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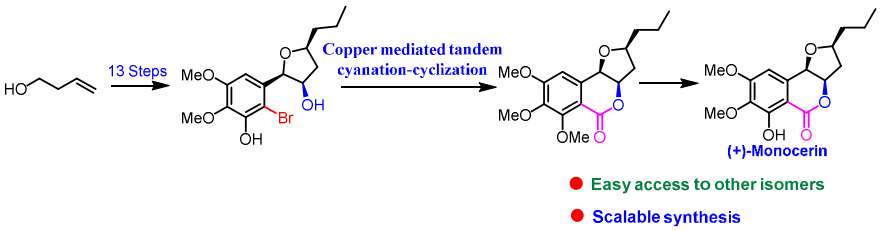

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A simple and novel synthesis of (+)-monocerin was achieved in 15 steps and 15.5% overall yield from 3-buten-1-ol employing hydrolytic kinetic resolution, Julia olefination, intramolecular tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization and a novel copper mediated tandem cyanation-cyclization as the key steps.

Introduction

Natural products symbolize the significant portion of current drug market and they play a crucial role in the discovery of new drug therapies. Hence total synthesis of biologically active natural products is a constant challenge for many scientists in the area of drug discovery around the globe. Monocerin **1** and its analogues are polyketide natural products[1] which are attractive synthetic targets due to their fascinating architecture (Figure 1). Monocerin was first isolated by Aldridge *et al*. in 1970 from the culture filtrates of *Helminthosporium monoceras* as a anti-powdery mildew (Erisyphe graminis) of wheat.[2] In 1979, Grove and co-workers noticed monocerin as an insecticidal constituent of the entomogenous fungus Fusarium larvarum Fukel.[3] Later on monocerin, dihydroisocoumarins and their analogues (Figure 1) were isolated from several other fungal species[3,4] exhibiting a broad spectrum of biological activities like antifungal,[4a] phytotoxic,[4b] plant pathogenic[4c] and insecticidal activity.[5]

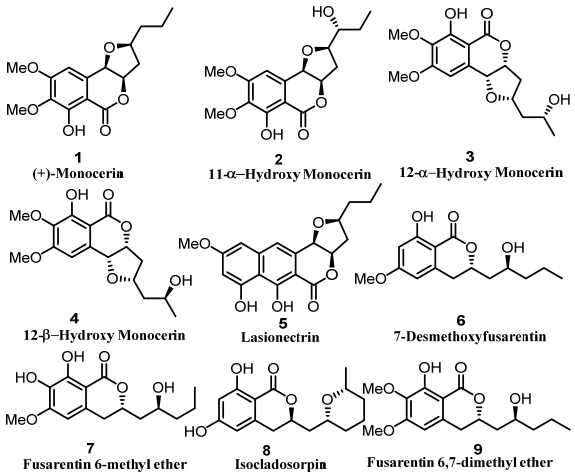


Figure 1. Polyketide (**1**,**2**,**3**,**4**,**5**) and dihydroisocoumarin (**6**,**7**,**8**,**9**) natural products

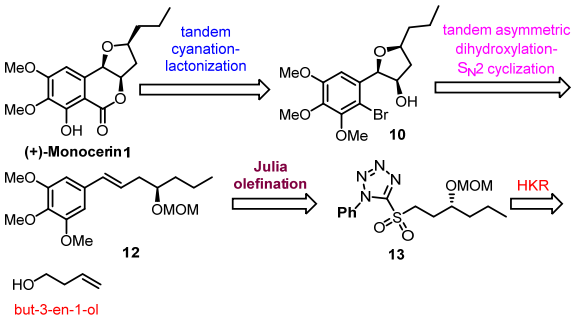
In 2008, Sriubolmas and co-workers identified the antiplasmodial activity[6] of monocerin 1 (IC_{50} value of 0.68 μM) against the multidrug-resistant K1 strain of *Plasmodium Falciparum.* Monocerin and its analogues were proved to be non specific toxic and nonspecific inhibitor of seed germination by interference with selected stages of the cell division cycles.[7] Its structure contains a 4-oxyisochroman-1-one skeleton and a 2,3,5-trisubstituted tetrahydrofuran, which are fixed with all-cis stereochemistry.

While the first synthesis of monocerin was reported by Mori *et al.* in 1989,[8] the Simpson group subsequently described its biomimetic synthetic path way.[9] In recent years monocerin and its analogues have attracted a great deal of interest, consequently several syntheses of this molecule were reported.[10] While She *et al*. reported its synthesis via an intramolecular nucleophilic trap of a quinonemethide intermediate through benzylic oxidation using PIFA,[10a] Lee and co- workers described its synthesis through radical cyclization of a vinylic ether.[10b]

We, herein report a simple and efficient synthesis of (+)-monocerin employing hydrolytic kinetic resolution, Julia-Kochienski olefination, intramolecular tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization and novel copper-mediated tandem cyanation-lactonization of a substituted bromo benzene derivative as the key steps.

Results and Discussion

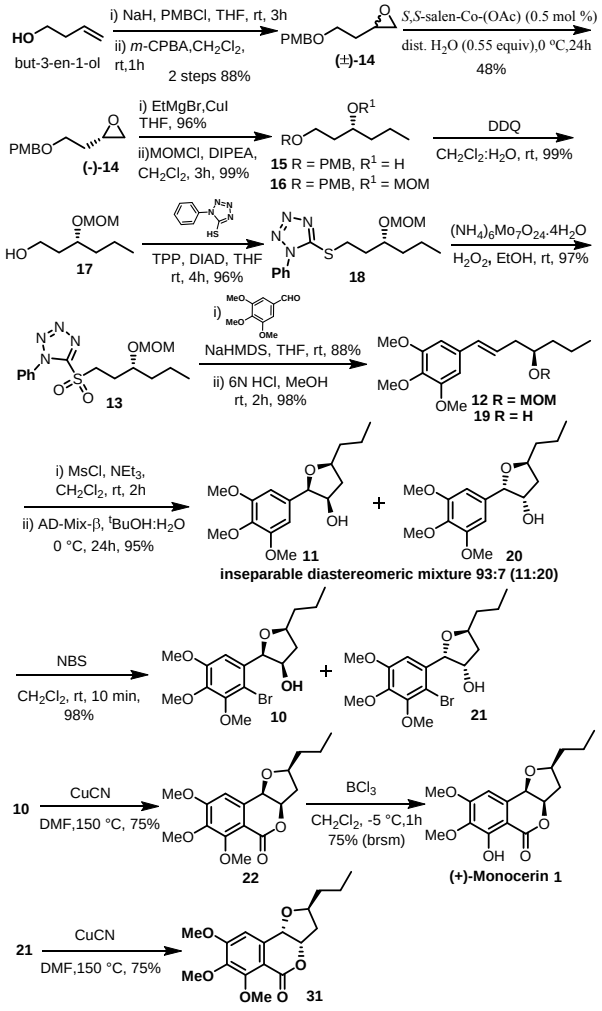
The retrosynthetic analysis of (+)-monocerin **1** is visualized based on the linear approach as outlined in Scheme 1. We envisioned that the target molecule **1** could be prepared by tandem



