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A Scalable Total Synthesis of Et-743 and Lurbinectedin

*Weiming He, Zhigao Zhang and Dawei Ma**

Abstract: An efficient and scalable approach for total synthesis of Et-743 and lubinectedin (about 1.6% overall yield in 26 total steps from Cbz-protected (*S*)-tyrosine) is described, and features the use of a common advanced intermediate to create the right and left parts of these antitumor drugs, and a light-mediated remote C-H bond activation to assemble a benzo[1,3]dioxole-embodied intermediate.

Et-743 (trabectedin, Figure 1) is the first marine natural product used clinically as a drug and is approved for treatment of advanced soft tissue sarcoma.[1] Mechanistically, this agent displays potent antiproliferative activity by binding to the minor groove of DNA with preference for GC-rich triplets and subsequently forming covalent adducts with the N2 position through its carbinolamine unit.[2] During the past decades, intensive structure-activity relationship (SAR) studies of Et-743 and related marine natural products have been conducted,[3] leading to the discovery of some new and promising anti-tumor drugs. For example, lurbinectedin (PM1183),[4] is in phase III clinical trials for treatment of small-cell lung cancer and hereditary breast cancers, while zalypsis is in phase II studies for treatment of advanced/metastatic endometrial or cervical cancer.[5]

Due to the limited natural availability of Et-743 (1.0 g from about 1.0 ton of tunicate), the development of practical syntheses of Et-743 and related antitumor drugs accessible in sufficient quantity is highly desirable.[1a] In the field of natural product synthesis, Et-743 has become one of the most challenging target molecules, and has attracted much attention from the synthetic community.[1,6-9] In 1996, Corey group reported the first total synthesis of Et-743,[6] in which an intermolecular Strecker reaction and an internal Mannich bisannulation were used for elaboration of tetrahydroisoquinoline core structure in combination with a C-S bond forming cyclization and a Pictet-Spengler reaction to create the bridged 10-membered lactone and spiro ring system. Later, Fukuyama,[7,9] Zhu,[8] Danishefsky[10] and Williams[11] groups reported three additional elegant total syntheses along with several formal synthetic routes. However, these routes remain far from practical preparation of Et-743, largely because of the requirement of de novo synthesis of unnatural amino acid residues (for installing right and left parts of Et-743). The current synthetic approach, either asymmetric hydrogenation of the corresponding dehydrophenalanine derivatives or asymmetric induction using chiral auxiliaries, not only requires the employment of expensive reagents that are difficult to access, but also increases the numbers of total synthetic steps (about 40-60 steps). Indeed, the current manufacturing route of Et-743 is a semi-synthesis using cyanosafracin B as the starting material, which still requires 21 synthetic steps with ~1% overall yield.[12] Herein, we wish to describe a more efficient and practical de novo route for the synthesis of Et-743 and lubinectedin.

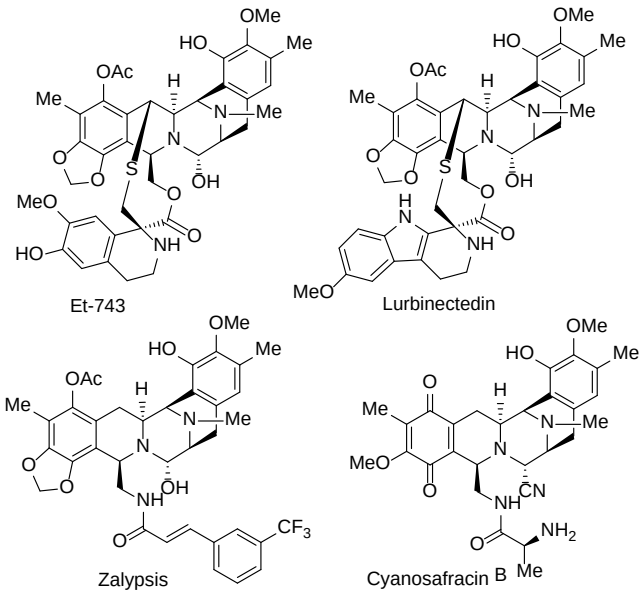

Figure 1. Structures of Et-743, lurbinectedin and related anti-tumor agents.

