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Synthetic Studies on Ecteinascidin-743: Constructing a Versatile Pentacyclic Intermediate for the Synthesis of Ecteinascidins and Saframycins

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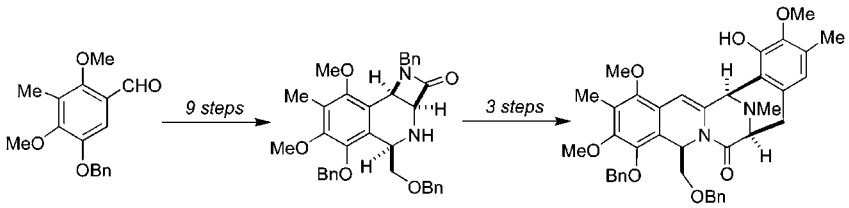
ABSTRACT



The asymmetric synthesis of a highly functionalized pentacyclic tetrahydroisoquinoline relevant to the ecteinascidin, saframycin, safracin, and renieramycin family of antitumor alkaloids is described.

Ecteinascidin (ET)-743 (**1**) is a natural product isolated from the marine tunicate *Ecteinascidia turbinata*,[1] which has been demonstrated to be a highly promising, exceedingly potent antitumor agent currently in phase II/III clinical trials.[2] The novel structure of ET-743 combined with the meager availability from natural sources and the unique mechanism of action of this drug[3] have made this substance a very attractive and important synthetic target.

The first total synthesis of ET-743 was accomplished by Corey and co-workers.[4] Later, Corey, Schreiber, and co-workers prepared a simpler synthetic analogue of ET-743 (phthalascidin, Pt-650) that exhibited virtually the same cytotoxity as the natural product.[5] In 2000, a semisynthesis of Et-743 from cyanosfracin B was described,[6] and more recently, a total synthesis of ET-743 was accomplished by Fukuyama and co-workers.[7]

In addition to Et-743, the structurally related safracins,[8] saframycins,[9] and renieramycins[10] are also potent antitumor antibiotics that contain densely functionalized tetrahydroiso-

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quinoline ring systems constituted from similar amino acid components. As part of a program directed toward efficient, asymmetric total syntheses of these substances and mechanistically inspired analogues for biochemical and biological evaluation,[11] we report here a potentially general and concise

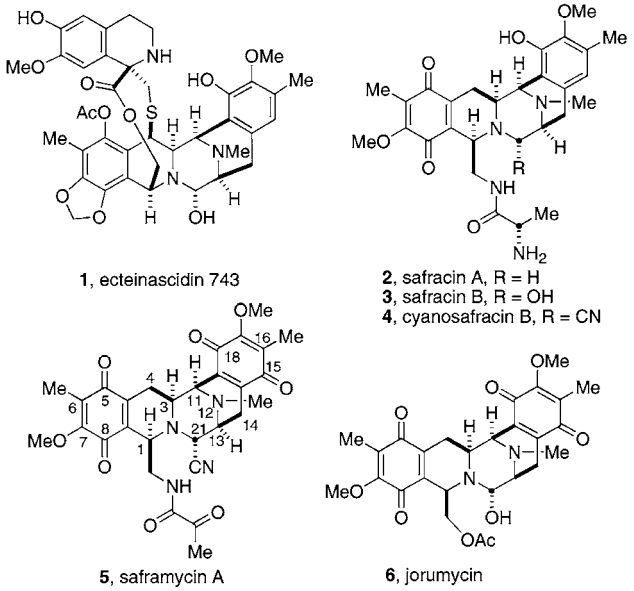
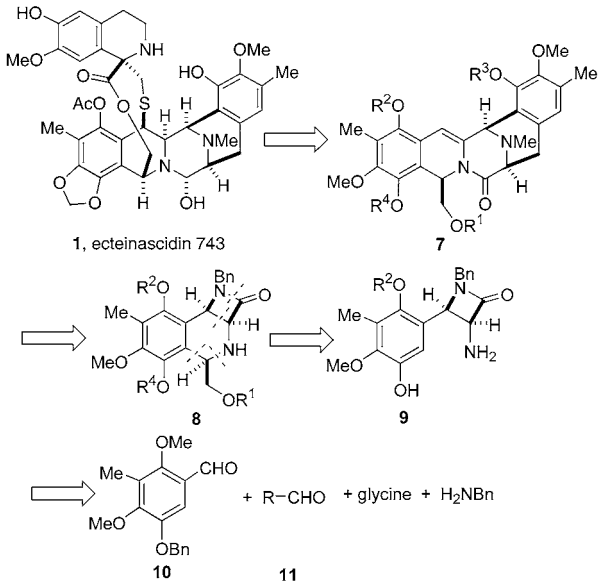


Figure 1. Structures of Et-743, safracins, saframycin A, and jorumycin.

