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A simple route to the syntheses of both enantiomers of *trans*-oak lactone and (+)-*cis*-oak lactone

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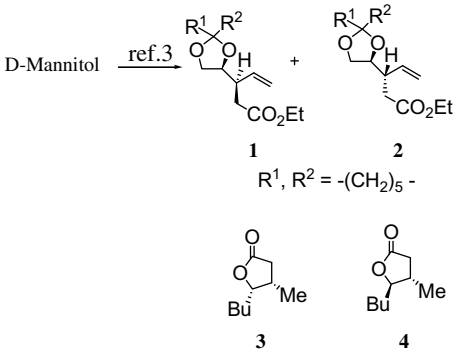
ABSTRACT

Stereocontrolled syntheses of both enantiomers of *trans*-oak lactone and (+)-*cis*-oak lactone have been achieved from a common precursor.

Natural products containing a substituted γ-butyrolactone unit are of considerable interest due to their important biological profiles.[1] Differentially protected succinate[2] is an extremely useful synthon for the synthesis of substituted butyrolactones. We have recently[3] developed a route for the synthesis of enantiopure masked succinates **1** and **2** from D-mannitol (Scheme 1). The wide applicability of these succinates has been demonstrated by the synthesis of both enantiomers of pseudo-nucleosides,[4] pseudo-sugars,[5] fused γ-butyrolactones[6] and substituted butyrolactones.[7] The (4*S*,5*S*)-*cis*- and (4*S*,5*R*)-*trans*-5-*n*-butyl-4-methyl γ-butyrolactones **3** and **4**, known as oak lactones, are extracted from wood in alcoholic beverages during fermentation and/or storage in oak barrels. The aroma of alcoholic beverages is believed to be due to the presence of a pure enantiomer of these lactones.[8]

Due to the non-availability of an efficient methodology for the synthesis of all the enantiomers of oak lactones, efforts towards evaluation of their sensory properties are lacking. Several approaches to the synthesis of these lactones have been reported.[9] Many of these approaches provide only one enantiomer of either the *cis*-lactone **3** or the *trans*-lactone **4**. Recently, an approach to the synthesis of both enantiomers of *cis*- and *trans*-oak lactone was reported by Brown et al.[8] Herein, we report an enantiodivergent route for the synthesis of both enantiomers of *trans*-oak lactone and (+)-*cis*-oak lactone from succinates **1** and **2**.

The advantageous feature of the present approach is the synthesis of both *cis*- and *trans*-oak lactones from a common succinate derivative **1** or **2**. The succinate derivative **1** produces one enantiomer whilst **2** produces its antipode. The major challenge towards this end is the stereocontrolled introduction of the butyl and methyl substituents on the carbon backbone of **1** and **2** with *syn* orientation for *cis*-oak lactone and *anti* orientation for *trans*-oak lactone. The desired stereodivergency has been achieved by reversing the sequence of introduction of the methyl and butyl groups. Enolate alkylation of the ester **1** with MeI followed by addition of *n*-BuLi to the aldehyde derived from the ester moiety provided the *cis* disposed Bu and Me groups for *cis*-oak lactone whilst an aldol-type condensation of the same enolate with *n*-pentanal followed by conversion of the ester unit of the succinate to a Me group provided the *trans* disposed Bu and Me groups for *trans*-oak lactone in a stereocontrolled fashion.



Scheme 1.

Alkylation of the lithium enolate of the ester **1** with MeI gave mainly compound **5**[10] in greater than 90% diastereomeric purity

