Synthesis of the Esperamicin A_1 Trisaccharide

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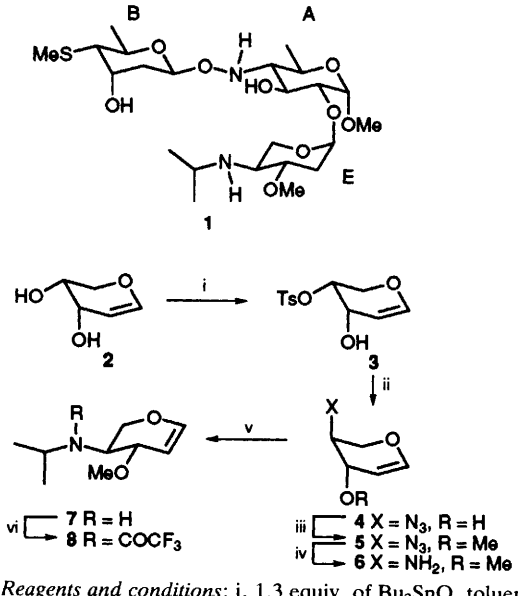
The total synthesis of the trisaccharide of the esperamicin antibiotics from adapted monosaccharidic precursors is described.

The unusual oligosaccharide found in the antitumour antibiotics esperamicins[1] and calicheamicins[2] is mainly responsible for the sequence selectivity observed in DNA cleavage.[3] There is now considerable evidence for complexation of the oligosaccharidic moiety into the minor groove of the duplex nucleic acid before enediyne activation and DNA cleavage initiation.[4] Several synthetic solutions have been proposed for the construction of this oligosaccharide in both the esperamicin[5] and calicheamicin[6] series. Synthetic models of this oligosaccharide are necessary for a better understanding of the factors influencing DNA binding selectivity and could pave the way to fully synthetic sequence-selective DNA ligands. Our group has already described a new approach to the hydroxylamino glycosidic linkage[7] and two syntheses of the thio-sugar (*B*-ring).[8] We now report a new synthesis of the amino pentose (*E*-ring)[9] and the total synthesis of **1**, the methyl glycoside of the natural trisaccharide found in esperamicins.

The preparation of the *E*-ring precursor began with D-arabinal **2**, available from D-arabinose in 53% overall yield.[10] Direct tosylation with the stannylene method[11] gave a 55–60% isolated yield of the crystalline 4-*O*-tosylarabinal **3**† without any of the isomeric 3-*O*-tosylated product. Nucleophilic nitrogen introduction was best done with sodium azide in HMPA at 60 °C to give the hydroxy azide **4** in 76% yield. Because of the high volatility of **5** and **6**, the sequence from **4** to **7** was carried out without purification of the intermediates. Thus, alcohol **4** was methylated to **5** which was reduced to amine **6** with the Staudinger reaction.[12]

Reductive alkylation of crude **6** with acetone[13] gave the secondary amine **7**,‡ immediately protected as the trifluoroacetamide **8**. The overall yield from **4** to **8** was 54%.§

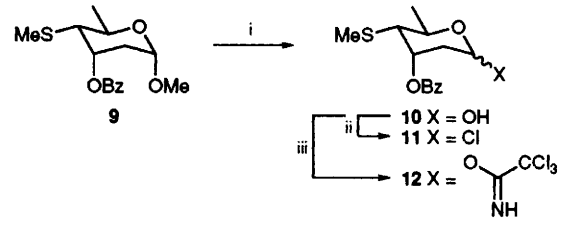
The anomeric activation of the *B*-ring started by acid hydrolysis of the methyl glycoside **9**[8] which gave the hemiacetal **10** in 86% yield as a 3 : 1 mixture of the β- and α-anomers.