method to construct densely functionalized pentacyclic tetrahydroisoquinoline ring systems that represent the "western" sector of Et-743 that should prove useful for the asymmetric total synthesis of several members of this family of natural products and congeners. Our approach is based on the use of sequential asymmetric Staudinger and Pictet–Spengler cyclization reactions.[11]

Our retrosynthetic strategy for Et-743 is illustrated in Scheme 1. It was anticipated that the Staudinger reaction between an imine derived from aldehyde **10** and a chiral *N*-protected ketene would afford the *cis*-relationship at C-3 and C-4 (ecteinascidin numbering). After removal of the chiral auxiliary and deprotection of the phenolic residue, the

Scheme 1. Retrosynthetic Analysis of Et-743



chiral amino phenol **9** would be subjected to a Pictet–Spengler reaction to form tetrahydroisoquinoline **8** that embodies all the requisite functionality to tackle the planned asymmetric synthesis of Et-743 and bioxalomycin. We have previously reported a racemic model study along these lines[11] and now describe an asymmetric approach that specifically provides the western half of Et-743 in the optically pure form.

In a separate report, we described the asymmetric synthesis of the amino acid component (**18**).[12] Herein, we describe an asymmetric synthesis of the tetrahydroisoquinoline **8** that represents the "Western" sector of Et-743 and the coupling of these two fragments culminating in the construction of the pentacyclic core of the ecteinascidin, saframycin, and related alkaloids.

As shown in Scheme 2, the Staudinger reaction[13] was accomplished by condensing benzylamine with aldehyde **10** in refluxing benzene to afford the corresponding imine in quantitative yield. The ketene of the optically pure acid chloride **12** was prepared at −78 °C by the addition of triethylamine and the benzyl imine obtained from **10** was added and the reaction warmed to 0 °C, which afforded, after workup, β-lactam **13** in excellent yield.

Reductive removal of the chiral auxiliary and the benzyl ether was accomplished by hydrogenolysis over $Pd(OH)_2$ to afford the corresponding amino phenol, which upon treatment with methylglyoxylate afforded **14** in 84% yield as a single stereoisomer.[14] The relative stereochemistry of this substance was determined by comparison of ^{1}H NMR coupling constants to a related racemic substance for which an X-ray crystal structural analysis on a Pictet–Spengler cyclization

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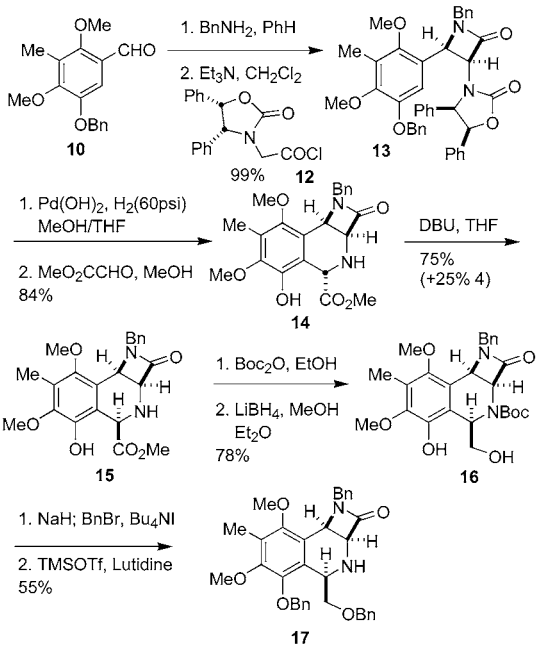
(14) It should be noted that the free phenol was found to be essential for a successful Pictet–Spengler cyclization reaction to proceed. Related substrates containing the methylenedioxy moiety or simple aryl methyl ethers failed to afford the corresponding Pictet–Spengler products.

