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Convenient route to enantiopure substituted butyrolactones: application in a formal synthesis of both enantiomers of enterolactone

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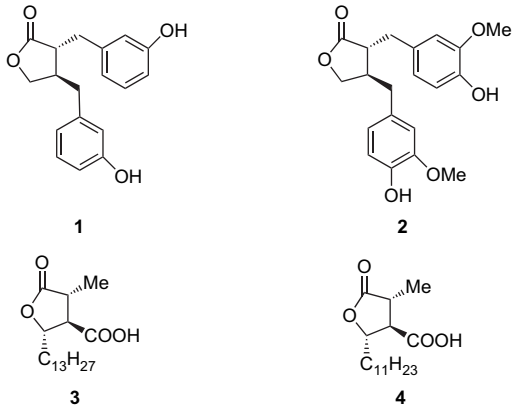
Abstract—A simple route for the synthesis of enantiopure substituted γ-butyrolactones involving a highly diastereoselective alkylation of an enantiomerically pure substituted latent succinate ester is described. This route provides entry into both enantiomers of 3,4-disubstituted butyrolactones from a single enantiomer, 2,3-di-*O*-cyclohexylidine-*R*-(+)-glyceraldehyde. The synthetic potential of this methodology has been demonstrated by a formal synthesis of both enantiomers of enterolactone.

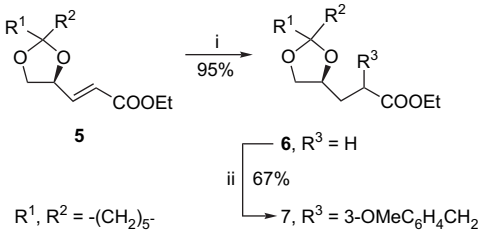
1. Introduction

Natural products containing substituted butyrolactone as the core structure are of considerable interest due to their important biological profile.[1] The lignan[2] lactones such as enterolactone **1** and arctigenin **2** are classic examples of bioactive disubstituted butyrolactones. Recent investigations by Lin and co-workers[3] have shown that enterolactone **1** inhibits breast and colon cancer and suppresses the growth of prostate cancer cells. Arctigenin **2** and its analogs have also been shown[4] to be potent inhibitors of HIV-type 1 integrase. Roccellaric acid **3**[5] and nephrosteranic acid **4**[5c,6] are representative examples of bioactive trisubstituted butyrolactones. Due to interesting biological activities associated with them, considerable attention has been focussed[7] on the development of efficient methodologies for the stereocontrolled construction of substituted butyrolactones. Herein, we report a stereocontrolled route that provides access to disubstituted as well as trisubstituted butyrolactones in enantiomerically pure form. The strategy is illustrated with a formal synthesis of both enantiomers of enterolactone.[8]



2. Results and discussion

We envisaged that the enantiopure and differentially protected succinate **6** (Scheme 1) would be an ideal synthon for sequential introduction of two different substituents based on enolate alkylation prior to its transformation to butyrolactone. Diastereoselection during alkylation of the ester **6** might be expected to arise through π-face discrimination of the metal enolate, which would possibly be chelated with the dioxolane ring. The ester **6** was prepared by catalytic hydrogenation of the unsaturated ester **5**, which



Scheme 1. (i) H_2, 10% Pd/C, EtOH; (ii) LDA, THF/HMPA, 3-MeO$C_6H_4CH_2$Br, −78 °C to rt.

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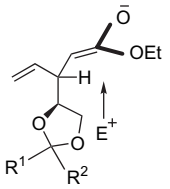
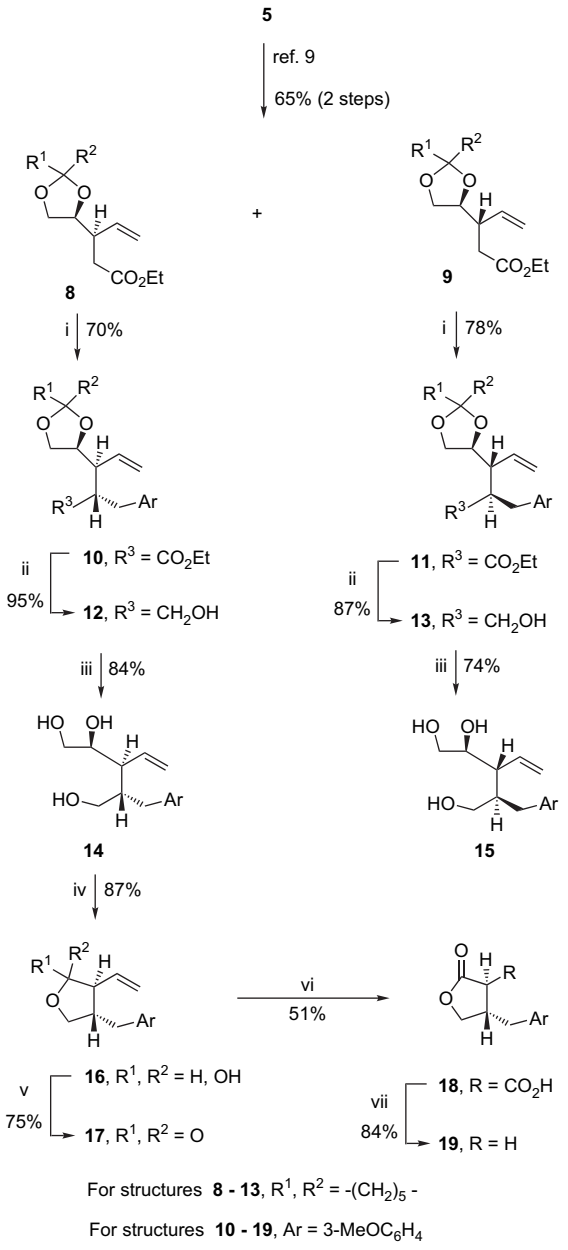


