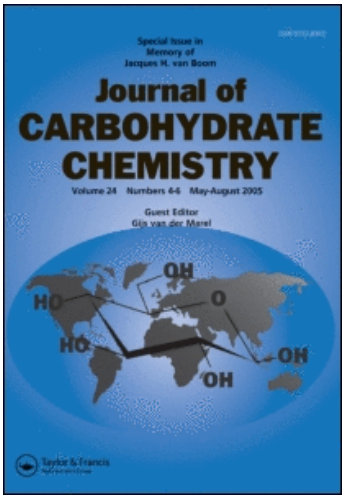


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# $SN^2$ Displacement of Carbohydrate Triflates by 9-Oximes of Erythromycin A and Of a Tylosin Derivative

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# $S_N2$ DISPLACEMENT OF CARBOHYDRATE TRIFLATES BY 9-OXIMES OF ERYTHROMYCIN A AND OF A TYLOSIN DERIVATIVE

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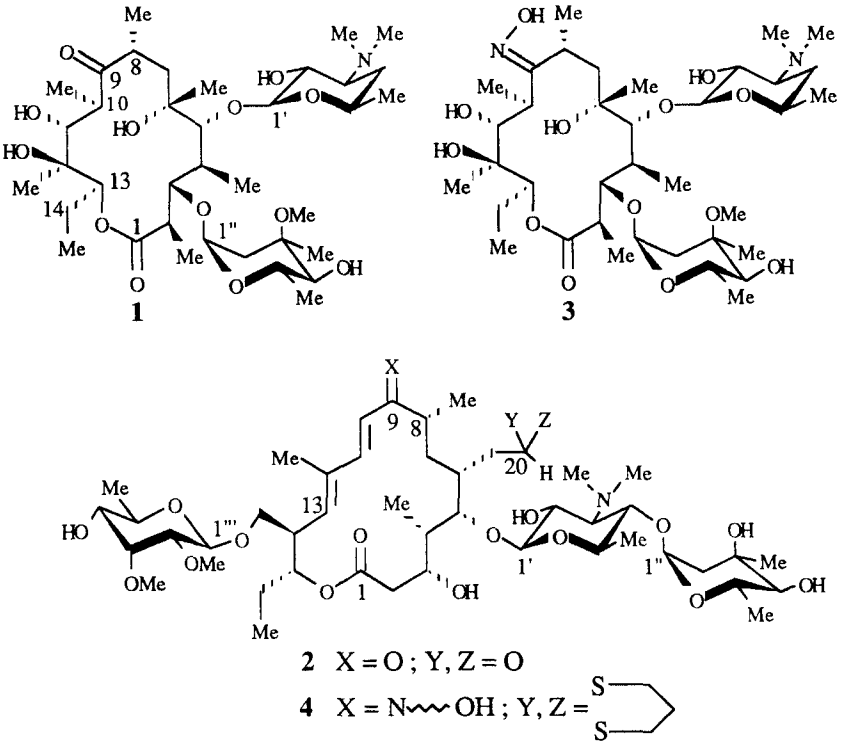
## ABSTRACT

The preparation of 9-*O*-glycosyloxime derivatives of erythromycin A (**1**) and tylosin (**2**) is reported. Access to this new class of macrolides was achieved from (*E*)-9-oxime of erythromycin A (**3**) and 9-oxime of tylosin 20-(1,3-dithiane) (**4**), by successful displacement of triflates of suitably protected carbohydrates.

## INTRODUCTION

Medicinal and veterinary utility of macrolide antibiotics has never been contested since their discovery.[1] However, these antibiotics and their metabolites have been shown to induce hepatic cytochrome P450 and to produce, in some cases, a suicide-type inhibitory complex after *N*-demethylation and oxidation of their *N*-dimethylamino function.[2] This hepatotoxicity could not simply be avoided by chemical modification of the tertiary amine since this group was recognised as essential for the binding of the antibiotic agent with its ribosomal target in bacteria.[3] The ionization state of the tertiary amine (pKa effect),[4] the steric hindrance around the dimethylamino group and the hydrophobicity of the molecule[5] seem to be three factors of significance which affect the interaction of these antibiotics with




**Scheme 1**



cytochrome P450. Focusing on hydrophobicity, the introduction of additional hydroxyl groups on erythromycin A (**1**) and tylosin (**2**) was thought to contribute to a better tolerance.

These hydroxyl groups could be brought by an additional carbohydrate, linked to the aglycone moiety of these macrolides *via* an oxime at the C-9 position. Choice of an oximic linkage was justified considering the potential antibacterial activity of previously reported 9-*O*-ether oxime derivatives of tylosin[6] (**2**) and erythromycin A[7] (**1**). In the latter case, these derivatives were prevented from extensive acidic decomposition at biological pH.[8] Only a few methods of preparation of *O*-glycosyloxime derivatives are reported in the literature. Pozo and Gotor[9] have disclosed an enzymatic approach, but their method is limited to a small range of substrates and its application, if possible, would have required full protection of the hydroxy groups of the macrolides to avoid competitive glycosylation. Glycosyloxime derivatives can also be obtained by condensation of *O*-glycosylhydroxylamine derivatives[10] with aldehydes or ketones[11] (Figure 1, route A). In view of both the versatility of this

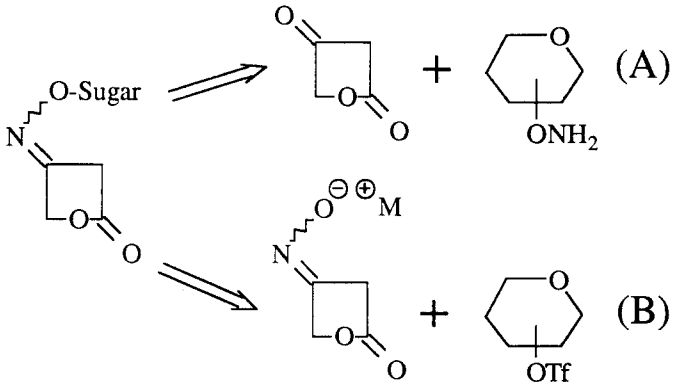



**Figure 1.** Strategies towards *O*-glycosyloxime derivatives of macrolides.



methodology and the high nucleophilicity of *O*-glycosylhydroxylamines, as demonstrated by Tronchet *et al*,[11a] we decided to first explore this route although the ketone function of tylosin (**2**) and especially erythromycin A (**1**) were only poorly reactive. Whatever the experimental conditions applied,[13] the desired *O*-glycosyloxime derivatives were not detected in the crude reaction mixtures. Thus we alternatively designed a new strategy based on a coupling reaction between carbohydrate bearing triflates and oximate ions of compounds **3** and **4** (Figure 1, route B).

## RESULTS AND DISCUSSION

The successful reaction between the (*E*)-9-oxime of erythromycin A[7] (**3**) and the readily accessible 1,2;3,4-di-*O*-isopropylidene-6-*O*-[(trifluoromethyl)sulfonyl]-α-D-galactopyranoside[14] (**5**) confirmed the feasibility of this approach (Scheme 2).

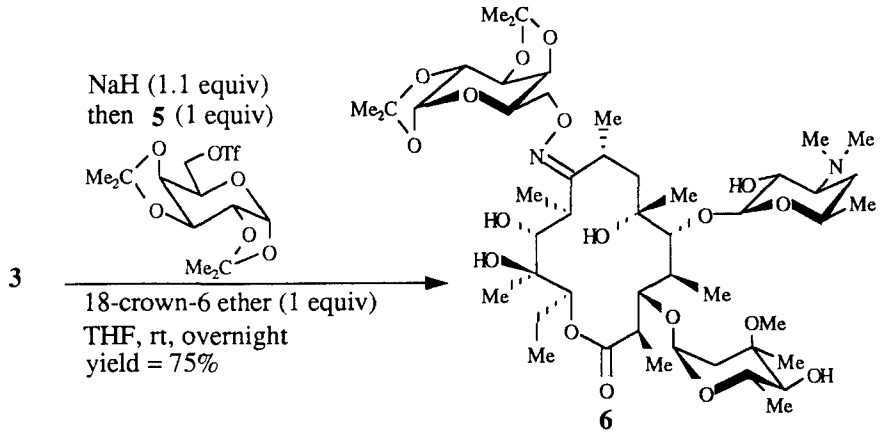
Thus, the synthesis of various triflated carbohydrates was undertaken (Scheme 3). The choice of the protecting groups was suggested by:

(a) the putative stability of the triflates,

(b) the compatibility of their removal with the functionalities of acid and base sensitive macrolides,

(c) the requirement of a single deprotection step.

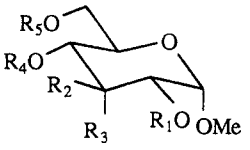
Primary triflate **8** was obtained from methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside[15] using Binkley's procedure[16] in 84% yield. Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-[(trifluoromethyl)sulfonyl]-α-D-galactopyranoside (**10**) was obtained from the



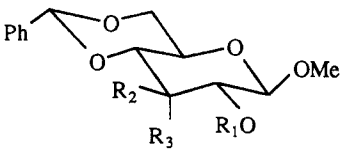

**Scheme 2**



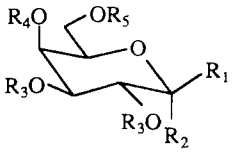
corresponding alcohol **9** as mentioned in the literature.[17] For the preparation of triflate **14**, we switched from ester to 4-methoxybenzyl ether protective groups to avoid possible intramolecular displacement of the triflate by the 3-*O* ester group.[18] Etherification[19] of diol **11**[20] with 4-methoxybenzyl chloride (MPMCl) in DMSO afforded **12** in 80% yield. Regioselective acetal ring opening of this intermediate with sodium cyanoborohydride and trifluoroacetic acid in DMF[20] gave methyl 2,3,6-tri-*O*-(4-methoxybenzyl)-α-D-glucopyranoside (**13a**) in 88% together with 5% of its regioisomer **13b**. Triflation of compound **13a** with triflic anhydride and pyridine in $CH_2Cl_2$ afforded triflate **14** in 89% yield. Benzylation of methyl 4,6-*O*-benzylidene-2-*O*-[(trifluoromethyl)sulfonyl]-α-D-glucopyranoside[21] (**15**) with benzyltrichloroacetimidate and a catalytic amount of triflic acid[22] furnished the known triflate **16** in improved yield compared to the literature.[23] The synthesis of triflates **18**, **20**, **22** and **24** was achieved starting from the corresponding alcohols **17**[24], **19**[25], **21**[26] and **23**[27] by treatment with triflic anhydride and pyridine in $CH_2Cl_2$ in 86%, 81%, 89% and 93% yield, respectively. Nucleophilic substitution of triflate **24** with tetraacetylammonium acetate at room temperature in DMF led to intermediate **25** in 94% yield. Zemplen deprotection of the acetate in quantitative yield followed by triflation with triflic anhydride and pyridine in $CH_2Cl_2$ furnished the particularly unstable compound **27** in 51% yield. Regioselective reductive ring opening of benzyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside[28] (**28**) with boron-trimethylamine complex and aluminium chloride in THF[29] afforded benzyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside[30] (**29**) as a sole product in 76% yield. Treatment of compound **29** with triflic anhydride and pyridine in $CH_2Cl_2$ furnished compound **30** in 95% yield.



