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A S_NAr Based Facile Synthesis of Triaryl Diethers, Degradation Products of Vancomycin and Related Glycopeptide Antibiotics

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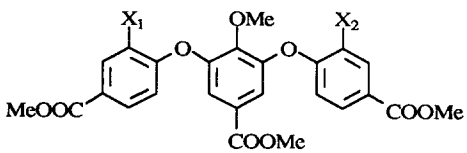
Abstract: A mild and efficient procedure has been developed for the synthesis of triaryl diethers and has been applied to the synthesis of **1**, **2** and **3**, degradation products from glycopeptide antibiotics of the vancomycin family

Besides actidinoidic acid[1] (biarylbisaminoacid), triaryl diethers are substructures common to all the glycopeptide antibiotics of the vancomycin family,[2] a synthetically challenging and clinically important group of natural products. While much progress has been made in the past few years,[3] the development of mild and convenient procedures for preparing triaryl diethers having correctly functionalized aromatic rings is a matter of current interest.[4]

We report herein a facile synthesis of properly substituted triaryl diethers and application of this method to the synthesis of degradation products (**1**, **2**, **3**) of the vancomycin family glycopeptides (Figure 1).



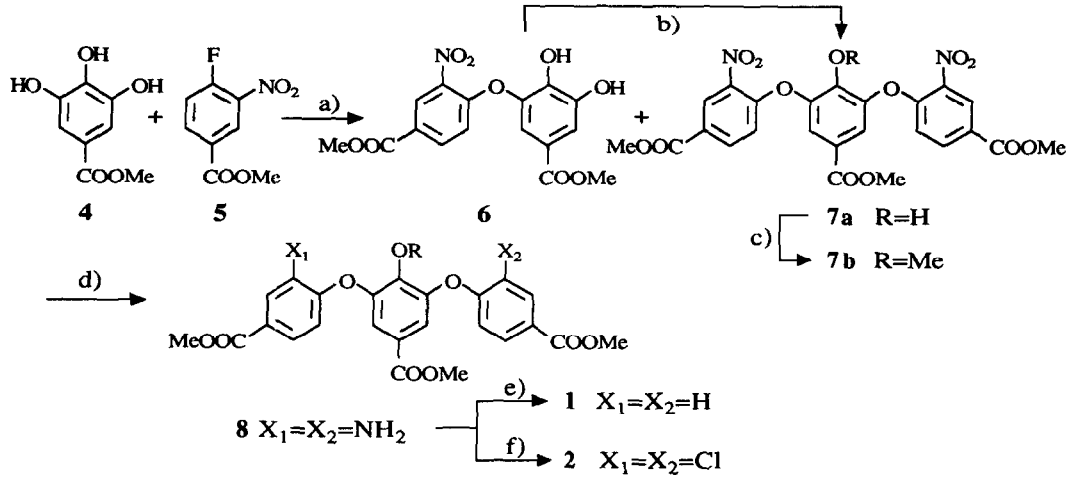
1 : X_1=X_2=H (from ristocetin,[5] A35512B[6])
2 : X_1=X_2=Cl (from vancomycin,[7] teicoplanin[8])
3 : X_1=H, X_2=Cl (from actaplanin,[9] avoparcin[10] and actinoidin[11])

Figure 1

Methyl gallate **4** and methyl 3-nitro-4-fluoro-benzoate **5**[12] were employed in our S_NAr based approach, for which compound **5** was structurally designed as to carry a NO_2 group, not only serving together with the ester group to activate the leaving group F^-, but also to provide an access to the substitution pattern (X_1, X_2=H, Cl) required on *ortho* to the aryl ether linkage.

While the high reactivity of **5** towards the nucleophilic attack was anticipated, the major concern was the regioselectivity in reactions with compound **4**.[13] Experimentally, it was found after repeated trials that controlled addition of **5** (1 eq), at r.t., into a solution of **4** in dry DMF in the presence of K_2CO_3 led to total consumption of **5** after 1h and gave a mixture of **6**, **7a** and trace amount of 4-arylated methyl gallate derivative. Then the addition

of a second eq. of **5** led after 5 hrs to an increased amount of **7a**, concomitantly with the disappearance of **6** (TLC). Finally, treatment of the above reaction mixture with methyl iodide in the same pot provided compound **7b** in 80% yield after column chromatography.



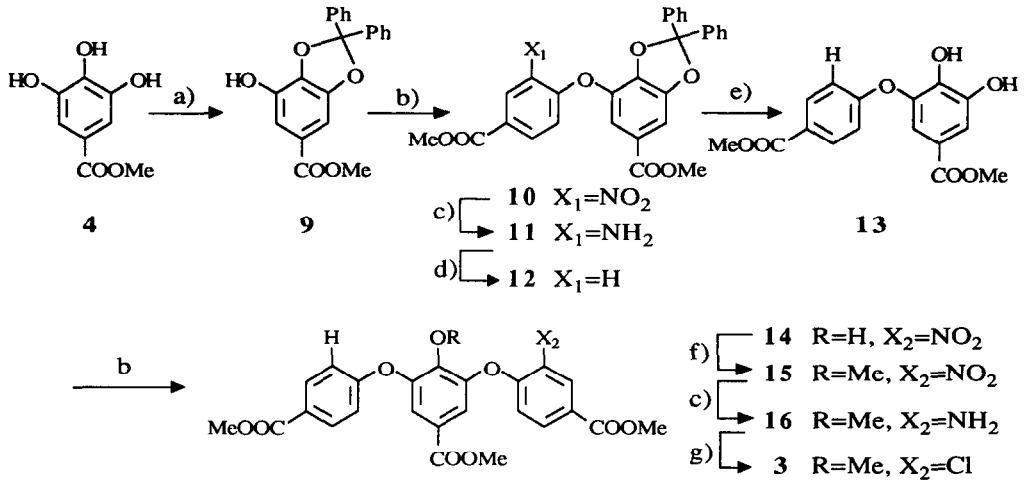
Reagents and conditions: a) K_2CO_3(1 eq), DMF, rt, 1hr; b) K_2CO_3(1 eq.), 5 (1 eq.), rt, 5hrs; c) K_2CO_3(5eq.), CH_3I (2.5eq.), rt, 2days, 80%; d) Fe-$FeSO_4$(3:1), H_2O, reflux, 24 hrs, 90%; e) TBN, DMF, 65°C, 0.5 hrs, 50%; f) TBN, $CuCl_2$,CH_3CN, 60°C, 15 hrs,74%

