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Titanocene (III) chloride mediated radical induced synthesis of (−)-methylenolactocin and (−)-protolichesterinic acid

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ABSTRACT

Enantioselective synthesis of two *anti*-tumor antibiotics, (−)-methylenolactocin and (−)-protolichesterinic acid, has been achieved through titanocene(III) chloride mediated radical cyclization reaction starting from commercially available D-mannitol. Titanocene(III) chloride (Cp_2TiCl) was prepared in situ from commercially available titanocene dichloride (Cp_2TiCl_2) and zinc dust in THF.

1. Introduction

The α-methylene-γ-butyrolactone ring system is an important building block for a major class of biologically active natural products.[1] The biological activities of such compounds may be attributed to the α,β-unsaturated carbonyl moiety, which mainly acts as a Michael acceptor of different biological nucleophiles. Paraconic acid[2] is probably one of the simple classes of naturally occurring γ-butyrolactone derivative with a carboxylic acid group at C-4 position with an *exo*-methylene or methyl group at C-3 position. But substitution pattern varies at C-5 and obviously stereochemical relationship also varies with the substituent on the adjacent carbon.[2] Most of these densely functionalized paraconic acid molecules are biologically active and some of them are isolated in both optically active form.

Since, aforesaid compounds exhibit important biological activities such as antifungal, *anti*-tumor, antibacterial etc., the synthesis of such lactones have attracted considerable attention to the organic chemists. Therefore, designing a general strategy for the synthesis of such densely functionalized molecules in both active forms is still desirable. We report here mainly the synthesis of two paraconic acids, (−)-methylenolactocin and (−)-protolichesterinic acid through radical cyclization reaction starting from the easily accessible (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde. Methylenolactocin, an isomerization prone *anti*-tumor antibiotic was isolated from culture filtrate of *Penicilium* sp.[3,4,6f] and protolichesterinic acid with antibacterial properties was isolated from *Cetrariaislandica*.[4,6f] Both of them are effective in inhibiting the growth of gram positive bacteria. A number of reports has been found in the literature for the synthesis of methylenolactocin and protolichesterinic acid in racemic[5] as well as in optically active forms.[6] But most of the reported asymmetric methods suffer from generality, use of toxic reagents, number of steps, and moderate yield. It is noteworthy that although (+)-protolichesterinic acid is widely distributed in *Parmelia* sp., but both (+) and (−) antipodes have been isolated from different sources of *Cetraria*.[6h]

The radical chemistry in organic synthesis has become an inevitable tool in recent years due to the mildness and desired stereochemical outcome. Due to several difficulties associated with the use of tributyltin hydride as a radical source, titanocene(III) chloride (Cp_2TiCl) has widely been explored for the homolytic cleavage of epoxides to generate a carbon-centered radical, which has subsequently been used for the synthesis of complex organic molecules.[7] Titanocene(III) chloride (Cp_2TiCl) was prepared from commercially available titanocene dichloride and zinc dust in THF.[7a] In continuation to our studies[8] toward the synthesis bioactive natural products, we have now achieved the total synthesis (−)-methylenolactocin (**1a**) and (−)-protolichesterinic (**1b**) through radical cyclization reaction using titanocene(III) chloride as the radical initiator.

2. Results and discussion

Thus, (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde (**2**) on treatment with appropriate Grignard reagent (RMgX)[9] yielded the

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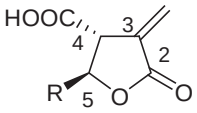
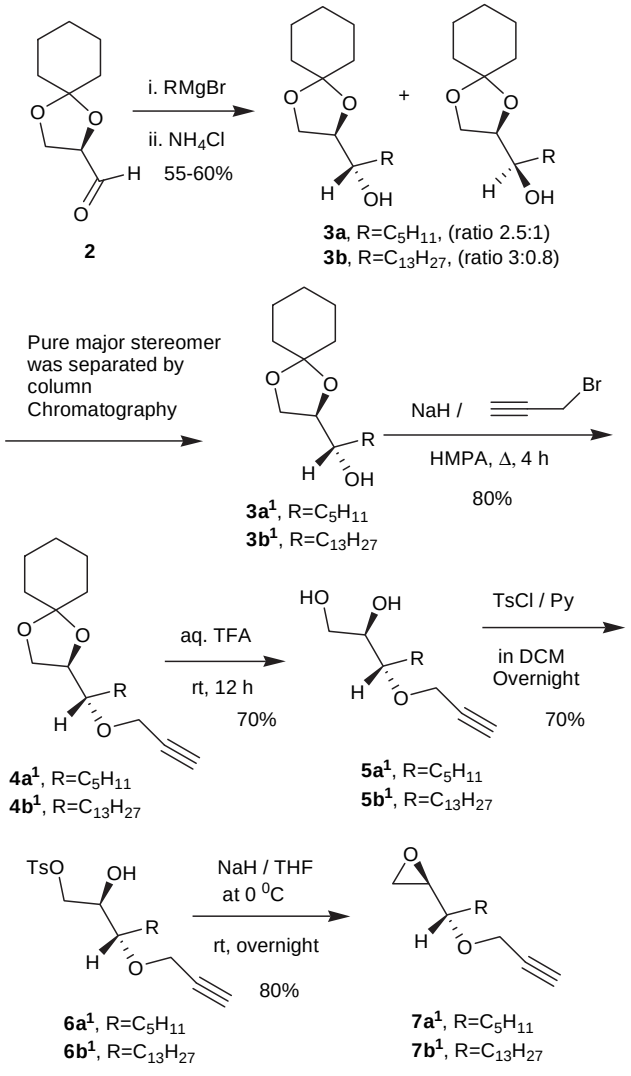