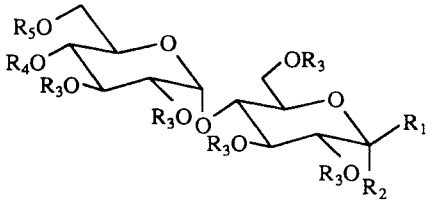
| | R1 | R2 | R3 | R4 | R5 |
|---|---|---|---|---|---|
| **7** | Ac | OAc | H | Ac | H |
| **8** | Ac | OAc | H | Ac | Tf |
| **11** | H | OH | H | 4-MeOPh-CH | |
| **12** | MPM | OMPM | H | 4-MeOPh-CH | |
| **13a** | MPM | OMPM | H | OH | OMPM |
| **13b** | MPM | OMPM | H | OMPM | OH |
| **14** | MPM | OMPM | H | OTf | OMPM |
| **15** | Tf | OH | H | Ph-CH | |
| **16** | Tf | OBn | H | Ph-CH | |
| **17** | Bn | OH | H | Ph-CH | |
| **18** | Bn | OTf | H | Ph-CH | |
| **19** | Bn | H | OH | Ph-CH | |
| **20** | Bn | H | OTf | Ph-CH | |



| | R1 | R2 | R3 |
|---|---|---|---|
| **21** | H | OBn | H |
| **22** | Tf | OBn | H |
| **23** | Bn | OH | H |
| **24** | Bn | OTf | H |
| **25** | Bn | H | OAc |
| **26** | Bn | H | OH |
| **27** | Bn | H | OTf |



| | R1 | R2 | R3 | R4 | R5 |
|---|---|---|---|---|---|
| **9** | H | OMe | Bz | H | Bz |
| **10** | H | OMe | Bz | Tf | Bz |
| **28** | OBn | H | Bn | Ph-CH | |
| **29** | OBn | H | Bn | H | Bn |
| **30** | OBn | H | Bn | Tf | Bn |



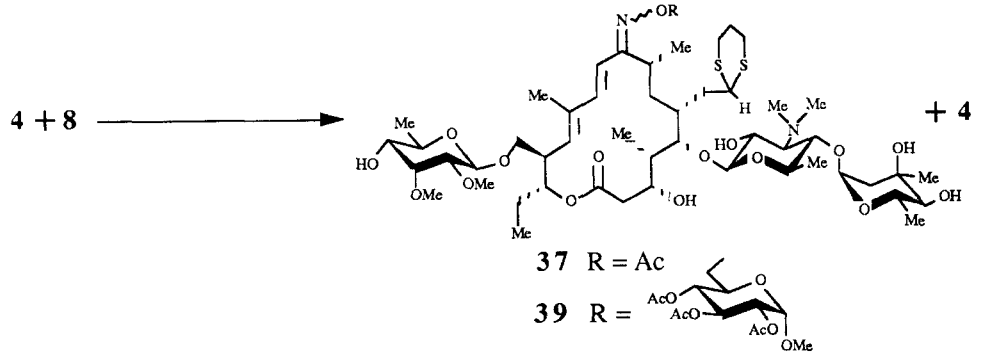
| | R1 | R2 | R3 | R4 | R5 |
|---|---|---|---|---|---|
| **31** | H,OH | OH,H | H | H | H |
| **33** | OMe | H | Ac | Ac | Ac |
| **34** | OMe | H | Bn | Ph-CH | |
| **35** | OMe | H | Bn | H | Bn |
| **36** | OMe | H | Bn | Tf | Bn |

(MPM = 4-Methoxyphenylmethyl)

**Scheme 3.** Preparation of carbohydrate triflates.

Treatment of maltose monohydrate (**31**) with acetic anhydride and a catalytic amount of perchloric acid in glacial acetic acid followed by addition of 30% hydrobromic acid in glacial acetic acid afforded 2,3,6,2',3',4',6'-hepta-*O*-acetyl-α-D-maltosyl bromide (**32**), which was further transformed to the corresponding methyl-β-D-glycoside **33** *via* a Koenigs-Knorr reaction in the presence of mercuric (II) cyanide in MeOH in 61% overall yield. Deesterification of **33** was carried out using the Zemplen procedure; the crude

**Table 1.** Optimization of the coupling reaction conditions.



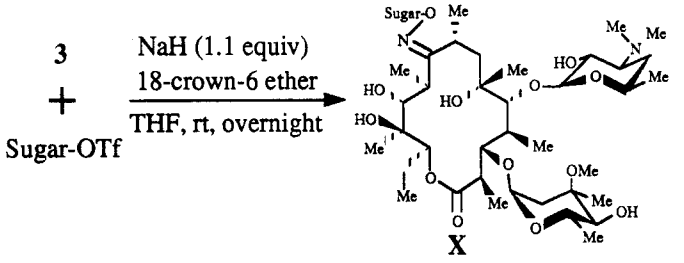

| Entry | Experimental conditions | Yields (%) 37 | 39 | 4 |
|---|---|---|---|---|
| 1 | THF, rt triflate added to anion | 14 | 25 | 50 |
| 2 | THF, rt anion added to triflate | traces | 44 | 37 |
| 3 | THF, rt 18-crown-6 ether anion added to triflate | traces | 53 | 25 |
| 4 | THF/DMPU 5:2, rt anion added to triflate | traces | 48 | 40 |

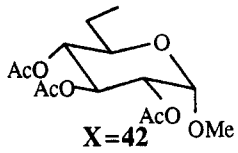
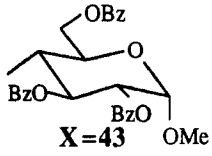
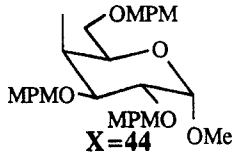
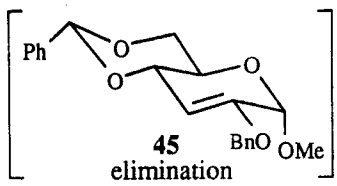


product was treated with dimethoxytoluene in the presence of a catalytic amount of *p*-toluenesulfonic acid in DMF.[32] After removal of the excess reagent and solvent, the residue was treated with sodium hydride and benzyl bromide in DMF to give **34** in 68% overall yield. Regioselective reductive acetal ring opening of compound **34** with boron-trimethylamine complex and aluminium chloride in THF[29] afforded alcohol **35** as a sole product in 70% yield. Treatment of **35** with triflic anhydride and pyridine in $CH_2Cl_2$ furnished triflate **36** in 84% yield.

Having prepared these triflates, their nucleophilic substitution with compounds **3** and **4** was undertaken. Direct addition of triflate **8** in solution in THF into the oximate ion of compound **4** in THF at room temperature led mainly to the formation of undesired products [e.g., **37** or methyl 2,4-di-*O*-acetyl-3,6-anhydro-α-D-glucopyranoside (**38**)] together with recovered starting material rather than to compound **39** (Table 1, entry 1).

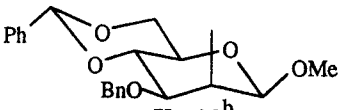
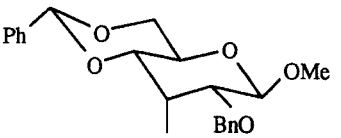
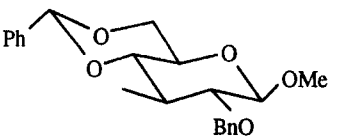
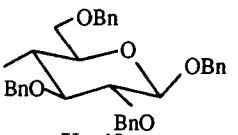
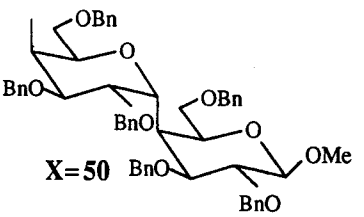
**Table 2.** *O*-Glycosyloxime derivatives of erythromycin A.




| Entry | Sugar-OTf | Temperature | Sugar Compound | Yield (%) |
|---|---|---|---|---|
| 1 | **8** | rt |  **X=42** | 61 |
| 2 | **10** | rt |  **X=43** | 65 |
| 3 | **14** | rt |  **X=44** | 82 |
| 4 | **16** | reflux | no reaction | - |
| 5 | **18**[a] | rt | no reaction | - |
| 6 | **18** | reflux |  **45** elimination | - |

(continued)

**Table 2.** (continued)

| Entry | Sugar-OTf | Temperature | Sugar Compound | Yield (%) |
|---|---|---|---|---|
| 7 | **20**[a] | rt | elimination **45** | |
| 8 | **22**[a] | reflux |  **X=46**[b] | 60 |
| 9 | **24**[a] | rt |  **X=47** | 70 |
| 10 | **27** | 0°C |  **X=48** | 47 |
| 11 | **30** | rt |  **X=49** | 90 |
| 12 | **36** | rt |  **X=50** | 65 |

a. See note 33.
b. Obtained as a *Z* and *E* mixture of oximes.

The importance of these side reactions was, however, controlled using an inverse procedure (i.e., dropwise addition of the oximate ion into the triflate in solution in THF) (Table 1, entry 2) and almost avoided when 18-crown-6 ether or a cosolvent was used (Table 1, entries 3 and 4). Reproducing the above optimum conditions, 9-[*O*-(methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranosid-4-yl)oxime] of tylosin 20-(1,3-dithiane) (**40**) and 9-{*O*-[methyl 2,3,6-tri-*O*-(4-methoxybenzyl)-α-D-glucopyranosid-4-yl]oxime} of tylosin 20-(1,3-dithiane) (**41**) were obtained in 63 and 72% yield starting from triflates **10** and **14**, respectively. These substancially improved yields may reflect the greater stability of triflates **10** and **14** towards the applied basic conditions.

In the same manner, *O*-glycosyloxime derivatives of erythromycin A (**1**) were prepared using compound **3** as nucleophile (Table 2). Results were strongly dependent on the nature of the triflates and particularly on their anomeric configuration. Methyl 2-*O*- or 3-*O*-[(trifluoromethyl)sulfonyl]-α-D-glycopyranoside derivatives did not react or led to elimination products. Triflate **16** (Table 2, entry 4) was recovered unchanged whereas the isomer **22** led to a mixture of oximes (*Z* and *E*) **46**,[34] when the reaction was run at reflux, in 70% yield (Table 2, entry 8). The difference of reactivity of triflates **16** and **22** is surprising and may be explained by more unfavorable dipolar interactions at the transition state for the former compound.[35] Triflate **24** and its unstable stereomer **27** smoothly afforded the corresponding *O*-glycosyloxime derivatives **47** and **48** at room temperature or 0 °C, respectively (Table 2, entries 9 and 10). In contrast, the lack of reactivity of triflate **18** (Table 2, entry 5) may be attributed to 1,3-dipolar interactions with the anomeric methoxy group. Under forcing conditions (Table 2, entry 6), this substrate reacted preferentially to give methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hex-2-enopyranoside (**45**). Starting from isomer **20**, the same unsaturated carbohydrate was obtained from room temperature (Table 2, entry 7). The formation of this elimination product was in agreement with recent observations.[33b] Reasonable yields of *O*-glycosyloxime derivatives were obtained starting from primary triflates (Table 2, entry 1 and Scheme 2) or from axial (Table 2, entries 2 and 11) or equatorial (Table 2, entries 3 and 12) 4-*O*-triflated derivatives regardless of the anomeric configuration.