Figure 1.

in turn was obtained from 2,3-di-*O*-cyclohexylidene-*R*-(+)-glyceraldehyde following the literature procedure.[9] Alkylation of the enolate generated (LDA) from the ester **6** with 3-methoxy benzyl bromide proceeded smoothly but non-stereoselectively to give a 1:1 mixture of the alkylated products **7** in 85% yield. The distant chiral center thus failed to induce any diastereoselectivity during enolate alkylation.

We next considered the possibility of inducing diastereoselectivity through alkylation of ester having a β substituent such as the readily available latent succinate **8** or **9**. Houk and co-workers[10] proposed a model to predict the stereochemical outcome during addition of an electrophile to α-chiral C–C double bonds. According to this model, electrophiles add through an orientation (Fig. 1) in which the small substituent (H in the present case) of the chiral center lies onto the side of the double bond minimizing the 1,3-allylic strain between the small substituent and the substituent (OEt or the enolate O) on the double bond giving rise to the anti-Felkin product. Fleming and co-workers[11] have extensively investigated the addition of various electrophiles to α-chiral C–C double bond including alkylation of α-chiral enolates, which in accord with Houk's model yielded the anti-Felkin product predominantly irrespective of the *E*/*Z* geometry of the olefin. Based on the above findings, we predicted that alkylation of the enolate of the ester **8** or **9**[12] would take place preferentially from the face of the smallest group (H atom in this case) present in the chiral center to produce predominantly **10** and **11**, respectively. Once the diastereomerically pure compound is obtained, the vinyl group can either be removed through oxidation to a carboxylic acid followed by decarboxylation or modified to provide a desired substituent in the lactone to be prepared. With this background, the esters **8** and **9** were prepared as a chromatographically separable mixture (1:1) in 65% yield in two steps from the ester **5** according to the procedure[9] developed earlier in this laboratory. Alkylation of lithium enolate generated from the ester **8** with 3-methoxy benzyl bromide afforded the ester **10** along with the other diastereoisomer in a 5:1 ratio. The pure ester **10** was obtained in 70% yield after column chromatography. The gross structure of the product **10** was easily determined from spectroscopic data. The stereochemical assignment to **10** is based on its transformation to the trans-disubstituted lactone **18** (Scheme 2). Similarly, alkylation of the enolate of the ester **9** gave the alkylated product **11** along with the other diastereomers in a ratio of approximately 5:1. The pure diastereoisomer **11** was obtained in 78% yield after chromatographic separation.

After successfully attaining reasonably good level of stereocontrol during alkylation, we next focused on the transformation of the ester **10** to the trans-disubstituted lactone **17**

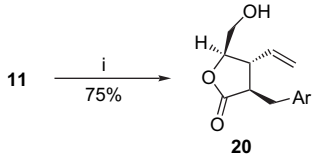


Scheme 2. (i) LDA, THF/HMPA, 3-$MeOC_6H_4CH_2Br$, −78 °C to rt; (ii) $LiAlH_4$, THF, rt; (iii) $HOAc/H_2O$, rt; (iv) $NaIO_4$, CH_3CN/H_2O; (v) Jones oxidation; (vi) $RuCl_3 \cdot xH_2O$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$ and then Jones reagent; (vii) toluene, reflux.

as delineated in Scheme 2. The ester **10** was reduced with lithium aluminum hydride in diethyl ether to produce the alcohol **12** in 95% yield. Acid catalyzed deketalization of the spiroketal in **12** afforded the triol **14** in 84% yield. Periodate cleavage of the vicinal diol in **14** afforded a 1:1 mixture of lactol epimers **16** in 87% yield. The lactol **16** without further purification was directly oxidized with Jones reagent to afford the disubstituted lactone **17**, $[\alpha]_D^{25}$ +15.2 (*c* 1.8, $CHCl_3$) in 75% yield. Following a similar sequence the ester **11** was converted to the enantiomer of the lactone **17**, $[\alpha]_D^{25}$ −15.5 (*c* 2.4, $CHCl_3$), through oxidation of the *ent*-lactol **16**, which in turn was obtained from periodate cleavage of the diastereoisomeric triol **15**. Thus, both the enantiomers of the disubstituted lactone **17** can be obtained from 2,3-di-*O*-cyclohexylidine *R*-(+)-glyceraldehyde.

