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Regioselectivity of Pictet–Spengler cyclization reactions to construct the pentacyclic frameworks of the ecteinascidin–saframycin class of tetrahydroisoquinoline antitumor antibiotics

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Abstract—The regiochemical outcome of Pictet–Spengler cyclization reactions directed toward the preparation of the pentacyclic core of the ecteinascidin class of antitumor antibiotics has been investigated on two different phenolic substrates. In one substrate, the assistance of an incipient benzylamine group at C-4 is postulated to direct the cyclization in favor of the pentacyclic framework of ET-743, which bears a hydroxyl group at C-18. Conversely, cyclization of an alternative substrate lacking a heteroatom at C-4 favors the opposite regiochemical outcome, primarily affording an unnatural pentacyclic core bearing a hydroxyl group at C-16.

In 1990, the isolation of the ecteinascidins, a new family of tetrahydroisoquinoline alkaloids[1] was reported from the marine tunicate *Ecteinascidin tubinata*.[2] Among these compounds, ecteinascidin 743 (Et-743, Yondelis™, **1**) is presently in phase II/III clinical trials due to its exceedingly low nanomolar activity against different tumor cell lines (Fig. 1).[3,4] It has been demonstrated that Et-743 (**1**) binds to guanine in the minor groove of DNA at the reactive C-21 carbinolamine position. The DNA–drug adduct exhibits a bend or widening in the minor groove of the DNA component, presumably due to the steric requirements of the GH-subunit of Et-743 (**1**). It has been postulated that this bend in DNA disrupts DNA–protein binding and may be, in part, a foundation for the enhanced activities of Et-743 over related agents. Recently, Et-743 was demonstrated to halt the DNA nucleotide excision repair (NER) mechanism in cells.[4] The restricted natural availability of Et-743 (**1**) from the tunicate has been overcome through semi-synthesis of multigram quantities from the more readily available metabolite cyanosafracin B (**2a**). Cyanosafracin B (**2a**) is available in kilogram quantities through bacterial fermentation. The route, developed by Cuevas and Manzanares at PharmaMar, supports current clinical trials.[5] Closely related to the ecteinascidins, safracins **2a**–**c** were isolated in 1983 from *Pseudomonas fluorescens* and also display potent antimicrobial and antitumor activities.[6]

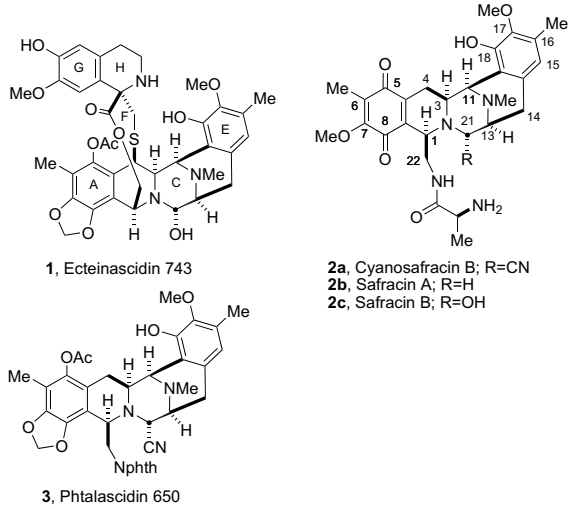

Figure 1. Ecteinascidin 743, the safracins and phtalascidin 650.

