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Synthesis of Analogues of the Calicheamicin γ_1^I Oligosaccharide as Potential DNA Ligands

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Abstract: The chemical synthesis of two analogues of the calicheamicin γ_1^I oligosaccharide is described.

The oligosaccharide portion of the esperamicins[1] and calicheamicins[2] plays a key role in the drug-DNA[3] interaction and it is largely responsible for the selectivity and specificity of DNA cleavage.[3-4] Earlier studies have determined the roles of carbohydrate rings D and E,[4] the aromatic ring-C,[5] and the β N-O glycosidic bond[6] on DNA-drug recognition events.

In this paper we report the total synthesis of oligosaccharides **1** and **2** which are analogues of the calicheamicin oligosaccharide in which these compounds possess a basic chain E' in place of carbohydrate ring E with or without the rhamnopyranosyl unit D. (Figure 1)

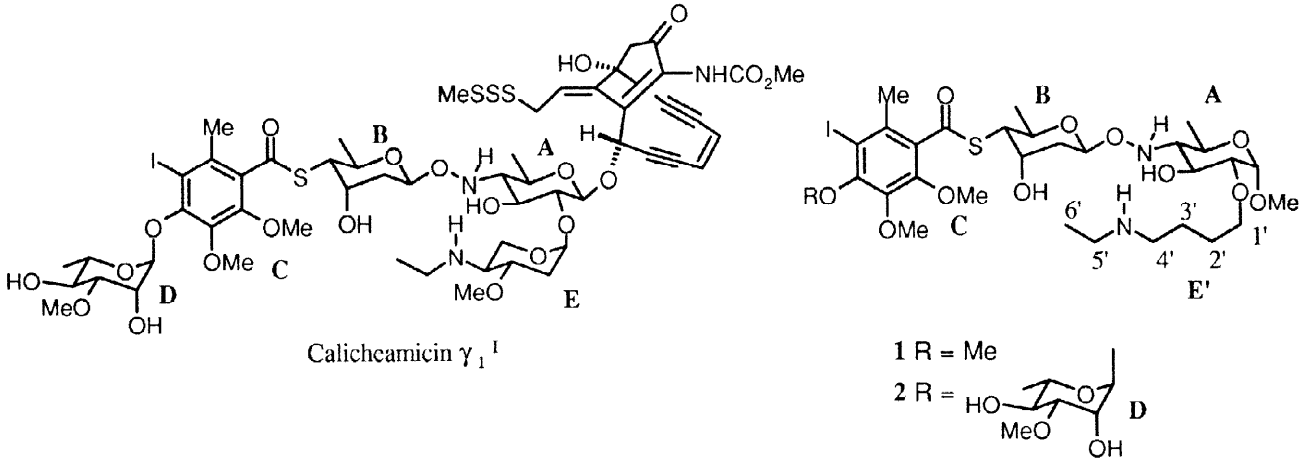

Figure 1. Structures of calicheamicin γ_1^I and analogues of calicheamicin γ_1^I oligosaccharide **1** and **2**