## CONCLUSION

In this paper, the first examples of substitution of carbohydrate triflates by oximate ions have been described. Given the poor nucleophilicity compared to the basicity of these ions, the issue of the coupling reaction is strongly dependent on the nature of the triflate.

Application of this reaction allowed the entry to a new class of macrolides, the 9-*O*-glycosyloximes of erythromycin A and tylosin. The antibacterial activity of the described compounds after liberation of all the hydroxyl groups from the respective esters, ethers and acetals will be reported upon permission of our industrial partner.

## EXPERIMENTAL

**General methods.** Meltings points were determined with a Reichert-Jung apparatus and are not corrected. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Thin-layer chromatography (TLC) was performed using E. Merck plates of silica gel 60 with fluorescent indicator. Visualization was effected by spraying plates with 5% $H_2SO_4$ in ethanol followed by heating at 120-140 °C. Flash chromatography was conducted with silica gel (0.040-0.063 mm, E. Merck). THF was distilled over sodium/benzophenone, DMF, DMSO and pyridine were distilled over $CaH_2$. $CH_2Cl_2$ was distilled over $P_2O_5$ and MeOH over magnesium. Nuclear magnetic resonance ($^1H$ and $^{13}C$ NMR) spectra were recorded in $CDCl_3$ on Bruker WP 200, Bruker WP 300 and Bruker WP 300 spectrometers. Chemical shifts are recorded in ppm ($\delta$) relative to tetramethylsilane as internal standard. For clarity, chemical shifts of aromatic hydrogens and carbons have been omitted. CIMS and FABMS spectra were obtained on AEI-SM-9 and SM-80 spectrometers, respectively. High resolution mass spectra (HRMS) were run on a VG-ZAB-SEQ spectrometer by the Service Central d'Analyse, Vernaison. Elemental analyses were performed by the microanalytical laboratory at the ICSN, Gif sur Yvette. In NMR data, "' and "" for compounds **6**, **42**, **43**, **44**, **46**, **47**, **48**, **49** and **39**, **40**, **41**, respectively, refer to the newly introduced carbohydrate moiety. '" and "" for compound **50** refer to the galactose and the glucose moiety of the disaccharide, respectively.

**General procedure A for trifluoromethanesulfonylation of carbohydrates (13a, 17, 19, 21, 23, 26, 29, 35).** A mixture of the carbohydrate substrate (1 equiv) and pyridine (2 equiv) in $CH_2Cl_2$ (3 mL/mmol of carbohydrate) was treated with trifluoromethanesulfonic anhydride (1.15 to 1.8 equiv) at -20 °C under argon. The reaction was stirred for 2 hours, then warmed up to room temperature. After completion (monitored by TLC), the reaction was quenched with water. The mixture was then extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to furnish a residue which was further purified by flash chromatography on silica gel.

**General procedure B for the coupling reactions between trifluoromethanesulfonates (8, 10, 14, 24, 30, 36) and oximes (3) and (4).**

A mixture of oxime (1 equiv) and 18-crown-6 ether (0.3 to 1 equiv) in THF (5 mL/mmol of oxime) was treated with sodium hydride (1.1 equiv) [sodium hydride (60% dispersion in mineral oil) was washed with heptane] at room temperature, under argon. After stirring during 20 minutes, the mixture was slowly transferred into a solution of triflate (1 equiv) in THF (5 mL/mmol of oxime). The reaction was stirred at room temperature overnight then quenched by adding Florisil® and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

**(*E*) -9-[ *O* -(1,2;3,4-di- *O* -isopropylidene-α-D-galactopyranosid-6-yl) oxime] of erythromycin A (6).** To a mixture of (*E*)-9-oxime of erythromycin A **3** (618 mg, 0.83 mmol) and 18-crown-6 ether (304 mg, 0.83 mmol) in THF (4 mL) was added, under argon, sodium hydride (20 mg) [sodium hydride (60% dispersion in mineral oil, 33 mg) was washed with heptane]. The mixture was then stirred for 20 min at room temperature. A solution of triflate **5** (426 mg, 1.08 mmol) in THF (5 mL) was then added dropwise *via* a syringe into the solution. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the residue purified by flash chromatography (eluent dichloromethane/methanol/concd ammonia 10:1:0.05 v/v/v) to afford compound **6** (625 mg, 75%) as a foam: Rf 0.46 (dichloromethane/methanol/concd ammonia 15:1:0.05 v/v/v); $[\alpha]_D$ -58 (*c* 0.8, chloroform); $^1H$ NMR (200 MHz) δ 1.00 (d, 3H, $J_{8,8Me}$ = 7 Hz, 8-$CH_3$), 1.30, 1.35, 1.43 and 1.50 (4s, 12H, 2 C($CH_3$)$_2$), 4.33 (dd, 1H, $J_{1''',2'''}$ = 5.1 Hz, $J_{2''',3'''}$ = 2.5 Hz, H-2'''), 4.42 (d, 1H, $J_{1',2'}$ = 7.2 Hz, H-1'), 4.62 (dd, 1H, $J_{3''',4'''}$ = 7.6 Hz, H-3'''), 4.86 (d, 1H, $J_{1'',2''}$ = 5 Hz, H-1''), 4.98 (dd, 1H, $J_{13,14ax}$ = 2 Hz, $J_{13,14eq}$ = 11 Hz, H-13), 5.55 (d, 1H, H-1'''); $^{13}C$ NMR (50 MHz) δ 15.1 (10-$OCH_3$), 18.6 (8-$CH_3$), 24.5, 24.6, 26.0 and 26.3 (4 $CH_3$), 25.8 (C-8), 33.0 (C-10), 65.9 (C-5'''), 72.8 (C-6'''), 71.0, 71.1 and 71.2 (C-2''', C-3''' and C-4'''), 96.5 (C-1'''), 108.4 and 109.4 (2 C($Me$)$_2$), 171.0 (C-9); FABMS (positive) *m/z* 1013 $(M+Na)^+$, 991 $(M+H)^+$, 833 $(M+H-(Cladinose-H))^+$. HRMS Calcd for $C_{49}H_{87}N_2O_{18}$ (991.5954). Found: 991.5957.

**Methyl 2,3,4-tri-*O*-acetyl-6-*O*-[(trifluoromethyl)sulfonyl]-α-D-glucopyranoside (8).** A solution of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside[15] **7** (1.51 g, 4.71 mmol) was converted to the triflate **8** following a literature procedure.[16] Compound **8** (1.84 g, 84%) was obtained after flash chromatography (eluent ether/pentane 3:2 v/v) as an unstable syrup; Rf 0.43 (ethyl acetate/heptane 1:1 v/v); $^1H$ NMR (200 MHz) δ 2.02, 2.07 and 2.09 (3s, 9H, 3 $CH_3$), 3.45 (s, 3H, $OCH_3$), 4.12 (ddd, 1H, $J_{4,5}$ = 3 Hz, $J_{5,6a}$ = 9.8 Hz, $J_{5,6b}$ = 5.5 Hz, H-5), 4.50-4.58 (m, 2H, H-6a and H-6b), 4.88 (dd, 1H, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = 10.1 Hz, H-2), 4.98 (d, 1H, H-1), 5.00 (dd, 1H, $J_{3,4}$ = 10.1 Hz, H-4), 5.50 (t, 1H, H-3); $^{13}C$ NMR (50 MHz) δ 20.2, 20.5 and 20.5 (3 $CH_3$), 55.7 ($OCH_3$),

67.0 (C-5), 68.6 (C-4), 69.7 and 70.5 (C-2 and C-3), 73.9 (C-6), 96.8 (C-1), 118.6 (q, J = 320.4 Hz, $CF_3$), 169.6 and 170.0 (3 $OCOCH_3$); FABMS (positive) *m/z* 475 $(M+Na)^+$.

**Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-[ (trifluromethyl) sulfonyl) ]-α-D-galactopyranoside (10).** Methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside[17] **9** (1.52 g, 3 mmol) was reacted with trifluoromethanesulfonic anhydride (0.76 mL, 4.5 mmol) in the presence of pyridine (0.47 mL, 6 mmol) following general procedure A. Compound **10** (1.79 g, 84%) was obtained after flash chromatography (eluent ethyl acetate/heptane 3:7 v/v) followed by crystallization from EtOH: Rf 0.53 (ethyl acetate/heptane 1:1 v/v); mp 136 °C (dec) (lit.[17] mp 137-138 °C); $[\alpha]_D$ +101 (*c* 1, chloroform) [lit.[17] $[\alpha]_D$ +103.6 (*c* 1, chloroform)]; $^1H$ NMR (200 MHz): identical to the literature; $^{13}C$ NMR (50 MHz) δ 56.2 ($OCH_3$), 61.6 (C-6), 66.0, 67.7 and 68.4 (C-2, C-3 and C-5), 83.1 (C-4), 97.7 (C-1), 118.5 (q, J = 321 Hz, $CF_3$), 165.9 (3 $OCOCH_3$); FABMS (positive) *m/z* 661 $(M+Na)^+$.

Anal. Calcd for $C_{29}H_{25}F_3O_{11}S$ (638.58): C, 54.54; H, 3.95; S, 5.02. Found: C, 54.69; H, 4.02; S, 4.80.

**Methyl 2,3-di-*O*-(4-methoxybenzyl)-4,6-*O*-(4-methoxybenzylidene)-α-D-glucopyranoside (12).** Methyl 4,6-*O*-(4-methoxybenzylidene)-α-D-glucopyranoside[20] **11** (2.6 g, 8.32 mmol) was dissolved in DMSO (40 mL) and added dropwise, under argon, to a suspension of sodium hydride (519 mg, 21.63 mmol) [sodium hydride (60% dispersion in mineral oil, 865 mg) was washed with heptane] in DMSO (35 mL) and stirred at room temperature for 30 min. 4-Methoxybenzyl chloride (3.38 mL, 24.96 mmol) was then added dropwise and the reaction mixture was further stirred overnight at room temperature. Crude **12** was precipitated by addition of a few drops of cold water. The solid was filtered and washed with water and heptane. Finally, crystallization from EtOH furnished compound **12** as a white solid (3.7 g, 80%): Rf 0.38 (ethyl acetate/heptane 1:1 v/v); mp 123-125 °C; $[\alpha]_D$ +46 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 3.40 (s, 3H, 1-$OCH_3$), 3.81 and 3.82 (2s, 3 and 6H, 3 $OCH_3$), 3.99 (dd, 1H, $J_{2,3}$ = 8.4 Hz, $J_{3,4}$ = 8.3 Hz, H-3), 4.22 (dd, 1H, $J_{1,2}$ = 3.6 Hz, H-2), 4.52 (d, 1H, H-1), 4.58-4.81 (m, 4H, 2 $CH_2Ar$), 5.42 (s, 1H, H-7); $^{13}C$ NMR (50 MHz) δ 55.4 (4 $OCH_3$), 62.5 (C-5), 69.2 (C-6), 73.5 and 75.0 (2 $CH_2Ar$), 78.4, 79.0 and 82.3 (C-2, C-3 and C-4), 99.5 (C-1), 101.4 (C-7); CIMS *m/z* 553 $(M+H)^+$.

Anal. Calcd for $C_{31}H_{36}O_9$ (503.38): C, 67.38; H, 6.57. Found: C, 67.43; H, 6.65.

