New Synthetic Technology for the Synthesis of Aryl Ethers: Construction of C-O-D and D-O-E Ring Model Systems of Vancomycin

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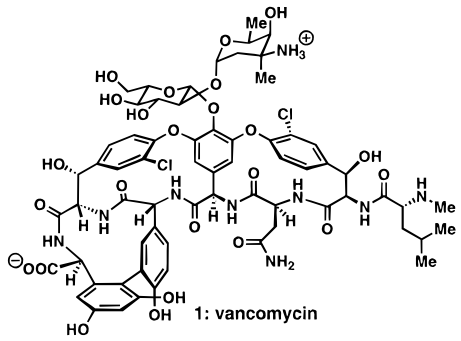
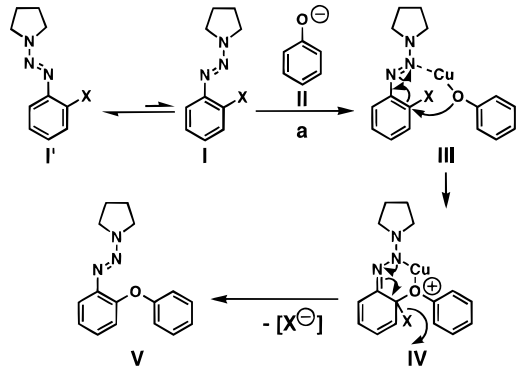
The aryl ether linkage is frequently encountered both in natural products and designed molecules. Much chemistry[1] has recently been extended for the construction of such systems, particularly as they relate to vancomycin type structures.[2] These glycopeptide antibiotics are becoming increasingly important as clinical agents against a growing number of drug resistant bacterial strains and have been the target of synthesis by several groups.[3] Although several cyclic diaryl ether systems related to vancomycin have been reported, a number of challenges still remain in this field. In this paper we report a new method for the construction of aryl ethers and its application to the synthesis of vancomycin (**1**) model D-O-E (**9**) and C-O-D (**15**) ring systems.



The design of this new reaction was based on the mechanistic rationale shown in Scheme 1. A triazene unit[4] was, thus, strategically placed *ortho* to a leaving group on the aromatic nucleus of substrate **I** to serve both as a potential "electron sink" and to attract the attacking nucleophilic species derived from

Scheme 1. Strategy and Presumed Mechanistic Rationale for the Triazene Based Synthesis of Diaryl Ethers



II through coordination with a suitable metal counterion[5] (e.g., Cu(I), see structure **III**, Scheme 1). This scenario was expected to lead to the desired diaryl ether **V** via intermediate **IV**. Triazenes are easily prepared and can be converted to a variety of functional groups such as halides, amines, and phenols.[6]

As demonstrated in Table 1, the triazene approach to aryl ethers is highly efficient and quite general. After considerable experimentation it was discovered that *o*-haloaryl triazenes react smoothly with phenols in the presence of K_2CO_3 and CuBr·Me_2S in MeCN−pyr (*ca.* 5:1) at 80 °C to afford, in good to excellent yields, diaryl ethers and triaryl bis-ethers. It is interesting to note that 2,6-disubstituted triazenes (entries 6−13, Table 1) react faster, and often more efficiently, than the corresponding monosubstituted aryl triazenes (entries 1−5, Scheme 1). This observation, which is in accord with the proposed mechanism, can be explained by assuming a preference for conformation **I′** for the *o*-monosubstituted aryl triazenes,[7] an option not available to the 2,6-disubstituted aryl triazenes. From among the halides, iodides and bromides exhibited the best mobilities for this reaction. Thiophenols also enter this process to produce triaryl bis-thioethers (e.g., entry 13, Table 1).

The D-O-E vancomycin model system **9** (Scheme 2) was successfully synthesized as follows. *p*-Aminobenzoic acid was converted to the dibromo derivative **2** by bromination of its methyl ester (>95%). Reduction of **2** with lithium aluminium hydride gave alcohol **3** (93%) which was subjected to diazotization[8] followed by quenching of the diazonium salt with pyrrolidine to give triazene **4** in 73% overall yield. Conversion of **4** to the corresponding azide via a Mitsunobu displacement[9] with Ph_3P, diethyl diazodicarboxylate (DEAD), and DPPA (**5**, 82%) was followed by reduction to an amino group[10] with Ph_3P and H_2O (**6**, 80%). Coupling of triazene **6** with dipeptide **7**[11] with EDC and HOBt gave tripeptide **8** (45%), setting the stage for the macrocyclization reaction. Treatment of precursor **8** with CuBr·Me_2S (2.5 equiv), K_2CO_3 (2.5 equiv), and pyridine (3.0

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(11) Peptide **7** was prepared, in 85% overall yield, by coupling commercially available *N*-Boc-(*R*)-tyrosine with (*S*)-alanine methyl ester using EDC and HOBt as coupling reagents in DMF, followed by hydrolysis of the methyl ester using aqueous LiOH and MeOH.