R = C_5H_{11}, (-)-Methylenolactocin (**1a**)
R = $C_{13}H_{27}$, (-)-Protolichesterinic acid (**1b**)

diasteromeric alcohols **3a** (mixture of two isomers, ratio 2.5:1) or **3b** (mixture of two isomers, ratio 3:0.8). The pure major isomer **3a**[1] or **3b**[1] was separated by column chromatography and was reacted with propargyl bromide in the presence of NaH in HMPA/THF to furnish the propargyl ether **4a**[1] or **4b**[1] in good yield (Scheme 1).[10] The *erythro*-selectivity of the addition of Grignard reagent with



Scheme 1.

the aldehyde **2** to afford **3a**[1] or **3b**[1] as the major product can be explained with the analogy reported by Mulzer et al.[11] Not only the bulky cyclohexylidene moiety but also the metal used (magnesium) control the nucleophilic attack at *Si* face (Cram direction) at the neighboring prochiral carbonyl center of **2** favoring the formation of **3a**[1] or **3b**[1] (Fig. 1). Deprotection of the cyclohexylidene group in **4** using aqueous TFA yielded the diol **5**. Selective monotosylation of the primary alcohol in **5** by TsCl and excess of pyridine in CH_2Cl_2 produced the tosyl derivative **6** in good yield. Compound **6** on

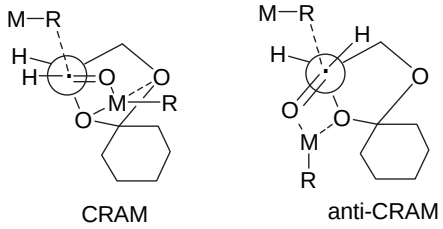
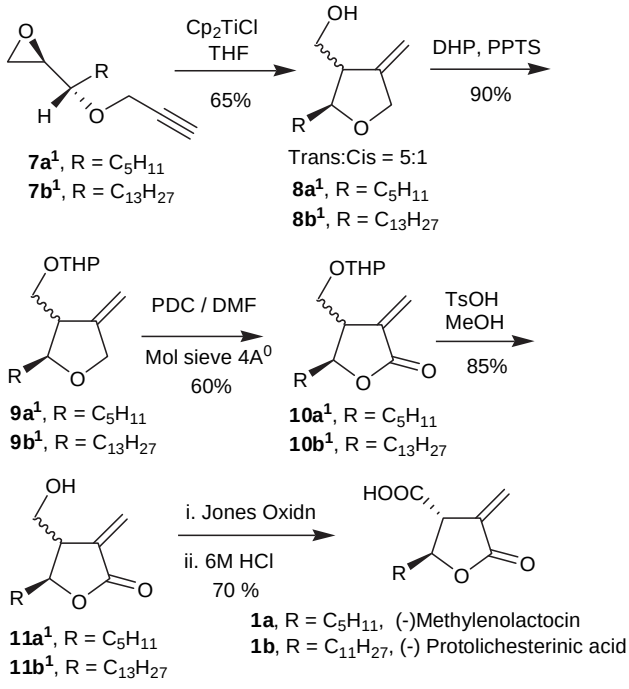


Figure 1.

treatment with NaH in THF furnished the epoxide **7**. The epoxide **7** was subjected to radical cyclization reaction using Cp_2TiCl in THF to produce the tetrahydrofuran derivative **8** as a mixture two isomer (trans/cis, 5:1) (Scheme 2). At this stage, two isomers could not be separated by usual chromatographic methods. The crude cyclized product **8** was then converted to the corresponding THP-ether **9** with dihydropyran and PPTS in CH_2Cl_2 in excellent yield. The crude THP-ether **9** was then subjected to PDC oxidation in DMF to yield the butyrolactone **10** as a mixture of two isomers in a ratio of 5:1. Without further separating two isomers the crude lactone **10** was treated with PTS-OH in MeOH to furnish the alcohol **11**. The crude alcohol **11** was subjected to Jones oxidation[12] and the crude product obtained after usual work-up was treated with 6 M HCl in benzene/THF (1:1) mixture to furnish solely the trans isomer **1**. Probably, in strong acidic conditions epimerization[13] took place to give the thermodynamically more stable (−)-methyleneolactocin (**1a**) from **11a**[1] and (−)-protolicheterinic acid (**1b**) from **11b**[1] in good overall yield. Fortunately, no trace of the isomerization of the *exo* double bond was observed in the crude product under the acidic condition.



Scheme 2.