We next planned to introduce the second benzyl substituent through alkylation of the enolate of the lactone **17** toward the synthesis of enterolactone **1**. Unfortunately, attempted alkylation of the enolate of the lactone **17** produced an inseparable mixture of several products. We thus decided to convert the vinyl group to the corresponding acid. The lactone **17** was subjected to RuO_4 oxidation producing, instead of the expected lactonic acid **18**, an intractable mixture of products. The lactonic acid **18** could finally be obtained in 51% yield from the lactol **16** through a sequence of RuO_4 and Jones oxidation. The coupling constant (J=9.3 Hz)[13] of the hydrogen at C-3, which appeared as a doublet at δ 3.36, indicated that the benzyl group and the carboxylic acid group are trans to each other. This confirmed that the vinyl group and the benzyl group in the ester **10** are trans to each other. Refluxing a toluene solution of the carboxylic acid **18** for 16 h effected smooth decarboxylation giving rise to β-arylmethyl γ-butyrolactone **19**.[14] The ^{1}H and ^{13}C NMR spectra of the lactone **19** prepared in this way are comparable to those reported in the literature.[8j] In general, β-arylmethyl butyrolactones are intermediates to vast number of lignan lactones. For example, the lactone **19** obtained in this way, having $[\alpha]_D^{23}$ +6.5 (*c*, $CHCl_3$) [lit.[8j] $[\alpha]_D^{25}$ +6.15 (*c* 1.86, $CHCl_3$)] has been converted to (−)-enterolactone **1** in two steps. Similarly, the *ent*-lactone **17** obtained from the ester **9** has been converted to the enantiomer of the lactone **19**, $[\alpha]_D^{25}$ −5.9 (*c* 0.8, $CHCl_3$) [lit.[8e] $[\alpha]_D^{25}$ −6.76 (*c* 1.04, $CHCl_3$)]. The *ent*-lactone **19** has been converted to (+)-enterolactone.[8e] Thus, a formal synthesis of the both enantiomers of enterolactone **1** from a single enantiomer, 2,3-di-*O*-cyclohexylidine *R*-(+)-glyceraldehyde has been achieved.

The synthesis of trisubstituted butyrolactone can be illustrated as delineated in Scheme 3. The ester **11** was hydrolyzed with aqueous ethanolic potassium hydroxide under reflux. The resulting alkaline solution was heated at 80 °C with 80% aqueous acetic acid to afford after chromatographic purification the trisubstituted lactone **20** in 75% yield. The vinyl group in the lactone **20** is a latent carboxylic acid while the hydroxymethyl group at C-5 can be elaborated to the desired alkyl chain. Thus, the route depicting the synthesis of the trisubstituted lactone **20** from 2,3-di-*O*-cyclohexylidine-*R*-(+)-glyceraldehyde will be of great significance for the synthesis of lactones such as **3** and **4** with carboxylic acid as one of the substituents.



Scheme 3. (i) KOH, $EtOH/H_2O$, reflux then $HOAc/H_2O$, reflux.

3. Conclusion

We have developed a simple route for the construction of both enantiomers of 3,4-disubstituted butyrolactones. This route has been extended to the synthesis of a trisubstituted butyrolactone. The potential of the strategy has been illustrated by a formal enantiodivergent synthesis of both enantiomers of enterolactone **1** from *R*-(+)-2,3-di-*O*-cyclohexylidine glyceraldehyde.

4. Experimental

4.1. General

All reactions were carried out under a blanket of nitrogen. A usual work up of the reaction mixture consists of extraction with diethyl ether, washing with brine, drying over anhydrous Na_2SO_4, and removal of the solvent in vacuo. Column chromatography was carried out with silica gel (60–120 mesh). Petroleum ether refers to the fraction having bp 60–80 °C. Peak positions in ^{1}H and ^{13}C NMR spectra are indicated in parts per million downfield from internal TMS in δ units. NMR spectra were taken in $CDCl_3$ at 300 MHz for ^{1}H and 75 MHz for ^{13}C. ^{13}C peaks' assignment is based on DEPT experiment. IR spectra for liquids were recorded as neat.