Scheme 1. Retrosynthetic route to (+)-monocerin

cyanation-cyclization of a substituted tetrahydrofuran alcohol **10** which could be derived via tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization of olefin **12**. The olefin **12** could be prepared by Julia–Kocienski olefination reaction between trimethoxy benzaldehyde and sulfone **13.** Compound **13** in turn could be derived from commercially available 3-buten-1-ol via hydrolytic kinetic resolution.

As illustrated in scheme 2, our synthesis began with the commercially available 3-buten-1-ol. This upon hydroxy group protection using PMBCl followed by oxidation using *m*CPBA gave (±)-**14**, which was subjected to Jacobsen's HKR[11] protocol using (*S*,*S*)-salen-Co^{III}(OAc) catalyst to give the enantiopure epoxide (-)-**14**[12] and diol. The epoxide ring opening[12,13] with ethyl magnesium bromide ((-)-**14**→**15**) followed by protection of hydroxy group with MOM chloride using diisopropylethylamine as a base gave the MOM ether **16** in almost quantitative yield. Subsequent oxidative removal of 4-methoxy benzyl group with DDQ afforded the alcohol **17** in excellent yield.

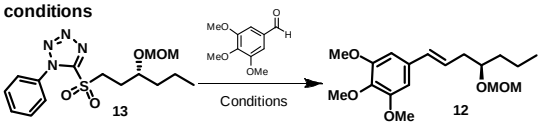


Scheme 2. Total synthesis of (+)-Monocerin **1** and formal synthesis of its stereoisomer **31**

Next, we sought to synthesize the olefin fragment **12.** Initially we attempted at the Horner-Wittig reaction of 3,4,5-trimethoxy phenylmethylenephosphonate with aldehyde derived from **17** under various conditions to obtain **12.** For example, use of different bases such as NaH (1.5 to 6 equiv), n-BuLi, KO^{t}Bu and NaHMDS (2 equiv) etc. to bring the above transformation was a total failure. Raising the temperature from 0 °C to rt and reflux temperature in various solvents such as THF or DMF also did not work.

Hence we modified the strategy and proceeded with Julia-Kocienski olefination reaction to obtain the required olefin **12**. Thus the primary alcohol **17** was converted to sulfide **18** under Mitsunobu conditions using 1-phenyl-1*H*-tetrazole-5-thiol as a nucleophile in the presence of TPP/DIAD. Oxidation of sulfide **18** with ammonium heptamolybdate and H_2O_2 afforded sulfone **13.**[14] Having sulfone **13** in hand we wanted to optimize the Julia–Kocienski[15] olefination conditions screening various bases such as KHMDS, NaHMDS under prematallate conditions at -78 °C to 0 °C. However under none of above conditions the product formation could be observed. Then we switched over to the Barbier conditions using NaHMDS as a base at -78 °C to 0 °C, however it gave only 10% of the desired product. Notably increasing the temperature from -78 °C to rt under Barbier conditions resulted in improvement of yields up to 30%. Eventually, further raising the temperature from 0 °C to rt, afforded the desired product **12** in 88% yield (Table 1).

Table 1. Optimization of Julia-Kocienski olefination reaction conditions



S.No	Reaction Condition	yield (%)	*E:Z*
1.	Prematellate[a] KHMDS, THF,-78 °C	No reaction	-
2.	Prematellate KHMDS, THF,-78 °C to 0 °C	No reaction	-
3.	Prematellate NaHMDS, THF,-78 °C to rt	No reaction	-
4.	Prematellate NaHMDS, THF, 0 °C to rt	No reaction	-
5.	Barbier[b] NaHMDS, THF,-78 °C to 0 °C	10%[c]	*E* only
6.	Barbier NaHMDS, THF,-78 °C to rt	30%[c]	*E* only
7.	**Barbier NaHMDS, THF, 0 °C to rt**	**88%[c]**	***E* only**

[a] base first added to sulfone followed by aldehyde addition, [b] base added to a mixture of sulfone and aldehyde [c]isolated yield

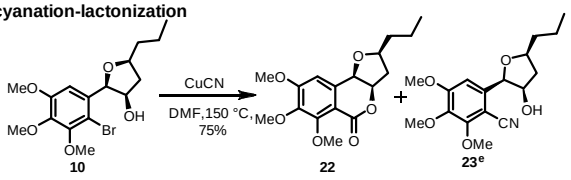
Compound **12** was subjected to MOM deprotection with 6 N HCl to give the alcohol **19** in 98% yield. Now the stage was set for the synthesis of *cis*- substituted tetrahydrofuran hydroxyl compound **11** via intramolecular tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization following Marshall's protocol.[12a] Thus the alcohol **19** was converted into its mesylate followed by Sharpless asymmetric dihydroxylation[16] using AD-mix-β in ^{t}BuOH/H_2O (1:1) to afford the inseparable mixture of key *cis* and *trans*-substituted tetrahydrofuran **11** and **20** (93:7) respectively in 95% yield. The formation of major cis-substituted tetrahydrofuran alcohol thus obtained could be attributed to the well-established steric preference of the AD-mix reagents and presumed S_N2 nature of cyclization reaction leading to the inversion of configuration at the reacting centre. The results obtained are analogous to those reported in a preliminary

communication,[12a] by Marshall *et al*. where the synthesis of *cis* and *trans*- 2,5-disubstituted and 2,3,5-trisubstituted tetrahydrofuran was achieved from δ and ε–mesyloxy α, β-unsaturated esters by tandem dihydroxylation and in situ S_N2 cyclization sequence. It may be pertinent to mention here that this protocol is amenable to the other stereoisomers of monocerin by simply taking the (*R*)-enantiomer of epoxide **14** and changing the ligand in the dihydroxylation step. Selective aromatic bromination of **11** & **20** with NBS in CH_2Cl_2 afforded the bromobenzene derivatives **10** & **21** in 98% yield. At this stage the two diastereomers could be separated easily by silica gel column chromatography.

