

DISSERTATION

SYNTHETIC STUDIES OF ECTEINASCIDIN 743 AND FENNEBRICIN B

Submitted by

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## ABSTRACT

### SYNTHETIC STUDIES OF ECTEINASCIDIN 743 AND FENNEBRICIN B

Ecteinasidin 743 (Et-743, trabectedin or Yondelis®) possesses an impressive antitumor activity that it was approved for treatments of several cancer types worldwide. Since this natural product only presents as a trace amount in the nature, the main supply of this drug for research and commercial use is from laboratory synthesis. Many syntheses of Et-743 have been reported including three total syntheses, two formal syntheses and two semisyntheses. The biological activities of fennebricin B were unknown due to the scarcity of this natural product. However, fennebricin B share a common pentacyclic core with Et-743, thus may also possess interesting biological activities.

Our group completed our formal synthesis of the natural product in 2008, featuring the Pictet-Spengler reaction to construct the pentacyclic core of Et-743. Our work, however, also produced both desired and undesired pentacycle with almost no selectivity. We herein described an improved formal synthesis of Et-743 employing bromine auxiliary to generate the pentacyclic core of Et-743 with the desired regioisomer as the single product. This approach was also utilized in the synthetic studies toward the total synthesis of fennebricin B.

## ACKNOWLEDGEMENTS

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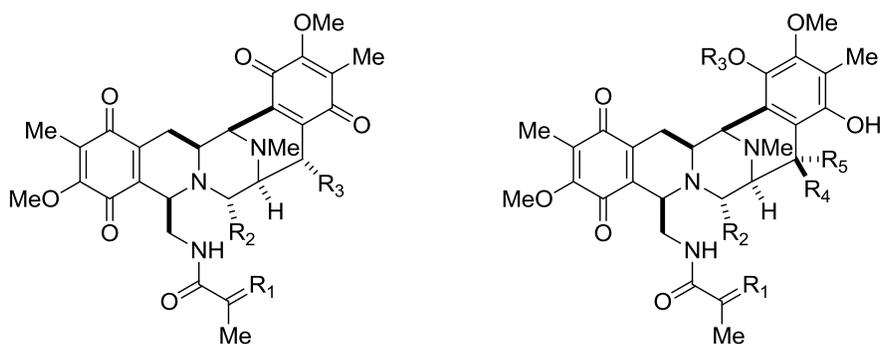
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# Chapter 1 – Introductions

## 1.1 Ecteinasclidin-743 (Et-743) and fennebricin B

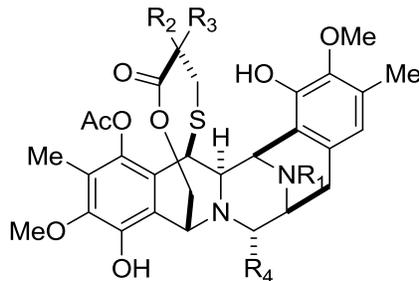
The tetrahydroisoquinoline (THIQ) family contains a large number of biological active natural products, divided into several sub-families including: saframycin, renieramycin, safracin, naphthyridinomycin, quinocarcin and ecteinasclidin (figure 1).<sup>1</sup> Among them, ecteinasclidin 743 (Et-743, **1**), commercial name is trabectedin or Yondelis®, possesses the most potent antitumor activity against a variety of cancer cell types (figure 2).<sup>2</sup> Et-743 was isolated in 1990 by Rhinehart and coworkers from tunicate extract *Ecteinasclidin turbinata*, and its structure was confirmed via X-ray crystal structure of its N12-oxide derivative in 1992 by Sakai *et al.*<sup>3,4</sup> Years later, after its first isolation, bacterial symbiont *Candidatus Endoecteinasclidia frumentensis* was recognized as the producer of this natural product.<sup>5-7</sup> As seen in figure 2, Et-743 is made up of three highly functionalized THIQ units A, B and C. Units A and B form a rigid pentacyclic core, connecting to the last unit via a 10-membered macrolactone-bridge. This structure was believed to efficiently form hydrogen bonds with the targeted DNAs and promote DNA alkylation leading to Et-743's antitumor activity.<sup>8,9</sup>

Saframycin or renieramycin family

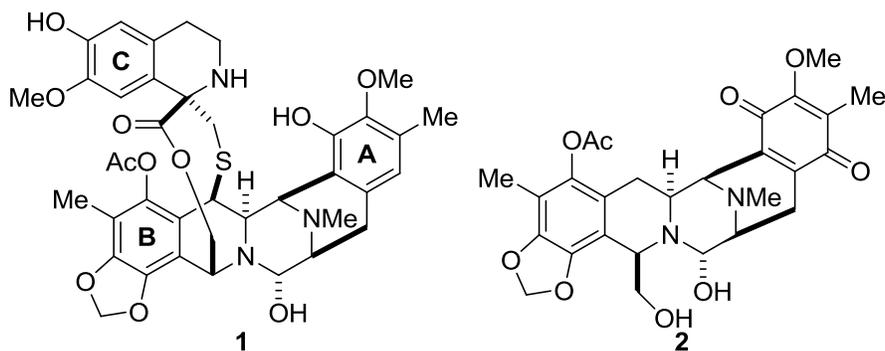




## Ecteinascidins



**Figure 1:** General structure of the tetrahydroisoquinoline family.



**Figure 2:** Structure of Et-743 (1) and fennebricin B (2).

Fennebricin B (2) was isolated in 2014 from the extract of dorid nudibranch (figure 2). The biological activity of fennebricin B is unknown since it is only present as a trace amount. However, the synthesis of this natural product is appealing to us because it is structurally related to Et-743, thus promising interesting effects on biological systems.

### 1.2 Biological activity of Et-743

Both Et-743 and Et-729 were found to have remarkable *in situ* antitumor activity against several cancer cell types (table 1).<sup>10</sup> However, studies on Et-729 were impossible at the time due to its scarcity; hence, little was known about this natural product. Et-743, on the other hand, was the most abundant from the extract making it a more attractive target for drug development.<sup>3</sup>

**Table 1:** Bioactivities of the Ets. L1210 = murine lymphocytic leukemia cells; P388 = murine lymphoblastic cells; A549 = human lung carcinoma; HT29 = human colon carcinoma; MEL28 = human melanoma; CV-1 = monkey kidney cells; PS = protein synthesis inhibition; DNA = DNA synthesis inhibition; RNA = RNA synthesis inhibition; DNAP = DNA polymerase inhibition; RNAP = RNA polymerase inhibition; Bs = *Bacillus subtilis*.<sup>11</sup>

	IC <sub>50</sub> (ng/mL)						IC <sub>50</sub> (µg/mL)					µg/dics
	L1210	P388	A549	HT29	MEL28	CV-1	PS	DNA	RNA	DNAP	RNAP	Bs
Et-743	5.0	0.2	0.2	0.5	5.0	1.0	>1	0.1	0.03	2.0	0.1	0.02
Et-729	<1.0	0.2	0.2	0.5	5.0	2.5	>1	0.2	0.02	1.5	0.05	0.08
Et-815	25	2.5	5.0	5.0		5.0		>1	0.1		5.0	0.75
Et-759B		5.0	5.0	5.0	10	25	>1	0.7	0.5		>1	3.90
Et-745B	25	5.0	10	10		25		>1	0.5		3.0	
Et-759C		1.0	2.5	2.5		2.5	2.5		>1	0.5	>5	0.1
Et-745		10	20	25	50	50		>1	0.3		5.0	6.50
Et-731		100	100	100	200	200	>1					6.20
Et-736		0.5	1.0	2.5	2.5	2.5	0.5	0.4	0.1		0.5	0.38
Et-722		1.0	1.0	2.0	2.0	5.0	0.9	0.4	0.1	>1	0.5	0.70
Et-594		10	20	25	25	25	0.8	0.5	0.5		1.0	0.37
Et-597		2.0	2.0	2.0	2.0	2.5	0.7	0.08	0.01		0.25	0.14
Et-583		10	10	10	5.0	25	1.0	1.0	0.4		0.5	0.74

*In vitro* studies on human cancer tissues and xenografts revealed that continuous exposures of Et-743 can be beneficial (table 2). This result also illustrated that soft tissue sarcomas are the most suitable targets of Et-743.

**Table 2:** Antitumor activity of Et-743 against human tumor colonies after one-hour exposure (1HR) versus continuous exposure (CE).<sup>12</sup>

Tumor type	0.1 nM		1.0 nM		10 nM		100 nM		1000 nM	
	1HR	CE	1HR	CE	1HR	CE	1HR	CE	1HR	CE
Ovary	0%	0%	11%	22%	20%	45%	0%	58%	0%	67%
Breast	0%	0%	0%	0%	0%	40%	20%	79%	40%	100%
Non-small cell lung	0%	0%	0%	0%	0%	50%	–	69%	–	85%
Colon	0%	0%	0%	0%	0%	50%	–	43%	–	71%
Melanoma	–	–	–	–	–	71%	–	88%	–	86%
Kidney	0%	0%	0%	0%	0%	43%	0%	50%	0%	67%
Sarcoma	0%	0%	0%	0%	100%	75%	–	67%	–	67%
Corpus uteri	–	–	–	–	–	67%	–	67%	–	67%
Peritoneum	0%	0%	0%	0%	50%	100%	–	–	–	–
Head/neck	0%	0%	0%	0%	0%	100%	–	–	–	–
Lymphoma	–	–	–	–	–	0%	–	0%	–	0%
Pancreas	–	–	–	–	–	100%	–	100%	–	100%
Mesothelioma	–	–	–	–	–	100%	–	100%	–	100%
Prostate	–	–	–	–	–	0%	–	0%	–	0%
Stomach	–	–	–	–	–	0%	–	0%	–	100%

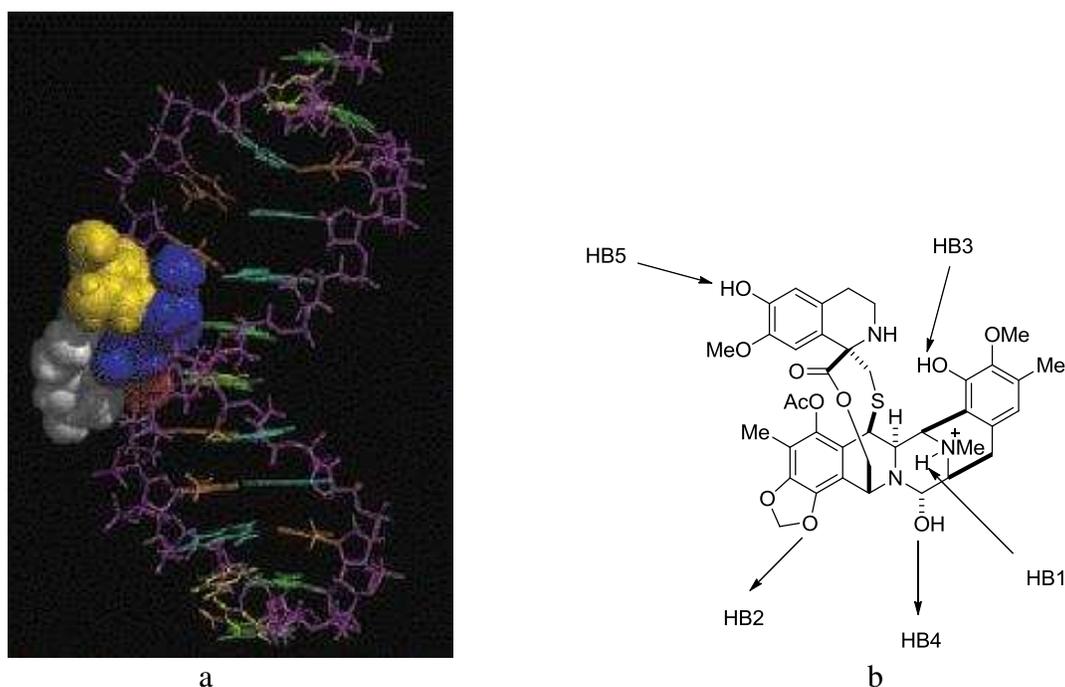
### 1.3 Mode of action of Et-743

Early studies of Et-743 on biological systems showed that Et-743 inhibits DNA-binding proteins, including NF-Y, TATA binding protein, E2F, and SRF/TCF, activates the formation of topoisomerase I-mediated cleavage complexes, and interrupts microtubule arrangement at micromolar concentration.<sup>13-16</sup> These were obviously not the major effects of Et-743 on tumor cells since they were detected at suprapharmacological concentrations. However, follow-up studies of Et-743 on transcription factor NF-Y by Zwicker and Muller found that preincubation of NF-Y with Et-743 prior to the addition of DNA stops DNA transcription at a significantly lower concentration of Et-743, although still at a higher concentration than its pharmacological concentration.<sup>17</sup> This result explains the delay in S-phase progression and accumulation of cells in G2/M phase observed by Simoens and coworkers in their study of Et-743's effect on the cell cycle.<sup>18</sup>

The study of Jin and coworkers of Et-743 on human colon carcinoma cell line SW 620 found that Et-743 inhibits the multidrug resistant gene 1 (MDR1) promoter activation via interfering with the binding of NF-Y to other coactivators.<sup>19</sup> This transcription suppression happens within the range of Et-743's pharmacological concentration, at 50nM, suggesting a mode of action of Et-743 independent of DNA alkylation.

Despite the early evidences of Et-743's activities on transcription factors and cell cycles, the best known and accepted mechanism of action of Et-743 today involves DNA alkylation, leading to DNA double-strand breaks (DSBs) and cell apoptosis. Figure 3a illustrated a binding event of Et-743 to the minor groove of DNA at the N2 of a guanine, bending the target DNA toward the major groove and forming a DNA adduct.<sup>8,20-23</sup> The alkylation of Et-743 to target DNA is reversible with the assistance of hydrogen bonds (HB) between Et-743 and the neighboring

nucleotides (figure 3b).<sup>24</sup> Seaman and Hurley demonstrated that HB1, HB2 and HB3 optimize and position HB4 to the alkylating site.<sup>25</sup> The protonated N12 also serves as a proton donor to promote formation of the iminium ion from the carbinolamine (N2), thus aiding DNA alkylation of the natural product.<sup>21</sup> 5'-**CGG**, **TGG**, **GGC**, **AGC** sequences, where the middle bold **G** is the site of alkylation, were identified to maximize the HB network on both strands of the DNA, and hence, become Et-743's favorite targets.<sup>24</sup> Although there are numerous favored sequences found along DNAs, formation of Et-743-DNA adducts was not efficient, suggesting a more complex interaction between Et-743 and the intracellular environment.<sup>20,26</sup>



**Figure 3:** (a) Et-743-DNA complex. (b) Hydrogen-bond network of Et-743 to DNA. The arrows represent the direction of the hydrogen bonds from a donor to an acceptor.<sup>11</sup>

Doxorubicin and vinblastine are traditional treatments of several cancers and also two known substrates of P-glycoprotein (P-gp). Et-743 was found to suppress P-gp via interaction with the two GC rich sequences of MDR1 promoter on P-gp/MDR1 overexpressing cell lines, KB-8-5 and KB-C-2, leading to sensitivity reversal of these cell lines over the conventional treatments.<sup>27</sup> Although Et-743 was proved a substrate of overexpressing P-gp cell-lines, such as those found in

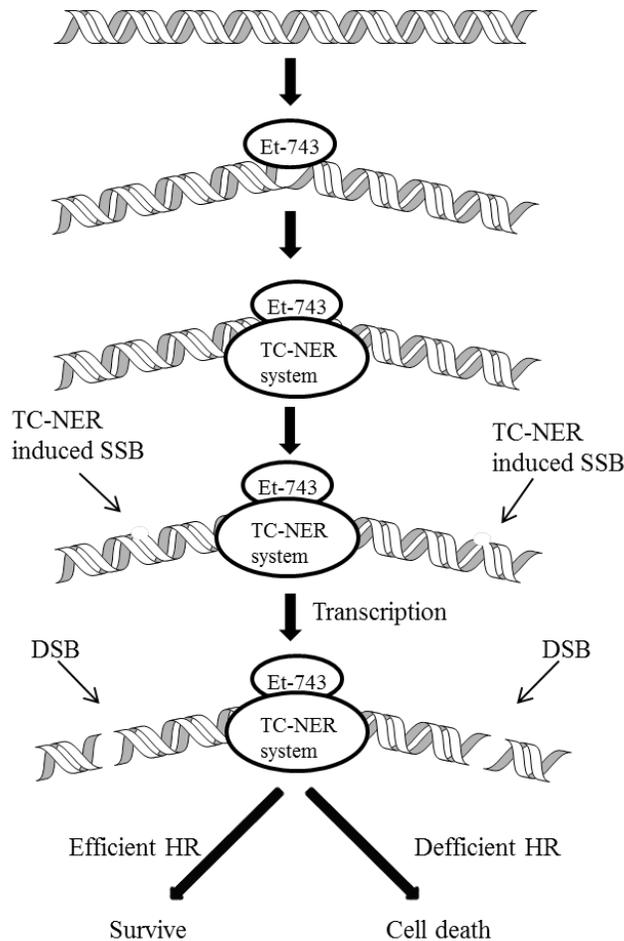
LLC-PK1 pig kidney and Madine-Darby Canine kidney cells, the P-gp levels of human cell lines does not affect cellular Et-743 level.<sup>28</sup> This result supports the combination treatment of Et-743 with either doxorubicin or vinblastine in more advanced sarcomas showing resistance to these well-known drugs.

Et-743 is significantly selective to Ewing sarcoma and myxoid/round cell liposarcoma type I and II. Studies of Et-743 on these sarcoma subtypes illustrated that Et-743 binds exclusively to the binding sites of the fusion proteins FUS-CHOP and EWS-FLI1.<sup>29,30</sup> This event causes the dissociation of these transcription factors from the promoters, leading to a halt in tumor initiation from these proteins, hence explaining Et-743's selectivity over these specific sarcomas.<sup>31-34</sup>

Most known DNA alkylating agents, such as cisplatin and mitomycin C, work efficiently when there is a deficient nucleotide excision repair (NER) system. Et-743, on the other hand, depends heavily on a proficient NER system, transcription-coupled (TC) NER specifically, to efficiently produce its antitumor activity.<sup>35-37</sup> The TC-NER system is known for its role in repairing transcription adducts caused by transcription errors. In the presence of Et-743, the DNA-Et-743 adduct will also recruit the TC-NER system; however, the repair does not happen properly, leading to irreversible single-strand breaks (SSBs), then double-strand breaks (DSBs) during replication (figure 4).<sup>31,36,38,39</sup> An efficient homologous recombination (HR) repair can recognize and save the cell by fixing these Et-743-induced DSBs. However, cancer cells normally lack this HR repair mechanism, and hence will undergo apoptosis.<sup>38,40</sup>

Studies on a simpler bacterial nuclease UvrABC system from Hurley group revealed a mechanism unrelated to DSB-induced apoptosis.<sup>41</sup> As shown in figure 5, the DNA-Et-743 adduct recruits the UvrABC system to the alkylating site. In case of unfavored DNA sequences, Et-743 either dissociates from the adduct, or is cleaved by this repair system, resulting in

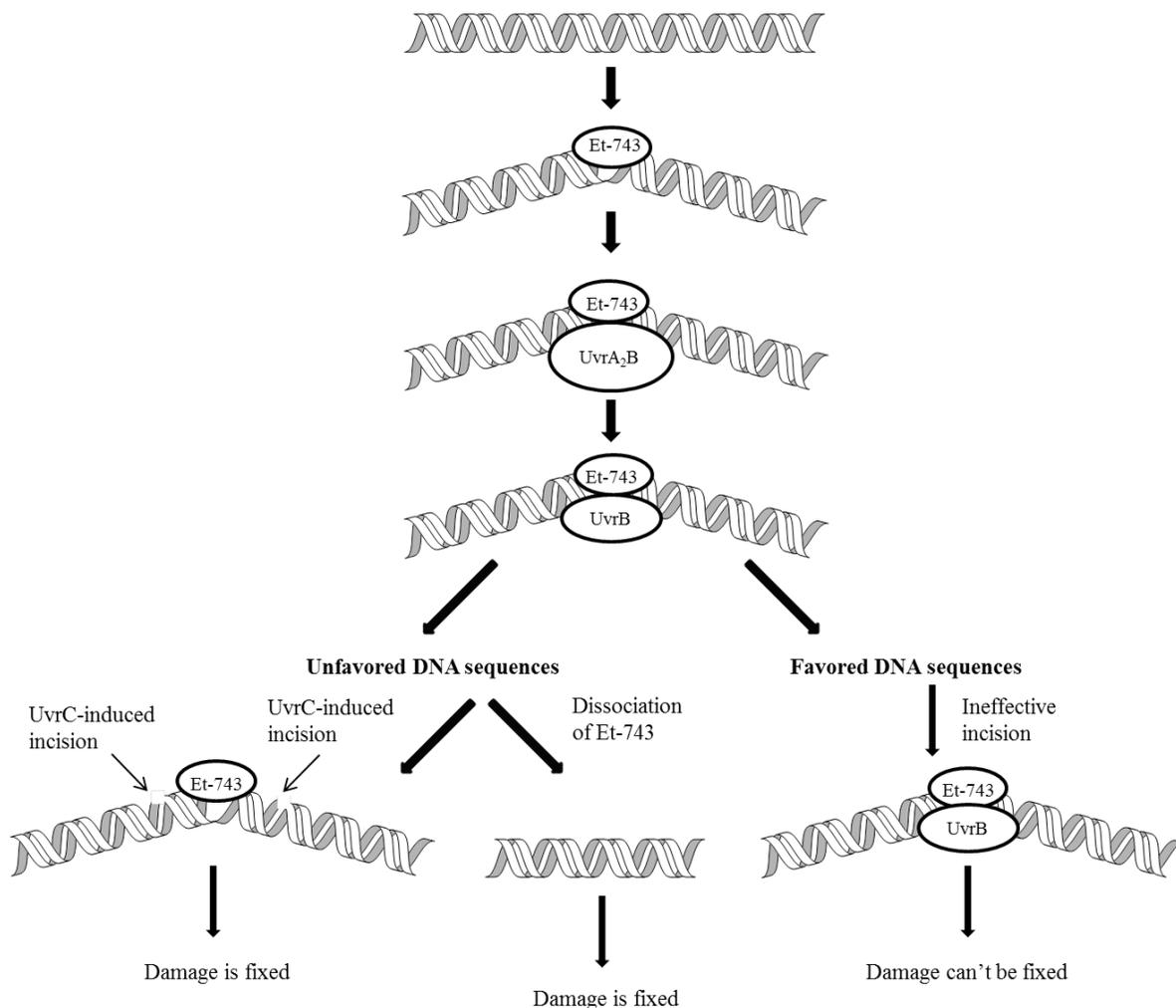
surviving cells. At favored sequences, the damage cannot be repaired efficiently, causing the deformed DNA and cell death.



