Synthesis of the *CD* and *E* Ring Systems of the Calicheamicin γ_1^I Oligosaccharide

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Syntheses of the *CD* and *E* ring systems of calicheamicin γ_1^I as compounds (**2**) and (**3**) (for *CD*) and (**4**) and (**5**) (for *E*) in their naturally occurring forms are reported.

The intriguing molecular structures of the calicheamicins[1] coupled with their phenomenal potencies as antibiotics and antitumour agents and their unusual mode of action prompted a flurry of research activities in recent times. Most of the synthetic efforts in this area have so far focused on biological mimics,[2] the bicyclic enediyne skeleton,[3] and the carbohydrate–aromatic fragment[4] of these molecules. In this communication we report the synthesis of the *CD* and *E* ring systems of calicheamicin γ_1^I (**1**), the most prominent member of the calicheamicin family of antibiotics, as compounds (**2**) and (**3**) (for *CD*) and (**4**) and (**5**) (for *E*) in their naturally occurring forms.

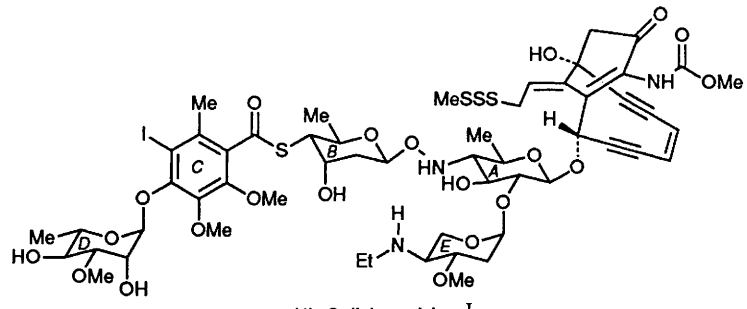
Scheme 1 outlines the stereoselective construction of the *CD* systems (**2**) and (**3**) from the readily available fragments (**6**)† and (**10**).[4a] Thus, (**6**) was selectively methylated at the 3-hydroxy group with Bu^n_2SnO–CsF–MeI[5] to afford compound (**7**)‡ (65% yield, plus 30% recovered starting material). Acetylation of (**7**) afforded (**8**) (95% yield), a derivative designed to undergo selective α-glycosidation due to neighbouring group participation, as desired in the present synthetic sequence. Fluoride (**9**) was generated from (**8**) upon exposure to *N*-bromosuccinimide (NBS) and diaminosulphur trifluoride (DAST)[6] (85%). Coupling of (**9**) with (**10**) under the influence of $AgClO_4$–$SnCl_2$[6,7] proceeded smoothly to afford, stereospecifically, glycoside (**11**) in 80% yield. Deacetylation of (**11**) under standard conditions furnished the requisite *CD* system as the dihydroxy methyl ester (**2**),§ in quantitative yield.

Bis(silylation) of (**2**) (92%) followed by di-isobutylaluminium hydride (DIBAL) reduction (90%) gave alcohol (**13**) *via* derivative (**12**). Finally, ruthenium chloride–sodium periodate

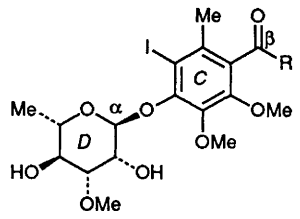
† This compound was prepared from L-rhamnose in ca 60% overall yield by the following sequence: (i) Ac_2O, dimethylaminopyridine (DMAP), CH_2Cl_2, 25 °C; (ii) $SnCl_4$–PhSH, CH_2Cl_2, 0 °C; (iii) K_2CO_3–MeOH, 25 °C.

‡ All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogenous materials.