3. Conclusions

In conclusion, we have synthesized two *anti*-tumor antibiotics (−) methylenolactocin and (−) protolichesterinic acid through radical cyclization reaction starting from inexpensive D-mannitol as a chiral pool using titanocene(III) chloride as a radical initiator. We believe that by applying the same synthetic sequences,

(+)-methylenolactocin and (+)-protolichesterinic acid can also be synthesized starting with the minor isomer of **3a** and **3b**, respectively.

4. Experimental

4.1. General

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with Bruker DPX 300 and Bruker AVANCE III 500 spectrometer using tetramethyl silane as the internal standard. IR spectra were recorded on Shimadzu FT IR-8300. Column chromatography was performed on silica gel (60–120 mesh) and preparative TLC was performed using pre-coated silica 60 F 254 plates (0.2 mm). High-resolution mass spectra were obtained using a Qtof Micro YA263 instrument. Diethyl ether and tetrahydrofuran were freshly distilled from sodium. Methylene chloride was freshly distilled over calcium hydride. Light petroleum of boiling range 60–80 °C was used for chromatography. Elemental analyses were done in the Inorganic Chemistry Department of this Institute using 2400 Series II CHNS analyzer.

*4.1.1. Synthesis of **3a**[1] and **3b**[1].* To a stirred solution of Grignard reagent at −50 °C [prepared by the treatment of the halide (RX) (0.075 mol) with a suspension of Mg (1.92 g, 0.08 g equiv) in THF (100 mL)] was added **2** (5.1 g, 0.03 mol) in THF (60 mL) over a period of 1 h. The mixture was stirred at −50 °C for 3 h at room temperature overnight. Saturated aqueous NH_4Cl was added to the reaction mixture followed by extraction with ether (3×10 mL). The combined organic layer was washed with water (10 mL) and brine (5 mL), and finally dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography over silica gel (15% ethyl acetate/light petroleum, R_f=0.70) to afford resulting in separation of the pure major isomer **3a**[1] (3.0 g, 43%) as a viscous oil. $[\alpha]_D^{25.7}$ −8.70 (*c*, 4.32 in $CHCl_3$); IR (neat): 3491, 2900, 1464, 1448, 1043 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (t, *J*=6.5 Hz, 3H), 1.12–1.57 (m, 18H), 3.64–3.72 (m, 2H), 3.80–3.90 (m, 1H), 3.94–4.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.6, 23.8, 23.9, 25.0, 25.2, 25.6, 25.8, 31.8, 32.7, 34.9, 36.2, 64.2, 70.8, 78.4, 109.5; HRMS calcd for $C_{14}H_{26}O_3Na$ $[M+Na]^+$ 265.178, found 265.178.

*4.1.1.1. Minor isomer of **3a**.* Yield 17%. R_f=0.79 (15% ethyl acetate/light petroleum); $[\alpha]_D^{26.0}$ +6.2 (*c*, 1.60 in $CHCl_3$); IR (neat): 3462, 3316, 2950, 1454, 1272, 1109 cm^{-1}; ^{1}H NMR (300 MHz): δ 0.88 (t, *J*=6.7 Hz, 3H), 1.25–1.42 (m, 24H), 1.59–1.84 (m, 13H), 3.54–3.60 (m, 1H), 3.71–3.87 (m, 2H), 3.93–4.03 (m, 1H); ^{13}C NMR (75 MHz): δ 14.2, 22.8, 23.9, 24.0, 24.0, 25.9, 26.8, 29.5, 29.6, 29.7, 29.8, 32.0, 32.8, 35.0, 36.8, 37.1, 62.4, 76.6, 81.3, 109.2; HRMS calcd for $C_{22}H_{42}O_3Na$ $[M+Na]^+$ 337.3032, found 337.3030.

Compound **3b**[1] (43.4%) was prepared following the same procedure described for **3a**[1]: R_f=0.40 (5% ethyl acetate/light petroleum); $[\alpha]_D^{26.2}$ −5.45 (*c*, 1.91 in $CHCl_3$); IR (neat): 3454, 3300, 2900, 1464, 1448, 1280, 1101 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.5 Hz, 3H), 1.26–1.44 (m, 26H), 1.45–1.65 (m, 8H), 3.77–3.81 (m, 1H), 3.87–3.90 (m, 1H), 3.94–3.96 (m, 1H), 4.01–4.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.8, 23.9, 24.1, 25.3, 25.9, 29.5, 29.6, 29.7, 29.8, 32.0, 32.7, 35.0, 36.3, 64.2, 70.8, 78.4, 109.5; HRMS calcd for $C_{22}H_{42}O_3Na$ $[M+Na]^+$ 377.3032, found 377.3035.

*4.1.1.2. Minor isomer of **3b**.* Yield 11.6%. R_f=0.48 (5% ethyl acetate/light petroleum); $[\alpha]_D^{24.4}$ +11.4 (*c*, 1.00 in $CHCl_3$); IR (neat): 3450, 2933, 2860, 1448, 1280, 1101 cm^{-1}; ^{1}H NMR (300 MHz): δ 0.82 (t, *J*=6.6 Hz, 3H), 1.14–1.34 (m, 8H), 1.36–1.80 (m, 10H), 3.41–3.62 (m, 1H), 3.64–3.70 (m, 2H), 3.87–3.96 (m, 1H); ^{13}C NMR (75 MHz): δ 14.0, 22.5, 23.8, 24.0, 24.3, 25.1, 25.6, 26.8, 31.8, 33.3, 34.9, 36.6, 65.8, 72.4, 81.1, 109.9; HRMS calcd for $C_{14}H_{26}O_3Na$ $[M+Na]^+$ 265.178, found 265.170.