Our next task was to convert bromo compund **10** into the corresponding cyano using CuCN in DMF[17] at reflux temperature conditions followed by acid mediated cyclization[18] to give the desired product **22**. Initially the formation of desired product **22** was not observed by attempting the reaction of **10** with CuCN (1.0 equiv.) in DMF at 100 °C and only the starting material was recovered (Table 2, entry 1).

Surprisingly, when the reaction was carried out at 150 °C, instead of the expected product **23**, the cyclized product **22** was directly obtained albeit in low yield (Table 2, entry 2)**.** This provided incentive for an extensive study to explore the copper-mediated tandem cyanation-lactonization of **10.** To improve the yield, when 2 equiv of CuCN was used, we could isolate compound **22** in moderate yield (Table 2, entry 3). When the same reaction was carried out with 3 equiv of CuCN at 150 °C, the desired cyclized product **22** was obtained in 75% yield (Table 2, entry 4).

Table 2. Optimization for copper cyanide mediated tandem cyanation-lactonization



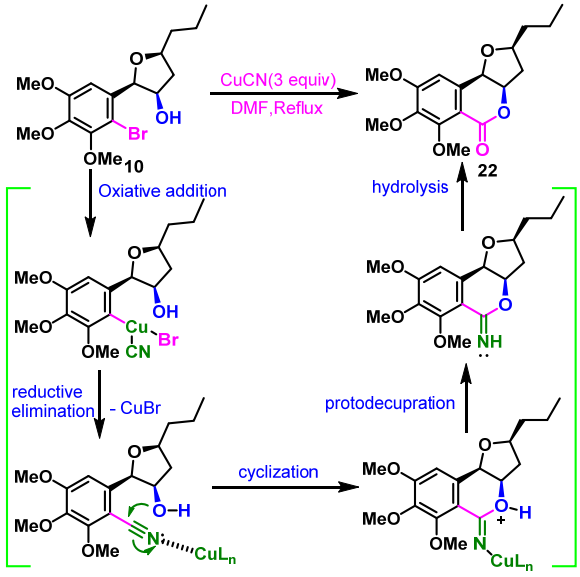
S.No	Equivalents of CuCN	temperature	Yield[a](%)(22)
1.	1	100 °C	0[b]
2.	1	150 °C	22%[c]
3.	2	150 °C	46%[d]
4.	**3**	**150 °C**	**75%**

[a]isolated yield,[b]Quantitative recovery of the starting material.[c,d]Recovery of most of the starting material.[e]no cyano product was observed

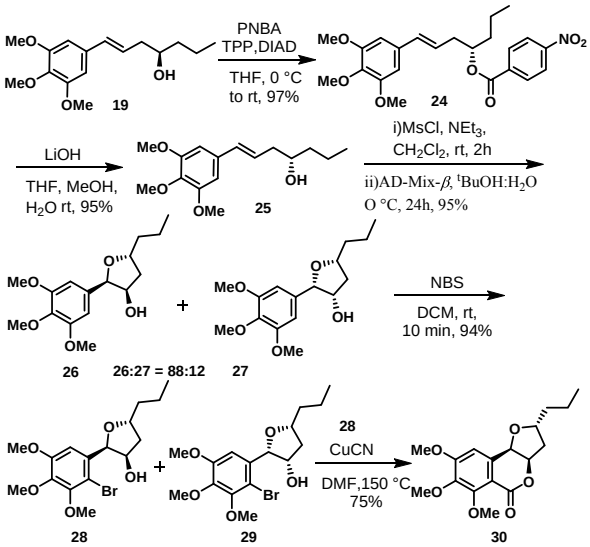
To the best of our knowledge, there has been no reports of the synthesis of 6-membered lactone ring through copper-mediated tandem cyanation-cyclization of a substituted bromo benzene tetrahydrofuran alcohol.

Mechanistically, the reaction is expected to proceed via the formation of oxidative addition of aryl bromide with copper cyanide followed by reductive elimination to give the cyano intermediate. This on further coordination with copper as Lewis acid facilitates the attack of alcoholic group. Subsequent protodecupration and hydrolysis eventually leads to the desired cyclized product **22** (Scheme 3).

Finally selective demethylation of methoxy group from **22** using boron trichloride gave the target molecule monocerin **1** in 75% yield. In the same manner, we have also accomplished the formal synthesis of (*S*,*S*,*S*) and (*R*,*R*,*R*) isomers of monocerin **31** & **30** respectively (Schemes 2 & 4). In our method, the synthesis of target molecule **1** was accomplished in 15 steps in an overall 15.5% yield. Our synthesis of **1** proved to be an efficient in comparison with literature reports (Mori *et al.*[8] 14 steps, 6.6% yield; She *et al.*[10a] 12 steps, 12.25% yield; Lee *et al.*[10b] 10 steps, 7.7% yield; Stephen *et al.*[10c] 8 steps, 6.5% yield; Fang *et al.*[10d] 11 steps 5% yield).



Scheme 3. Plausible mechanism for Copper mediated tandem cyanation-lactonization



Scheme 4: Formal synthesis of (2*R*,3a*R*,9b*R*)-6,7,8-trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5*H*-furo[3,2-*c*]isochromen-5-one **30**

Conclusions

In summary we have developed a novel copper mediated tandem cyanation-cyclization method for the synthesis of (+)-monocerin

and its stereoisomers. The present method is applicable for the preparation of polyketide and dihydroisocoumarin natural products containing lactone moiety through the intramolecular carbonylative coupling of aryl halide and alcohol. Our approach is suitable for the large-scale synthesis of **1** and its analogues. Currently synthesis of other analogues of monocerin such as 11-hydroxy monocerin and 12-hydroxy monocerin is under progress in our laboratory.

