

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 calicheamicins¹ 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 fragment⁴ 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 $\text{Bu}_3\text{SnO}-\text{CsF}-\text{MeI}$ 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 $\text{AgClO}_4-\text{SnCl}_2$ ^{6,7} proceeded smoothly to afford, stereospecifically, glycoside (11) in 80% yield. Deacetylation of (11) under standard conditions furnished the

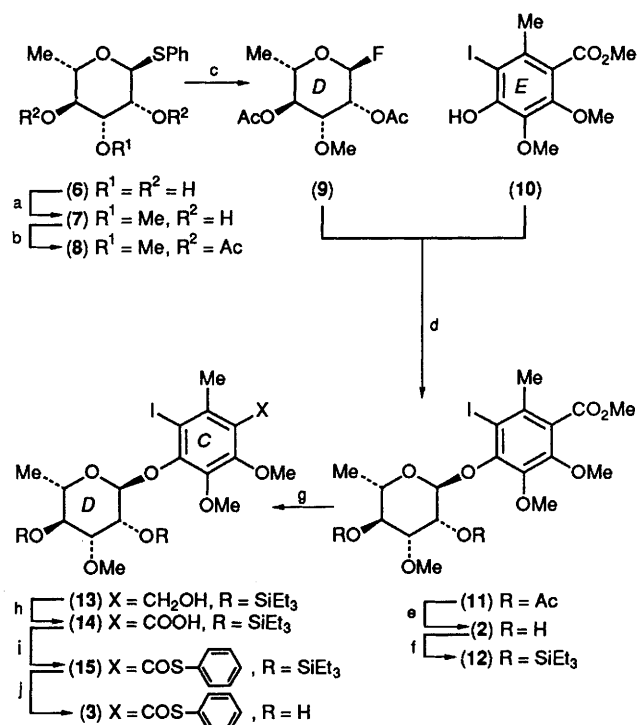
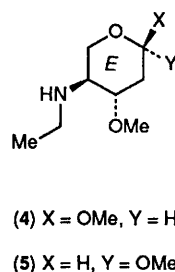
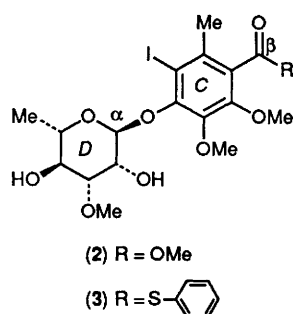
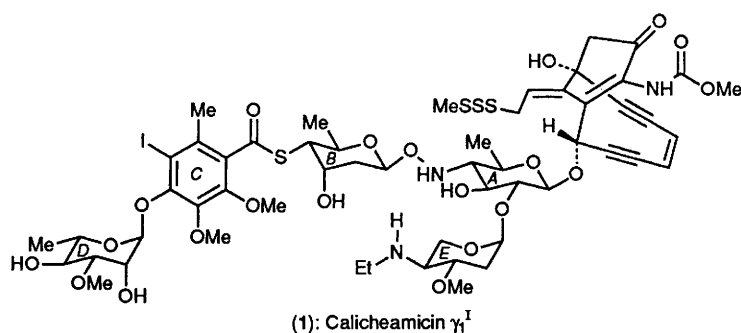
requisite *CD* system as the dihydroxy methyl ester (2),§ in quantitative yield.

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

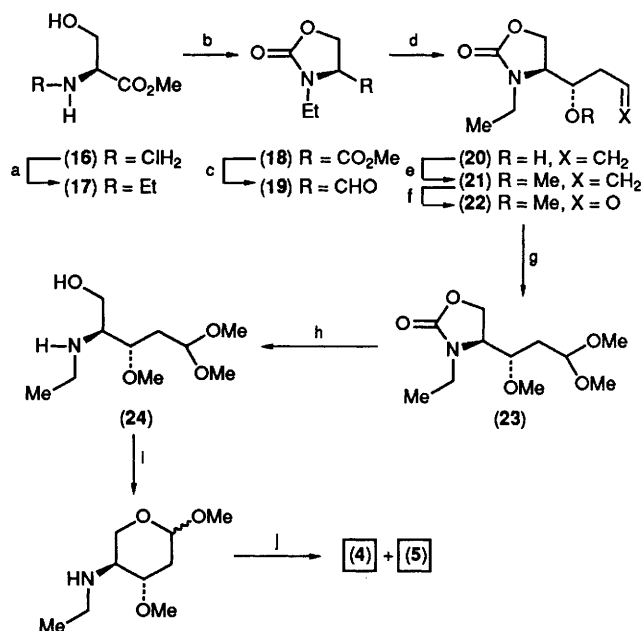
§ Selected physical properties of compounds (2)–(5). (2): R_f 0.20 (silica, 70% EtOAc in light petroleum); mp 137 °C; $[\alpha]_D^{23} -47.4^\circ$ (c 0.5, CHCl_3); IR (CHCl_3) ν_{max} 3600m, 2950m, 1750s, 1450s, 1400s, 1380s, 1280s cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.72 (s, 1 H, H-1), 4.45 (s, 1 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; $[\alpha]_D^{23} -36.2^\circ$ (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); $[\alpha]_D^{23} -56.7^\circ$ (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); $[\alpha]_D^{25} +99.7^\circ$ (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, $\text{H}_2\text{C}-\text{N}$), 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).