§ Selected physical properties of compounds (2)—(5). (**2**): R_f 0.20 (silica, 70% EtOAc in light petroleum); mp 137 °C; $[\alpha]_D^{23}$ −47.4° (*c* 0.5, $CHCl_3$); IR($CHCl_3$) ν_{max} 3600m, 2950m, 1750s, 1450s, 1400s, 1380s, 1280s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (s, 1 H, H-1), 4.45 (s, 1 H, H-2), 4.23-4.13 (m, 1 H, H-5), 3.90 (s, 3 H, H_3CO), 3.86 (s, 3 H, H_3CO), 3.84—3.81 (m, 4 H, H_3CO, H-3), 3.62 (dd, *J* 9.5, 9.4 Hz, H-4), 3.55 (s, 3 H, H_3CO), 2.44, 2.37 (br.s, 1 H, HO), 2.34 (s, 3 H, H_3C-aromatic), 1.27 (d, *J* 6.2 Hz, H-6). (**3**): R_f 0.23 (silica, 70% EtOAc in light petroleum); mp 140 °C; $[\alpha]_D^{23}$ −36.2° (*c* 0.35, $CHCl_3$); IR($CHCl_3$) ν_{max} 3600m, 3026m, 3010m, 2939m, 1685s, 1478s, 1458m cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49—7.45 (m, 2 H, aromatic), 7.40—7.37 (m, 3 H, aromatic), 5.67 (d, *J* 1.4 Hz, 1 H, H-1), 4.42 (dd, *J* 2.8, 1.4 Hz, 1 H, H-2), 4.21—4.11 (m, 1 H, H-5), 3.89 (s, 3 H, H_3CO), 3.80—3.76 (m, 4 H, H_3CO, H-3), 3.58 (dd, *J* 9.4, 9.4 Hz, H-4), 3.51 (s, 3 H, H_3CO), 2.39 (s, 3 H, H_3C-aromatic) 2.34, 2.26 (br.s, 1 H, HO), 1.24 (d, *J* 6.3 Hz, 3 H, H-6). (**4**): R_f 0.27 (silica, 10% MeOH in EtOAc); $[\alpha]_D^{23}$ −56.7° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3012m, 2969s, 2937s, 2911s, 2834m, 1466m, 1446m, 1376m, 1358w, 1248m, 1202m, 1154m, 1127s cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 4.66 (dd, *J* 3.6, 2.2 Hz, 1 H, H-1), 3.79 (dd, *J* 11.0, 4.7 Hz, 1 H, H-5 *eq*), 3.61—3.51 (m, 2 H, H-5 *ax*, H-3), 3.15 (s, 3 H, H_3CO), 3.03 (s, 3 H, H_3CO), 2.74 (ddd, *J* 9.7, 9.0, 4.7 Hz, 1 H, H-4), 2.52—2.38 (m, 2 H, H_2CN), 2.11 (ddd, *J* 12.7, 4.5, 2.2 Hz, 1 H, H-2 *eq*), 1.47 (ddd, *J* 12.7, 10.5, 3.6 Hz, 1 H, H-2 *ax*), 1.30 (br.s, 1 H, HN), 0.91 (t, *J* 7.1 Hz, 3 H, H_3C). (**5**): R_f = 0.18 (silica, 10% MeOH in EtOAc); $[\alpha]_D^{25}$ +99.7° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2971s, 2836s, 2700s, 2457m, 1584m, 1449m, 1392m, 1239m, 1191m cm^{-1}; ^1H NMR (300 MHz, C_6D_6)δ 4.14–4.07 (m, 2 H, H-5 *eq*, H-1), 3.37 (s, 3 H, H_3CO), 3.07 (dd, *J* 9.6, 9.0 Hz, 1 H, H-5 *ax*), 3.07—3.00 (m, 4 H, H-3, H_3CO), 2.66 (ddd, *J* 9.0, 9.0, 4.5 Hz, 1 H, H-4), 2.46—2.33 (m, 2 H, H_2C-N), 2.13 (ddd, *J* 12.4, 4.5 2.4 Hz, 1 H, H-2 *eq*), 1.96 (br.s, 1 H, HN), 1.59 (ddd, *J* 12.4, 10.5, 8.9 Hz, 1 H, H-2 *ax*), 0.89 (t, *J* 7.1 Hz, 3 H, H_3C).