**Methyl 2,3,6-tri-*O*-(4-methoxybenzyl)-α-D-glucopyranoside (13a).** A solution of trifluoroacetic acid (2.62 mL, 25.5 mmol) in DMF, precooled at 0 °C, was added dropwise to a stirred mixture containing compound **12** (933 mg, 1.7 mmol), sodium cyanoborohydride (1.06 g, 17 mmol) and 3Å molecular sieves in DMF (12 mL). The reaction mixture was kept at room temperature during 24 hours and then, filtered through Celite®. The filtrate was poured into ice-cold saturated aqueous sodium hydrogen

carbonate. The aqueous layer was extracted three times with $CH_2Cl_2$. The combined extracts were washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent ethyl acetate/heptane 4:6 v/v) to furnish compound **13a** (830 mg, 88%) as a colorless syrup and its regioisomer **13b** (46 mg, 5%), which was crystallized from EtOH.

Description of compound **13a**: Rf 0.43 (ethyl acetate/heptane 1:1 v/v); $[\alpha]_D$ +2 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 2.2 (br s, 1H, 4-OH), 3.32 (s, 3H, 1-$OCH_3$), 3.42 (dd, 1H,$J_{5,6a}$ = 3.4 Hz, $J_{6a,6b}$ = 9.4 Hz, H-6a), 3.49 (br d, 1H, H-6b), 3.75 (s, 9H, 3 $OCH_3$), 4.42 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.48-4.63 (m, 5H, $CH_2Ar$), 4.84 (d, 1H, J = 11.1 Hz, CH*H*Ar); $^{13}C$ NMR (50 MHz) δ 54.5 (4 $OCH_3$), 68.8 (C-6), 69.9 and 70.2 (C-4 and C-5), 72.0, 72.5 and 74.3 ( 3 $CH_2Ar$), 78.9 and 80.7 (C-2 and C-3), 97.8 (C-1); FABMS (positive) *m/z* 561 $(M+Li)^+$.

Anal. Calcd for $C_{31}H_{38}O_9$ (554.64): C, 67.13; H, 6.91. Found: C, 67.06; H, 6.95.

Description of regioisomer **13b** : Rf 0.15 (ethyl acetate/heptane 1:1 v/v); mp 79-80 °C; $[\alpha]_D$ +1 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 1.77 (br s, 1H, 6-OH), 3.35 (s, 3H, 1-$OCH_3$), 3.78 and 3.82 (2s, 3 and 6H, 3 $OCH_3$), 3.96 (t, 1H, $J_{2,3} = J_{3,4}$ = 9 Hz, H-3), 4.50 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 4.52-4.96 (m, 6H, 3 $CH_2Ar$); $^{13}C$ NMR (50 MHz) δ 55.2 and 55.3 (4 $OCH_3$), 62.0 (C-6), 70.7 (C-5), 73.1, 74.7 and 75.4 (3 $CH_2Ar$), 77.3 (C-4), 79.8 and 81.8 (C-2 and C-3), 98.3 (C-1); CIMS *m/z* 555 $(M+H)^+$.

Anal Calcd for $C_{31}H_{38}O_9$ (554.64): C, 67.13; H, 6.91. Found: C, 67.25; H, 6.95.

**Methyl 2,3,6-tri-*O*-(4-methoxybenzyl)-4-*O*-[(trifluoromethyl)sulfonyl]-α-D-glucopyranoside (14).** Compound **13a** (815 mg, 1.47 mmol) was reacted with trifluoromethanesulfonic anhydride (0.45 mL, 2.65 mmol) in the presence of pyridine (0.41 mL, 2.94 mmol) following general procedure A. Compound **14** (898 mg, 89%) was obtained after flash chromatography (eluent diethylether/pentane 3:2 v/v) as an unstable syrup: Rf 0.54 (ethyl acetate/heptane 1:1 v/v); $[\alpha]_D$ +31 (*c* 0.43, chloroform); $^1H$ NMR (200 MHz) δ 3.30 (s, 3H, 1-$OCH_3$), 3.78 (s, 9H, 3 $OCH_3$), 4.31-4.52 (m, 4H, H-1, H-3, H-4 and C*H*HAr), 4.52-4.92 (m, 5H, $CH_2Ar$); $^{13}C$ NMR (50 MHz) δ 55.0 (3 $OCH_3$), 55.5 (1-$OCH_3$), 67.2 (C-6), 67.6 (C-5), 73.1, 73.1 and 75.0 (3 $CH_2Ar$), 77.5 (C-3), 79.8 and 81.6 (C-2 and C-4), 97.8 (C-1), 118.5 (q, J = 320.4 Hz, $CF_3$); FAB-MS *m/z* 709 $(M+Na)^+$.

**Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-[(trifluoromethyl)sulfonyl]-α-D-glucopyranoside (16).** To a stirred solution of methyl 4,6-*O*-benzylidene-2-*O*-[(trifluoromethyl)sulfonyl]-α-D-glucopyranoside[21] **15** (1.75 g, 4.23 mmol) and benzyl-2,2,2-trichloroacetimidate (1.18 mL, 6.34 mmol) in a mixture of cyclohexane/$CH_2Cl_2$ 2:1 (v/v) (42 mL) was added, a catalytic amount of trifluoromethanesulfonic acid (211 μL) at room temperature, under argon. The mixture was stirred until the starting material had

completely reacted as monitored by TLC. The crystalline trichloroacetamidate was removed by filtration through Celite® and the filtrate washed with aqueous saturated sodium hydrogen carbonate and water. The organic layer was dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Coumpound **16** (1.28 g, 60%) was obtained after flash chromatography (eluent ethyl acetate/heptane 2:8 v/v) followed by crystallization from $Et_2O$/heptane as a white solid: Rf 0.36 (ethyl acetate/heptane 2:8 v/v); mp 93-94°C (dec); $[\alpha]_D$ +27 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 3.48 (s, 3H, 1-$OCH_3$), 3.70 (t, 1H, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4), 3.73 (dd, 1H, $J_{5,6ax} = 12$ Hz, $J_{6ax,6eq} = 9.7$ Hz, H-6ax), 3.88 (ddd, 1H, $J_{5,6eq} = 4.1$ Hz, H-5), 4.13 (t, 1H, $J_{2,3} = 9.3$ Hz, H-3), 4.32 (dd, 1H, H-6eq), 4.75 (dd, 1H, $J_{1,2} = 3.6$ Hz, H-2), 4.76 (d, 1H, J = 10.9 Hz, C*H*HPh), 4.87 (d, 1H, CH*H*Ph), 4.98 (d, 1H, H-1), 5.56 (s, 1H, H-7); $^{13}C$ NMR (50 MHz) δ 55.7 (1-$OCH_3$), 62.3 (C-5), 68.7 (C-6), 75.1 ($CH_2Ph$), 75.2 (C-3), 82.0 (C-4), 83.7 (C-2), 97.7 (C-1), 101.6 (C-7), 118.6 (q, J = 320.4 Hz, $CF_3$); CISM *m/z* 505 $(M+H)^+$.

**Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-[(trifluoromethyl)sulfonyl]-α-D-glucopyranoside (18).** Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside[24] **17** (1.12 g, 3 mmol) was reacted with trifluoromethanesulfonic anhydride (0.757 mL, 4.5 mmol) in the presence of pyridine (0.485 mL, 6 mmol) following general procedure A. Compound **18** (1.30 g, 86%) was obtained after flash chromatography (eluent diethylether/heptane 4:6 v/v) followed by crystallization from $Et_2O$-heptane: Rf 0.18 (diethylether/heptane 1:1 v/v); mp 91-92 °C (dec); $[\alpha]_D$ +9 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 3.38 (s, 3H, $OCH_3$), 4.26 (dd, 1H, $J_{5,6eq} = 4.1$ Hz, $J_{6ax,6eq} = 9.6$ Hz, H-6eq), 4.50 (d, 1H, $J_{1,2} = 3.5$ Hz, H-1), 4.53 (d, 1H, J = 12.2 Hz, C*H*HPh), 4.80 (d, 1H, CH*H*Ph), 5.17 (t, 1H, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-3), 5.55 (s, 1H, H-7); $^{13}C$ NMR (50 MHz) δ 55.7 ($OCH_3$), 62.6 (C-5), 68.8 (C-6), 73.8 ($CH_2Ph$), 77.3 and 78.7 (C-2 and C-4), 84.7 (C-3), 99.0 (C-1), 101.6 (C-7), 118.6 (q, J = 320.5 Hz, $CF_3$); CIMS *m/z* 505 $(M+H)^+$.

Anal. Calcd for $C_{22}H_{23}F_3O_8S$ (504.48): C, 52.38; H, 4.59; S, 6.36. Found: C, 52.19; H, 4.58; S, 6.41.

**Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-[(trifluoromethyl)sulfonyl]-α-D-allopyranoside (20).** Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-allopyranoside[25] **19** (40 mg, 0.11 mmol) was reacted with trifluoromethanesulfonic anhydride (27.12 μL, 0.17 mmol) in the presence of pyridine (86.08 μL, 0.22 mmol) following general procedure A. Compound **20** (44 mg, 82%) was obtained after flash chromatography (eluent diethylether/pentane 1:2 v/v) as a syrup: Rf 0.45 (ethyl acetate/heptane 1:1 v/v); $[\alpha]_D$ -5 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 3.46 (s, 3H, $OCH_3$), 3.60 (t, 1H, $J_{1,2} = J_{2,3} = 4$ Hz, H-2), 3.63 (d, 1H, $J_{4,5} = 10$ Hz, H-4), 3.69 (t, 1H, $J_{5,6ax} = J_{6ax,6eq} = 10$ Hz, H-6ax), 4.20 (dt, 1H, $J_{5,6eq} = 5.1$ Hz, 5-H), 4.35 (dd, 1H,

H-6eq), 4.62 (d, 1H, J = 12.7 Hz, C*H*HPh), 4.72 (d, 1H, H-1), 4.84 (d, 1H, CH*H*Ph), 5.45 (br s, 1H, H-3), 5.54 (s, 1H, H-7); $^{13}C$ NMR (50 MHz) δ 56.3 ($OCH_3$), 58.1 (C-5), 69.2 (C-6), 71.6 ($CH_2Ph$), 72.2 (C-2), 75.5 (C-4), 80.7 (C-3), 98.5 (C-1), 102.4 (C-7), 118.6 (q, J = 320.5 Hz, $CF_3$); FABMS (positive) *m/z* 505 $(M+H)^+$.

**Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-[(trifluoromethyl)sulfonyl]-β-D-glucopyranoside (22).** Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside[26] **21** (405 mg, 1.09 mmol) was reacted with trifluoromethanesulfonic anhydride (0.275 mL, 1.64 mmol) in the presence of pyridine (0.176 mL, 2.18 mmol) following general procedure A. Compound **22** (490 mg, 89%) was obtained as a white solid after flash chromatography (eluent ethyl acetate/pentane 3:7 v/v) followed by crystallization from a mixture of $Et_2O$-heptane: Rf 0.42 (ethyl acetate/heptane 3:7 v/v); mp 104 °C (dec); $[\alpha]_D$ -51 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 3.58 (s, 3H, $OCH_3$), 3.77 (t, 1H, $J_{5,6ax} = J_{6ax,6eq} = 10.3$ Hz, H-6ax), 3.88 (dd, 1H, $J_{2,3} = 7.8$ Hz, $J_{3,4} = 8.4$ Hz, H-3), 4.41 (dd, 1H, $J_{5,6eq} = 4$ Hz, H-6eq), 4.52 (d, 1H, $J_{1,2} = 7.9$ Hz, H-1), 4.61 (dd, 1H, H-2), 4.80 (d, 1H, J = 10.6 Hz, C*H*HPh), 4.93 (d, 1H, CH*H*Ph), 5.59 (1H, s, H-7); $^{13}C$ NMR ($CDCl_3$, 50 MHz): δ 57.6 ($OCH_3$), 66.4 (C-5), 68.5 (C-6), 75.0 ($CH_2Ph$), 77.7 (C-3), 81.7 (C-4), 84.8 (C-2), 101.5 (C-1 and C-7), 118.6 (q, J = 320.4 Hz, $CF_3$); CIMS *m/z* 505 $(M+H)^+$.

Anal. Calcd for $C_{22}H_{23}F_3O_8S$ (504.48): C, 52.38; H, 4.59; S, 6.36. Found: C, 52.61; H, 4.38; S, 6.28.

**Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-[(trifluoromethyl)sulfonyl]-β-D-glucopyranoside (24).** Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside[27] **23** (1.2 g, 3.23 mmol) was reacted with trifluoromethanesulfonic anhydride (0.81 mL, 4.84 mmol) in the presence of pyridine (0.53 mL, 6.45 mmol) following general procedure A. Compound **24** (1.5 g, 93%) was obtained as white solid after flash chromatography (eluent diethylether/pentane 1:3 v/v), followed by crystallization from $Et_2O$: Rf 0.57 (ethyl acetate/heptane 1:1 v/v); mp 85-87 °C (dec); $[\alpha]_D$ -36 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 3.58 (s, 3H, $OCH_3$), 3.80 (t, 1H, $J_{3,4} = J_{4,5} = 9.4$ Hz, H-4), 3.82 (t, 1H, $J_{5,6ax} = J_{6ax,6eq} = 10.6$ Hz, H-6ax), 4.43 (dd, 1H, $J_{5,6eq} = 5.1$ Hz, H-6eq), 4.58 (d, 1H, $J_{1,2} = 9.4$ Hz, H-1), 4.76 (d, 1H, J = 10.4 Hz, C*H*HPh), 4.89 (d,1H, CH*H*Ph), 4.96 (t, 1H, $J_{2,3} = 9.4$ Hz, H-3), 5.56 (s, 1H, H-7); $^{13}C$ NMR (50 MHz) δ 57.7 ($OCH_3$), 65.7 (C-5), 68.5 (C-6), 75.2 ($CH_2Ph$), 77.9 (C-2), 79.2 (C-4), 85.9 (C-3), 101.4 (C-7), 105.1 (C-1), 118.5 (q, J = 320.6 Hz, $CF_3$); FABMS (positive): *m/z* 505 $(M+H)^+$.

**Methyl 3-*O*-acetyl-2-*O*-benzyl-4,6-*O*-benzylidene-β-D-allopyranoside (25).** To a stirred solution of triflate **24** (800 mg, 1.59 mmol) in DMF (10 mL) was added, under argon, anhydrous tetraethylammonium acetate (1.24 g, 4.77 mmol) in one portion at

room temperature. The mixture was stirred until the starting material had completely reacted as monitored by TLC. The crude mixture was then diluted in $Et_2O$ and washed with water. The organic layer was dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent ethyl acetate/heptane 3:7 v/v) to afford compound **25** (600 mg, 94%) as a colorless syrup: Rf 0.37 (ethyl acetate/heptane 3:7 v/v); $[\alpha]_D$ -38 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 2.21 (s, 3H, $CH_3$), 3.42 (dd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 2.8 Hz, H-2), 3.60 (s, 3H, $OCH_3$), 3.60 (dd, 1H, $J_{3,4}$ = 2.8 Hz, $J_{4,5}$ = 10.1 Hz, H-4), 3.74 (t, 1H, $J_{5,6ax} = J_{6ax,6eq}$ = 10.1 Hz, H-6ax), 3.95 (dt, 1H, $J_{5,6eq}$ = 4.7 Hz, H-5), 4.39 (dd, 1H, H-6eq), 4.67 (d, 1H, J = 11.8 Hz, C*H*HPh), 4.72 (d, 1H, H-1), 4.74 (d, 1H, CH*H*Ph), 5.52 (s, 1H, H-7), 5.85 (t, 1H, H-3); $^{13}C$ NMR (50 MHz) δ 21.0 ($CH_3$), 57.3 ($OCH_3$), 63.9 (C-5), 68.1 (C-3), 69.2 (C-6), 72.4 ($CH_2Ph$), 76.1 and 76 9 (C-2 and C-4), 101.4 (C-7), 102.5 (C-1), 170.1 ($OCOCH_3$); CIMS *m/z* 415 $(M+H)^+$, 383 $(M+H-H_2O)^+$.

Anal. Calcd for $C_{23}H_{26}O_7$ (414.46): C, 66.65; H, 6.33. Found: C, 66.72; H, 6.21.

**Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-allopyranoside (26).** To a stirred solution of compound **25** (550 mg, 1.37 mmol) in MeOH (7 mL) was added sodium methylate (74 mg, 1.37 mmol) at room temperature. The mixture was stirred at room temperature until the starting material had completely reacted as monitored by TLC. The solvent was then evaporated under reduced pressure and the residue triturated with $Et_2O$ to furnish compound **26** (485 mg, 95%) as a white solid: Rf 0.20 (ethyl acetate/heptane 3:7 v/v); mp 122-123 °C, $[\alpha]_D$ -45 (*c* 1, chloroform), $^1H$ NMR (200 MHz) δ 3.28 (dd, 1H, $J_{1,2}$ = 8 Hz, $J_{2,3}$ = 3.8 Hz, H-2), 3.48 (dd, 1H, $J_{3,4}$ = 2 Hz, $J_{4,5}$ = 10.1 Hz, H-4), 3.53 (s, 3H, $OCH_3$), 3.67 (t, 1H, $J_{5,6ax} = J_{6ax,6eq}$ = 10.1 Hz, H-6ax), 3.99 (dt, 1H, $J_{5,6eq}$ = 5 Hz, H-5), 4.27 (br s, 1H, H-3), 4.35 (dd, 1H, H-6eq), 4.66 (d, 1H, J = 12.1 Hz, C*H*HPh), 4.72 (d, 1H, H-1), 4.81 (d, 1H, CH*H*Ph), 5.55 (s, 1H, H-7); $^{13}C$ NMR (50 MHz) δ 57.1 ($OCH_3$), 62.5 (C-5), 68.1 (C-3), 69.0 (C-6), 72.5 ($CH_2Ph$), 77.3 and 78.6 (C-2 and C-4), 101.7 (C-7), 102.2 (C-1); CIMS *m/z* 373 $(M+H)^+$.

Anal. Calcd for $C_{21}H_{24}O_6$ (372.42): C, 67.73; H, 6.49. Found: C, 67.90; H, 6.63.

**Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-[(trifluoromethyl)sulfonyl]-β-D-allopyranoside (27).** Alcohol **26** (358 mg, 0.96 mmol) was reacted with trifluoromethanesulfonic anhydride (0.25 mL, 1.48 mmol) in the presence of pyridine (0.155 mL, 1.92 mmol) following general procedure A. Unstable triflate **27** (247 mg, 51%) was obtained after flash chromatography (eluent ethyl acetate/pentane 3:7 v/v) followed by crystallization from $Et_2O$-heptane: Rf 0.33 (ethyl acetate/heptane 3:7 v/v); mp (dec); $[\alpha]_D$ -32 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 3.48 (dd, 1H, $J_{1,2}$ = 7.5 Hz, $J_{2,3}$ = 3 Hz, H-2), 3.62 (3H, s, $OCH_3$), 3.68 (dd, 1H, $J_{3,4}$ = 2 Hz, $J_{4,5}$ = 10.2 Hz, H-4), 3.77

(t, 1H, $J_{5,6ax} = J_{6ax,6eq}$ = 10.2 Hz, H-6ax), 3.97 (dt, 1H, $J_{5,6eq}$ = 4.6 Hz, H-5), 4.44 (dd, 1H, H-6eq), 4.77 (d, 1H, H-1), 4.84 (s, 2H, $CH_2Ph$), 5.36 (br s, 1H, H-3), 5.55 (s, 1H, H-7); $^{13}C$ NMR (50 MHz) δ 57.6 ($OCH_3$), 63.6 (C-5), 69.1 (C-6), 73.5 ($CH_2Ph$), 74.6 and 75.8 (C-2 and C-4), 84.1 (C-3), 102.4 and 102.5 (C-1 and C-7), 118.6 (q, J = 320 Hz, $CF_3$); CIMS *m/z* 505 $(M+H)^+$.

**Benzyl 2,3,6-tri-*O*-benzyl-4-*O*-[ (trifluoromethyl) sulfonyl ]-β-D-galactopyranoside (30).** Benzyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside **29** (400 mg, 0.74 mmol) was reacted with trifluoromethanesulfonic anhydride (231 μL, 1.33 mmol) in the presence of pyridine (122 μL, 1.48 mmol) following general procedure A. Compound **30** (473 mg, 95%) was obtained after flash chromatography (eluent diethylether/pentane 1:4 v/v) as a syrup: Rf 0.27 (ethyl acetate/heptane 1:4 v/v); $[\alpha]_D$ +1 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 3.61 (dd, 1H, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 2.7 Hz, H-3), 4.52 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.44-5.02 (m, 8H, 4 $CH_2Ph$), 5.42 (d, 1H, H-4); $^{13}C$ NMR (50 MHz) δ 67.4 (C-6), 71.4 (C-5), 71.4, 73.2, 73.9 and 75.8 (4 $CH_2Ph$), 78.2 and 78.6 (C-2 and C-3), 82.0 (C-4), 102.7 (C-1), 118.6 (q, J = 320.1 Hz, $CF_3$); FABMS (positive) *m/z* 673 $(M+H)^+$.

**Methyl 2,3,6,2',3',6'-hexa-*O*-benzyl-β-D-maltoside (35).** A mixture of methyl 2,3,6,2',3'-penta-*O*-benzyl-4',6'-*O*-benzylidene-β-D-maltoside **34** (2.85 g, 3.18 mmol), borane-trimethylamine complex (1.4 g, 19.1 mmol) and 4Å molecular sieves in THF (50 mL) was stirred, under argon, for 30 minutes at room temperature. Aluminium chloride (2.65 g, 19.1 mmol) was then added in several portions and the reaction monitored by TLC. After completion (3 hours), the molecular sieves were filtered on Celite® and the filtrate treated with Dowex 50 ($H^+$) resin. The mixture was filtered and coconcentrated three times with MeOH under reduced pressure. The residue was finally purified by flash chromatography (eluent ethyl acetate/heptane 1:4 v/v) to afford compound **35** (2 g, 70%) as a syrup: Rf 0.55 (ethyl acetate/heptane 1:1 v/v); $[\alpha]_D$ +27 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 3.60 (s, 3H, $OCH_3$), 4.08 (br t, 1H, $J_{5,6}$ = 9 Hz, H-5), 4.35 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.35-5.10 (m, 12H, 6 $CH_2Ph$), 5.69 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'); $^{13}C$ NMR (50 MHz) δ 56.9 ($OCH_3$), 69.5 and 70.0 (C-6 and C-6'), 70.9 and 71.6 (C-4' and C-5'), 73.1 (C-5), 74.5 (C-4), 73.0, 73.5, 73.7, 73.9, 74.8 and 75.3 (6 $CH_2Ph$), 79.2 (C-2'), 81.4 (C-3'), 82.3 (C-2), 84.8 (C-3), 96.7 (C-1'), 104.7 (C-1); FABMS (positive) *m/z* 897 $(M+H)^+$.