4.1.1. Ethyl 3-[(2*S*)-1,4-dioxaspiro[4.5]dec-2-yl]propanoate 6. A solution of the unsaturated ester **5** (800 mg, 3.33 mmol) in ethanol (8 mL) was stirred magnetically in the presence of 10% Pd/C as catalyst in an atmosphere of hydrogen for 5 h. The catalyst was filtered off and the solvent was removed in vacuo to afford the ester **6** (770 mg, 95%) as a colorless liquid; $[\alpha]_D^{25}$ −5.2 (*c* 1.5, $CHCl_3$); IR: ν_{max} 1738 cm^{-1}; ^{1}H NMR: δ 1.24 (3H, t, J=7.2 Hz), 1.37 (3H, br s), 1.57 (10H, m), 1.79–1.89 (2H, m), 2.32–2.48 (2H, m), 3.52 (1H, t, J=7.5 Hz), 3.99–4.15 (3H, m); ^{13}C NMR: δ 14.3 (CH_3), 23.9 (CH_2), 24.1 (CH_2), 29.0 (CH_2), 30.6 (CH_2), 35.2 (CH_2), 36.6 (CH_2), 60.5 (CH_2), 68.8 (CH_2), 74.6 (CH), 109.5 (C), 173.2 (CO); HRMS (ESI): calcd for $C_{13}H_{22}O_4Na$ (M+Na)$^+$, 265.1416; found, 265.1417.

4.1.2. Ethyl 3-[(2*S*)-1,4-dioxaspiro[4.5]dec-2-yl]-2-(3-methoxybenzyl)propanoate 7. To a magnetically stirred solution of LDA [prepared from *n*-BuLi (1 mL, 1.64 mmol, 1.6 M in hexane)] and diisopropyl amine (0.29 mL, 2 mmol) in THF (4 mL)], cooled to −78 °C, was added a solution of the ester **6** (200 mg, 0.82 mmol) in THF (1 mL). After addition is complete, the temperature of the bath was slowly raised to −30 °C. The reaction mixture was again cooled to −78 °C. HMPA (0.25 mL) followed by 3-methoxy benzyl bromide (329 mg, 1.64 mmol) was added to it. Stirring was continued for 4 h at −78 °C. The reaction mixture was then quenched by addition of saturated aqueous ammonium chloride. Usual work up of the reaction mixture with diethyl ether followed by column chromatography [petroleum ether/ethyl acetate (9:1)] afforded an inseparable diastereoisomeric mixture (1:1) of the ester **7** (200 mg, 67%); $[\alpha]_D^{25}$ −4.4 (*c* 2.8, $CHCl_3$); IR: ν_{max} 1732, 1601, 1585 cm^{-1}; ^{1}H NMR (of the mixture): δ 1.14 (3H, t, J=7.2 Hz), 1.35 (2H, br s), 1.52–1.65 (8H, m), 1.9–2.1 (1H, m), 2.71–2.79 (2H, m), 2.91 (2H, m), 3.43 (1H, t, J=6.9 Hz), 3.75 (3H, s), 3.94–4.07 (4H, m), 6.73 (3H, m), 7.16 (1H, t, J=7.8 Hz); ^{13}C NMR: δ 14.15 (CH_3), 14.18 (CH_3), 23.8 (CH_2), 23.9 (CH_2), 24.01 (CH_2), 24.05 (CH_2), 25.2 (CH_2), 35.1 (CH_2), 35.2 (CH_2), 35.6 (CH_2), 35.8 (CH_2), 36.60 (CH_2), 36.63 (CH_2), 44.1 (CH), 44.8 (CH), 55.1 (CH_3), 60.4 (CH_2), 69.04 (CH_2), 69.08 (CH_2), 73.7 (CH), 73.8 (CH), 109.4 (C), 109.6 (C), 111.84 (CH), 111.86 (CH), 114.6 (CH), 121.37 (CH), 121.39 (CH), 129.34 (CH), 129.37 (CH), 140.42 (C), 140.5 (C), 159.6 (C), 175.06 (CO), 175.2 (CO); HRMS (ESI): calcd for $C_{21}H_{30}O_5Na$ (M+Na)$^+$, 385.1991; found, 385.1998.

