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An Unusually Facile SNAr 14-Membered Biaryl Ether Macrocyclization Reaction Suitable for Preparation of the Cycloisodityrosine Subunit of Bouvardin, Deoxybouvardin and Related Agents

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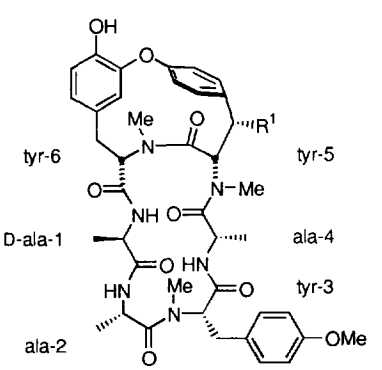
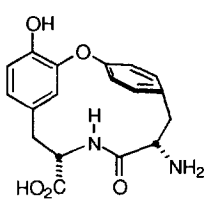
Abstract. A facile synthesis of the core cycloisodityrosine 14-membered ring system is detailed based on a key intramolecular SNAr biaryl ether ring closure.

Bouvardin (**1**) and deoxybouvardin (**2**), bicyclic hexapeptides isolated from *Bouvardia ternifolia*,[1] constitute the initial members of a growing class of potent antitumor antibiotics now including RA-I - RA-XIV.[2,3] The agents have been shown to inhibit protein synthesis through eukaryotic 80S ribosomal binding with inhibition of both amino acyl *t*-RNA binding and peptidyl *t*-RNA translocation and this is presently thought to be the site of action for their productive antitumor activity.[4]





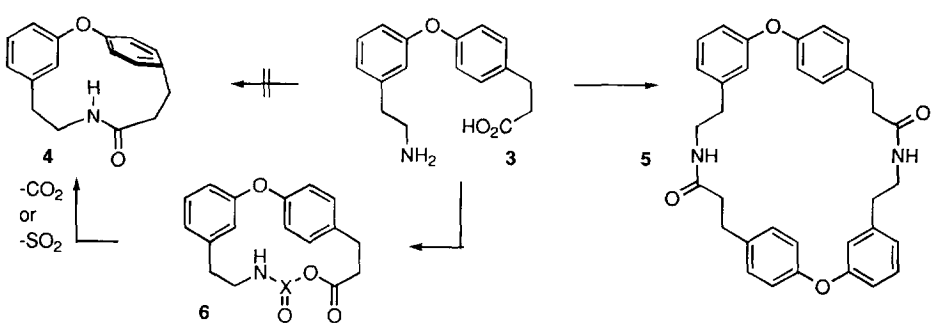
cycloisodityrosine

1 R^1 = OH, bouvardin
2 R^1 = H, deoxybouvardin

In contrast to initial expectations,[1,2] the 14-membered cycloisodityrosine-derived subunit has been shown to constitute the agents pharmacophore[5] and its incorporation into the bicyclic natural products results in its adoption of a conformation possessing an inherently disfavored cis amide central to its structure. Until recently, efforts to examine the role of the cycloisodityrosine subunit and related agents have been hampered by their synthetic inaccessibility. Conventional macrolactamization techniques including transannular lactamizations,[6] Ullmann macrocyclizations with C^3-O^2 bond closure,[6,7] and intramolecular oxidative phenol couplings[8] have failed to provide the 14-membered ring biaryl ethers although Yamamura's 2-step modifications in the latter approach has provided the core 14-membered ring systems in low conversions.[9,10] In recent efforts, we disclosed the unusually successful implementation of a general C^1-O^2 Ullmann macrocyclization reaction for the preparation of such 14-membered biaryl ethers (45-60%)[11] and have reported the

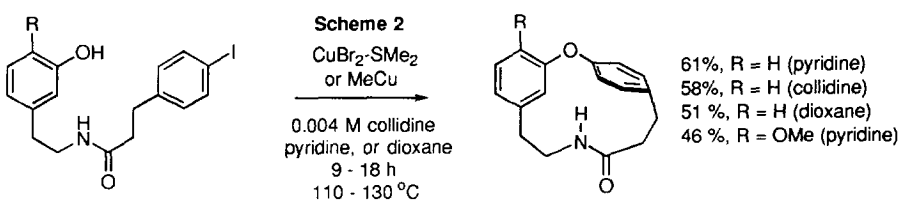
successful application of the methodology in the total syntheses of deoxybouvardin and RA-VII,[6,12] piperazinomycin,[13] bouvardin,[14] combretastatin D_2[15] and its surprisingly successful extrapolation to the core 16-membered ring systems found in vancomycin ($\leq$ 55%).[16] Subsequent to these studies, Beugelman, Zhu and coworkers have expanded the scope of such cyclization strategies through use of the intramolecular SNAr reaction of *o*-fluoronitroaromatics. First applied in the intermolecular preparation of biaryl ethers,[17,18] the studies have since been expanded to include examples of intramolecular cyclizations for the formation of 17-membered and 16-membered biaryl ethers[19,20] modeled on our Ullmann cyclization strategy.[5,6,11-16] The recent report of its use in a model intramolecular cyclization for the 14-membered F-O-G biaryl ring system of teicoplanin[21] has provided the incentive for us to disclose our related studies on the preparation of the cycloisodityrosine-derived 14-membered biaryl ether ring system. Unlike the cycloisodityrosine 14-membered biaryl ring system which has not been successfully closed by macrolactamization procedures, the teicoplanin 14-membered biaryl ring system examined by Beugelman and Zhu has been successfully closed by conventional macrolactamization procedures.[22] Consequently, the examination of the former may be viewed as being a unique vehicle in which to assess the viability of the intramolecular SNAr cyclization for the preparation of such refractory biaryl ethers.