**Figure 4:** Mode of action of Et-743, dependent on DNA replication.

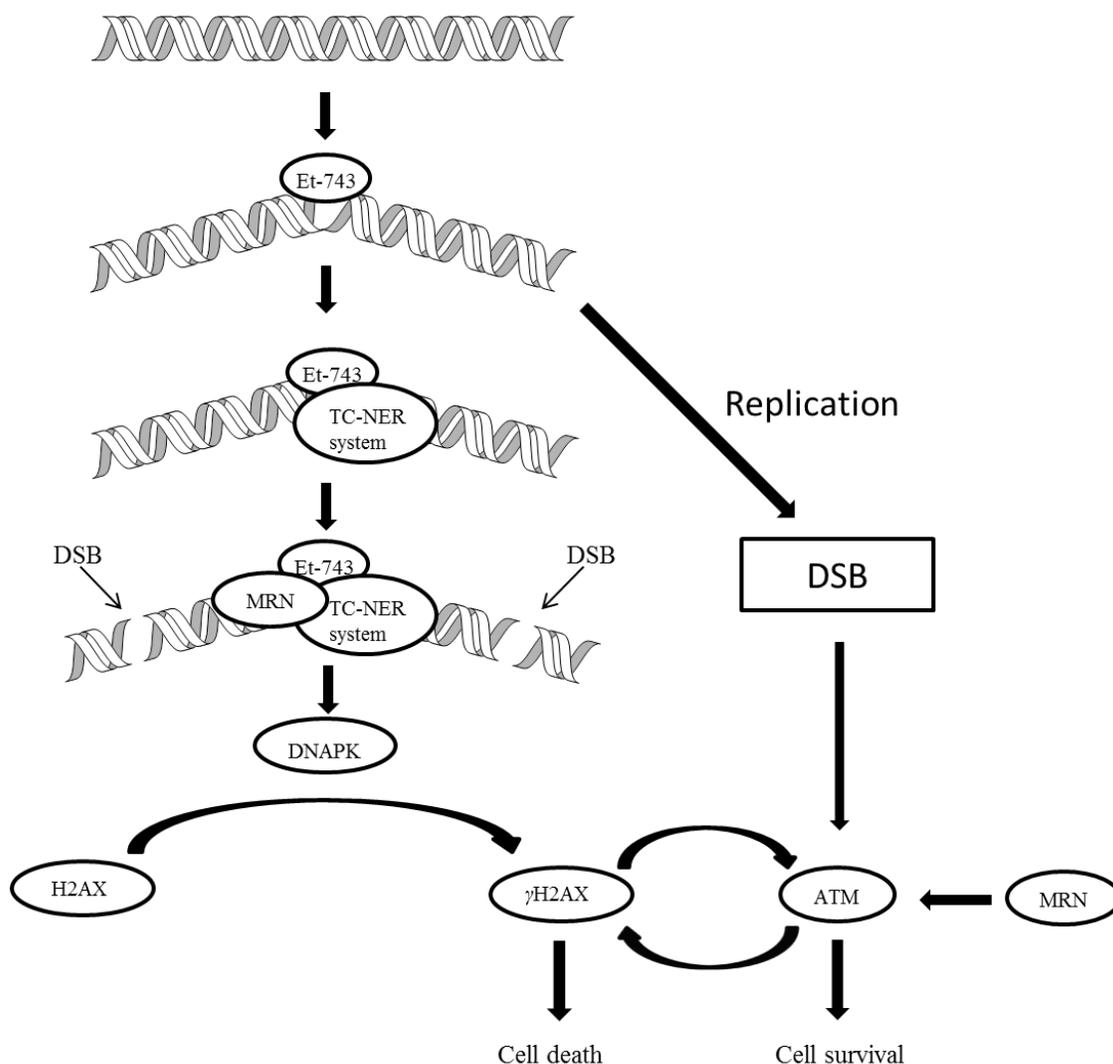
A more recent study by Guirouilh-Barbat *et al.* supports DSB pathway hypothesis, however, via a more complex mechanism.<sup>42</sup> The group proposed that Et-743-induced DNA DSBs via two pathways: one depends on transcription, and the other depends on replication. The transcription dependent pathway involves the formation of SSBs as described earlier (figure 6). The presence of TC-NER-induced SSBs recruits the Mre11-Rad50-Nbs1 (MRN) system to the adduct site, causing DSBs. In the presence of DSBs, DNA-dependent protein kinase (DNAPK) will phosphorylates serine 139 of H2AX protein ( $\gamma$ H2AX) around DSB sites, triggering cell

apoptosis. Furthermore,  $\gamma$ H2AX activates ataxia telangiectasia-mutated (ATM) gene, which in turn will amplify cell death signal by phosphorylating more H2AX proteins. Et-743 was also found to directly cause DSBs via replication, which will turn on the ATM gene, contributing to initiating cell apoptosis. The MRN system and the activation of ATM gene also plays a role in initiating DNA-damage checkpoints; thus the DNA-Et-743 adduct can be repaired and the cell can survive.<sup>43</sup>



**Figure 5:** Incision effectiveness at unfavored DNA sequences versus favored DNA sequences.

Aside from DNA-alkylating activities, Et-743 was found to modulate the tumor's microenvironment by reducing blood vessels and mononuclear phagocytes around the tumor. This activity will activate tumor's extrinsic apoptotic pathways, leading to cell death.<sup>44</sup>

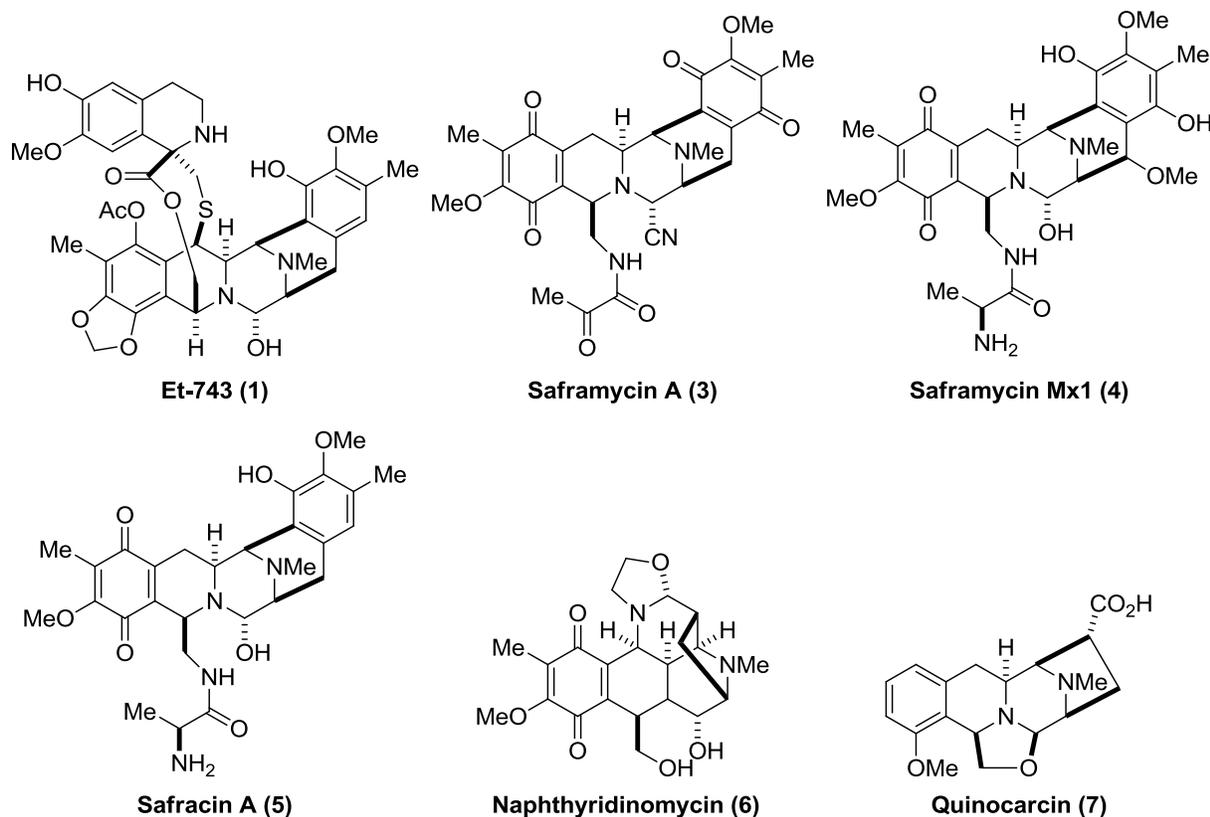


**Figure 6:** Et-743-induced DSBs mediated by TC-NER and MRN independent of replication.

### 1.4 Biosynthesis of Et-743

The studies of Et-743's biosynthesis have long been a challenge to the research community due to the inability to culture the bacterial symbiont *Candidatus Endoecteinascidia frumentensi* and the small amount of the isolated ecteinascidins. Despite these hurdles, some information of Et-743 production in nature was obtained indirectly from what we know about the related THIQ

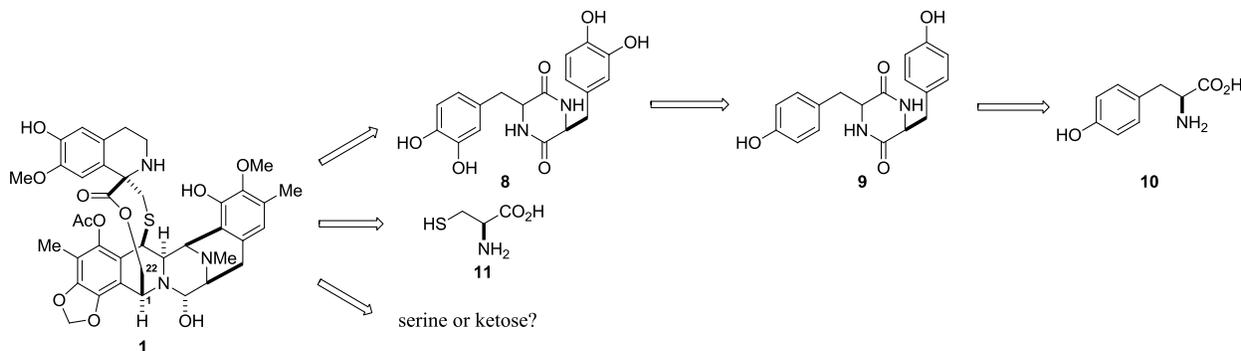
family members. As shown in figure 7, Et-743 shares a core THIQ structure with saframycin B (3),<sup>45</sup> saframycin Mx1 (4),<sup>46</sup> safracin A (5),<sup>47</sup> naphthyridinomycin (6),<sup>48</sup> and quinocarcine (7).<sup>49,50</sup> Since we have knowledge of how these THIQ representatives are produced in nature, we can derive the biosynthesis of Et-743 using limited information obtained from radioactive labeling studies and DNA collected from the tunicate consortium.



**Figure 7:** Structural similarity between Et-743 (1) and saframycin B (3), saframycin Mx1 (4), safracin A (5) and naphthyridinomycin (6).

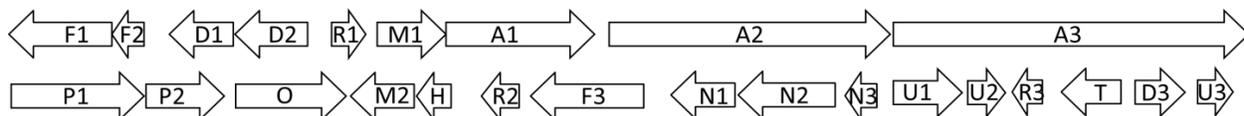
<sup>14</sup>C-Radiolabeled diketopiperazines (DKPs) 8 and 9 were found to incorporate in Et-743 when treated with the tunicate extract (figure 8).<sup>51</sup> The incorporation of <sup>14</sup>C-labeled tyrosine, on the other hand, was not conclusive since it is a common substrate for several biological pathways. Cysteine (11) was identified as a precursor of the macrolactone-bridge.<sup>52</sup> The most controversial information on Et-743 biosynthesis is the precursor to make up the C1-C22 moiety. Serine was originally proposed as the precursor of this  $\alpha$ -hydroxyethyl moiety, but no evidence

was found to support this proposal. A more recent study of Peng's group revealed the role of ketoses in the biosynthesis of naphthyridinomycin (**6**) and quinocarcin (**7**), that  $\alpha$ -hydroxyethyl-thiamine pyrophosphate, generated from ketose phosphates, made up the  $\alpha$ -hydroxyethyl moiety of these two natural products.<sup>53</sup> Since Et-743 also shares this structure, we speculate that its biosynthesis involves a similar ketose pathway.



**Figure 8:** Possible precursors of Et-743 biosynthesis.

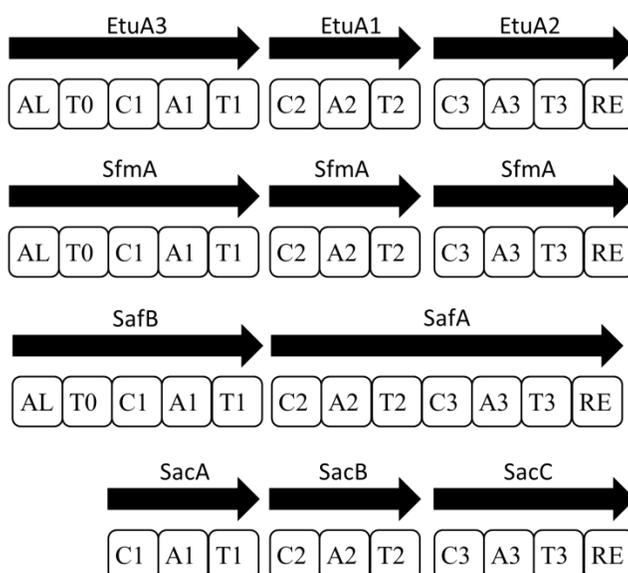
The genome responsible for the biosynthesis of Et-743 was solved by Sherman's and Williams' groups in 2011.<sup>7</sup> They applied metagenomic sequencing methodology on the tunicate consortium to overcome the difficulty of growing the bacterial symbiont. The genome pool was analyzed by comparing to the known biosynthetic pathways of saframycin A (Sfm) (**3**), saframycin Mx1 (Saf) (**4**) and safracin A (Sac) (**5**).<sup>54-56</sup> Their work resulted in the gene cluster (figure 9), which was then translated to the enzymes linked to the biosynthesis of Et-743 (Etu).<sup>7</sup>



**Figure 9:** Gene cluster encoding the biosynthesis of Et-743. A: NRPS; D: DNA processing; F: fatty acid biosynthesis; H: hydrolase; M: methyltransferases; N: amidotransferases; O: monooxygenase; P: pyruvate cassette; R: regulatory enzymes; T: drug transporter; U: unknown function.

Homology between Et-743 core modular nonribosomal peptide synthetase (NRPS) proteins and those of saframycin B, saframycin Mx1, and safracin A was used to construct Et-743 NRPS domains (figure 10). Et-743 NRPS contains three modules Etu1, Etu2 and Etu3, including a

common starter domain (AL-T) on Etu3 and a common reductive domain (RE) on Etu1, uniquely found in THIQ biosynthetic pathways. Furthermore, the biosynthesis of THIQ family, and also Et-743, was demonstrated to be non-collinear, in contrast to conventional NRPSs, which are usually collinear.<sup>57,58</sup> Also the discovery of C domain of SfmC serving as a Pictet-Spenglerase in the formation of the mono- and bis-THIQ intermediates of saframycin synthesis gave rise to a hypothesis that the correspondent C domain in EtuA2 is a Pictet-Spenglerase as well.<sup>59</sup>



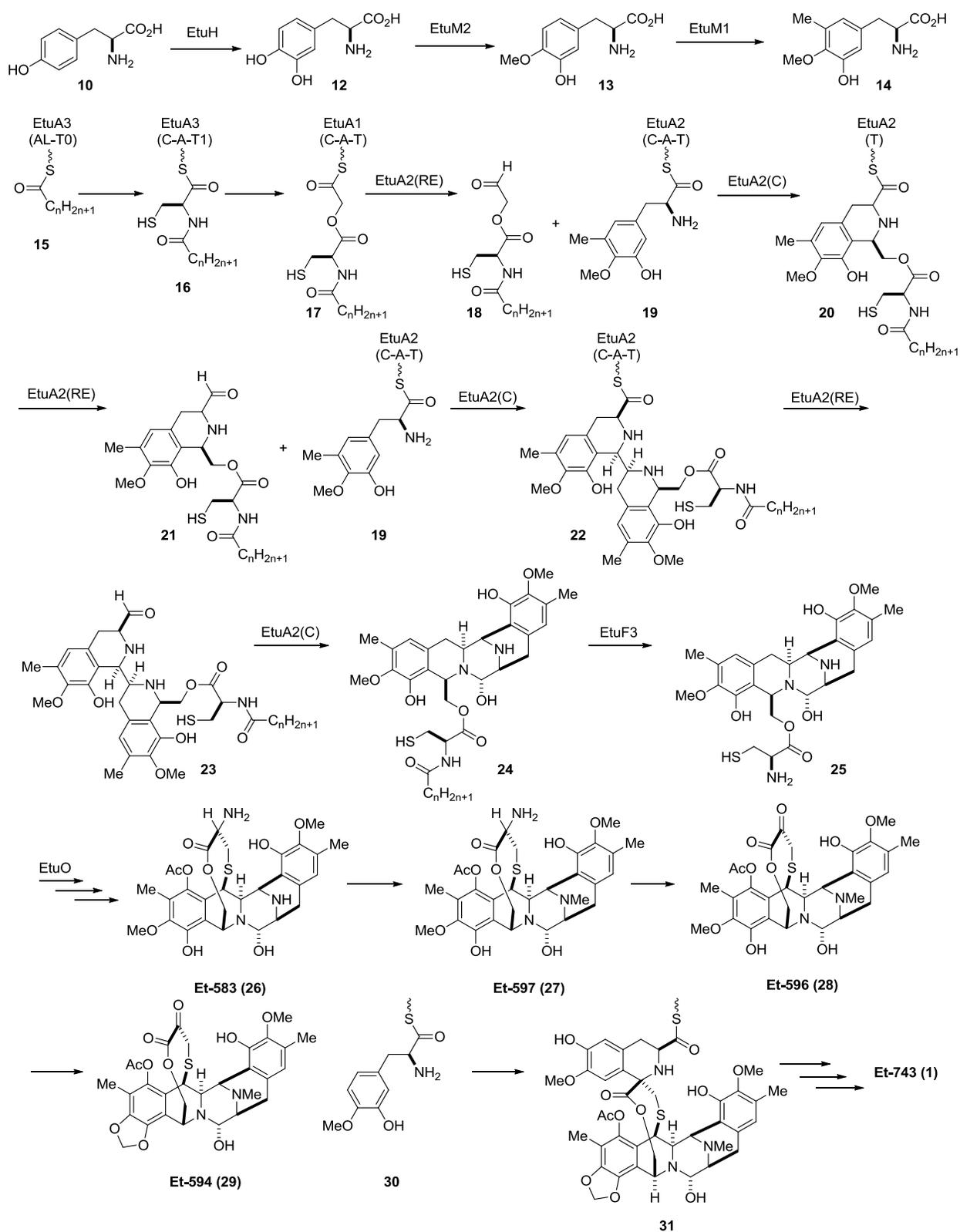
**Figure 10:** Et-743 NRPS proteins. AL: acyl ligase; T: thiolation; C: condensation; A: adenylation; RE: reduction.

The enzymatic catalysis of Et-743 synthesis is illustrated in scheme 1. Tyrosine derivative **14** was proposed a precursor of Et-743 biosynthesis. It is generated in the nature by first hydroxylation of L-tyrosine (**10**) by EtuH, followed by formation of the methyl ether moiety by EtuM2. EtuM1 was predicted to methylate intermediate **13** as previously seen in the biosynthetic pathways of saframycin B and safracin A.<sup>60</sup>

The biosynthesis of Et-743 is started with the activation of a long chain fatty acid by a serine at the starter domain AL-T. Insertion of a glycolic acid followed by reductive elimination yields

aldehyde **18**, which will condense with thioester **19** (the activated form of **14**) to furnish the first THIQ unit A of Et-743 (**20**). Reductive release of **20** gives aldehyde **21**, which undergoes Pictet-Spengler reaction with a second thioester **19** to generate bis-THIQ intermediate **22**. Carbinolamine **24** is formed by reductive release of **22**, followed by instant intramolecular condensation of the resulting aldehyde with the secondary amine under catalysis of C domain on EtuA2. The removal of the fatty acid chain can be done by EtuF, and the installation of the final phenol on THIQ unit A can be achieved by EtuO, a FAD-dependent monooxygenase homologue of SfmO2 and SacJ.<sup>56,61</sup>

The question of how intermediate **25** is transformed into Et-743 still remains unsolved. However, analyzing the isolated Ets can provide an insight of the final steps in the biosynthesis of the natural product. Intermediate **25** is converted to Et-583 (**26**), which is then methylated to provide Et-597 (**27**). Transamination of **27** happens to give Et-596 (**28**), and the dioxymethylene moiety is formed to furnish Et-594 (**29**). Condensation of Et-594 with tyrosine derivative **30** will generate **31**, which will be converted to Et-743 via a reductive release mechanism.



Scheme 1: Proposed biosynthetic pathway of Et-743.

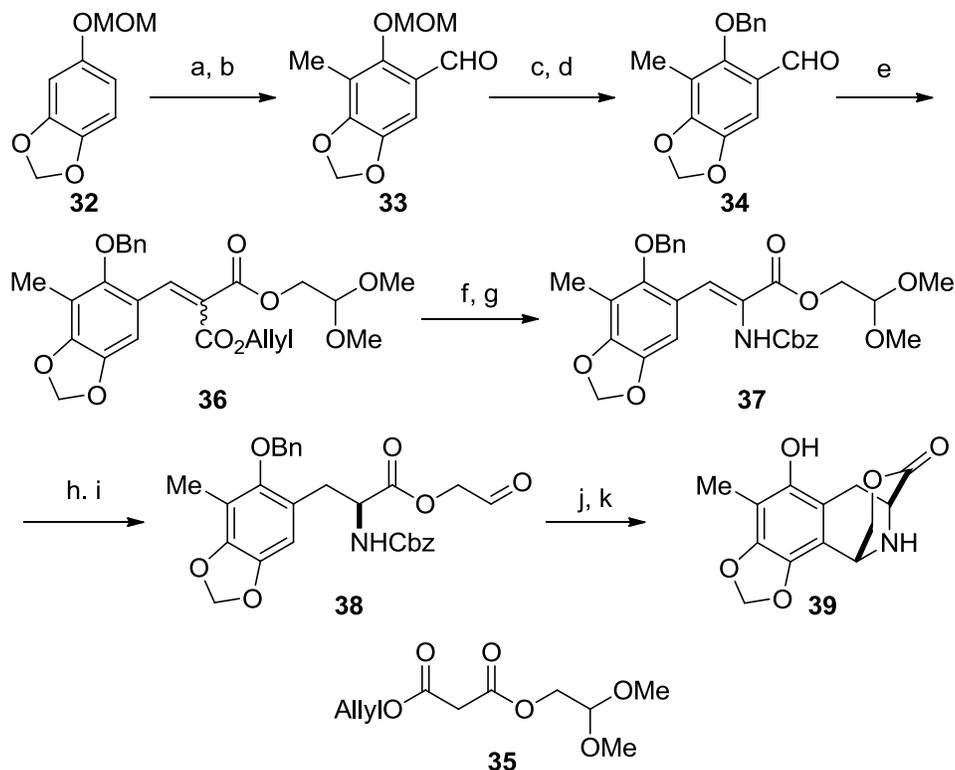
## 1.5 Total syntheses of Et-743

### 1.5.1 Corey total synthesis of Et-743

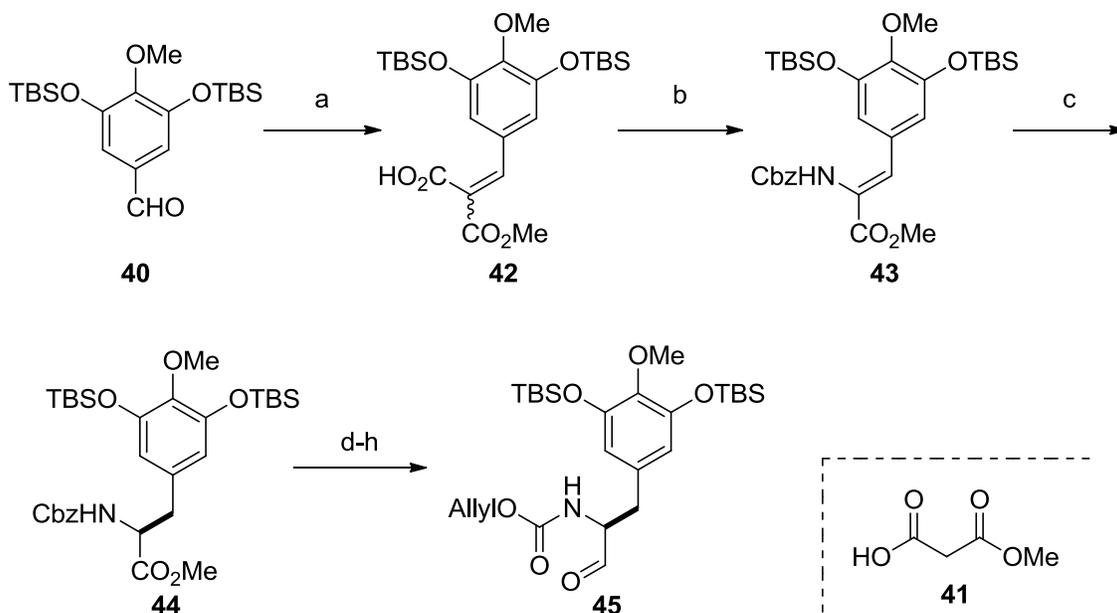
The first and pioneering synthesis of Et-743 was published by Corey and coworkers in 1996.<sup>62</sup> MOM-protected sesamol (**32**) was ortho methylated at C-2, followed by ortho formylation at C-5, forming **33** exclusively (scheme 2). Subsequent cleavage of the MOM-protecting group then protecting the resulting phenol with a benzyl group provided benzaldehyde **34**. Treatment of **34** with malonate **35** under catalysis of piperidine in the presence of acetic acid gave allyl ester **36**. Allyl ester cleavage, followed by Curtius rearrangement in the presence of benzyl alcohol produced **37**. Asymmetric hydrogenation of **37** was taken place under catalysis of Rh[(COD)-(R,R)-DiPAMP]<sup>+</sup>BF<sub>4</sub><sup>-</sup> in 97% yield (96% *ee*) and the resulting product was treated with methyl sulfonic acid at low temperature to furnish aldehyde **38**. Bridged lactone **39** was prepared by first treating **38** with boron trifluoride etherate and 4Å molecular sieves, then submitting the resulting lactone to palladium-catalyzed hydrogenation.

The synthesis of the right hand fragment was done under similar approach (scheme 3). Ester **42** was prepared from the condensation of aldehyde **40** with monomethyl malonate (**41**). Curtius rearrangement of **42** proceeded and the resulting isocyanate was trapped with benzyl alcohol to form protected amine **43**. Subsequent asymmetric hydrogenation of **43** formed amino ester **44**, which was then converted to aldehyde **45** via protecting group swap and reduction.