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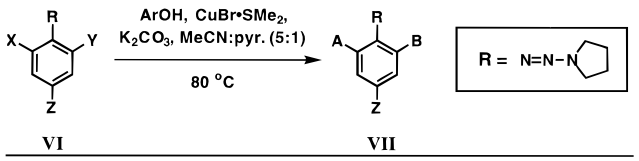
Table 1. Synthesis of Triaryl Ether via Reaction of Triazenes with Phenols

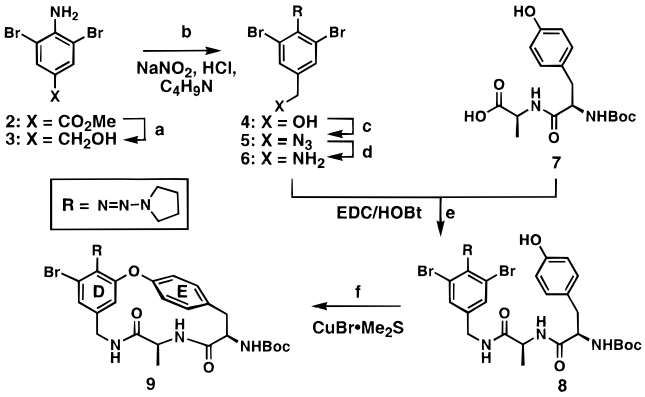


VI VII

	VI: Substrate				VII: Product		Time	Yield
Entry	X	Y	Z	ArOH	A	B	(h)	(%)
1[a]	H	I	H	PhOH	PhO	H	16	78
2[a]	H	Br	H	PhOH	PhO	H	16	65
3[a]	H	Br	H	*o*-Cl-C_6H_4OH	*o*-Cl-C_6H_4OH	H	16	70
4[a]	H	Br	H	*p*-Me-C_6H_4OH	*p*-Me-C_6H_4OH	H	16	64
5[a]	H	Br	H	*o*-Cl-*p*-Me-C_6H_3OH	*o*-Cl-*p*-Me-C_6H_3O	H	16	67
6[b]	I	I	Me	PhOH	PhO	A	4	83
7[b]	Br	Br	Me	PhOH	PhO	A	5	89
8[b]	Br	Br	Br	PhOH	PhO	A	2	91
9[b]	Br	Me	Me	PhOH	PhO	Me	5	56
10[b]	Br	Br	Me	*o*-Cl-C_6H_4OH	*o*-Cl-C_6H_4O	A	5	78
11[b]	Br	Br	Me	*p*-Me-C_6H_4OH	*p*-Me-C_6H_4O	A	5	70
12[b]	Br	Br	Me	*o*-Cl-*p*-Me-C_6H_3OH	*o*-Cl-*p*-Me-C_6H_3O	A	4	74
13[b]	Br	Br	Me	PhSH	PhS	A	4	84

[a] Amounts: 1.2 equiv of ArOH; 5.0 equiv of CuBr•SMe_2; 5.0 equiv of K_2CO_3. [b] Amounts: 2.4 equiv of ArOH; 10.0 equiv of CuBr•SMe_2; 10.0 equiv of K_2CO_3.

Scheme 2. Synthesis of D-O-E Cyclic Aryl Ether **9**[a]

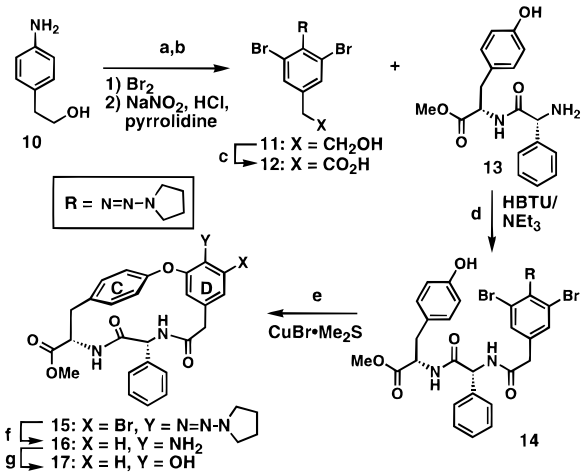


[a] Reagents and conditions: (a) 3.0 equiv of LAH, THF, 0 °C, 4 h, 93%; (b) 1.3 equiv of $NaNO_2$, 5 equiv of 12 N HCl, THF−H_2O (10:1), 0 °C, 0.5 h; then 10 equiv of pyrrolidine, satd. aq. K_2CO_3, 1 h, 73%; (c) 1.5 equiv of Ph_3P, 1.5 equiv of DEAD, then 1.5 equiv of DPPA, THF, 25 °C, 2 h, 82%; (d) 2.0 equiv of Ph_3P, 10 equiv of H_2O, THF, 45 °C, 8 h, 80%; (e) 1.5 equiv of **7**, 3 equiv of EDC, 1.5 equiv of HOBt, DMF, 0 °C, 8 h, 45%; (f) 2.5 equiv of K_2CO_3, 2.5 equiv of CuBr•Me_2S, 3 equiv of pyridine, MeCN (0.01 M), 75 °C, 6 h, 54% (87% conversion) (DPPA = $(PhO)_2P(O)N_3$, EDC = 1-ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride, HOBt = *N*-hydroxybenzotriazole).

