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De Novo Highly Stereocontrolled Synthesis of 2,6-Dideoxy-C-3-Branched Carbohydrates by Use of 2,6-Anhydro-2-Thio Sugar: L-Cladinose and Its C-3 Epimer

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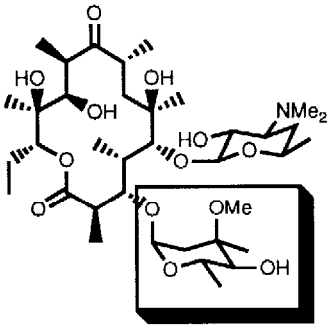
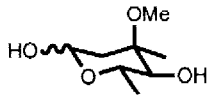
Summary: L-Cladinose (**1**) and its C-3 epimer **2** were synthesized through a highly stereoselective addition of methyl anion to the C-3 carbonyl groups of α-anomer **9** and β-anomer **10** having 2,6-anhydro-2-thio structures, respectively, which were prepared from the common intermediate **6** in stereocontrolled fashion.

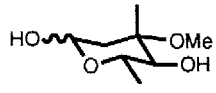
In biological means, sugar parts of natural products have been paid considerable attention as well as their aglycones. In the connection with the projects aimed at development of methodology for stereocontrolled synthesis of natural products, we have recently reported the use of 2,6-anhydro-2-thio sugar for a highly stereoselective and powerful glycosylation[1] Further, in our extended studies of this projects, we have investigated the efficient use of 2,6-anhydro-2-thio sugar for stereocontrolled synthesis of 2,6-dideoxy-C-3-branched carbohydrates[2]. In this communication, we wish to describe the syntheses of L-cladinose (**1**)[3] which is a sugar moiety of erythromycin A, and its C-3 epimer **2** which is an unnatural novel sugar, by a highly stereocontrolled addition of methyl anion to the carbonyl function at C-3 position of 2,6-anhydro-2-thio sugar as a key step.