Experimental Section:

2-(2-((4-Methoxybenzyl)oxy)ethyl)oxirane (±)-14:

To a stirred solution of but-3-en-1-ol (5.0 g, 69.33 mmol) in THF (100 mL) was added NaH (4.0 g, 90.14 mmol) at 0 °C and stirred well for 20 min at rt. Then PMBCl (11.8 ml, 83.22 mmol) was added to the reaction mixture at 0 °C followed by addition of TBAI (2.5 g, 6.9 mmol) and stirred at rt for 3h. The reaction mixture was quenched with ice water and extracted with EtOAc (3 x 50 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using (petroleum ether:EtOAc, 91:9) as eluent provided the PMB protected compound (12.8 g, 96%) yield as a colourless liquid. ^{1}H NMR (200MHz, $CDCl_3$) d 7.36 - 7.25 (m, 2 H), 6.97 - 6.85 (m, 2 H), 5.86 (tdd, *J* = 6.7, 10.3, 17.1 Hz, 1 H), 5.20 - 5.01 (m, 2 H), 4.48 (s, 2 H), 3.83 (s, 3 H), 3.52 (t, *J* = 6.8 Hz, 2 H), 2.39 (tq, *J* = 1.3, 6.7 Hz, 2 H); ^{13}C NMR (125MHz, $CDCl_3$) d 159.1, 135.3, 130.5, 129.2, 116.3, 113.7, 72.5, 69.3, 55.2, 34.2.

To a stirred solution of above compound (12.0 g, 62.4 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added *m*-CPBA (50%) (32.31 g, 93.62 mmol).The reaction mixture was stirred at room temperature for 1h and quenched by saturated Na_2CO_3 solution, extracted with CH_2Cl_2,washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using (petroleum ether:EtOAc, 9:1) as eluent to yield the epoxide (±)-**14** (11.9 g, 92%) as a colourless liquid. ^{1}H NMR (200MHz, $CDCl_3$) d 7.35 - 7.22 (m, 2 H), 6.96 - 6.85 (m, 2 H), 4.49 (s, 2 H), 3.83 (s, 3 H), 3.68 - 3.56 (m, 2 H), 3.15 - 3.03 (m, 1 H), 2.85 - 2.76 (m, 1 H), 2.54 (dd, *J* = 2.8, 5.1 Hz, 1 H), 2.03 - 1.69 (m, 2 H).

(*S*)-2-(2-((4-Methoxybenzyl)oxy)ethyl)oxirane (-)-14:

Epoxide (±)-**14** (6 g, 28.83 mmol) and (*S,S*)-salen-Co(III)-OAc (95.7 mg, 0.0144 mmol) in isopropyl alcohol (0.285 ml) was stirred at 0 °C for 5 min, and then distilled water (0.285 ml, 15.84 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using petroleum ether : EtOAc (9:1) to afford (-)-**14** (2.88 mg, 48%) as a yellow colour syrupy liquid Continued chromatography with petroleum ether : EtOAc (1:1) provided the diol as a brown coloured liquid. $[\alpha]_D^{27}$: -13.1 (*c* 1.0, $CHCl_3$) {lit.[19] $[\alpha]_D^{26}$: −13.9° (*c* 1.0, $CHCl_3$)}; IR (neat ,cm^{-1}) : ν_{max} 2997, 2924, 1611, 1511, 1416, 1316, 1243, 1174, 1088, 906, 817, 753, 709; ^{1}H NMR (200 MHz , $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 4.47 (s, 2 H), 3.82 (s, 3 H), 3.67 - 3.54 (m, 2 H), 3.16 - 2.96 (m, 1 H), 2.79 (t, *J* = 4.5 Hz, 1 H), 2.53 (dd, *J* = 2.7, 4.9 Hz, 1 H), 2.03 - 1.70 (m, 2 H);^{13}C NMR (50 MHz , $CDCl_3$) δ 159.2, 130.3, 129.2, 113.8, 72.7, 66.7, 55.2, 50.1, 47.1, 32.9; HRMS (ESI) for $C_{12}H_{16}O_3Na$ $(M + Na)^+$ found 231.0992, calcd 231.0992.

(*R*)-1-((4-Methoxybenzyl)oxy)hexan-3-ol 15:

To a stirred solution of epoxide (-)-**14** (2.0 g, 9.61 mmol) and CuI (183 mg, 0.961mmol) in dry THF (60 mL), was added, 1M solution of ethyl magnesium bromide in THF (14.4 ml, 14.4 mmol, 1M solution in THF) drop-wise at 0 °C and stirred for 1h. The mixture was quenched with a saturated NH_4Cl solution (5 mL). The layers were separated, the aqueous layer extracted with EtOAc (3x10 mL), the combined organic extracts were washed with brine (2x5 mL), followed by 25% NH_4OH solution (5 ml) and dried over Na_2SO_4, evaporated to dryness and silica gel column chromatographic purification (petroleum ether:EtOAc, 89:11) of the crude product gave **15** (2.2 g, 96%) as a yellow colour oil. $[\alpha]_D^{26}$: + 8.41° (*c* 0.53, $CHCl_3$); IR (neat, cm^{-1}) : ν_{max} 3444, 2956, 1612, 1512, 1245, 1085, 1032, 817, 707; ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.32 - 7.20 (m, 2 H), 6.96 - 6.83 (m, 2 H), 4.46 (s, 2 H), 3.81 (s, 4 H), 3.74 - 3.57 (m, 2 H), 3.00 - 2.81 (m, 1 H), 1.80 - 1.66 (m, 2 H), 1.55 - 1.24 (m, 4 H), 1.03 - 0.81 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.2, 137.5, 129.5, 127.3, 96.1, 77.6, 76.4, 58.3, 54.7, 35.4, 32.4, 25.0, 23.2, 21.5; HRMS (ESI) for $C_{14}H_{22}O_3Na$ $(M + Na)^+$ found 261.1461, calcd 261.1461.