As depicted in Figure 2, we believed that Et-743 and lubinectedin could be assembled from hexacyclic amino nitrile **1** by using a macrocyclization method that was initially developed by Corey and coworkers,[6] and has also been applied in other semi- and total syntheses of Et-743.[7-9,12] The amino nitrile **1** could be prepared from amino alcohol **2** through an intramolecular Strecker reaction, while **2** could be obtained via a Pictet–Spengler reaction between aldehyde **3** and (*S*)-5-(2-amino-3-hydroxypropyl)-2-methoxy-3-methylphenol **4**.[13] The aldehyde **3** could be synthesized from phenol **5** via protection and subsequent oxidation, and the phenol **5** could be prepared from tetrahydroisoquinoline **6** using an unusual remote C-H functionalization method.[14] If this proposal works well, we will be able to install both the right part and left part of Et-743 using a same intermediate **4** that could be prepared from Cbz protected (*S*)-tyrosine in 7 steps.[15] Obviously, this strategy will greatly minimize the overall synthetic steps.

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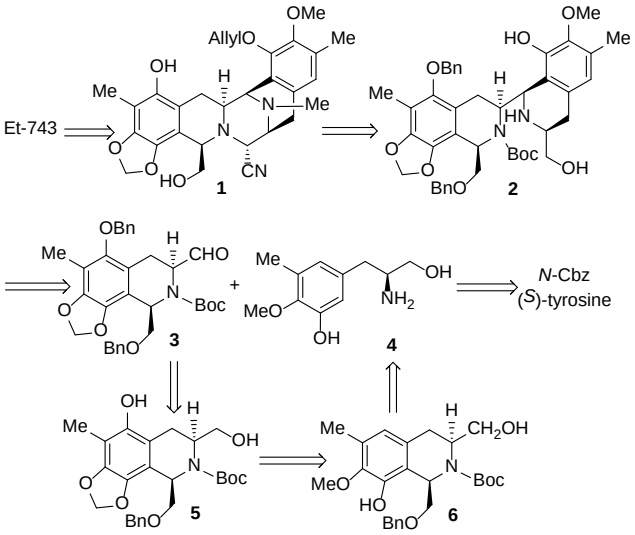
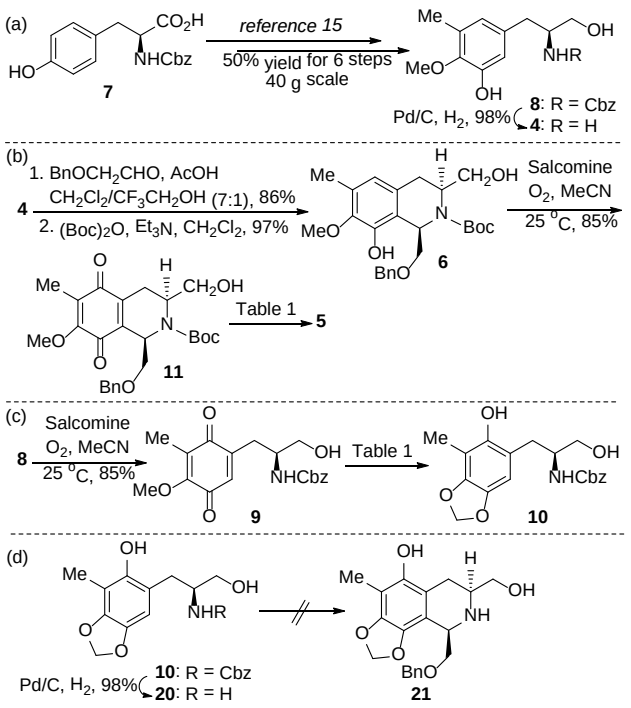


Figure 2. Retrosynthetic analysis of Et-743.

