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Synthesis of a Novel Analogue of the BCD Carbohydrate Domain of Calicheamicin γ_1^I

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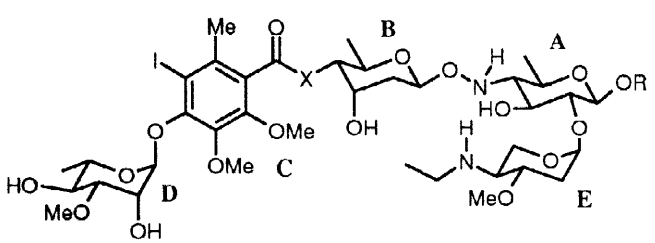
Abstract: The efficient preparation of a novel analogue of the BCD oligosaccharide domain of Calicheamicin γ_1^I is described in which the thioester linkage found in the natural product is replaced by an ester group.

To further probe which structural features of the carbohydrate domain[1] of calicheamicin γ_1^I are responsible for selective DNA recognition,[1b, 2] we decided to examine the role of the sulfur atom of the thioester group. In this paper, we report the synthesis of the hemiacetal **3**, a key intermediate required for the synthesis of the novel calicheamicin γ_1^I oligosaccharide analogue **2** (Figure 1).



1 (X = S), Calicheamicin γ_1^I oligosaccharide
2 (X = O),

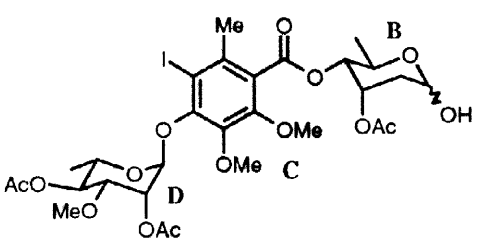


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Figure 1: Structures of calicheamicin γ_1^I oligosaccharide **1**, analogue **2** and hemiacetal **3**

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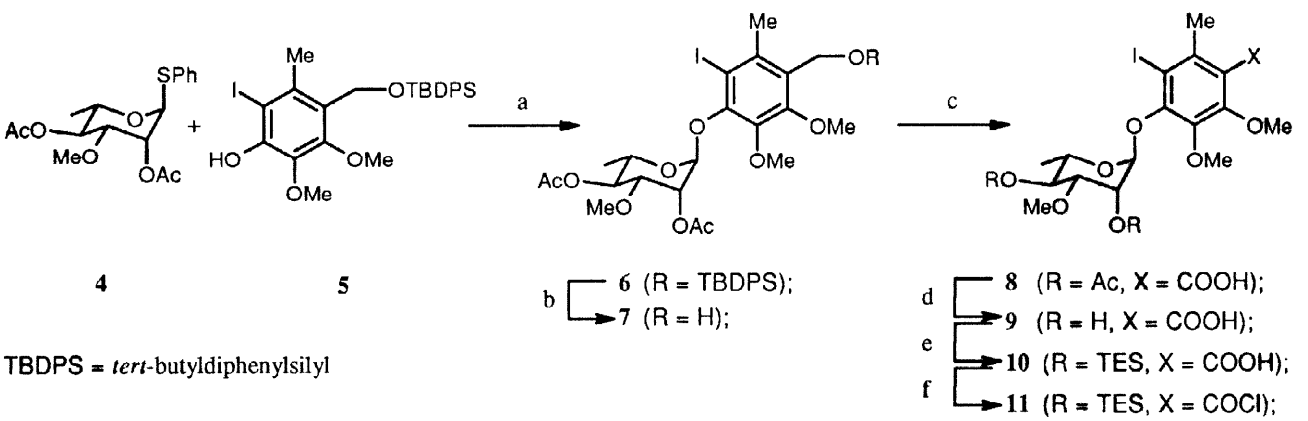
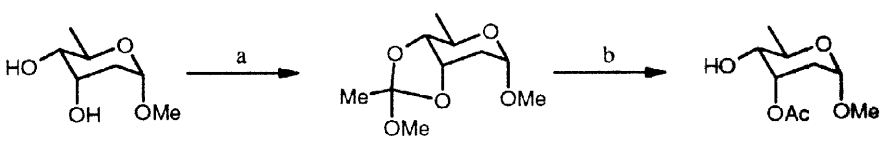
Retrosynthetic analysis led us to conclude that analogue **2** could be derived from coupling of the hemiacetal **3** and an appropriate AE fragment. The participation of the acetate group at the 3-position[3] of B-ring hemiacetal **3** should allow the β-glycoside to be formed as the major product. Further disconnections led us to propose that hemiacetal **3** could be made by coupling of an arylsaccharide CD with carbohydrate ring B.