Strecker reaction between THIQ **39** and aldehyde **45** was accomplished, followed by allylation of the phenol gave **46** (scheme 4). After the reduction of the lactone, the TBS group was removed and the resulting phenol was treated with methyl sulfonic acid to furnish pentacycle **47**. The less hindered phenol underwent trifluoromethanesulfonation, followed by silylation of the aliphatic hydroxyl group and protection of the remaining phenol as a



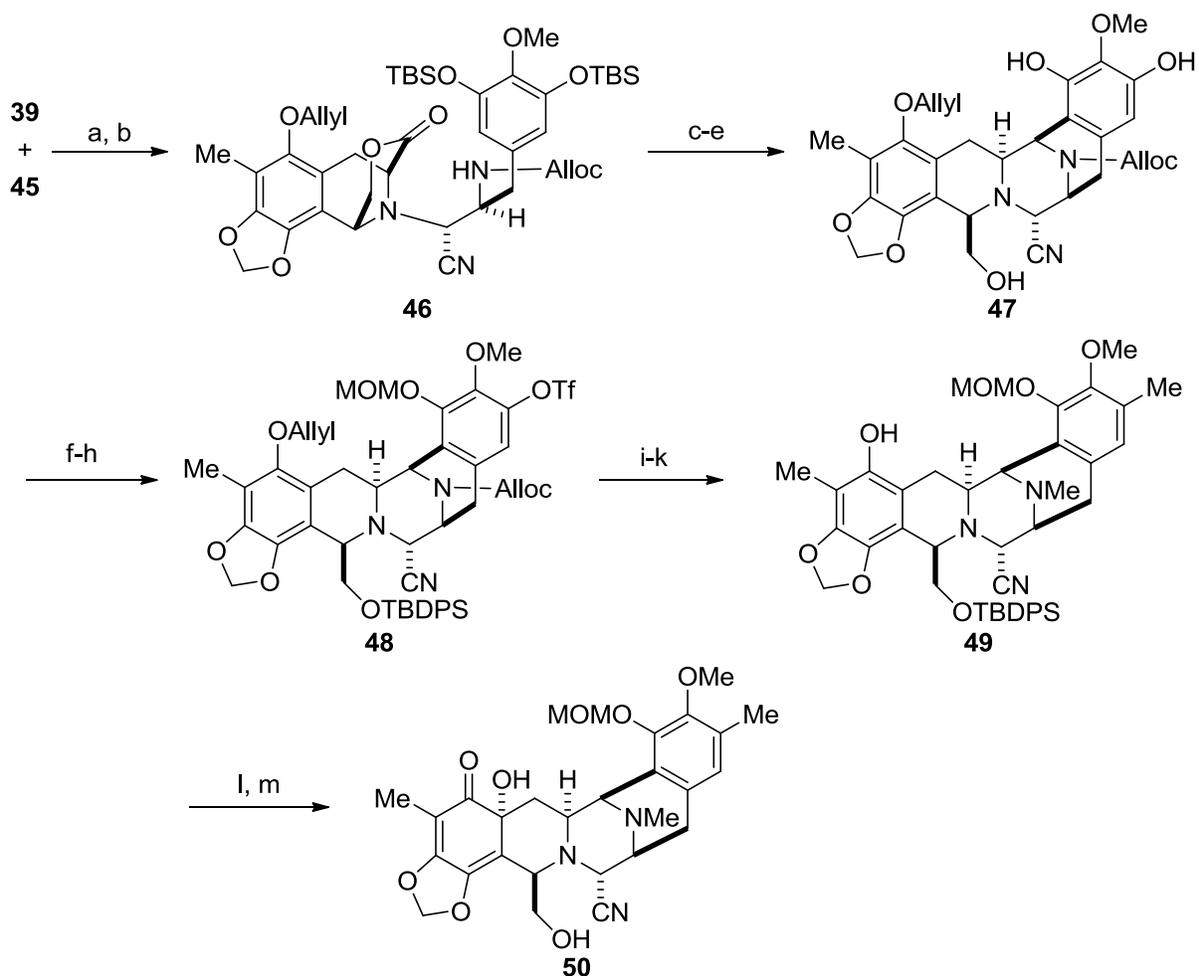
**Scheme 2:** Reagents and conditions (a) BuLi, TMEAD, 0°C, then MeI, -78°C to 23°C, 87%; (b) BuLi, -30°C, then DMF, 0°C, 64%; (c) MeSO<sub>3</sub>H, 0°C; (d) NaH, BnBr, 86% (2 steps); (e) **35**, piperidine, AcOH, MS 4Å, 99%; (f) Et<sub>3</sub>N/HCO<sub>2</sub>H, Pd(PPh<sub>3</sub>)<sub>4</sub>; (g) (PhO)<sub>2</sub>P(O)N<sub>3</sub>, Et<sub>3</sub>N, MS 4Å, then 70°C, BnOH, 93% (2 steps); (h) Rh[(COD)-(R,R)-DiPAMP]<sup>+</sup>BF<sub>4</sub><sup>-</sup>, H<sub>2</sub> (3 atm) (97%, 96% ee); (i) BF<sub>3</sub>•OEt<sub>2</sub>, H<sub>2</sub>O; (j) BF<sub>3</sub>•OEt<sub>2</sub>, MS 4Å, 73% (2 steps); (k) 10% Pd/C, H<sub>2</sub>, quant.



**Scheme 3:** Reagents and conditions (a) **41**, piperidine, AcOH, MS 3Å, 92%; (b) (PhO)<sub>2</sub>P(O)N<sub>3</sub>, Et<sub>3</sub>N, MS 4Å, then 70°C, BnOH, 89%; (c) Rh[(COD)-(R,R)-DiPAMP]<sup>+</sup>BF<sub>4</sub><sup>-</sup>, H<sub>2</sub>

(45 psi) (quant., 96% ee); (d) 10% Pd/C, H<sub>2</sub>, quant.; (e) AllocCl, py., 93%; (f) 0.2M HCl, AcOH; (g) TBSCl, imid., 95% (2steps); (h) DIBAL, -78°C, 90%.

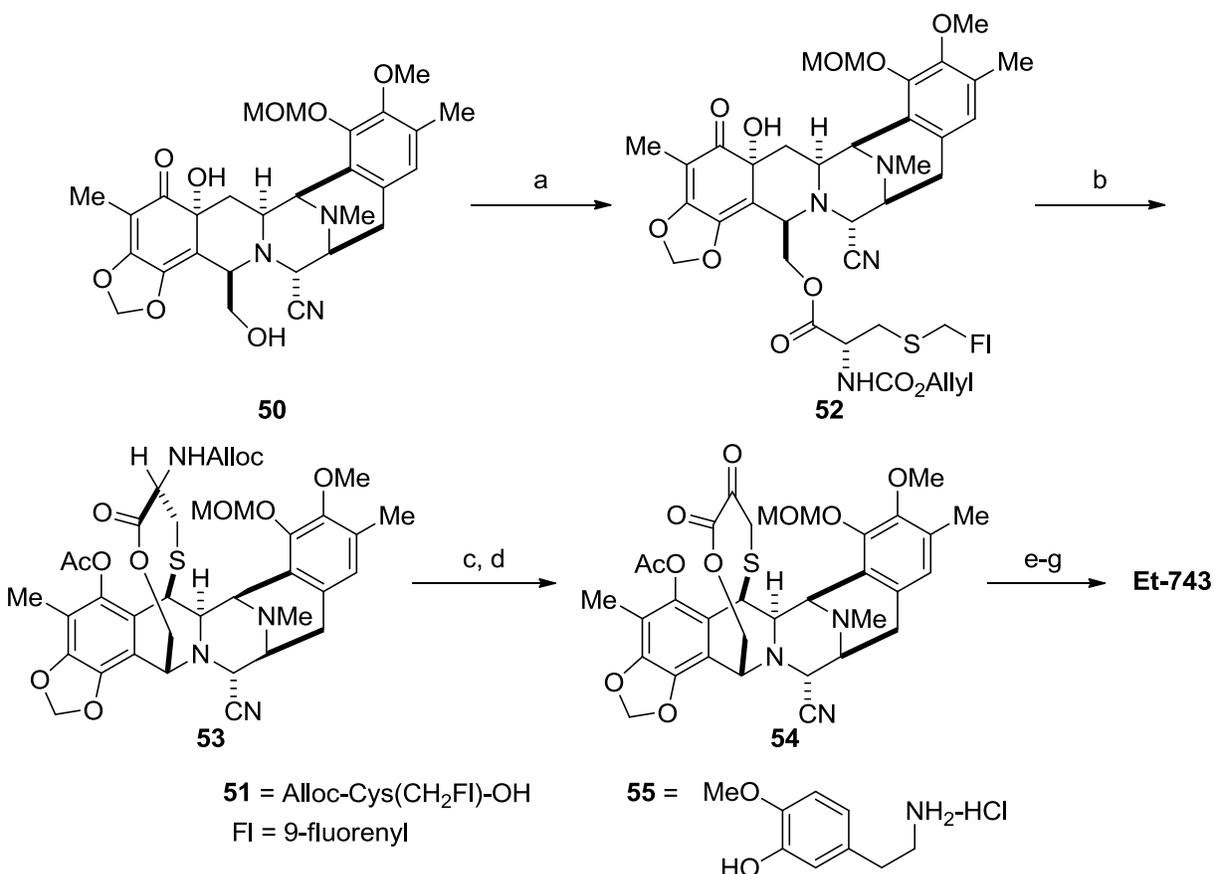
methoxymethyl ether to provide pentacyclic core **48**. Concomitant cleavage of allyl- and alloc-protecting group was done in quantitative yield, and the resulting amine was methylated, followed by Stille coupling in excess amount of tetramethyl tin to form intermediate **49**. Dihydroxy dienone **50** was generated by oxidation and desilylation of intermediate **49**.



**Scheme 4:** Reagents and conditions (a) AcOH, KCN; (b) AllylBr, Cs<sub>2</sub>CO<sub>3</sub>, 87% (2steps); (c) DIBAL, -78°C; (d) KF•2H<sub>2</sub>O; (e) MeSO<sub>3</sub>H, MS 3Å, 55% (3 steps); (f) Tf<sub>2</sub>NPh, Et<sub>3</sub>N, DMAP, 72%; (g) TBDPSCl, DMAP, 89%; (h) MOMBr, *i*Pr<sub>2</sub>NEt, 92%; (i) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Bu<sub>3</sub>SnH, AcOH, quant.; (j) CH<sub>2</sub>O, NaBH<sub>3</sub>CN, AcOH, 95%; (k) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, SnMe<sub>4</sub>, LiCl, 83%; (l) (PhSeO)<sub>2</sub>O; (m) TBAF, 75% (2 steps).

The final steps in Corey synthesis started with esterification of dienone **50** with cysteine derivative **51** (scheme 5). The bridged lactone **53** was made via the formation of quinone

methide intermediate and the replacement of the 9-fluorenyl group to the thiolated ion, followed by acylation of the newly formed phenol. After the removal of the alloc-protecting group, the newly formed amine was converted to  $\alpha$ -keto lactone **54** by biomimetic transamination. The reaction of **54** with amine **55** in the presence of silica gel furnished the THIQ unit C of Et-743. The final step in this synthesis involved the cleavage of the MOM-protecting group and the replacement of CN by OH to produce Et-743.

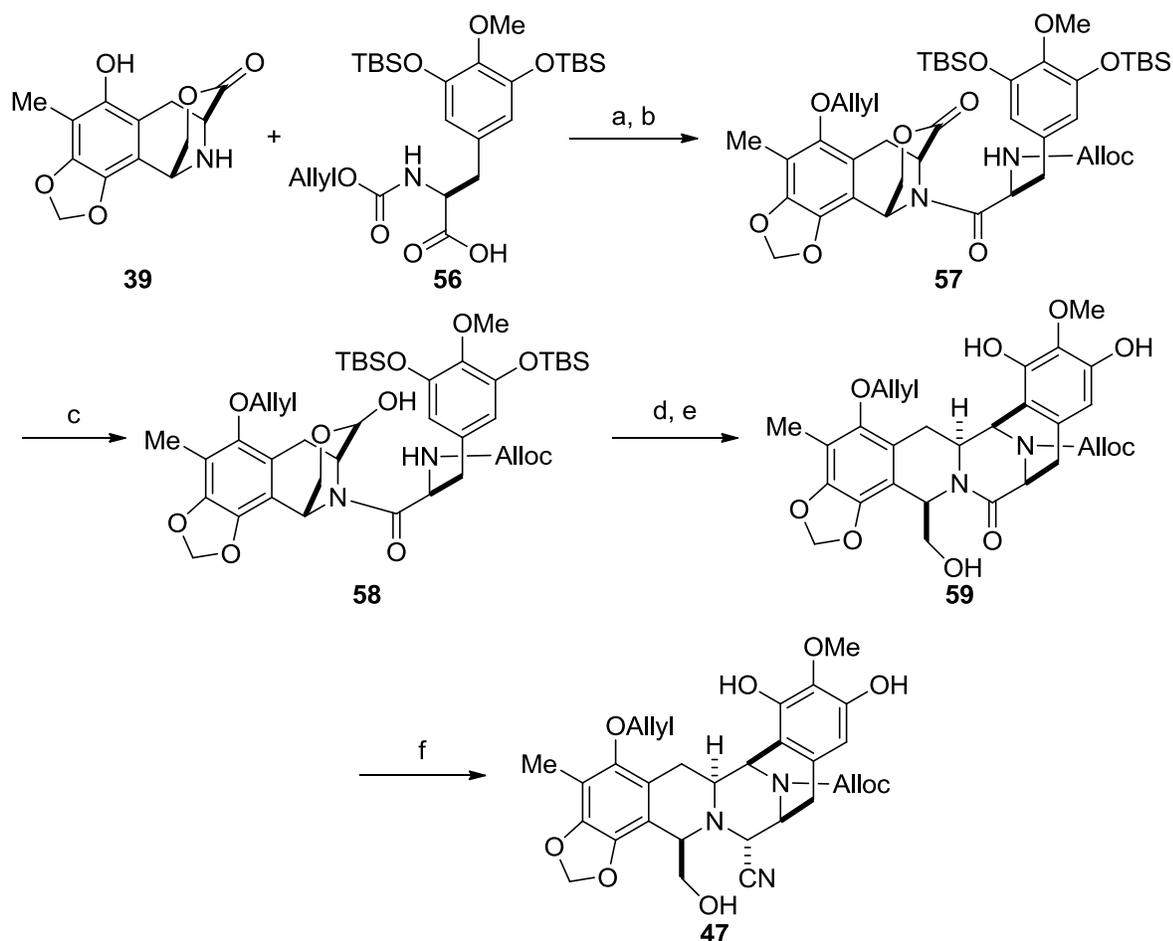


**Scheme 5:** Reagents and conditions (a) **51**, EDCI, DMAP, 91%; (b) DMSO, Tf<sub>2</sub>O; *i*-Pr<sub>2</sub>NEt; *t*BuOH; (Me<sub>2</sub>N)<sub>2</sub>CN*t*-Bu; Ac<sub>2</sub>O, 79%; (c) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Bu<sub>3</sub>SnH, AcOH, 84%; (d) [*N*-methylpyridinium-4-carboxaldehyde]<sup>+</sup>T, DBU, (CO<sub>2</sub>H)<sub>2</sub>, 70%; (e) silica gel, **55**, 82%; (f) TFA, H<sub>2</sub>O; (g) AgNO<sub>3</sub>, H<sub>2</sub>O.

### 1.5.2 Corey's improved synthesis of Et-743

Although their first synthetic route was able to supply Et-743 for clinical trials, Corey and Martinez published an improved synthetic route toward intermediate **47** (scheme 6) since the

former synthesis toward this intermediate was not scalable.<sup>63</sup> Amide **57** was produced by coupling of lactone **39** and acid **56** (prepared by an analogous route as seen in scheme 2), then allylation of the phenol. Partial reduction of the lactone provided **58**, which was then subjected to acid-catalyzed intramolecular Pictet-Spengler reaction after desilylation to give pentacyclic core **59**. Partial reduction of this intermediate furnish pentacycle **47** and the synthesis of Et-743 was accomplished following the route described earlier.



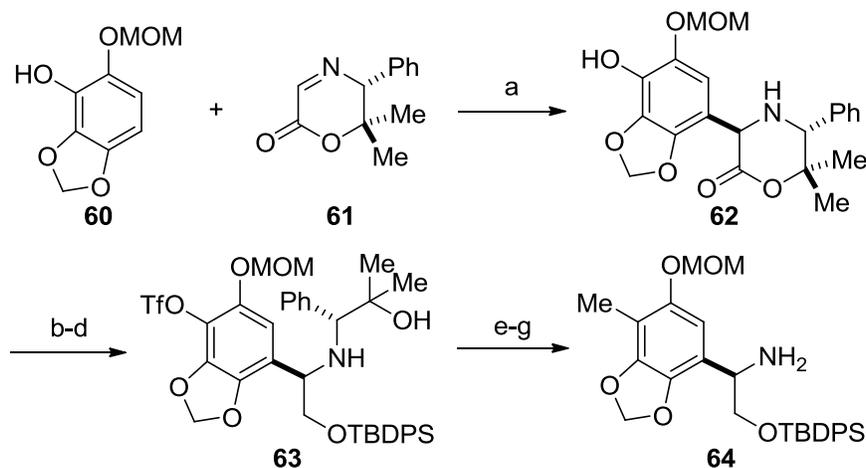
**Scheme 6:** Reagents and conditions (a) CIP, HOAT, Et<sub>3</sub>N, 0°C to 23°C; (b) AllylBr, Cs<sub>2</sub>CO<sub>3</sub>, 81% (2 steps); (c) LiAlH<sub>2</sub>(OEt)<sub>2</sub>, -78°C, 95%; (d) KF, MeOH; (e) 0.6M TfOH, BHT, 45°C, H<sub>2</sub>O, CF<sub>3</sub>CH<sub>2</sub>OH, 89% (2 steps); (f) LiAlH<sub>2</sub>(OEt)<sub>2</sub>, 0°C, then AcOH, 4.8M KCN, 87%.

Corey's first and improved syntheses of Et-743 illustrated that it is possible to generate the congested *tris*-tetrahydroisoquinoline structure of Et-743. More significantly, these syntheses

exploited late-stage biomimetic transamination reaction to construct the THIQ C unit of Et-743 that would be utilized by other synthetic groups in their syntheses of Et-743.

### 1.5.3 Fukuyama's first total synthesis of Et-743

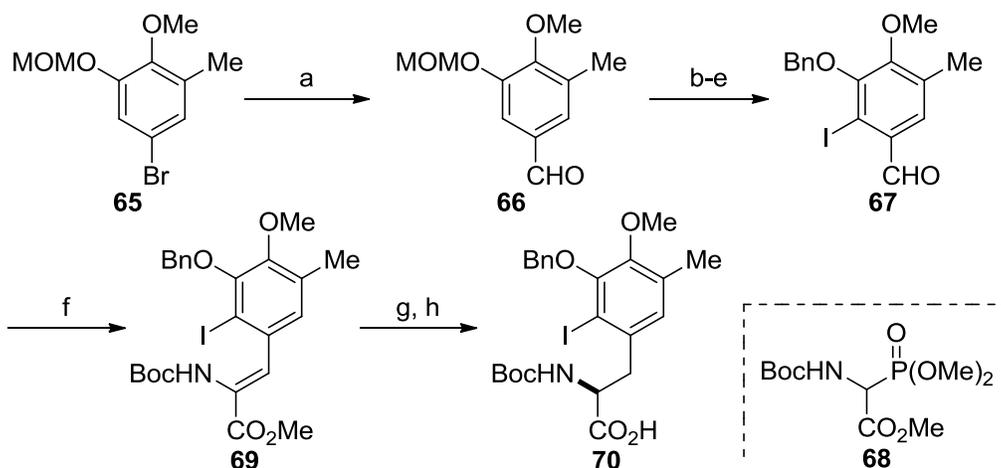
Fukuyama and coworkers published their first total synthesis of Et-743 in 2002.<sup>64</sup> Their synthesis commenced with the Mannich-type reaction of phenol **60** and chiral template **61** to produce intermediate **62** (scheme 7).<sup>65</sup> Amine **63** was prepared by trifluoromethanesulfonation of the phenol, reductive opening of the lactone and silylation of the resulting alcohol. Subsequent palladium-catalyzed cross-coupling reaction of **63** with methyl zinc chloride furnished the required C-2 methyl on the aromatic ring.<sup>66</sup> The resulting amino alcohol was subjected to oxidative cleavage to give amine **64**, which would become the THIQ A unit of Et-743.



**Scheme 7:** Reagents and conditions (a) TFA,  $-10^{\circ}\text{C}$ , 89%; (b)  $\text{Tf}_2\text{O}$ , py.,  $0^{\circ}\text{C}$ , 90%; (c)  $\text{NaBH}_4$ , MeOH,  $0^{\circ}\text{C}$ , 85%; (d) TBDPSCl, imidazole, 91%; (e)  $\text{MeZnCl}$ ,  $\text{PdCl}_2(\text{PPh}_3)_2$ , reflux, 97%; (f)  $\text{Pb}(\text{OAc})_4$ ,  $0^{\circ}\text{C}$ ; (g)  $\text{NH}_2\text{OH}\cdot\text{HCl}$ ,  $\text{NaOAc}$ , 89% (2 steps).

The right-hand fragment (THIQ B unit) was made by first conversion of the bromide **65** to aldehyde **66** (scheme 8). The introduction of the iodide was done by treating aldehyde **66** with *n*-butyl lithium, followed by addition of iodide. Replacing the MOM-protecting group for a benzyl protecting group and simultaneously removal of the dimethyl acetal provided

intermediate **67**, which was then submitted to Horner-Wadsworth-Emmon reaction to form **69**. Rhodium-catalyzed asymmetric hydrogenation of **69**, followed by hydrolysis of the methyl ester gave *N*-Boc amino acid **70** in high yield and enantiomeric excess.<sup>67</sup>



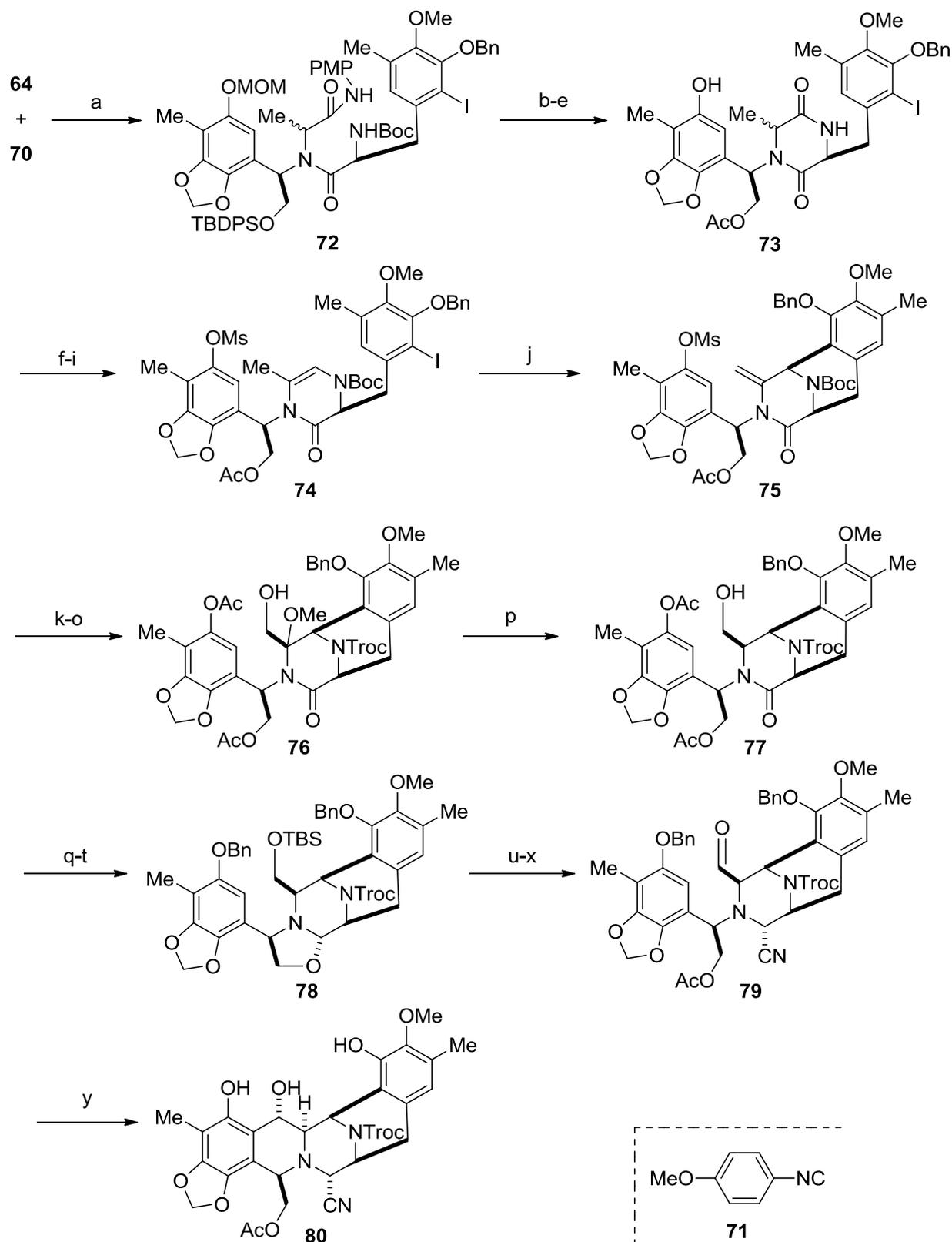
**Scheme 8:** Reagents and conditions (a) BuLi,  $-60^{\circ}\text{C}$ , then DMF, 79%; (b)  $\text{HC}(\text{OMe})_3$ , CSA, 94%; (c) BuLi,  $0^{\circ}\text{C}$ , then  $\text{I}_2$ ; (d) conc. HCl, THF, 72% (2 steps); (e) BnBr,  $\text{K}_2\text{CO}_3$ , reflux, 98%; (f) **68**, TMG, 93%; (g)  $\text{Rh}[(\text{COD})-(S,S)\text{-Et-DuPHOS}]^+\text{OTf}^-$ ,  $\text{H}_2$  (500 psi),  $50^{\circ}\text{C}$ , 99%, 94% *ee*; (h) LiOH,  $0^{\circ}\text{C}$  to rt, quant.