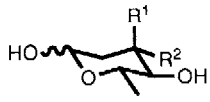
Erythromycin A



1



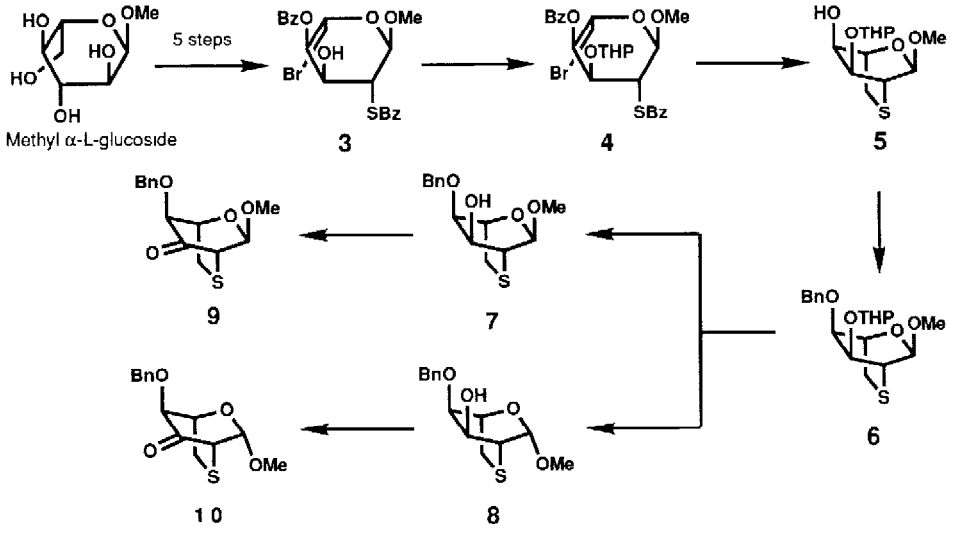
2



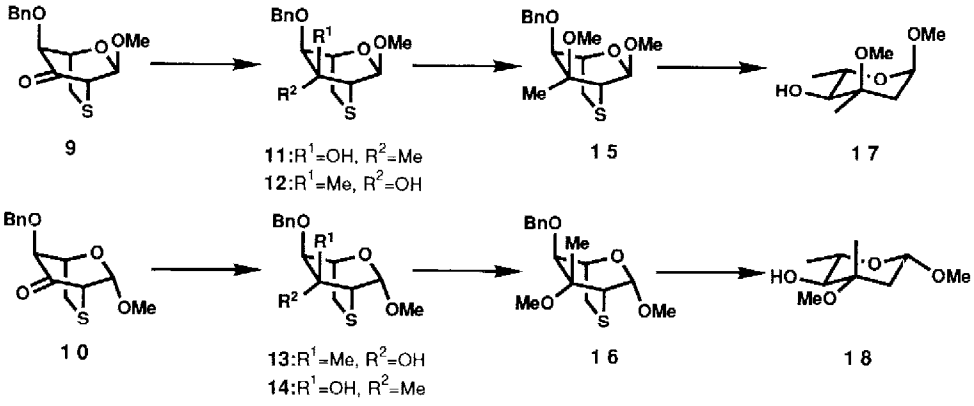
19: R^1=OH, R^2=Me
20: R^1=H, R^2=OMe
21: R^1=H, R^2=OH

From methyl α-L-glucoside, compound **3** was synthesized in 5 steps in good overall yield according to the literatures [4]. Treatment of **3** with 3.0 equiv. of dihydropyran in the presence of catalytic amounts of 10-DL-camphorsulfonic acid and MS 4A in CH_2Cl_2 (0°C, 2h) gave **4**[5] in 97% yield. Basic hydrolysis (25°C, 3h) of **4** with 3.0 equiv. of NaOMe in MeOH caused the construction of 2,6-anhydro-2-thio bridge with deprotection of benzoyl groups to afford **5**[5] in 98% yield.

Benzylation of **5** by standard way (2.0 equiv BnBr, 2.0 equiv NaH, DMF) produced **6**[5] in 98% yield. When **6** was treated with $BF_3 \cdot Et_2O$ (0.2 equiv) in MeOH at 0°C for 0.5h to give stereospecifically the deprotected α-anomer **7**[5](mp 46.5~47.0°C, $[\alpha]_D$ -110°, (c 0.89, $CHCl_3$)) in 97% yield. On the other hand, when treated with TMSOTf (0.2 equiv) in MeOH at 40°C for 1.5h, the thermodynamically stable β-anomer **8**[5](mp 85.5~86°C, $[\alpha]_D$ +17.0°, (c 0.79, $CHCl_3$)) was predominantly obtained in 65 % yield with 19% of α-anomer. The combination of the configuration of anomeric position and 2,6-anhydro-2-thio structure expectedly played a crucial role for the highly stereocontrolled addition of methyl anion to the carbonyl function at C-3 position of **9** and **10** as described below. Each of C-3 hydroxy products **7** and **8** was oxidized by Dess-Martin periodate[6] to give cleanly the ketones **9**[5]($[\alpha]_D$ +89.6°, (c 0.79, $CHCl_3$)) and **10**[5]($[\alpha]_D$ +198°, (c 0.72, $CHCl_3$)) in 97 and 99% yields, respectively.



