediated aldol reaction of the lactone **3** with the 6-bromopipernal **4a** in THF at −78 °C produced the aldol product **7** as a 1:1 mixture of diastereomers, determined by ^{1}H NMR analysis of the crude mixture. After workup, the crude lactone alcohol **7** was fully reduced with *in situ* prepared $CaBH_4$ (from $CaCl_2$ and $NaBH_4$) in THF. Again after workup, the crude mono-*O*-TBS protected tetraol **8** was treated with 50% aqueous HCl in THF at rt. The desilylation and subsequent dehydrative cyclization gave exclusively dibromo sesamin **9** as a white solid. The consumption of starting compound and the formation of intermediate product of each step was monitored by TLC and MS analysis. The overall yield for the three step synthesis of dibromosesamin **9** from lactone **3** without purification of intermediate compounds was found to be very high (72%).

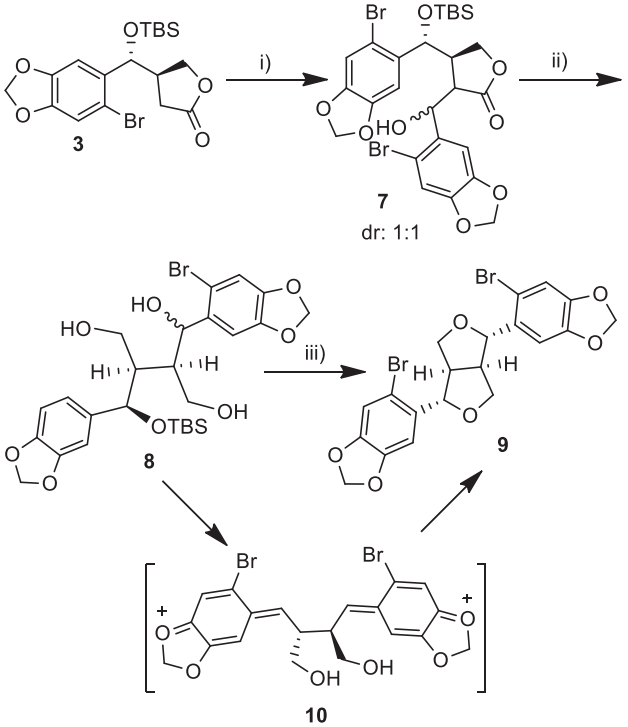
The stereoselective formation of thermodynamically stable *exo-exo* furofuran lignan from a mixture of diastereomeric tetraol could be rationalized from the generation of a common quinoid intermediate **10**.

Debromination of compound **9** can provide the natural (+)-sesamin **1** and additionally the bromo-functionality can be utilized for the late functionalization to synthesize the analogues of sesamin. So we put our effort for the debromination of **7** (Table 1). Metal halogen exchange protocol using *n*-BuLi, Mg and Turbo Grignard reagent (*i*-

PrMgCl.LiCl) gave either poor yield of desired product **1** along with decomposition/intractable mixture or no reaction (entries 1–5). Pd-catalyzed hydrogenation using *i*-PrOH and molecular hydrogen (H_2) were also not successful (entries 6 and 7). Interestingly, $Pd(OAc)_2$ catalyzed transfer hydrogenation using sodium formate gave the desired desbromo product, sesamin **1** in 43% yield (entry 9). To our delight, changing the catalyst to $Pd_2(dba)_3$ afforded the smooth reaction with excellent yield (96%; entry 10).



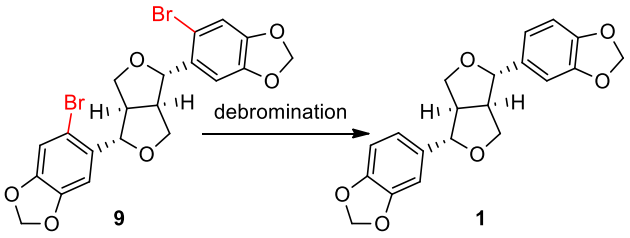
Scheme 2. Synthesis of enantiopure lactone 3 [7c].