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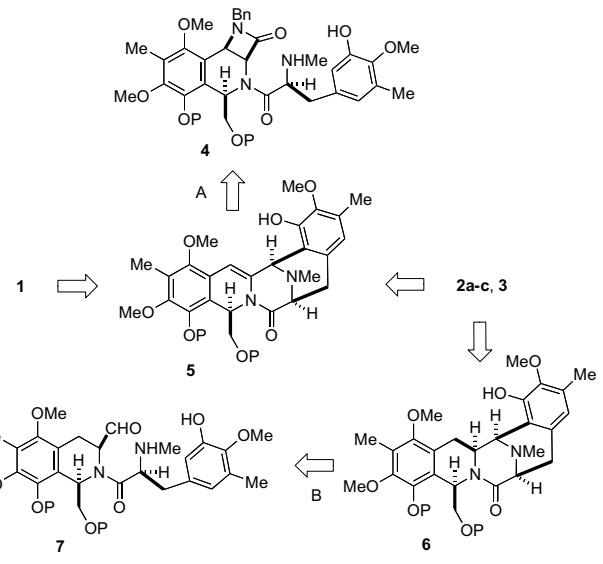
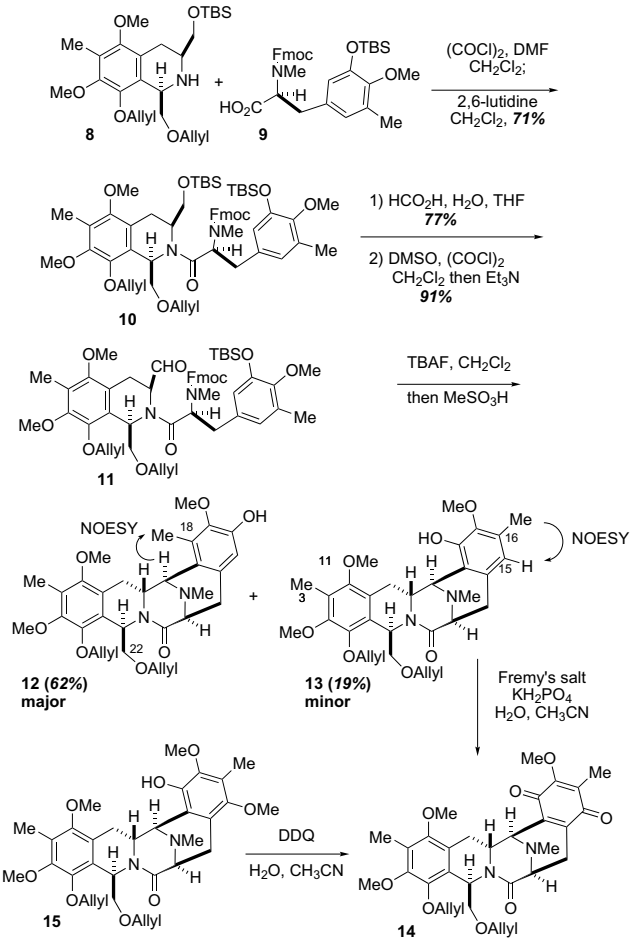
The structural challenges associated with Et-743 (**1**) have attracted significant attention from the synthetic community. Corey reported the first total synthesis of **1** in 1996.[7] Subsequently, Corey and Schreiber reported a simplified analogue of **1**, phthalascidin 650 (Pt-650, **3**),[8] which exhibited comparable biological activity. Fukuyama[9] and Zhu[10] have also completed the total synthesis of Et-743 (**1**), and Danishefsky has described a formal synthesis.[11] Additionally, Zhu has prepared the putative biosynthetic precursors of **1**, Et-597, and Et-583,[12] and Kubo has published synthetic studies toward safracins **2**.[13]

We previously described a reductive opening/Pictet–Spengler cyclization cascade sequence from β-lactam **4** to form the C3–C4 unsaturated pentacycle **5** (Scheme 1, route A).[14] Recently, this strategy was successfully employed in our total synthesis of cribrostatin 4.[15] We conjectured that the C3–C4 alkene of **5** was also flexibly poised to deliver either Et-743 (**1**), safracins **2**, or Pt-650 (**3**). Specifically, functionalization of the alkene group in **5** would ultimately permit formation of the macrocyclic ring of Et-743 through closure at C-4. Alternatively, saturation of the alkene group in **5** could deliver the core of the safracins and Pt-650. The C3–C4 saturated pentacyclic skeleton of the safracins **6** could also be obtained through a Pictet–Spengler cyclization of the C3–C4 saturated amino aldehyde **7** (route B).[16]