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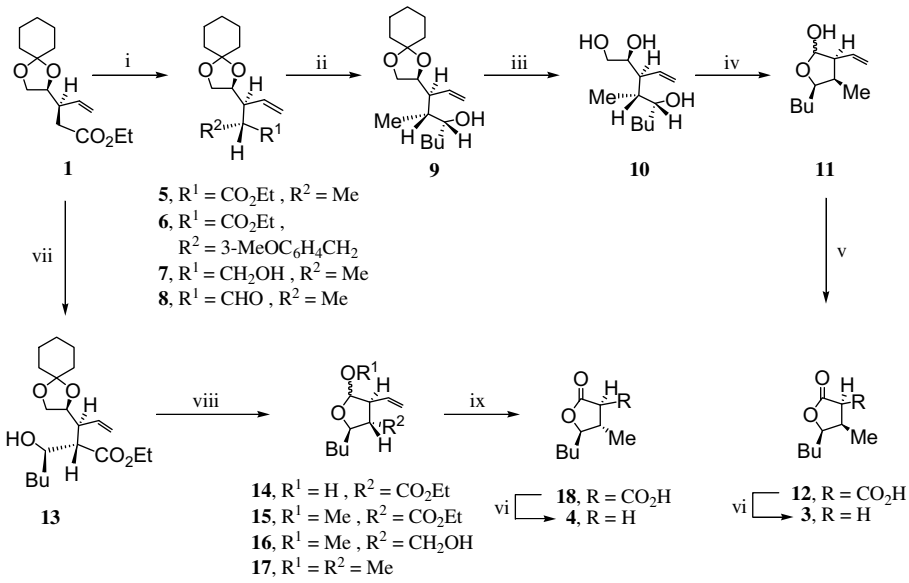


Scheme 2. Reagents and conditions: (i) LDA, THF, HMPA, −70 °C, MeI, 2.5 h, 71%; (ii) (a) LAH, Et_2O, rt, 2.5 h, 90%; (b) DMP, CH_2Cl_2, rt, 6 h, 95%; (c) *n*-BuLi, THF, −78 °C, 1.5 h, 76%; (iii) AcOH–H_2O, rt, 18 h, 90%; (iv) CH_3CN–H_2O, $NaIO_4$, rt, 1.5 h, 90%; (v) $RuCl_3{\cdot}xH_2O$, $NaIO_4$, CH_3CN, H_2O, CCl_4, rt, 3 h, 74%; (vi) toluene, 120 °C, 8 h, 85% for **3**; 92% for **4**; (vii) LDA, THF, HMPA, −70 °C, *n*-pentanal, 2.5 h, 75%; (viii) (a) AcOH–H_2O, $NaIO_4$, rt, 5 h, 85%; (b) MeOH, HCl (37%), rt, 18 h, 81%; (c) LAH, Et_2O, rt, 2.5 h, 91%; (d) TsCl, CH_2Cl_2, Py, DMAP; (e) LAH, THF, rt, 3 h, 83%; (ix) (a) AcOH–H_2O, 50 °C, 4 h, 80%; (b) $RuCl_3{\cdot}xH_2O$, $NaIO_4$, CH_3CN, H_2O, CCl_4, rt, 3 h, 77%.

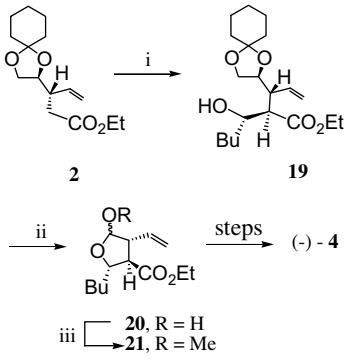
in 71% yield (Scheme 2). Stereochemical assignment of **5** was based on analogy[7] with the formation of **6** on alkylation of the same enolate with 3-methoxybenzyl bromide. The ester **5** was then reduced with $LiAlH_4$ and the resulting alcohol **7** was oxidized with Dess–Martin periodinane (DMP) to yield the aldehyde **8** in excellent yield. Addition of *n*-BuLi to the aldehyde produced a mixture of the hydroxy compound **9** and its diastereoisomer in a 6:1 ratio in reasonably good yield. The structure of the major addition product was predicted as **9** based on the Felkin–Anh model. This assignment was confirmed by its transformation to *cis*-oak lactone **3**. The mixture of hydroxy compound **9** and its minor diastereoisomer was treated with aqueous acetic acid. The resulting mixture of products after column chromatography provided pure triol **10** as the major product in 79% yield. Treatment of **10** with $NaIO_4$ in aqueous acetonitrile afforded the lactol **11** in excellent yield. The lactol **11** was subjected to oxidation with RuO_4 to give the keto-acid **12** in 74% yield. Finally, heating a solution of this keto-acid in toluene under reflux effected smooth decarboxylation to produce (+)-*cis*-oak lactone **3** in 85% yield. The spectral data and optical rotation observed for the lactone obtained in this way were found to be closely comparable with those reported in the literature.[8,9b,11]

