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Enantiodivergent synthesis of (−)-methylenolactocin and (+)-methylenolactocin from D-mannitol

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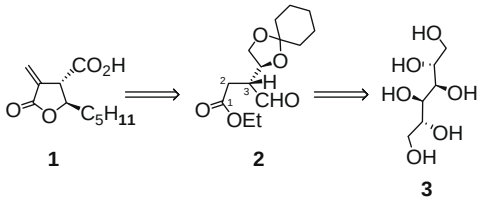
ABSTRACT

An enantiodivergent synthesis of both enantiomers of methylenolactocin is described through stereocontrolled addition of *n*-pentyl magnesium bromide to two D-mannitol-derived diastereomerically related aldehydes having an α-chiral center with a β hetero atom.

Natural products containing a substituted γ-butyrolactone unit with a carboxylic acid at β position, commonly known as paraconic acids,[1] are ubiquitous. Many of these compounds exhibit a wide range of interesting biological activities. Among them, methylenolactocin **1**[2] has attracted considerable attention because of its strong antitumor, antibiotic activity, and densely functionalized structure. A number of approaches have been developed for the synthesis of **1** in racemic[3,4] as well as in enantiomerically pure form.[5] The asymmetric route, reported so far, mainly dealt with the synthesis of the natural enantiomer, (−)-methylenolactocin. However, only a few approaches address the synthesis of (+)-methylenolactocin. As part of our continued interest[6] in asymmetric synthesis of natural products containing γ-lactone unit, we planned to develop a strategy that would afford both enantiomers of methylenolactocin from a single enantiomer.

A major challenge in the synthesis of methylenolactocin is the control of trans stereochemistry between the 4,5-substituents. However, total stereocontrol was observed only in a few approaches. We visualized that addition of an appropriate nucleophilic species to the aldehyde **2** would proceed stereoselectively (Scheme 1). The ketal unit would play the crucial role in dictating the stereochemical outcome. Generation of the carboxylic acid moiety from the ketal unit at a latter stage would accomplish the synthesis of **1**. Thus, while **2** would provide one enantiomer of methylenolactocin, its C-3 diastereoisomer would provide the other enantiomer.

To begin with, D-mannitol was transformed to the masked succinates **4** and **5** following the protocol developed earlier by us[7] (Scheme 2). Oxidative cleavage (OsO_4–$NaIO_4$) of the vinyl group in **4** afforded the aldehyde **2**[8] in 80% yield. Synthesis of methylenolactocin from **2** required stereocontrolled addition of the appropriate nucleophilic species to the aldehyde group in **2**. In case, addition of a Grignard reagent to the aldehyde **2** having an α-chiral center proceeds through Felkin-Anh model **6**, a trans disubstituted product **7** is expected (Fig. 1). However, the aldehyde **2** has also an oxygen atom at β to the aldehyde unit and addition might proceed through a chelated intermediate **8**. This would give rise to a cis disubstituted product **9**. Addition of Grignard reagent to an aldehyde having an α-chiral center with a hetero atom at β position has been reported to proceed non-stereoselectively.[9] With this background, the aldehyde **2** was allowed to react with *n*-pentyl magnesium bromide. To our delight, addition to the aldehyde **2** proceeded in a highly stereoselective fashion with spontaneous lactonization of the hydroxy-ester **7** (R = *n*-C_5H_{11}) to give exclusively the lactone **10** in 60% yield (Scheme 2). The lactone **10** could



Scheme 1. A retrosynthetic route to methylenolactocin.

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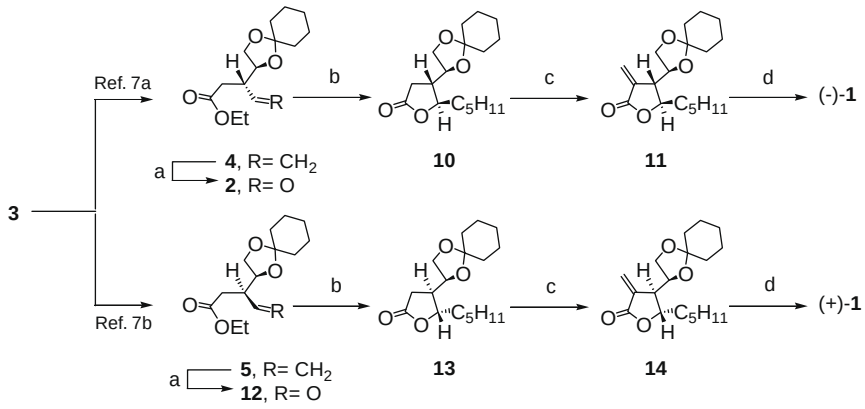

Scheme 2. Synthesis of (−)- and (+)-methylenolactocin. Reagents and conditions: (a) OsO_4–$NaIO_4$, THF–H_2O (2:1), 80–82%; (b) *n*-$C_5H_{11}MgBr$, THF, rt, 60–62%; (c) LDA, THF, HCHO then MsCl, DCM, Et_3N, 24 h, 50% in two steps; (d) (i) CH_3CO_2H–H_2O (4:1); (ii) Jones reagent, acetone, 58–60% in two steps.