The addition of methyl anion of Grignard reagent (MeMgBr) to the α-anomer **9** gave predominantly the α-methyl-β-hydroxy product **11**[5,7]($[\alpha]_D$ -101°, (c 0.99, $CHCl_3$)) in several temperatures, while treatment of **9** with MeLi caused the decomposition of **9**. Highly stereocontrolled addition was best effected by treatment of **9** with 4.0 equiv of MeMgBr in Et_2O at –75°→–25°C for 1.5h to afford **11** in 85% yield with 9% of its C-3 epimer **12**[5,7]($[\alpha]_D$ -30.5°, (c 1.09, $CHCl_3$)). In dramatic contrast to this fact, the addition of MeMgBr or MeLi to the β-anomer **10** generated exclusively the C-3 epimer, β-methyl-α-hydroxy product **13**[5,7]($[\alpha]_D$ +50.2°, (c 0.71, $CHCl_3$)) in both cases. The best stereocontrolled addition was observed by treatment of **10** with 3.0 equiv. of MeLi in Et_2O at -98°C for 0.5h to afford **13** in 92% yield with 7% of its C-3 epimer **14**[5,7](mp 102.5~103°C, $[\alpha]_D$ +53.9°, (c 0 52, $CHCl_3$)). Thus, both C-3 epimers were synthesized in good overall yields with high stereocontrol. On the next stage, **11** and **13** were O-methylated (2.0 equiv MeI, 2.0 equiv NaH, DMF, 25°C, 30min) to afford **15**[5]($[\alpha]_D$ -128°, (c 0.84, $CHCl_3$)) and **16**[5](mp 80.5~81°C, $[\alpha]_D$ +68.8°, (c 0.59, $CHCl_3$)) respectively, which were subjected to



desulfurization with de-O-benzylation by hydrogenolysis[1a] in the presence of Raney-Ni (W4) in EtOH-dioxane at 40°C to give the desired 2,6-dideoxy compounds **17**[5,8,9]([α]$_D$ -143°, (c 3.00, H_2O)) and **18**[5]([α]$_D$ +46.8°, (c 0.57, EtOH)) in 79 and 75% overall yields respectively. Finally, hydrolyses of the methyl glycoside of **17** and **18** in acidic condition (0.6N HCl, 25°C, 24h)[3a] proceeded smoothly to give L-cladinose (**1**)[3,5,8]([α]$_D$ -22.8°, (c 2.60, H_2O)) and its C-3 epimer **2**[5,10]([α]$_D$ -9.5°, (c 0.40, H_2O)) in 90 and 87% yields respectively.

In conclusion, *de novo* highly stereocontrolled syntheses of 2,6-dideoxy-C-3-branched carbohydrates, L-cladinose and its C-3 epimer were achieved by effective assistance of the combination of 2,6-anhydro-2-thio structure and the configuration of anomeric position. Although such demonstrations are now in progress, similarly, mycarose (**19**), oleandrose (**20**), olivose (**21**) and their C-3 epimers have been stereospecifically synthesized by the present methodology. The results will be published elsewhere in detail.

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References and Notes:

1) (a) K. Toshima, S. Mukaiyama, T. Ishiyama, and K. Tatsuta, *Tetrahedron Lett.*, **31**, 3339 (1990); (b) K. Toshima, S. Mukaiyama, T. Ishiyama, and K. Tatsuta, *Tetrahedron Lett.*, **31**, 6361 (1990).
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3) (a) E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, and K. Gerzon, *J. Am. Chem. Soc.*, **76**, 3121 (1954); (b) D. M. Lemal, P. D. Pacht, and R. B. Woodward, *Tetrahedron*, **18**, 1275 (1962); (c) G. B. Howarth and J. K. N. Jones, *Can. J. Chem.*, **45**, 2253 (1967); (d) B. Flaherty, W. G. Overend, N. R. Williams, *J. Chem. Soc., (C)*, **1966**, 398; (e) J. Yoshimura, *Adv. Carbohydr. Chem. Biochem.*, **42**, 69 (1984); (f) E. R. Koft, P. Dorff, and R. Kullnig, *J. Org. Chem.*, **54**, 2936 (1989); (g) C. H. Heathcook and S. H. Montgomery, *Tetrahedron Lett.*, **26**, 1001 (1985); (h) S. H. Montgomery, M. C. Pirrung, and C. H. Heathcook, *Carbohydr. Res.*, **202**, 13 (1990).
4) See references and notes cited in Ref. 1a.
5) All compounds were purified by silica gel column chromatography and were fully characterized by spectroscopic means and elemental analyses. Optical rotations were