4.1.3. (2*S*,3*S*)-Ethyl 2-(3-methoxybenzyl)-3-[(2*S*)-1,4-dioxaspiro[4.5]dec-2-yl]pent-4-enoate 10. Following the above procedure, the enolate of the ester **8** (400 mg, 1.5 mmol) generated with LDA [prepared from *n*-BuLi (1.87 mL, 3 mmol, 1.6 M in hexane) and diisopropyl amine (0.53 mL, 3.8 mmol)] was alkylated with 3-methoxy benzyl bromide (600 mg, 3 mmol) to afford after column chromatography (petroleum ether/ether (9:1)] the ester **10** (410 mg, 70%) as colorless oil; $[\alpha]_D^{25}$ +14.9 (*c* 1.2, $CHCl_3$); ^1H NMR: δ 1.04 (3H, t, *J*=7 Hz), 1.50–1.65 (10H, m), 2.47 (1H, m), 2.66 (1H, dd, *J*=13, 11 Hz), 2.83–2.98 (3H, m), 3.63 (1H, t, *J*=7.6 Hz), 3.77 (3H, s), 3.93–4.08 (3H, m), 5.16 (1H, dd, *J*=15, 1.8 Hz), 5.31 (1H, dd, *J*=10, 1.8 Hz), 5.73–5.86 (1H, m), 6.74–6.88 (3H, m), 7.15 (1H, t, *J*=7.8 Hz); ^{13}C NMR: δ 13.0 (CH_3), 23.8 (CH_2), 24.1 (CH_2), 25.3 (CH_2), 34.7 (CH_2), 35.8 (CH_2), 37.4 (CH_2), 49.2 (CH), 49.5 (CH), 55.2 (CH_3), 60.3 (CH_2), 66.9 (CH_2), 75.6 (CH), 108.5 (C), 111.8 (CH), 114.6 (CH), 120.2 (CH_2), 121.4 (CH), 129.3 (CH), 134.6 (CH), 139.9 (C), 158.5 (C), 173.7 (CO). HRMS (ESI): calcd for $C_{23}H_{32}O_5Na$ $(M+Na)^+$, 411.2148; found, 411.2147.

4.1.4. (2*R*,3*R*)-Ethyl 2-(3-methoxybenzyl)-3-[(2*S*)-1,4-dioxaspiro[4.5]dec-2-yl]pent-4-enoate 11. The enolate of the ester **9** (400 mg, 1.5 mmol) generated on treatment with LDA [prepared from *n*-BuLi (1.86 mL, 3 mmol, 1.6 M in hexane) and diisopropyl amine (0.53 mL, 3.75 mmol)] was alkylated with 3-methoxy benzyl bromide (600 mg, 3 mmol) to afford after chromatography [petroleum ether/ether (9:1)] the ester **11** (405 mg, 78%) as colorless oil; $[\alpha]_D^{25}$ +7.9 (*c* 1.5, $CHCl_3$); ^1H NMR: δ 1.01 (3H, t, *J*=7.2 Hz), 1.32 (3H, br s), 1.51 (7H, m), 2.56–2.88 (4H, m), 3.58 (1H, t, *J*=7.2 Hz), 3.70 (3H, s), 3.88–4.03 (4H, m), 5.07–5.13 (2H, m), 5.47–5.60 (1H, m), 6.64–6.72 (3H, m), 7.08 (1H, t, *J*=7.8 Hz); ^{13}C NMR: δ 14.5 (CH_3), 24.3 (CH_2), 24.4 (CH_2), 25.6 (CH_2), 35.0 (CH_2), 35.6 (CH_2), 36.8 (CH_2), 49.8 (CH), 51.5 (CH), 55.5 (CH_3), 60.6 (CH_2), 68.5 (CH_2), 76.2 (CH), 110.5 (C), 112.2 (CH), 114.9 (CH), 119.8 (CH_2), 121.8 (CH), 129.5 (CH), 134.9 (CH), 141.9 (C), 159.9 (C), 174.5 (CO). HRMS (ESI): calcd for $C_{23}H_{32}O_5Na$ $(M+Na)^+$, 411.2148; found, 411.2144.

4.1.5. (2*S*,3*S*)-2-(3-Methoxybenzyl)-3-[(2*S*)-1,4-dioxaspiro[4.5]dec-2-yl]pent-4-en-1-ol 12. A solution of the ester **10** (225 mg, 0.6 mmol) in diethyl ether (5 mL) was added to a magnetically stirred suspension of lithium aluminum hydride (24 mg, 0.64 mmol) in diethyl ether (5 mL) at rt. The reaction mixture was stirred at rt for 4 h. On cooling to 0 °C, the reaction mixture was quenched by sequential addition of water (25 µl), aqueous sodium hydroxide (75 µl, 15%), and water (75 µl). Stirring was continued for additional 15 min. The precipitated white solid was filtered out. The filtrate after drying was concentrated and the residual mass was chromatographed [petroleum ether/ether (4:1)] to afford the hydroxy compound **12** (190 mg, 95%); $[\alpha]_D^{25}$ +15.9 (*c* 1.0, $CHCl_3$); ^1H NMR: δ 1.20–1.60 (10H, m), 1.97 (1H, br s), 2.18 (1H, m), 2.31 (1H, m), 2.64 (1H, dd, *J*=9, 13.8 Hz), 2.75 (1H, br s), 2.83 (1H, dd, *J*=5.7, 13.8 Hz), 3.48 (1H, m), 3.65 (1H, t, *J*=7.8 Hz), 3.77 (3H, s), 3.98 (1H, t, *J*=7.8 Hz), 4.37–4.41 (1H, m), 5.05–5.25 (2H, m), 5.91–6.00 (1H, m), 6.72–6.79 (3H, m), 7.18 (1H, t, *J*=7.8 Hz); ^{13}C NMR: δ 24.1 (CH_2), 25.2 (CH_2), 35.1 (CH_2), 35.4 (CH_2), 35.9 (CH_2), 46.3 (CH), 46.6 (CH), 55.2 (CH_3), 61.4 (CH_2), 67.4 (CH_2), 74.5 (CH), 109.7 (C), 111.0 (CH), 114.9 (CH), 118.9 (CH_2), 121.6 (CH), 129.5 (CH), 136.1 (CH), 142.1 (C), 159.5 (C). HRMS (ESI): calcd for $C_{21}H_{30}O_4Na$ $(M+Na)^+$, 369.2042; found, 369.2046.