(*R*)-1-Methoxy-4-(((3 methoxymethoxy)hexyl)oxy) methyl)benzene 16:

To a solution of alcohol **15** (2.0 g, 8.4 mmol) in dry CH_2Cl_2 (40 mL) was added diisopropylethylamine (3.12 mL, 17.64 mmol) at 0 °C. To this mixture MOM chloride (0.94 ml, 12.6 mmol) was added slowly with further stirring for 2h at the room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL), brine, dried over Na_2SO_4 and concentrated to give crude **16**. It was purified by silica gel column chromatography using (petroleum ether-EtOAc, 93:7) as eluent to furnish **16** as colourless oil (2.34 g, 99%); $[\alpha]_D^{27}$: -4.39° (*c* 1.02, $CHCl_3$); IR (neat, cm^{-1}) : $\nu_{max.}$ 2933, 1512, 1246, 1138, 1034, 951, 821, 750, 606; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (br. s., 2 H), 6.88 (d, *J* = 8.2 Hz, 2 H), 4.64 (s, 2 H), 4.44 (s, 2 H), 3.81 (s, 3 H), 3.71 (t, *J* = 5.6 Hz, 1 H), 3.54 (t, *J* = 6.4 Hz, 2 H), 3.37 (s, 3 H), 1.85 - 1.75 (m, 2 H), 1.54 - 1.32 (m, 4 H), 0.92 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 130.5, 129.3, 113.7, 95.7, 74.9, 72.6, 66.7, 55.5, 55.3, 37.0, 34.7, 18.4, 14.2; HRMS (ESI) for $C_{16}H_{26}O_4Na$ $(M + Na)^+$ found 305.1723, calcd 305.1723.

(*R*)-3-(Methoxymethoxy)hexan-1-ol 17:

To a solution of PMB ether **16** (2.0 g, 7.08 mmol) in dry CH_2Cl_2 : H_2O (38:2) mL was added DDQ (1.93 g, 8.5 mmol) at 0 °C with further stirring for 2h at the room temperature. The reaction mixture was quenched with addition of cold water, stirred for 30 min then sat.$NaHCO_3$ solution was added, stirred for 30 min.

Then filtered through celite. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with sat.$NaHCO_3$ (2x15 mL), brine, dried over Na_2SO_4 and concentrated to give crude **17**. It was purified by silica gel column chromatography using petroleum ether-EtOAc (86:14) as eluent to furnish **17** as a yellow colour oil (1.12 g, 99%). $[\alpha]_D^{27}$: - 58.22° (*c* 1.08, $CHCl_3$); IR (neat, cm^{-1}) : ν_{max}. 3385, 2956, 2933, 1095, 1029, 915; ^1H NMR (500 MHz, $CDCl_3$) δ 4.70 (d, *J* = 6.7 Hz, 1 H), 4.66 (d, *J* = 7.0 Hz, 1 H), 3.86 - 3.70 (m, 3 H), 3.41 (s, 3 H), 2.15 - 1.91 (m, 1 H), 1.86 - 1.79 (m, 1 H), 1.73 - 1.65 (m, 1 H), 1.62 - 1.55 (m, 1 H), 1.53 - 1.45 (m, 1 H), 1.41 - 1.32 (m, 2 H), 0.93 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 95.9, 76.4, 59.9, 55.8, 36.8, 36.5, 18.5, 14.2; HRMS (ESI) for $C_8H_{18}O_3Na$ $(M + Na)^+$ found 185.1148, calcd 185.1148.

(*R*)-5-((3-(Methoxymethoxy)hexyl)thio)-1-phenyl-1H-tetrazole 18:

To the solution of resulting alcohol **17** (0.5 g, 3.08 mmol) in dry THF (5 mL) were added PPh_3 (1.78 g, 6.78 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (0.824 g, 4.62 mmol) and DIAD (1.33 ml, 6.78 mmol) at 0 °C and it was allowed to stir for 2h at room temperature. THF was concentrated and crude product was purified by silica gel column chromatography using petroleum ether-EtOAc, (91:9) as eluent to furnish **18** as a yellow colour oil (954 mg, 96%); $[\alpha]_D^{26}$: - 14.06 ° (*c* 1.48, $CHCl_3$); IR (neat, cm^{-1}) : ν_{max} 2955, 2931, 1596, 1499, 1385, 1032, 915, 759, 711; ^1H NMR (200 MHz, $CDCl_3$) δ 7.64 - 7.51 (m, 5 H), 4.72 - 4.60 (m, 2 H), 3.78 - 3.63 (m, 1 H), 3.61 - 3.41 (m, 2 H), 3.40 - 3.35 (m, 3 H), 2.18 - 1.88 (m, 2 H), 1.61 - 1.25 (m, 4 H), 0.97 - 0.86 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 133.7, 130.0, 129.7, 123.8, 95.6, 76.0, 55.7, 36.4, 33.8, 29.5, 18.4, 14.1; HRMS (ESI) for $C_{15}H_{22}O_2N_4NaS$ $(M + Na)^+$ found 345.1353, calcd 345.1356.

(*R*)-5-((3-(Methoxymethoxy)hexyl)sulfonyl)-1-phenyl-1H-tetrazole 13:

To a solution of compound **18** (0.9 g, 2.79 mmol) in absolute EtOH (10 mL) was added $(NH_4)_6Mo_7O_{24}.4H_2O$ (1.72 g, 1.39 mmol) dissolved followed by H_2O_2 (1.47 mL, 12.55 mmol) at 0 °C and it was allowed to stir for 8h at room temperature. The reaction mixture was quenched with addition of cold sat.Na_2SO_3 solution at 0 °C, filtered through celite. The solvent was evaporated and then the residue was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product which was purified by silica gel column chromatography using petroleum ether-EtOAc, (90:10) as eluent to furnish **13** as a light yellow colour semi solid (960 mg, 97%); $[\alpha]_D^{25}$: - 4.43° (*c* 1.0, MeOH){lit.[15c] for *S* isomer $[\alpha]_D^{23}$= + 8.60° (*c* 0.91, $CHCl_3$); IR (neat ,cm^{-1}) : ν_{max} . 2958, 2932, 1595, 1339, 1149, 1036, 761, 688; ^1H NMR (200 MHz, $CDCl_3$) δ 7.82 - 7.53 (m, 5 H), 4.71 - 4.61 (m, 2 H), 3.99 - 3.69 (m, 3 H), 3.40 (s, 3 H), 2.35 - 1.97 (m, 2 H), 1.52 - 1.28 (m, 4 H), 0.99 - 0.89 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 133.0, 131.4, 129.7, 125.1, 95.7, 75.2, 55.8, 52.6, 36.3, 26.6, 18.4, 14.0; HRMS (ESI) for $C_{15}H_{22}O_4N_4NaS$ $(M + Na)^+$ found 377.1254, calcd 377.1254.