*4.1.2. Synthesis of **4a**[1] and **4b**[1].* To a stirred suspension of sodium hydride (595 mg, 60% dispersion, 24.8 mmol) in a mixture of dry THF (25 mL) was added dropwise a solution of alcohol **3a**[1] (1.5 g, 6.2 mmol) in dry THF (25 mL) at 0 °C under N_2. Then HMPA (0.5 mL) was added to the reaction mixture. Then, a solution of propargyl bromide (950 mg, 8.06 mmol) in dry THF (20 mL) was added dropwise at 0 °C over 30 min. The reaction mixture was refluxed for 4 h and then stirred overnight at room temperature. The reaction mixture was then carefully quenched with ice-water. After removal of most of THF under reduced pressure, the resulting residue was extracted with diethyl ether (3×30 mL). The combined ether extract was washed with water (10 mL), brine (5 mL), and finally dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a viscous liquid, which was purified by column chromatography over silica gel (5% ethyl acetate/light petroleum, R_f=0.76) to furnish **4a**[1] (1.4 g, 80%) as a viscous liquid. $[\alpha]_D^{25.0}$ +1.24 (*c*, 6.07 in $CHCl_3$); IR (neat): 3310, 2935, 2115, 1448, 1163, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, *J*=6.7 Hz, 3H), 1.30–1.63 (m, 18H), 2.41 (t, *J*=2.4 Hz, 1H), 3.60–3.65 (m, 1H), 3.88–3.97 (m, 1H), 3.99–4.08 (m, 2H), 4.29 (d, J=2.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.7, 24.0, 24.2, 24.9, 25.3, 31.2, 32.1, 35.1, 36.3, 58.1, 65.7, 74.1, 77.6, 78.5, 80.5, 109.7; HRMS calcd for $C_{17}H_{28}O_3Na$ $[M+Na]^+$ 303.1936, found 303.1937.

Compound **4b**[1] (72%) was prepared from **3b**[1] following the similar procedure described for the **4a**[1]. R_f=0.50 (2% ethyl acetate/light petroleum); $[\alpha]_D^{27.1}$=+2.51 (*c*, 4.95 in $CHCl_3$); IR (neat): 3312, 2926, 2852, 2115, 1464, 1448, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, *J*=6.5 Hz, 3H), 1.19–1.56 (m, 35H), 2.34 (t, *J*=2.4 Hz, 1H), 3.53–3.56 (m, 1H), 3.81–3.99 (m, 2H), 4.21 (d, *J*=2.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.7, 23.8, 24.0, 25.1, 25.2, 29.3, 29.5, 29.6, 29.6, 31.1, 31.9, 34.9, 36.1, 58.0, 65.5, 73.9, 77.5, 78.3, 80.4, 109.5; HRMS calcd for $C_{25}H_{44}O_3Na$ $[M+Na]^+$ 415.3188, found 415.3187.

*4.1.3. Synthesis of **5a**[1] and **5b**[1].* Compound **4a**[1] (1.0 g, 3.6 mmol) was stirred with water–trifluoroacetic acid (1:2) for 12 h at room temperature. The reaction mixture was extracted with ethyl acetate (3×30 mL) and the combined organic layer was washed with brine (5 mL) then dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue obtained was chromatographed over silica gel (50% ethyl acetate/light petroleum, R_f=0.44) to furnish the diol **5a**[1] (535 mg, 75%) as a viscous oil. $[\alpha]_D^{27.8}$ +21.41 (*c*, 1.66 in $CHCl_3$); IR (neat): 3408, 3308, 2955, 2860, 2115, 1456, 1261, 1089 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J*=7 Hz, 3H), 1.27–1.36 (m, 6H), 1.42–1.62 (m, 2H), 2.45 (t, *J*=2.3 Hz, 1H), 2.56 (br s, 2H), 3.61–3.61 (m, 1H), 3.68–3.75 (m, 3H), 4.20 (dd, *J*=2.5, 16 Hz, 1H), 4.29 (br d, *J*=16 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.7, 25.1, 30.4, 32.1, 57.9, 63.3, 72.8, 74.7, 80.2, 81.0; HRMS calcd for $C_{11}H_{20}O_3Na$ $[M+Na]^+$ 223.131, found 223.1312.

Compound **5b**[1] prepared from **4b**[1] following the similar procedure described for **5a**[1] (70%) as a crystalline solid. R_f=0.24 (30% ethyl acetate/light petroleum). Mp 53–55 °C (ethyl acetate/light petroleum); $[\alpha]_D^{25.7}$ +9.12 (*c*, 7.10 in $CHCl_3$); IR (KBr): 3367, 3265, 2918, 2125, 1462, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (t, *J*=7 Hz, 3H), 1.16–1.23 (m, 21H), 1.38–1.40 (m, 3H), 2.39 (t, *J*=2.5 Hz, 1H), 3.56–3.72 (m, 4H), 4.14 (dd, *J*=2.5 Hz, 16 Hz, 1H), 4.23 (dd, *J*=2.5 Hz, 16 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.8, 25.4, 29.1, 29.4, 29.6, 29.7, 29.9, 29.9, 30.1, 30.3, 32.0, 45.0, 57.8, 62.0, 63.3, 72.9, 74.6, 80.7; HRMS calcd for $C_{19}H_{36}O_3Na$ $[M+Na]^+$ 335.2562, found 335.2565.