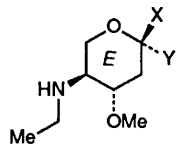


(1): Calicheamicin γ_1^I



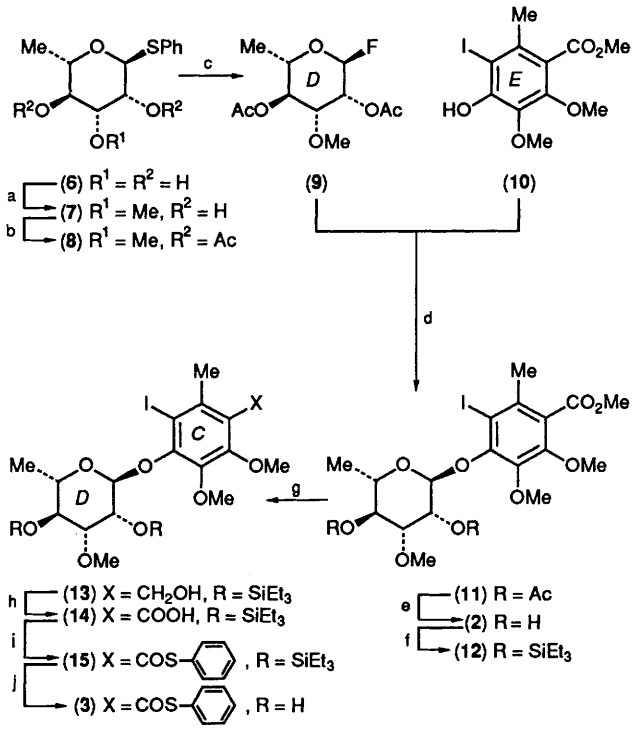
(2) R = OMe

(3) R = S-Ph

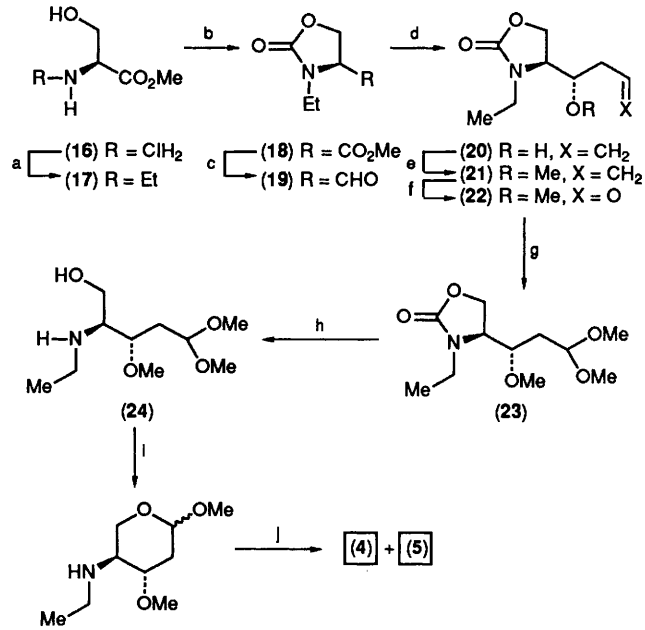


(4) X = OMe, Y = H

(5) X = H, Y = OMe



Scheme 1. *Synthesis of the DC systems* (**2**) *and* (**3**). *Reagents and conditions:* (a) 1.1 equiv. of Bu^n_2SnO, MeOH, 65 °C, 2 h, then dimethylformamide (DMF), 4 equiv. of MeI, 1.1 equiv. of CsF, 25 °C, 12 h, 65%, plus 30% starting material (**6**); (b) 3.0 equiv. of Ac_2O, 3.5 equiv. of Et_3N, DMAP cat., CH_2Cl_2, 0—25 °C, 2 h, 95%; (c) 2.0 equiv. of DAST, 1.4 equiv. of NBS, CH_2Cl_2, −78 to 0 °C, 3 h, 85%; (d) 1.0 equiv. of (**10**), 2.0 equiv. of (**9**), 4.0 equiv. of $SnCl_2$, 4.0 equiv. of $AgClO_4$, 4 Å molecular sieves, CH_2Cl_2, −20 to 0 °C, 12 h, 80%; (e) 0.5 equiv. of K_2CO_3, MeOH, 25 °C, 2 h, 100%; (f) 2.5 equiv. of $Et_3SiOSO_2CF_3$, 3.0 equiv. of 2,6-lutidine, CH_2Cl_2, −20 to 0 °C, 1 h, 92%; (g) 2.5 equiv. of DIBAL, CH_2Cl_2, −78 to 0 °C, 2 h, 90%; (h) 0.02 equiv. of $RuCl_3$ hydrate, 4.0 equiv. of $NaIO_4$, CCl_4–MeCN–H_2O (2 : 2 : 3), 0 to 25 °C, 3 h, 75%; (i) 1.5 equiv. of $PhOP(O)Cl_2$, 4.0 equiv. of pyridine, 2.0 equiv. of PhSH, dimethoxyethane, 0—25 °C, 1 h, 90%; (j) 2.2 equiv. of Bu_4NF, tetrahydrofuran (THF), 0 °C, 0.5 h, 90%.