Anal. Calcd for $C_{55}H_{60}O_{11}$ (897.08): C, 73.64; H, 6.74. Found: C, 73.36; H, 6.98.

**Methyl 2,3,6,2',3',6'-hexa-*O*-benzyl-4'-*O*-[(trifluoromethyl)sulfonyl]-β-D-maltoside (36).** Alcohol **35** (705 mg, 0.79 mmol) was reacted with

trifluoromethanesulfonic anhydride (239 μL, 1.42 mmol) in the presence of pyridine (128 μL, 1.58 mmol) following general procedure A. Compound **36** (676 mg, 84%) was obtained after flash chromatography (eluent ethyl acetate/pentane 3:7 v/v) as an unstable syrup: Rf 0.62 (ethyl acetate/heptane 1:1 v/v); $[\alpha]_D$ +41 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 3.61 (3H, $OCH_3$), 5.69 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1'); $^{13}C$ NMR (50 MHz) δ 56.8 ($OCH_3$), 67.4 (C-6'), 68.7 (C-5'), 69.0 (C-6), 72.7 (C-5), 74.4 (C-4), 72.6, 73.2, 73.6, 74.4 and 75.0 (6 $CH_2Ph$), 77.7 (C-3'), 79.6 (C-4'), 81.8 (C-2'), 82.1 (C-2), 84.5 (C-3), 95.8 (C-1'), 104.7 (C-1), 118.6 (q, J = 320 Hz, $CF_3$); FABMS (positive) *m/z* 1029 $(M+H)^+$.

**9-*O*-Acetyloxime of tylosin 20-(1,3-dithiane) (37).** Rf 0.53 (dichloromethane/methanol/concd ammonia 20:1:0.05 v/v/v); $^1H$ NMR (200 MHz) δ 2.01 and 2.08 ($OCOCH_3$); $^{13}C$ NMR (50 MHz) δ 12.5 (8-$CH_3$), 20.7 and 20.9 ($OCOCH_3$), 26.1 ($SCH_2CH_2$), 26.1 (2 $SCH_2$), 35.1 and 40.2 (C-8), 44.6 (C-20), 138.4 (C-13), 160.2 (C-9), 169.8 and 170.1 ($OCOCH_3$); FABMS (positive) *m/z* 1085 $(M+Na)^+$, 1063 $(M+H)^+$.

**Methyl 2,4-di-*O*-acetyl-3,6-anhydro-α-D-glucopyranoside (38).** Rf 0.1 (ethyl acetate 1:1 v/v); $^1H$ NMR (300 MHz) δ 2,01 and 2.13 (2s, 6H, 2 $OCOCH_3$), 3.50 (s, 3H, $OCH_3$), 3.92 (dd, 1H, $J_{5,6a}$ = 1.6 Hz, $J_{6a,6b}$ = 8.6 Hz, H-6a), 4.13 (d, 1H, H-6b), 4.48 (t, 1H, $J_{4,5}$ = 1.6 Hz, H-5), 4.56 (t, 1H, $J_{2,3} = J_{3,4}$ = 3.6 Hz, H-3), 4.66 (dd, 1H, H-4), 4.93 (d, 1H, $J_{1,2}$ = 2.6 Hz, H-1), 5.03 (dd, 1H, H-2); $^{13}C$ NMR (62.5 MHz) δ 20.7 and 20.8 (2 OCO*C*H3), 58.0 ($OCH_3$), 67.9 (C-2), 68.2 (C-6), 69.7 (C-3), 71.0 (C-4), 73.4 (C-5), 96.7 (C-1), 169.9 (2 $OCOCH_3$). CIMS *m/z* 261 $(M+H)^+$, 229 (M+H-MeOH)+.

**9-[*O*-(Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosid-6-yl)oxime] of tylosin 20-(1,3-dithiane) (39).** 9-Oxime of tylosin 20-(1,3-dithiane) **4** (500 mg, 0.42 mmol) was reacted with triflate **8** (189 mg, 0.42 mmol) in the presence of 18-crown-6 ether (155 mg, 0.42 mmol) following general procedure B. Compound **39** (292 mg, 53%) was obtained after flash chromatography (eluent dichloromethane/methanol/concd ammonia 20:1:0.05 v/v/v) as a white foam: Rf 0.59 (dichloromethane/methanol/concd ammonia 20:1:0.05 v/v/v); $^1H$ NMR (200 MHz) δ 3.22 (s, 3H, 1""-$OCH_3$), 5.02 (d, 1H, $J_{1"",2""}$ = 4.7 Hz, H-1""); $^{13}C$ NMR (50 MHz) δ 12.4 (8-$CH_3$), 20.7 and 20.8 (3 $OCOCH_3$), 26.2 ($SCH_2CH_2$), 26.2 (2 $SCH_2$), 35.1 and 40.3 (C-8), 44.5 (C-20), 54.9 (1""-$OCH_3$), 67.2 (C-5""), 71.0, 71.0 and 71.1 (C-2"", C-3"" and C-4""), 72.8 (C-6""), 96.4 (C-1""), 138.3 (C-13), 160.7 (C-9), 169.7 and 170.0 (3 $OCOCH_3$); FABMS (positive) *m/z* 1345 (M+Na)+, 1323 (M+H)+. HRMS Calcd for $C_{62}H_{103}N_2O_{24}S_2$ (1323.6342. Found: 1323.6315.

**9-[*O*-(Methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranosid-4-yl)oxime] of tylosin 20-(1,3-dithiane) (40).** Compound **4** (1g, 1 mmol) was reacted with triflate **10** (625 mg, 1 mmol) in the presence of 18-crown-6 ether (364 mg, 1 mmol) following general procedure B. Product **40** (926 mg, 63%) was obtained after flash chromatography (eluent dichloromethane/methanol/concd ammonia 20:1:0.05 v/v/v) as a foam: Rf (dichloromethane/methanol/concd ammonia 10:1:0.05 v/v/v); $^1$H NMR (200 MHz) δ 3.46 (1""-$OCH_3$), 5.14 (d, 1H, $J_{1"",2""}$ = 3.1 Hz, H-1""), 6.08 (t, 1H, $J_{2"",3""} = J_{3"",4""}$ = 9.6 Hz, H-3""); $^{13}$C NMR (50 MHz) δ 12.1 (8-$CH_3$), 25.8 ($SCH_2CH_2$), 26.0 (2 $SCH_2$), 35.1 and 41.0 (C-8), 44.1 (C-20), 55.0 (1""-$OCH_3$), 63.5 (C-6""), 67.7 (C-5""), 69.9 (C-3""), 72.5 (C-2""), 77.4 (C-4""), 95.7 (C-1""), 162.8 (C-9), 165.0, 165.8 and 165.8 (3 *O*COBz); FABMS (positive) *m/z* 1509 $(M+H)^+$. HRMS Calcd for $C_{77}H_{109}N_2O_{24}S_2$ (1509.6812). Found: 1509.6873.

**9-{*O*-[Methyl 2,3,6-tri-*O*-(4-methoxybenzyl)-α-D-galactopyranosid-4-yl]oxime} of tylosin 20-(1,3-dithiane) (41).** Compound **4** (642 mg, 0.62 mmol) was reacted with triflate **14** (475 mg, 0.62 mmol) in the presence of 18-crown-6 ether (70 mg, 0.20 mmol) following general procedure B. Compound **41** (694 mg, 72%) was obtained after flash chromatography (eluent dichloromethane/methanol/concd ammonia 20:1:0.05 v/v/v) as a foam: Rf 0.58 (dichloromethane/methanol/concd ammonia 10:1:0.05 v/v/v); $^1$H NMR (200 MHz) δ 3.38 (s, 3H, 1""-$OCH_3$), 4.51 (d, 1H, $J_{1"",2""}$ = 2.4 Hz, H-1""); $^{13}$C NMR (50 MHz) δ 12.7 and 12.9 (8-$CH_3$), 26.2 ($SCH_2CH_2$), 26.2 (2 $SCH_2$), 36.1 and 40.6 (C-8), 45.6 (C-20), 55.3 (1""-$OCH_3$ and 3 $OCH_3$), 68.9 and 69.2 (C-5""), 69.5 (C-6""), 71.0, 73.2 and 73.6 (C-4""), 99.1 (C-1""), 137.4 (C-13), 160.5 (C-9); FABMS (positive) *m/z* 1557 $(M+H)^+$. HRMS Calcd for $C_{80}H_{121}N_2O_{24}S_2$ (1557.7751). Found: 1557.7712.

**(*E*)-9-[*O*-(Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosid-6-yl)oxime] of erythromycin A (42).** (*E*)-9-oxime of erythromycin A **3** (400 mg, 0.53 mmol) was reacted with triflate **8** (242 mg, 0.53 mmol) in the presence of 18-crown-6 ether (200 mg, 0.53 mmol) following general procedure B. Compound **42** (243 mg, 61%) was obtained after flash chromatography (eluent dichloromethane/methanol/concd ammonia 15:1:0.05 v/v/v) as a foam: Rf 0.40 (dichloromethane/methanol/concd ammonia 10:1:0.05); $[\alpha]_D$ -3 (*c* 0.34, chloroform); $^1$H NMR (300 MHz) δ 1.00 (d, 3H, $J_{8,8Me}$ = 7 Hz, 8-$CH_3$), 1.96 and 2.02 (2s, 3 and 6H, 3 $CH_3$), 2.66 (br q, 1H, $J_{10,10Me}$ = 7 Hz, H-10), 2.86 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{2,2Me}$ = 7.5 Hz, H-2), 3.22 (s, 3H, 1'"-$OCH_3$), 3.38 (s, 3H, 3"-$OCH_3$), 3.52 (d, 1H, $J_{4,5}$ = 7.8 Hz, H-5), 3.61 (br s, 1H, H-11), 4.15 (dd, 1H, $J_{5,6"'b}$ = 1.4 Hz, $J_{6"'a,6"'b}$ = 13 Hz, H-6'"b), 4.32 (br s, 1H, OH), 4.43 (d, 1H, $J_{1',2'}$ = 7.2 Hz, H-1'), 4.88 (dd, 1H, $J_{1"',2"'}$ = 4.7 Hz, $J_{2"',3"'}$ = 10.3 Hz, H-2'"), 4.94 (d, 1H, $J_{1",2"}$ = 5 Hz, H-1"), 5.02 (d,

1H, H-1'''), 5.07 (t, 1H, $J_{3,4} = J_{4,5} = 10.3$ Hz, H-4'''), 5.13 (br d, 1H, $J_{13,14ax} = 10$ Hz, H-13), 5.48 (t, 1H, H-3'''); $^{13}C$ NMR (62.5 MHz) δ 14.6 (10-$CH_3$), 19.0 (8-$CH_3$), 20.8 and 20.9 (3 $CH_3$), 26.6 (C-8), 32.2 (C-10), 56.0 (1'''-$OCH_3$), 67.8 (C-5'''), 69.3 (C-4'''), 70.8 and 71.1 (C-2''' and C-3'''), 71.9 (C-6'''), 97.0 (C-1'''), 169.7 and 170.0 (3 $OCOCH_3$), 171.8 (C-9); FABMS (positive) *m/z* 1073 $(M+Na)^+$, 1051 $(M+H)^+$, 893 $[M+H-(Cladinose-H)]^+$. HRMS Calcd for $C_{50}H_{87}N_2O_{21}$ (1051.5801). Found: 1051.5837.