Reagents & Conditions: i) LiHMDS, **4a**, -78 °C 6 h; ii) $NaBH_4$, $CaCl_2$, THF/MeOH 6 h; iii) 1:4 THF/ HCl (50% aq)

Scheme 3. Optimization of sequential one-pot synthesis of dibromosesamin 9 from lactone 3.

Table 1
Optimization of debromination reaction.[a]



entry	reagent/s	solvent	time (h)	temp (°C)	yield[b] (%)
1	n-BuLi	THF	1	−78	20
2	Mg (I_2 cat.)	THF	4	25	NR
3	Mg (I_2 cat.)	THF	12	60	<10
4	^{i}PrMgCl.LiCl	THF	2	25	NR
5	^{i}PrMgCl.LiCl	THF	12	60	NR
6	$Pd(OAc)_2/K_2CO_3$	^{i}PrOH	12	70	NR
7	$Pd(OH)_2/H_2$	EtOAc	6	25	NR
8	$Pd/C/H_2$	EtOH	12	25	15
9	$Pd(OAc)_2/PPh_3/HCO_2Na$	DMF	12	80	43
10	$Pd_2(dba)_3/HCO_2Na$	DMF	12	80	96

[a] All the reactions were performed under N_2 atmosphere with 50 mg scale. Concentration of the reaction was maintained 0.1 M.
[b] Isolated yield. NR = no reaction (starting material recovered).

After standardization of each step we focused on the scalability and pot-economy. For this purpose, we made our effort to carry out the first three steps aldol, reduction and desilylative-cyclization in "one-pot" (pot economy) using same THF without workup and purification of intermediate compounds (Scheme 4). After the LiHMDS mediated aldol reaction of TBS-lactone **3** (2 g, 4.65 mmol) and 6-bromopiperonal **4a**, the reaction was treated with the stoichiometric amount of AcOH to destroy the excess Li-reagent. It was then reacted with *in situ* prepared $CaBH_4$ in THF. The complete reduction to **8** was monitored by MS analysis. After completion, it was quenched with solid NH_4Cl and stirred. The solid residue was filtered off and the filtrate containing tetraol **8** (THF solution) was treated with 50% aqueous HCl. After stirring for 24 h at rt, it produced white precipitate. On filtration, it gave sufficiently pure dibromo sesamin **9**. This was used for the debromination without any purification. $Pd_2(dba)_3/HCO_2Na$ mediated debromination of **9** afforded the targeted (+)-sesamin **1** (1.06 g, 64%) after purification by crystallization from diethyl ether. We thus accomplished the chromatography-free "two-pots" gram-scale asymmetric total synthesis of (+)-sesamin using only one workup at debromination step. NMR and optical rotation of the synthesized (+)-sesamin **1** are in well agreement with the literature [6f].

The similar protocol can be utilized for the synthesis of other *exo-exo* furofuran lignans varying the aldehyde in aldol step. Accordingly, "two-pots" asymmetric total synthesis of hetero-biaryl furofuran lignan, (+)-aschantin **2** was commenced from 2 g of lactone **3** and 3,4,5-trimethoxy benzaldehyde **4b** (Scheme 5). Gratifyingly, without any complication we achieved the chromatography-free "two-pots" asymmetric total synthesis of (+)-aschantin **2** with excellent selectivity in high overall yield (0.93 g, 50%).

Spectral and optical rotation data of synthesized (+)-aschantin **2** are also in good agreement with the literature [6c].

Additionally, to demonstrate the late stage functionalization of bromo-functionality of aryl unit, the dibromo sesamin **9** was subjected to the Suzuki coupling reaction with phenyl boronic acid using $Pd_2(dba)_3$ as a catalyst (Scheme 6). It underwent smooth coupling reaction and afforded the diphenyl substituted sesamin **12** in good yield.