(*R,E*)-1,2,3-Trimethoxy-5-(4-(methoxymethoxy)hept-1-en-1-yl)benzene 12:

To a mixture of compound **13** (930 mg, 2.62 mmol) and trimethoxybenzaldehyde (514 mg, 2.62 mmol) in dry THF (10 mL) was added NaHMDS (4.64 ml, 1M in THF, 4.64 mmol) dropwise at 0 °C and it was stirred at room temperature for 3h. The reaction mixture was quenched with addition of sat.NH_4Cl solution. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give crude **12**. It was purified by silica gel column chromatography using petroleum ether-EtOAc (90:10) as eluent to furnish **12** as colourless oil (749 mg, 88 %, *E* only); $[\alpha]_D^{26}$: + 18.46° (*c* 1.31, $CHCl_3$); IR (neat, cm^{-1}) : ν_{max} 2956, 2930, 1581, 1506, 1416, 1327, 1150, 1124, 1006, 966, 838, 779; ^1H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 2 H), 6.36 (d, *J* = 15.6 Hz, 1 H), 6.24 - 6.08 (m, 1 H), 4.76 - 4.66 (m, 2 H), 3.91 - 3.83 (m, 9 H), 3.74 - 3.66 (m, 1 H), 3.40 (s, 3 H), 2.53 - 2.37 (m, 2 H), 1.58 - 1.35 (m, 4 H), 1.01 - 0.91 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 137.3, 133.3, 132.0, 126.1, 103.0, 95.4, 60.9, 56.0, 55.5, 38.0, 36.6, 18.7, 14.1; HRMS (ESI) for $C_{18}H_{28}O5Na$ $(M + Na)^+$ found 347.1826, calcd 347.1829.

***(R,E)*-1-(3,4,5-Trimethoxyphenyl)hept-1-en-4-ol 19:**

To a solution of compound **12** (700 mg, 2.15 mmol) in methanol (14 ml), was added 6N HCl (14 ml) drop wise at rt and stirring was continued for 2h (reaction was monitored by TLC).The reaction was quenched by using sat.$NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give crude **19**. It was purified by silica gel column chromatography using petroleum ether-EtOAc, (85:15) as eluent to furnish **19** as a white solid (592 mg, 98%); mp.: 70-71 °C; $[\alpha]_D^{27}$: - 11.27 (*c* 1.8, $CHCl_3$); IR (neat, cm^{-1}) : ν_{max} 3412, 2955, 2929, 1580, 1453, 1237, 1150, 1006, 966, 838; ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 2 H), 6.41 (d, *J* = 15.7 Hz, 1 H), 6.17 (td, *J* = 7.5, 15.4 Hz, 1 H), 3.90 - 3.81 (m, 9 H), 3.79 - 3.72 (m, 1 H), 2.53 - 2.39 (m, 1 H), 2.38 - 2.24 (m, 1 H), 1.68 - 1.62 (m, 1 H), 1.54 - 1.37 (m, 4 H), 0.96 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 137.2, 132.7, 132.5, 125.6, 102.8, 70.6, 60.6, 55.7, 40.7, 38.8, 18.6, 13.7; HRMS (ESI) for $C_{16}H_{24}O_4Na$ $(M + Na)^+$ found 303.1566, calcd 303.1567.

(2*R*,3*R*,5*S*)-5-Propyl-2-(3,4,5-trimethoxyphenyl) tetrahydrofuran 11:

To a solution of compound **19** (200 mg, 0.713 mmol) in dry CH_2Cl_2 was added triethylamine (0.4 ml, 2.84 mmol) at 0 °C. To this mixture mesyl chloride (0.11 ml, 1.42 mmol) was added slowly with further stirring for 2h at the room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 8 mL). The combined organic layers were washed with water (3 x 8 mL), brine, dried over Na_2SO_4 and concentrated to give crude mesylate.

To a solution of crude mesylate in $^{t}BuOH/H_2O$ (1:1, 12 mL) were added AD-mix-β (357 mg, 1.4 gm/mmol) and methanesulfonamide (25.5 mg, 100 mg/mmol) at 0 °C and the reaction mixture was allowed to stir for 24h at 0 °C temperature. The reaction was quenched by addition of Na_2SO_3 (360 mg, 1.48 mg/mmol) and stirred for 1h at room temperature until it became colourless. EtOAc was used for extraction and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product which was purified by silica gel column chromatography using petroleum ether-EtOAc, (80:20) as eluent to furnish **11** as a colourless oil (200 mg, 95%), which contains 7% of other diastereomer **20** (inseparable) confirmed by ^{1}H NMR spectroscopy; $[\alpha]_D^{28}$: - 51.35° (*c* 1.85, $CHCl_3$); IR (neat, cm^{-1}) : ν_{max} 3470, 2955,2940, 1590, 1418, 1232, 1125, 920, 781; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 2 H), 4.75 (d, *J* = 3.7 Hz, 1 H), 4.40 - 4.33 (m, 1 H), 4.09 - 3.99 (m, 1 H), 3.87 (s, 6 H), 3.84 (s, 3 H), 2.49 - 2.39 (m, 1 H), 1.90 - 1.81 (m, 1 H), 1.80 - 1.73 (m, 1 H), 1.70 - 1.40 (m, 4 H), 0.99 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 137.4, 132.4, 103.7, 103.4, 84.9, 84.3, 78.6, 78.1, 77.2, 74.6, 73.9, 60.8, 56.1, 40.7, 40.2, 38.5, 38.3, 19.4, 19.1, 14.1; HRMS (ESI) for $C_{16}H_{24}O_5Na$ $(M + Na)^+$ found 319.1514, calcd 319.1516.