Refluxing two building blocks **64** and **70** with acetaldehyde and *p*-methoxyphenyl isocyanide **71** in methanol gave intermediate **72** (scheme 9).<sup>68</sup> Diketopiperazine **73** was synthesized by 1) desilylation of **72**, 2) acylation of the resulting alcohol, 3) simultaneous cleavage of the MOM ether and Boc group, and 4) refluxing the resulting amine in ethyl acetate. Methylsulfonylation of phenol **73** was followed by Boc-protection of the lactam, then partial reduction of this lactam and dehydration to produce alkene intermediate **74**. Intramolecular Heck reaction of this intermediate yielded tricycle **75**.<sup>69</sup> Protecting group swap was done and the resulting *N*-Troc-*O*-Ac intermediate was submitted to epoxidation condition, followed by acid-catalyzed opening of the resulting epoxide to furnish methoxyalcohol **76**. Subsequent reduction of **76** in the presence of trifluoroacetic acid happened exclusively on the less hindered side producing alcohol **77**, which was then protected with a TBS group. The synthesis of carbinolamine **78** was achieved by

removal of both acetyl group, followed by selective benzylation of the resulting phenol and partial reduction of the amide. Treating **78** with trimethylsilyl cyanide and boron trifluoride etherate yielded aminonitrile product, which was then converted to acetate ester. Subsequent desilylation and oxidation of the silyl ether moiety provided aldehyde **79**, which underwent aldol-type reaction after the cleavage of the benzyl ether, yielding pentacyclic core **80**.

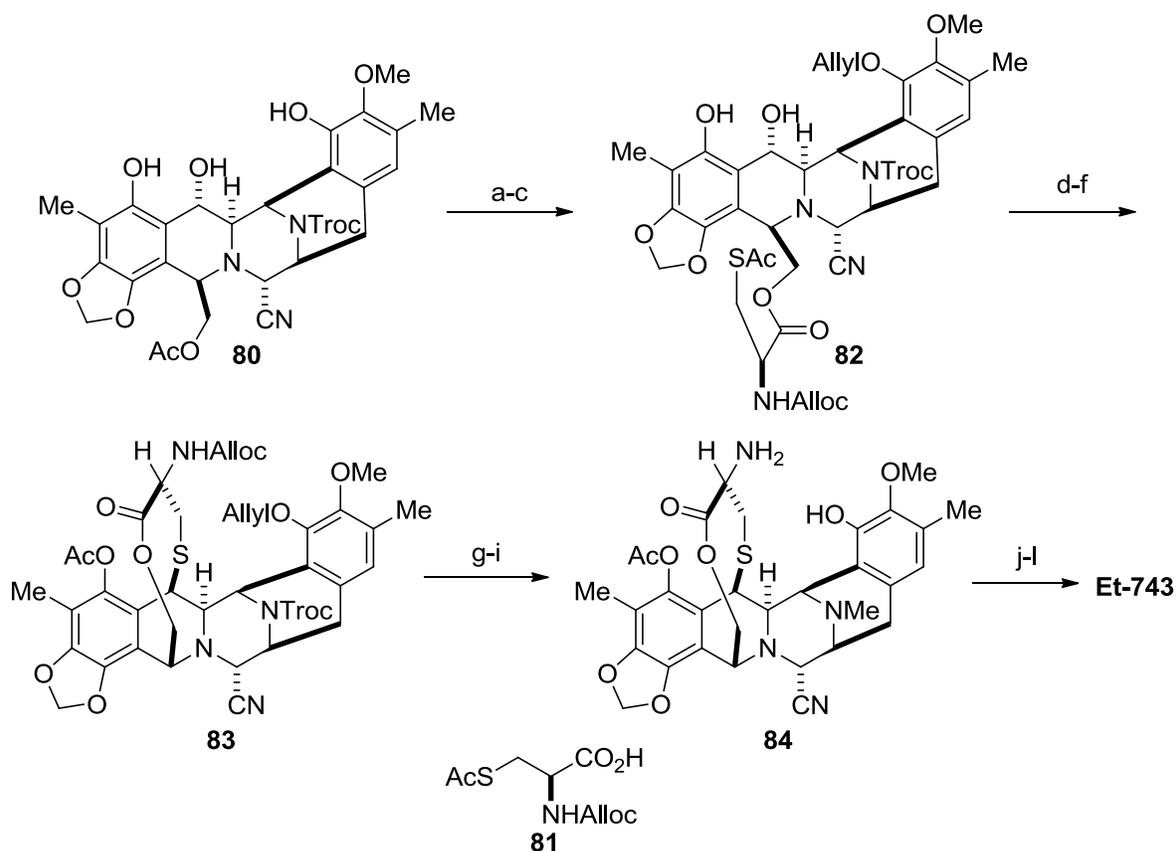
The less hindered phenol was selectively protected with an allyl group, and the acetate moiety was hydrolyzed to give an alcohol, which was then condensed with L-cysteine derivative to furnish intermediate **82** (scheme 10). Deacylation of **82**, followed by acid-catalyzed macrocyclization produced the macrolactone bridge of Et-743, which was then acylated at the phenol to yield **83**. Sequential *N*-Troc deprotection, methylation of the resulting amine, and concomitant cleavage of the allyl and alloc protecting groups generated intermediate **84**. **84** was transformed into Et-743 via similar approach seen in Corey's synthesis of the natural product, including biomimetic transamination of the  $\alpha$ -aminoester, Pictet-Spengler reaction of the newly form  $\alpha$ -ketoester with amine **55**, and replacement of the aminonitrile to a carbinolamine.

In summary, Fukuyama successfully assembled all components of the pentacyclic core via Ugi reaction. Albeit the high yielding in individual steps, the approach is insufficient for industrial preparation of Et-743 due to numerous protecting steps required.



**Scheme 9:** Reagents and conditions (a) **71**, MeCHO, MeOH, reflux, 90%; (b) TBAF, 89%; (c) Ac<sub>2</sub>O, py, DMAP, 93%; (d) TFA, anisole; (e) EtOAc, reflux, 87% (2 steps); (f) MsCl, py,

0°C, 91%; (g) Boc<sub>2</sub>O, DMAP, 97%; (h) NaBH<sub>4</sub>, H<sub>2</sub>SO<sub>4</sub>, 0°C; (i) CSA, quinoline, toluene, reflux, 88% (2 steps); (j) Pd<sub>2</sub>(dba)<sub>3</sub> (5 mol %), P(*o*-tol)<sub>3</sub> (20 mol %), Et<sub>3</sub>N, reflux, 83%; (k) NaOH, MeOH, H<sub>2</sub>O, reflux; (l) Ac<sub>2</sub>O, py, DMAP, 93% (2 steps); (m) TFA; (n) TrocCl, NaHCO<sub>3</sub>, 74% (2 steps); (o) DMDO, 0°C, then CSA, 90%; (p) NABH<sub>3</sub>CN, TFA, 0°C, 94%; (q) TBSCl, imidazole, 92%; (r) guanidinium nitrate, NaOMe, 40°C, 85%; (s) BnBr, K<sub>2</sub>CO<sub>3</sub>, reflux, 91%; (t) Red-Al, 0°C, 82%; (u) TMSCN, BF<sub>3</sub>•OEt<sub>2</sub>, 0°C, 73%; (v) Ac<sub>2</sub>O, py, DMAP, 92%; (w) HF, quant.; (x) Dess-Martin periodinane, 92%; (y) Pd/C, H<sub>2</sub>, 84%.

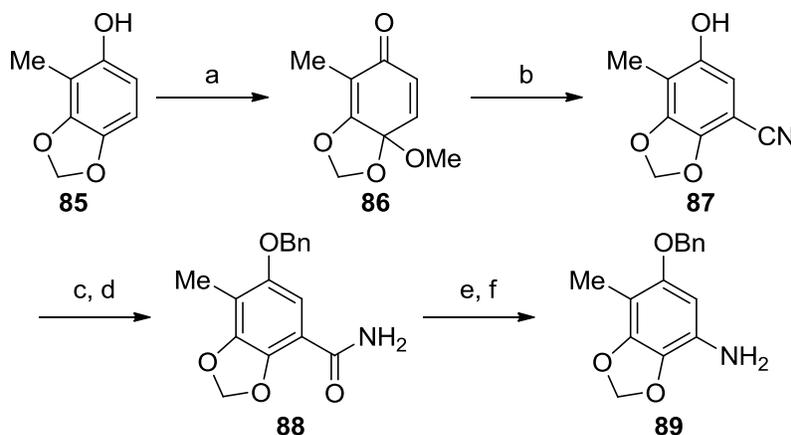


**Scheme 10:** Reagents and conditions (a) AllylBr, *i*-Pr<sub>2</sub>NEt, reflux, 89%; (b) K<sub>2</sub>CO<sub>3</sub>, MeOH, 99%; (c) **81**, EDCI, DMAP, 94%; (d) NH<sub>2</sub>NH<sub>2</sub>, 98%; (e) TFA, CF<sub>3</sub>CH<sub>2</sub>OH; (f) Ac<sub>2</sub>O, py, DMAP, 71%; (g) Zn, AcOH, 92%; (h) HCHO, AcOH, NaBH<sub>3</sub>CN, 96%; (i) Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, AcOH, Bu<sub>3</sub>SnH, 89%; (j) 4-formyl-1-methylpyridinium benzenesulfonate, then DBU, then citric acid, 54%; (k) NaOAc, **55**, 96%; (l) AgNO<sub>3</sub>, 93%.

#### 1.5.4 Fukuyama's second total synthesis of Et-743

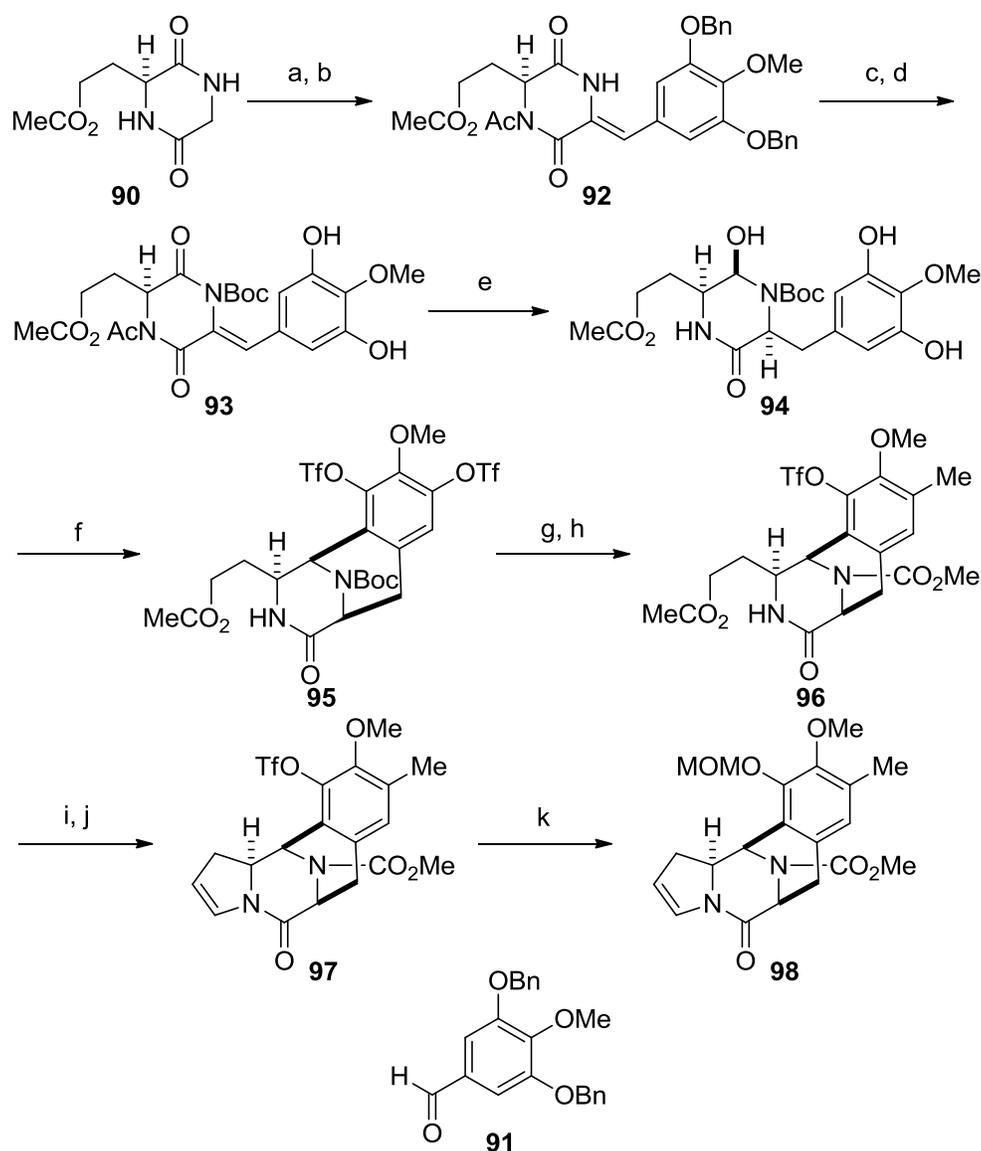
In an effort to achieve a more practical synthetic route to Et-743, Fukuyama and coworkers published their second total synthesis of Et-743 in 2013.<sup>70</sup> The synthesis started with the oxidation of phenol **85** in methanol to generate dienone **86**, which was subsequently treated with sodium cyanide to give **87** (scheme 11).<sup>71</sup> Benzoylation of the phenol, followed by hydrolysis of

the resulting nitrile provided amide **88**, which underwent Hoffmann rearrangement to furnish the left hand aromatic fragment **89**.



**Scheme 11:** Reagents and conditions (a)  $\text{PhI}(\text{OAc})_2$ , MeOH,  $0^\circ\text{C}$ ; (b) NaCN,  $0^\circ\text{C}$  to rt, 37% (2 steps); (c) BnBr,  $\text{K}_2\text{CO}_3$ ; (d) aq  $\text{H}_2\text{O}_2$ ,  $\text{K}_2\text{CO}_3$ ; (e)  $\text{PhI}(\text{OAc})_4$ , KOH,  $0^\circ\text{C}$ ; (f) LiOH, EtOH,  $\text{H}_2\text{O}$ , reflux, 83% (4 steps).

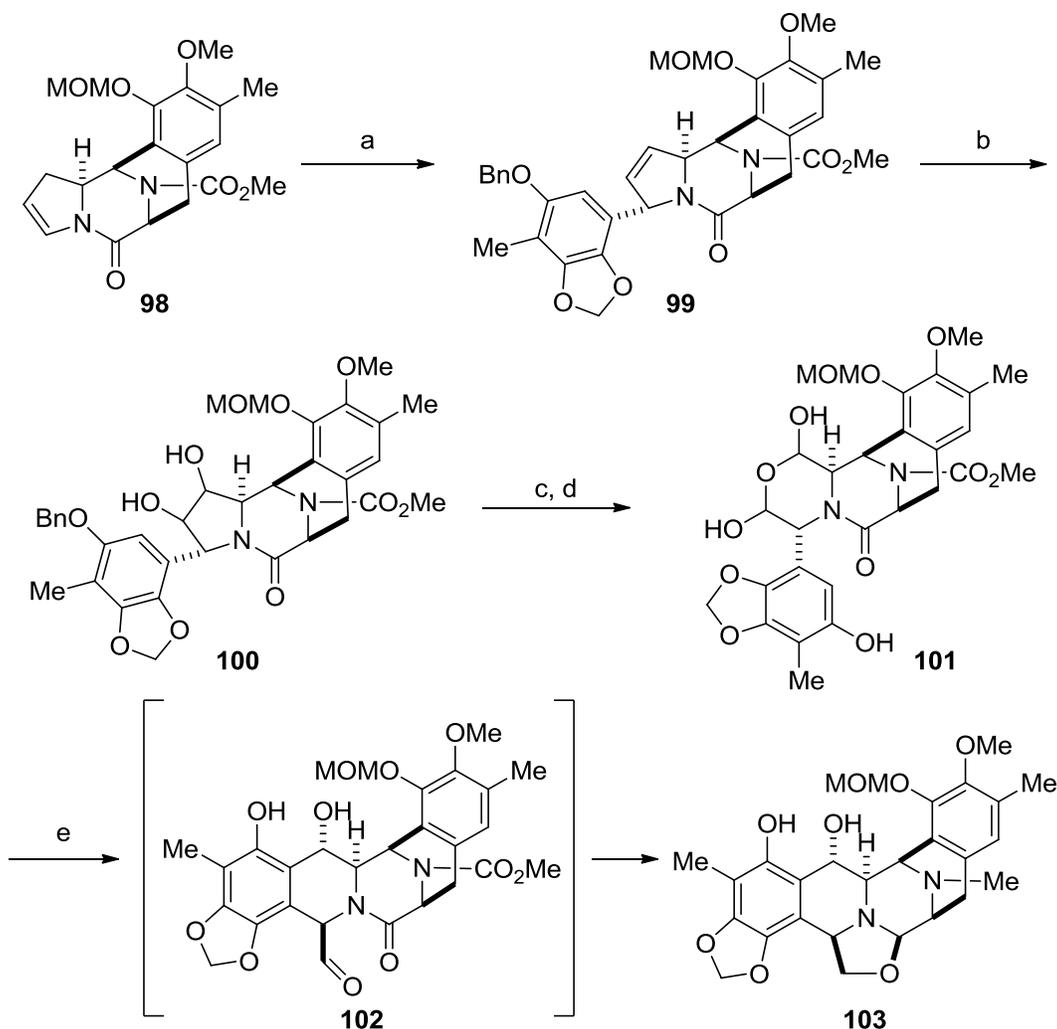
The synthesis of the right hand fragment commenced with diacylation of diketopiperazine **90** (scheme 12).<sup>72</sup> Perkin condensation of the resulting product with aldehyde **91** provided intermediate **92**. Boc-protecting group was introduced and the benzyl groups were removed to yield **93**, which was then partially reduced to carbinolamine **94**. Treatment of **94** with trifluoroacetic acid generated the cyclized product via an N-acyliminium ion intermediate, which was submitted to non-selective trifluoromethanesulfonylation to furnish compound **95**. Selective Suzuki-Miyaura coupling of **95** with trimethylboroxine happened at the less hindered triflate, followed by protecting group swap of the amine afforded intermediate **96**. Selective reduction of the methylester moiety and subsequent dehydration of the product yielded alkene **97**. The desired right hand fragment **98** was made by hydrolysis of the remaining triflate, followed by MOM-protection of the resulting phenol.



**Scheme 12:** Reagents and conditions (a)  $\text{Ac}_2\text{O}$ ,  $130^\circ\text{C}$ , 80%; (b) **91**,  $t\text{-BuOK}$ ,  $-78^\circ\text{C}$  to rt; DBU,  $0^\circ\text{C}$ ; (c)  $\text{Boc}_2\text{O}$ , DMAP, quant. (2steps); (d)  $\text{H}_2$  (750 psi), Pd/C; (e)  $\text{H}_2\text{NNH}_2\cdot\text{H}_2\text{O}$ ; evaporation;  $\text{NaBH}_4$ , MeOH,  $0^\circ\text{C}$ , 57% (2 steps); (f) TFA,  $\text{CF}_3\text{CH}_2\text{OH}$ ; evaporation;  $\text{PhNTf}_2$ , DMAP,  $\text{Cs}_2\text{CO}_3$ , 88%; (g) trimethylboroxine,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{K}_3\text{PO}_4$ ,  $100^\circ\text{C}$ , 92%; (h) HCl;  $\text{ClCO}_2\text{Me}$ ,  $\text{NaHCO}_3$ ,  $0^\circ\text{C}$ , 91%; (i) *L*-selectride,  $-42^\circ\text{C}$ ; (j) CSA, toluene, relax, 55% (2 steps); (k) aq KOH; MOMCl,  $0^\circ\text{C}$ , 95%.

The coupling of the two fragments was done by first converting the left hand amine to a diazonium salt, followed by Heck reaction with the right hand fragment, providing intermediate **99** as a single stereo- and regio-isomer (scheme 13).<sup>73</sup> Dihydroxylation of the alkene furnished **100**, which was submitted to oxidative cleavage and debenzoylation to give phenol **101**.

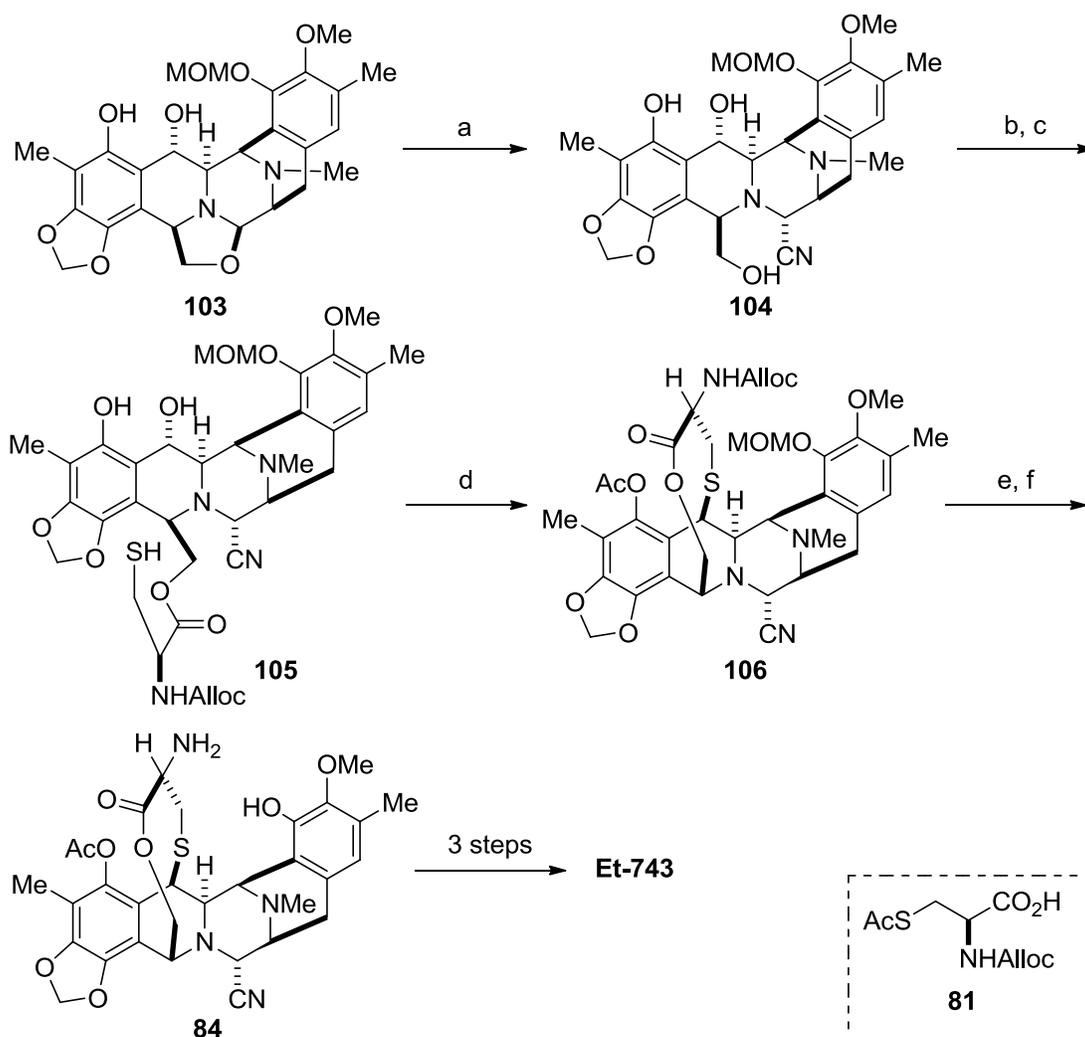
Pentacycle **103** was produced by heating **101** to promote aldol-type reaction of the phenol moiety and the dialdehyde, followed by treatment with Red-Al to form the oxazolidine ring.



**Scheme 13:** Reagents and conditions (a) **89**,  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $t\text{-BuONO}$ ,  $-15^\circ\text{C}$  to  $0^\circ\text{C}$ , then **98**,  $\text{Pd}_2(\text{dba})_3$ ,  $\text{NaOAc}$ ; (b)  $\text{OsO}_4$ ,  $\text{K}_3[\text{Fe}(\text{CN})_6]$ ,  $\text{K}_2\text{CO}_3$ , quinuclidine $\cdot\text{HCl}$ ,  $\text{MeSO}_2\text{NH}_2$ ,  $t\text{-BuOH}$ , 93% (2 steps); (c)  $\text{H}_5\text{IO}_6$ ,  $0^\circ\text{C}$ , 87%; (d)  $\text{H}_2$ ,  $\text{Pd/C}$ ; (e)  $m\text{-xylene}$ ,  $120^\circ\text{C}$ ; Red-Al,  $-42$  to  $60^\circ\text{C}$ , 76% (2 steps).

