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Application of Efficient Glycosylation of 2,6-Anhydro-2-thio Sugar to The Total Synthesis of Erythromycin A

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Abstract: *The total synthesis of erythromycin A (1) from (9S)-9-dihydroerythronolide A (2) was achieved efficiently by the highly stereoselective and powerful glycosylation of 2,6-anhydro-2-thio sugar **9** as a key step.*

A most typical and clinically important macrolide antibiotic, erythromycin A (**1**) has been studied for a long time and still undoubtedly one of the most challenging molecules for many organic chemists. Although a number of synthetic studies of erythromycins including some elegant total syntheses of erythronolides have been reported[1], complete total synthesis of erythromycin A possessing two sugars, L-cladinose and D-desosamine, was only announced by R. B. Woodward and his co-workers in 1981[2]. One of the highest barriers in front of us after the aglycone synthesis seems to be the introduction of the acid sensitive 2,6-dideoxy sugar, L-cladinose to the extremely low reactive C-3-hydroxyl function of aglycone[2]. Recently, we introduced the highly stereoselective and powerful glycosylation of 2,6-anhydro-2-thio sugar for the synthesis of 2,6-dideoxy-α-glycosides[3] and the highly stereocontrolled synthesis of 2,6-dideoxy-C-3-branched carbohydrates by use of 2,6-anhydro-2-thio sugar[4]. So, we have applied these novel methodologies to the total synthesis of erythromycin A. In this communication, we wish to describe the efficient total synthesis of erythromycin A from (9*S*)-9-dihydroerythronolide A (**2**) by successful application of the glycosylation of 2,6-anhydro-2-thio sugar **9**.

Our synthesis began with the conversion of (9*S*)-9-dihydroerythronolide A (**2**), which was first synthesized by Kinoshita *et al.*[5] and easily prepared from natural erythromycin A[6], to **3**[7] in 87% yield by the selective protection (5.0 equiv. p-anisaldehyde dimethylacetal, 0.2 equiv. CSA, CH_2Cl_2, -30°C, 72h) of C-3 and 5 hydroxyl functions with the p-methoxybenzylidene group. Selective isopropylidenation (6.0 equiv. 2-methoxypropene, 1.0 equiv. PPTS, CH_2Cl_2, 25°C, 1.5h) of **3** followed by reductive deprotection (H_2, cat. $Pd(OH)_2$, 25°C, 2h) of p-methoxybenzylidene group of **4**[7] gave the first key intermediate **5**[7] in 95% overall yield. Glycosylation of **5** with **6**[2] by the modified Woodward procedure (5.2 equiv. **6**, 6.4 equiv. AgOTf, MS 4A, CH_2Cl_2-toluene, Ar, 0°→25°C, 4h) was proceeded regio- and stereo-selectively to afford the desired glycosylated product **7**[7] in 63% yield. Next oxidation (2.0 equiv. mCPBA, $CHCl_3$, 25°C, 20min) of the N-Me_2 group in **7** gave the second key intermediate **8**[7] in 99 % yield. The second glycosylation to the C-3-

hydroxy group of **8**, predictively, posed an extremely hard problem, which was due to the low reactivity by the sterically crowded nature of C-3-hydroxy group and the formation of hydrogen bond between its hydroxy group and C-1 carbonyl group. On this stage, our glycosylation protocol showed sharp contrast with the vast number of other methods and worked efficiently. The glycosylation of **8** with activated 2,6-anhydro-2-thio sugar **9**[7], which was easily synthesized (5.0 equiv. Me_3SiSPh, 1.2 equiv. TMSOTf, CH_2Cl_2, -10°C, 10min,[3a,8] 96%) from **10**[4], in the presence of 1.1 equiv. of NIS, 0.7 equiv. of TfOH[9] and MS 4A in degassed CH_2Cl_2 under Ar at -35°C for 10min proceeded smoothly to give the desired α-glycoside **15**[7] *in 90% yield* with high stereocontrol as an only isolated product. In contrast to this fact, glycosylations of **8** with **11**[7], **12**[7], **13**[7] or **14**[2,7] by some appropriate conditions[10] were not effective and the corresponding glycosylated products were not isolated at all or isolated in miserable yields. Further, as the glycosidic bond of 2,6-anhydro-2-thio sugar was more stable than that of the corresponding 2,6-dideoxy sugar in acidic conditions, deisopropylidenation of **15** in 50% AcOH-H_2O at 40°C for 24h afforded **16**[7] in 66% yield with minimal cleavage of the glycosidic bond of cladinose moiety in **15**. Treatment of **16** with H_2 in the presence of catalytic amounts of Raney-Ni (W4) in EtOH caused the desulfurization of 2,6-anhydro-2-thio sugar, reduction of N-oxide and removal of benzyl and carbomethoxy groups at the same time to give (9*S*)-9-dihydroerythromycin A (**17**)[7,11] in 54% yield. To selectively oxidize the C-9 hydroxyl function of **17**, N-Me_2 group of **17** was again oxidized by 2.0 equiv. of mCPBA in $CHCl_3$ at 25°C for 10min to give **18**[7] in 99% yield. The selective oxidation was effected by the treatment of **18** with 1.3 equiv. of $(n\text{-}Bu_3Sn)_2O$ and 1.3 equiv. of Br_2[12] in CH_2Cl_2 at 25°C for 24h to afford the desired 9-keto compound **19**[7,13] in 58% yield. Finally, N-oxide of **19** was reduced by hydrogenolysis (H_2, Raney-Ni (W4), EtOH, 25°C, 1h) to give **1** in 84% yield. **1** was identical with an authentic sample of natural erythromycin A[14] by ^{1}H-NMR, $[\alpha]_D$ and TLC behaviors in several solvent systems.

