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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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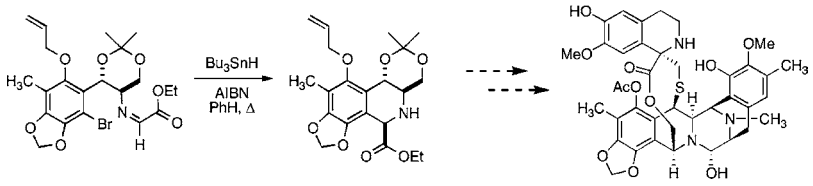
ABSTRACT



The asymmetric synthesis of a highly functionalized tetrahydroisoquinoline relevant to the total synthesis of Et-743 is described. The key step involves a highly diastereoselective radical cyclization on a glyoxalimine derivative.

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 IC_{50} values in the 0.1 ∼ 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 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]

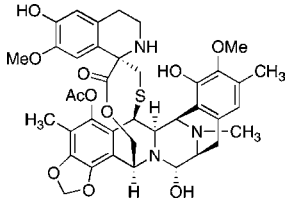


Figure 1. Ecteinascidin 743, **1**.

(1) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669−1730.
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(3) (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202−9203. (b) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993−996. (c) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552−6554. (d) Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2005**, *128*, 87−89. (e) Zheng, S.; Chan, C.; Furuuchi, T.; Wright, B. J. D.; Zhou, B.; Guo, J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1754−1759. (f) Cuevas, C.; Pérez, M.; Martín, M. J.; Chicharro, J. L.; Fernández-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de la Calle, F.; García, J.; Polanco, C.; Rodríguez, I.; Manzanares, I. *Org. Lett.* **2000**, *2*, 2545−2548.

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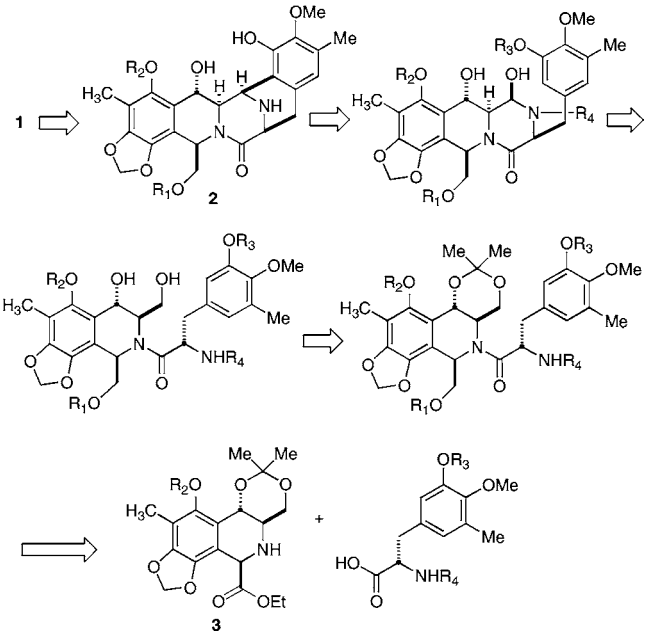
Our laboratory has been developing the assembly of tetrahydroisoquinoline natural products and has reported syntheses of quinocarcinamide,[4] tetrazomine,[5] renieramycin G, and jorumycin.[6] We have targeted Et-743 by a convergent route that envisions coupling of a suitably functionalized tyrosine derivative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

Scheme 1. Retrosynthetic Analysis of Ecteinascidin 743



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.