4.1.6. (2*R*,3*R*)-2-(3-Methoxybenzyl)-3-[(2*S*)-1,4-dioxaspiro[4.5]dec-2-yl]pent-4-en-1-ol 13. Following the above procedure, the ester **11** (270 mg, 0.7 mmol) was reduced with lithium aluminum hydride (29 mg, 0.76 mmol) to afford the hydroxy compound **13** (210 mg, 87%); $[\alpha]_D^{25}$ +4.2 (*c* 2, $CHCl_3$); ^1H NMR: δ 1.25–1.68 (10H, m), 2.0 (1H, br s), 2.19 (1H, s), 2.32–2.47 (2H, m), 2.83 (1H, m), 3.46 (1H, dd, *J*=5.1, 11.7 Hz), 3.58 (1H, t, *J*=8.1 Hz), 3.71 (1H, dd, *J*=3, 11.6 Hz), 3.79 (3H, s), 3.96 (1H, dd, *J*=5.7, 8.2 Hz), 4.09 (1H, m), 5.15–5.20 (2H, m), 5.55–5.67 (1H, m), 6.72–6.79 (3H, m), 7.18 (1H, t, *J*=8 Hz); ^{13}C NMR: δ 24.1 (CH_2), 24.2 (CH_2), 25.2 (CH_2), 34.6 (CH_2), 35.6 (CH_2), 36.6 (CH_2), 45.6 (CH), 50.4 (CH), 55.2 (CH), 62.2 (CH_2), 69.2 (CH_2), 76.1 (CH), 110.3 (C), 111.4 (CH), 115.0 (CH), 118.9 (CH_2), 121.8 (CH), 129.4 (CH), 136.3 (CH), 142.8 (C), 159.7 (C). HRMS (ESI): calcd for $C_{21}H_{30}O_4Na$ $(M+Na)^+$ 369.2042; found, 369.2040.

4.1.7. (2*S*,3*S*,4*S*)-5-(3-Methoxyphenyl)-3-vinylpentane-1,2,4-triol 14. A solution of the hydroxy compound **12** (200 mg, 0.58 mmol) in aqueous acetic acid (5 mL, 80%) was stirred at rt for 18 h. The reaction mixture was diluted with ethyl acetate (10 mL). The entire mass was transferred into a separatory funnel and washed successively with 10% aqueous NaOH (3×3 mL) and brine (2×5 mL), dried, and concentrated in vacuum. The residual mass was chromatographed [petroleum ether/ethyl acetate (2:3)] to afford the triol **14** (130 mg, 84%); $[\alpha]_D^{25}$ +7.3 (*c* 1.0, $CHCl_3$); ^1H NMR: δ 1.94–2.00 (1H, br s), 2.14–2.22 (2H, m), 2.45 (1H, dd, *J*=10, 14 Hz), 2.77 (1H, dd, *J*=4.5, 14 Hz), 3.42–3.73 (6H, m), 3.77 (3H, s), 3.98 (1H, br s), 5.06 (1H, dd, *J*=1.8, 17.4 Hz), 5.18 (1H, dd, *J*=1.8, 10.2 Hz), 5.93 (1H, m), 6.70–6.75 (3H, m), 7.18 (1H, t, *J*=7.5 Hz); ^{13}C NMR: δ 35.5 (CH_2), 44.7 (CH), 48.7 (CH), 61.5 (CH_2), 65.8 (CH_2), 70.8 (CH), 111.3 (CH), 115.10 (CH), 115.13 (CH), 118.6 (CH_2), 121.6 (CH), 129.5 (CH), 136.7 (CH), 142.3 (C), 159.7 (C). HRMS (ESI): calcd for $C_{15}H_{22}O_4Na$ $(M+Na)^+$, 289.1416; found, 289.1418.