*4.1.4. Synthesis of **6a**[1] and **6b**[1].* To a stirred solution of **5a**[1] (930 mg, 4.65 mmol) and excess of pyridine (3 ml) in dry CH_2Cl_2 (20 mL) at

0 °C was added *p*-toluenesulfonyl chloride (1.06 g, 5.58 mmol) in portions during 1 h. After stirring for 12 h at room temperature, the mixture was poured into ice-water. The organic layer was separated, and the aqueous portion was extracted with CH_2Cl_2 (3×30 mL). The combined organic extract was washed successively with aqueous 2 M HCl (5 mL), water (5 mL), brine (5 mL), and finally dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by column chromatography of the residue obtained over silica gel (20% ethyl acetate/light petroleum) afforded the monotosylated derivative **6a**[1] (1.2 g, 75%) as a viscous liquid. R_f=0.25 (10% ethyl acetate/light petroleum); $[\alpha]_D^{26.9}$ +12.61 (*c*, 3.65 in $CHCl_3$); IR (neat): 3524, 3504, 3286, 2955, 2929, 2117, 1359, 1176, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, *J*=6.6 Hz, 3H), 1.25–1.39 (m, 6H), 1.42–1.50 (m, 2H), 2.42 (t, *J*=2.4 Hz, 1H), 2.44 (s, 3H), 3.54–3.56 (m, 1H), 3.87–3.88 (m, 1H), 4.04–4.24 (m, 4H), 7.35 (d, *J*=8 Hz, 2H), 7.80 (d, *J*=8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 21.8, 22.6, 24.6, 29.9, 31.9, 57.7, 71.0, 71.5, 74.7, 79.2, 80.0, 128.1, 130.1, 132.8, 145.2; HRMS calcd for $C_{18}H_{26}O_5SNa$ $[M+Na]^+$ 377.1399, found 377.1395.

Compound **6b**[1] (75%) was prepared from **5b**[1] following similar procedure described for **6a**[1]. R_f=0.60 (20% ethyl acetate/light petroleum). $[\alpha]_D^{25.7}$ +10.34 (*c*, 4.55 in $CHCl_3$); IR (neat): 3545, 3290, 2924, 2117, 1458, 1359, 1176, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, *J*=7 Hz, 3H), 1.21–1.31 (m, 24H), 2.40 (t, *J*=2.0 Hz, 1H), 2.4 (s, 3H), 3.5–3.57 (m, 2H), 3.87–3.90 (m, 1H), 4.05–4.23 (m, 3H), 7.54 (d, *J*=8 Hz, 2H), 7.80 (d, *J*=9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 21.8, 22.8, 25.1, 26.4, 28.6, 29.5, 29.7, 29.8, 29.8, 30.0, 32.1, 44.2, 57.7, 69.7, 71.1, 71.5, 74.7, 79.3, 80.0, 128.0, 130.0, 132.9, 145.0; HRMS calcd for $C_{26}H_{42}O_5S$ $[M+H]^+$ 467.2831, found 467.2973.

4.1.5. Synthesis of ***7a***[1] *and* ***7b***[1]. To a stirred suspension of sodium hydride (80 mg, 60% dispersion, 4 mmol) in dry THF (20 mL) at 0 °C was added dropwise a solution of mono tosylate derivative **6a**[1] (400 mg, 1.13 mmol) in dry THF (10 mL) under N_2 for 30 min. The reaction mixture was stirred for 1 h at 0 °C at room temperature for overnight. It was then carefully quenched with ice-water. After removal of most of THF under reduced pressure, the resulting residue was extracted with diethyl ether (3×30 mL). The combined ether extract was washed with water (10 mL) and brine (5 mL), and finally dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a viscous liquid, which was purified by column chromatography over silica gel (5% ethyl acetate/light petroleum, R_f=0.65) to furnish **7a**[1] (175 mg, 85%) as a viscous liquid. $[\alpha]_D^{26.8}$ +27.92 (*c*, 1.23 in $CHCl_3$); IR (neat): 3308, 2956, 2860, 2115, 1464, 1261, 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.82 (t, *J*=6.6 Hz, 3H), 1.19–1.28 (m, 4H), 1.30–1.38 (m, 1H), 1.41–1.9 (m, 1H), 1.50–1.57 (m, 2H), 2.35 (t, *J*=2.5 Hz, 1H), 2.70–2.74 (m, 2H), 2.82–2.85 (m, 1H), 3.31–3.34 (m, 1H), 4.16 (AB_q, further coupled with acelylenic proton, *J*=15.5, 2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 21.5, 23.7, 30.8, 31.6, 44.4, 52.1, 56.4, 73.2, 76.4, 79.0; HRMS calcd for $C_{11}H_{18}O_2Na$ $[M+Na]^+$ 205.1204, found 205.1201.

