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Synthetic Studies on Et-743. Asymmetric, Stereocontrolled Construction of the Tetrahydroisoquinoline Core via Radical Cyclization on a Glyoxalimine

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ABSTRACT





Members of the tetrahydroisoquinoline family of alkaloids display a wide range of biological properties such as antitumor and antimicrobial activities.¹ Of particular significance within this family is Ecteinascidin 743 (Et-743, **1**, Figure 1), which possesses extremely potent cytotoxic activity with in vitro IC₅₀ values in the 0.1 \sim 1 ng/mL range in several cell lines (measure of RNA, DNA, and protein synthesis inhibition). Et-743 is currently in stage II/III clinical trials for the treatment of ovarian, endometrial, and breast cancers, and several sarcoma lines.² The scarcity of the natural product



Figure 1. Ecteinascidin 743, 1.

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from marine sources renders Et-743 an important target for synthesis. Corey reported the first total synthesis in 36 steps with an overall yield of 0.72%.^{3a} A second-generation synthesis improved the overall yield to 2.04% but still in 36 steps.^{3b} Fukuyama has achieved a total synthesis of Et-743 in 50 steps and 0.56% overall yield.^{3c} Recently, Zhu has reported a 31-step synthesis in 1.7% overall yield.^{3d} Danishefsky has also reported a formal total synthesis^{3e} via a pentacyclic core of Et-743 that intercepts a late stage of Fukuyama's route. A semisynthesis from cyanosafracin B has also been accomplished by a group at PharmaMar.^{3f}

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Our laboratory has been developing the assembly of tetrahydroisoquinoline natural products and has reported syntheses of quinocarcinamide,⁴ tetrazomine,⁵ renieramycin G, and jorumycin.⁶ We have targeted Et-743 by a convergent route that envisions coupling of a suitably functionalized tyrosine derivative with the complete tetrahydroisoquinoline core (Scheme 1). We have successfully deployed this strategy,



with the present objective of construction of pentacycle 2, in the synthesis of (-)-renieramycin G and (-)-jorumycin.⁶

The synthesis of a tetrahydroisoquinoline such as 3 can be problematic because of the acid sensitivity of the benzylic hydroxyl, particularly because it is ortho to the phenolic hydroxyl of the aromatic ring and thus has a high propensity for ortho-quinone methide formation. The Pictet-Spengler reaction has been widely used in the construction of tetrahydroisoquinolines,⁷ but the typically highly acidic conditions are not compatible with the substrate and products desired in this synthesis. Recognizing this issue, Zhu has developed very mild conditions for the Pictet-Spengler closure of a cis-acetonide species that provided a 1,3-trans-tetrahydroisoquinoline analogous to 3 that subsequently required epimerization at C1.8 We targeted a trans-acetonide that was predicated on obviating a late-stage E2 elimination of this stereogenic center that might also allow for a facile construction of the C-S bond constituting the macrocyclic core.

The failure to induce any trace of ring closure by the Pictet–Spengler reaction for a *trans*-acetonide containing

substrate suggested that there are severe steric and/or electronic factors in these glyoxalimine substrates. Rather than constructing a substrate dependent upon π -nucleophilicity, we decided to investigate an intramolecular radical closure onto a glyoxalimine.

The literature provides precedent for tetrahydroisoquinoline formation by radical reaction of imines,^{9,10} but it has not been extensively utilized in natural product synthesis.¹¹ Typical problems associated with radical reactions were anticipated such as the formation of undesired 5-*exo* cyclization products and simple hydrogen atom quenching of the aryl radical. The kinetics of these processes for aldimine substrates have been studied by Warkentin.¹² These studies concluded that the 6-*endo* product was favored when concentrations of Bu₃SnH were low, so slow dropwise addition of AIBN/Bu₃SnH to a dilute solution of the substrate was found to be optimal. The yields of tetrahydroisoquinoline formation ranged from 50 to 78% for a variety of aldimine substrates.

More recently, Johnston has developed a radical method of aryl amination using aryl halides via 5-*exo* cyclization onto ketimines.¹³ This work contrasted the reactivity of aldimines and ketimines, but of particular importance to our studies toward Et-743 is their report of an attempted cyclization of a glyoxalimine substrate.^{13b} They observed tetrahydroisoquinoline as the major product in 55% yield arising from an undesired (in their case) 6-*endo* cyclization. Although this reaction was not further explored, we considered a radical ring closure on a glyoxalimine to have potential as a powerful tool for the preparation of highly functionalized tetrahydroisoquinolines such as **3**.

Substrate synthesis began with Borchardt's catechol 4^{14} that was regioselectively brominated to generate 5 (92% yield) (Scheme 2). Conversion of catechol 5 to the methyl-



enedioxy aldehyde **6** was accomplished using bromochloromethane in a sealed vessel (69% yield). Baeyer–Villiger oxidation using *m*CPBA provided bromophenol **7** as an offwhite solid following hydrolysis of the resulting formate intermediate (73% yield).

Stereoselective aldol condensation of the titanium phenolate of 7 with (R)-Garner's aldehyde¹⁵ was accomplished

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using the method of Casiraghi¹⁶ (Scheme 3). The *anti* product was isolated following allyl protection of the phenol to provide **9** as an off-while solid (65% yield, two steps). Subsequent hydrolysis of the oxazolidine and formation of the *trans*-acetonide (84% yield, two steps) provided **10** as an oil that cleanly underwent *N*-Boc deprotection using Ohfune's protocol¹⁷ (76% yield) to afford the desired free amine **11** as a stable crystalline solid. This procedure to prepare **11** has been performed on a multigram scale.

With **11** in hand, the glyoxalimine intermediate was readily obtained by condensation with ethyl glyoxalate. Following isolation by filtration through Celite and concentration, the radical ring closure commenced with slow addition of Bu_3 -SnH and AIBN via syringe pump (over 5.5 h) to a refluxing dilute solution of the glyoxalimine. Concentration and KF/ silica chromatography¹⁸ of the crude reaction mixture

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provided solid **3** as a single diastereomer (58% yield, two steps).¹⁹ The relative stereochemistry of **3** was secured and corroborated NMR data by X-ray crystallography.²⁰

Examination of the crude ¹H NMR reveals the formation of a single diastereomer in the radical closure and exclusive 6-*endo* regioselectivity. In addition to **3** and tin impurities visible in the NMR, an aromatic proton arising from hydride quenching of the aryl radical suggests a \sim 6.6:1 ratio of **3** to reduced substrate. Slower addition rates (over 18 or 36 h) did not improve the isolated yield of **3**.

The diastereoselectivity of this reaction stands in stark contrast to numerous Pictet–Spengler cyclizations on related substrates^{6,8,21} that provide tetrahydroisoquinolines exclusively as the 1,3-*trans*-diastereomers. We can rationalize the *cis* diastereoselectivity of this radical process using the Beckwith–Houk chairlike transition state model for intramolecular radical ring closures (Figure 2).²²



Figure 2. Chairlike transition state of the aryl radical.

The lowest-energy chair conformation adopted by the *trans*-acetonide of the substrate results in both the glyoxalimine and aryl substituent being in an equatorial disposition. In this conformation, 1,3-diaxial steric effects and allylic strain interactions are minimized in the forming ring.

In summary, the concise asymmetric synthesis of the tetrahydroisoquinoline core of Et-743 has been accomplished utilizing a highly diastereoselective *6-endo* radical cyclization on a glyoxalimine. Efforts are underway to apply this approach to other imine systems and to appy the application of this technology to a practical total synthesis of Et-743 and congeners.

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Supporting Information Available: Complete experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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