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SYNTHESIS OF DIARYL ETHERS FROM TYROSINE DERIVATIVES

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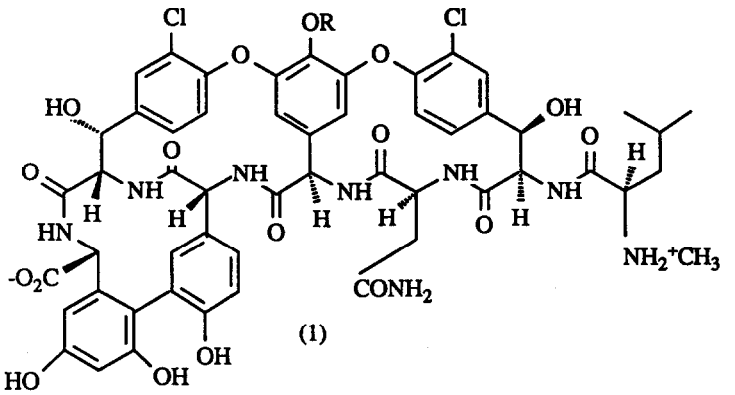
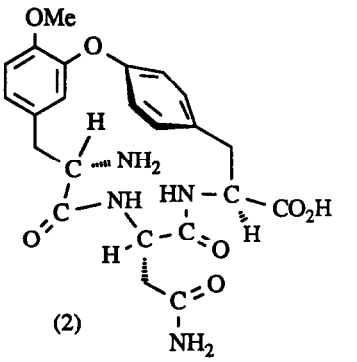
Abstract: Diaryl ethers of tyrosine, maintaining optical activity, have been formed through the reaction of a tyrosine derivative with an aryl iodonium salt.

Of late, there has been an increased interest in the glycopeptide class of antibiotics because of their activity against multiple resistant Staphylococcus aureus (MRSA)[1]. This interest has been reflected by a vastly expanded number of reports of new glycopeptides whose structures, while they vary markedly in substitution, all contain the polycyclic heptapeptide core of vancomycin (1)[2]. The phenolically linked amino acid residues, either as biphenyls or as diaryl ethers, constitute an unusual feature of the structure and presumably are involved in the maintenance of conformational ridigity. Recently, two other natural products, OF 4949 (2)[3], and K13[4], have been isolated which also contain tyrosine residues which are linked in a ring as a diaryl ether. We report here an approach to ethers related to these natural products.



(1)



(2)

The classical and most widely used synthesis of diphenyl ethers, the Ullmann reaction[5], requires forcing conditions not compatible with amino acids containing base- or heat-sensitive functionality. This problem led Hamilton[6] to adopt a method involving displacement, by phenolate (or phenoxide), of a tosylate from an activated dinitro-tyrosine derivative. Evans[7] has tackled the formation of the diethers of tyrosine by using the Ullmann reaction to yield diphenyl ethers prior to the construction of amino acid side chains. Recently, however, Boger and Yohannes[8] have developed conditions for the Ullmann condensation giving coupled products without amino acid racemisation. In a related approach Pearson[9] chose to use an aryl manganese complex to facilitate activation, while Still[10] has prepared similar thioethers by a photochemical $S_{RN}1$ reaction.

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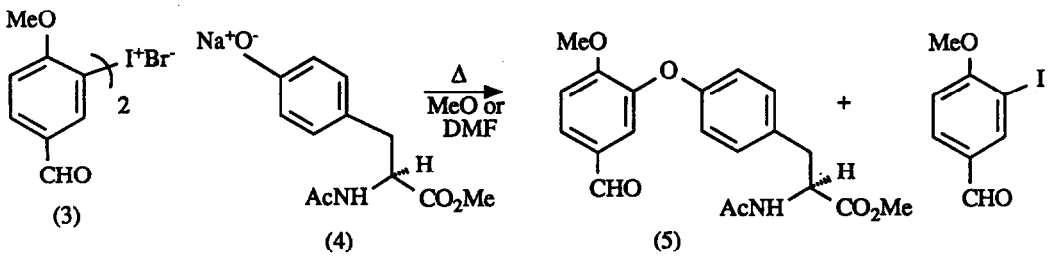
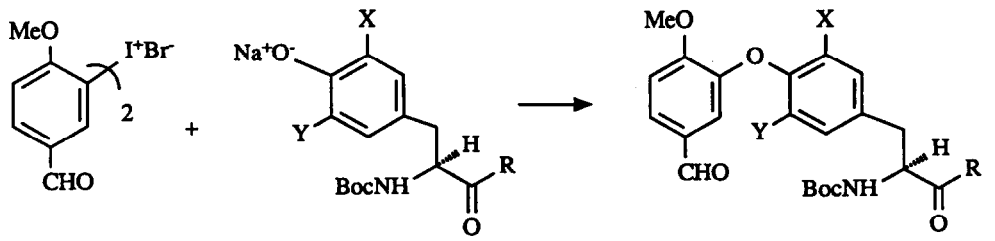
We were interested to find a few reports of aryl iodonium salts undergoing displacement reactions with phenols and, in particular, tyrosine derivatives were treated with aryl iodonium salts to give thyroxines without loss of stereochemical integrity.[11]