Compound **7b**[1] (75%) was prepared from **6b**[1] following similar procedure described for **7a**[1]. R_f=0.38 (5% ethyl acetate/light petroleum); $[\alpha]_D^{27.2}$ −15.68 (*c*, 3.91 in $CHCl_3$); IR (neat): 3310, 2924, 2115, 1458, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, *J*=10 Hz, 3H), 1.19–1.07 (m, 20H), 1.49–1.58 (m, 4H), 2.34 (t, *J*=2.4 Hz, 1H), 2.71–2.72 (m, 2H), 2.81–2.84 (m, 1H), 3.29–3.33 (m, 1H), 4.10–4.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.7, 25.0, 29.3, 29.5, 29.6, 29.6, 29.7, 31.9, 32.6, 45.4, 53.1, 57.4, 74.2, 80.0; HRMS calcd for $C_{19}H_{34}O_2Na$ $[M+Na]^+$ 317.2457, found 317.2456.

4.2. General procedure for Cp_2TiCl mediated radical cyclization of 7a[1]. Synthesis of 8a[1]

A solution of titanocene dichloride (564 mg, 2.2 mmol) in dry THF (25 mL, not deoxygenated) was stirred with activated zinc dust (360 mg, 5.5 mmol) for 1 h under argon (activated zinc dust was prepared by washing 20 g of commercially available zinc dust with 60 mL of 4 M HCl and thorough washing with water and finally with dry acetone and then drying in vacuo). The resulting green solution was then added dropwise to a stirred solution of the epoxide **7a**[1] (200 mg, 1.1 mmol) in dry THF (25 ml) at room temperature under argon during 1 h. The reaction mixture was stirred for overnight and was decomposed with 10% H_2SO_4 (10 mL). Most of the solvent was removed under reduced pressure, and the residue was extracted with diethyl ether (4×30 mL). The combined ether layer was washed with saturated $NaHCO_3$ (2×25 mL) and finally dried (Na_2SO_4). After removal of the solvent under reduced pressure the crude residue was purified by column chromatography over silica gel (20% ethyl acetate/light petroleum, R_f=0.30) to afford the cyclized alcohol **8a**[1] (mixture of two isomers in 1:5 ratio) as a viscous liquid (130 mg, 65%). IR (neat): 3400, 2955, 2931, 1458, 1039 cm^{-1}; ^1H NMR (300 MHz): δ 0.88 (t, *J*=6.5 Hz, 3H), 1.24–1.37 (m, 6H), 1.45–1.57 (m, 2H), 2.45–2.48 (m, 1H), 3.63–3.73 (m, 2H), 3.84 (m, 2H), 4.23–4.39 (m, 2H), 5.00–5.04 (m, 2H); ^{13}C NMR (75 MHz): δ 14.2, 22.7, 25.8, 32.0, 34.6, 51.6, 63.3, 70.5, 80.3, 82.3, 105.2, 149.6; Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.52; H, 10.70.

Compound **8b**[1] was synthesized from **7b**[1] following similar procedure described for **8a**[1]. R_f=0.37 (20% ethyl acetate/light petroleum). Yield 64%; IR (neat): 3400, 2924, 1465, 1041 cm^{-1}; ^1H NMR (500 MHz): δ 0.88 (t, *J*=7 Hz, 3H), 1.21–1.29 (m, 20H), 1.46–1.49 (m, 2H), 1.55–1.59 (m, 3H), 2.45–2.48 (m, 1H), 3.67 (dd, *J*=5.5, 11 Hz, 1H), 3.74 (dd, *J*=6, 11 Hz, 1H), 3.86 (dd, *J*=6.5, 12.5 Hz, 1H), 4.26–4.39 (2 AB br d, *J*=13.5 Hz, 2H), 5.02–5.04 (m, 2H); ^{13}C NMR (75 MHz): δ 14.2, 22.8, 26.8, 29.5, 29.7, 29.7, 29.7, 32.1, 34.7, 51.6, 63.3, 70.6, 82.3, 105.2, 149.7; calcd for $C_{19}H_{36}O_2$: C, 76.96; H, 12.24. Found: C, 76.45; H, 11.96.

4.2.1. Synthesis of ***9a***[1] *and* ***9b***[1]. A solution of the alcohol **8a**[1] (120 mg, 0.65 mmol), 3,4-dihydro-2*H*-pyran (120.5 mg, 1.43 mmol), and pyridinium-*p*-toluenesulfonate (10 mol %) in dry CH_2Cl_2 (15 mL) was stirred for 5 h at room temperature under N_2. The resulting reaction mixture was diluted with CH_2Cl_2 (15 mL), washed with saturated $NaHCO_3$ (3×25 mL), and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the crude residue was purified by column chromatography over silica gel (2% ethyl acetate/light petroleum) to afford **9a**[1] (165 mg, 95%) as a viscous liquid. IR (neat): 3074, 2941, 2866, 1444, 1350, 1222 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, *J*=6.5 Hz, 3H), 1.19–1.31 (m, 6H), 1.46–1.52 (m, 8H), 1.54–1.67 (m, 2H), 3.41–3.46 (m, 2H), 3.63–3.81 (m, 3H), 4.16–4.33 (m, 2H), 4.88–4.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 19.3, 19.6, 22.7, 22.7, 25.6, 25.8, 30.7, 30.8, 32.0, 32.0, 34.7, 34.8, 48.7, 49.1, 62.0, 62.3, 68.9, 69.1, 70.7, 70.8, 83.5, 83.8, 98.8, 99.3, 104.8, 105.0, 149.9, 150.0; HRMS calcd for $C_{16}H_{28}O_3Na$ $[M+Na]^+$ 291.1936, found 291.1938.