Scheme 2. Asymmetric Staudinger Sequence

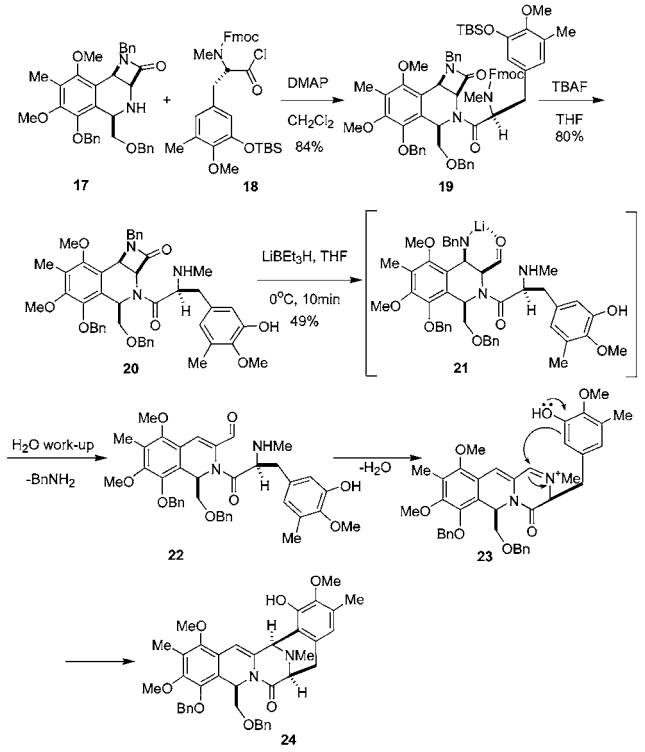


product has been secured.[15] As expected, on the basis of our previous racemic study, the relative stereochemistry of **14** at C-1 possessed the undesired *anti*-configuration.

Epimerization of the *anti*-carbomethoxy group of **14** with DBU in THF at room temperature afforded a 75% yield of the desired *syn*-isomer **15** plus 25% of recovered **14**, which could be readily separated and recycled. The secondary amine of **15** was selectively protected by treatment with Boc_2O in ethanol and reduction of the carbomethoxy group to the corresponding alcohol was accomplished by treatment with $LiBH_4$−MeOH in refluxing ether in excellent yield to afforded **16** in 78% yield. Benzyl protection of both the primary alcohol and the phenol was achieved by treatment with NaH and BnBr in the presence of a catalytic amount nBn_4NI. Next, the Boc group was removed by treatment with TMSOTf and lutidine to afford the tetrahydroisoquinoline **17** in 55% isolated yield.

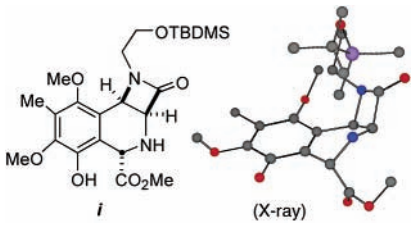
The amino acid was converted into the corresponding acid chloride by treatment with oxalyl chloride and then coupled to the amine in the presence of DMAP to afford the peptide **19** in 84% yield.[16] Both the Fmoc and TBS protecting groups were removed in a single operation by treatment with TBAF, which afforded the phenolic amine **20** in 80% isolated yield. Exposure of **20** to $LiBEt_3H$ in THF at 0 °C remarkably furnished the desired pentacyclic compound **24** directly in one step in 49% yield.

Scheme 3



The conversion of **20** into **24** is envisioned to proceed by initial partial reduction of the β-lactam to the amine-coordinated lithium complex **21** that obviates over-reduction of the incipient aldehyde. Extensive experience on related compounds in our hands and a search of the literature has revealed that the reduction of β-lactams directly to aldehydes is a synthetically challenging reaction for which few good solutions exist.[17] Elimination of benzylamine occurs spontaneously under the reaction conditions to afford the α,β-unsaturated aldehyde **22** that subsequently suffers cyclization of the secondary amine on the aldehyde to generate the key iminium ion species **23**. Regioselective intramolecular Pictet−Spengler cyclization finally affords the pentacyclic compound **24** without contamination of the alternative regioisomer.[18] The pentacyclic compound **24** contains the olefinic moiety at C3−C4 (saframycin numbering) that is flexibly poised for either saturation to the saframycins and related compounds or functionalization at C-4 for closure of the sulfur-containing macrocyclic ring of the ecteinasci-

(15) The relative stereochemistry of model compound ***i*** was secured by X-ray analysis, confirming the *trans*-configuration at the C-1 position. Comparison of ^{1}H NMR data of the pre-Pictet−Spengler β-lactam used to prepare ***i*** to that of **21** was used to establish the relative stereochemistry of **21**.



(16) The coupling with the acid chloride **18** in the presence of DMAP did not lead to detectable racemization.

(17) A search of the literature did not reveal any general methods for the reduction of β-lactams to aldehydes. For a pertinent reference, see: Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263−5277.

(18) In the Pictet−Spengler reaction, the regioselectivity of the observed product was secured by ^{1}H NMR nOe studies.

dins.[19] The retention of the oxidation state of the C-4 carbon atom (saframycin numbering) from the initial tricyclic β-lactam should prove to be very versatile, particularly for the ecteinascidins, since this was a difficult problem in the Corey total synthesis approach,[4] as well as the semisynthetic approach to the ecteinascidins that was based on benzylic C-4 oxidation of saframycin.[6]

In summary, the optically pure, densely functionalized pentacyclic tetrahydroisoquinoline **24** was prepared in 12 steps, with an overall yield of 12%. Efforts to utilize this intermediate and the approach outlined for the concise asymmetric synthesis of the ecteinascidin, saframycin families, and related alkaloids are currently under study in these laboratories.

(19) All new compounds gave satisfactory spectroscopic and analytical data consistent with the assigned structures (see Supporting Information).

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Supporting Information Available: Complete spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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