We next focused on the synthesis of the *trans*-oak lactone **4** from the same succinate ester **1**. Reaction of the lithium enolate of the ester **1** with *n*-pentanal afforded the aldol product **13** (Scheme 2) in 75% yield as the main product. The assignment of relative stereochemistry to the substituents in **13** was based on the stereochemical outcome in analogous[12] aldol condensation of the enolate of the ester **1** with aromatic aldehydes. This assignment was confirmed by its transformation to the *trans*-oak lactone **4**. Acid induced deprotection of the ketal in **13** followed by periodate cleavage of the resulting diol produced a 1:1 anomeric mixture of the lactol **14**. For conversion of the carbethoxy group to an Me group, the lactol **14** was first treated with MeOH–HCl to produce the acetal **15** in 81% yield. The ester group in **15** was then reduced to give the alcohol **16**. Reduction of the tosylate derived from the alcohol **16** produced **17** in an overall excellent yield.

Deacetalization of **17** followed by RuO_4 oxidation gave the keto-acid **18** in excellent yield. Finally, decarboxylation of the keto-acid **18** was achieved thermally to produce (+)-*trans*-oak lactone **4** in 92% yield.

For the synthesis of (−)-*trans*-oak lactone, the lithium enolate of the ester **2** was allowed to react with *n*-pentanal to afford the hydroxy-ester **19** in very good yield with excellent diastereoisomeric purity (Scheme 3). Successive treatment of the hydroxy-ester **19** with aqueous acetic acid—sodium metaperiodate gave the hemiacetal **20**. The latter on treatment with MeOH–HCl produced the acetal **21**, an enantiomer of **15**. The acetal **21** was then converted to (−)-*trans*-oak lactone following the steps employed for conversion of the acetal **15** to (+)-**4**. Thus, both (+)-*trans*-oak lactone and (−)-*trans*-oak lactone can be synthesized from D-mannitol through the esters **1** and **2**, respectively. We have illustrated above the synthesis of (+)-*cis*-oak lactone from the ester **1**. Following an identical protocol, the succinate derivative **2** is expected to produce (−)-*cis*-oak lactone **3**.

In conclusion, we have developed a stereocontrolled route for the syntheses of both *cis*-oak lactone and *trans*-oak lactone from a common precursor. This approach also afforded both enantiomers of *trans*-oak lactone and (+)-*cis*-oak lactone and offers the possibility of synthesizing (−)-*cis*-oak lactone.



Scheme 3. Reagents and conditions: (i) LDA, THF, HMPA, −70 °C, *n*-pentanal, 2.5 h, 78%; (ii) AcOH-H_2O, $NaIO_4$, 50 °C, 6 h, 82%; (iii) MeOH, HCl (37%), rt, 18 h, 84%.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.026.