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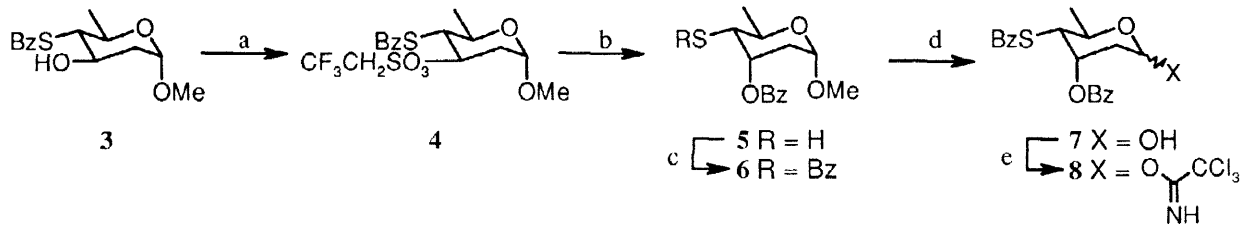
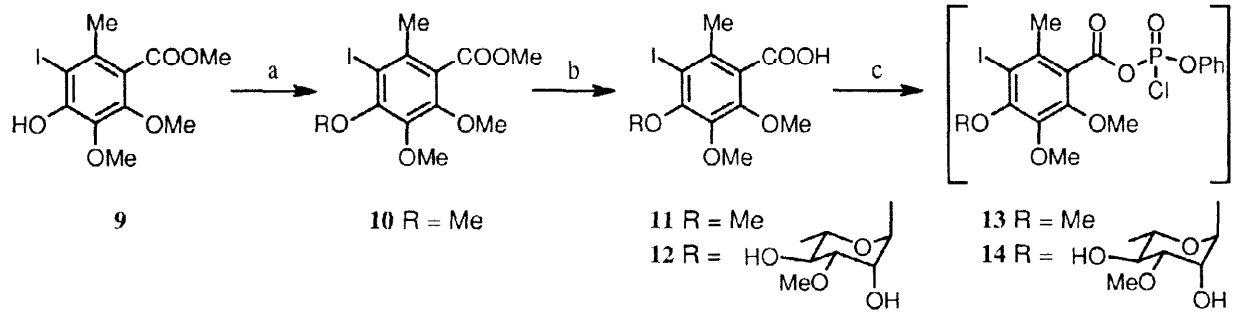
Our strategy is based on the coupling of the fully deprotected disaccharide ABE' with aromatic unit C (or CD) using the selective formation of a thioester.[7] Conversion of alcohol **3**[8] into tresylate[9] **4** (Scheme 1) and subsequent heating at reflux in a mixture of $ClCH_2CH_2Cl$/pyridine/H_2O gave thiol **5**[8] in 68% yield over the two steps. The use of the trifluoroethanesulfonate ester was critical for the high yielding conversion of **3** into **5**. Benzoylation of thiol **5** provided **6** which was hydrolysed under acidic conditions to give hemiacetal **7** as a 1:3 mixture of α and β anomers. Final hemiacetal activation using Schmidt's conditions[10] furnished exclusively the β-trichloroacetimidate **8**.



Scheme 1. (a), 2,2,2-trifluoroethanesulfonyl chloride, pyridine, CH_2Cl_2, 0°C → rt, 2 h; (b), $ClCH_2CH_2Cl$/pyridine/H_2O, reflux, 1 h, 68% (over 2 steps); (c), BzCl, pyridine, 0°C → rt, 5 h, 88%; (d), H_2O:AcOH (2:1), reflux, 2 h, 85%; (e), CCl_3CN, DBU, CH_2Cl_2, rt, 1 h.

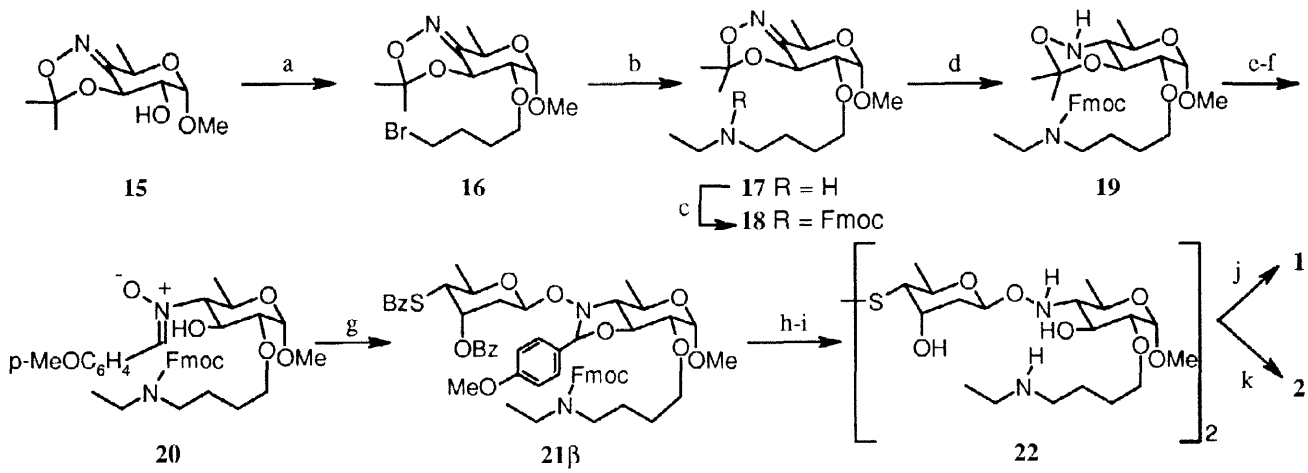
The preparation of the ring C **13** (Scheme 2) began with a methylation of known phenol **9**[11] to give ester **10** (94%) and subsequent saponification provided carboxylic acid **11** in 95% yield which was then activated with phenyldichlorophosphate[12] yielding mixed anhydride **13**. A similar procedure was used for the preparation of CD fragment **14** from 3-*O*-methyl rhamnose substituted benzoic acid **12**.[7, 13] In this case, formation of the mixed anhydride was performed in the presence of 2,4-di-*O*-unprotected rhamnose residue.