As outlined in Scheme 1, we started our synthesis by preparing alcohol **8** from Cbz protected (*S*)-tyrosine according to a known procedure.[15] This 6-step synthesis could be easily scaled up to decagram scale in 50% overall yield. Hydrogenolysis of **8** afforded the amino alcohol **4** (a), which was subjected to a Pictet–Spengler reaction[13a] and subsequent protection with $(Boc)_2O$ provided the tetrahydroisoquinoline **6** in 82% overall yield. After oxidation of the phenol **6** to quinone **11**, we were ready to study the formation of benzo[1,3]dioxole via a light-mediated remote C-H bond activation to obtain alcohol **5** (b). In a parallel procedure, transformation of trisubstituted phenol **8** to tetrasubstituted phenol **10** was also examined through a light-mediated reaction of quinone **9** (c).



Scheme 1. Preparation of the tetrahydroisoquinoline **5**.

The benzo[1,3]dioxole unit existing in numerous natural products is believed to form biogenetically via oxidation of the corresponding monomethyl-catechol moiety with cytochrome P450 enzymes.[16] During their synthetic study towards taiwaniaquinol A, Gademann and coworkers observed that benzo[1,3]dioxole unit could be elaborated via photolysis of a methoxyquinone precursor.[14] This study stimulated us to try photolysis of quinones **9** and **11** to convert them to the corresponding benzo[1,3]dioxole products **10** and **5**. As indicated in Table 1, we initially tried the reaction under Gademann's conditions (sunlight, ether),[14a] and found that the desired oxidative cyclization products **10** and **5** could be obtained in moderate yields (entry 1). To avoid the influence of the variable intensity of sunlight on the efficiency, various light sources including 365 nm UV lamp, medium-pressure Hg lamp, and white LED light were employed, albeit with no further improvement (entries 2-4). Gratifyingly, blue LED light (with a narrow wavelength range centered at 450 nm) proved more effective (entry 5). Since the excitation efficiency could be crucial to the outcome of this triplet state-mediated cyclization, the excitation spectra of quinone **11** were carefully examined and a pronounced solvent effect was observed, with the spectrum in THF showcasing the highest efficiency and the largest overlap with blue LED irradiation spectrum (Figure 3). Thus, switching the solvent from ether to THF dramatically increased the reaction yields (entry 6), while other examined solvents all gave poor yields (entries 7-9). Under the optimized conditions the formation of **5** could be scaled up to multi-decagrams without compromising the yield. Application of a scalable C-H functionalization to quinone **11** proved essential in our synthesis because an alternate route to furnish the skeleton of the tetrahydroisoquinoline **5** by Pictet–Spengler reaction of the amine **20**, which had derived from **10**, failed to give the desired cyclization product **21** under various conditions (Scheme 1, (d)), presumably because of steric hindrance.

Table 1. Light-mediated remote C-H functionalization of **9** and **11**.[a]

Entry	Conditions	Yield of **10** (%)[b]	Yield of **5** (%)[b]
1	Sunlight, Et_2O	44	41
2	UV light (365 nm), Et_2O	44	39
3	Medium-pressure Hg lamp, Et_2O	38	31
4	White light, Et_2O	41	42
5	Blue light, Et_2O	51	48
6	Blue light, THF	83	84
7	Blue light, *t*-BuOH	19	22
8	Blue light, toluene	40	41
9	Blue light, acetone	2	7

[a] Reaction conditions: **9** or **11** (0.5 mmol), solvent (5 mL), RT, 2 h. [b] The yield was determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard.

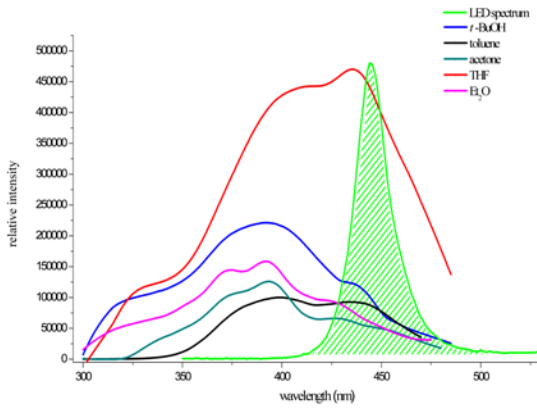


Figure 3. Excitation spectra of the quinone **11** and the blue LED irradiation spectrum.