The last few steps in this synthesis involved the formation of the macrolactone-bridge and the C-ring via similar approach as seen in their first total synthesis of Et-743. Oxazolidine **103** was converted to aminonitrile **104** by treatment with potassium cyanide (scheme 14). Esterification, followed by deacylation afforded compound **105**, which was then treated with trifluoroacetic acid to form the macrolactone and acylated at the phenol moiety to give intermediate **106**. MOM

and Alloc deprotection of this intermediate generated known compound **84**, and the synthesis of Et-743 from **84** was accomplished in three known steps described in their previous synthesis of Et-743.

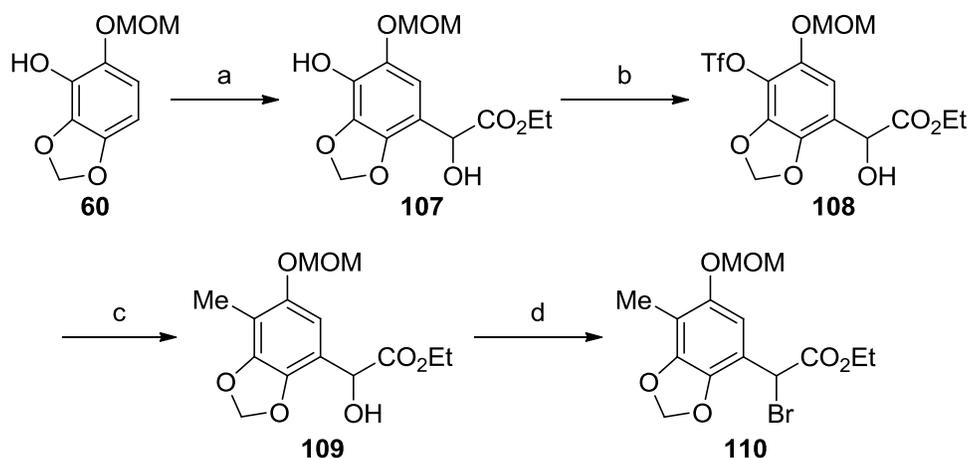


**Scheme 14:** Reagents and conditions (a) KCN, AcOH, 98%; (b) **81**, EDCI, DMAP, 92%; (c) H<sub>2</sub>NNH<sub>2</sub>.H<sub>2</sub>O, 85%; (d) TFA, CF<sub>3</sub>CH<sub>2</sub>OH; toluene, evaporation; Ac<sub>2</sub>O, py, 55%; (e) TFA, 64%; (f) (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>, AcOH, Bu<sub>3</sub>SnH, 95%.

### 1.5.5 Zhu's synthesis of Et-743

In 2005, Zhu and coworkers published their total synthesis of Et-743.<sup>74</sup> Methoxymethyl ether **60** was converted to ester **107** when treated with ethyl glyoxalate (scheme 15).<sup>64</sup> Intermediate **110** was made by selective trifluoromethane sulfonation of the phenol, followed by

Suzuki-Miyaura cross coupling of the resulting triflate with trimethyl boroxine and the replacement of the benzylic alcohol with a bromine.<sup>75,76</sup>

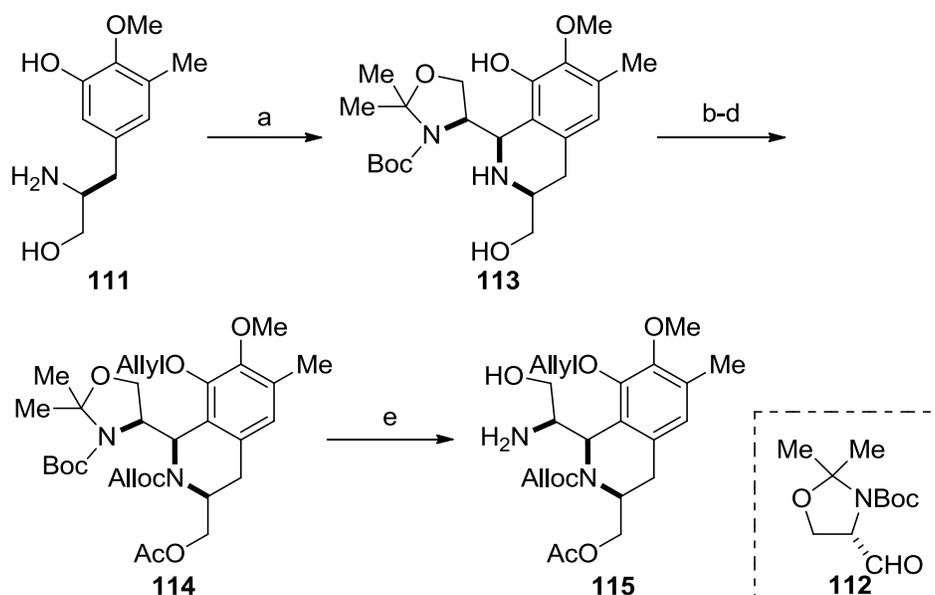


**Scheme 15:** Reagents and conditions (a) LiCl, MS 3 Å, HFIP, toluene, ethyl glyoxylate, 97%; (b) 4-nitrophenyltriflate, K<sub>2</sub>CO<sub>3</sub>, 94%; (c) trimethyl boroxine, K<sub>3</sub>PO<sub>4</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, dioxane, reflux, 93%; (d) SOBr<sub>2</sub>, benzotriazole, 91%.

The synthesis of the right hand side fragment started with the condensation of the known aminoalcohol **111** and *L*-Garner's aldehyde **112** (scheme 16).<sup>77-80</sup> The resulting product **113** was protected with alloc and allyl protecting group, followed by acylation of the primary alcohol to yield intermediate **114**. Subsequent treatment of **114** with trifluoroacetic acid furnished desired aminoalcohol **115**.

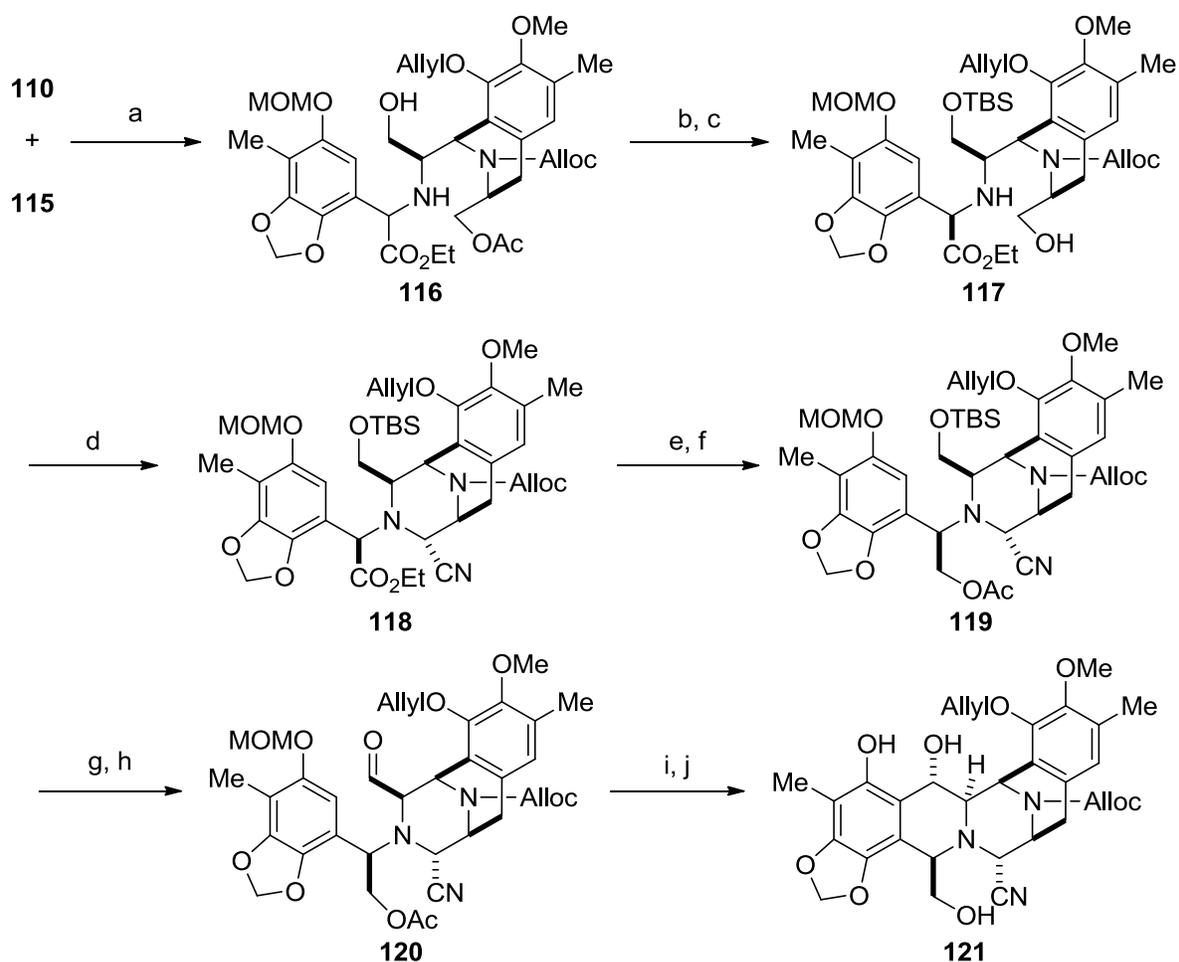
Coupling of the two building blocks **110** and **115** generated alcohol **116**, which was then protected with a silyl protecting group (scheme 17). The stereocenter of the ethyl ester moiety was resolved, and the acetyl ester was cleaved at the same time when treated with potassium carbonate giving intermediate **117** as a single diastereomer. **117** was submitted to oxidation condition to produce an aldehyde, which underwent Strecker reaction spontaneously to give aminonitrile **118**. Reduction of the ethyl ester, followed by acylation of the resulting alcohol furnished intermediate **119**, which was then converted to aldehyde **120** by removal of the TBS-

protecting group and oxidation of the resulting alcohol. **120** was submitted to acid-catalyzed cleavage of the methoxymethyl ether, then basic condition to produce pentacycle **121**.

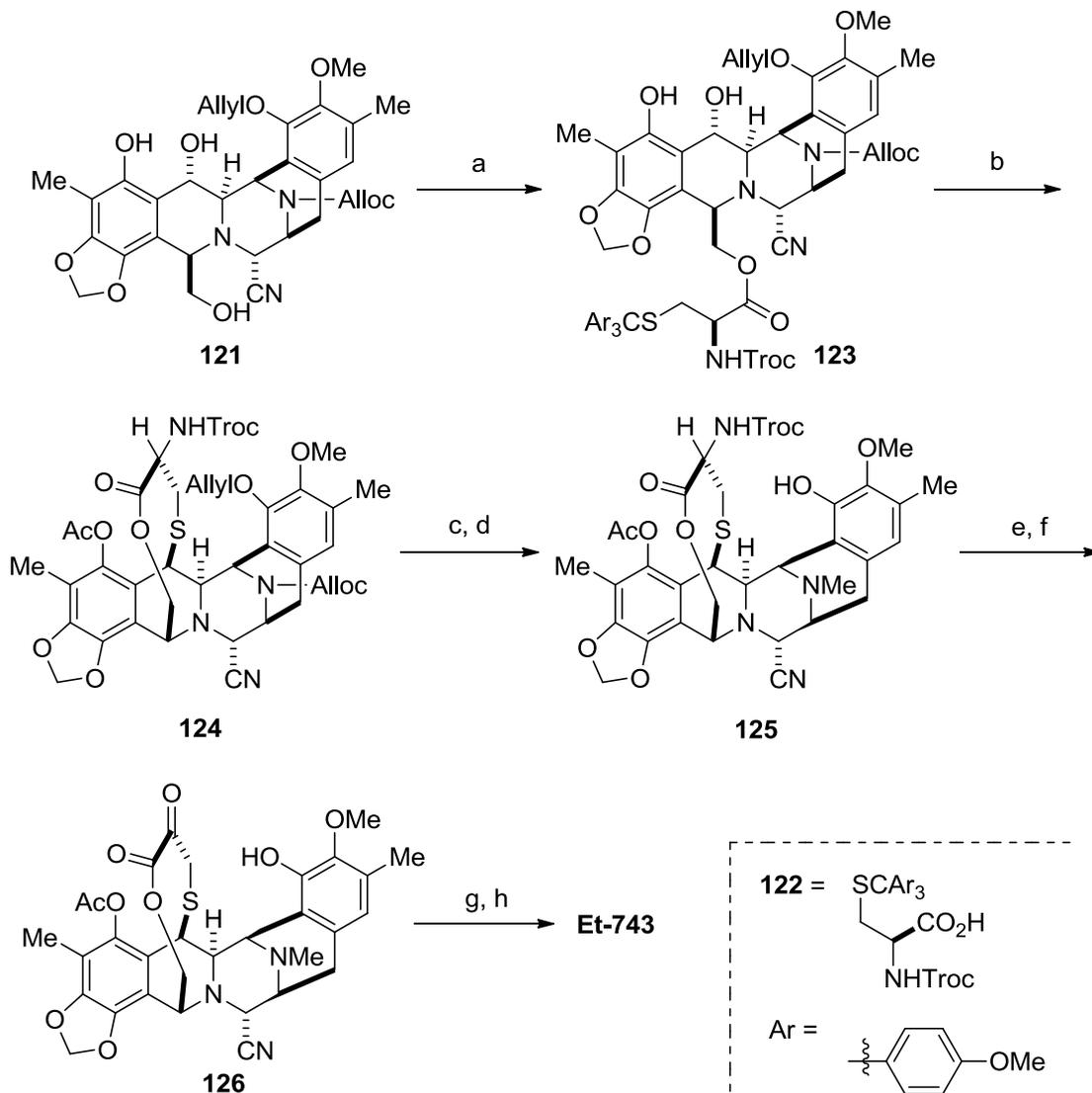


**Scheme 16:** Reagents and conditions (a) **112**, AcOH, CF<sub>3</sub>CH<sub>2</sub>OH, MS 3 Å, 84%; (b) AllocCl, NaHCO<sub>3</sub>, 88%; (c) AllylBr, Cs<sub>2</sub>CO<sub>3</sub>, 86%; (d) Ac<sub>2</sub>O, py, DMAP, 92%; (e) TFA, 72%.

The finishing steps in Zhu's synthesis of Et-743 were done in a similar methodology seen in Fukuyama's synthesis of Et-743 with some modification of the protecting groups. The less hindered hydroxyl of **121** underwent esterification with acid **122** to give ester **123**. The macrolactone-bridge was made under acidic condition after the formation of the free thiol, and the remaining phenol was acylated to furnish intermediate **124**. Allyl and alloc deprotection, followed by reductive amination yielded **125**, which was converted to ketoester **126** under troc-deprotection and transamination conditions. Intermediate **126** was transformed into Et-437 under same conditions reported by Corey and coworkers.



**Scheme 17:** Reagents and conditions (a)  $\text{Et}_3\text{N}$ , 68%; (b) TBSCl, imid., 97%; (c)  $\text{K}_2\text{CO}_3$ , 94%; (d) Dess-Martin periodinane, then TMS-CN,  $\text{ZnCl}_2$ , 78%; (e)  $\text{LiBH}_4$ , MeOH,  $0^\circ\text{C}$ , 80%; (f)  $\text{Ac}_2\text{O}$ , py., DMAP, 92%; (g)  $\text{HF}\cdot\text{H}_2\text{O}$ , 91%; (h) Dess-Martin periodinane, 93%; (i) TFA, 95%; (j)  $\text{K}_2\text{CO}_3$ , 96%.



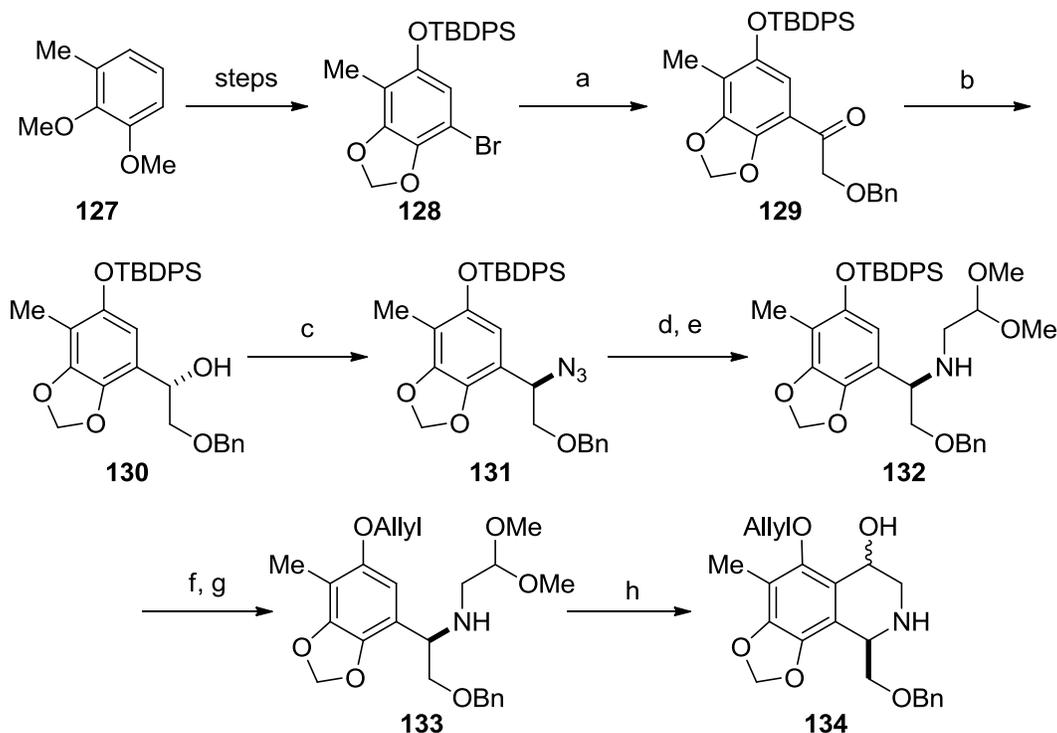
**Scheme 18:** Reagents and conditions (a) **122**, EDCI, DMAP, 95%; (b) TFA, then Ac<sub>2</sub>O, py., DMAP, 77%; (c) Bu<sub>3</sub>SnH, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, AcOH, 87%; (d) NaBH<sub>3</sub>CN, AcOH, HCHO, 96%; (e) Zn, AcOH, 92%; (f) 4-formyl-1-methylpyridinium benzenesulfonate, sat. aq. oxalic acid, DBU, 53%; (g) **55**, NaOAc, 97%; (h) AgNO<sub>3</sub>, H<sub>2</sub>O, 92%.

## 1.6 Formal syntheses of Et-743

### 1.6.1 Danishefsky's formal synthesis of Et-743

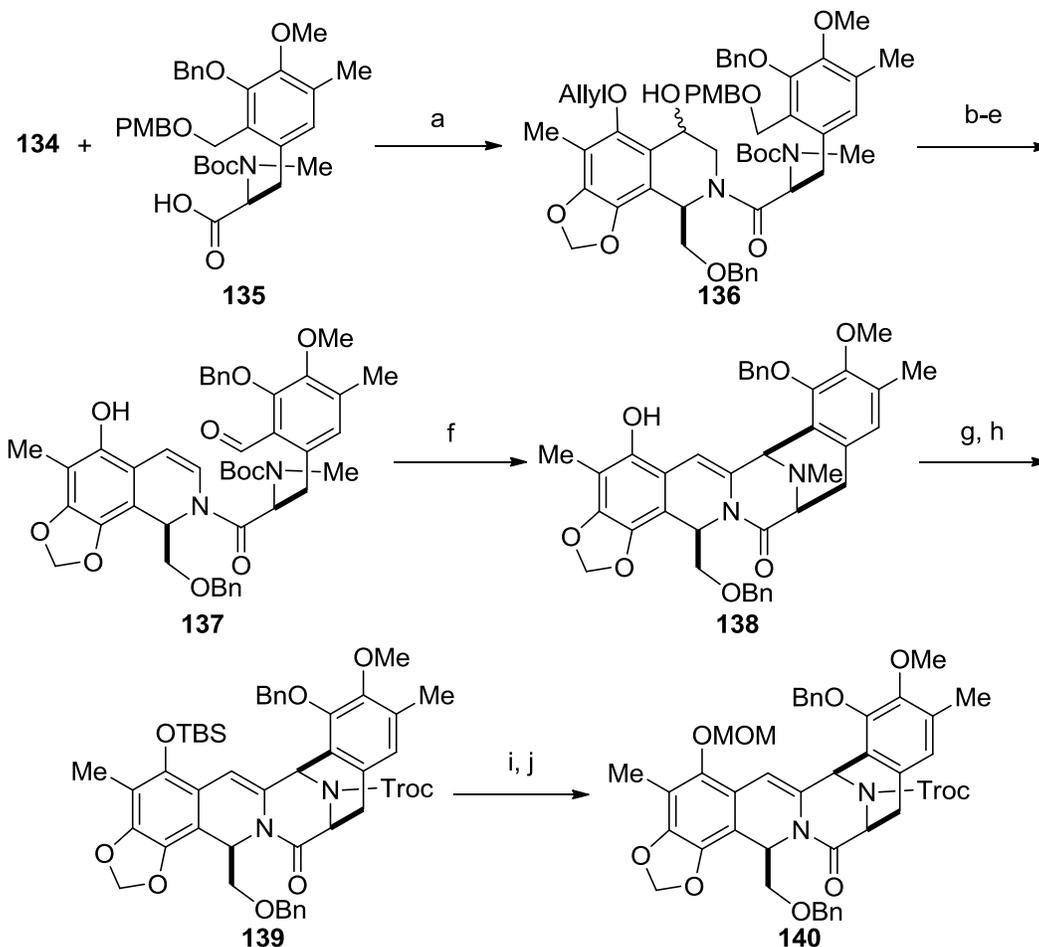
The first formal synthesis of Et-743 was reported by Danishefsky and coworkers in 2006.<sup>81</sup> Phenyl bromide **128**, which was made from commercially available 2,3-dimethoxy toluene (**127**), was lithiated and reacted with Weinreb amide of benzyloxyglycolic acid to afford ketone

**129** (scheme 19).<sup>82,83</sup> Asymmetric hydrogenation of this ketone produced alcohol **130**,<sup>84</sup> which underwent Mitsunobu reaction to give azide **131**. Hydrogenation of the azide, followed by reductive amination with 2,2-dimethoxy acetaldehyde generated acetal **132**. Desilylation and allylation of the resulting phenol yielded **133**, which can be transformed into THIQ **134** when treated with hydrochloric acid.



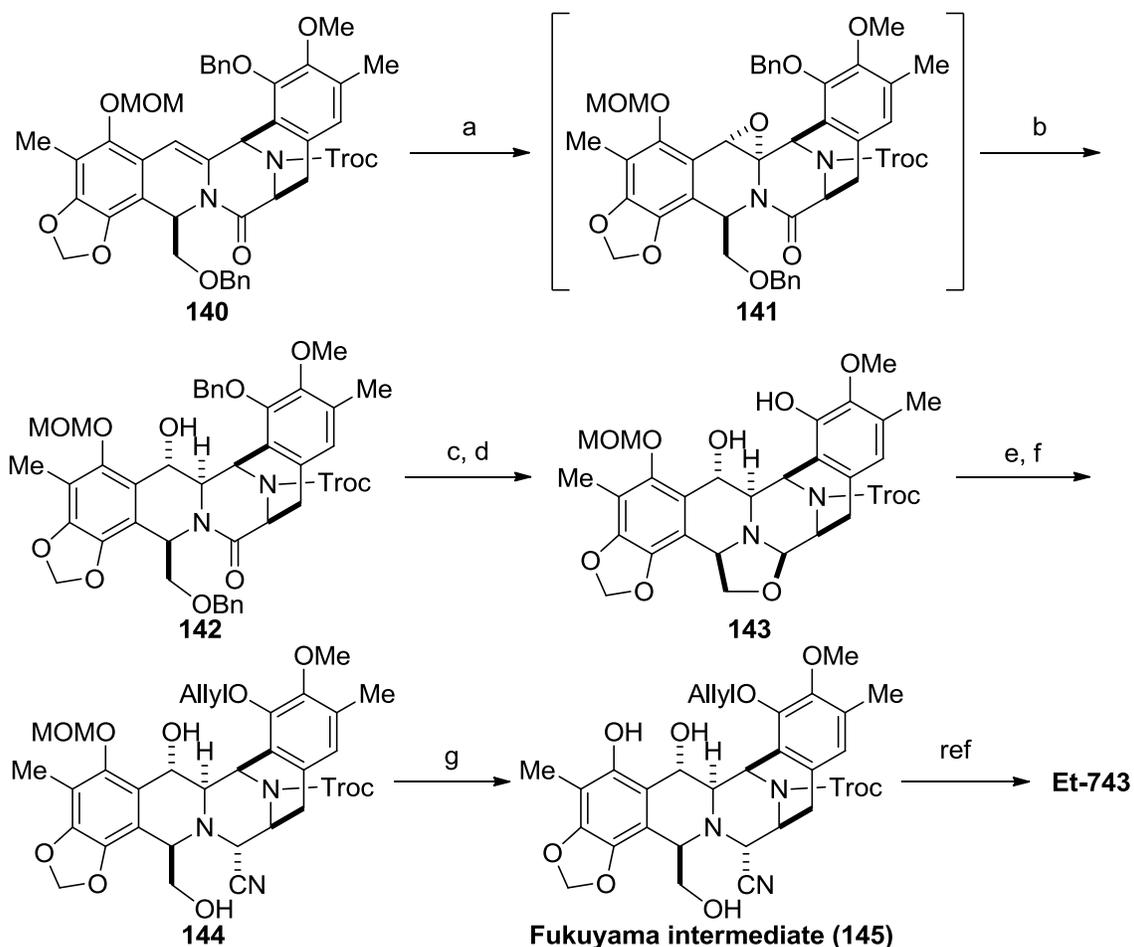
**Scheme 19:** Reagents and conditions (a) BuLi, Me(MeO)NC(O)CH<sub>2</sub>OBn, 80%; (b) RuCl[(*R,R*)-Ts-DPEN](*p*-cymene), HCO<sub>2</sub>H, Et<sub>3</sub>N, 78%; (c) DPPA, DBU, 89%; (d) H<sub>2</sub> (1 atm), Pd/C, 80%; (e) (MeO)<sub>2</sub>CHCHO, AcOH, NaCNBH<sub>3</sub>, Mg<sub>2</sub>SO<sub>4</sub>, 0 to 65°C; (f) TBAF, 94% (2 steps); (g) AllylBr, NaH, 0 to 25°C, 84%; (h) 7M HCl, 0 to 25°C, 90%.