In an effort to investigate the preparation of **6** from **7** (Scheme 1, route B), tetrahydroisoquinoline **8**, representing the western half of **7**, was coupled with the acid chloride derived from amino acid **9**, representing the eastern half of **7**, to deliver **10** (Scheme 2). Selective deprotection of the primary alcohol group in **10** with formic acid and water was followed by a Swern oxidation to afford the desired aldehyde **11**. With **11** in hand, the stage was set to form the pentacyclic core of **2** and **3** through the key Pictet–Spengler reaction. Simultaneous removal of the *N*-Fmoc and *O*-TBS groups in **11** was accomplished with TBAF resulting in an iminium ion intermediate, after which methanesulfonic acid was then added in situ to promote subsequent ring-closure and pentacycle formation. Interestingly, this transformation resulted in the formation of two C-3 *epi* pentacyclic regioisomers, **12** and **13**, in a 3.3:1 ratio, respectively, based on ^{1}H NMR analysis. The unusual epimerization at C-3 was consistent with observations from our prior total syntheses of 3-*epi*-renieramycin G, renieramycin G, 3-*epi*-jorumycin and jorumycin.[16] Furthermore, formation of E-ring regioisomer **12** as the major product indicated that the cyclization had preferentially occurred *para* to the phenolic group in **11**. Conversely, the minor product **13** was derived from cyclization *ortho* to the phenolic group in **11**. The regiochemistries of **12** and **13** were secured by NOESY correlations between H-11 and the C-18 Me-group and between H-15 and the C-16 Me-group, respectively. The trans-relationship between H-3 and H-11 in **12** and **13** was verified by ^{1}H NMR through coupling constants ($J_{H3–H11} = 0$ Hz). Moreover, the structure of the minor product **12** was further verified through oxidation with Fremy's salt to quinone **14**, which was also successfully generated from compound **15**, an intermediate in the synthesis of 3-*epi*-jorumycin.[16]



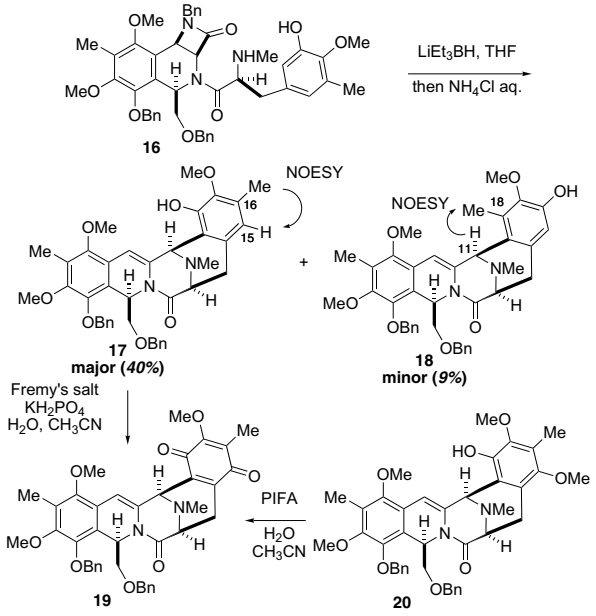
Scheme 1. Retrosynthetic analysis.



Scheme 2. Pictet–Spengler cyclization of C3–C4 saturated aldehyde **11**.

The observed epimerization at C3 in **11** could potentially be avoided by pre-forming a hemiaminal unit through the aldehyde and amine groups, prior to conducting the Pictet–Spengler cyclization. This strategy was successfully demonstrated in our syntheses of jorumycin and renieramycin G.[16] Unfortunately, however, the regiochemical outcome afforded through the cyclization of **11** remains unsuitable for the synthesis of the safracins or Pt-650. Historically, methods have been successfully devised to selectively access pentacyclic intermediates bearing the appropriate E-ring regiochemical relationship for the ecteinascidin family of natural products. In their studies toward Et-743 (**1**) Corey and co-workers employed a symmetric 3,5-dihydroxy aryl residue, representing the E-ring, to circumvent regioselectivity issues intrinsic to *mono*-hydroxy phenol cyclization substrates. Subsequent differentiation of the less hindered hydroxy position through activation as the corresponding triflate group followed by cross-coupling with $SnMe_4$ afforded the correctly functionalized E ring.[7] Alternatively, Kubo and Fukuyama utilized an E-ring precursor bearing a bromide group *para* to the phenolic hydroxyl group, which successfully blocked this position and promoted exclusive *ortho* cyclization.[17] However, despite the elegance and utility of these strategies, an enhanced understanding of the factors influencing the regiochemical outcome of cyclizations of substrates capable of affording both *ortho*- and *para*-products would certainly be useful and would perhaps obviate the need for blocking groups or post-cyclization manipulations at the E-ring unit.