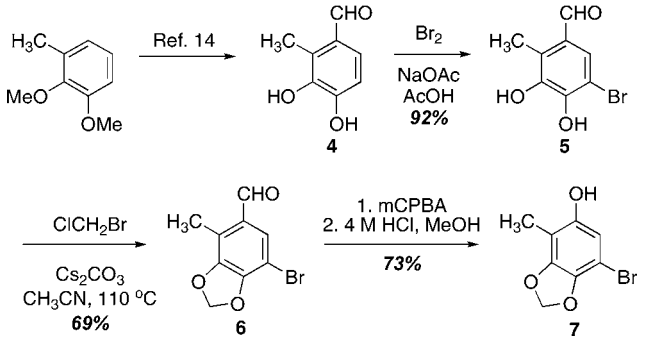
The failure to induce any trace of ring closure by the Pictet−Spengler reaction for a *trans*-acetonide containing substrate suggested that there are severe steric and/or electronic factors in these glyoxalimine substrates. Rather than constructing a substrate dependent upon π-nucleophilicity, we decided 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 Bu_3SnH were low, so slow dropwise addition of AIBN/Bu_3SnH 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-

Scheme 2. Synthesis of 3-Bromophenol **7**



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

Stereoselective aldol condensation of the titanium phenolate of **7** with (*R*)-Garner's aldehyde[15] was accomplished

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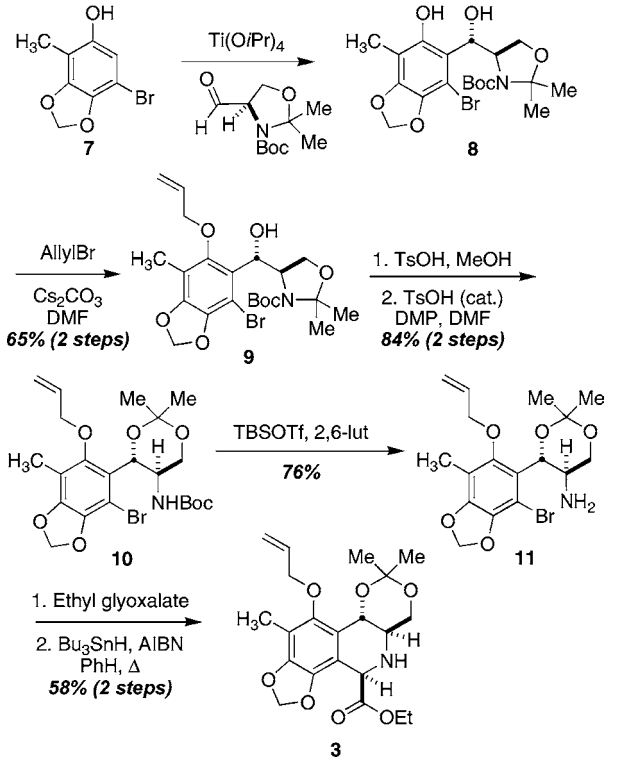
(8) (a) De Paolis, M.; Chiaroni, A.; Zhu, J. *Chem. Commun.* **2003**, 2896−2897. (b) Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397−4408.

(9) Tomaszewski, M. J.; Warkentin, J.; Werstiuk, N. H. *Aust. J. Chem.* **1995**, *48*, 291−321.

Scheme 3. Substrate Assembly and 6-Endo Radical Closure



using the method of Casiraghi[16] (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 protocol[17] (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 chromatography[18] of the crude reaction mixture 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 ^{1}H 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 ~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]

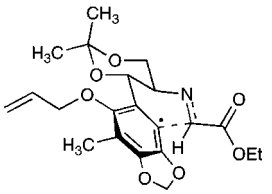


Figure 2. Chairlike transition state of the aryl radical.

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.

Acknowledgment. We gratefully acknowledge financial support from the National Institutes of Health (Grant CA85419). This paper is dedicated to Prof. Yoshito Kishi on the occasion of his 70th birthday.

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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(17) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870−876.

(18) Effective removal of tin impurities from Bu_3SnH-mediated reactions: Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004**, 1968−1969.

(19) Working with 2.5 mmol of **11**. The reaction has been performed on 0.125−2.5 mmol (50 mg−1 g) of **11** and consistently provides **3** with isolated yields of 58−61%.

(20) Details of the X-ray crystal structure determination are to be published elsewhere.

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