The observed regioselectivity was understandable by assuming that the reaction is thermodynamically controlled. Due to the conjugating effect of the ester function, the kinetic acidity of the 4-hydroxy group might be higher than that of the two lateral hydroxy groups[13]. As a consequence, the conjugate base of the 3- or 5-hydroxy group should be more nucleophilic.

From compound **7b**, the access to **1** and **2** was straightforward via a common intermediate **8**,[14] resulting from the simultaneous reduction of both nitro groups.[15] The triaryl diether **1**[5, 16] was thus obtained in 50% yield by treating **8** with t-butylnitrite (TBN) in DMF[17] while the dichloro derivative **2**[7, 16] was prepared by treating **8** with TBN and $CuCl_2$ in acetonitrile at 60°C.[18] The spectral data of synthetic compounds **1** and **2** were in good agreement with reported values.[5,7]

The route to **3** was also based upon the S_NAr reaction, but protection of the 3,4-hydroxy groups of **4** *prior* to the substitution step is necessary to secure ultimately the differential conversion of each nitro group (X_1=H, X_2=Cl). Thus, methyl gallate **4**, protected as diphenylmethylene ketal derivative **9**, underwent a smooth and efficient reaction with **5** to give the nitrobiarylether **10**.[14] Reduction of nitro to amino group followed by reductive deamination furnished compound **12**. Alternatively, **12** was prepared by treating **9** with the less

activated methyl 4-fluorobenzoate[19] instead of **5**. Although this route is shorter, harsh conditions (80°C for 30 hrs in DMF) were required, and the yield was moderate (40%).



Reagents and conditions: a) Ph_2CCl_2, 170°C, 79%; b) K_2CO_3, methyl 3-nitro-4-fluoro-benzoate, DMF, rt, 100% c) Fe-$FeSO_4$-H_2O, 75% ; d) TBN, DMF, 65°C, 1 hrs, 74%; e) AcOH-H_2O (4:1), reflux, 24 hrs, 84%; f) K_2CO_3, CH_3I, DMF, 82%; g)TBN, $CuCl_2$, CH_3CN, 60°C, 10 hrs, 45%

Deprotection of **12** afforded **13**, which was used as the nucleophile in a second S_NAr reaction with **5** to give **14** in a highly regioselective way. Methylation was effected by methyl iodide in the same pot and compound **15** was obtained in 82% isolated yield. Finally, a sequence of simple group transformations led to **3**,[10,16] identical to the degradation product, in 32% overall yield.

In conclusion, we have developed a very mild and a high yielding approach to symmetrically or unsymmetrically substituted triaryl diethers **1**, **2** and **3**. The method could find application in the synthesis of triaryl diethers containing a racemization prone amino acid moiety and for the ring closure step of appropriate linear precursors to peptidic macrocycles of the size encountered in vancomycin and related antibiotics. Investigations aimed at those targets are in progress.

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16 **1**: m.p., 85-86°C (Lit[5]: 67°C); IR (cm^{-1}): 3021, 1719, 1600, 1575, 1505, 1340, 1284, 1163, 728; ms(m/z): 467(M+H)$^+$, 435, 202, 149; H^1NMR($CDCl_3$): 3.75(s, OMe, 3H), 3.87(s, OMe, 3H), 3.91(s, 2xOMe, 6H), 6.92(d, J=8.8 Hz, 4H), 7.65(s, 2H); 8.05(d, J=8.8 Hz, 4H); Microanalysis: Calc%: C, 64.38; H, 4.74; Found%: C, 64.37; H, 4.77. **2**: m.p., 113-114°C (Lit[7]: 112-114); IR (cm^{-1}): 3022, 1720, 1600, 1575, 1425, 1325, 1254, 1228, 790; ms(m/z): 538, 536, 534, 507, 505, 503; H^1NMR($CDCl_3$): 3.86, 3.87, 3.90 (s, MeO, 12H), 6.84(d, J=8.6 Hz), 7.56(s, 2H), 7.88(dd, J=2 and 8.6 Hz, 2H), 8.18(d, J=2 Hz, 2H); Microanalysis: Calc%: C, 56.11; H, 3.74; Found%: C, 56.31; H, 3.56. **3**: Oil; IR(cm^{-1}): 3021, 1719, 1600, 1575, 1505, 1437, 1336, 1286, 1252, 1163, 788; ms(m/z): 503, 501(M+H)$^+$, 471, 469, 467, 391, 383, 381, 347; H^1NMR($CDCl_3$): 3.83, 3.87, 3.90, 3.93 (s, 4xMeO, 12H), 6.84(d, J=8.5Hz, 1H), 7.0(d, J=8.7 Hz, 2H), 7.59, 7.64(d, J=2 Hz, 2H), 7.9(dd, J=2 and 8.5 Hz), 8.05(d, J=8.7 Hz, 2H), 8.17(d, J=2 Hz, 1H).

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