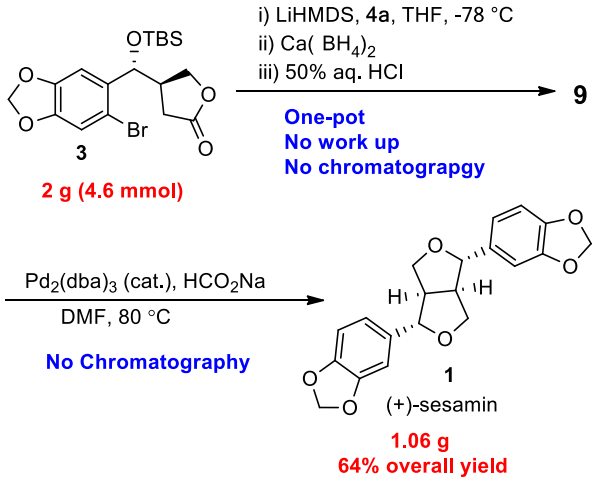
3. Conclusion

In summary, we have demonstrated a pot- and step-economy general protocol for the asymmetric synthesis of both homo- and hetero-biaryl furofuran lignans, in particular, containing at least one methylenedioxy arene unit. A highly efficient "two-pots" gram-scale asymmetric total synthesis of (+)-sesamin and (+)-aschantin have been showcased, which involve only one work up and free from any chromatographic purification. Thus the developed protocol reduces the amounts of solvent use, waste, time, labor and the cost. Additionally, the synthesized furofuran core containing bromoarene unit can be easily functionalized in late stage to other analogues.

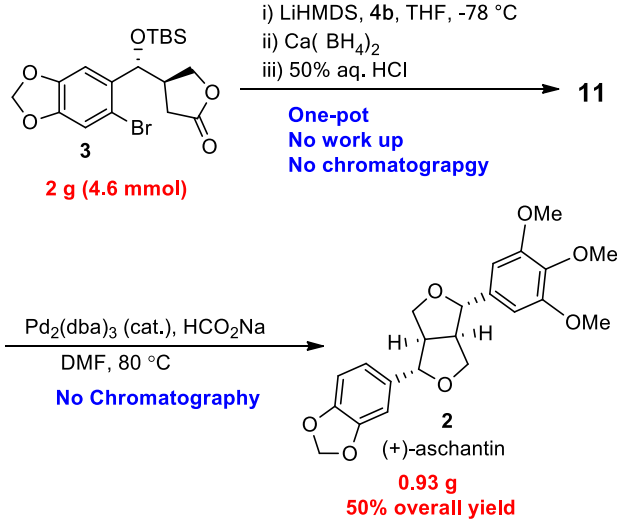
4. Experimental section

4.1. General methods

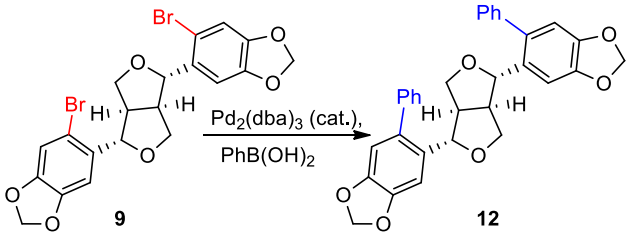
All the reactions were carried out under an atmosphere of argon using oven-dried glassware. Commercially available reagents were



Scheme 4. Gram Scale chromatography free synthesis of (+)-sesamin.



Scheme 5. Gram Scale chromatography free synthesis of (+)-aschantin.



Scheme 6. Synthesis of sesamin analogue.

purchased and used without further purification. Solvents were dried and distilled following standard literature procedure. Flash column chromatography was performed using silica gel (230–400 mesh) when required. Analytical TLC was performed on aluminium-backed plates coated with silica gel 60 with F_{254} indicator and compounds were visualized by irradiation of UV light. The ^{1}H NMR spectra were recorded with 400 MHz and 800 MHz and ^{13}C NMR spectra recorded with 100 MHz and 200 MHz using $CDCl_3$ or DMSO-d_6. ^{1}H NMR chemicals shift are expressed in ppm(δ) relative to δ = 7.27 for $CDCl_3$ and δ = 2.50 for DMSO-d_6. ^{13}C NMR chemical shift are expressed in ppm(δ) relative to δ = 77.00 for $CDCl_3$ and δ = 39.51 for DMSO-d_6 resonance. HRMS and Electron spray ionization (ESI) mass spectrometry (MS) experiment were performed on Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS. Optical rotation value was measured on a Digipol 781 M6U Automatic Polarimeter. Enantiomeric excess (*ee*) was measured by HPLC analysis with chiral stationary phase. The melting points (mps) were determined using a STUART SMP30 melting point apparatus and are uncorrected.