mesured using a 0.5dm tube at 25°C. Selected significant ^{1}H-NMR spectra (270 Mz, $CDCl_3$) [δ (TMS), J(Hz)] are the following. **7**: δ=2.52 (1H, dd, J=11.8 and 1.6, H-6), 2.86 (1H, dd, J=2.2 and 2.2, H-2), 2.97 (1H, dd, J=11.8 and 5.0, H-6'), 3.45 (3H, s, OMe), 3.68 (1H, dd, J=8.4 and 1.9, H-4), 3.96 (1H, d, J=12.0, OH), 4.28 (1H, dddd, J=12.0, 8.4, 2.2 and 1.8, H-3), 4.37 (1H, ddd, J=5.0, 1.9 and 1.6, H-5), 4.64 and 4.89 (each 1H, ABq, J=12.2, CH_2Ph), 5.15 (1H, dd, J=2.2 and 1.8, H-1). **8**: δ=2.50 (1H, ddd, J=11.8, 3.6 and 0.3, H-6), 3.04 (1H, ddd, J=3.8, 3.6 and 0.3, H-2), 3.27 (1H, dd, J=11.8 and 3.2, H-6'), 3.53 (3H, s, OMe), 3.61 (1H, d, J=3.9, H-4), 3.85 (1H, d, J=7.8, OH), 4.23 (1H, dd, J=3.6 and 3.2, H-5), 4.43 (1H, ddd, J=7.8, 3.9 and 3.8, H-3), 4.71 (2H, s, CH_2Ph), 5.16 (1H, d, J=3.6, H-1). **9**: δ=2.68 (1H, dd, J=11.6 and 2.0, H-6), 3.16 (1H, d, J=2.2, H-2), 3.17 (1H, dd, J=11.6 and 4.0, H-6'), 3.47 (3H, s, OMe), 3.80 (1H, d, J=1.8, H-4), 4.56 (1H, ddd, J=4.0, 2.0 and 1.8, H-5), 4.82 and 4.97 (each 1H, ABq, J=12.2, CH_2Ph), 5.24 (1H, d, J=2.2, H-1). **10**: δ=2.73 (1H, dd, J=11.6 and 3.0, H-6), 3.32 (1H, d, J=2.8, H-2), 3.41 (1H, dd, J=11.6 and 2.4, H-6'), 3.57 (1H, s, OMe), 4.15 (1H, d, J=1.0, H-4), 4.46 (1H, ddd, J=3.0, 2.4 and 1.0, H-5), 4.85 and 5.01 (each 1H, ABq, J=12.2, CH_2Ph), 5.22 (1H, d, J=2.8, H-1). **11**: δ=1.54 (3H, d, J=0.8, C3-Me), 2.49 (1H, dd, J=11.6 and 1.6, H-6), 2.60 (1H, d, J=2.0, H-2), 2.94 (1H, dd, J=11.6 and 4.8, H-6'), 3.19 (1H, d, J=1.6, H-4), 3.49 (3H, s, OMe), 4.33 (1H, ddd, J=4.8, 1.6 and 1.6, H-5), 4.50 and 4.95 (each 1H, ABq, J=12.2, CH_2Ph), 4.65 (1H, d, J=0.8, OH), 5.22 (1H, d, J=2.0, H-1). **13**: 1.52 (3H, d, J=0.8, C3-Me), 2.59 (1H, ddd, J=11.6, 3.2 and 1.0, H-6), 2.79 (1H, dd, J=3.6 and 1.0, H-2), 3.26 (1H, dd, J=11.6 and 2.4, H-6'), 3.54 (1H, s, H-4), 3.72 (1H, d, J=0.8, OH), 4.19 (1H, dd, J=3.2 and 2.4, H-5), 4.63 and 4.73 (each 1H, ABq, J=12.2, CH_2Ph), 5.05 (1H, d, J=3.6, H-1). **17**: δ=1.22 (3H, s, C3-Me), 1.28 (3H, d, J=6.4, H-6), 1.53 (1H, dd, J=15.2 and 4.4, H-2), 2.27 (1H, d, J=15.2, H-2'), 2.32 (1H, d, J=11.0, OH), 3.02 (1H, dd, J=11.0 and 9.8, H-4), 3.26 (3H, s, OMe), 3.32 (3H, s, OMe), 3.85 (3H, dq, J=9.8 and 6.4, H-5), 4.60 (1H, d, J=4.4, H-1). **18**: δ=1.25 (3H, s, C3-Me), 1.35 (3H, d, J=6.2, H-6), 1.63 (1H, dd, J=12.4 and 10.0, H-2), 2.05 (1H, dd, J=12.4 and 2.1, H-2'), 2.08 (1H, d, J=2.0, OH), 3.22 (3H, s, OMe), 3.31 (1H, dd, J=9.6 and 2.0, H-4), 3.43 (1H, dd, J=9.6 and 6.2, H-5), 3.49 (1H, s, OMe), 4.41 (1H, d, J=10.0 and 2.1, H-1). α-anomer of **1**: δ=1.30 (3H, s, C3-Me), 1.31 (3H, d, J=6.0, H-6), 1.60 (1H, dd, J=14.8 and 4.0, H-2), 2.05 (1H, d, J=11.0, OH), 2.24 (1H, dd, J=14.8 and 1.6, H-2'), 3.04 (1H, dd, J=11.0 and 10.8, H-4), 3.37 (3H, s, OMe), 3.92 (1H, dq, J=10.8 and 6.0, H-5), 4.83 (1H, d, J=10.8, OH), 5.07 (1H, ddd, J=10.8, 4.0 and 1.6, H-1). β-anomer of **1**: δ=1.25 (3H, s, C3-Me), 1.30 (3H, d, J=6.0, H-6), 1.34 (1H, dd, J=14.2 and 9.8, H-2), 2.11 (1H, d, J=11.0, OH), 2.33 (1H, dd, J=14.2 and 1.9, H-2'), 2.98 (1H, dd, J=11.0 and 9.0, H-4), 3.25 (3H, s, OMe), 3.32 (1H, d, J=6.0, OH), 3.67 (1H, dq, J=9.0 and 6.0, H-5), 4.92 (1H, ddd, J=9.8, 1.9 and 6.0, H-1). **2**+**2'**[10] ($CDCl_3$ + D_2O): δ=3.23 (s, OMe), 3.24 (s, OMe), 3.29 (s, OMe), 3.37 (s, OMe), 4.86 (dd, J=8.0 and 2.0), 4.90 (dd, J=6.6 and 1.9), 5.35 (dd, 4.4 and 0.4), 5.58 (dd, J=7.6 and 2.0), (other peaks are very complicated).

6) D. B. Dess and J. C. Martin, *J. Org. Chem.*, **48**, 4155 (1983).

7) The stereochemistry of C3-Me was ascertained by the observation of nuclear Overhauser enhancement of the H-4 upon irradiation at a C3-Me resonance frequency.

8) The spectral data including ^{1}H-NMR and $[\alpha]_D$ were in accord with those of authentic samples which were prepared from natural erythromycin A[3a] and isolated by silica gel column chromatography in our laboratories.

9) The optical rotations of methyl α-cladinoside in Ref. 3c and 3d are unfortunately incorrect! These are originally compared with the data in Ref. 3a. However, in Ref. 3a, the stereochemistry of anomeric position of methyl cladinoside was not discussed, and we confirmed that the methyl cladinoside which was obtained from erythromycin A according to the Ref. 3a, was a mixture of both anomers (α/β=1/4.9) by ^{1}H-NMR analysis.

10) **2** was isolated as a mixture of the pyranose form **2** and its furanose form **2'**.[5]

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