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Synthesis of Analogues of the *O*-β-D-Ribofuranosyl Nucleoside Moiety of Liposidomycins. Part 2: Role of the Hydroxyl Groups upon the Inhibition of MraY

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Abstract—*O*-β-D-Ribofuranosyl nucleoside **I** is the minimal structural entity of liposidomycins that maintains enzyme inhibitory activity on MraY. A set of compounds with hydroxyl patterns different from **I** has been synthesized. The presence of a hydroxyl group in the 3″ position is essential for the activity. The 3′-deoxy derivative (**IV**), however, shows a 5-fold improved potency.

Translocase (MraY) is an essential enzyme for bacteria.[1] It catalyzes a key step during the synthesis of precursors of peptidoglycan, before their assembly[2] around the bacterial cell. Compounds **I** and **II** (Fig. 1) that are simplified analogues of liposidomycins[4] (LPMs), have recently been shown as inhibitors of MraY. Their design was the result of a thorough SAR analysis between liposidomycins (LPMs), and tunicamycins (TCMs),[5] another family of naturally occurring inhibitors of translocase. The amino group and the uracil moiety in this family of molecules play a crucial role in the protein–inhibitor interaction.[6]

In order to assess the importance of the remaining polar functions of **I**, we have undertaken the synthesis of molecules related to **I**, missing at least one hydroxyl group (Table 1).

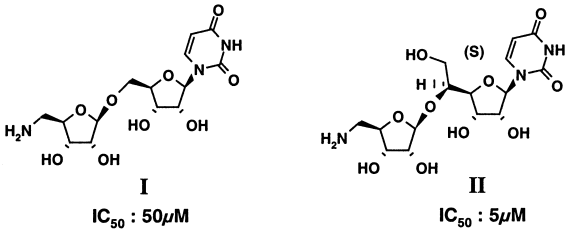

Figure 1.

Condensation of **1**[3] with **2**[7] (Scheme 1), in the presence of tin tetrachloride, led to **3**. Intermediate **3** was successively submitted to methanolysis, and to reduction with PPh_3 and H_2O to provide **III**.[8]

Condensation of **4**[3] with **5**[9] (Scheme 2), in the presence of mercury cyanide gave **6**. Deprotection of the acetonide group was accomplished by using 60% aqueous acetic acid. Acetylation of the crude compound gave **7**. The introduction of the uracil moiety was performed using a standard Vorbruggen procedure[10] to give the nucleoside **8**. Methanolysis of **8** and subsequent reduction of the crude compound in the presence of PPh_3 and H_2O in THF, gave the desired analogue **IV**.[11]

Concomitant protection of the 5″ and 3″ hydroxyl groups of **9**[3] with 1,3-dichloro 1,1,3,3-tetraisopropyl disiloxane in pyridine gave **10** (Scheme 3). Thiocarbonylation of **10** was accomplished with phenyl chlorothionoformate in the presence of DMAP leading to **11**. Deoxygenation of the 2″ position of **11** was performed with tributyltin hydride and AIBN to give **12**. Regeneration of the hydroxyl groups in 5″ and 3″ positions was achieved with tetrabutylammonium fluoride in THF to give **13**. Tosylation of the 5″ hydroxyl group was performed with toluenesulfonyl chloride in pyridine. Tosylate substitution was carried out on the crude

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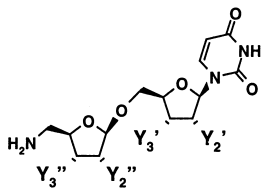
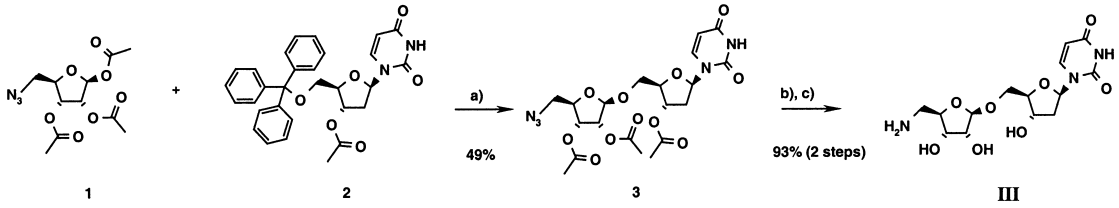
Table 1.