O-TBS lactone **3** was prepared in grams scale following our earlier protocol [7c].

4.2. Synthesis of (1S,3aR,4S,6aR)-1,4-bis(6-bromobenzo[d][1,3]dioxol-5-yl)tetrahydro-1H,3H-furo[3,4-c]furan 9

Step 1: Synthesis of compound **7**: To an oven dried two-necked RB was added TBS-lactone **3** (0.1 g, 0.23 mmol) in THF (2 mL). It was cooled to −78 °C. LiHMDS (0.28 mL, 0.28 mmol, 1 M in THF) was added to it and stirred for 45 min. 6-bromopiperonal **4a** (0.073 g, 0.32 mmol) in THF (1 mL) was added to the reaction mixture and stirred for additional 6 h at the same temperature. After complete consumption of the TBS Lactone **3**, the reaction mixture was quenched by 1M AcOH solution in THF. The temperature of the mixture was then raised to room temperature. It was diluted with H_2O (20 mL). The aqueous part was extracted with EtOAc (3 × 35 mL). The combined organic layer was washed with brine (10 mL) and was dried over Na_2SO_4. The solvent was evaporated under *vacuum* to afford the crude compound as a gummy yellow liquid. It was triturated before using for the Step 2 without further purification (0.18 g crude weight). HRMS (ESI-TOF) *m/z* (M + Na)$^+$ calcd for $C_{26}H_{30}^{79}Br^{81}BrO_8SiNa^+$ 680.9954; found 680.9932.

Step 2: Synthesis of compound **8**: To the THF (1 mL) solution of crude **7** was added to *in situ* generated $CaBH_4$ ($CaCl_2$ 0.153 g, 1.38 mmol; $NaBH_4$ 0.105 g, 2.76 mmol) in THF/MeOH (1:1; 2 mL) at 0 °C. It was allowed to stir at room temperature for 6 h. The completion of the reaction was monitored by mass spectroscopy analysis. The reaction was quenched with solid NH_4Cl and then filtered through celite pad. The filtrate was collected. The solvent was evaporated out under *vacuum* to afford the title compound **8** as a colourless gummy liquid (0.16 g). HRMS (ESI-TOF): *m/z* (M + Na)$^+$ calcd for $C_{26}H_{34}^{79}Br^{81}BrO_8SiNa^+$ 685.0267; found 685.0229.

Step 3: Synthesis of compound **9**: To the THF (1 mL) solution of compound **8** was added 50% aqueous HCl (4 mL) at 0 °C. The reaction mixture was then allowed to stir at room temperature for 48 h. The whole mixture was diluted with H_2O (20 mL) and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent evaporation under *vacuum* gave the crude product which was purified by column chromatography (Hexanes/EtOAc 9:1) and afforded compound **9** as a white solid (0.086 g, 72% over three steps). R_f 0.6 (Hexanes/EtOAc 9:1); $[\alpha]_D^{20}$ = −12 (c = 0.97 $CHCl_3$); mp 188–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 2H), 6.95 (s, 2H), 5.98 (d, J = 1.2 Hz, 2H), 5.96 (d, J = 1.2 Hz, 2H), 5.09 (d, J = 2.8 Hz, 2H), 4.48 (pseudo t (dd), J = 8.4 Hz 2H), 4.18 (dd, J = 9.2, 4.8 Hz, 2H), 2.94 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.61, 147.49, 134.74, 112.76, 111.81, 106.81, 101.74, 84.50, 73.50, 54.21.; HRMS (ESI-TOF) *m/z* (M + Na)$^+$ calcd for $C_{20}H_{16}^{79}Br_2O_6Na^+$/$C_{20}H_{16}^{79}Br^{81}BrO_6Na^+$/$C_{20}H_{16}^{81}Br_2O_6Na^+$ 532.9206, 534.9186 and 536.9165; found 532.9202, 534.9188 and 536.9164, respectively.