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10. All new compounds were characterized on the basis of ^{1}H NMR, ^{13}C NMR and HRMS data. Physical characteristics for selected compounds: Compound **5**: $[\alpha]_D^{25}$ +31 (*c* 0.6, $CHCl_3$); ^{1}H NMR (from mixture): (300 MHz, $CDCl_3$): δ 1.11 (3H, d, *J* = 6.9 Hz), 1.25 (3H, t, *J* = 7 Hz), 1.36 (2H, br s), 1.53–1.57 (8H, m), 2.42 (1H, m), 2.64 (1H, m), 3.60 (1H, t, *J* = 7.5 Hz), 3.93 (1H, t, *J* = 7.5 Hz), 4.12 (3H, m), 5.05–5.23 (2H, m), 5.23–5.73 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 15.6, 24.1, 25.4, 34.9, 35.9, 41.2, 49.2, 60.5, 67.1, 74.4, 75.9, 109.6, 119.6, 134.5, 176.1; HRMS (ESI) calcd for $C_{16}H_{26}O_4Na$ $(M+Na)^+$, 305.1729; found, 305.1728. Compound **10**: $[\alpha]_D^{25}$ +13.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR: (300 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 6.9 Hz), 0.91 (3H, d, *J* = 6.9 Hz), 1.24–1.51 (6H, m), 1.76 (1H, m), 2.12 (1H, m), 3.32 (3H, br), 3.48 (2H, m), 3.79 (1H, m), 3.92 (1H, m), 5.05 (1H, d, *J* = 17 Hz), 5.14 (1H, dd, *J* = 1.8, 10.5 Hz), 5.88–6.00 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 14.2, 22.8, 28.8, 34.6, 40.3, 50.3, 65.9, 70.1, 71.6, 117.9, 137.2; HRMS (ESI) calcd for $C_{12}H_{24}O_3Na$ $(M+Na)^+$, 239.1623; found, 239.1627. Compound **3**: $[\alpha]_D^{25}$ +74 (*c* 0.4, $CHCl_3$) (lit.[11] $[\alpha]_D^{25}$) +76; ^{1}H NMR: (300 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* = 6.9 Hz), 1.01 (3H, d, *J* = 6.9 Hz), 1.18–1.67 (6H, m), 2.19 (1H, dd, *J* = 16.5, 3.6), 2.57 (1H, m), 2.70 (1H, dd, *J* = 7.8, 16.8), 4.41 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0, 22.7, 28.2, 29.7, 33.1, 37.7, 83.8, 177.1; HRMS (ESI) calcd for $C_{18}H_{32}O_4Na$ $(2M+Na)^+$, 335.2198; found, 335.2190. Compound **13**: $[\alpha]_D^{25}$ +32 (*c* 0.6, $CHCl_3$); ^{1}H NMR (from mixture): (300 MHz, $CDCl_3$): δ 0.84 (3H, partly resolved t, *J* = 6.6 Hz), 1.21–1.53 (19H, m), 2.49–2.84 (3H, m), 3.55–4.17 (6H, m), 5.04–5.22 (2H, m), 5.77 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$):δ 14.1, 14.3, 22.6, 23.8, 23.9, 25.2, 27.8, 32.9, 34.7, 35.7, 46.3, 53.7, 60.6, 66.6, 70.8, 75.5, 109.7, 119.6, 134.6, 173.2; HRMS (ESI) calcd for $C_{20}H_{34}O_5Na$ $(M+Na)^+$, 377.2304; found, 377.2301. Compound **16**: $[\alpha]_D^{25}$ −8.3 (*c* 0.2, $CHCl_3$); ^{1}H NMR: (300 MHz, $CDCl_3$): δ 0.90 (3H, t, *J* = 7 Hz), 1.35 (3H, m), 1.47–1.60 (3H, m), 1.71 (1H, s), 2.41 (1H, m), 2.91 (1H, dd, *J* = 7.5, 9.6 Hz), 3.32 (3H, s), 3.63 (2H, m), 3.84 (1H, m), 4.68 (1H, s), 5.13 (1H, d, *J* = 12 Hz), 5.21 (1H, d, *J* = 17 Hz), 5.75 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.8, 28.8, 37.3, 48.7, 52.8, 54.5, 61.8, 81.8, 108.6, 118.3, 134.7; HRMS (ESI) calcd for $C_{12}H_{22}O_3Na$ $(M+Na)^+$, 237.1467; found, 237.1468. Compound **4**: $[\alpha]_D^{25}$ +93 (*c* 0.2, $CHCl_3$) (lit.[11] $[\alpha]_D^{25}$) +96; ^{1}H NMR: (300 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* = 6.4 Hz), 1.13 (3H, d, *J* = 6.3 Hz), 1.20–1.75 (6H, m), 2.16–2.21 (2H, m), 2.67 (1H, dd, *J* = 12, 21 Hz), 4.00 (1H, dt, *J* = 7.5, 3.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 17.6, 22.6, 27.9, 33.8, 36.2, 37.2, 87.6, 176.8; HRMS (ESI) calcd for $C_{18}H_{32}O_4$ $(2M+H)^+$, 313.2373; found, 313.2371.
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