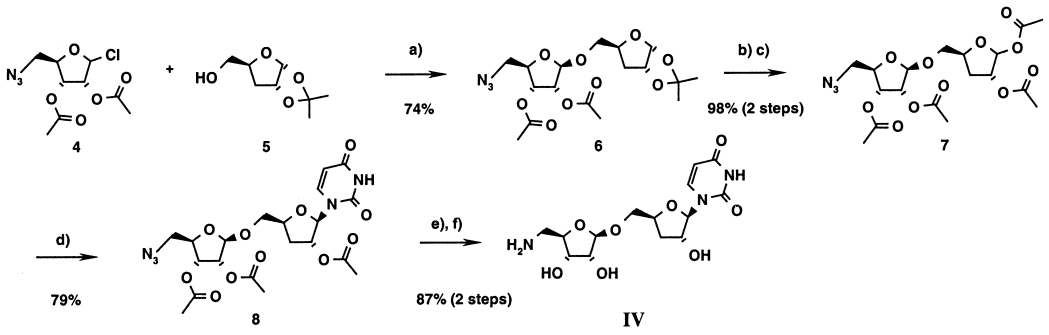
	Y2′	Y3′	Y2″	Y3″
III	H	OH	OH	OH
IV	OH	H	OH	OH
V	OH	OH	H	OH
VI	OH	OH	OH	H
VIII	H	H	OH	OH

compound with sodium azide in DMF leading to the azido compound **14**. The acetonide protecting group was cleaved off with 60% aqueous acetic acid and the azido group hydrogenolyzed to give **V**.[12]

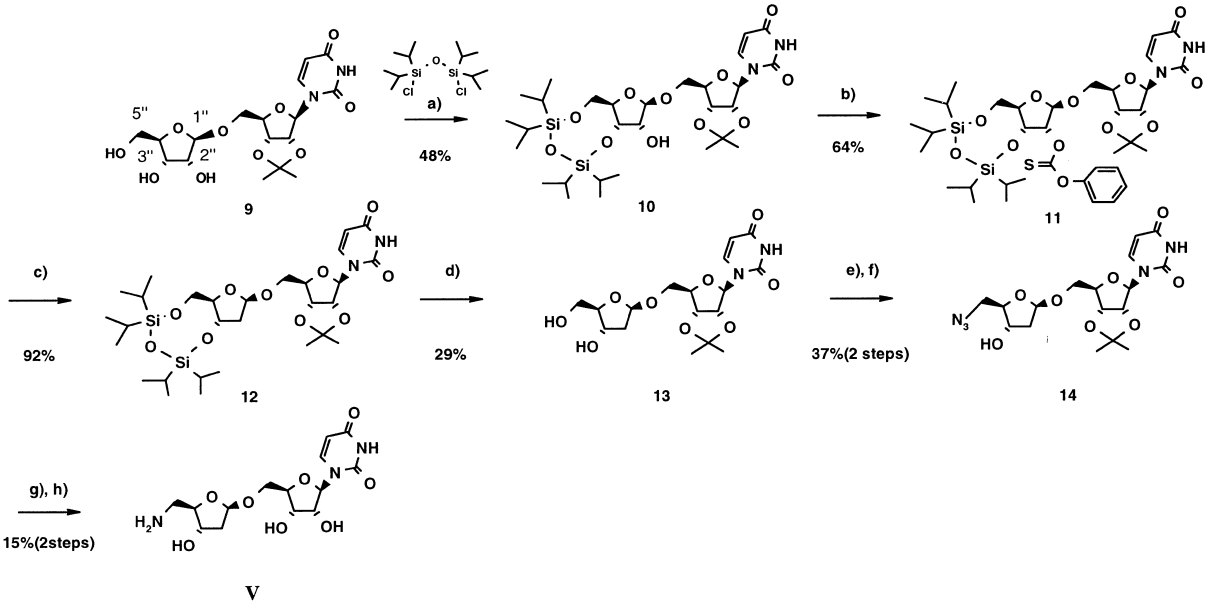
Compound **16** was prepared by silylation of the 5′ position of **15** (commercially available) with trimethylsilyl chloride in the presence of DIEA and subsequent protection of the uracil imide group with Boc anhydride and DMAP as base (Scheme 4). Compound **18** was synthesized from **17**,[9] after cleavage of the acetonide protecting group and acetylation of resulting hydroxyls. Compounds **16** and **18** were coupled using trimethylsilyl triflate as catalyst to provide **19**. Methanolysis of **19**, followed by reduction of the azido group with