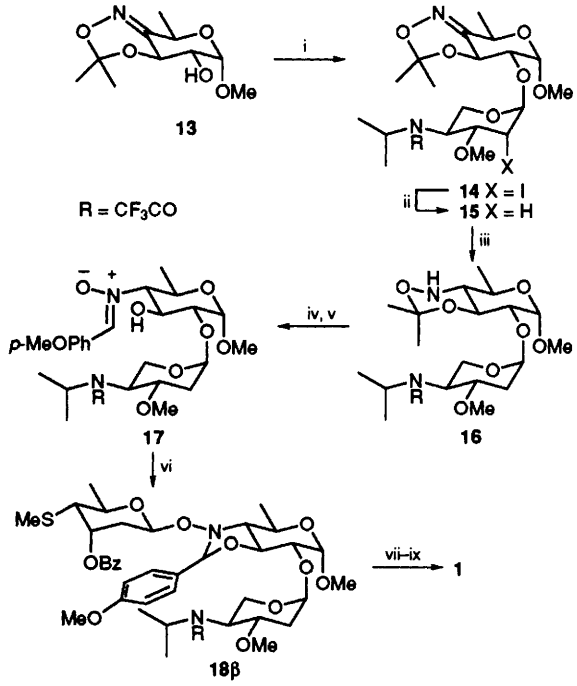
Scheme 1 *Reagents and conditions*: i, 1.3 equiv. of Bu_2SnO, toluene, reflux, then 1.5 equiv. of NBu_4Br, 1.2 equiv. of TsCl, 70 °C, 30 min, 60%; ii, 1.5 equiv. of NaN_3, HMPA, 60 °C, 74%; iii, NaH, 1.5 equiv. of MeI, THF, 0 °C; iv, 1.2 equiv. of PPh_3, THF : H_2O, 10 : 1, room temp., 24 h; v, $NaBH_3CN$, acetone, Pr^iOH, pH 3, room temp.; vi, 2 equiv. $(CF_3CO)_2O$, NEt_3, room temp., 54% from **4**

Both anomeric chloride **11** (α : β ratio, 3 : 1) or trichloroacetimidate **12** (β only) were prepared in high yield from **10** using the Vilsmeier's reagent[14] or Schmidt's conditions.[15] It was anticipated that the axial benzoyl group at O_3 of **11** or **12** would favour a β-selective glycosylation reaction.[16]

The oligosaccharide assembly started by the *N*-iodosuccinimide-assisted iodoglycosylation[17] of glycal **8** with alcohol **13**[7] which provided the *trans*-diaxial disaccharide **14** exclusively in 74% yield. Radical dehalogenation proceeded to the deoxyglycoside **15** smoothly (87%). Classical reduction of the oxime bond of **15** with sodium cyanoborohydride in acidified methanol,[13,18] successful on a model disaccharide,[7] gave stereospecifically the expected hydroxylamine **16**, however, in only 15% yield together with 79% of recovered starting



Scheme 2 *Reagents and conditions*: i, H_2O : $MeCO_2H$, 2 : 1, reflux, 2 h, 86%; ii, Vilsmeir reagent, CH_2Cl_2; iii, 10 equiv. of CCl_3CN, 0.5 equiv. of DBU, CH_2Cl_2, room temp., 1 h



Scheme 3 *Reagents and conditions*: i, 1.5 equiv. of **8**, 1.5 equiv. of NIS, MeCN, MS 4 Å, −30 to 0 °C, 74%; ii, 2 equiv. of Bu_3SnH, toluene, 70 °C, 87%; iii, 20 equiv. of $NaBH_3CN$, 15 equiv. of $BF_3{\cdot}OEt_2$, CH_2Cl_2 : THF, 1 : 1, −20 °C, 74% plus 7% of recovered starting material; iv, 0.3 mol dm^{-3} HCl in MeOH : H_2O, 3 : 1, room temp.; v, 1.3 equiv. of *p*-anisaldehyde, toluene, reflux, 1 h, 97% from **16**; vi, 2 equiv. of **12**, 2 equiv. of AgOTf, CH_2Cl_2, MS 4 Å, 0 °C, 2 h, 90%; vii, 5% DDQ, CH_3CN : H_2O, 9 : 1, room temp., 73%; viii, K_2CO_3, MeOH, room temp., 15 h, 94%; ix, aqueous 5 mol dm^{-3} KOH, room temp., 47% plus 11% of the recovered starting material

material. After numerous trials, this reduction was carried out with $NaBH_3CN$ in a 1 : 1 mixture of CH_2Cl_2 and THF in the presence of 15 equiv. of $BF_3.OEt_2$[5b] (74% yield). In every case, only the *gluco*-configuration was obtained for the now completed *A*-ring.[7] Deprotection of the ketal and nitrone formation furnished **17** in nearly quantitative yield.