Scheme 2. (a), Me_2SO_4, K_2CO_3, acetone, rt, 24 h, 94%; (b), 2.5 N NaOH, MeOH, reflux, 6 h, 95%; (c), $PhOPOCl_2$, pyridine, 1,2-dimethoxyethane, 0°C → rt, 1 h.

Alkylation of **15**[14] with 2 equivalents of 1,4 dibromobutane in the presence of sodium hydride gave **16** in 61% yield (Scheme 3), without formation of any disubstituted compound. Displacement of the remaining bromide from **16** with $EtNH_2$ gave secondary amine **17** which was directly converted into Fmoc protected amine **18** (76%, 2 steps). Reduction of the oxime bond of **18** with $NaBH_3CN$ in the presence of BF_3:Et_2O gave **19** in 86% yield with solely the *gluco* configuration.[14, 15] Hydrolysis of the ketal protecting group in **19** followed by condensation of the resultant hydroxylamine with 4-methoxybenzaldehyde provided nitrone **20** (82%, 2 steps).

Subsequent coupling of this nitrone with trichloroacetimidate **8** under the influence of AgOTf[16] at -20°C gave an unseparable mixture of α and β anomers **21** in 92% yield (β:α 5.8:1).[15, 17] This selectivity, unusual for a glycosylation reaction involving a 2-deoxyglycoside, can be explained by the participation of the benzoyl group at the 3-position of ring B.[18, 7b] Removal of the aminoacetal was achieved with a catalytic amount of DDQ[19] in a mixture of CH_3CN and H_2O (88%). At this stage, the β-anomer[20] was easily separated from the unwanted α-anomer by chromatography. Removal of the benzoyl and Fmoc groups was performed in one step using MeOH and K_2CO_3 to afford disulfide **22** in 72% yield. This appropriately functionalized oligosaccharide unit **22** was now ready for coupling with activated esters **13** and **14**. Disulfide **22** was initially reduced with *n*-Bu_3P in 1,2-dimethoxyethane to the thiolate and then added to a solution of mixed anhydride **13** to provide compound **1**[21] in 53% yield.[7] Alternatively, using mixed anhydride **14** in this coupling protocol gave analogue **2**[22] in 72% yield. In both cases, we have only observed the formation of the desired thioester, no competing ester or amide bond formation was observed.