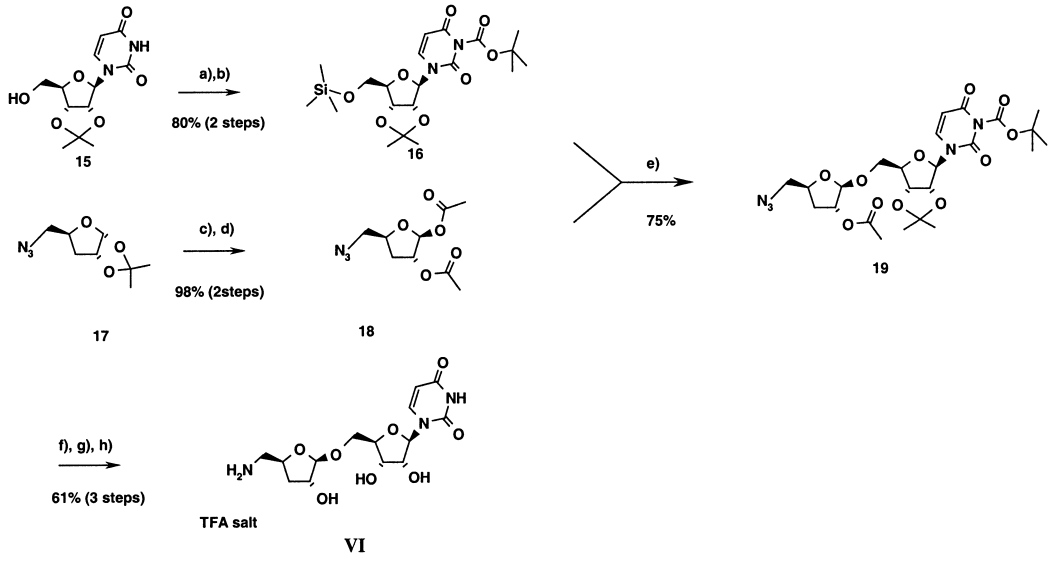
Scheme 1. (a) $SnCl_4$, CH_2Cl_2, 3 h, rt; (b) MeONa, MeOH, 18 h, rt; (c) PPh_3, THF, H_2O, 18 h, rt; (d) TFA/H_2O (7:3), 30 min, rt.



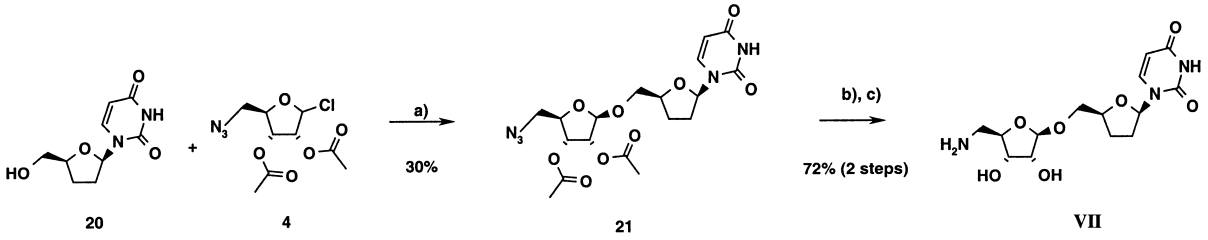
Scheme 2. (a) $Hg(CN)_2$, $ClCH_2CH_2Cl$, 18 h, rt; (b) 60% CH_3CO_2H aq, 10 h, 60 °C; (c) Ac_2O, pyridine, 3 h, rt; (d) *O*-*O*′-bis(trimethylsilyl)uracil, TMSOTf, CH_3CN, 3 h, rt; (e) MeONa, MeOH, 18 h, rt; (f) PPh_3, THF, H_2O, 18 h, rt.