Scheme 2. *Synthesis of E ring* (**4**) *and* (**5**). *Reagents and conditions:* (a) 1.0 equiv. of Et_3N, MeOH, 0 °C, 10 min, then 1.0 equiv. of MeCHO, 0 °C, 2 h, then 2.0 equiv. of $NaBH_4$, 0 °C, 1 h, 64%; (b) 1.1 equiv. of carbonyldi-imidazole, MeCN, 80 °C, 66%; (c) 1.05 equiv. of DIBAL, CH_2Cl_2, −78 °C, 3 h, 75%; (d) 1.3 equiv. of (−)-β-methoxydiisopinocampheylborane, 1.3 equiv. of allylmagnesium bromide, THF, −78 to 25 °C, 14 h, then (ref. 12) pH 7 buffer; MeOH–30% H_2O_2 (3 : 1), 0 °C, 1 h, 75%; (e) 1.2 equiv. of Ag_2O, 5 equiv. of MeI, DMF, 40 °C, 12 h, 92%; (f) ozone, CH_2Cl_2–MeOH (1 : 1), −78 °C, then 2.0 equiv. of $P(OMe)_3$, −78 to 25 °C, 1.5 h, 91%; (g) MeOH, Amberlyst-15, 25 °C, 14 h, 85%; (h) 1.5 equiv. of NaOH, MeOH–H_2O (2 : 1), 90 °C, 1 h, 96%; (i) 1.5 equiv. of HCl, MeOH, 25 °C, 1 h, 88%; (j) recrystallization from EtOAc.

oxidation[8] of (**13**) at −20 °C afforded carboxylic acid (**14**) (75%) which was successfully coupled to benzenethiol under the influence of $PhOP(O)Cl_2$[9] to furnish the phenylthio ester (**15**) in 90% yield. Finally, desilylation of (**15**) gave the targeted *CD* ring system (**3**)§ (90%).

The synthesis of the two isomers of the carbohydrate unit *E*, compounds (**4**) (1*R*) and (**5**) (1*S*), proceeded from serine methyl ester hydrochloride (**16**) as shown in Scheme 2. Thus, reductive alkylation of (**16**) with acetaldehyde and sodium borohydride[10] produced the monoalkylated amine (**17**) in 66% yield. Oxazolidinone formation with carbonyldi-imidazole in refluxing acetonitrile gave (**18**) (64%) which was reduced with DIBAL to the aldehyde (**19**) in good yield. Stereoselective addition of an allyl group to the aldehyde function of (**19**) was achieved *via* the action of (−)-β-methoxydi-isopinocampheylborane[11] and allylmagnesium bromide leading to a single isomer (**20**) (in 75% yield). Methylation of (**20**) (Ag_2O-MeI, 92%) followed by ozonolysis (91%) led to methoxy aldehyde (**22**) *via* compound (**21**). Acetalization of (**22**) proceeded smoothly in MeOH under acid catalysis leading to compound (**23**) (85%) which was then exposed to basic conditions to produce the amino alcohol (**24**) in 96% yield. Finally, cyclization of (**24**) in methanol with anhydrous hydrogen chloride furnished a mixture of the methoxy isomers (**4**) (1*R*) and (**5**) (1*S*) which were separated by recrystallization from ethyl acetate to give pure compounds (**4**)§¶ and (5).§

The described chemistry demonstrates efficient technology for the construction of the crucial bonds α (glycosidic) and β (thioester) linking carbohydrate units *D* and *B* to the aromatic moiety *C* of the calicheamicin γ_1^I oligosaccharide. Furthermore, the reported sequences render readily available derivatives of the *CD* and *E* ring systems of the calicheamicins for DNA binding studies and further synthetic and bio-organic investigations.

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¶ The optical purity of (**4**) was determined at its *N*-acetyl derivative and found to be $[\alpha]_D^{25}$ −99.0° (*c* 0.96, $CHCl_3$); lit[4c] $[\alpha]_D^{20}$ −96.0° (*c* 0.9, $CHCl_3$).

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