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A New Route to Isodityrosine-derived Cyclic Peptides:Application to K-13

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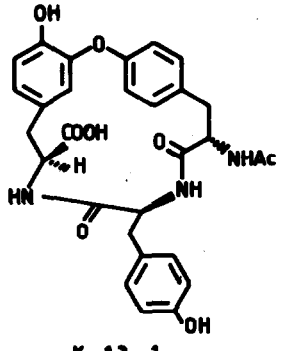
Abstract: A versatile approach suitable for isodityrosine derived cyclic peptides, and its application to K-13 have been described.

The family of cyclic peptides containing oxidatively coupled aromatic nuclei ranging from tyrosine derived peptides such as K-13[1], OF-4949[2] to the structurally complex glycopeptides antibiotics representing vancomycin and ristocetin have emerged[3] as worthy targets because of their impressive biological profiles. For example K-13 (1) is known to be an inhibitor of angiotensin converting enzyme[4a] while OF-4949 I-IV (2) are inhibitors of aminopeptidase



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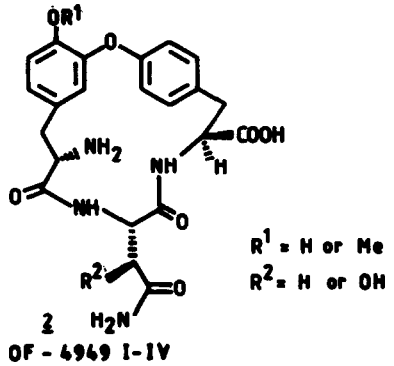

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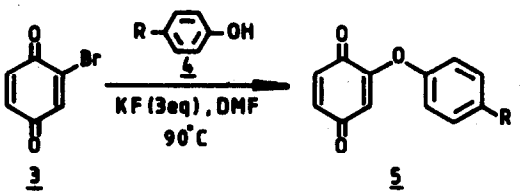
B[4]. The syntheses of these molecules primarily involve building of isodityrosine derived units and the strategy reported by various groups focuses mainly on the Ullmann ether synthesis[5] or thallium (III) nitrate promoted oxidative coupling[6]. Syntheses of isodityrosine directly by coupling tyrosine derivatives has been illustrated but in very low yields[5c]. Other approaches[7a] using this reaction but employing structurally simple p-bromobenzaldehyde[5c] or p-iodobenzoic acid[5d] improved the yield of the coupled product which in turn was elaborated to the amino acid side chain. Evans group[5c] employed oxidative coupled cinnamic acid to fabricate the isodityrosine skeleton of K-13 and OF-4949. In these laboratories, the synthesis of K-13 was earlier reported in which the advantage of having an electron withdrawing nitro substituent was used to prepare biphenyl ether linkage[7b]. The TTN oxidative phenolic coupling formed the basic premise in the synthesis of a variety of isodityrosine derived cyclic peptides reported by Yamamura et al[6] with moderate yields.

We have developed a conceptually different process as a tactical devise to form diphenyl ether linkages suitable for the synthesis of isodityrosine derived peptides. The fundamental approach features displacement of the bromine atom of 2-bromobenzoquinone[8] with phenolic derivatives (4) providing aryloxybenzoquinone (5) in good yields followed by manipulation of



5a R = CH_3 (85%)

5b R = H (79%)

5c R = CHO (78%)

5d R = (S)-CH_2-CH(NHBoc)COOMe (81%)

5e R = (S)-CH_2-CH(NHBoc)COOBn (80%)

benzoquinone skeleton to the corresponding aryl amino acid for which we relied on the Pd catalyzed cross coupling reaction[9] of aryl triflate with allyl tributyltin and the Sharpless asymmetric dihydroxylation reaction[10].

In our preliminary investigations 2-bromobenzoquinone (**3**) was coupled with p-cresol in the presence of KF (3.0 equi.) (DMF, 90°, 3h) to afford the 2-aryloxybenzoquinone derivative (**5a**) in 85% yield. We observed that K_2CO_3 instead of KF could also be used in the coupling reaction with marginal yield improvement. We further demonstrated that benzyl N-Boc-L-tyrosinate containing chiral amino acid side chain and labile functional group distribution could also be used as a suitable coupling partner in the above reaction (KF, DMF, 90°) giving **5d-e** in 80% yield. The efficacy of this reaction was substantiated with a number of displacement reactions carried out with a variety of phenoxides. It should be pointed out that the conditions for this displacement were mild and the chiral amino acids groups were tolerated in the phenoxide without any degree of racemisation[11].

