Synthesis of L-Cladinose Using Enantioselective Desymmetrization

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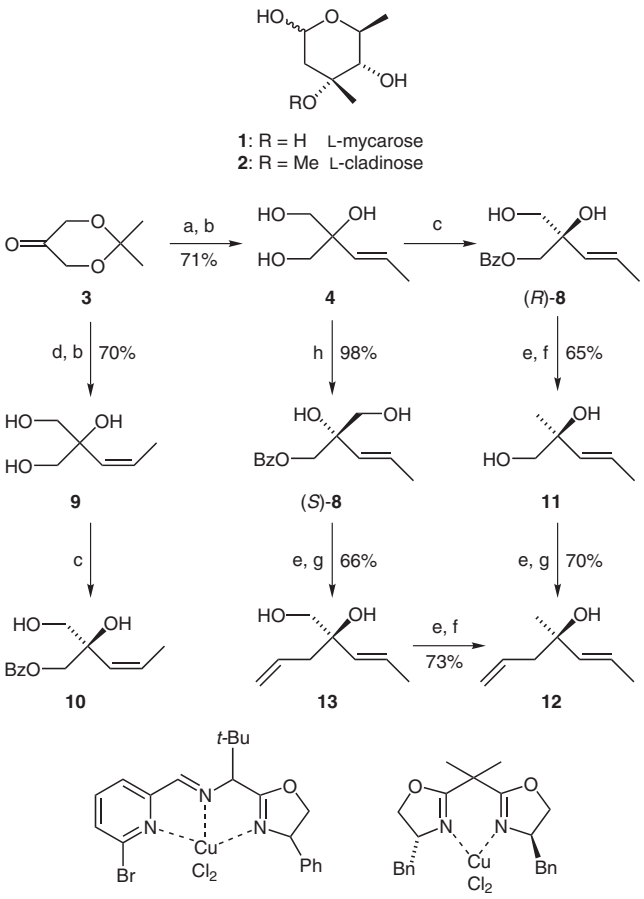
Abstract: L-Cladinose, a neutral sugar found in erythromycins and azithromycins, has been synthesized efficiently using enantioselective monobenzoylation of 2-propenylglycerol in the presence of the imine-$CuCl_2$ catalysts to elaborate the stereogenic quaternary center.

Key words: L-mycarose, L-cladinose, desymmetrization, quaternary centers, imine-$CuCl_2$

A branched neutral sugar L-mycarose (**1**, 2,6-dideoxy-3*C*-methyl-L-ribohexose; Scheme 1) is present[1] in magnamycin (cabomycin),[2] erythromycins C and D,[3] tylosin,[4] mithramycin,[5] spiramycin,[6] leucomycin,[7] and kedarcidin chromophore.[8] Its 3-methyl ether L-cladinose (**2**; Scheme 1) is attached to erythromycins A, B, F, and G.[3] Since the first nonstereoselective synthesis of mycarose disclosed from acetoacetaldehyde dimethyl acetal,[9] their several synthetic routes have been reported through methyl Grignard additions to ketones[10] and aldol condensation[11] in the formation of the tertiary alcohol functionality. All the approaches have exploited the preexisting asymmetric center(s) to induce the desired stereochemistry with relatively low stereoselectivity. In connection with our recently developed enantioselective desymmetrization to install hydroxyl-containing quaternary centers,[12] we have been engaged in synthetic studies on natural products embedded with the stereogenic quaternary centers. One of our on-going targets is azithromycin A, an erythromycin A derived semisynthetic macrolide antibiotic comprising L-cladinose.[13] Herein, we describe an enantioselective synthesis of L-cladinose (**2**; Scheme 1) using the desymmetrizing monobenzoylation to introduce the requisite tertiary alcohol functionality.