Our synthetic work began with the construction of the requisite arylsaccharide CD. Glycosylation of thioglycoside **4**[4] with phenol **5**[3c] in the presence of *N*-iodosuccinimide[5] and a catalytic amount of TMSOTf gave aryl α-L-rhamnoside **6**[6] in 68% yield as the sole product (Scheme 1). Deprotection and subsequent oxidation of the resultant primary hydroxyl group using ruthenium tetroxide[3c] gave acid **8** in 45% yield over the 2 steps. Removal of the acetate groups[7] and subsequent reprotection of the hydroxyl groups as silyl ethers was uneventful. Finally, the carboxylic acid **10** was activated for coupling by conversion into acid chloride **11**.[4]



Scheme 1: (a), NIS, TMSOTf, CH_2Cl_2, 4 Å mol. sieves, 0°C, 68%; (b), *n*-Bu_4NF, THF, rt, 75%; (c), $RuCl_3$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$, 0°C → rt, 60%; (d), H_2O_2, LiOH, THF/H_2O 3/1, rt, 79%; (e), TESOTf, pyridine, DMAP, CH_2Cl_2, rt, 80%; (f), $(COCl)_2$, CH_2Cl_2, rt.

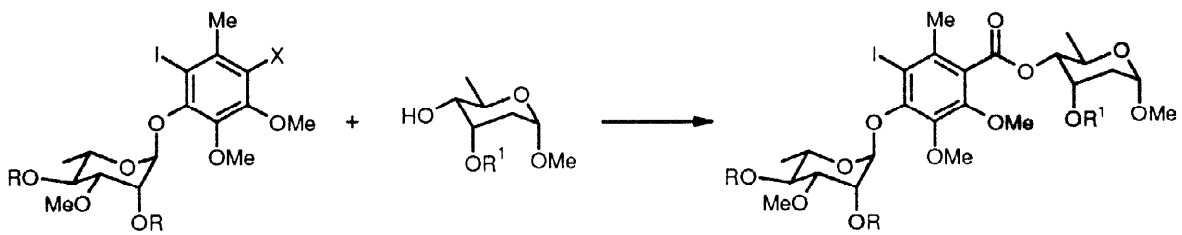
The preparation of the B-ring component is summarised in Scheme 2. Diol **12**,[8] available in 6 steps from the commercially available methyl α-D-glucopyranoside, was treated with trimethyl orthoacetate in the presence of camphorsulphonic acid to give orthoester **13**. Subsequent regioselective hydrolysis of this material under acidic conditions[9] provided alcohol **14** in 67% overall yield.



12 13 14

Scheme 2: (a), $MeC(OMe)_3$, camphorsulphonic acid, toluene; (b), AcOH 80%, rt, 67% (2 steps).

Several methods were attempted to couple the two components together (Table 1). Treatment of carboxylic acid **8** with **14** in the presence of DCCI[10] and a catalytic amount of DMAP gave none of the desired product (Entry 1). When the reaction was carried out using 3 or 4 equivalents of DMAP, we observed migration of the acetate group from O-3 to O-4 within carbohydrate **14**. Coupling of the carboxylic acid **11**[4] with alcohol **14** in the presence of Et_3N and catalytic amount of DMAP yielded the expected ester **17** but in a very low yield. Again migration of the acetate group within carbohydrate **14** was observed and carboxylic acid **10** was recovered due to the hydrolysis of acid chloride **11** (Entry 2). To increase the nucleophilicity of the hydroxyl group, we prepared the alkoxide of carbohydrate ring-B. To this end, compound **15**, synthesised by a literature procedure,[3b] was treated with *n*-BuLi in THF to produce the corresponding lithium alkoxide. Upon addition of acid chloride **11**, ester **18** was produced in 17% yield (Entry 3). Much better results were achieved using the corresponding sodium alkoxide, in this way, ester **18**[11] could be obtained in 67% yield (Entry 4).



8 - 11

14 (R^1 = Ac);
15 (R^1 = THP);