The preference for the formation of compound **12** from the Pictet–Spengler cyclization of **11** was not consistent with the regiochemical outcome observed in our previously reported reductive opening/Pictet–Spengler cyclization sequence through β-lactam **16** (Scheme 3).[14,18]

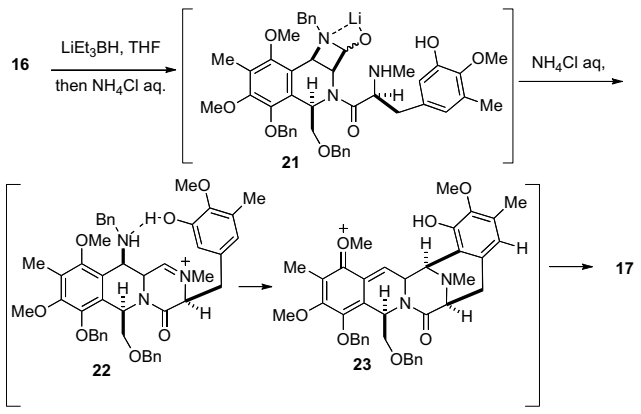


Scheme 3. Reductive opening/Pictet–Spengler sequence from β-lactam **16**.

Therefore, an effort was made to rationalize these findings. Initially, a more thorough analysis of the reductive opening/Pictet–Spengler cyclization sequence confirmed the production of two regioisomers, **17** and **18**, in a 4:1 ratio, respectively, based on ^{1}H NMR analysis. Although the structure of compound **17** was originally secured through ^{1}H NMR NOE studies,[14] additional ^{1}H NMR NOESY experiments further verified the correlation between H-15 and the C-16 Me-group. The structure of compound **17** was unequivocally confirmed through oxidation with Fremy's salt to quinone **19**, which was identical to the quinone obtained by PIFA oxidation of **20**, an intermediate in our synthesis of cribrostatin 4.[15] The structure of the minor regioisomer **18** was also secured by NOESY experiments (correlation between H-11 and the C-18 Me-group).

Successful and rigorous verification of our previously reported results,[14] lead us to propose the following pathway to explain the two distinct cyclization outcomes (Scheme 4). Partial reduction of the β-lactam unit in **16** would lead to the coordinated lithium complex **21**, which also serves to prevent over-reduction of the corresponding aldehyde group. Following aqueous quench with NH_4Cl, condensation of the secondary amine group onto the hemi-aminal unit in **21** would generate the key iminium ion intermediate **22**. Within intermediate **22**, a postulated hydrogen bonding interaction between the C-4 benzylic amine and the E-ring phenolic residue would direct the Pictet–Spengler cyclization *ortho*- to the phenol. Finally, spontaneous elimination of the C-4 benzylamine group occurs through the intermediacy of *ortho*-quinone methide **23** to afford the C3–C4 unsaturated pentacycle **17** as the major product. The minor pentacycle regioisomer **18** (Scheme 3) may arise from a pathway whereby C-4 benzylamine elimination, potentially through intermediate **22**, occurred prior to ring-closure onto the incipient iminium ion.

In summary, we have postulated the assistance of an incipient benzylamine group at C-4, which was derived from β-lactam **16** in a reductive opening/Pictet–Spengler reaction sequence, to direct the formation of the pentacyclic framework of the ecteinascidin family of



Scheme 4. Postulated pathway for the reductive opening/Pictet–Spengler sequence of β-lactam **16**.

antitumor antibiotics. In the absence of a heteroatom at C-4 (compound **11**), Pictet–Spengler cyclization resulted in the preferential formation of an unnatural regioisomer at the E-ring position. The transformation of **17** into the safracins and the ecteinascidins is currently under investigation in our group.[19] We are also pursuing the introduction of a C-4 hydroxyl group into our Pictet–Spengler cyclization substrate prior to forming the pentacyclic core of Et-743.[20]

Acknowledgments

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Supplementary data

Supplementary data (complete experimental procedures and NMR spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.113.

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