4.1.8. (2*S*,3*R*,4*R*)-5-(3-Methoxyphenyl)-3-vinylpentane-1,2,4-triol 15. Following the above procedure deketalization of the dioxolane derivative **13** (210 mg, 0.6 mmol) was achieved to afford the triol **15** (120 mg, 74%); $[\alpha]_D^{25}$ +9.8 (*c* 2.2, $CHCl_3$); ^1H NMR: δ 2.25 (2H, m), 2.47 (1H, br t), 2.79 (1H, m), 3.37–3.45 (2H, m), 3.51–3.70 (6H, m), 3.76 (3H, s), 5.12 (2H, m), 5.52–5.61 (1H, m), 6.70–6.77 (3H, m), 7.16 (1H, t, *J*=7.5 Hz); ^{13}C NMR: δ 33.9 (CH_2), 43.2 (CH_2), 48.3 (CH), 55.3 (CH_3), 62.5 (CH_2), 71.7 (CH), 111.3 (CH), 115.1 (CH), 119.2 (CH_2), 121.6 (CH), 129.5 (CH), 135.8 (CH), 142.7 (C), 159.7 (C). HRMS (ESI): calcd for $C_{15}H_{22}O_4Na$ $(M+Na)^+$, 289.1416; found, 289.1417.

4.1.9. (3*S*,4*S*)-4-(3-Methoxybenzyl)-tetrahydro-3-vinylfuran-2-ol 16. To a solution of the triol **14** (110 mg, 0.41 mmol) in aqueous acetonitrile (4 mL, 60%), $NaIO_4$ (175 mg, 0.82 mmol) was added. The resulting suspension was stirred at rt for 1.5 h. Usual work up of the reaction

mixture with diethyl ether afforded the lactol **16** (85 mg, 87%) as a 1:1 diastereoisomeric mixture; ^{1}H NMR: δ 2.23–2.53 (3H, m), 2.84 (1H, dt, J=4, 10 Hz), 3.51 (1H, t, J=8.4 Hz), 3.70 (3H, s), 3.83 (1H, t, J=7.2 Hz), 4.02 (1H, t, J=8.4 Hz), 5.02–5.28 (3H, m), 5.66–5.75 (1H, m), 6.60–6.66 (3H, m), 7.10 (1H, t, J=7.8 Hz); ^{13}C NMR: δ 37.8 (CH_2), 38.2 (CH_2), 42.8 (CH), 47.1 (CH), 55.5 (CH_3), 57.4 (CH_3), 72.4 (CH_2), 73.1 (CH_2), 99.9 (CH), 103.7 (CH), 118.8 (CH), 114.8 (CH), 117.7 (CH_2), 118.8 (CH_2), 121.4 (CH), 129.8 (CH), 134.2 (CH), 137.1 (CH), 142.0 (C), 142.1 (C), 160.1 (C). HRMS (ESI): calcd for $C_{14}H_{18}O_3Na$ $(M+Na)^+$, 257.1154; found, 257.1140.

4.1.10. (3*S*,4*S*)-4-(3-Methoxybenzyl)-dihydro-3-vinyl-furan-2(3*H*)-one 17. Jones reagent was added to a magnetically stirred ice-cold solution of the lactol **16** (50 mg, 0.2 mmol) in acetone (1 mL) till the color of the reagent persisted. The reaction mixture was extracted with diethyl ether (3×4 mL). The combined extract was washed sequentially with 2% aqueous NaOH (2 mL) and brine (4 mL), dried, and concentrated. The residual mass was chromatographed [petroleum ether/ether (5:1)] to afford the lactone **17** (35 mg, 75%); $[\alpha]_D^{25}$ +6.8 (c 1.8, $CHCl_3$); IR: ν_{max} 1774 cm^{-1}; ^{1}H NMR: δ 2.58–2.74 (2H, m), 2.87–3.00 (2H, m), 3.80 (3H, s), 3.94 (1H, t, J=9.0 Hz), 4.27 (1H, t, J=9 Hz), 5.33 (2H, m), 5.76 (1H, m), 6.74 (3H, m), 7.23 (1H, t, J=7.8 Hz); ^{13}C NMR: δ 37.6 (CH_2), 43.4 (CH), 49.8 (CH), 55.3 (CH_3), 71.2 (CH_2), 111.9 (CH), 114.8 (CH), 120.3 (CH_2), 121.1 (CH), 129.9 (CH), 131.8 (CH), 139.3 (C), 160.0 (C), 176.7 (CO). HRMS (ESI): calcd for $C_{14}H_{16}O_3Na$: $(M+Na)^+$ 255.0997; found, 255.0993.