**(*E*)-9-[*O*-(Methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranosid-4-yl)oxime] of erythromycin A (43).** (*E*)-9-oxime of erythromycin A **3** (543 mg, 0.73 mmol) was treated with triflate **10** (328 mg, 0.73 mmol) in the presence of 18-crown-6 ether (270 mg, 0.73 mmol) following general procedure B. Compound **43** (650 mg, 65%) was obtained after flash chromatography (eluent dichloromethane/methanol/concd ammonia 10:1:0.05 v/v/v) as a foam: Rf 0.39 (dichloromethane/methanol/concd ammonia 10:1:0.05); $[\alpha]_D$ +5 (*c* 0.46, chloroform); $^1H$ NMR (250 MHz) δ 1.00 (d, 3H, $J_{8,8Me} = 7$ Hz, 8-$CH_3$), 2.66 (br d, 1H, $J_{10,10Me} = 6.9$ Hz, H-10), 3.21 (s, 3H, 3''-$OCH_3$), 3.28 (dd, 1H, $J_{1',2'} = 7.2$ Hz, $J_{2',3'} = 10.3$ Hz, H-2'), 3.38 (s, 3H, 1'''-$OCH_3$), 3.63 (br s, 1H, H-11), 4.73 (d, 1H, $J_{1'',2''} = 4.7$ Hz, H-1''), 4.92 (dd, 1H, $J_{1''',2'''} = 3.5$ Hz, $J_{2''',3'''} = 9.6$ Hz, H-2'''), 5.11 (d, 1H, H-1'''), 5.17 (br d, 1H, $J_{13,14ax} = 10.6$ Hz, H-13), 6.08 (t, 1H, $J_{3''',4'''} = 9.6$ Hz, H-3'''); $^{13}C$ NMR (50 MHz) δ 14.6 (10-$CH_3$), 18.5 (8-$CH_3$), 26.6 (C-8), 34.4 (C-10), 55.6 (1'''-$OCH_3$), 62.9 (C-6'''), 67.7 (C-5'''), 69.9 (C-3'''), 72.5 (C-2'''), 78.8 (C-4'''), 97.1 (C-1'''), 165.9 and 166.4 (3 *O*COBz), 172.5 (C-9); FABMS (positive) *m/z* 1237 $(M+H)^+$ and 1079 $[M+H-(Cladinose-H)]^+$. HRMS Calcd for $C_{65}H_{93}N_2O_{21}$ (1237.6271). Found: 1237.6279.

**(*E*)-9-{*O*-[Methyl 2,3,4-tri-*O*-(4-methoxybenzyl)-α-D-galactopyranosid-4-yl]oxime} of erythromycin A (44).** (*E*)-9-oxime of erythromycin A **3** (373 mg, 0.50 mmol) was treated with triflate **14** (342 mg, 0.50 mmol) in the presence of 18-crown-6 ether (56 mg, 0.15 mmol) following general procedure B. Compound **44** (550 mg, 82%) was obtained after flash chromatography (dichloromethane/methanol/concd ammonia 20:1:0.05 v/v/v) as a foam: Rf 0.46 (dichloromethane/methanol/concd ammonia 20:1:0.05 v/v/v); $[\alpha]_D$ -19 (*c* 1, chloroform); $^1H$ NMR (300 MHz) δ 1.00 (d, 3H, $J_{8,8Me} = 7$ Hz, 8-$CH_3$), 2.92 (d, 1H, $J_{4'',5''} = 9.7$ Hz, H-4''), 3.32 (s, 3H, 3''-$OCH_3$), 3.37 (s, 3H, 1'''-$OCH_3$), 3.70 (s, 9H, 3 $OCH_3$), 3.88 (d, 1H, $J_{4,5} = 8$ Hz, H-5), 4.41 (d, 1H, $J_{1',2'} = 7.2$ Hz, H-1'), 4.51 (d, 1H, $J_{1''',2'''} = 3.4$ Hz, H-1'''), 4.43-4.63 (m, 6H, H-4''', C*H*HAr and 2 $CH_2Ar$), 4.72 (d, 1H, J = 13 Hz, CH*H*Ar), 4.76 (d, 1H, $J_{1'',2''} = 4.6$ Hz, H-1''), 5.12 (dd, 1H, $J_{13,14ax} = 10.6$ Hz, $J_{13,14eq} = 2.5$ Hz, 13-H); $^{13}C$ NMR (62.5 MHz) δ 14.5 (10-$CH_3$), 18.8 (8-$CH_3$), 26.5 (C-8), 32.8 (C-10), 55.2 (3 $OCH_3$), 55.3 (1'''-$OCH_3$),

68.3 (C-6'''), 68.8 (C-5'''), 71.0, 72.8 and 73.1 (3 $CH_2Ar$), 75.3 (C-2'''), 76.8 (C-3'''), 77.7 (C-4'''), 98.8 (C-1'''), 171.0 (C-9); FABMS (positive) *m/z* 1285 $(M+H)^+$. HRMS Calcd for $C_{68}H_{105}N_2O_{21}$ (1285.7210). Found: 1285.7251.

**Methyl 2-*O*-benzyl-4,6-*O*-(4-methoxybenzyl)-3-deoxy-α-D-*erythro*-hex-2-enopyranoside (45).** Rf 0.34 (ethyl acetate/heptane 3:7 v/v); $[\alpha]_D$ +23 (*c* 1, chloroform); $^1H$ NMR (200 MHz) δ 3.48 (s, 3H, $OCH_3$), 3.79 (t, 1H, $J_{5,6ax} = J_{6ax,6eq}$ = 9.5 Hz, H-6ax), 3.97 (dt, 1H, $J_{5,6eq}$ = 4.1 Hz, H-6eq), 4.81 (s, 1H, H-1), 4.78 (d, 1H, J = 14.5 Hz, C*H*HPh), 4.82 (d, 1H, CH*H*Ph), 5.05 (br s, 1H, H-3), 5.55 (s, 1H, H-7); $^{13}C$ NMR (50 MHz) δ 56.2 ($OCH_3$), 65.2 (C-5), 69.2 and 69.8 (C-6 and $CH_2Ph$), 76.2 (C-4), 96.9 (C-3), 98.5 (C-1), 102.0 (C-7), 153.1 (C-2); CIMS *m/z* 355 $(M+H)^+$, 323, 249 and 247.

**9-[*O*-(Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosid-2-yl)oxime] of erythromycin A (46).** To a mixture of (*E*)-9-oxime of erythromycin A **3** (300 mg, 0.40 mmol) and 18-crown-6 ether (45 mg, 0.12 mmol) in THF (2 mL) was added, under argon, sodium hydride (11 mg, 0.44 mmol) [sodium hydride (60% dispersion in mineral oil, 19 mg) was washed with heptane]. The mixture was stirred for 20 minutes at room temperature and then transferred via a syringe to a mixture of triflate **22** (202 mg, 0.44 mmol) in THF (2 mL). The reaction mixture was refluxed for 3 hours. After cooling, the reaction was quenched with Florisil® and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent dichloromethane/methanol/concd ammonia 10:1:0.05 v/v/v) to furnish a 70:30 mixture (as determined by NMR) of *Z* and *E* oximes **46** (260 mg, 60%) as a foam: Rf 0.36 (dichloromethane/methanol/concd ammonia 10:1:0.05); $^1H$ NMR (300 MHz) δ 4.30-4.50 (m, 4H, H-1', H-1''', H-2'''(*E*) and H-6'''eq), 4.68-4.80 (m, 1H, H-2'''(*Z*)), 4.82 (d, 1H, $J_{1'',2''}$ = 4.3 Hz, H-1''(*E*)), 4.87 (d, 1H, $J_{1'',2''}$ = 4.3 Hz, H-1''(*Z*)), 5.22 (d, 1H, $J_{13,14ax}$ = 10.7 Hz, H-13(*E*)), 5.29 (d, 1H, $J_{13,14ax}$ = 10.7 Hz, 13-H(*Z*)), 5.54 (s, 1H, H-7'''(*E*)), 5.64 (s, 1H, H-7'''(*Z*)); $^{13}C$ NMR (62.5 MHz) (*Z* isomer) δ 14.9 (10-$CH_3$), 19.1 (8-$CH_3$), 26.5 (C-8), 33.1 (C-10), 57.3 (1'''-$OCH_3$), 67.2 (C-5'''), 69.8 (C-6'''), 72.1 ($CH_2Ph$), 75.2 (C-3'''), 79.1 (C-4'''), 80.6 (C-2'''), 101.7 (C-1''' and C-7'''), 170.2 (C-9); (*E* isomer) δ 11.3 (10-$CH_3$), 19.1 (8-$CH_3$), 34.4 (C-10), 35.5 (C-8), 57.3 (1'''-$OCH_3$), 67.4 (C'''-5), 68.9 (C-6'''), 72.1 ($CH_2Ph$), 75.8 (C-3'''), 79.7 (C-4'''), 80.6 (C-2'''), 101.7 (C-1''' and C-7'''), 168.3 (C-9); FABMS (positive) *m/z* 1125 $(M+Na)^+$, 1103 $(M+H)^+$, 945 (M+H-(Cladinose-H))$^+$. HRMS Calcd for $C_{58}H_{91}N_2O_{18}$ (1103.6267). Found: 1103.6260.