Scheme 3. (a) 1,3-Dichloro 1,1,3,3-tetraisopropyl disiloxane, pyridine, 3 h, rt; (b) ClC(S)OPh, DMAP, CH_3CN, 3 h, rt; (c) Bu_3SnH, AIBN, $PhCH_3$, 3 h, 80 °C; (d) TBAF, THF, 3 h, rt; (e) TsCl, pyridine, 18 h, rt; (f) NaN_3, DMF, 18 h, 70 °C; (g) 60% CH_3CO_2H aq, 4 h, 60 °C; (h) Pd/C, H_2, MeOH, 30 min, rt.



Scheme 4. (a) TMSCl, DIEA, THF, 30 min, rt; (b) $(BOC)_2O$, DMAP(cat.), TEA, THF, 2 h, rt; (c) 60% CH_3CO_2H aq, 2 h, 70 °C; (d) Ac_2O, pyridine, 3 h, rt; (e) TMSOTf (cat. 10%), CH_2Cl_2, −10 °C, 24 h; (f) MeONa, MeOH, 2 h, rt; (g) PPh_3, THF, H_2O, 72 h, rt; (h) TFA/H_2O (7:3), 30 min, rt.



Scheme 5. (a) $Hg(CN)_2$, $ClCH_2CH_2Cl$, rt, 18 h; (b) MeONa, MeOH, rt, 18 h; (c) Pd–C, H_2, MeOH, 30 min, rt.

Table 2.

	I	III	IV	V	VI	VII
IC_{50} (μM) on translocase	50	80	10	115	>1000	120

PPh_3 in the presence of water, and subsequent cleavage of the remaining protecting groups with 70% aqueous trifluoroacetic acid, gave rise to **VI**.[13]

Condensation of **4**[3] with **20** (commercially available), in the presence of mercury(II) cyanide gave **21** (Scheme 5). Methanolysis of **21** and subsequent hydrogenolysis of the crude compound gave **VII**.[14]

The inhibitory activity (IC_{50}) of these compounds was determined by using the assay mentioned in previous publications.[3,6] Results are summarized in Table 2.

According to these results, it appears that only the hydroxyl in position 3″ is crucial for the inhibition of MraY. Removal of the 2′-hydroxyl induced a slight decrease in activity, whereas the effect is more pronounced when the 2″ hydroxyl or both 2′ and 3′ hydroxyls are removed. Conversely, the absence of the 3′ hydroxyl gave rise to an inhibitor (**IV**), which was five times more potent.

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8. Analytical data for **III**: ^1H NMR (400 MHz, D_2O): 2.41 (m, 2H, H2′a, H2′b), 2.81 (dd, 1H, $J=8$, 13.5 Hz, H5″a), 3.06 (dd, 1H, $J=3.5$, 13.5 Hz, H5″b), 3.67 (dd, 1H, $J=5$, 11.5 Hz, H5′a), 4.02–4.11 (m, 5H, H4′, H5′b, H2″, H3″, H4″), 4.50 (m, 1H, H3′), 5.05 (s, 1H, H1″), 5.87 (d, 1H, $J=8$ Hz, H5), 6.28 (t, 1H, $J=6$ Hz, H1′), 7.71 (d, 1H, $J=8$ Hz, H6). MS (FAB): $360+=(M+H^+)$.
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11. Analytical data for **IV**: ^1H NMR (400 MHz, D_2O): (acetic acid salt): 1.92 (s, CH_3, acetic acid salt), 2.07 (m, 2H, H3′a,