In conclusion, this work showed not only the total synthesis of erythromycin A from (9*S*)-9-dihydroerythronolide A but also the promising potentiality of our glycosylation method in the synthesis of large and complex natural products.

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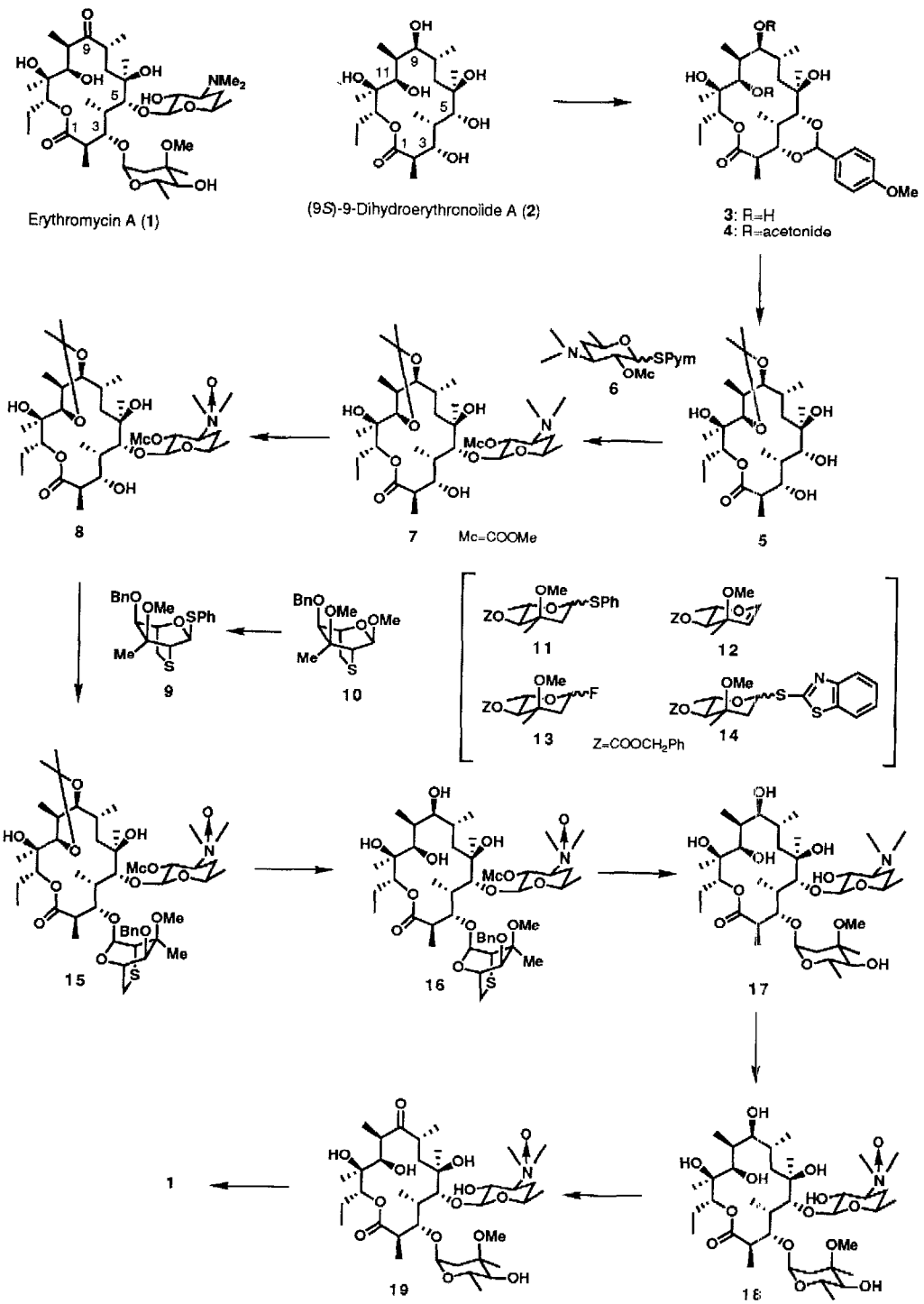
Erythromycin A (1)
(9S)-9-Dihydroerythronolide A (2)
3: R=H
4: R=acetonide
6
5
7
Mc=COOMe
8
9
10
11
12
13
14
Z=COOCH2Ph
15
16
17
18
19
1

Garrant, K. Hayakawa, W. Heggie, D. P. Hesson, D. Hoppe, I. Hoppe, J. A. Hyatt, D. Ikeda, P. A. Jacobi, K. S. Kim. Y. Kobuke, K. Kojima, K. Krowicki, V. J. Lee, T. Leutert, S. Malchenko, J. Martens, R. S. Matthews, B. S. Ong, J. B. Press, T. V. Rajan Babu, G. Rousseau, H. M. Sauter, M. Suzuki, K. Tatsuta, L. M. Tolbert, E. A. Truesdale, I. Uchida, Y. Ueda, T. Uyehara, A. T. Vasella, W. C. Vladuchick, P. A. Wade, R. M. William, and H. N. -C. Wong, *J. Am. Chem. Soc.*, **103**, 3210, 3213 and 3215 (1981).

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