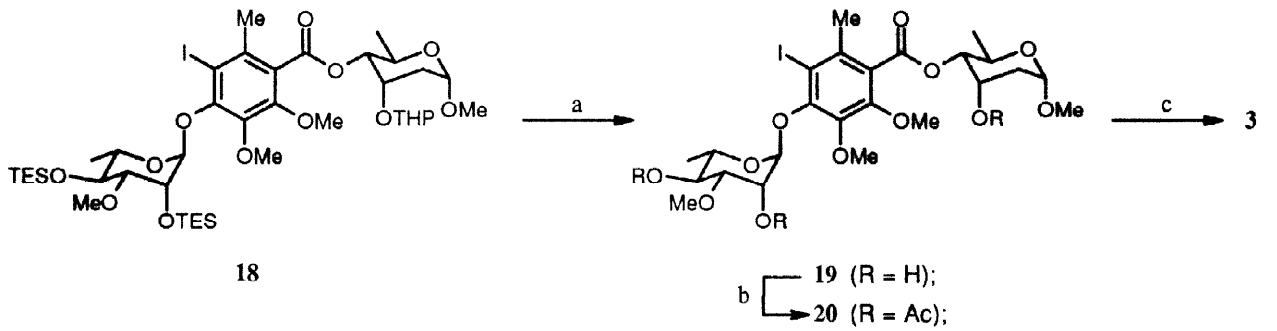
16 (R = R^1 = Ac);
17 (R = TES, R^1 = Ac);
18 (R = TES, R^1 = THP);

Table 1.

Entry	R	X	R^1	conditions and reagents	Yield	Product
1	Ac	COOH	Ac	DCCI, DMAP, CH_2Cl_2, 0°C → rt	0%	**16**
2	TES	COCl	Ac	Et_3N, DMAP, CH_2Cl_2, rt	10%	**17**
3	TES	COCl	THP	*n*-BuLi,[a] THF, 0°C → rt	17%	**18**
4	TES	COCl	THP	NaH,[b] THF, 0°C → rt	67%	**18**

[a] Acid chloride **11** in THF was added after 1h to a stirred solution of **15** in presence of *n*-BuLi at 0°C. [b] Acid chloride **11** in THF was added after 1h to a stirred solution of **15** in presence of NaH at 0°C.

Having successfully prepared **18** in acceptable yield, the removal of TES and THP groups of **18** was performed in one step using 1% HCl in dry MeOH[3b] to provide solely the α-methyl glycoside **19** in 75% yield (Scheme 3). Acetylation of **19** followed by hydrolysis of the acetal yielded hemiacetal **3**[12] as a 1:3-4 mixture of α- and β-anomers.



Scheme 3. (a), 1% HCl in dry MeOH, 0°C, 75%; (b), Ac_2O, pyridine, rt, 83%; (c), H_2O/AcOH 2/1, reflux, 73%, β/α 3-4/1.

In conclusion, we have described an efficient synthesis of hemiacetal **3** in good yield. The coupling reaction of unit CD with unit B was achieved in an acceptable yield by using the sodium salt of carbohydrate **15**. Further work is currently in progress to complete the synthesis of calicheamicin γ_1^I oligosaccharide analogue **2**.

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References and notes

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6. Selected NMR data for the α-anomer: δ_H ($CDCl_3$) 4.03 (dd, 1H, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 10.0 Hz, H-3), 5.56 (d, 1H, $J_{1,2}$ 2.0 Hz, H-1), 5.79 (dd, 1H, $J_{1,2}$ 2.0 Hz, $J_{2,3}$ 3.5 Hz, H-2).
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11. All new compounds gave satisfactory ^{1}H-NMR data.
12. NMR data for the β-anomer: δ_H ($CDCl_3$) 1.20 (d, 3H, $J_{5,6}$ 6.5 Hz, H-6), 1.37 (d, 3H, $J_{5,6}$ 6.0 Hz, H-6), 1.86 (ddd, 1H, $J_{2ax,1}$ 9.0 Hz, $J_{2ax,3}$ 2.5 Hz, $J_{2eq,2ax}$ 14.5 Hz, H-2Bax), 2.08 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.17 (s, 3H, OAc), 2.27 (ddd, 1H, $J_{2eq,1}$ 2.0 Hz, $J_{2eq,3}$ 4.0 Hz, $J_{2eq,2ax}$ 14.5 Hz, H-2Beq), 2.35 (s, 3H, CH_3), 2.88 (d, 1H, $J_{1,OH}$ 6.5 Hz, OH), 3.44 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.04 (dd, 1H, $J_{4,3}$ 10.0 Hz, $J_{3,2}$ 3.0 Hz, H-3D), 4.13 (m, 1H, H-5), 4.33 (m, 1H, H-5), 4.90 (dd, 1H, $J_{4,3}$ 3.0 Hz, $J_{4,5}$ 9.5 Hz, H-4B), 5.10 (t, 1H, $J_{3,4} = J_{4,5}$ 10.0 Hz, H-4D), 5.16 (m, 1H, H-1B), 5.58 (m, 1H, H-3B), 5.63 (d, 1H, $J_{1,2}$ 2.0 Hz, H-1D), 5.74 (dd, 1H, $J_{1,2}$ 2.0 Hz, $J_{3,2}$ 3.0 Hz, H-2D).