Scheme 3. (a), 1,4 dibromobutane, NaH, DMF, 0°C → rt, 3 h, 61%; (b), $EtNH_2$, DMF, rt, 10 h; (c), FmocCl, K_2CO_3, THF:H_2O 2.5:1, 0°C, 45 min, 76% from **16**; (d), $NaBH_3CN$, BF_3:Et_2O, CH_2Cl_2, -30°C, 1 h 15, 86%; (e), 0.3 M HCl in MeOH:H_2O 3:1, rt, 1 h 30; (f), 4-MeOPhCHO, toluene, reflux, 1 h, 82% from **19**; (g), **8**, AgOTf, CH_2Cl_2, -20°C, 4 Å molecular sieves, 2 h, 92%; (h), DDQ, CH_3CN:H_2O 9:1, 0°C, 1 h, 88%; (i), K_2CO_3, MeOH, rt, 2 h, 72%; (j), *n*-Bu_3P, 1,2-dimethoxyethane, 0°C, 1 h then **13**, rt, 24 h, 53%; (k), *n*-Bu_3P, 1,2-dimethoxyethane, 0°C, 1 h then **14**, rt, 24 h, 72%.

We have undertaken some preliminary studies to evaluate the DNA binding properties of these novel oligosaccharides. The CD spectrum of oligosaccharide **2** was recorded in the presence of oligonucleotide 5'-d(CCCGGTCCTAAG) using conditions described by Ellestad.[23] Although we observed some small effects which indicated that oligosaccharide **2** was binding the double strand DNA, problems with the solubility of these analogues precluded a detailed study.

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17 NMR analysis of this mixture was further complicated by the formation of a new chiral center of the aminoacetal.

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20 *Selected NMR data for the β-anomer*: δ_H ($CDCl_3$) 1.94 (ddd, 1H, , $J_{2eq,2ax}$ 14.0 Hz, $J_{2ax,3}$ 3.0 Hz, $J_{2ax,1}$ 10.0 Hz, H-2axB), 2.22 (ddd, 1H, , $J_{2eq,2ax}$ 14.0 Hz, $J_{2eq,3}$ 2.5 Hz, $J_{2eq,1}$ 2.0 Hz, H-2eqB), 5.05 (dd, 1H, $J_{1,2eq}$ 2.0 Hz, $J_{1,2ax}$ 10.0 Hz, H-1B), 5.58 (m, 1H, $J_{3,4} = J_{3,2ax}$ 3.0 Hz, $J_{3,2eq}$ 2.5 Hz, H-3B).

21 *Selected physical data for 1*: colorless oil; $[\alpha]_D^{20}$ +28° (c 0.63, $CHCl_3$); δ_H ($CDCl_3$) 1.10 (t, 3H, $J_{5',6'}$ 7.5 Hz, H-6'), 1.32 (d, 3H, $J_{5,6}$ 6.5 Hz, H-6A), 1.37 (d, 3H, $J_{5,6}$ 6.5 Hz, H-6B), 1.61 (m, 4H, H-2', H-3'), 1.75 (m, 1H, $J_{2eq,2ax}$ 13.5 Hz, $J_{2eq,3}$ 3.0 Hz, $J_{2eq,1}$ 10.0 Hz, H-2axB), 1.98 (ddd, 1H, $J_{2eq,2ax}$ 13.5 Hz, $J_{2eq,3}$ 3.0 Hz, $J_{2eq,1}$ 2.0 Hz, H-2eqB), 2.31 (s, 3H, CH_3), 2.34 (td, 1H, $J_{3,4} = J_{4,5}$ 9.5 Hz, $J_{4,NH}$ 2.0 Hz, H-4A), 2.63 (q, 2H, $J_{5',6'}$ 7.5 Hz, H-5'), 2.64 (m, 2H, H-4'), 3.24 (dd, 1H, $J_{2,1}$ 3.5 Hz, $J_{2,3}$ 9.5 Hz, H-2A), 3.38 (s, 3H, OCH_3), 3.56 (m, 1H, H-1'), 3.68 (m, 1H, H-1'), 3.68 (dd, 1H, $J_{4,3}$ 2.5 Hz, $J_{4,5}$ 10.5 Hz, H-4B), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.89 (dq, 1H, $J_{5,6}$ 6.5 Hz, $J_{5,4}$ 10.5 Hz, H-5B), 4.00 (dq, 1H, $J_{5,6}$ 6.5 Hz, $J_{5,4}$ 9.5 Hz H-5A), 4.14 (t, 1H, $J_{3,4} = J_{2,3}$ 9.5 Hz, H-3A), 4.27 (m, 1H, H-3B), 4.73 (d, 1H, $J_{2,1}$ 3.5 Hz, H-1A), 5.02 (dd, 1H, $J_{1,2eq}$ 2.0 Hz, $J_{1,2ax}$ 10.0 Hz, H-1B), 6.60 (d, 1H, $J_{4,NH}$ 2.0 Hz, NHO); δ_C ($CDCl_3$) 192.05, 150.31, 143.62, 132.92, 130.30, 117.69, 109.98, 99.68, 97.78, 94.32, 81.85, 77.50, 71.19, 68.76, 68.03, 66.05, 64.27, 61.89, 60.97, 60.69, 55.14, 51.96, 49.21, 44.02, 27.74, 26.76, 24.91, 19.23, 18.31, 14.75.