Glycosylation at the oxygen atom of the disaccharidic nitrone **17** with chloride **11** proved very difficult to handle because, under the conditions used (trifluoromethane sulfonate activation in CH_2Cl_2 at low temperature), chloride **11** eliminated giving the corresponding glycal before the glycosylation event. However, silver trifluoromethanesulfonate-promoted[19] glycosylation of **17** with the trichloroacetimidate **12** gave the trisaccharide **18** in a high yield (90%). As already noticed in model studies,[7] an aminoacetal was formed by attack of the electrophilic carbon of a transient *O*-glycosyl nitrone salt by the free hydroxy group at C_3 of the *A*-unit resulting in the simultaneous formation of the *A*–*B* hydroxylamino ring junction and protection of the oxygen at position 3 of ring *A*. The stereoselectivity of the newly formed anomeric centre was 5 : 1 with the major product being the expected β-anomer,¶ readily separated from the minor α-anomer¶ by chromatography. The sequential deprotection of trisaccharide **18**β was effected as follows. First, due to the high sensitivity of the β-2-deoxy glycosidic linkage in **18**β to acids, removal of the aminoacetal protecting group was best performed with a catalytic amount of dichlorodicyano quinone in wet acetonitrile[20] (73% yield). Cerium ammonium nitrate was also effective although the reaction was more difficult to control. Secondly, the benzoyl group was cleanly removed with K_2CO_3 in methanol (94%) and cleavage of the amide bond provided the ABE trisaccharide **1**.‖

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Footnotes

† All new compounds gave satisfactory spectral and analytical data.

‡ Bulb to bulb distillation (bp 70 °C, 15 mm Hg) gave an analytical sample of **7**. $[\alpha]_D^{20}$ + 176 (*c* 1.34, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 6.50 (d, 1 H, $J_{1,2}$ 6.2 Hz, H_1), 4.91 (m, 1 H, $J_{1,2}$ 6.2, $J_{2,3}$ 4.7, $J_{2,4}$ 1.4 Hz, H_2), 3.97 (ddd, 1 H, $J_{5,5'}$ 11.0, $J_{5,4}$ 3.5, $J_{5,3}$ 1.4 Hz, H_5), 3.92 (dd, 1 H, $J_{5',5}$ 11.0, $J_{5',4}$ 2.3 Hz, $H_{5'}$), 3.49–3.45 (m, 1 H, H_3), 3.37 (s, 3 H, OCH_3), 2.97 (m, 1 H, J_{H,CH_3} 6.2 Hz, H-isopropyl), 2.93–2.89 (m, 1 H, H_4), 1.06 and 1.08 (2 d, 6 H, $J_{CH_3,H}$ 6.2 Hz, 2 CH_3-Pr^i).

§ Introduction of the trifluoroacetamido group on the *E*-ring gave rise to rotational isomers. Consequently, all intermediates in the synthesis show two sets of signals in their ^1H NMR spectra in $CDCl_3$ at 298 K. The relative proportions of these rotamers are as follows: **8**, 7 : 1; **14**, 19 : 1; **15**, 5 : 1; **16**, 2 : 1; **17**, 6 : 4; **18**β, 2 : 1.

¶ Compound **18**β, $[\alpha]_D^{20}$ +23, was obtained as a single isomer on the newly formed aminoacetalic centre. However, the α-isomer **18**α was a 7 : 3 mixture of diastereoisomers at this centre.

‖ *Selected ^1H NMR data* for **1**: δ 5.22 (bt, *J* 3.0 Hz, H_{1E}), 4.98 (dd, *J* 10.2, 2.0 Hz, H_{1B}), 4.74 (d, *J* 3.8 Hz, H_{1A}), 4.26 (t, *J* 9.8 Hz, H_{3A}), 4.11–4.09 (m, H_{3B}), 3.95 (dq, *J* 9.8, 6.3 Hz, H_{5A}), 3.77 (dq, *J* 10.5, 6.3 Hz, H_{5B}), 3.70 (dd, *J* 11.2, 4.5 Hz, H_{5E}), 3.66–3.60 (m, H_{5E}), 3.59 (dd, *J* 9.8, 3.8 Hz, H_{2A}), 3.39 and 3.36 (2 s, 2 OCH_3), 2.91 (m, *J* 6.5 Hz, H-Pr^i), 2.72 (dt, *J* 9.0, 4.5 Hz, H_{4E}), 2.48 (dd, *J* 10.5, 2.6 Hz, H_{4B}), 2.33 (ddd, *J* 12.7, 4.5, 2.5 Hz, H_{2Eeq}), 2.31 (t, *J* 9.8 Hz, H_{4A}), 2.12 (m, *J* 13.5, 3.1, 2.0 Hz, H_{2Beq}), 2.11 (s, SCH_3), 1.58 (ddd, *J* 13.5, 10.2, 3.7 Hz, H_{2Bax}), 1.54 (ddd, *J* 12.7, 10.2, 3.0 Hz, H_{2Eax}), 1.39 and 1.29 (2 d, *J* 6.3 Hz, $H_{6A,6B}$), 1.10 (bd, *J* 6.5 Hz, CH_3-Pr^i).

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