The First Examples of S_NAr-based Macrocyclisation: Synthesis of Model Carboxylate-Binding Pockets of Vancomycin

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Model carboxylate-binding pocket *C*–O–*D* rings of vancomycin and related glycopeptides were efficiently synthesized by intramolecular S_NAr reaction.

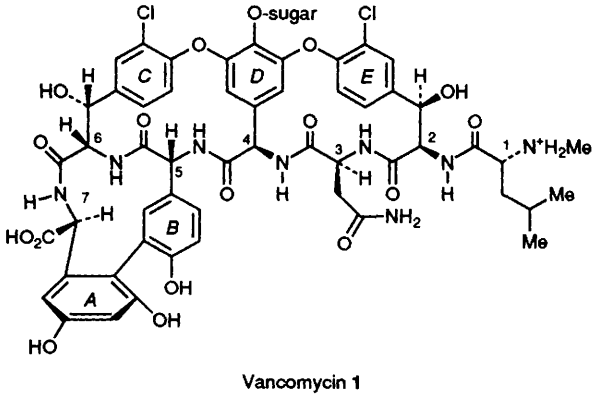
Glycopeptides of the vancomycin **1** (Fig. 1) family have received much attention owing to their effective antibiotic activities.[1] The molecular architecture of this class of natural products has intrigued synthetic chemists for decades.[2] While progress towards the synthesis of racemisation prone arylglycine amino acids[3] has been made in past few years, the development of efficient methods that permit the synthesis of the characteristic 16-membered macrocyclic ring of vancomycin and related antibiotics of this family is still required.[4]

Hamilton *et al.*[5a] and Crimmin *et al.*[5b] have reported the synthesis of model *C*–O–*D* and *D*–O–*E* rings by a macrolactamization procedure in less than 10% yield. However, in related studies, Williams *et al.*[6a] and Pearsons *et al.*[6b] failed to get the macrocyclic compound based on the same strategy. Yamamura *et al.*[7a] and Evans *et al.*[7b] have developed an elegant approach based on thallium(III) promoted intramolecular oxidative coupling procedure. Very recently, Boger *et al.*[4] have detailed an intramolecular Ullmann reaction towards this end. Nevertheless, the yield from the above mentioned methods is still moderate and furthermore, introduction of one chlorine atom into the aromatic *C* and *E* ring *ortho* to the arylether linkage is less than evident.

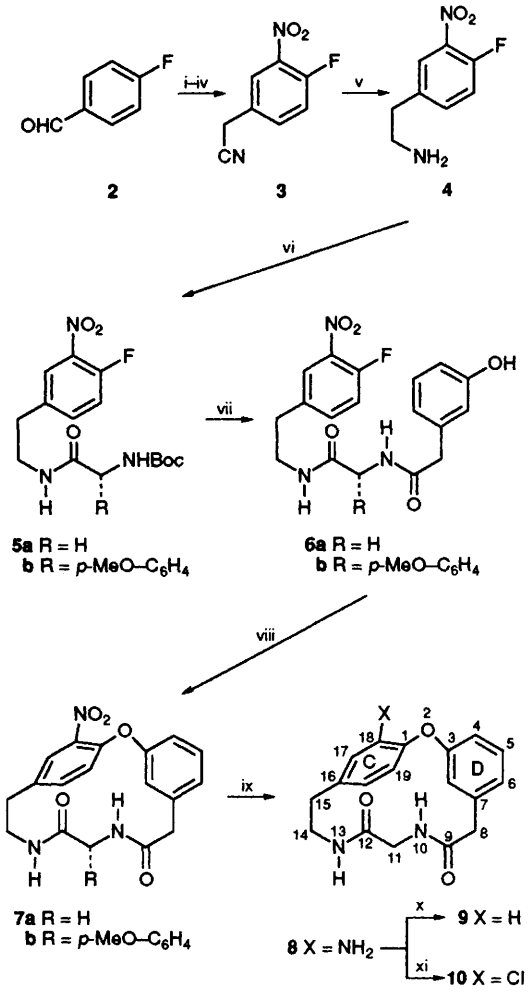
Recently, we reported a S_NAr based synthesis of triaryl diethers,[2] degradation products of all glycopeptides of the vancomycin family, starting from methyl gallate and methyl 3-nitro-4-fluoro-benzoate. The characteristic features of this method are high yield, mild conditions, and more importantly, easy conversion of the nitro group into appropriate functional group (Cl or H) found in the natural products of the vancomycin family. As a logical extension of this work, we turned our attention to the synthesis of a 16-membered ring system *via* intramolecular S_NAr reaction and we report herein our preliminary result.