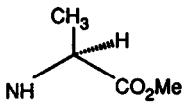
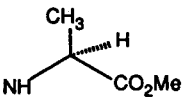
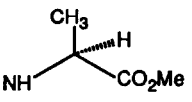
While the use of iodonium salts was indicated for the coupling, the methods for their preparation, electrophilic aromatic substitution under highly acidic conditions, restricted the choice of substituents. Indeed, the examples in the literature were monosubstituted with simple alkyl- and halo-aromatics predominating. We finally chose the iodonium salt (3) which contained the aldehyde as an easily and selectively manipulable group. The iodonium salt (3) was prepared by treating anisaldehyde with iodosyl sulphate.[12] The sodium phenolate of the tyrosine derivative (4) was heated with the salt (3) in methanol at reflux overnight to produce a disappointingly low yield (8%) of the ether (5). Changing the solvent to a more polar medium (DMF) to favour ionic reaction pathways, as well as increasing the reaction temperature (90-95°C), led to a much improved yield (59%).



(mp 135-6°)
($[\alpha]_D^{20} = 22.4$, c = 1 MeOH)

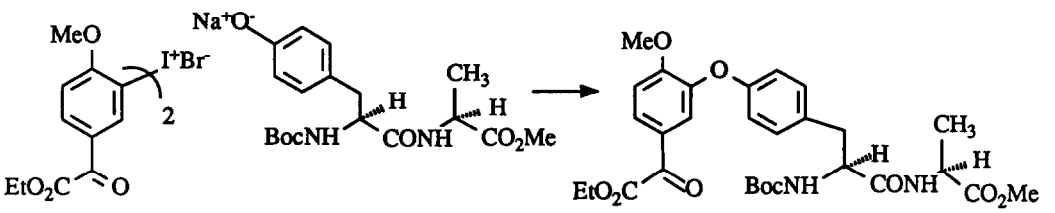
Pleasingly, extension of this methodology to derivatives containing the more easily removed t-butoxycarbonyl group gave no problems and the products were available in moderate to good yield (see table). In almost all cases, the starting tyrosine was not completely consumed and 10-30% was recovered, presumably due to side reactions of the iodonium salts. This situation was not improved by increasing reaction times or temperatures, nor increasing the excess of iodonium salt. Use of halogenated tyrosines (entries 3, 4 and 5) improved the yield of ether product, presumably due to an increased nucleophilicity of the phenolic moiety.



Entry[a]	X	Y	R	%[b]	(mp, a)[c]
1	H	H	OMe	51	(95-6, 43.2°)
2[d]	H	H	OMe	42	(99-100, -43.7°)
3	Cl	H	OMe	67	(gum, e)
4	Br	Br	OMe	70	(gum, -3.2°)
5	Cl	H		66	(120-21, -3.6°)
6	H	H		55	(132-5, -6.6°)
7[d]	H	H		31	(136-7, -10.2)

a) L-isomer unless otherwise stated; b) isolated yields; c) $[\alpha]_D^{20}$ at 1% concentration in methanol; entries 1 and 2 carried out in $CHCl_3$ since their rotation in methanol was <1°; d) D-tyrosine residue; e) $[\alpha]_D^{20}$ not determined.

Our attention then turned to the problem of optical purity. Reaction of an enantiomeric pair of derivatives (entries 1 and 2) gave products of equal but opposite optical rotation. This, taken with the fact that recovered starting materials have unchanged rotations, implies that no racemisation occurred during the reaction. In the cases where a dipeptide was studied (entries 5, 6 and 7) only a single diastereomer was produced as judged by NMR. The related iodonium salt [13] (6), when treated with the dipeptide (7), gave the ether (8) which now bears an extra carboxylate.



(6) (7) (8) 30% yield

The use of these ethers as precursors for cyclic analogues related to the binding pocket of vancomycin is described separately.

Acknowledgements: We thank Dr. P. Edwards for helpful discussions during the course of this work.

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Compound (3); mp 204-5° (HCO_2H), $\delta_H((CD_3)_2SO)$, 4.00 (3H, s, MeO), 7.41 (1H, d, J = 8.6Hz, H-3), 8.11 (1H, dd, J = 8.6, 1.9Hz, H-4), 8.71 (1H, d, J = 1.9Hz, H-6) and 9.92 (1H, s, CHO).

13. Compound (6); mp 148-9° (EtOH), δ_H ($(CD_3)_2SO$), 1.30 (3H, t, J = 7Hz, $CO_2CH_2\underline{CH_3}$), 3.98 (3H, s, MeO), 4.40 (2H, q, J = 7Hz, $CO_2\underline{CH_2}CH_3$), 7.37 (1H, d, J = 8.5Hz, H-3), 8.17 (1H, dd, J = 8.5, 2Hz, H-4) and 8.73 (1H, d, J = 2Hz, H-6).

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