4.3. Synthesis of (+)-sesamin 1

To an oven dried two-necked RB was added compound **9** (0.08 g, 0.157 mmol) in DMF (0.8 mL). HCO_2Na (0.053 g, 0.78 mmol) was added to that solution. Argon was flushed for 10 times into this mixture. Pd_2dba_3 (0.0072 g, 0.0078 mmol) was added then and argon was flushed for additional 3 times. The mixture was heated to 80 °C for 12 h. After completion of the reaction, water (25 mL) was added to that. The aqueous part was extracted with EtOAc (3 × 35 mL). The combined organic layer was washed with brine, dried over Na_2SO_4. Solvent evaporation under *vacuum* gave the crude product which was purified by column chromatography (0.053 g 96%). R_f 0.35 (Hexanes/EtOAc 9:1); $[\alpha]_D^{27}$ = +68 (c = 0.5 $CHCl_3$) [lit [6f]. +68.9 in $CHCl_3$]; mp 124–126 °C [lit[8]. 122–123 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 6.81 (d, AB type, J = 8.5 Hz, 2H), 6.78 (d, AB type, J = 8.5 Hz, 2H), 5.96 (s, 4H), 4.72 (d, J = 3.4 Hz, 2H), 4.24 (pseudo t, J = 7.6 Hz, 2H), 3.88 (dd, J = 9.3, 3.1 Hz, 2H), 3.06 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.93, 147.08, 134.98, 119.36, 108.17, 106.48, 101.06, 85.77, 71.68, 54.29; HRMS (ESI-TOF) *m/z* (M + Na)$^+$ calcd for $C_{20}H_{18}O_6Na^+$ 377.0980; found 377.1001.

4.4. Synthesis of 5-bromo-6-((1S,3aR,4S,6aR)-4-(3,4,5-trimethoxyphenyl)tetrahydro-1H,3H-furo[3,4-c]furan-1-yl)benzo[d][1,3]dioxole 11

Step 1: To an oven dried two-necked RB was added TBS-lactone **3** (0.1 g, 0.23 mmol) in THF (2 mL). It was cooled to −78 °C. LiHMDS (0.28 mL, 0.28 mmol, 1 M in THF) was added to it and stirred for 45 m. 3, 4, 5-trimethoxybenzaldehyde **4b** (0.063 g, 0.32 mmol) in THF (1 mL) was added to the reaction mixture and stirred for additional 6 h at the same temperature. After completion of the reaction the reaction was quenched by 1M AcOH solution in THF. The temperature of the mixture was then raised to room temperature. It was diluted with H_2O (20 mL). The aqueous part was extracted with EtOAc (3 × 35 mL). The combined organic layer was washed with brine (10 mL) and was dried over Na_2SO_4. The solvent was evaporated under *vacuum* to afford the crude aldol product as a gummy yellow liquid. It was triturated before using for the Step 2 without further