[†] 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) $\text{SnCl}_4-\text{PhSH}$, CH_2Cl_2 , 0 °C; (iii) $\text{K}_2\text{CO}_3-\text{MeOH}$, 25 °C.

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



Scheme 1. Synthesis of the DC systems (2) and (3). Reagents and conditions: (a) 1.1 equiv. of Bu₂SnO, 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 Ac₂O, 3.5 equiv. of Et₃N, DMAP cat., CH₂Cl₂, 0–25 °C, 2 h, 95%; (c) 2.0 equiv. of DAST, 1.4 equiv. of NBS, CH₂Cl₂, –78 to 0 °C, 3 h, 85%; (d) 1.0 equiv. of (10), 2.0 equiv. of (9), 4.0 equiv. of SnCl₂, 4.0 equiv. of AgClO₄, 4 Å molecular sieves, CH₂Cl₂, –20 to 0 °C, 12 h, 80%; (e) 0.5 equiv. of K₂CO₃, MeOH, 25 °C, 2 h, 100%; (f) 2.5 equiv. of Et₃SiOSO₂CF₃, 3.0 equiv. of 2,6-lutidine, CH₂Cl₂, –20 to 0 °C, 1 h, 92%; (g) 2.5 equiv. of DIBAL, CH₂Cl₂, –78 to 0 °C, 2 h, 90%; (h) 0.02 equiv. of RuCl₃ hydrate, 4.0 equiv. of NaIO₄, CCl₄–MeCN–H₂O (2:2:3), 0 to 25 °C, 3 h, 75%; (i) 1.5 equiv. of PhOP(O)Cl₂, 4.0 equiv. of pyridine, 2.0 equiv. of PhSH, dimethoxyethane, 0–25 °C, 1 h, 90%; (j) 2.2 equiv. of Bu₄NF, 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 Et₃N, MeOH, 0 °C, 10 min, then 1.0 equiv. of MeCHO, 0 °C, 2 h, then 2.0 equiv. of NaBH₄, 0 °C, 1 h, 64%; (b) 1.1 equiv. of carbonyldi-imidazole, MeCN, 80 °C, 66%; (c) 1.05 equiv. of DIBAL, CH₂Cl₂, –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% H₂O₂ (3:1), 0 °C, 1 h, 75%; (e) 1.2 equiv. of Ag₂O, 5 equiv. of MeI, DMF, 40 °C, 12 h, 92%; (f) ozone, CH₂Cl₂–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–H₂O (2:1), 90 °C, 1 h, 96%; (i) 1.5 equiv. of HCl, MeOH, 25 °C, 1 h, 88%; (j) recrystallization from EtOAc.

oxidation⁸ of (13) at –20 °C afforded carboxylic acid (14) (75%) which was successfully coupled to benzenethiol under the influence of PhOP(O)Cl₂⁹ 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 borohydride¹⁰ produced the monoalkylated amine (17) in 66% yield. Oxazolidinone formation with carbonyldiimidazole 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-isopinocampheylborane¹¹ and allylmagnesium bromide leading to a single isomer (20) (in 75% yield). Methylation of (20) (Ag₂O-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 γ₁¹ 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 $[\alpha]_{\text{D}}^{25} -99.0^\circ$ (*c* 0.96, CHCl₃); lit^{4c} $[\alpha]_{\text{D}}^{20} -96.0^\circ$ (*c* 0.9, CHCl₃).

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