Amino acid coupling of THIQ **134** with a known tyrosine derivative **135** gave rise to amide **136** (scheme 20).<sup>85</sup> Intermediate **137** was generated by a four step sequence including cleavage of the PMB group, dehydration of the benzylic alcohol, oxidation of the primary alcohol and cleavage of the allyl group. Treating **137** with difluoroacetic acid at an elevated temperature afforded desired pentacycle **138**, which underwent protecting group modification to yield **140**.



**Scheme 20:** Reagents and conditions (a) BOPCl, Et<sub>3</sub>N, 85%; (b) DDQ, pH 7.00 buffer, 90%; (c) Cu(OTf)<sub>2</sub>, 61%; (d) Dess-Martin periodinane, 94%; (e) (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>, Bu<sub>3</sub>SnH, AcOH, 93%; (f) F<sub>2</sub>CHCO<sub>2</sub>H, MgSO<sub>4</sub>, 100°C, 42-58%; (g) TBSOTf, Et<sub>3</sub>N, quant.; (h) TrocCl, TBAI, 110°C, 92%; (i) TBAF, 0°C; (j) MOMCl, *i*-Pr<sub>2</sub>NEt, 79% (2 steps).

Intermediate **142** was produced by first epoxidation of **140** and reductive opening of the resulting epoxide (scheme 21). Concomitant cleavage of both benzyl groups was accomplished under low pressure hydrogenation without modifying the Troc protecting group. The resulting product was partially reduced to give oxazolidine **143**. Allylation of the phenol, followed by introduction of the aminonitrile yielded **144**, which was converted to **145**, intercepting Fukuyama's total synthesis of Et-743.

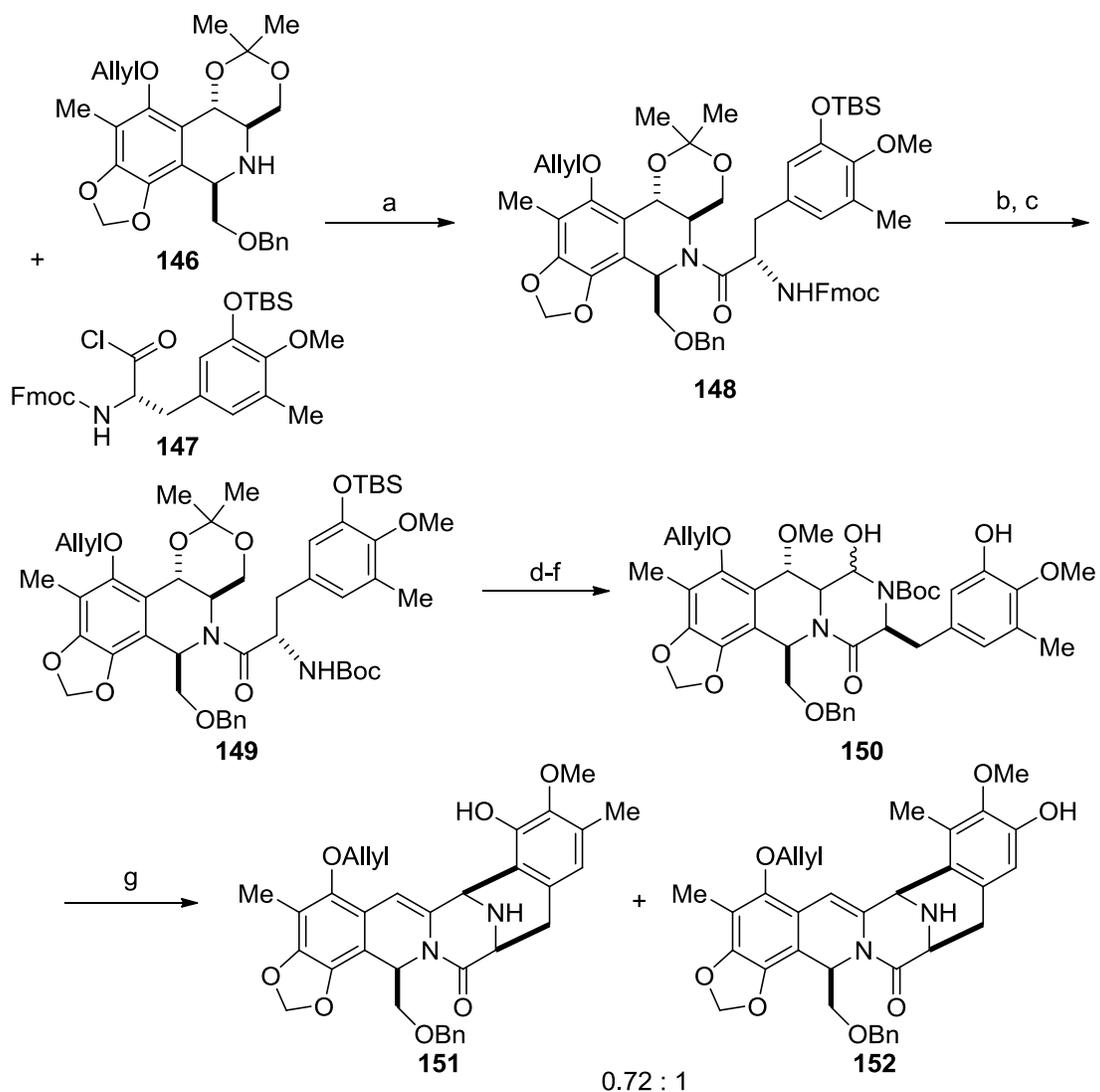


**Scheme 21:** Reagents and conditions (a) DMDO, 0 to 25°C; (b) NaBH<sub>3</sub>CN, 78%; (c) H<sub>2</sub> (1 atm), Pd/C, 77%; (d) DIBAL, BuLi, 0°C, 78%; (e) AllylBr, *i*-Pr<sub>2</sub>NEt, 50°C, 66%; (f) KCN, AcOH, 79%; (g) TFA, 54%.

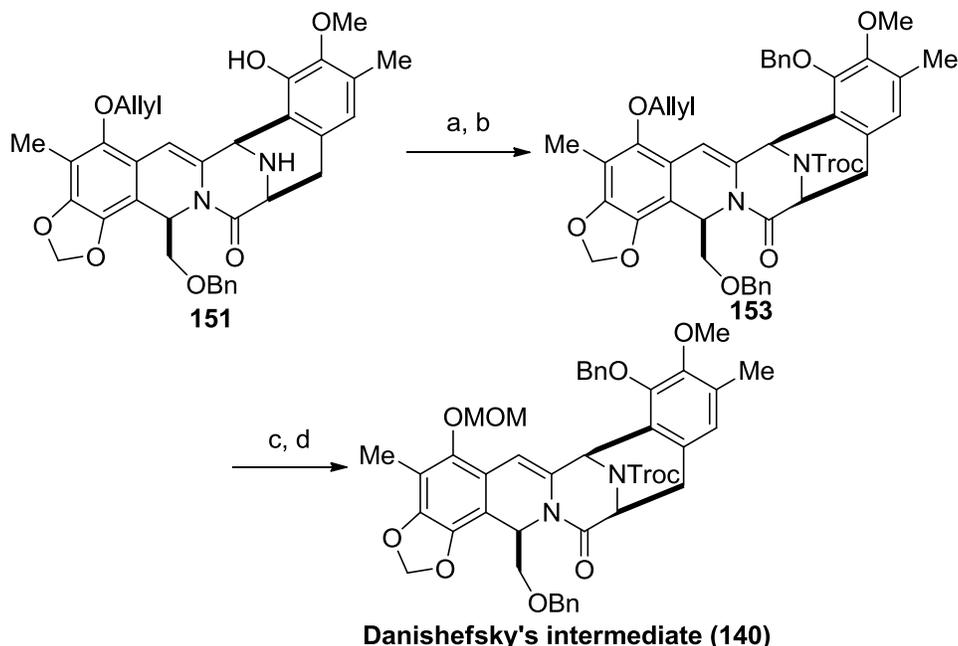
### 1.6.2 Williams' formal synthesis of Et-743

In 2010, our group also published a formal synthesis of Et-743 intercepting an intermediate in Danishefsky's formal synthesis of Et-743.<sup>86</sup> The synthesis commenced with amino acid coupling of known THIQ **146** and tyrosine derivative **147** to furnish amide **148** (scheme 22).<sup>87,88</sup> Fmoc protecting group was converted to Boc protecting group, and the resulting product (**149**) underwent a series of reactions including acetonide cleavage, desilylation and oxidation of the primary alcohol to give carbinolamine **150**. Pictet-Spengler reaction of **150** afforded two regioisomers **151** and **152** with almost no selectivity. Protecting group modification of the

desired pentacycle (**151**) gave rise to known compound **140** (scheme 23), concluding our formal synthesis of the natural product.



**Scheme 22:** Reagents and conditions (a) 2,6-lutidine, 70%; (b)  $\text{Et}_2\text{NH}$ ; (c)  $\text{Boc}_2\text{O}$ , 90% (2 steps); (d) dry Dowex 50W-X8, dry MeOH (90%); (e) TBAF, 95%; (f) Swern oxidation; (g) TFA, anisole, 72% (2 steps).



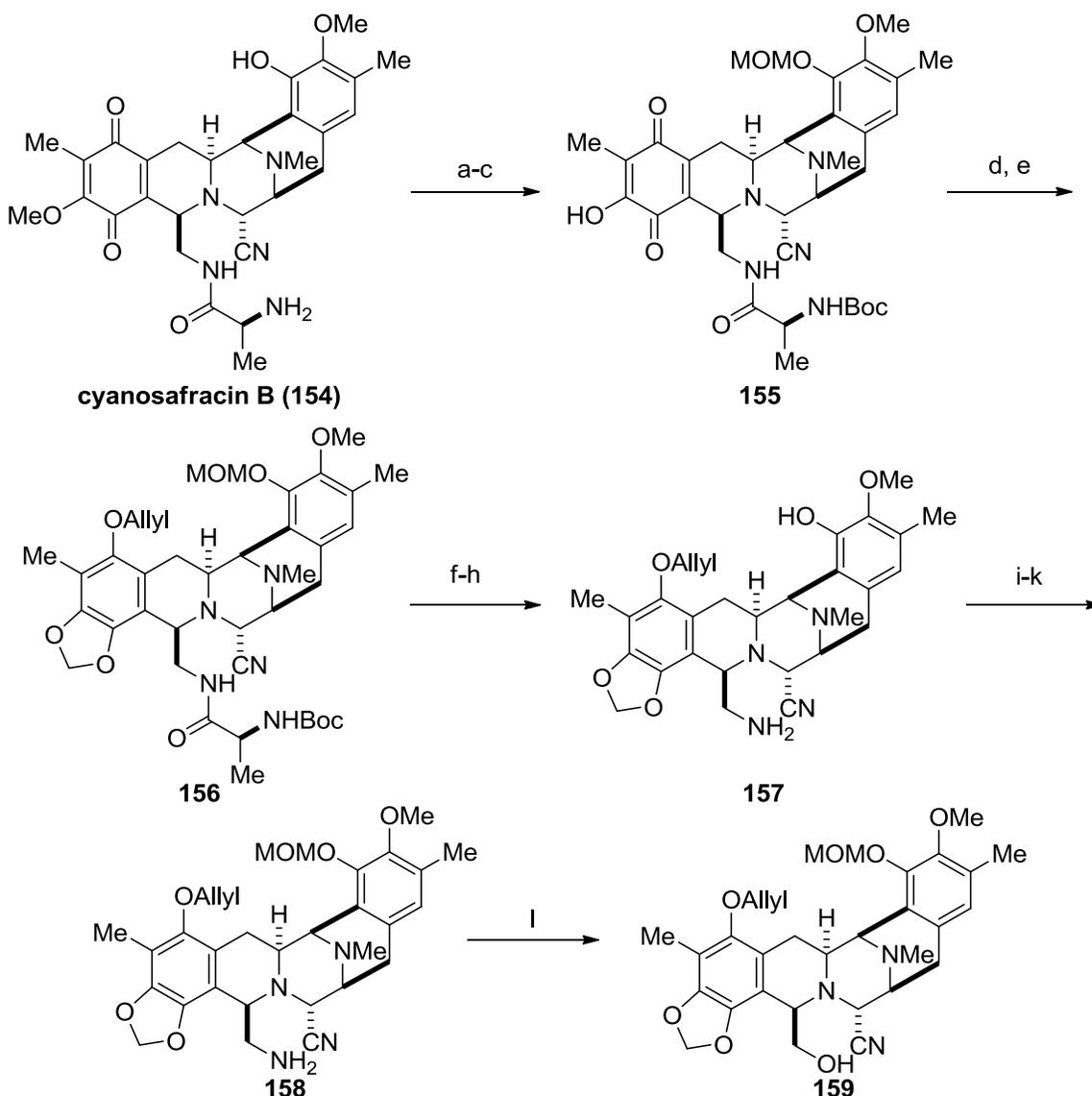
**Scheme 23:** Reagents and conditions (a) TrocCl, py., 0°C; (b) BnBr, K<sub>2</sub>CO<sub>3</sub>, TBAI, 85% (2 steps); (c) pyrrolidine, Pd(PPh<sub>3</sub>)<sub>4</sub>; (d) MOMBr, *i*-Pr<sub>2</sub>NEt, 56% (2 steps).

## 1.7 Semisynthesis of Et-743

### 1.7.1 Pharma Mar's semisynthesis of Et-743

Albeit a number of successful syntheses of Et-743 and aquaculture of the tunicate, obtaining enough Et-743 to supply for clinical trials and lab studies is still a challenge for synthetic chemists. Cuevas and coworkers from Pharma Mar reported a multigram scale semisynthesis of Et-743 from cyanosafraicin B (**154**), a fermentation product of *Pseudomonas fluorescens*.<sup>89,90</sup> Boc and MOM protection of cyanosafraicin B was carried out and the methoxy quinone was hydrolyzed to afford quinone **155** (scheme 24). Reduction of the quinone gave rise to a triol, which was converted to dioxymethylene **156** by treatment with bromochloromethane under basic condition and allylation of the remaining phenol. Boc-deprotection, treatment with phenyl isothiocyanide and Edman degradation of the resulting thiourea yielded amine **157**. Temporary Troc protection of the primary amine, followed by MOM protection of the phenol and immediate

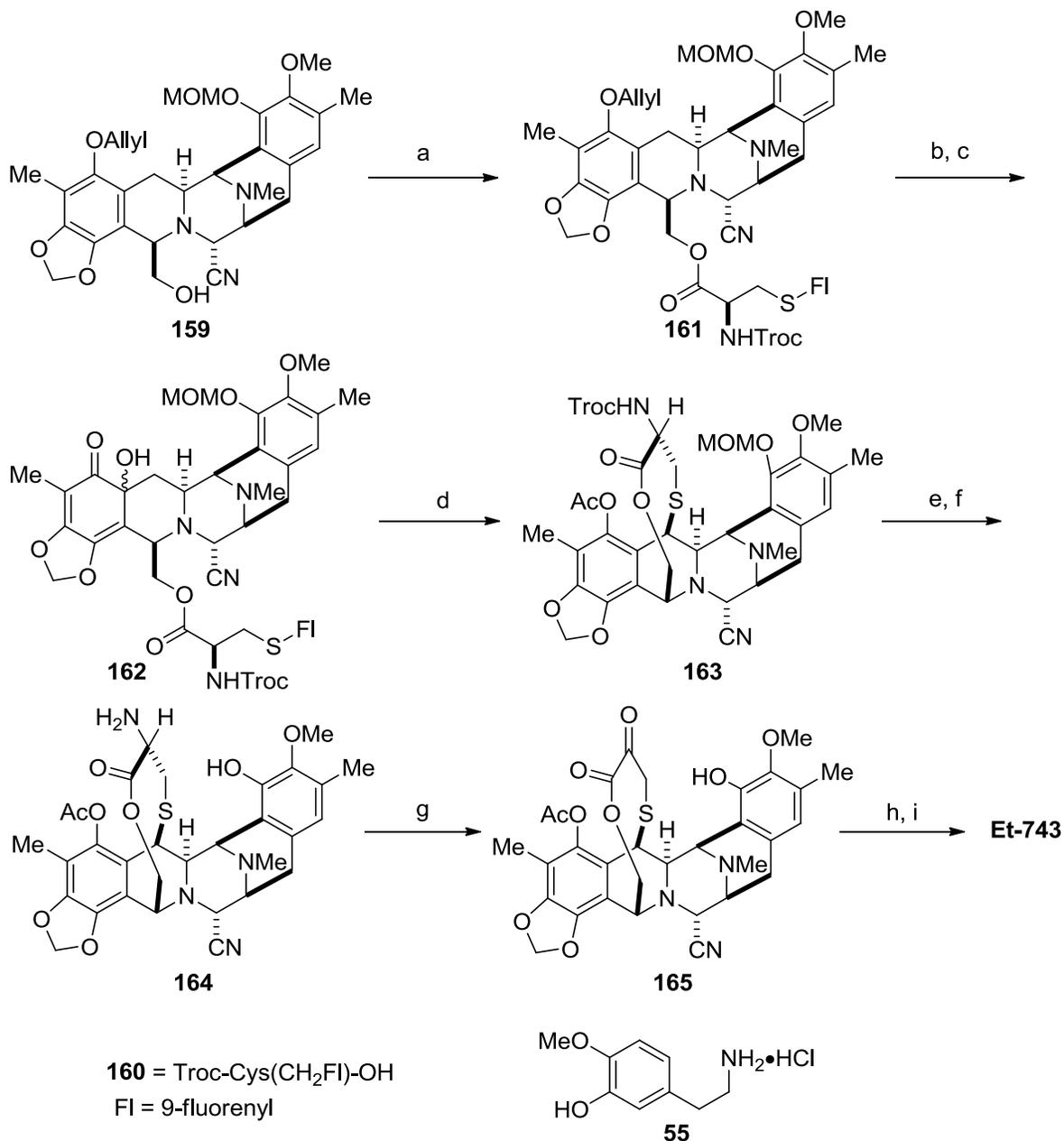
cleavage of Troc protecting group generated amine **158**, which was transformed into alcohol **159** in the presence of sodium nitrite and acetic acid.



**Scheme 24:** Reagents and conditions (a)  $\text{Boc}_2\text{O}$ , 81%; (b)  $\text{MOMBr}$ ,  $i\text{-Pr}_2\text{NEt}$ , DMAP,  $40^\circ\text{C}$ , 83%; (c) 1M  $\text{NaOH}$ ,  $\text{MeOH}$ , 68%; (d)  $\text{H}_2$ , 10%  $\text{Pd/C}$ ;  $\text{BrCH}_2\text{Cl}$ ,  $\text{Cs}_2\text{CO}_3$ ,  $110^\circ\text{C}$ ; (e)  $\text{AllylBr}$ ,  $\text{Cs}_2\text{CO}_3$ , 56% (2 steps); (f)  $\text{TFA}$ , 95%; (g)  $\text{PhNCS}$ , 87%; (h)  $\text{HCl}$ , 82%; (i)  $\text{TrocCl}$ ,  $\text{py.}$ ,  $0^\circ\text{C}$ , 98%; (j).  $\text{MOMBr}$ ,  $i\text{-Pr}_2\text{NEt}$ , DMAP,  $40^\circ\text{C}$ , 88%; (k)  $\text{Zn}$ ,  $\text{AcOH}$ , 83%; (l)  $\text{NaNO}_2$ ,  $\text{AcOH}$ , 50%.

The last steps in this synthesis were accomplished via *ortho*-quinone intermediate, a strategy employed by Corey and coworkers in their synthesis of Et-743 (scheme 25). **159** was couple with cysteine derivative **160** to provide ester **161**. Subsequent deallylation and oxidation of the

resulting phenol yielded intermediate **162**, which was converted to macrocyclic intermediate **163** using same condition described in scheme 5. Removal of the MOM and Troc protecting groups furnished amine **164**, which underwent biomimetic transamination affording ketone **165**. Pictet-Spengler reaction of **165** with known intermediate **55**, followed by treatment of the resulting product with aqueous solution of silver nitrate generated Et-743.



**Scheme 25:** Reagents and conditions (a) **160**, EDCI, DMAP, 95%; (b) Bu<sub>3</sub>SnH, (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>, AcOH, 90%; (c) (PhSeO)<sub>2</sub>O, -10°C, 91%; (d) DMSO, Tf<sub>2</sub>O; *i*-Pr<sub>2</sub>NEt; *t*-BuOH;

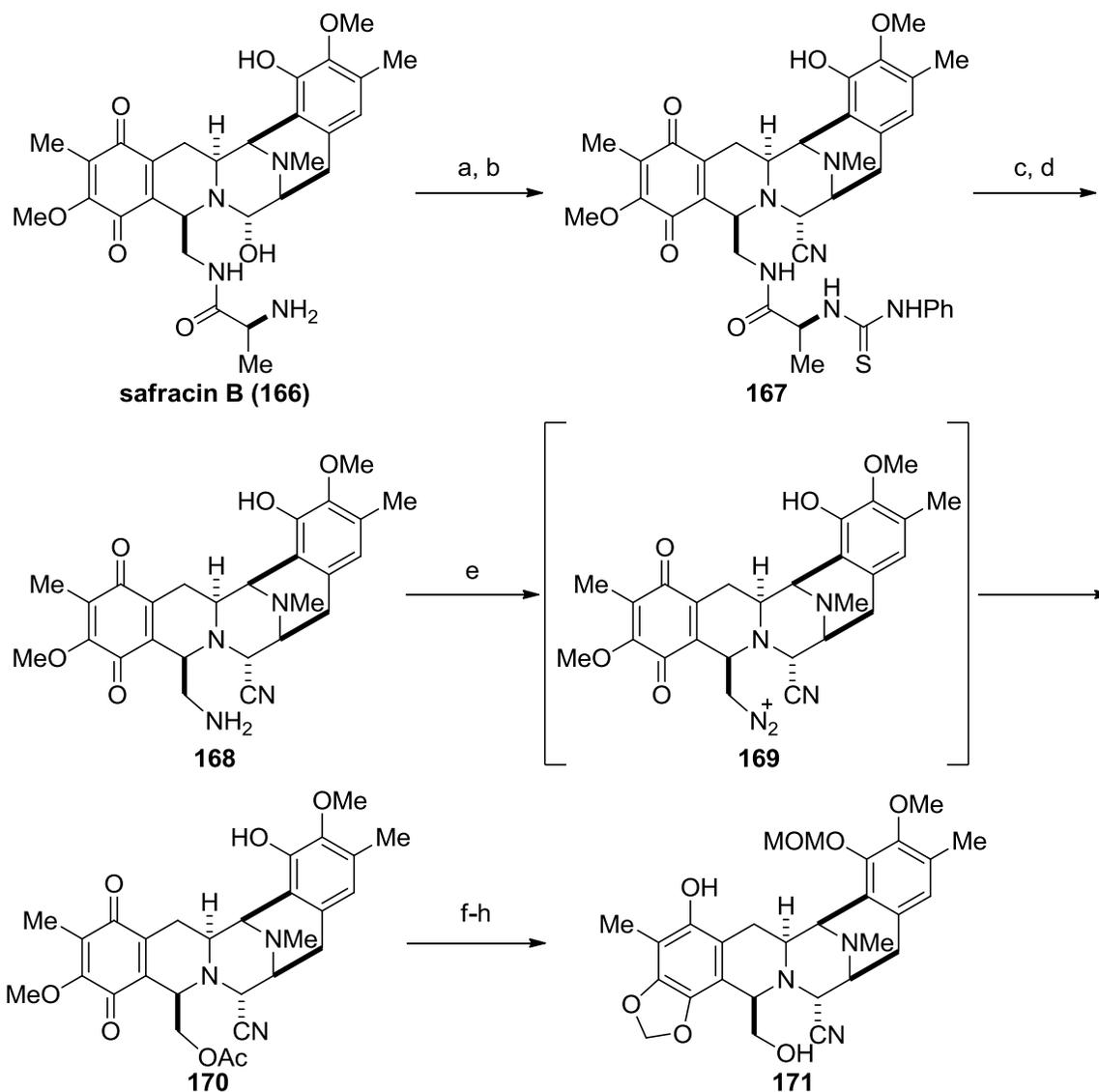
(Me<sub>2</sub>N)<sub>2</sub>CN*t*-Bu; Ac<sub>2</sub>O, 58%; (e) TMSCl, NaI; (f) Zn, AcOH, 70°C, 77% (2 steps); (g) [*N*-methylpyridinium-4-carboxaldehyde]<sup>+</sup>I<sup>-</sup>, DBU, (CO<sub>2</sub>H)<sub>2</sub>, 57%; (h) **55**, silica gel, 18, 90%; (i). AgNO<sub>3</sub>, H<sub>2</sub>O, 90%.