The synthesis began with preparation of the desymmetrization substrate glycerol **4** (Scheme 1). The known ketone **3**[14] was coupled with the propenyllithium generated by transmetalation of *trans*-1-bromo-1-propene and then hydrolyzed to afford the triol **4** in 71% overall yield (Scheme 1). While the desymmetrization of **4** using the imine-$CuCl_2$ catalyst **5** furnished 98% of the monobenzoate (*R*)-**8** with 91% ee,[12a] the bisoxazoline-$CuCl_2$ catalyst **7** induced much inferior stereoselectivity (28% ee) and 91% chemical yield. Due to the potential utility of the desymmetrization product, the *cis*-isomeric triol **9**, procured by the similar sequence to **4**, was also subjected to the monobenzoylation to give the expected monobenzoate **10** in 85–90% yield with 82% ee using **5** but merely 29% ee in the presence of **7** (Scheme 1).



Scheme 1 *Reagents and conditions*: a) *trans*-MeCH=CHBr, *t*-BuLi, THF, –78 °C; b) dilute aq HCl, MeOH, r.t.; c) **5** (20 mol%) or **7** (5 mol%), BzCl, Et_3N, THF, r.t.; d) *cis*-MeCH=CHBr, *t*-BuLi, THF, –78 °C; e) MsCl, Et_3N, CH_2Cl_2, –78 °C, then DBU, r.t.; f) Red-Al, THF, 0 °C; g) CH_2=CHMgBr, CuI, THF, –40 to –20 °C; h) **6** (20 mol%), BzCl, Et_3N, THF, r.t.

For the synthesis of the target L-cladinose, the enantiomerically enriched diol (*R*)-**8** was mesylated and then cyclized with DBU in one pot to give rise to the epoxide in 81% yield (Scheme 1). Subsequently, it was reductively deoxygenated and concomitantly debenzoylated by Red-Al to deliver the allylic alcohol **11** in 80% yield (Scheme 1).

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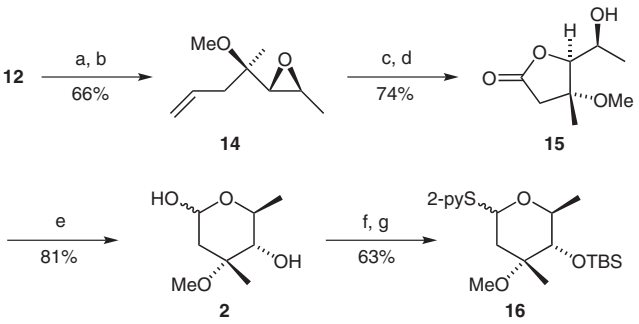
After conversion of **11** into the corresponding epoxide in 79% yield by the one-pot mesylation–cyclization process, the epoxide was exposed to vinyl Grignard reagent in the presence of CuI to offer the diene **12** in 89% yield (Scheme 1).[15] Alternatively, **12** could be derived from the monobenzoate (*S*)-**8** enantiomeric to (*R*)-**8** by switching the orders of the reductive epoxide opening and the cuprate-driven epoxide substitution. The desymmetrization of **4** with the catalyst **6** supplied (*S*)-**8** with the expected level of enantioselectivity (91% ee), which was functionalized to the epoxide in 81% yield by the one-pot operation. Treatment of the generated epoxide with vinyl anion effected substitution as well as debenzoylation to render the diol **13** in 81% yield (Scheme 1). Reductive removal of the primary hydroxyl group of **13** was carried out via epoxide formation with Red-Al to provide the diene **12** in 73% overall yield (Scheme 1).