Scheme 1



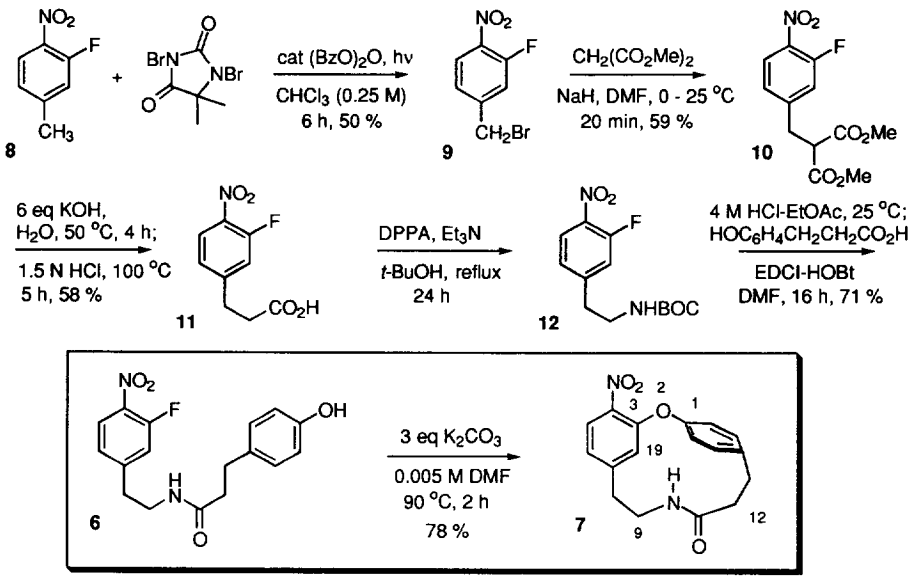
Representative of such efforts, repeated past efforts to close **3** employing a range of macrolactamization procedures including the use of DPPA,[23] EDCI-HOBt,[24] DCC, and the activated pentafluorophenyl ester[25] failed to provide **4** and provided **5** as the sole cyclization product, Scheme 1.[6] The use of polymer-supported activating agents (polystyrene-PrCl[26] and -SO_2Cl),[27] carbonyldimidazole[28] or dipyridyl sulfite[29] did not alter the course of the reaction. The latter macrocyclizations which could proceed by initial 16-membered ring formation and subsequent collapse of an intermediate anhydride **6** to the 14-membered ring (-CO_2, -SO_2) provided convincing evidence that direct macrolactamization may not be readily successful.

Scheme 2



In contrast, the intramolecular Ullmann reaction with C^1-O^2 bond closure proved viable for direct formation of the appropriately functionalized 14-membered biaryl ethers (Scheme 2). Routine conversions of 45-60% were realized under moderately dilute reaction conditions (0.004 M) including the reactions of substrates bearing an alkoxy group ortho to the participating phenol.

Scheme 3



For direct comparison, The substrate **6** was chosen for examination of the SNAr closure. Notably, although its closure product 7 bears the appropriate aromatic substitution for conversion to the functionalization found in the cycloisodityrosine biaryl ether ($NO_2 \rightarrow OR$), it is derived from a ring closure (C^3-O^2 bond formation) with the reversed orientation than that employed for the Ullmann reaction (O^2-C^1 bond formation). Without optimization, the substrate **6** was prepared in six steps from **8** as detailed in Scheme 3. Although no reaction was observed at 25 °C, treatment of **6** with K_2CO_3 (3 equiv) in anhydrous DMF under moderately dilute reaction conditions (0.005 M) at 90 °C for 2 h cleanly provided 7[30] in superb conversions (78%). Diagnostic of the successful closure to the 14-membered ring, the product 7 exhibited a characteristic, strongly shielded C19-H at δ 5.36 (s, $CDCl_3$). Thus, the SNAr modification of the classical Ullmann biaryl ether coupling strategy for macrocyclization of the cycloisodityrosine 14-membered biaryl ether ring system proceeds exceptionally well under comparatively mild conditions. Extensions of these studies to the improved preparation of the naturally-derived cycloisodityrosine subunits of **1-2** and related agents and their extension to our efforts on vancomycin[16] are in progress and will be reported in due course.

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30. For 4-nitro-11-oxo-2-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (7): yellow solid; mp 207-209 °C (EtOH-hexane); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.88 (d, 1H, J = 8.4 Hz, C5-H), 7.33 (d, 2H, J = 8.5 Hz, C15-H and C18-H), 7.07 (d, 2H, J = 8.5 Hz, C16-H and C17-H), 6.72 (d, 1H, J = 8.4 Hz, C6-H), 5.36 (s, 1H, C19-H), 4.84 (bs, 1H, NH), 3.33 (dt, 2H, J = 4.4, 7.5 Hz, CH_2NH), 3.07 (t, 2H, J = 6.3 Hz, CH_2Ar), 2.76 (t, 2H, J = 5.4 Hz, CH_2Ar), 2.32 (t, 2H, J = 6.3 Hz, CH_2CO); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 171.7, 156.7, 155.4, 147.1, 139.4, 131.2, 125.5, 124.0, 121.2, 116.5, 115.4, 41.0, 39.0, 31.9, 31.3; IR (neat) ν_{max} 3391, 3268, 2930, 1639, 1588, 1516, 1347, 1223 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 313.1175 (M^+ + H, $C_{17}H_{16}N_2O_4$ requires 313.1188).

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