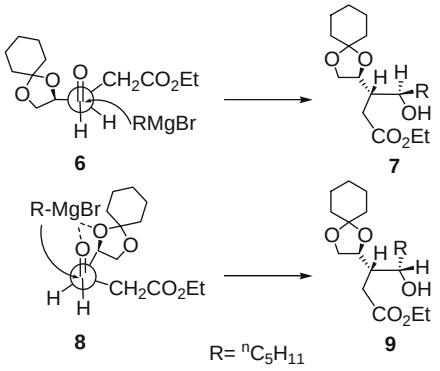

Figure 1. Possible modes of RMgX addition.

also arise by the addition of *n*-pentyl magnesium bromide through a seven-membered chelate involving the ethyl ester oxygen. However, it is difficult to ascertain the actual reaction path involved for the observed stereochemical outcome. The stereochemical assignment to the lactone **10** was confirmed after its transformation to methylenolactocin as described below. α-Methylenation of the lactone **10** was achieved by reaction of its lithium enolate with formaldehyde followed by treatment of the resulting hydroxymethyl derivative with methane sulfonyl chloride in the presence of excess triethyl amine to afford the lactone **11** in overall good yield. α-Methylene lactone **11** was transformed to (−)-methylenolactocin **1** through acid-catalyzed deketalization and Jones oxidation of the resulting diol. Methylenolactocin, $[\alpha]_D^{23}$ −6.46 (*c* 0.5, MeOH) (lit.[5a] $[\alpha]_D^{23}$ −6.7 (*c* 0.5, MeOH), thus obtained exhibits spectral data closely comparable to those reported in the literature.

A similar protocol was followed for synthesis of (+)-methylenolactocin from the succinate derivative **3**. Treatment of **5** with OsO_4–$NaIO_4$ led to the aldehyde **12** in 82% yield. Addition of *n*-pentyl magnesium bromide to the aldehyde **12** gave the lactone **13** in 62% yield as the only isolable product. The lactone **13** was then transformed to (+)-methylenolactocin **1**, $[\alpha]_D^{23}$ +6.5 (*c* 1.5, MeOH) through the α-methylene lactone **13** using the protocol described above for transformation of **7** to (−)-**1**.

In conclusion, we have developed a simple route for the synthesis of both enantiomers of methylenolactocin. The key step involves stereocontrolled addition of *n*-pentyl magnesium bromide to the aldehyde moiety of two diastereomerically related masked succinate derivatives having an α-chiral center prepared from D-mannitol.

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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.2009.10.011.

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8. All new compounds were characterized on the basis of IR, ^1H, ^{13}C NMR and HRMS data. Physical characteristics for selected compounds: Compound **10**: $[\alpha]_D^{27}$ −35.8 (*c* 2.2, $CHCl_3$); IR: ν_{max} 1778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 6 Hz), 1.25–1.66 (17H, m), 1.88 (1H, m), 2.32 (1H, m), 2.56 (1H, dd, *J* = 8.7, 18 Hz), 2.63 (1H, dd, *J* = 7.5, 18 Hz), 3.53 (1H, t, *J* = 7 Hz), 4.06 (1H, t, *J* = 6.8 Hz), 4.13–4.16 (1H, m), 4.34 (1H, q, *J* = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.6 (CH_2), 23.8 (CH_2), 24.0 (CH_2), 25.1 (CH_2), 25.2 (CH_2), 29.7 (CH_2),

31.6 (CH_2), 34.7 (CH_2), 35.1 (CH_2), 36.1 (CH_2), 43.5 (CH), 67.2 (OCH_2), 74.5 (OCH), 82.5 (CH), 110.4 (C), 176.3 (CO); HRMS (ESI) calcd for $C_{17}H_{28}O_4Na$ $(M+Na)^+$, 319.1884; found 319.1885. Compound **11**: $[\alpha]_D^{27}$ +4.6 (*c* 0.4, $CHCl_3$); IR: ν_{max} 1766 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, t, *J* = 6 Hz), 1.24–1.61 (18H, m), 2.96 (1H, br s), 3.62 (1H, t, *J* = 7.4 Hz), 4.01 (1H, t, *J* = 7.2 Hz), 4.22 (1H, q, *J* = 6 Hz), 4.33 (1H, br s), 5.77 (1H, s), 6.34 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 22.4 (CH_2), 23.7 (CH_2), 23.9 (CH_2), 24.5 (CH_2), 25.0 (CH_2), 31.3 (CH_2), 34.4 (CH_2), 36.2 (CH_2), 36.4 (CH_2), 46.8 (CH), 65.9 (OCH_2), 76.4 (OCH), 79.2 (OCH), 110.3 (C), 124.9 (CH_2), 135.4 (CH_2), 169.8 (CO); HRMS (ESI) calcd for $C_{18}H_{28}O_4Na$ $(M+Na)^+$, 331.1885; found 331.1887. Compound (−)-**1**: $[\alpha]_D^{26}$ −6.46 (*c* 0.5, MeOH); IR: ν_{max} 1743, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 6.7 Hz), 1.21–1.33 (6H, m), 1.67–1.78 (2H, m), 3.61–3.63 (1H, m), 4.81 (1H, q, *J* = 5.9 Hz), 6.02 (1H, d, *J* = 2.4 Hz), 6.46 (1H, d, *J* = 2.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.5 (CH_2), 24.5 (CH_2), 31.4 (CH_2), 35.8 (CH_2), 49.6 (CH), 79.1 (OCH), 126.1 (CH_2), 132.6 (CH_2), 168.5 (CO), 173.9 (COOH); HRMS (ESI) calcd for $C_{11}H_{16}O_4Na$ $(M+Na)^+$, 235.0943; found 235.0946.

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