purification (0.176 g crude weight). HRMS (ESI-TOF): *m/z* $(M + Na)^+$ calcd for $C_{28}H_{37}^{79}BrO_9SiNa^+$ 649.1267; found 649.1215.
Step 2: To the THF (1 mL) solution of the above aldol compound was added to *in situ* generated $CaBH_4$ ($CaCl_2$ 0.153 g, 1.38 mmol; $NaBH_4$ 0.105 g, 2.76 mmol) in THF/MeOH (1:1; 2 mL) at 0 °C. It was allowed to stir at room temperature for 6 h. At this stage, the mass spectroscopy analysis showed the complete conversion to tri-ol. The reaction was quenched with solid NH_4Cl and then filtered through celite pad. The filtrate was collected. The solvent was evaporated out under *vacuum* to afford the *O*-TBS-tetraol as a colourless gummy liquid (0.16 g). HRMS (ESI-TOF): *m/z* $(M + Na)^+$ calcd for $C_{28}H_{41}^{79}BrO_9SiNa^+$ 651.1601; found 651.1525.
Step 3. Synthesis of compound **11**: To the THF (1 mL) solution of the above crude tetraol was added 50% aqueous HCl (2 mL) at 0 °C and then raised it to room temperature. The reaction was stirred for an additional 48 h. The whole mixture was diluted with H_2O (20 mL) and the aqueous layer was extracted with EtOAc (3 × 35 mL). The combined organic layer was washed with brine, dried over Na_2SO_4. Solvent evaporation under *vacuum* gave the crude product which was purified by column chromatography (Hexanes/EtOAc 8:2) and afforded the compound **11** as a yellowish solid (0.069 g. 62% over three steps). R_f 0.4 (Hexanes/EtOAc 4:1); $[\alpha]_D^{20} = +17$ (c = 0.51 $CHCl_3$); mp 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.96 (s, 1H), 6.58 (s, 2H), 5.98 (d, J = 3.5 Hz, 2H), 5.10 (d, J = 3.8 Hz, 1H), 4.67 (d, J = 6.0 Hz, 1H), 4.50 (pseudo t (dd), J = 8.5 Hz, 1H), 4.28 (dd, J = 9.2, 6.6 Hz, 1H), 4.11 (dd, J = 9.3, 5.7 Hz, 1H), 4.03 (dd, J = 9.3, 3.9 Hz, 1H), 3.88 (s, 6H), 3.84 (s, 3H), 3.11–2.92 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 147.6, 147.5, 137.4, 136.5, 134.8, 112.9, 111.9, 106.6, 102.8, 101.8, 85.6, 85.5, 74.1, 71.7, 60.8, 56.1, 54.6, 54.; HRMS (ESI-TOF): *m/z* $(M + Na)^+$ calcd for $C_{22}H_{23}^{79}BrO_7Na^+$/$C_{22}H_{23}^{81}BrO_7Na^+$ 479.0700 and 481.0680; found 479.0695 and 481.0682, respectively.

4.5. Synthesis of (+)-aschantin 2

To an oven dried two-necked RB were added compound **11** (0.06 g, 0.12 mmol) and HCO_2Na (0.041 g, 0.6 mmol) in DMF (0.6 mL). Argon was flushed for 10 times into this mixture. Pd_2dba_3 (0.005 g, 0.044 mmol) was added then and argon was flushed for additional 3 times. The mixture was heated to 80 °C for 12 h. After completion of the reaction, water (20 mL) was added to that. The aqueous part was extracted with EtOAc (3 × 35 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent evaporation under *vacuum* gave the crude product which was purified by column chromatography (Hexanes/EtOAc 8:2) and gave aschantin 2 as a colourless solid (0.53 g, 91%). R_f 0.25 (Hexanes/EtOAc 4:1); $[\alpha]_D^{27} = +64.1$ (c = 0.32 $CHCl_3$) [lit [6c]. +65 in $CHCl_3$]; mp 122–124 °C [lit [6c]. 122 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.82 (d, J = 8 Hz, 1H), 6.79 (d, J = 8 Hz, 1H), 6.58 (s, 2H), 5.96 (s, 2H), 4.75–4.70 (m, 2H), 4.28 (td, J = 9.5, 6.0 Hz, 2H), 3.93–3.90 (m, 2H), 3.88 (s, 6H), 3.85 (s, 3H), 3.08 (q, J = 5.0, 4.1 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 147.6, 147.5, 137.4, 136.5, 134.8, 112.9, 111.9, 106.6, 102.8, 101.8, 85.6, 85.5, 74.1, 71.7, 60.8, 56.1, 54.6, 54.; HRMS (ESI-TOF): *m/z* $(M + H)^+$ calcd for $C_{22}H_{25}O_7^+$ 401.1600; found 401.1593.