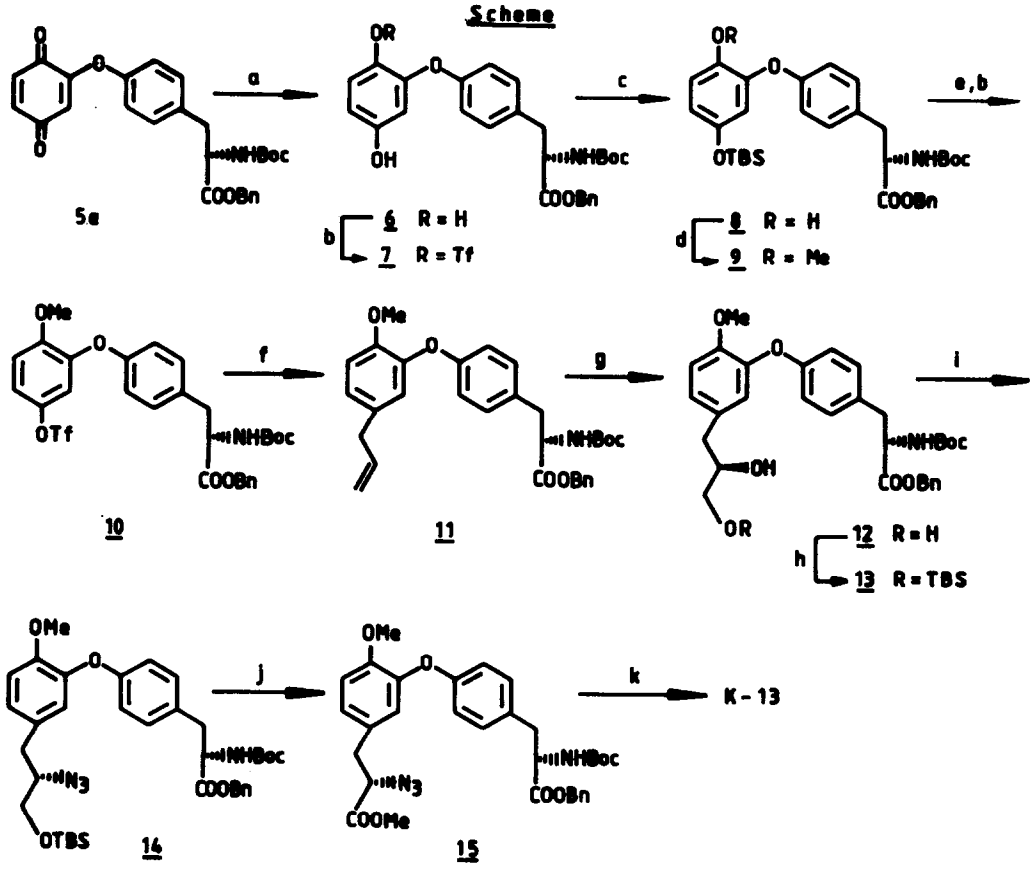
Inspired by the success of this reaction, we then directed our efforts towards the synthesis of K-13. Compound **5e** was chosen as the starting point for this exploration. Subsequent reduction of **5e** with dithionite ($Na_2S_2O_4$, H_2O, $CHCl_3$, RT, 1h) provided the hydroquinone (**6**) in almost quantitative yield. Its direct trifluoromethanesulfonylation [Py., $(CF_3SO_2)_2O$, DCM, RT, 2h] afforded the 1-O-triflate derivative **7** which indicated the higher reactivity of 1-hydroxyl group probably due to hydrogen bonding (as steric factors suggest that the 4-hydroxyl group should be the preferred site of reaction). Therefore to obtain the 4-O-triflate derivative, we first reacted hydroquinone (**6**) with TBS-Cl (Et_3N, DCM, 0°, 5h) and then methylated with DMS/K_2CO_3 in acetone (Δ, 2h) to generate **9** in 70% overall yield. Successive desilylation (Bu_4NF, THF, RT, 1h) and trifluoromethanesulfonylation of **9** then gave the requisite 4-O-triflate derivative **10.**