H3′b), 3.06 (dd, 1H, $J=9.5$, 13.5 Hz, H5″a), 3.39 (dd, 1H, $J=3$, 13.5 Hz, H5″b), 3.71 (dd, 1H, $J=5$, 12 Hz, H5′a), 4.54 (m, 1H, H2′), 4.12–4.23 (m, 4H, H5′b, H2′, H3′, H4′), 4.64 (m, 1H, H4′), 5.11 (s, 1H, H1″), 5.83 (d, 1H, $J=1$ Hz, H1′), 5.86 (d, 1H, $J=8$ Hz, H5), 7.78 (d, 1H, $J=8$ Hz, H6); MS (ESI): $360+=(M+H^+)$.

12. Analytical data for **V**: ^{1}H NMR (400 MHz, CD_3OD): 2.11 (ddd, 1H, $J=5.5$, 7, 13 Hz, H2″a), 2.24 (ddd, 1H, $J=2$, 7, 13 Hz, H2″b), 2.73 (dd, 1H, $J=8$, 13 Hz, H5″a), 2.89 (dd, 1H, $J=4$, 13 Hz, H5″b), 3.60 (m, 1H, H5′a), 3.87 (m, 1H, H4″), 4.05–4.15 (m, 4H, H5′b, H2′, H3′, H4′), 4.24 (dt, 1H, $J=5$, 7 Hz, H3″), 5.27 (dd, 1H, $J=2$, 5.5 Hz, H1″), 5.72 (d, 1H, $J=8$ Hz, H5), 5.86 (d, 1H, $J=3.5$ Hz, H1′), 7.85 (d, 1H, $J=8$ Hz, H6). MS (SIMS): $360+=(M+H^+)$.

13. Analytical data for **VI** (trifluoroacetate form): ^{1}H NMR (400 MHz, CD_3OD): 1.92 (ddd, 1H, $J=4.5$, 9, 14 Hz, H3″a), 2.22 (ddd, 1H, $J=7$, 14 Hz, H3″b), 2.94 (dd, 1H, $J=9.5$, 13 Hz, H5″a), 3.27 (dd, 1H, $J=2.5$, 13 Hz, H5″b), 3.74 (dd, 1H, $J=5$, 11.5 Hz, H5′a), 4.12 (dd, 1H, $J=2.5$, 11.5 Hz, H5′b), 4.24 (m, 1H, H4′), 4.28 (dd, 1H, $J=5$, 6 Hz, H3′), 4.35 (dd, 1H, $J=4$, 5 Hz, H2′), 4.40 (d, 1H, $J=4.5$ Hz, H2″), 4.59 (ddt, 1H, $J=2.5$, 7, 9 Hz, H4″), 5.11 (s, H1″), 5.90 (d, 1H, $J=4$ Hz, H1′), 5.92 (d, 1H, $J=8$ Hz, H5), 7.74 (d, 1H, $J=8$ Hz, H6). MS (ESI): $360+=(M+H^+)$.

14. Analytical data for **VII**: ^{1}H NMR (400 MHz, D_2O): 1.87–2.55 (m, 4H, H2′a, H2′b, H3′a, H3′b), 2.89 (dd, 1H, $J=8.5$, 13 Hz, H5″a), 3.17 (dd, 1H, $J=3$, 13 Hz, H5″b), 3.63 (dd, 1H, $J=5.5$, 11.5 Hz, H5′a), 4.04 (dd, 1H, $J=2.5$, 11.5 Hz, H5′a), 4.02–4.16 (m, 3H, H2″, H3″, H4″), 4.34 (m, 1H, H4′), 5.06 (s, 1H, H1″), 5.86 (d, 1H, $J=8$ Hz, H5), 6.12 (dd, 1H, $J=3$, 7 Hz, H1′), 7.79 (d, 1H, $J=8$ Hz, H6). MS (ESI): $344+=(M+H^+)$.