(2*R*,3*R*,5*S*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol 10:

To a solution of alcohol **11** (100 mg, 0.337 mmol) in CH_2Cl_2 (3 mL) was added NBS (66 mg, 0.371 mmol) and the mixture was stirred at 25 °C for 10 min. After the reaction was complete (reaction was monitored by TLC), it was quenched with sat. $Na_2S_2O_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 4 mL), washed with water and combined organic phases were dried over Na_2SO_4 and concentrated to give the crude bromo compound, which was then purified by column chromatography over silica gel using petroleum ether-EtOAc (90:10) to give brominated alcohol **10** (124 mg, 98%) as a colourless oil. It contains 8.7 mg of other diastereomer **23;** $[\alpha]_D^{28}$: - 55° (*c* 2.2, $CHCl_3$); IR (neat, cm^{-1}) : ν_{max} 2935, 2866, 1569, 1481, 1428, 1166, 1012, 812, 773; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1 H), 4.99 (d, *J* = 4.1 Hz, 1 H), 4.76 - 4.69 (m, 1 H), 4.02 (td, *J* = 6.9, 13.7 Hz, 1 H), 3.91 - 3.85 (m, 9 H), 2.50 (td, *J* = 6.8, 14.3 Hz, 1 H), 1.90 - 1.81 (m, 1 H), 1.76 - 1.62 (m, 3 H), 1.56 - 1.41 (m, 2 H), 0.99 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 150.5, 142.4, 132.1, 108.1, 107.4, 84.3, 77.7, 71.8, 61.0, 56.0, 40.5, 38.3, 19.4, 14.2; HRMS (ESI) for $C_{16}H_{23}O_5BrNa$ $(M + Na)^+$ found 397.0618, calcd 397.0621.

(2*S*,3a*R*,9b*R*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5H-furo[3,2c]isochromen-5-one 22:

Bromo alcohol **10** (100 mg, 0.267 mmol) was taken in dry DMF (1.0 mL) and CuCN (71 mg, 0.802 mmol) was added to it. The entire solution was refluxed under N_2 for 12h (monitored by TLC). The reaction mixture was then cooled to room temperature, and diluted with water (3 mL) and EtOAc (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by column chromatography using an eluent dichloromethane-EtOAc (95:5) to give cyclised product **22** (64 mg, 75%) as a colourless oil; $[\alpha]_D^{27}$: + 23.2 °(*c* 0.53, $CHCl_3$) {(lit.[8] $[\alpha]_D^{21}$ = + 22.8° (*c* 2.76, $CHCl_3$)}; IR (neat, cm^{-1}) : ν_{max} 2923, 2853, 1717, 1592, 1461, 1366, 1256, 1110, 1009, 844, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1 H), 5.01 - 4.92 (m, 1 H), 4.52 (d, *J* = 2.7 Hz, 1 H), 4.19 - 4.10 (m, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 3.89 (s, 3 H), 2.52 (ddd, *J* = 5.7, 8.6, 14.2 Hz, 1 H), 2.16 (dd, *J* = 5.4, 14.2 Hz, 1 H), 1.77 - 1.68 (m, 1 H), 1.64 - 1.56 (m, 1 H), 1.48 - 1.34 (m, 2 H), 0.91 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.9, 156.5, 144.3, 132.5, 111.2, 108.1, 79.5, 79.0, 75.1, 61.8, 61.1, 56.2, 39.0, 38.1, 19.2, 13.9; HRMS (ESI) for $C_{17}H_{23}O_6$ $(M + H)^+$ found 323.1483, calcd 323.1489.

(2*S*,3a*R*,9b*R*)-6-Hydroxy-7,8-dimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5H-furo[3,2-c]isochromen-5-one 1:

To a solution of lactone **22** (48 mg, 0.148 mmol) in dry CH_2Cl_2 (1 mL) was added BCl_3 (1.0 M, 0.163 mL, 0.163 mmol) at -10 °C under Argon. The mixture was stirred at -5 °C for 1h and quenched with saturated aqueous $NaHCO_3$ (1 mL), The mixture was extracted with CH_2Cl_2 (3 x 4 mL), and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuum and purified by column chromatography using an eluent petroleum ether:EtOAc (60:40) to give **(+)-monocerin 1** (11.3 mg, 75% yield, brsm) as colourless oil; $[\alpha]_D^{26}$ = + 53° (*c* 1, $CHCl_3$) {(lit[2]. $[\alpha]_D^{25}$ = +53° (*c* 1, $CHCl_3$)}; IR (neat, cm^{-1}) : ν_{max} 2956, 2924, 1663, 1520, 1456, 1274, 1119, 1013, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1 H), 6.60 (s, 1 H), 5.06 (dd, *J* = 3.1, 5.3 Hz, 1 H), 4.55 (d, *J* = 3.2 Hz, 1 H), 4.17 - 4.08 (m, 1 H), 3.96 (s, 3 H), 3.91 (s, 3 H), 2.60 (ddd, *J* = 6.4, 8.4, 14.5 Hz, 1 H), 2.17 (dd, *J* = 6.0, 14.5 Hz, 1 H), 1.74 - 1.67 (m, 1 H), 1.63 - 1.59 (m, 1 H), 1.45 - 1.35 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 158.7, 156.3, 137.3, 131.1, 104.3, 102.0, 81.2, 78.7, 74.5, 60.7, 56.2, 39.0, 38.0, 19.1, 14.0; HRMS (ESI) for $C_{16}H_{21}O_6$ $(M + H)^+$ found 309.1331, calcd 309.1333.

(*S*,*E*)-1-(3,4,5-Trimethoxyphenyl)hept-1-en-4-yl-4-nitrobenzoate 24:

To the solution of alcohol **19** (0.2 g, 0.713 mmol) in dry THF (5 mL) were added PPh_3 (0.393 g, 1.49 mmol), *p*-nitrobenzoic acid (PNBA) (0.143 g, 0.856 mmol) and diisopropylazodicarboxylate (DIAD) (0.29 ml, 1.49 mmol) at 0 °C and it was allowed to stir for 1 h at room temperature. THF was concentrated and crude product was purified by silica gel column chromatography using petroleum ether:EtOAc, (94:6) as eluent to furnish **24** as a yellow colour oil (297 mg, 97%). $[\alpha]_D^{27}$: + 39.8° (*c* 1.03, $CHCl_3$); IR (neat ,cm^{-1}) : ν_{max} 2959, 2936, 1718, 1581, 1505, 1416, 1270, 1184, 1011, 964, 872, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 - 8.26 (m, *J* = 8.7 Hz, 2 H), 8.23 - 8.18 (m, *J* = 8.7 Hz, 2 H), 6.53 (s, 2 H), 6.39 (d, *J* = 15.6 Hz, 1 H), 6.15 - 6.06 (m, 1 H), 5.32 - 5.24 (m, 1 H), 3.88 - 3.83 (m, 9 H), 2.62 (t, *J* = 6.6 Hz, 2 H), 1.82 - 1.71 (m, 2 H), 1.53 - 1.40 (m, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ164.4, 153.3, 150.5, 137.7, 136.0, 133.1, 132.9, 130.6, 124.4, 123.5, 103.2, 75.4, 60.9, 56.1, 37.9,

35.8, 18.7, 13.9; HRMS (ESI) for $C_{23}H_{27}O_7NNa$ $(M + Na)^+$ found 452.1676, calcd 452.1680.