The allylic alcohol **12** was epoxidized not only chemoselectively but also stereoselectively in 83% yield using V(IV)-promoted *tert*-butyl hydroperoxide (Scheme 2).[16] The tertiary hydroxyl group of the resultant epoxy alcohol was methylated to produce the methyl ether **14** in 80% yield (Scheme 2).[17] After ozonolysis of **14**, the generated aldehyde was unsuccessfully attempted to form the desired pyranose or pyranoside via the corresponding furanosyl derivative under various acidic conditions in the presence of several nucleophiles such as H_2O, alcohol, thiol, etc. The ineffective synthetic plan led us to employ carboxylic acid rather than the aldehyde. The olefinic double bond of **14** was oxidatively cleaved in 86% yield and the resulting carboxylic acid was most efficiently cyclized to the butyrolactone **15** in 86% yield in the presence of 0.3 equivalents of $BF_3{\cdot}OEt_2$ (Scheme 2).[18] The requisite rearrangement of **15** to the six-membered lactone failed under various acidic or basic conditions. When **15** was reduced to the corresponding furanose with DIBAL-H, it was spontaneously rearranged to the pyranose to impart L-cladinose (**2**) in 81% yield (Scheme 2),[19] the spectral data of which were found to be identical with the reported.[11] In order to prepare the known glycosyl donor for our azithromycin synthesis, the synthetic L-cladinose (**2**) was silylated in the presence of $AgNO_3$ and then coupled with 2,2′-dithiodipyridine under Mitsunobu conditions to produce the thiocladinoside **16** in 63% overall yield (Scheme 2).[20]

In summary, a practical synthesis of L-cladinose has been completed through twelve steps from the readily available ketone **3** in 12.5% overall yield. The synthesis culminated in setting up the C_4-stereogenic quaternary center by our developed enantioselective desymmetrization of 2-substituted glycerols, which is considered of great synthetic utility to settle the abstruse installation of the hydroxyl-containing quaternary asymmetric carbons.



Scheme 2 *Reagents and conditions*: a) $VO(acac)_2$, *t*-BuO_2H, CH_2Cl_2, 0 °C to r.t. (83%); b) NaH, MeI, THF, 0 °C to r.t. (80%); c) $RuCl_3(H_2O)_n$, $NaIO_4$, CH_2Cl_2, MeCN, H_2O, 15 °C (80%); d) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to r.t. (86%); e) DIBAL-H, THF, –78 °C (81%); f) TBSCl, $AgNO_3$, pyridine, THF, r.t.; g) $(2\text{-pyS})_2$, $(n\text{-Bu})_3P$, CH_2Cl_2, r.t.