4.1.11. (3*R*,4*S*)-4-(3-Methoxybenzyl)-tetrahydro-2-oxo-furan-3-carboxylic acid 18. Sodium metaperiodate (107 mg, 0.5 mmol) was added to a magnetically stirred solution of the lactol **16** (50 mg, 0.2 mmol) in carbon tetrachloride (0.6 mL), acetonitrile (0.6 mL), and water (1.2 mL). A catalytic amount of $RuCl_3 \cdot xH_2O$ (2 mg) was added to this suspension and stirring was continued for 3 h. The reaction mixture was diluted with diethyl ether (10 mL) and filtered through a plug of cotton. The filtrate on drying was concentrated in vacuum. The residual mass was dissolved in acetone (1 mL) and to it was added Jones reagent drop wise till the color of the reagent persisted. The reaction mixture was extracted with diethyl ether (3×4 mL). The combined extract was washed with water (3 mL) and then with saturated aqueous sodium bicarbonate (2×2 mL). The organic extract was discarded. The combined alkaline extract on cooling to 0 °C was acidified with 12 N HCl. Usual work up of the acidic solution with diethyl ether afforded the acid **18** (30 mg, 51%); $[\alpha]_D^{25}$ +20.4 (c 0.9, $CHCl_3$); IR: ν_{max} 1776, 1732 cm^{-1}; ^{1}H NMR: δ 2.79 (1H, dd, J=8, 13.6 Hz), 2.97 (1H, dd, J=5.4, 13.5 Hz), 3.24–3.31 (1H, m), 3.36 (1H, d, J=9.3 Hz), 3.79 (3H, s), 4.03 (1H, t, J=8.7 Hz), 4.42 (1H, t, J=8.7 Hz), 6.78 (3H, m), 7.23 (1H, t, J=7.8 Hz); ^{13}C NMR: δ 37.7 (CH_2), 41.3 (CH), 51.3 (CH), 55.4 (CH_3), 71.5 (CH_2), 112.5 (CH), 114.8 (CH), 121.3 (CH), 130.1 (CH), 138.4 (C), 160.0 (C), 171.2 (CO), 172.3 (CO). HRMS (ESI): calcd for $C_{13}H_{14}O_5Na$ $(M+Na)^+$, 273.0739; found, 273.0735.

4.1.12. (*S*)-4-(3-Methoxybenzyl)-dihydrofuran-2(3*H*)-one 19. A solution of the acid **18** (10 mg, 0.036 mmol) in toluene (2 mL) was heated under reflux for 16 h. Removal of toluene in vacuum afforded the lactone **19** (7 mg, 84%); $[\alpha]_D^{25}$ +6.03 (c 1.0, $CHCl_3$); ^{1}H NMR: δ 2.29 (1H, dd, J=6.9, 17.4 Hz), 2.61 (1H, dd, J=7.8, 17.4 Hz), 2.73–2.90 (3H, m), 3.80 (3H, s), 4.04 (1H, dd, J=6.6, 9 Hz), 4.34 (1H, t, J=7.2 Hz), 6.69–6.79 (3H, m), 7.23 (1H, t, J=7.8 Hz); ^{13}C NMR: δ 34.4 (CH_2), 37.2 (CH), 39.1 (CH_2), 55.3 (CH_3), 72.8 (CH_2), 112.0 (CH), 114.8 (CH), 121.1 (CH), 129.9 (CH), 139.9 (C), 160.0 (C), 177.0 (CO). HRMS (ESI): calcd for $C_{12}H_{14}O_3Na$ $(M+Na)^+$, 229.0840; found, 229.0841.

4.1.13. (*R*)-5-Hydroxymethyl-(*R*)-3-(3-methoxybenzyl)-(*R*)-4-vinyl-dihydro-furan-2-one 20. The ester **11** (100 mg, 0.25 mmol) was heated under reflux with a solution made by dissolving KOH (70 mg, 1.25 mmol) in ethanol (5 mL) and water (0.5 mL) for 4 h. On cooling to rt, an aqueous solution of acetic acid (2 mL, 80%) was added and the resulting acidic solution was refluxed for another 4 h. The reaction mixture on cooling was neutralized by adding powdered sodium bicarbonate portionwise till evolution of carbon dioxide ceased. Usual work up of the reaction mixture with diethyl ether followed by column chromatography [petroleum ether/ethyl acetate (7:3)] afforded the lactone **20** (50 mg, 75%); $[\alpha]_D^{25}$ +51.6 (c 1.2, $CHCl_3$); IR: ν_{max} 1770 cm^{-1}; ^{1}H NMR: δ 2.27 (1H, br), 2.80 (2H, m), 3.00 (2H, m), 3.50 (1H, dd, J=4.5, 12.6 Hz), 3.77 (3H, s), 3.84 (1H, br d, J=12.6 Hz), 4.14 (1H, m), 5.06–5.15 (2H, m), 5.48–5.57 (1H, m), 6.76 (3H, m), 7.17 (1H, t, J=7.8 Hz); ^{13}C NMR: δ 34.4 (CH_2), 46.1 (CH), 48.1 (CH), 55.5 (CH_3), 61.7 (CH_2), 82.8 (CH), 112.6 (CH), 115.6 (CH), 119.9 (CH_2), 122.3 (CH), 129.8 (CH), 135.0 (CH), 139.4 (C), 160.0 (C), 177.3 (CO); HRMS (ESI): calcd for $C_{15}H_{18}O_4Na$ $(M+Na)^+$, 285.1103; found, 285.1101.

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