4.6. Gram-scale chromatography-free 'two-pots' total synthesis of (+)-sesamin 1

First-Pot: To an oven dried two-necked RB was added TBS-lactone **3** (2 g, 4.65 mmol) in THF (30 mL). It was cooled to −78 °C. LiHMDS (5.58 mL, 5.58 mmol, 1 M in THF) was added to it and stirred for 45 min. 6-bromopiperonal **4a** (1.12 g, 4.88 mmol) in THF (5 mL) was added to the reaction mixture and stirred for additional 6 h at the same temperature. After complete consumption of the TBS Lactone, it was allowed to warm to 0 °C and then the reaction mixture was quenched by 1M AcOH solution in THF. To this reaction mixture was added to *in situ* generated $CaBH_4$ ($CaCl_2$ 3.1 g, 27.9 mmol; $NaBH_4$ 2.12 g, 55.8 mmol) in THF/MeOH (1:1, 15 mL) at 0 °C. It was allowed to stir at room temperature for 6 h. At this stage, the mass spectroscopy analysis showed the complete conversion to tri-ol. The reaction was quenched with solid NH_4Cl and then filtered through celite pad. The filtrate was collected and the volume was reduced to 5 mL under *vacuum*. It was then cooled to 0 °C. 50% aqueous HCl (20 mL) was added to it. The reaction mixture was then allowed to stir at room temperature for 48 h. The whole mixture was diluted with H_2O (50 mL) and cooled to 10 °C. The white precipitate formed was filtered out and dried to get the compound **9** as a white solid (1.6 g, 66%). It was taken directly for the next reaction without further purification.

Second-Pot: To an oven dried two-necked RB was added compound **9** (1.6 g, 3.12 mmol) in DMF (14 mL). HCO_2Na (1.06 g, 15.6 mmol) was added to that solution. Argon was flushed for 10 times into this mixture. Pd_2dba_3 (0.142 g, 0.156 mmol) was added then and argon was flushed for additional 3 times. The mixture was heated to 80 °C for 12 h. After completion of the reaction, it was cooled to room temperature and then diluted with EtOAc (250 mL). The mixture was then filtered over a celite bed. The filtrate was collected. The solvent was evaporated out under *vacuum*. The crude obtained was crystallized from diethylether to afford the (+)-sesamin as a white solid (1.06 g, 96%). R_f 0.35 (Hexaness/EtOAc 9:1); $[\alpha]_D^{27} = +68$ (c = 0.5 $CHCl_3$) [lit [6f]. +68.9 in $CHCl_3$]; mp 124–126 °C [lit [8]. 122–123 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 6.81 (d, AB type, J = 8.5 Hz, 2H), 6.78 (d, AB type, J = 8.5 Hz, 2H), 5.96 (s, 4H), 4.72 (d, J = 3.4 Hz, 2H), 4.24 (pseudo t (dd), J = 7.6 Hz, 2H), 3.88 (dd, J = 9.3, 3.1 Hz, 2H), 3.06 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.93, 147.08, 134.98, 119.36, 108.17, 106.48, 101.06, 85.77, 71.68, 54.29; HRMS (ESI-TOF): *m/z* [$(M + Na)^+$ calcd for $C_{20}H_{18}O_6Na^+$ 377.1001; found 377.0984.

4.7. Gram-scale chromatography-free 'two-pot' total synthesis of (+)-aschantin 2

First-Pot: To an oven dried two-necked RB was added TBS-lactone **3** (2 g, 4.65 mmol) in THF (30 mL). It was cooled to −78 °C. LiHMDS (5.58 mL, 5.58 mmol, 1 M in THF) was added to it and stirred for 45 m. 3, 4, 5-trimethoxybenzaldehyde 5b (0.957 g, 4.88 mmol) in THF (5 mL) was added to the reaction mixture and stirred for additional 6 h at the same temperature. After completion of the reaction it was allowed to warm at 0 °C and then the reaction mixture was quenched by 1M AcOH solution in THF. To this reaction mixture was added to *in situ* generated $CaBH_4$ ($CaCl_2$ 3.1 g, 27.9 mmol; $NaBH_4$ 2.12 g, 55.8 mmol) in THF/MeOH (1:1; 15 mL) at 0 °C. It was allowed to stir at room temperature for 6 h. At this stage, the mass spectroscopy analysis showed the complete conversion to tri-ol. The reaction was quenched with solid NH_4Cl and then filtered through celite pad. Filtrate was collected and volume was reduced to 5 mL and keep at 0 °C and then 50% aqueous HCl (20 mL) was added to that and transferred it to room temperature and stirred for an additional 48 h. After completion of the reaction the whole mixture was diluted with H_2O (50 mL) and then cooled to 10 °C. The precipitate formed was filtered out to get the crude compound as a yellowish white solid. It was used for the next reaction without further purification (1.27 g. 57%).