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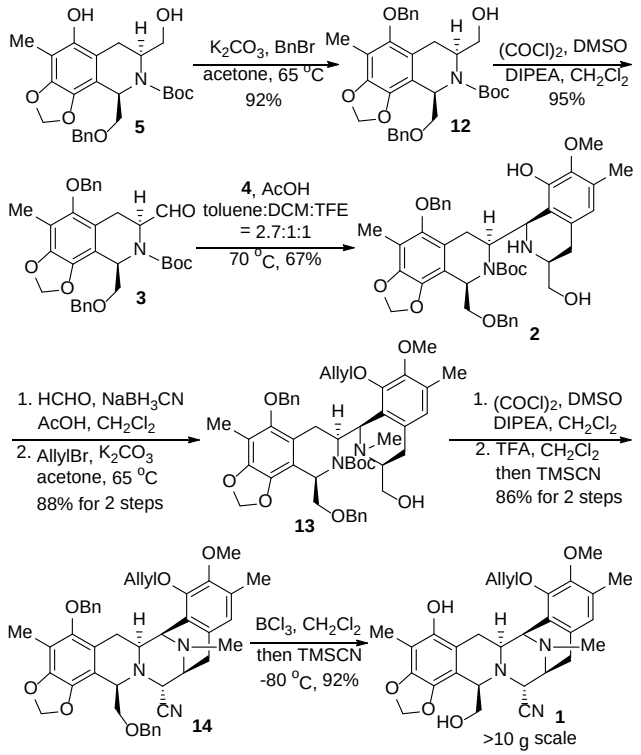
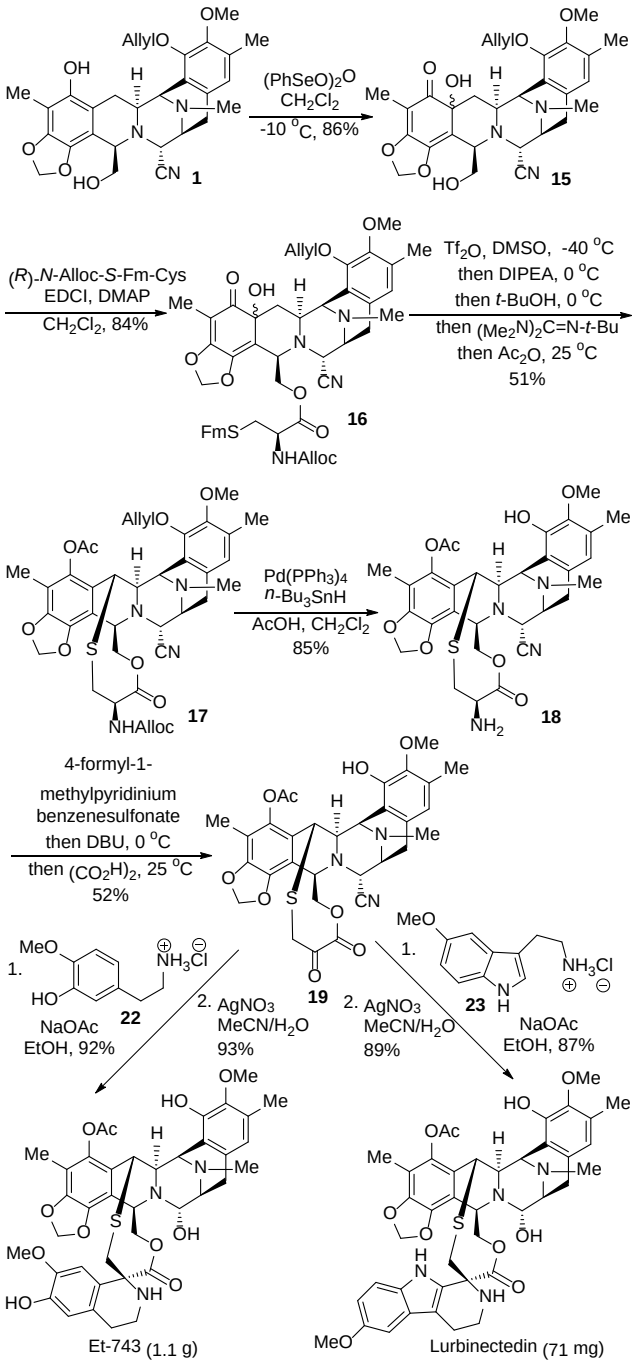
Protection of **5** with benzyl bromide produced alcohol **12** (Scheme 2), which was subjected to Swern oxidation to afford the aldehyde **3**. Intermolecular Pictet–Spengler reaction of **3** with the amino alcohol **4** proceeded smoothly under Chen's conditions[13] to provide cyclization product **2** as a major isomer in 67% yield. After the reductive amination to introduce the requisite methyl group, protection of the phenol unit in **2** with allyl group was conducted, affording amino alcohol **13** in 88% yield. Swern oxidation of **13** and subsequent deprotection and intramolecular Strecker reaction proceeded smoothly, giving the amino nitrile **14** in 86% overall yield. Next, treatment of **14** with boron trichloride to remove two benzyl protecting groups furnished the alcohol **1**. In large scale preparation (>10 g), we observed that partial hydrolysis of **1** occurred, and therefore some TMSCN was added to ensure the isolation of **1** in a good yield.