equiv) in degassed MeCN (0.01 M) at 75 °C for 3 h, led smoothly to the D-O-E ring system **9** in 54% yield (87% conversion).

The C-O-D vancomycin model system **15** was synthesized as shown in Scheme 3. (4-Aminophenyl)ethyl alcohol (**10**) was sequentially subjected to bromination, diazotization,[8] and reaction with pyrrolidine to furnish the triazene **11** (84% overall). Oxidation[12] of the primary alcohol of **11** with TEMPO and NaOCl gave the carboxylic acid **12** in 82% yield. Coupling of **12** with dipeptide **13**[13] with HBTU and Et_3N gave tripeptide **14** in 63% yield. The key cyclization reaction was then

Scheme 3. Synthesis of C-O-D Cyclic Aryl Ether **15**[a]



[a] Reagents and conditions: (a) 2.2 equiv of Br_2, AcOH, 25 °C, 0.5 h, 99%; (b) 1.3 equiv of $NaNO_2$, 5 equiv of 12 N HCl, THF−H_2O (10:1), 0 °C, 0.5 h; then 10 equiv of pyrrolidine, satd. aq. K_2CO_3, 1 h, 84%; (c) 1.5 equiv of TEMPO, 3 equiv of 5% aq. NaOCl, NaBr cat., Me_2CO, 0 °C, 2 h, 82%; (d) 1.5 equiv of HBTU, 2 equiv of 13, 1.5 equiv of NEt_3, DMF, 0 °C, 18 h, 63%; (e) 2.5 equiv of K_2CO_3, 2.5 equiv of CuBr•Me_2S, 3 equiv of pyridine, MeCN (0.01 M), 75 °C, 15 h, 77%; (f) Raney Ni, MeOH, Δ, 2 h, 71%; (g) (i) *t*-BuONO, BF_3•OEt_2, THF, −20 to −5 °C, 0.5 h; (ii) $Cu(NO_3)_2/Cu_2O$, H_2O, 25 °C, 3 h, 60% (TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl. HBTU = *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate).

performed by exposure of **14** to K_2CO_3 (2.5 equiv), CuBr•Me_2S (2.5 equiv), and pyridine (3.0 equiv) in degassed MeCH (0.01 M) at 75 °C for 15 h, furnishing cleanly, and without significant loss of stereochemical integrity,[14] the targeted C-O-D vancomycin ring model system **15** (77%).

Conversion of the synthesized triazenes to the corresponding phenols under acidic conditions (Dowex H^+ resin 50WX8-200, H_2O/MeCN, Δ, 10 min) was demonstrated with several acyclic aryl systems (e.g., **VI**, entry 7, Table 1, 92%).[6b] However, treatment of the cyclic triazene system **15** with the above conditions led to only traces of phenol **16**. After considerable experimentation it was found that reduction of **15** with Raney Ni cleanly furnished the amine **16** (71% yield), which in turn was converted to the phenol **17** upon diazotization and treatment with Cu(I)/Cu(II) (60% from **16**). The unusual behavior of triazene **15** is presumably due to the special conformational preferences of the monocyclic aryl ether, effects which may not necessarily be operating in the bicyclic system of vancomycin.

The described chemistry provides a new synthetic avenue to a wide variety of aryl ethers from readily available aniline derivatives. The method is mild enough to accommodate racemization-prone amino acids and to be successfully applied to the construction of vancomycin type model systems. Further studies in this field are in progress.[15]

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Supporting Information Available: Selected data for compounds **VI** and **VII** (entries 6−10 and 13, Table 1) and **4**−**17** (14 pages). See any current masthead page for ordering and Internet access instructions.

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(13) Peptide **13** was prepared by coupling (*S*)-tyrosine methyl ester with *N*-CBZ-(R)-phenylglycine using EDC and HOBt as coupling reagents in DMF, followed by deprotection of the *N*-terminal CBZ group by hydrogenolysis using $Pd(OH)_2$/C (10 mol %) in MeOH (91% overall yield).

(14) The phenylglycine epimer of **14** was prepared in an analogous manner and cyclized under identical conditions leading to the corresponding epimer of **15**. The reaction mixtures of both cyclizations showed, by ^1H NMR (500MHz), <5% epimerization of the phenylglycine residue.

(15) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.