Second-Pot: To an oven dried two-necked RB were added compound **11** (1.27 g, 2.65 mmol) and HCO_2Na (0.54 g 7.95 mmol) in DMF (5 mL). Argon was flushed for 10 times into this mixture.

Pd_2dba_3 (0.12 g 0.132 mmol) was added then and argon was flushed for additional 3 times. The mixture was heated to 80 °C for 12 h. After completion of the reaction, it was cooled to room temperature and then diluted with EtOAc (250 mL). The mixture was then filtered over a celite bed. The filtrate was collected. The solvent was evaporated out under vacuum. The crude obtained was crystalized from diethylether/hexaness to afford the title compound as a white solid (0.93 g, 91%). R_f 0.25 (Hexanes/EtOAc 4:1); $[\alpha]_D^{27}$ = +64.1 (c = 0.32 $CHCl_3$) [lit [6c]. +65 in $CHCl_3$] mp 122–124 °C [lit [6c]. 122 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.82 (d, J = 8 Hz, 1H), 6.79 (d, J = 8 Hz, 1H), 6.58 (s, 2H), 5.96 (s, 2H), 4.75–4.70 (m, 2H), 4.28 (td, J = 9.5, 6.0 Hz, 2H), 3.93–3.90 (m, 2H), 3.88 (s, 6H), 3.85 (s, 3H), 3.08 (q, J = 5.0, 4.1 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 147.6, 147.5, 137.4, 136.5, 134.8, 112.9, 111.9, 106.6, 102.8, 101.8, 85.6, 85.5, 74.1, 71.7, 60.8, 56.1, 54.6, 54.; HRMS (ESI-TOF): *m/z* $[(M + H)^+$ calcd for $C_{22}H_{25}O_7^+$ 401.1600; found 401.1604.

4.8. Synthesis of (1S,3aR,4S,6aR)-1,4-bis(6-phenylbenzo[d][1,3] dioxol-5-yl)tetrahydro-1H,3H-furo[3,4-c]furan 12

To a 10 mL oven dried double neck RB flask was added compound **9** (0.05 g, 0.098 mmol) in 1,4- dioxane: H_2O (9:1) (2.0 mL) under argon. Pd_2dba_3 (0.018 g, 0.019 mmol), K_3PO_4 (0.084 g, 0.392 mmol), tricyclohexylphosphine (0.011g, 0.039 mmol) and phenylboronic acid (0.028 g, 0.235 mmol) were subsequently added. The reaction mixture was then degassed with argon following freeze-pump-thaw technique. It was then heated to 100 °C on a preheated oil-bath for 8 h. Upon completion of the reaction, water (20 mL) was added and the organic mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (20 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product obtained was purified by column chromatography to afford the title compound (yield 0.041 g; 82%) as a white solid. mp 178–180 °C. R_f 0.25 (Hexanes/EtOAc 7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.32 (m, 6H), 7.23 (d, J = 7.2 Hz, 4H), 6.90 (s, 2H), 6.68 (s, 2H), 5.96 (s, 4H), 4.73 (d, J = 3.4 Hz, 2H), 3.70 (dd, J = 9.2, 6.6 Hz, 2H), 3.14 (dd, J = 9.2, 4.0 Hz, 2H), 2.77 (d, J = 3.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 146.4, 140.8, 134.8, 133.0, 129.4, 128.4, 127.2, 110.3, 105.8, 101.1, 82.7, 72.0, 55.0. HRMS (ESI-TOF): *m/z* $(M + Na)^+$ calcd for $C_{22}H_{22}O_9Na^+$ 529.1627; found 529.1619.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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