22 *Selected physical data for 2*: white solid, $[\alpha]_D^{20}$ -5° (c 0.54, $CHCl_3$); δ_H ($CDCl_3$) 1.26 (t, 3H, $J_{5',6'}$ 7.5 Hz, H-6'), 1.27 (d, 3H, $J_{5,6}$ 6.0 Hz, H-6D), 1.31 (d, 3H, $J_{5,6}$ 6.0 Hz, H-6A), 1.36 (d, 3H, $J_{5,6}$ 6.0 Hz, H-6B), 1.74 (m, 1H, H-2axB), 1.87 (m, 4H, H-2', H-3'), 2.00 (ddd, 1H, H-2eqB), 2.32 (s, 3H, CH_3), 2.41 (t, 1H, $J_{3,4} = J_{4,5}$ 10.0 Hz, H-4A), 2.74 (m, 1H, H-4'), 2.89 (q, 2H, $J_{5',6'}$ 7.5 Hz, H-5'), 2.89 (m, 1H, H-4'), 3.37 (s, 3H, OCH_3), 3.40 (dd, 1H, $J_{2,1}$ 3.5 Hz, $J_{2,3}$ 10.0 Hz, H-2A), 3.54 (s, 3H, OCH_3), 3.61 (t, 1H, $J_{3,4} = J_{4,5}$ 9.5 Hz, H-4D), 3.68 (dd, 1H, $J_{4,3}$ 2.5 Hz, $J_{4,5}$ 10.0 Hz, H-4B), 3.61-3.72 (m, 2H, H-1'), 3.80 (s, 3H, OCH_3), 3.81 (dd, 1H, $J_{2,3}$ 3.0 Hz, $J_{3,4}$ 9.5 Hz, H-3D), 3.82 (m, 1H, H-5A), 3.85 (s, 3H, OCH_3), 4.02 (dq, 1H, $J_{5,6}$ 6.0 Hz, $J_{5,4}$ 10.0 Hz, H-5B), 4.05 (t, 1H, $J_{3,4} = J_{2,3}$ 10.0 Hz, H-3A), 4.16 (dq, 1H, $J_{4,5}$ 9.5 Hz, $J_{5,6}$ 6.0 Hz, H-5D), 4.26 (m, 1H, H-3B), 4.45 (dd, 1H, $J_{1,2}$ 2.0 Hz, $J_{2,3}$ 3.0 Hz, H-2D), 4.75 (d, 1H, $J_{2,1}$ 3.5 Hz, H-1A), 5.06 (dd, 1H, $J_{1,2eq}$ 2.0 Hz, $J_{1,2ax}$ 10.0 Hz, H-1B), 5.69 (d, 1H, $J_{1,2}$ 2.0 Hz, H-1D), 6.65 (s, 1H, NHO); δ_C ($CDCl_3$) 192.22, 151.38, 150.63, 142.98, 133.45, 130.44, 129.20, 120.17, 102.56, 99.77, 97.28, 93.46, 80.82, 71.12, 70.38, 69.03, 68.18, 66.97, 61.66, 60.89, 57.18, 54.90, 51.95, 47.54, 25.33, 19.26, 18.38, 17.55.

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