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(15) Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3 H), 1.64 (br s, 1 H), 1.70 (d, *J* = 5.2 Hz, 3 H), 2.11–2.48 (m, 2 H), 5.07–5.21 (m, 2 H), 5.59 (d, *J* = 14.0 Hz, 1 H), 5.71–5.92 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 27.7, 47.2, 71.8, 118.7, 122.9, 133.9, 137.6. HRMS (EI): *m/z* calcd for $C_8H_{14}O$: 126.1044; found: 126.1041.
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(17) **Synthesis of Epoxide 14**
Vanadyl(acetylacetonate) (25 mg, 0.095 mmol) and *t*-BuO_2H (2.0 M in CH_2Cl_2, 2.38 mL, 4.76 mmol) were added to diene **12** (400 mg, 3.17 mmol) in CH_2Cl_2 (3 mL) at 0 °C in sequence. The mixture was stirred at 0 °C for 30 min and then at r.t. for 6 h. After quenching the excess peroxide with 10% aq $Na_2S_2O_3$ (10 mL), the following extraction with EtOAc (3 × 5 mL), drying over $MgSO_4$ (500 mg), filtration and evaporation under reduced pressure gave the crude product, which was separated by column chromatography (SiO_2, 230–400 mesh, EtOAc–hexane, 1:3) to furnish the desired epoxide (374 mg, 83%) along with the regioisomeric epoxide (35 mg, 7%). Sodium hydride (60% dispersion in mineral oil, 126 mg, 3.16 mmol) was added to the disubstituted epoxide (374 mg, 2.63 mmol) in THF (3 mL) at 0 °C portionwise. To the generated alkoxide was injected MeI (0.25 mL, 4.0 mmol), and the resulting solution was stirred at 0 °C for 15 min and then at r.t. for 3 h. After quenching the methylation with sat. NH_4Cl (3 mL), the workup was done by extraction with EtOAc (3 × 4 mL), drying with $MgSO_4$ (300 mg), filtration and evaporation in vacuo. The residual material was purified chromatographically (SiO_2, 230–400 mesh, EtOAc–hexane, 1:4) to render the epoxy methyl ether **14** (329 mg, 80%).
Compound **14**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 3 H), 1.33 (d, *J* = 5.2 Hz, 3 H), 1.91–2.10 (m, 2 H), 2.71 (d, *J* = 2.3 Hz, 1 H), 3.12 (qd, *J* = 5.2, 2.3 Hz, 1 H), 3.31 (s, 3 H), 5.10–5.25 (m, 2 H), 5.78–5.94 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3, 25.1, 39.1, 51.5, 52.6, 62.4, 63.5, 118.1, 133.6. HRMS (EI): *m/z* calcd for $C_9H_{16}O_2$: 156.1150; found: 156.1145.
(18) **Synthesis of Lactone 15**
To epoxide **14** (300mg, 1.92 mmol), dissolved in a mixture of CH_2Cl_2 (4 mL), MeCN (4 mL), and H_2O (6 mL), were added $NaIO_4$ (1.68 g, 7.87 mmol) and $RuCl_3·3H_2O$ (16 mg) sequentially at r.t., and the mixture was stirred at that temperature for 8 h. After addition of CH_2Cl_2 (50 mL) to the mixture, the resulting solution was washed with aq HCl (1.0 M, 30 mL) twice and then brine (20 mL) once. The remaining organic layer was dried over $MgSO_4$ (1 g), filtered and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, 230–400 mesh, EtOAc–hexane, 1:2) to give the corresponding carboxylic acid (267 mg, 80%). The carboxylic acid (267 mg, 1.53 mmol) in CH_2Cl_2 (4 mL) was stirred in the presence of $BF_3·OEt_2$ (58 μL, 0.46 mmol) at 0 °C for 10 min and then at r.t. for 5 h. After addition of H_2O (3 mL), the resulting solution was extracted with EtOAc (3 × 5 mL), the organic layer was dried over $MgSO_4$ (400 mg), filtered and evaporated in vacuo. The residue was separated by column chromatography (SiO_2, 230–400 mesh, EtOAc–hexane, 1:2) to afford the lactone **15** (229 mg, 86%).
Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.3 Hz, 3 H), 1.42 (s, 3 H), 2.52 (d, *J* = 17.1 Hz, 1 H), 2.66 (d, *J* = 17.1 Hz, 1 H), 3.24 (s, 3 H), 3.88–3.95 (m, 1 H), 4.06 (d, *J* = 7.1 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 20.4, 41.5, 51.1, 66.5, 80.6, 87.9, 174.0. HRMS (EI): *m/z* calcd for $C_8H_{14}O_4$: 174.0892; found: 174.0889.
(19) **Synthesis of L-Cladinose (2)**
Diisobutylaluminum hydride (1.0 M in THF, 2.87 mL, 2.87 mmol) was added to **15** (200 mg, 1.15 mmol) in THF (5 mL) dropwise at –78 °C and the resulting mixture was stirred at that temperature for 3 h. The reaction was quenched with a 4:1 mixture of MeOH and H_2O at –78 °C, and then the temperature was raised to r.t. After addition of sat. $NaHCO_3$ (0.5 mL) and $MgSO_4$ (200 mg) to the mixture, it was filtered using EtOAc (10 mL), and the organic layer was evaporated in vacuo. The remaining residue was purified by column chromatography (SiO_2, 230–400 mesh, EtOAc–hexane, 1:1) to deliver L-cladinose (**2**, 164 mg, 81%).
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