**(*E*)-9-[*O*-(Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-allopyranosid-3-yl)oxime] of erythromycin A (47).** (*E*)-9-oxime of erythromycin A **3** (1.2 g, 1.60 mmol) was treated with triflate **24** (807 mg, 1.60 mmol) in the presence of 18-crown-6

ether (180 mg, 0.48 mmol) following general procedure B. Compound **47** (1.23 g, 70%) was obtained after flash chromatography (eluent dichloromethane/methanol/concd ammonia 10:1:0.05 v/v/v) and crystallization from diethylether/heptane as a white solid: Rf 0.38 (dichloromethane/methanol/concd ammonia 10:1:0.05 v/v/v); mp 153-155 °C; $[\alpha]_D$ -72 (*c* 1, chloroform); $^1$H NMR (300 MHz) δ 1.00 (d, 3H, $J_{8,8Me}$ = 7 Hz, 8-$CH_3$), 2.59 (br d, 1H, $J_{10,10Me}$ = 7 Hz, H-10), 3.21 (s, 3H, 3"-$OCH_3$), 3.22-3.32 (2H, m, 2'-H and 2'''-H), 3.33 (1H, dd, $J_{3''',4'''}$ = 2.5 Hz, $J_{4''',5'''}$ = 9 Hz, H-4'''), 3.53 (s, 3H, 1'''-$OCH_3$), 3.78 (br s, 1H, H-11), 3.95 (m, 1H, H-5"), 4.08 (d, 1H, $J_{2,3}$ = 9.8 Hz, H-3), 4.25 (dd, 1H, $J_{5''',6'''eq}$ = 3.8 Hz, $J_{6'''ax,6'''eq}$ = 10 hz, H-6'''eq), 4.32 (t, 1H, $J_{2''',3'''}$ = 2.5 Hz, H-3'''), 4.42 (d, 1H, $J_{1',2'}$ = 6.7 Hz, H-1'), 4.53 (1H, d, J = 12.4 Hz, C*H*HPh), 4.62 (d, 1H, $J_{1''',2'''}$ = 8.2 Hz, H-1'''), 4.75 (d, 1H, $J_{1'',2''}$ = 4.9 Hz, H-1"), 4.78 (d, 1H, CH*H*Ph), 5.18 (br d, 1H, $J_{13,14ax}$ = 10.4 Hz, H-13), 5.36 (s, 1H, H-7'''); $^{13}$C NMR (50 MHz) δ 14.4 (10-$CH_3$), 18.6 (8-$CH_3$), 26.7 (C-8), 33.0 (C-10), 57.5 (1'''-$OCH_3$), 64.0 (C-5'''), 69.4 (C-6'''), 72.9 ($CH_2$Ph), 75.1 (C-2'''), 77.8 (C-4'''), 80.6 (C-3'''), 101.2 (C-7''') 103.4 (C-1'''), 170.0 (C-9); FABMS (positive) *m/z* 1125 $(M+Na)^+$, 1103 $(M+H)^+$. HRMS Calcd for $C_{36}H_{67}N_2O_{15}$ (1103.6266). Found: 1103.6320.

**(*E*)-9-[*O*-(Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosid-3-yl)oxime] of erythromycin A (48).** To a mixture of (*E*)-9-oxime of erythromycin A **3** (225 mg, 0.30 mmol) and 18-crown-6 ether (33 mg, 0.09 mmol) in THF (1.5 mL) was added, under argon, sodium hydride (8 mg, 0.33 mmol) [sodium hydride (60% dispersion in mineral oil, 14 mg) was washed with heptane]. The mixture was then stirred for 10 minutes at room temperature and then added dropwise via a syringe into a mixture of triflate **27** (151 mg, 0.3 mmol) in THF (1.5 mL) at 0 °C. The reaction mixture was then stirred for 10 hours at 0 °C before being quenched with Florisil®. The solvent was removed under reduced pressure and the residue purified by flash chromatography (eluent dichloromethane/methanol/concd ammonia 10:1:0.05 v/v/v) to afford compound **48** (155 mg, 47%) as a foam: Rf 0.37 (dichloromethane/methanol/concd ammonia 10:1:0.05); $[\alpha]_D$ -52 (*c* 0.93, chloroform); $^1$H NMR (300 MHz) δ 1.00 (d, 3H, $J_{8,8Me}$ = 7 Hz, 8-$CH_3$), 2.48 (ddd, 1H, $J_{2',3'}$ = 10.1Hz, $J_{3',4'ax}$ = 12 Hz, $J_{3',4'eq}$ = 2 Hz, H-3'), 2.52 (br q, 1H, $J_{10,10Me}$ = 6.9 Hz, H-10), 2.96 (d, 1H, $J_{4'',5''}$ = 8.4 Hz, H-4"), 3.16 (dd, 1H, $J_{1',2'}$ =7.2 Hz, H-2'), 3.22 (s, 3H, 3-$OCH_3$), 3.51 (s, 3H, 1'''-$OCH_3$), 3.52 (br s, 1H, H-11), 3.52 (t, 1H, $J_{1''',2'''} = J_{2''',3'''}$ = 8.8 Hz, H-2'''), 3.85 (d, 1H, $J_{2,3}$ = 11.1 Hz, H-3), 3.92 (dq, 1H, $J_{5'',5''Me}$ = 6.2 Hz, $J_{4'',5''}$ = 9.7 Hz, H-5"), 4.26 (d, 1H, H-1'), 4.27 (dd, 1H, $J_{3''',4'''}$ = 9.4 Hz, H-3'''), 4.42 (d, 1H, H-1'''), 4.61 (d, 1H, J = 10.3 Hz, C*H*HPh), 4.71 (d, 1H, $J_{1'',2''}$ = 4.7 Hz, H-1"), 4.78 (d, 1H, CH*H*Ph), 4.92 (dd, 1H, $J_{13,14ax}$ = 10.1 Hz, $J_{13,14eq}$ = 2.3 Hz, H-13), 5.46 (s, 1H, H-7'''); $^{13}$C NMR (50 MHz) δ 14.2 (10-$CH_3$), 18.4 (8-

$CH_3$), 26.4 (C-8), 32.9 (C-10), 56.9 (1'''-$OCH_3$), 65.7 (C-5'''), 68.4 (C-6'''), 74.5 ($CH_2Ph$), 78.3 and 78.7 (C-2''' and C-4'''), 82.7 (C-3'''), 101.3 (C-7'''), 102.2 (C-1'''), 171.6 (C-9); FABMS (positive) *m/z* 1125 $(M+Na)^+$, 1103 $(M+H)^+$. HRMS Calcd for $C_{58}H_{91}N_2O_{18}$ (1103.6267). Found: 1103.6293.

**(*E*)-9-[*O*-(Benzyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranosid-4-yl)oxime] of erythromycin A (49).** (*E*)-9-oxime of erythromycin A **3** (403 mg, 0.54 mmol) was treated with triflate **30** in the presence of 18-crown-6 ether (80 mg, 0.12 mmol) following general procedure B. Compound **49** (615 mg, 90%) was obtained after flash chromatography (eluent dichloromethane/methanol/concd ammonia 15:1:0.05 v/v/v) as a foam: Rf 0.32 (dichloromethane/methanol/concd ammonia 15:1:0.05); $[\alpha]_D$ -73 (*c* 1, chloroform); $^1H$ NMR (300 MHz) δ 1.00 (d, 3H, $J_{8,8Me}$ = 7 Hz, 8-$CH_3$), 2.61 (br q, 1H, $J_{10,10Me}$ = 7 Hz, 10-H), 2.90 (d, 1H, $J_{4'',5''}$ = 9.7 Hz, H-4''), 3.18 (dd, 1H, $J_{1',2'}$ = 7.1 Hz, $J_{2',3'}$ = 10.2 Hz, H-2'), 3.22 (s, 3H, 3''-$OCH_3$), 3.49 (d, 1H, $J_{4,5}$ = 7.3 Hz, H-5), 3.57 (dd, 1H, $J_{5,6'''a}$ = 3.9 Hz, $J_{6'''a,6'''b}$ = 10.9 Hz, H-6'''a), 3.73 (s, 1H, H-11), 3.91 (t, 1H, $J_{2''',3'''} = J_{3''',4'''}$ = 9.2 Hz, H-3'''), 4.09 (t, 1H, $J_{4''',5'''}$ = 9.2 Hz, H-4'''), 4.34 (d, 1H, H-1'), 4.47 (d, 1H, $J_{1''',2'''}$ = 7.5 Hz, H-1'''), 4.51-4.69 (m, 6H, 3 $CH_2Ph$), 4.72 (d, 1H, $J_{1'',2''}$ = 4.5 Hz, H-1''), 4.82 (d, 1H, J = 12 Hz, C*H*HPh), 4.84 (d, 1H, CH*H*Ph), 5.04 (dd, 1H, $J_{13,14ax}$ = 9.3 Hz, $J_{13,14eq}$ = 2.3 Hz, H-13); $^{13}C$ NMR (62.5 MHz) δ 14.9 (10-$OCH_3$), 18.8 (8-$CH_3$), 26.8 (C-8), 33.0 (C-10), 69.6 (C-6'''), 73.3 (C-5'''), 73.3 and 75.0 (4 $CH_2Ph$), 80.7 (C-3'''), 81.4 (C-2'''), 82.3 (C-2'''), 102.7 (C-1'''), 172.1 (C-9); FABMS (positive) *m/z* $(M+Na)^+$ and 1271 $(M+H)^+$. HRMS Calcd for $C_{71}H_{103}N_2O_{18}$ (1271.7206). Found: 1271.7269.

**(*E*)-9-{*O*-[2,3,6-Tri-*O*-benzyl-1-*O*-(methyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranosid-4-yl)-α-D-galactopyranosyl-4-yl]oxime} of erythromycin A (50).** (*E*)-9-oxime of erythromycin A **3** (473 mg, 0.63 mmol) was reacted with triflate **36** (650 mg, 0.63 mmol) in the presence of 18-crown-6 ether (70 mg, 0.19 mmol) following general procedure B. Compound **50** (770 mg, 75%) was obtained after flash chromatography (eluent dichloromethane/methanol/concd ammonia 10:1:0.05) as a foam: Rf 0.43 (dichloromethane/methanol/concd ammonia 10:1:0.05); $[\alpha]_D$ +4 (*c* 0.2, chloroform); $^1H$ NMR (300 MHz) δ 1.00 (d, 3H, $J_{8,8Me}$ = 7 Hz, 8-$CH_3$), 2.53 (br d, 1H, $J_{10,10Me}$ = 7.1 Hz, H-10), 3.51 (dd, 1H, $J_{5''',6'''a}$ = 2.1 Hz, $J_{6'''a,6'''b}$ = 7.4 Hz, H-6'''a), 3.58 (s, 3H, 1''''-$OCH_3$), 3.84 (dd, 1H, $J_{2''',3'''}$ = 10.7 Hz, $J_{3''',4'''}$ = 3.1 Hz, H-3'''), 4.32 (d, 1H, $J_{1''',2''''}$ = 7.7 Hz, H-1''''), 4.45 (d, 1H, $J_{1',2'}$ = 7.4 Hz, H-1'), 4.67 (d, 1H, H-4'''), 4.39-4.92 (m, 12H, 6 $CH_2Ph$), 4.86 (d, 1H, $J_{1'',2''}$ = 4.8 Hz, H-1''), 5.18 (dd, 1H, $J_{13,14ax}$ = 11 Hz, $J_{13,14eq}$ = 2.1 Hz, H-13), 5.71 (d, 1H, $J_{1''',2'''}$ = 3.7 Hz, H-1'''); $^{13}C$ NMR (62.5 MHz) δ 14.5 (10-$CH_3$), 18.8 (8-$CH_3$), 26.6 (C-8), 33.0 (C-10), 56.9 (1''''-$OCH_3$), 68.4

(C-6'''), 70.0 (C-6''''), 70.8 (C-5'''), 71.1, 73.4, 73.6 and 73.7 (4 $CH_2Ph$), 73.7 (C-5''''), 73.9 and 74.5 (2 $CH_2Ph$), 74.6 (C-4''''), 75.3 (C-2'''), 77.4 (C-3'''), 77.5 (C-4'''), 82.5 (C-2''''), 84.6 (C-3''''), 97.5 (C-1'''), 104.5 (C-1''''), 171.1 (C-9); FABMS (positive) *m/z* 1628 $(M+H)^+$. HRMS Calcd for $C_{92}H_{127}N_2O_{23}$ (1267.8830). Found: 1267.8892.

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