Compound **9b**[1] (90%) was prepared from **8b**[1] following similar procedure described for **9a**[1]. IR (neat): 2926, 1456, 1201, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, *J*=6.9 Hz), 1.25 (m, 18H), 1.52–1.82 (m, 12H), 2.5 (m, 1H), 3.48–3.53 (m, 1H), 3.71–3.86 (m, 3H), 4.27–4.35 (m, 2H), 4.58–4.64 (m, 1H), 4.95–5.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 19.3, 22.8, 25.6, 26.1, 26.2, 29.5, 29.7, 29.8, 29.8, 30.6, 30.7, 32.1, 34.7, 48.9, 62.2, 68.9, 70.7, 83.6, 98.9, 105.1, 150.0; HRMS calcd for $C_{24}H_{44}O_3Na$ $[M+Na]^+$ 403.3188, found 403.3186.

4.2.2. Synthesis of ***10a***[1] *and* ***10b***[1]. To a stirred solution of compound **9a**[1] (90 mg, 0.33 mmol) in dry DMF (4 mL) was added molecular sieves (4 Å) (50 mg) and pyridinium dichromate (1.4 g, 3.3 mmol) portion-wise at room temperature during 1 h. The reaction mixture was further stirred for 24 h, diluted with water (5 mL), and extracted with ethyl acetate (4×25 mL). The combined organic layer was washed with saturated $NaHCO_3$ (10 mL), water (4×5 mL),

and finally dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue obtained was chromatographed over silica gel (20% ethyl acetate/light petroleum) to furnish the lactone **10a**[1] (60 mg, 65%) as a light yellow viscous liquid. IR (neat): 2926, 2854, 1764, 1512, 1269, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J=6.5 Hz, 3H), 1.24–1.39 (m, 6H), 1.40–1.47 (m, 2H), 1.50–1.61 (m, 5H), 1.64–1.77 (m, 3H), 2.93–2.96 (m, 1H), 3.47–3.52 (m, 2H), 3.75–3.89 (m, 2H), 4.33–4.37 (m, 1H), 4.58–4.61 (m, 1H), 5.69–5.70 (m, 1H), 6.29–6.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 13.9, 19.2, 19.4, 22.5, 24.6, 24.6, 25.3, 25.6, 30.4, 30.4, 31.4, 31.5, 36.0, 36.0, 44.7, 44.9, 68.7, 68.9, 81.2, 81.2, 98.7, 99.3, 123.1, 123.2, 136.6, 136.7, 170.0; HRMS calcd for $C_{16}H_{26}O_4Na$ $[M+Na]^+$ 305.1729, found 305.1724.

Compound **10b**[1] (60%) was prepared from **9b**[1] following similar procedure described for **10a**[1]. IR (neat): 2924, 1766, 1465, 1271, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.80 (t, J=6.5 Hz, 3H), 1.08–1.22 (m, 23H), 1.31–1.40 (m, 2H), 1.40–1.58 (m, 6H), 1.61–1.70 (m, 2H), 2.87–2.88 (m, 1H), 3.32–3.46 (m, 2H), 3.70–3.82 (m, 2H), 4.27–4.29 (m, 1H), 4.51–4.54 (m, 1H), 5.62–5.64 (m, 1H), 6.22–6.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 22.8, 25.0, 25.1, 29.4, 29.5, 29.6, 29.7, 29.8, 30.5, 30.6, 30.7, 32.0, 36.2, 44.8, 45.0, 62.3, 62.5, 68.8, 69.0, 81.4, 81.4, 98.9, 99.4, 123.2, 123.4, 136.7, 136.9, 170.2; HRMS calcd for $C_{24}H_{42}O_4Na$ $[M+Na]^+$ 417.2981, found 417.2983.

*4.2.3. Synthesis of **11a**[1] and **11b**[1].* To a stirred solution of lactone **10a**[1] (60 mg, 0.2 mmol) in methanol (4 mL) was added *p*-toluenesulfonic acid monohydrate (10 mol %), and the reaction mixture was stirred for 3 h at room temperature. Most of the solvent was removed in vacuo and water (3 mL) was added to it. It was extracted with ethyl acetate (3×20 mL). The combined ethyl acetate extract was washed with saturated $NaHCO_3$ (5 mL), brine (5 mL), and finally dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue obtained was purified by column chromatography over silica gel (25% ethyl acetate/light petroleum) to afford the hydroxy lactone **11a**[1] (35 mg, 85%) as viscous oil. IR (neat): 3500, 3013, 2955, 2929, 1750, 1271 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.84 (t, J=6.5 Hz, 3H), 1.17–1.37 (m, 4H), 1.41–1.48 (m, 2H), 1.56–1.7 (m, 3H), 2.80 (m, 1H), 3.66–3.72 (m, 2H), 4.31–4.35 (m, 1H), 5.65 (d, J=2 Hz, 1H), 6.27 (d, J=3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.6, 24.8, 30.4, 36.2, 47.1, 64.1, 123.5, 137.4, 170.1; HRMS calcd for $C_{11}H_{18}O_3Na$ $[M+Na]^+$ 221.1154, found 221.1152.