### 1.7.2 Zhang and Sun's semisynthesis of Et-743

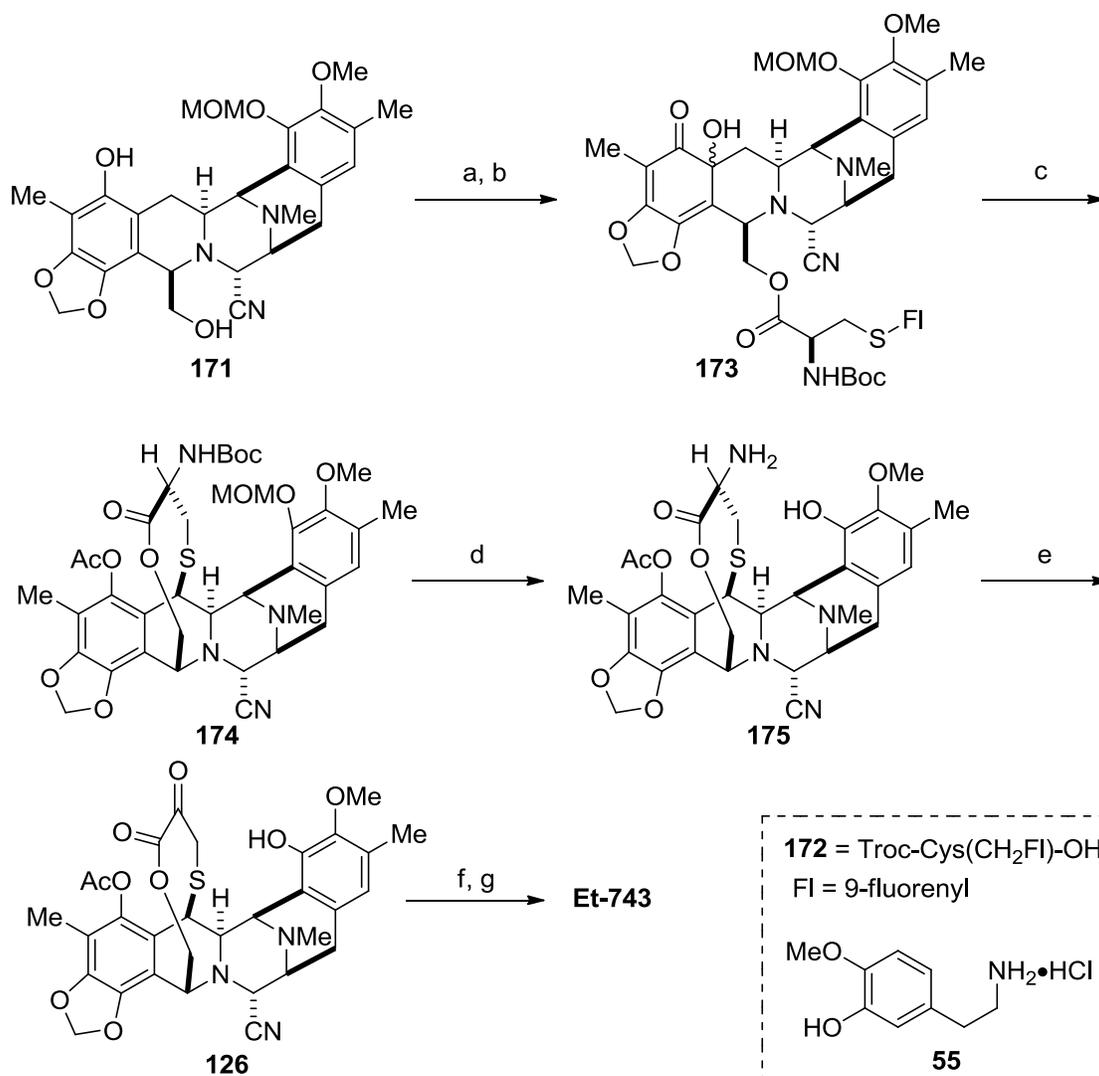
Most recently, Zhang and coworkers published their semisynthesis of Et-743 from safracin B (**166**), a fermentation product of bacteria *Pseudomonas fluorescens*.<sup>89,91</sup> As seen in scheme 26, safracin B was treated with phenyl isothiocyanide, followed by conversion of the carbinolamine to amino nitrile to give thiourea **167**. Early stage Edman degradation was performed giving a stable amine salt, which was treated with a solution of sodium bicarbonate to release its free amine (**168**). Treatment of **168** with sodium nitrite and acetic acid yielded unstable diazo intermediate **169**, which reacted with sodium acetate to generate acetyl ester **170**. Subsequent MOM protection of the phenol and hydrolysis of the methoxyquinone and the acetyl ester gave an intermediate, which was reduced and treated with bromochloromethane under basic condition to furnish pentacycle **171** with the desired dioxymethylene moiety.

Phenol **171** was oxidized prior to coupling with **172** to give ester **173** (scheme 27). The formation of the macrolactone **174** was performed under standard condition described in Corey's synthesis of Et-743. Concomitant cleavage of the Boc and MOM protecting groups furnished free amine **175**, which underwent biomimetic transamination to known ketoester **126**. The synthesis of Et-743 was completed with the formation of the THIQ C unit via Pictet-Spengler reaction, followed by treatment with copper (I) chloride to reinstall the carbinolamine moiety.

Compared to all other synthesis routes to Et-743, Zhang and Sun's synthesis has the least number of steps with a minimal protecting group manipulation. Although there are a few low yielding steps, this synthesis could potentially become the production route of commercial Et-743 in the future.



**Scheme 26:** Reagents and conditions (a) PhNCS; (b) NaCN, AcOH,  $-10^{\circ}\text{C}$ ; (c) MeOH, TMSCl,  $0^{\circ}\text{C}$ , 80% (3 steps); (d)  $\text{NaHCO}_3$ ; (e)  $\text{NaNO}_2$ , AcOH, then AcONa, 45%; (f) NaH, MOMBr,  $0^{\circ}\text{C}$ ; (g) LiOH, 0 to  $5^{\circ}\text{C}$ , 96% (2 steps); (h)  $\text{H}_2$ , 10% Pd/C;  $\text{BrCH}_2\text{Cl}$ ,  $\text{Cs}_2\text{CO}_3$ ,  $110^{\circ}\text{C}$ , 44%.



**Scheme 27:** Reagents and conditions (a) (PhSeO)<sub>2</sub>O, -10°C; (b) **172**, EDCI, DMAP, 0°C, 60% (2 steps); (c) DMSO, Tf<sub>2</sub>O; *i*-Pr<sub>2</sub>NEt; *t*-BuOH; (Me<sub>2</sub>N)<sub>2</sub>CN*t*-Bu; Ac<sub>2</sub>O, 50%; (d) TsOH, quant.; (e) *N*-methylpyridinium-4-carboxaldehyde benzenesulfonate, DBU, oxalic acid, 0°C, 51%; (f) **55**, NaOAc, 70%; (g) CuCl, H<sub>2</sub>O, 94%.

## 1.8 Et-743 syntheses – a summary

Table 3 is a summary of number of longest linear steps and overall yield from all the reported syntheses of Et-743 described in the previous sections. As shown in table 3, all syntheses resulted in low yielding of the natural product. Despite the low yields of the natural product from these syntheses, there were enough of Et-743 produced for drug development and clinical trials owing largely to the pioneering synthesis of Corey's group and, later on, to PharmaMar's

semisynthesis. We will not be surprised if someday, there will be an improved semisynthesis featuring less protecting group steps as seen in Zhang and Sun synthesis and better yield, which can be applied in the synthesis of Et-743 for more studies and also cancer treatments.

**Table 3:** Summary of reported syntheses of Et-743.

	Longest linear steps	Yield
Corey's total synthesis	36	2.04%
Fukuyama's 1 <sup>st</sup> total synthesis	50	0.56%
Fukuyama's 2 <sup>nd</sup> total synthesis	30	1%
Zhu's total synthesis	31	1.7%
Danishefsky's formal synthesis	38	0.037%
Williams' formal synthesis	41	< 0.1%
PharmaMar's semisynthesis	21	1%
Sun and Zhang's semisynthesis	15	1.5%

## 1.9 Therapeutic applications of Et-743

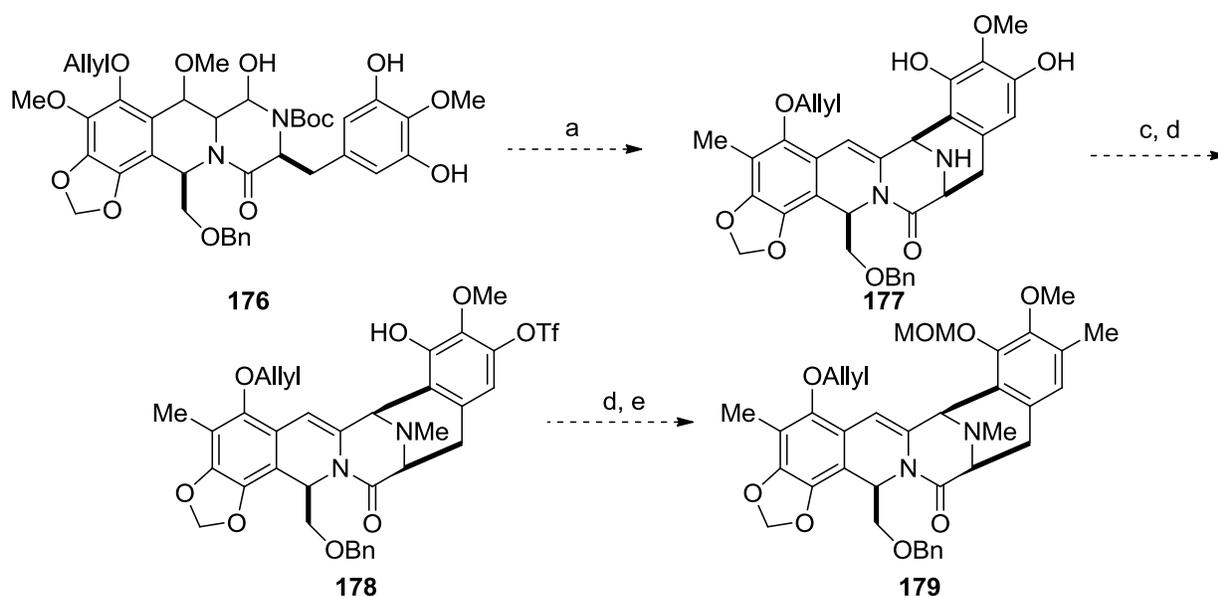
Et-743 is commercialized under the name trabectedin or Yondelis®. Clinical studies of Et-743 were performed at these three major centers, including the United States, the Europe and Japan. Phase II and III studies showed that hematological side effect, including neutropenia, febril neutropenia, thrombocytopenia and sepsis, is the most common toxicity of trabectedin but reversible. Liver damage was reported as the major non-hematological effect and this event can be relieved by dexamethasone pretreatment. Other common adverse events were also observed including fatigue, nausea, vomiting, renal failure, cardiac and muscular problems, alopecia and neural disorder.<sup>11</sup> In the United States, Et-743 was approved for the treatment of unresectable or metastatic liposarcoma or leiomyosarcoma previously treated with an anthracycline medicine. Trabectedin was approved for treatment of all types of soft tissue sarcoma due to its better progression-free survival (5.6 months) compared to best supportive care (0.9 months) in Japan.

It also received approval for the treatment of advanced ovarian and soft tissue sarcomas in combination with pegylated liposomal doxorubicin in several countries worldwide.<sup>92</sup>

## Chapter 2: Synthetic Studies of Et-743

### 2.1 Possible approaches to overcome the regioisomer issue

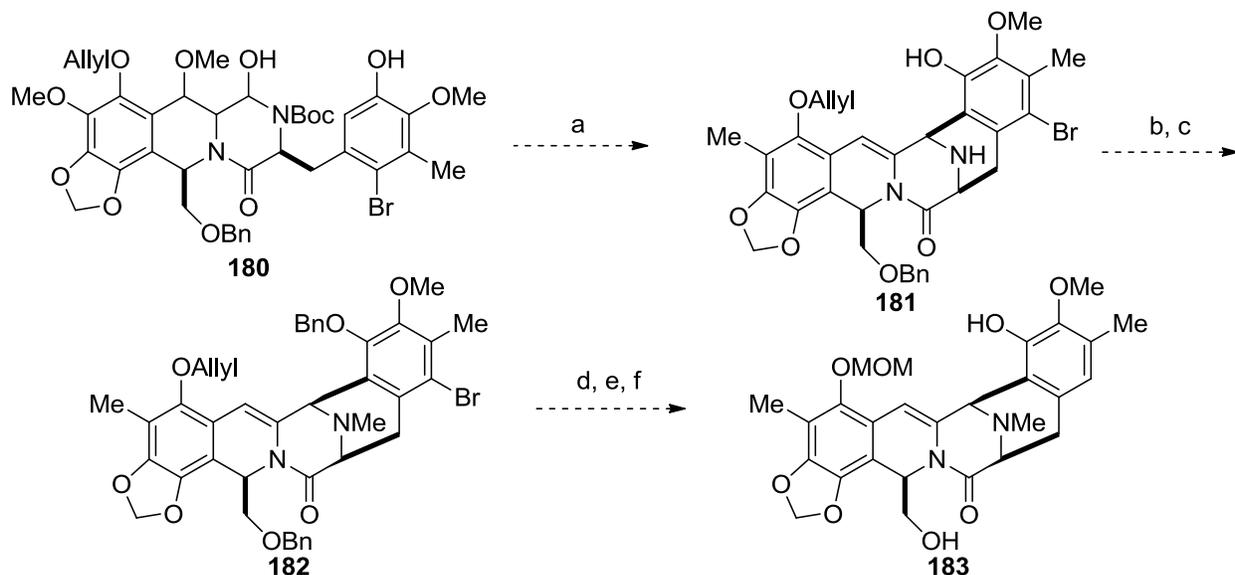
As seen in scheme 22 (section 1.6.2), our synthesis of the pentacyclic core of Et-743 resulted in two regioisomers with almost no selectivity. In an attempt to improve our synthesis, we proposed two approaches to overcome the regioisomer issue. We foresaw that carbinolamine **176**, containing the symmetrical eastern aromatic region, would cyclize to give a single isomer (scheme 28). The less hindered phenol could be selectively converted to a methyl substituent via Stille coupling after mono-sulfonylation and protection of the remaining phenol. This strategy was successfully employed by Corey's group in their synthesis of Et-743 (described in scheme 4); therefore, we are confident that this approach would lead to a completion of Et-743 synthesis.<sup>62</sup>



**Scheme 28:** Proposed synthetic route to pentacycle **179** via cyclization of the symmetrical diphenol **176**. Reagents and conditions (a) TFA, anisole; (b) HCHO, NaBH<sub>3</sub>CN; (c) Tf<sub>2</sub>NPh, Et<sub>3</sub>N; (d) MOMBr, *i*-Pr<sub>2</sub>NET; (e) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, SnMe<sub>4</sub>, LiCl.

Our second proposed synthetic route involved the cyclization of brominated intermediate **180** (scheme 29). We envisioned that the bromination reaction would be simple and effective and the

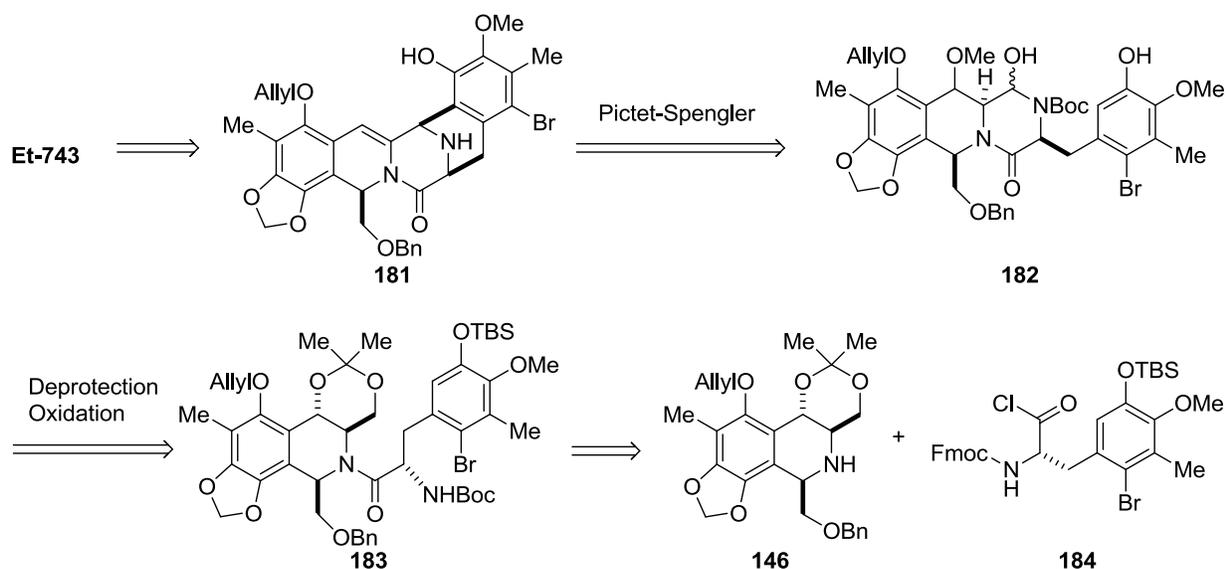
bromine cleavage after the cyclization step could happen concomitantly with one of the palladium-catalyzed step along the synthesis. Using bromine substituent as a blockage of undesired cyclization product has been reported in the syntheses of other THIQ alkaloids.<sup>93,94</sup> Furthermore, this strategy did not require an excess use of toxic tetramethyltin (20 equivalents), thus making it more appealing than the other synthetic route.



**Scheme 29:** Proposed cyclization of brominated intermediate **180**. Reagents and conditions(a) TFA, anisole; (b) HCHO, NaBH<sub>3</sub>CN; (c) BnBr, TBAI, *i*-Pr<sub>2</sub>NEt; (d) Pd(PPh<sub>3</sub>)<sub>4</sub>, Bu<sub>3</sub>SnH, AcOH; (e) MOMBr, *i*-Pr<sub>2</sub>NEt; (f) 10% Pd/C, H<sub>2</sub>.

## 2.2 Retrosynthesis

We suggested that Et-743 could be produced from brominated pentacycle **181**, which is a cyclization product of carbinolamine **182** (scheme 30). **182** could be generated from amide **183** via acetamide cleavage and oxidation of the resulting alcohol. We envisioned that **183** could be made from amino acid coupling reaction of known precursors **146** (THIQ fragment) and **184** (acid chloride fragment).



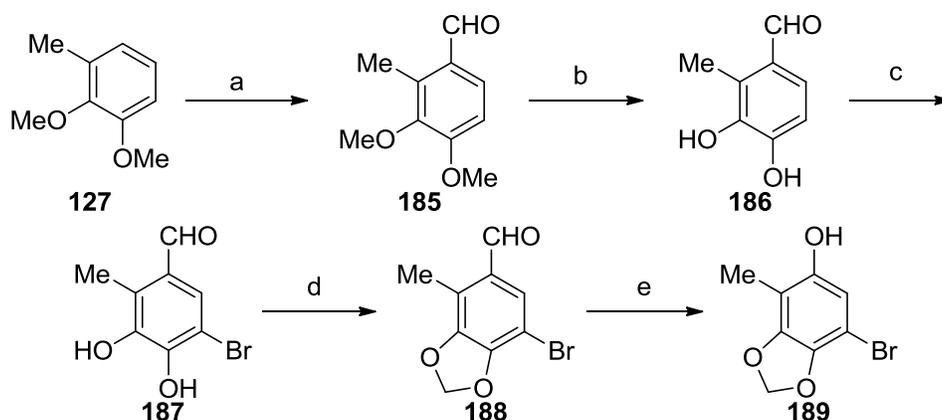
**Scheme 30:** Revised retrosynthesis of Et-743.

## 2.3 Synthesis of the THIQ fragment **146**

### 2.3.1 Synthesis of bromophenol **189**

My research in the Williams group started with the synthesis of known bromophenol **189**, a precursor in the THIQ fragment synthesis (scheme 31).<sup>87</sup> Commercially available 2,3-dimethoxytoluene (**127**) was formylated on 40-gram scale to give aldehyde **185** in 95% yield. De-methylation of aldehyde **185** with boron tribromide followed by bromination of the resulting phenol provided **187** in 61% yield over the two steps. The bromination reaction did not always go to completion, likely due to the presence of boron impurity from the de-methylation reaction, which could only be detected by mass spectrometry. The reaction resulted in an inseparable mixture of bromoaldehyde **187** and starting material **186**. Attempts to separate the mixture in a more advanced step or to brominate the more advanced intermediates of this mixture did not give any positive results. Therefore, only fractions of phenol **186** that could provide complete bromination product were carried on to the synthesis of the THIQ **146** and accounted for the

yield of the de-methylation reaction. The actual yield of this reaction was higher than reported here because the impure fractions were purified again to give more de-methylation product.

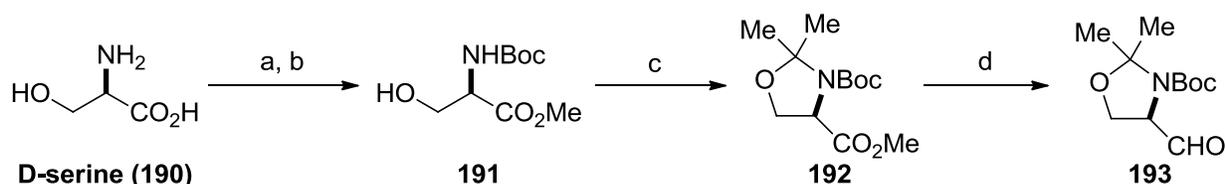


**Scheme 31:** Synthesis of known bromophenol **189**. Reagents and conditions (a)  $\text{MeOCHCl}_2$ ,  $\text{TiCl}_4$ ,  $0^\circ\text{C}$ , 95%; (b)  $\text{BBr}_3$ , 76%; (c)  $\text{Br}_2$ ,  $\text{NaOAc}$ ,  $\text{AcOH}$ , 80%; (d)  $\text{BrCH}_2\text{Cl}$ ,  $\text{Cs}_2\text{CO}_3$ ,  $110^\circ\text{C}$ , 67%; (e) (i) *m*-CPBA, (ii)  $\text{HCl}$ , 77%.

Bromoaldehyde **187** was treated with bromochloromethane in the presence of cesium carbonate to afford aldehyde **188** in 67% yield. Treatment of aldehyde **188** with Dakin oxidation condition furnished phenol **189** in 77% yield.

### 2.3.2 Synthesis of *D*-Garner's aldehyde (**193**)

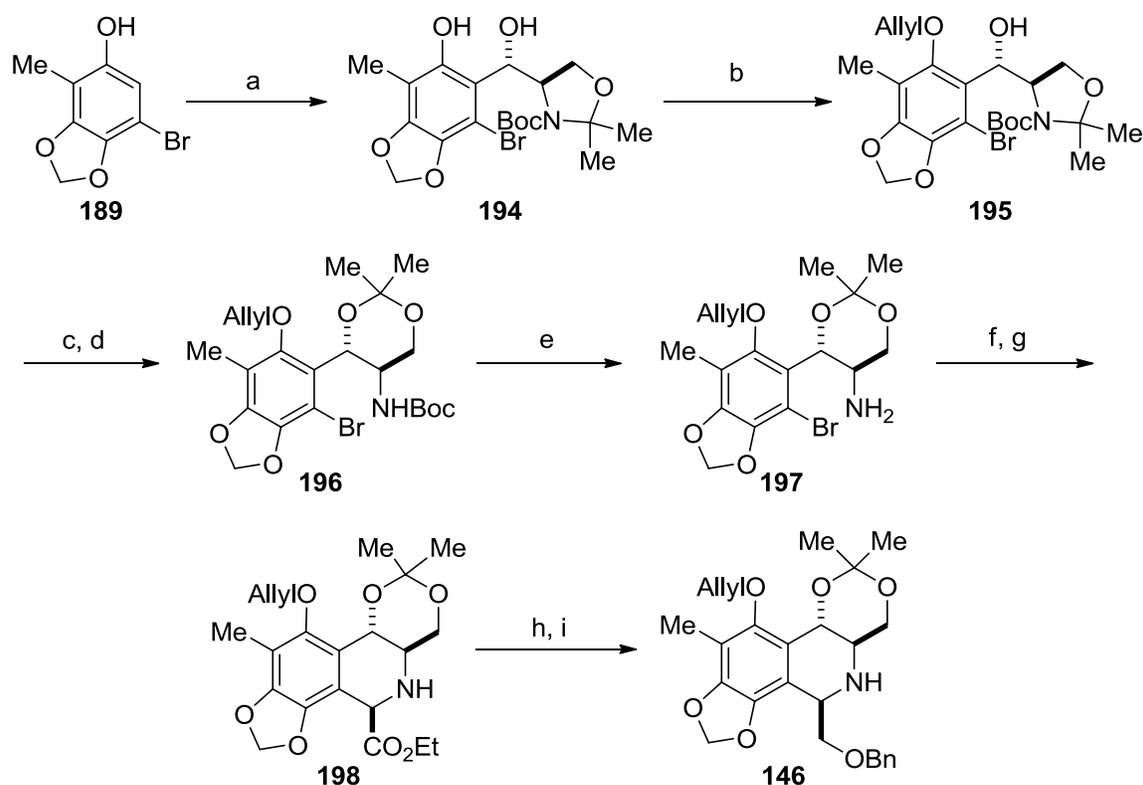
*D*-Garner's aldehyde was synthesized according to the published procedure by Garner and Park with modifications from Mckillop *et al.*<sup>78,79</sup> *D*-serine (**190**) was first refluxed with acyl chloride in methanol, followed by Boc-protection of the amine to yield methyl ester **191**. Subsequent treatment of **191** with 2,2-dimethoxypropane in the presence of boron trifluoride etherate provided **192**. *D*-Garner's aldehyde (**193**) was made by treating ester **192** with DIBAL at low temperature, and the crude product was used in the next step without purification.