Our next concern was to refunctionalise the benzoquinone skeleton into the corresponding aryl alanine derivative in optically pure form. Reaction of **10** with allyl tributyltin in the presence of LiCl (3.0 equi.) and $Pd(PPh_3)_4$ (0.02 equi.) in refluxing dioxane[9] (12h) gave the allyl derivative **11.** This C-C bond cross coupling reaction was found to be highly selective providing **11** in 80% yield; that the functional groups present in the tyrosine segment remained unaffected was particularly grtifying. Subsequent Sharpless asymmetric dihydroxylation reaction[10] of **11** with dihydroquinidine-p-chlorobenzoate as a chiral ligand (OsO_4, K_3FeCN_6, 1:1 H_2O-t.BuOH, RT, 24h) gave the diol **12** which was first silylated (TBS-Cl, Imid., DMAP, DCM,

RT, 3h) at the primary hydroxyl group and then by Mosher ester method, the diastereomeric excess of 62% was determined by using the ^{19}F-NMR spectroscopy[12].

Finally **13** was transformed (MsCl, Et_3N; NaN_3, DMF, 90°, 4h) into the azido derivative **14** via the mesylate. Jones oxidation (Jones reagent, CH_3COCH_3, RT, 2h) and consequent esterification (CH_2N_2, EtOEt), provided the key intermediate **15** (60% overall yield) whose spectroscopic analysis was found comparable with the reported data[13]. This key intermediate was earlier converted into K-13 by the Evans group[5c].

Scheme



a) Saturated aq. sodium dithionite, $CHCl_3$, 1h, 100%; b) 1.0 eq. Tf_2O, pyridine, CH_2Cl_2, 2h, 60%; c) 1.0 eq. TBDMS-Cl, TEA, CH_2Cl_2, 0°, 5h, 80%; d) 1.1 eq. $(CH_3)_2SO_4$, 3 eq. K_2CO_3, acetone refluxed, 2h, 87%; e) 1.6 eq., $Bu_4N^+F^-$, THF, RT, 1h, 97%; f) 1.03 eq. allyltributyltin, 0.02 eq. Pd(O), 3 eq. LiCl, refluxing dioxane, 12h, 80%; g) 0.5 eq. DHQDPCB, 3 eq. K_2CO_3, 3 eq. $K_3Fe(CN)_6$, 0.0125 eq. OsO_4, t-Butanol/H_2O (1:1 v/v), RT, 24 h, 94%; h) 1.1 eq. TBS-Cl, 2 eq. imid. Cat. DMAP, CH_2Cl_2, RT, 3h, 70%; i) 1.5 eq. MsCl, TEA, CH_2Cl_2, RT, 2h, 91%; ii) 3 eq. NaN_3, DMF, 90°C, 4h, 90%; j) i) Jones reagent, acetone, 2 h; ii) excess of CH_2N_2, ether, 73%; k) Ref. 5c.

In the preceeding lines we have demonstrated a simple approach to construct K-13 which in fact could be expanded to the entire gamut of natural products belonging to this class of antibiotics such as OF-4949, piperazinomycin, bouvardin, deoxybouradin etc. Efforts to improve the d.e. of the diol (**12**) by using recently developed cincona alkaloid derivatives are being pursued in these laboratories.

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13. Although compound **15** was a diastereomeric mixture (4:1), its ^{1}H NMR spectrum did not resolve: ^{1}H NMR data ($CDCl_3$, 200 MHz):δ 1.41 (s, 9H), 2.91 (dd, 1H, J = 8.4, 13.7 Hz), 2.96-3.11 (m, 3H), 3.73, 3.81 (2s, 6H), 4.01 (dd, 1H, J = 5.4, 8.4 Hz), 4.58 (m, 1H), 4.96 (d, 1H, J = 8.2 Hz), 5.10, 5.17 (ABq, 2H, J = 12.4 Hz), 6.75-6.85 (m, 3H), 6.9-7.05 (m, 4H), 7.2-7.4 (m, 5H).

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