Compound **11b**[1] (85%) was prepared from **10b**[1] following similar procedure described for **11a**[1]. IR (neat):3439, 2924, 2852, 1753, 1467, 1273, 1124 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.81 (t, J=6.5 Hz, 3H), 1.19–1.31 (m, 18H), 1.33–1.62 (m, 5H), 2.80–2.81 (m, 1H), 3.69 (m, 2H), 4.31–4.34 (m, 1H), 5.64 (s, 1H), 6.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.8, 25.1, 29.2, 29.5, 29.6, 29.7, 29.7, 29.8, 30.0, 32.0, 36.2, 45.0, 47.0, 62.1, 64.0, 81.1, 123.6, 136.5, 170.5; HRMS calcd for $C_{19}H_{34}O_3Na$ $[M+Na]^+$ 333.2406, found 333.2408.

*4.2.4. Synthesis of (−)-methylenolactocin (**1a**) from **11a**[1] and (−)-protolichesterinic acid (**1b**) from **11b**[1].* A solution of the hydroxy lactone **11a**[1] (40 mg, 0.3 mmol) in acetone (1 mL) was treated with freshly prepared Jones reagent at room temperature until a persistent orange color was observed. After 30 min of stirring at room temperature (progress of the reaction was monitored by TLC), 2-propanol was added and the reaction mixture was diluted with water (1 mL). Acetone was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (4×10 mL). The organic solvent was removed and the residue was dissolved in toluene (5 mL) and extracted with 10% of aqueous $NaHCO_3$ (3×3 mL). Aqueous bicarbonate layer was acidified with dil HCl and was extracted with CH_2Cl_2 (2×25 mL). The combined organic layer was washed with brine (5 mL) and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded a crude mass, which was dissolved in THF–benzene (1:1, 5 mL) and was heated at 70 °C with dil HCl (0.5 mL) for 3 h. It was extracted with CH_2Cl_2 (2×25 mL) and the combined organic layer was washed with brine (5 mL) and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded the pure acid **1a** as a crystalline solid (30 mg, 70%) the NMR spectra of which were identical[3] with (−)-methylenolactocin reported in the literature. Mp 82–84 °C (ethyl acetate/petroleum ether); $[\alpha]_D^{24.0}$ −17.13 (*c*, 1.96 in $CHCl_3$), reported $[\alpha]_D^{24.0}$ −18.80 (*c*, 1.34 in $CHCl_3$);[6c] IR (KBr): 3444, 3099, 2955, 1743, 1716, 1255 cm^{-1}; ^1H NMR (500 MHz): δ 0.90 (t, J=7 Hz, 3H), 1.32–1.33 (m, 4H), 1.41–1.63 (m, 2H), 1.71–1.77 (m, 2H), 3.62–3.64 (m, 1H), 4.79–4.83 (m, 1H), 6.02 (d, J=2.5 Hz, 1H), 6.46 (d, J=2.5 Hz, 1H); ^{13}C NMR (75 MHz): δ 14.0, 22.6, 24.6, 31.5, 35.8, 49.7, 79.1, 126.1, 132.6, 168.4, 174.4; HRMS calcd for $C_{11}H_{16}O_4Na$ $[M+Na]^+$ 235.0946, found 235.0944.

(−)-Protolichesterinic acid (**1b**) was prepared from **11b**[1] in 70% yield following the similar procedure described for **1a**. Mp 98–100 °C; $[\alpha]_D^{26.9}$ −12.24 (*c*, 1.23 in $CHCl_3$), reported $[\alpha]_D^{32.0}$ −10.40 (*c*, 0.46 in $CHCl_3$);[6f] IR (KBr): 3091, 2920, 2849, 1743, 1715, 1407, 1254, 1199 cm^{-1}; ^1H NMR (500 MHz): δ 0.88 (t, J=6.5 Hz, 3H), 1.22–1.33 (m, 17H), 1.72–1.75 (m, 5H), 3.62–3.63 (m, 1H), 4.80–4.82 (m, 1H), 6.02 (d, J=2.5 Hz, 1H), 6.46 (d, J=3, 1H); ^{13}C NMR (75 MHz): δ 14.2, 22.8, 25.1, 29.3, 29.5, 29.5, 29.6, 29.7, 29.8, 29.8, 32.0, 35.9, 49.6, 79.0, 125.9, 132.7, 168.3, 173.5; HRMS calcd for $C_{19}H_{32}O_4Na$ $[M+Na]^+$ 347.2198, found 347.2198.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.058. These data include MOL files and InChiKeys of the most important compounds described in this article.

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