(*S*,*E*)-1-(3,4,5-Trimethoxyphenyl)hept-1-en-4-ol 25:

To the solution of ester **24** (0.25 g, 0.582 mmol) in THF:MeOH:H_2O (3:2:1) (6 mL) was added LiOH.H_2O (0.029 g, 0.699 mmol at rt and it was allowed to stir for 1h at room temperature. Solvent was concentrated and to the residue was added sat.$NaHCO_3$ (5 ml) and extracted with EtOAc (3 x 5 ml). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Purification by column chromatography using an eluent petroleum ether:EtOAc (85:15) gave **25** (153 mg, 94% yield) as colourless oil. $[\alpha]_D^{27}$: + 11.16° (*c* 1.8, $CHCl_3$).

(2*R*,3*R*,5*R*)-5-Propyl-2-(3,4,5-trimethoxyphenyl) tetrahydrofuran-3-ol 26:

The same procedure was followed as described for the preperation of compound **11.** Compound **25** (40 mg, 0.142 mmol) was subjected to tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization to give **26** as a colourless oil (40 mg, 95%), which contains 12% of other diastereomer **27** (inseparable) confirmed by ^{1}H NMR spectroscopy. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 - 1.05 (m, 3 H) 1.36 - 1.61 (m, 4 H) 1.79 - 1.90 (m, 1 H) 2.27 (dd, *J*=13.07, 5.75 Hz, 1 H) 3.84 (s, 3 H) 3.87 (s, 6 H) 4.35 - 4.55 (m, 2 H) 5.00 (d, *J*=3.03 Hz, 1 H), 6.60 (s, 2 H).

(2*R*,3*R*,5*R*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol 28:

The same procedure was followed as described for the preparation of compound **10.** Bromination of alcohol **26&27** (20 mg, 0.202 mmol) yielded the brominated alcohol **28** (22 mg, 98%) as a colourless oil. It contains 3 mg of other diastereomer **29.** $[\alpha]_D^{25}$: - 43.54° (*c* 2.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (s, 1 H), 5.25 (d, *J* = 3.1 Hz, 1 H), 4.77 (t, *J* = 3.2 Hz, 1 H), 4.51 - 4.45 (m, 1 H), 3.90 - 3.87 (m, 9 H), 2.23 (dd, *J* = 5.5, 13.1 Hz, 1 H), 1.91 - 1.85 (m, 1 H), 1.77 - 1.70 (m, 1 H), 1.53 - 1.38 (m, 3 H), 0.98 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 150.6, 142.4, 132.5, 107.7, 107.5, 83.7, 78.4, 72.4, 61.0, 56.1, 40.8, 38.1, 19.2, 14.1.

(2*R*,3a*R*,9b*R*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5H-furo[3,2-c]isochromen-5-one 30 :

The same procedure was followed as described for the preparation of compound **22.** Bromo alcohol **28** (10 mg, 0.026 mmol) yielded cyclized product **30** (6.4 mg, 75%) as a colourless oil. $[\alpha]_D^{28}$: + 11.34° (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J*=7.21 Hz, 3 H), 1.48 - 1.59 (m, 2 H), 1.71 - 1.76 (m, 2 H), 1.94 (ddd, *J*=13.63, 9.60, 3.91 Hz, 1 H), 2.60 (dd, *J*=13.69, 5.87 Hz, 1 H), 3.89 (s, 3 H), 3.97 (s, 3 H), 3.96 (s, 3 H) 4.38 - 4.47 (m, 1 H), 4.76 (d, *J*=2.69 Hz, 1 H), 5.04 (t, *J*=3.06 Hz, 1 H), 6.77 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 158.1, 156.6, 144.2, 133.4, 108.0, 80.2, 79.5, 73.9, 61.8, 61.2, 56.2, 40.2, 38.3, 19.2, 14.0; HRMS (ESI) for $C_{17}H_{23}O_6$ $(M + H)^+$ found 323.1484, calcd 323.1489.

(2*S*,3*S*,5*S*)-2-(2-Bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol 21:

Compound **21** was obtained as a by product in the preparation of compound **10.** $[\alpha]_D^{27}$: + 39.58° (*c* 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1 H), 5.26 (d, *J* = 3.2 Hz, 1 H), 4.78 (t, *J* = 3.7 Hz, 1 H), 4.52 - 4.44 (m, 1 H), 3.91 - 3.88 (m, 9 H), 2.25 (dd, *J* = 5.5, 13.3 Hz, 1 H), 1.93 - 1.85 (m, 1 H), 1.78 - 1.71 (m, 1 H), 1.54 - 1.44 (m, 3 H), 1.01 - 0.97 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 150.6, 142.4, 132.5, 107.8, 107.5, 83.8, 78.5, 72.4, 61.0, 56.1, 40.8, 38.1, 19.2, 14.1.

(2*S*,3a*S*,9b*S*)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5H-furo[3,2-c]isochromen-5-one 31:

The same procedure was followed as described for the preparation of compound **22.** Bromo alcohol **21** (6 mg, 0.0801 mmol) yielded cyclized product **31** (3.8 mg, 75%, brsm) as a colourless oil. $[\alpha]_D^{27}$: - 10.5° (*c* 0.2 , $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 - 0.97 (m, 3 H) 1.49 - 1.57 (m, 2 H) 1.67 - 1.75 (m, 2 H) 1.94 (ddd, *J*=13.66, 9.69, 4.12 Hz, 1 H) 2.59 (dd, *J*=13.43, 5.80 Hz, 1 H) 3.89 (s, 3 H) 3.97 (d, *J*=4.27 Hz, 7 H) 4.39 - 4.46 (m, 1 H) 4.76 (d, *J*=2.75 Hz, 1 H) 5.04 (t, *J*=2.90 Hz, 1 H) 6.78 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 158.1, 156.5, 144.1, 133.4, 108.0, 80.2, 79.5, 73.9, 61.8, 61.2, 56.2, 40.1, 38.3, 19.2, 14.1.

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† Electronic Supplementary Information (ESI) available: Copies of NMR spectra (^{1}H&^{13}C) of all compounds. See DOI: 10.1039/c000000x/

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