Scheme 2. Assembly of the hexacyclic amino nitrile **1**. DIPEA = *N*,*N*-diisopropylethylamine; DCM = dichloromethane; TFE = 2,2,2-trifluoroethanol; TFA = trifluoroacetic acid; TMSCN = trimethylsilyl cyanide.

With multi-decagrams of the hexacyclic intermediate **1** in hand, we were able to achieve gram-scale synthesis of Et-743 as outlined in Scheme 3. Oxidation of the phenol **1** with benzeneseleninic anhydride through a position-selective angular hydroxylation gave dihydroxy dienone **15**,[6] which was condensed with (*R*)-*N*-Alloc-*S*-Fm-Cys to afford ester **16**. After macrocyclization according to Corey's one-pot procedure,[6] lactone **17** was obtained in 51% yield. Next, cleavage of both allyl and alloc protecting groups in **17** via Pd(0)-catalyzed reduction provided amine **18**, which was oxidized to produce keto ester **19**. Finally, Pictet–Spengler reaction of **19** with 2-(3-hydroxy-4-methoxyphenyl)ethylamine hydrochloride salt **22** followed by hydrolysis of the amino nitrile moiety delivered Et-743 (1.1 g) in 86% overall yield, while lurbinectedin was obtained by using 2-(5-methoxy-1*H*-indol-3-yl)ethanamine hydrochloride salt **23** as a condenser.



Scheme 3. Synthesis of Et-743 and lurbinectedin. EDCI = 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide; DMAP = 4-dimethylaminopyridine; Tf_2O = trifluoromethanesulfonic anhydride; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

In conclusion, we have accomplished an efficient and scalable synthesis of Et-743 (1.6% overall yield for 26 total steps from commercially available Cbz protected (*S*)-tyrosine) and lurbinectedin. This strategy has featured the employment of (*S*)-5-(2-amino-3-hydroxypropyl)-2-methoxy-3-methylphenol as the same intermediate to install the both sides of two target molecules and an effective light-mediated remote C-H bond activation to furnish the required benzo[1,3]dioxole-embodied key intermediate. We believe that the present synthetic route provides a practical and economical approach for manufacturing Et-743 and lurbinectedin, therefore solving the long-standing supply issue of these complex antitumor

drugs. Additionally, the efficient synthesis may stimulate further SAR studies of these marine natural products.

Key words: marine natural product; antitumor agent; C-H bond activation; cyclization; total synthesis

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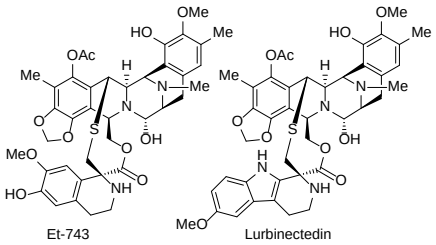
A Scalable Total Synthesis of Et-743 and Lurbinectedin



An efficient and scalable synthesis of Et-743 and lurbinectedin is achieved by employing a light-mediated remote C-H bond activation as the key step.