Precursors **6a** and **6b** needed for the macrocyclisation study were prepared according to Scheme 1. Commercially available 4-fluorobenzaldehyde **2** was converted to 3-nitro-4-fluorobenzylnitrile **3** by sequential nitration, reduction, bromination and cyanation (54% in 4 steps). Chemoselective reduction of nitrile group in the presence of nitro function was problematic until AlH_3[8] or sodium borohydride in the presence of 1 equiv. of TFA[9] were employed as reducing agents. Without further purification, the crude amine **4** was coupled with *N*-Boc glycine to afford amide **5a** in 87% overall yield. Mild acid deprotection of **5a** followed by amide bond formation with 3-hydroxyphenylacetic acid provided compound **6a**† in 94% yield, without any complication due to the presence of a free hydroxy group. The same sequence involving *p*-hydroxyphenylglycine led to compound **6b** in 26% overall yield ($[\alpha]_D$ = −54, *c* = 0.9, MeOH).

Treatment of DMF solution of **6a** with 4 equiv. of anhydrous potassium carbonate at room temp. for 6 h afforded a single compound in 95% isolated yield. Macrocyclisation was first run in 0.004 mol dm^{-3} concentration, however, we found that the high dilution technique was, in fact, not needed and macrocyclisation was routinely carried out in 0.01 mol dm^{-3} concentration. Under these conditions, possible side products derived from dimerisation and O-transacylations (inter- or intra-molecular) were not observed. The



Vancomycin **1**



Scheme 1 *Reagents and conditions:* i, HNO_3–H_2SO_4, 100%; ii, $NaBH_4$, diethyl ether, 87%; iii, PBr_3, toluene, 82% iv, Et_4NCN, MeCN, 75%; v, $LiAlH_4$–$AlCl_3$, 62%; vi, *N*-BOC-glycine, DCC, THF–CH_2Cl_2, 87% or (a) *N*-BOC-4-hydroxyphenylglycine, DCC, THF–CH_2Cl_2; (b) MeI, Me_2CO, K_2CO_3, 56%; vii, (a) TFA; (b) DCC, *m*-hydroxylphenylacetic acid, 94% for **6a** and 50% for **6b**; viii K_2CO_3–DMF, 0.01 mol dm^{-3}, 95%; ix, Fe–$FeSO_4$, 98%; x, Bu^tONO, DMF, 47%; xi, $NaNO_2$, conc. HCl, CuCl–$CuCl_2$, 52%

spectral data (^{1}H and ^{13}C NMR, IR and elemental analyses) of the product were consistent with the macrocyclic compound **7a**.‡ A comparison of ^{1}H NMR spectra shows an upfield shift of H-21 signal, from δ 6.75 in **6a** to δ 6.18 in **7a**. The equivalent proton in vancomycin is found at δ 5.65.[10] Further structure evidence was obtained by converting **7a** to the known compound **9** (see below).[4] It is worth noting that, for compound **6a**, protons attached to the same carbon (C-8, C-11, C-14 and C-15) are all magnetically and chemically non-equivalent in contrast to those of compound **9**.§ This may indicate that the conformation of **7a** is more rigid than that of **9** owing to the presence of the nitro function.

Macrocyclisation of compound **6b** under identical conditions led to the formation of two cyclic products (total yield 95%) from which compound **7b**‡ ($[\alpha]_D = -11$, $c = 0.2$, MeOH) was isolated in 55% yield. The structure of the second cyclised product (40%) was tentatively assigned as the atropoisomer of **7b**.¶

The potential of this approach was demonstrated by transforming the macrocyclic compound **7a** into the model *C*–O–*D* ring **9** found in ristocetin, actaplanin and actinoidin, or into the model compound **10** found in vancomycin and teicoplanin. Thus, reduction of nitro compound **7a** employing Fe–$FeSO_4$[11] as the reducing agent provided the corresponding amine **8** in excellent yield. Direct reductive deamination of **8** under Doyle's condition[12] gave **9** in 47% yield. Conversion of **8** and **10** was best realized by using modified Sandmeyer conditions.[13] We found that the yield could be improved when the reaction was run in degassed solvent. The successful preparation of compound **10** represents the first example where chlorine atom was correctly incorporated into the aromatic *C* ring.

In conclusion, mild and efficient conditions have been established for the preparation of 16-membered macrocycles related to the vancomycin family. To the best of our knowledge, these represent the first examples of S_NAr based macrocyclisation.[14]

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Footnotes

† All new compounds described herein gave spectral data consistent with the assigned structures.

‡ **7a**: mp 251–253 °C; IR: ν_{max}/cm^{-1} 3620, 3250–3550, 2975, 2928, 1669, 1596, 1530; MS (*m/z*): 355 (M^+, 65), 327, 298, 270, 241; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.78 (ddd, *J* 4.8, 8.7, 13.6 Hz, 1H, H-15); 2.95 (m, 1H, H-15); 3.42 (d, *J* 14.7 Hz, 1H, H-8); 3.48 (d, *J* 14.7 Hz, 1H, H-8); 3.55 (m, 1H, H-14); 3.68 (dd, *J* 3.8, 16.3 Hz, 1H, H-11); 3.79 (m, 1H, H-14); 3.95 (dd, *J* 6.0, 16.3 Hz, 1H, H-11); 5.95 (br s, 1H, NH); 6.18 (t, *J* 1.7 Hz, 1H, H-21); 6.29 (br s, 1H, NH); 6.89 (br d, *J* 7.4 Hz, 1H, H-6); 7.03 (d, *J* 8.3 Hz, 1H, H-19); 7.12 (dd, *J* 2.4, 8.0 Hz, 1H, H-4); 7.28 (t, *J* 8.0 Hz, 1H, H-5); 7.32 (dd, *J* 2.2, 8.3 Hz, 1H, H-20); 7.86 (d, *J* 2.2 Hz, 1H, H-17); ^{13}C NMR (CD_3OD, 62.5 MHz): δ 36.5, 40.0, 42.5, 43.1, 115.0, 117.3, 124.8, 125.6, 127.6, 130.9, 137.2, 139.1, 149.1, 161.1, 170.3, 173.3; satisfactory elemental analyses were obtained. **7b**: mp 283–284 °C; $[\alpha]_D = -11$, $c = 0.2$, MeOH; IR: ν_{max}/cm^{-1} 3200–3500, 2938, 1676, 1589, 1530, 1510, MS (*m/z*): 461 (M^+, 90), 431, 404; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.55 (m, 1H, H-15), 2.90–3.12 (m, 2H, H-15 and H-14), 3.31 (d, *J* 13.9 Hz, 1H, H-8), 3.51 (d, *J* 13.9 Hz, 1H, H-8), 3.76 (s, 3H, *Me*O), 4.10 (m, 1H, H-14), 5.32 (d, *J* 7.7 Hz, 1H, H-11), 6.12 (br d, *J* 7.14 Hz, 1H, NH-13), 6.31 (br s, 1H, H-21), 6.78 (d, *J* 8.5 Hz, 2H, aromatic protons of *p*-methoxyphenylglycine), 6.82 (d, *J* 7.3 Hz, 1H, H-19), 6.90 (d, *J* 7.3 Hz, H-6), 7.05 (m, 2H, H-20 and NH-10), 7.19 (d, *J* 8.5 Hz, 2H, aromatic protons of *p*-methoxyphenylglycine), 7.30 (m, 2H, H-4 and H-5), 7.99 (d, *J* 1.9 Hz, 1H, H-17); ^{13}C NMR (CD_3OD, 50.13 MHz), δ 36.1, 39.9, 43.7, 55.0, 55.8, 114.3, 114.6, 117.2, 124.2, 124.4, 126.5, 128.5, 130.2, 130.3, 136.0, 137.2, 160.0, 169.7, 170.0.

§ We thank Professor Boger for kindly providing us with the NMR spectra of compound **9**.

¶ This interesting observation as well as the structure evidences for this compound will be described elsewhere.

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