**Scheme 32:** Synthesis of *D*-Garner's aldehyde (**193**). Reagents and conditions (a)  $\text{AcCl}$ ,  $\text{MeOH}$ ; (b)  $\text{Boc}_2\text{O}$ ; (c) 2,2-dimethoxypropane,  $\text{BF}_3 \cdot \text{OEt}_2$ ; (d) DIBAL,  $-78^\circ\text{C}$ .

### 2.3.3 Synthesis of 146

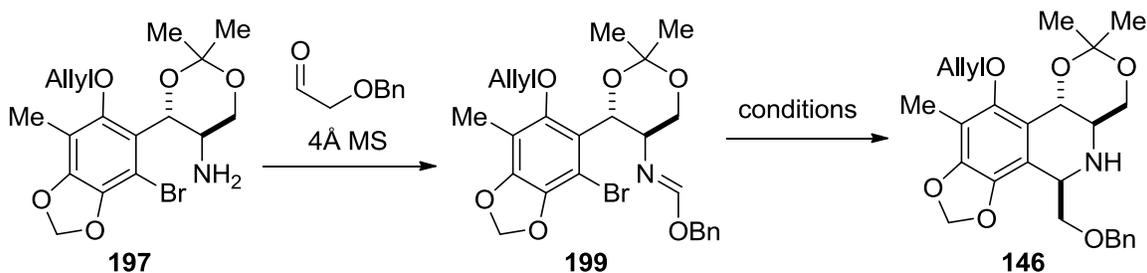
Bromophenol **189** underwent aldol type reaction with *D*-Garner's aldehyde (**193**) affording diol **194**.<sup>95</sup> Selective allylation of the phenol on **194** provided alcohol **195** (scheme 33). Removal of the acetonide under acidic condition and subsequent protection of the free alcohols with dimethoxypropane gave Boc-protected amine **196**. Removal of the Boc-protecting group under Ohfuné's condition yielded amine **197**.<sup>96</sup> Condensation of this amine with ethyl glyoxylate followed by radical-mediated cyclization of the resulting imine gave ester **198** in 54% yield over the two steps. Reduction of the ester and subsequent benzylation of the newly formed alcohol yielded the tetrahydroisoquinoline **146** in 73% overall yield.



**Scheme 33:** Synthesis of THIQ **146**. Reagents and conditions (a) *D*-Garner's aldehyde,  $\text{Ti}(\text{O-}i\text{-Pr})_4$ , 70%; (b) AllylBr,  $\text{Cs}_2\text{CO}_3$ , 73%; (c) TsOH, MeOH; (d) 2,2-dimethoxypropane, TsOH, yield; (e) (i) TBSOTf, 2,6-lutidine; (ii) KF, MeOH, 89%; (f) ethyl glyoxylate, 4Å molecular sieves; (g)  $\text{Bu}_3\text{SnH}$ , AIBN, 80°C, 54% (2 steps); (h) LAH; (i) NaH, BnBr, 73% (2 steps).

### 2.3.4 Attempts to bypass intermediate 198

Considering the total number of steps in the synthesis of Et-743, we sought to make intermediate **146** without going through ester **198**. Imine **199** was produced by treating amine **197** with benzyloxyacetaldehyde (scheme 34). The resulting imine was submitted to radical-induced cyclization conditions. Some desired product was observed under these conditions in entry 1, but the result was irreproducible. A Lewis acid was added to help activate the imine (entry 3) and accelerate the cyclization process in order to compete with the reduction reaction.<sup>97</sup> Unfortunately, the starting material was decomposed under these conditions as the Lewis acid acted to remove the acetonide and catalyzed the reverse aldol reaction. Efforts were placed on searching for a new source of hydrogen radical that would allow for cyclization before the hydride transfer occurs; however, no desired product **146** was obtained (entry 4 and 5). To this point, the tetrahydroisoquinoline **147** was synthesized according to scheme 33, as a shorter route could not be accessed.

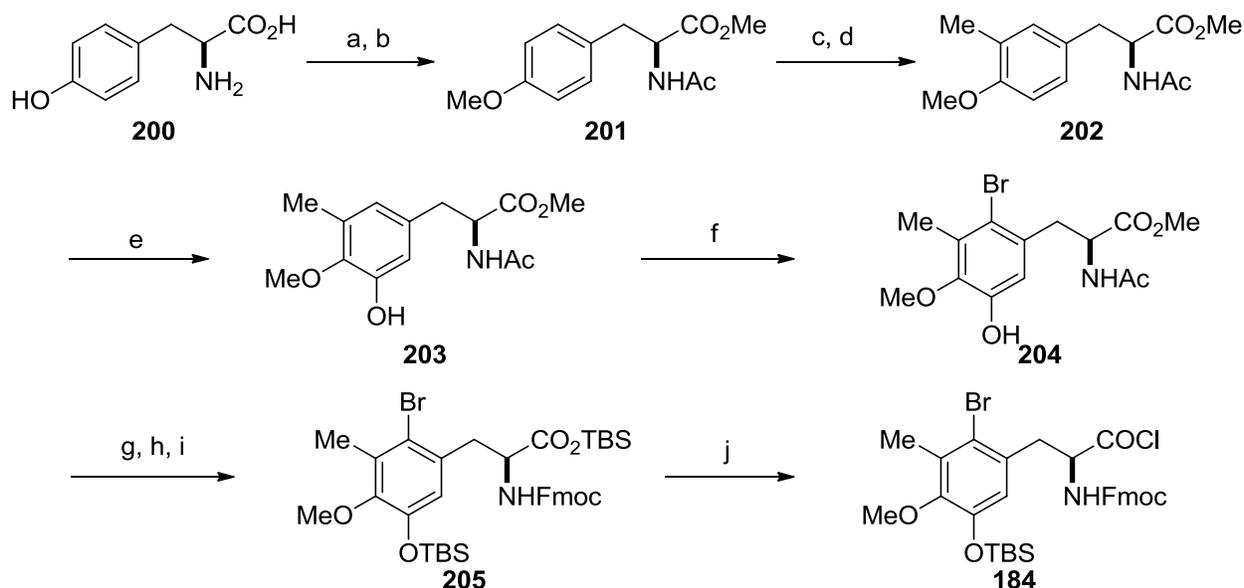


Entry	Conditions	Product <b>58</b>
1	Bu <sub>3</sub> SnH (2 eq.), AIBN (1.2 eq.), PhH, reflux	14-35%, irreproducible
2	Bu <sub>3</sub> SnH (4 eq.), AIBN (2.4 eq.), PhH, reflux	NR
3	Bu <sub>3</sub> SnH (2 eq.), AIBN (1.2 eq.), BF <sub>3</sub> .Et <sub>2</sub> O, PhH, reflux	Decomp.
4	1. Et <sub>3</sub> B, air, CH <sub>2</sub> Cl <sub>2</sub> , rt 2. NaHCO <sub>3</sub> , H <sub>2</sub> O	NR
5	Et <sub>3</sub> SiH or <i>i</i> Pr <sub>3</sub> SiH, AIBN, PhH, 80°C	NR

**Scheme 34:** Attempts to bypass intermediate **198**.

## 2.4 Synthesis of acid chloride fragment 184

The synthesis of the acid chloride (**184**) began with the acylation of the amine and the methylation of both the acid and the phenol of *L*-tyrosine (**200**) in 50-gram scale (79% yield over the two steps) (scheme 35). The synthesis of bromophenol **204** from **201** was adopted from the published procedure in the synthesis of (-)-renieramycin G, with some modification of the reaction conditions.<sup>93</sup> The *N*-acyl amino ester **201** underwent formylation followed by hydrogenation to provide compound **202** in 70% yield over the two steps. Formylation and Dakin oxidation of **202** yielded phenol **203** (48% yield over the 2 steps), which was then brominated at the position *para*- to the phenol giving **204** in 85% yield. Treatment of **204** with refluxing 6N HCl resulted in hydrolysis of the methyl ester and deacylation of the acyl amine. The resulting amino acid was treated with Fmoc-OSu, then with TBSCl to yield tyrosine derivative **205** in 63% yield over three steps. Acid chloride **184** was only prepared prior to the coupling with **146** by treatment of TBS ester **184** with oxalylchloride and dimethylformamide.



**Scheme 35:** Synthesis of acid chloride **184**. Reagents and conditions (a) Ac<sub>2</sub>O, H<sub>2</sub>O, reflux; (b) Me<sub>2</sub>SO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, reflux, 79% (2 steps); (c) MeOCHCl<sub>2</sub>, TiCl<sub>4</sub>; (d) 10% Pd/C, H<sub>2</sub> (50 psi),

70% (2 steps); (e) MeOCHCl<sub>2</sub>, TiCl<sub>4</sub>; (f) (i) *m*-CPBA; (ii) 12N HCl, 73%; (g) Br<sub>2</sub>, quant.; (h) 6N HCl, reflux; Fmoc-OSu, NaHCO<sub>3</sub>; (i) TBSCl, imidazole, 63% (3 steps); (j) (COCl)<sub>2</sub>, DMF.

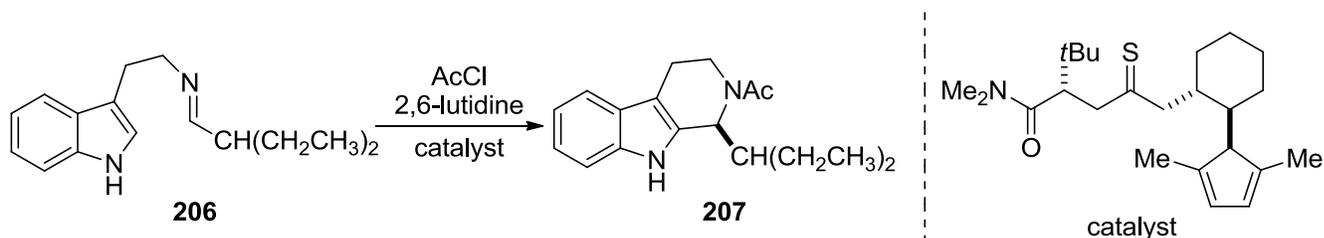
## 2.5 Pentacycle synthesis

### 2.5.1 *N*-Acyl Pictet-Spengler attempts

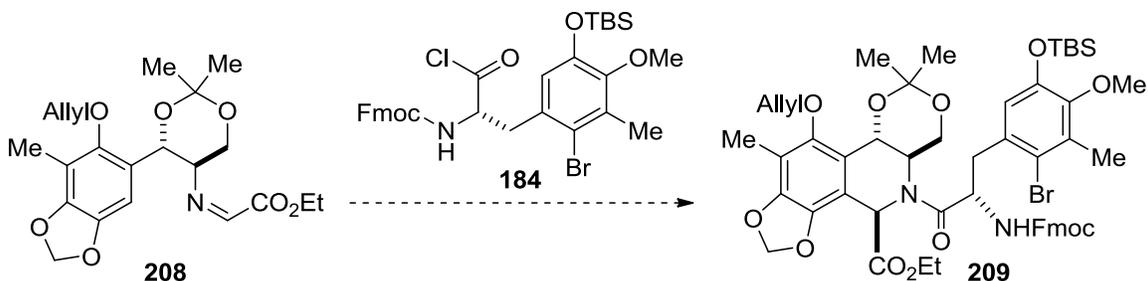
#### 2.5.1.1 Precedence

The radical-initiated cyclization reaction, although successfully generated the THIQ's precursor **146** (scheme 33), was a hurdle to scale up due to a large volume of solvent was used for a small amount of material and the restriction in the size of reaction containers. Furthermore, organic tin reagent is toxic and the reaction requires oxygen-free environment, making it an unpleasant reaction to deal with. Therefore, a more effective and less toxic method to construct this intermediate was seeking.

In 2004, Taylor and Jacobsen published the cyclization of indole **206** via Pictet-Spengler reaction of the *N*-acyl iminium ion (scheme 36).<sup>98</sup> There are reported successful applications of this more active intermediate in the synthesis of cyclized products, hence we considered the Pictet-Spengler of **208** as an alternative way to get to the pentacyclic core (scheme 37).<sup>99-102</sup>



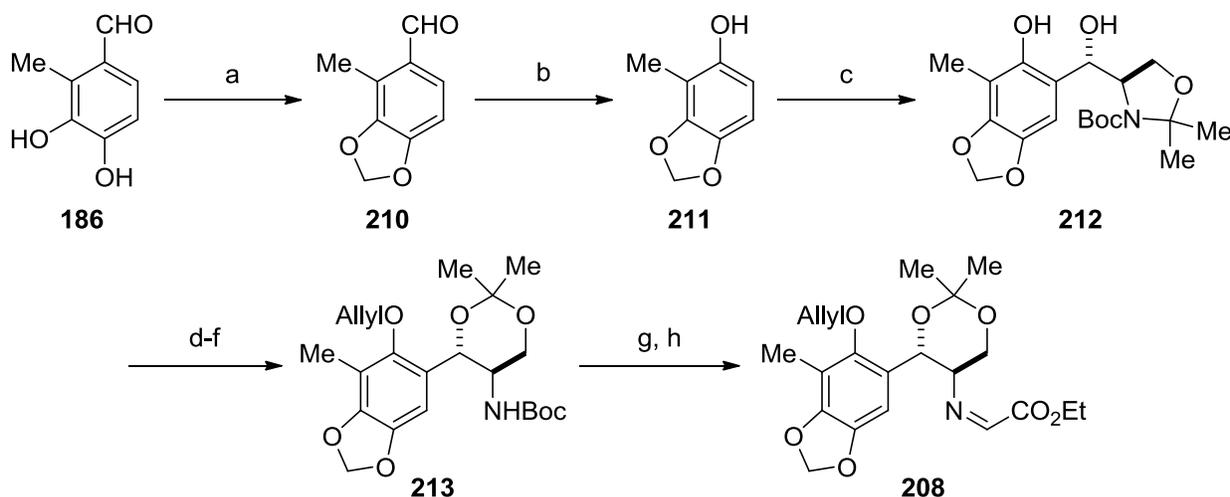
**Scheme 36:** Jacobsen's Pictet-Spengler reaction of the acyliminium ion.



**Scheme 37:** Proposed *N*-acyl Pictet-Spengler reaction.

### 2.5.1.2 Synthesis of precursor 208

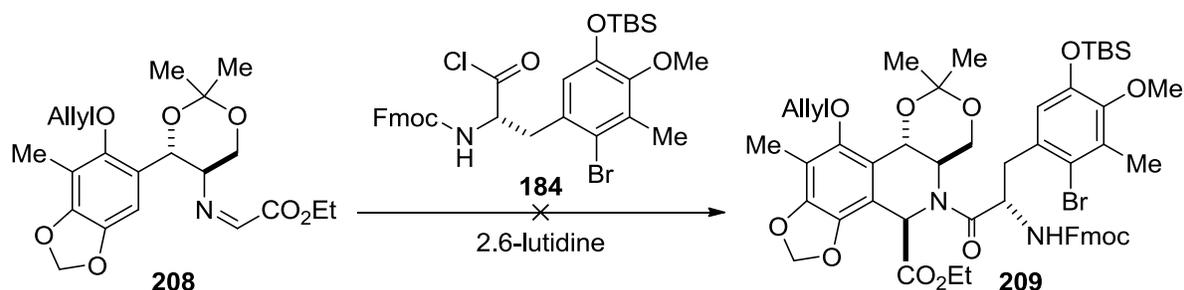
The substrate for *N*-acyl Pictet-Spengler reaction (**208**) was produced in a similar approach of the synthesis of intermediate **197** from Borchardt's aldehyde **186** in 53% yield (scheme 37). Dioxymethylene **210** was made from **197**, and then underwent Dakin oxidation to yield phenol **211**. Aldol-type reaction of **211** with *D*-Garner's aldehyde **193** in the presence of titanium tetraisopropoxide gave diol **212**. The phenol of **212** was selectively protected as an allyl ether, which was then treated with tosic acid, followed by reintroduction of the acetonide to furnish intermediate **213**. Subsequent Boc-deprotection of **213** gave an amine, which was converted to imine **208** when treated with ethyl glyoxalate.



**Scheme 38:** Synthesis of compound **208**. Reagents and conditions (a)  $\text{BrCH}_2\text{Cl}$ ,  $\text{Cs}_2\text{CO}_3$ ,  $110^\circ\text{C}$ , 53%; (b) *m*-CPBA; 4N HCl, 77%; (c) *D*-Garner's aldehyde (**193**),  $\text{Ti}(\text{O-}i\text{-Pr})_4$ , 79%; (d) AllylBr,  $\text{Cs}_2\text{CO}_3$ , 71%; (e) TsOH, MeOH; (f) 2,2-dimethoxypropane, TsOH, 61% (2 steps); (g) TBSOTf, 2,6-lutidine; KF, 80%; (h) ethyl glyoxalate, 4 Å MS.

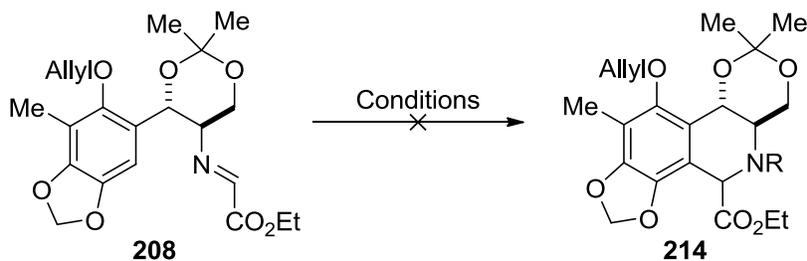
### 2.5.1.3 *N*-acyl Pictet-Spengler attempts

The reaction of imine **208** and acid chloride **184** yielded a complex mixture of products. Attempts to purify the mixture gave a few fractions with the right mass. However, the isolated yield of each fraction was low and the reaction was not reproducible. Therefore, we did not pursue this route further.



**Scheme 39:** Attempted direct *N*-acyl Pictet-Spengler.

We then considered using simpler protecting group to generate the iminium intermediate (scheme 40). AllocCl in THF did not yield any cyclized product. Switching the solvent to acetonitrile gave a product with the right mass. However, attempts to characterize the novel compound failed because the reaction was not reproducible and the deprotection was not successful. We encountered the same situation when using TeocCl to produce the iminium intermediate and other conditions did not give any sign of cyclization. Therefore, we stopped pursuing the alternative route to the THIQ western fragment of the molecule and the synthesis of this moiety was carried out as described in scheme 33.

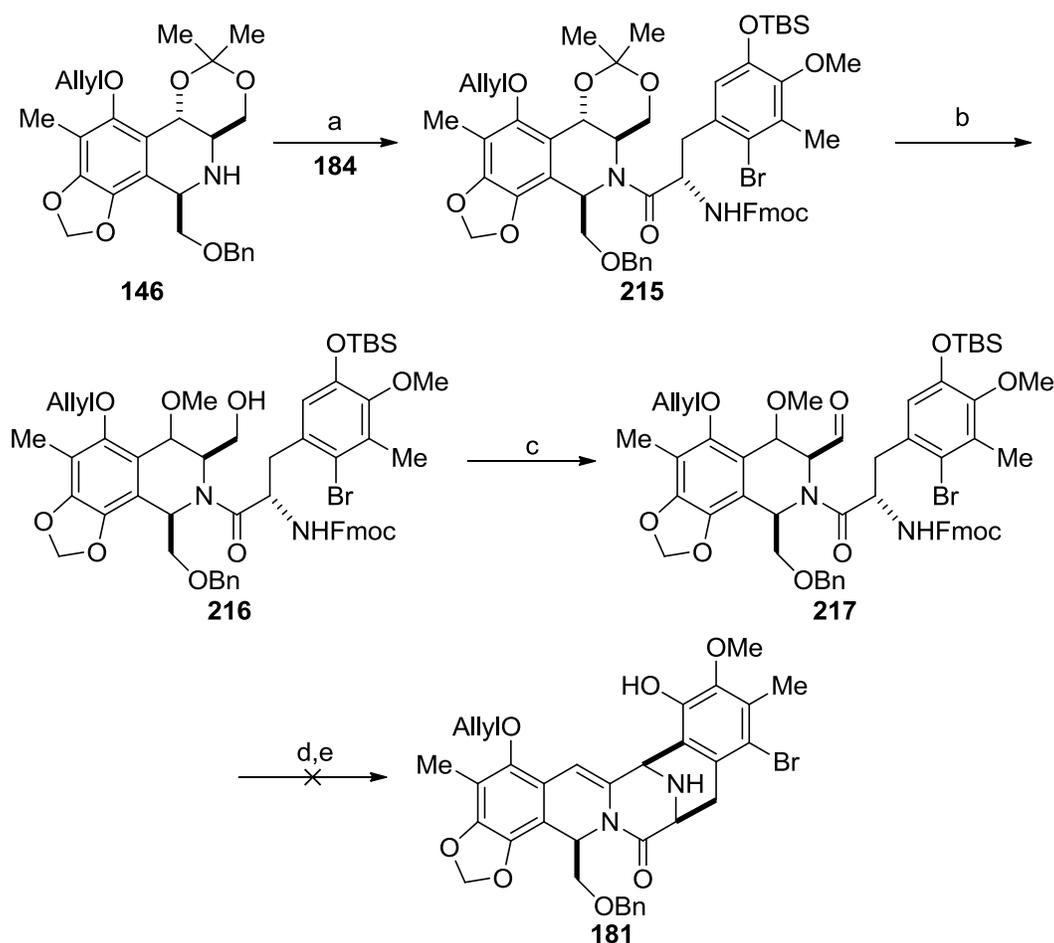


**Scheme 40:** Attempted *N*-acyl Pictet-Spengler. Reagents and conditions: AllocCl, THF, rt; AllocCl, MeCN rt to 80°C; TeocCl, MeCN, rt; phosgene; NVOCCl; Boc<sub>2</sub>O; BocCl; CbzCl; TrocCl; Ac<sub>2</sub>O.

### 2.5.2 First attempt to the pentacyclic core

The coupling of THIQ **146** and acid chloride **184** happened smoothly in the presence of 2,6-lutidine (scheme 41). However, the isolated yield of this reaction was low (54%). Observing that the work-up condition, saturated aqueous solution of ammonium chloride, might cause the deprotection of the acetonide protecting group, we switched to using a saturated aqueous solution

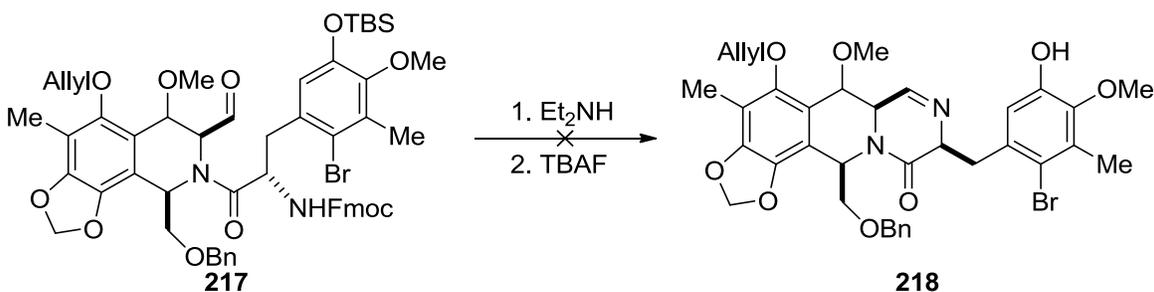
of sodium bicarbonate and this change increased the yield of the reaction to 82%. We envisioned that the Fmoc-protecting group could be cleaved in the presence of TBAF at the same time with the removal of the silyl protecting group; therefore, we bypassed the protecting swap of Fmoc to Boc as planned in our retrosynthesis. The synthesis was continued with the removal of the acetonide in dry methanol, followed by Swern oxidation of the resulting alcohol to give aldehyde **217**. Subsequent cleavage of the silyl and Fmoc protecting groups, followed by treatment of the resulting residue with trifluoroacetic acid did not give the desired pentacycle **181** as expected.



**Scheme 41:** First attempt of pentacycle synthesis. Reagents and conditions (a) 2,6-lutidine, 82%; (b) Dowex 50W-X8, dry MeOH, 89%; (c) (COCl)<sub>2</sub>, DMSO, then Et<sub>3</sub>N, -78°C; (d) TBAF; (e) TFA.

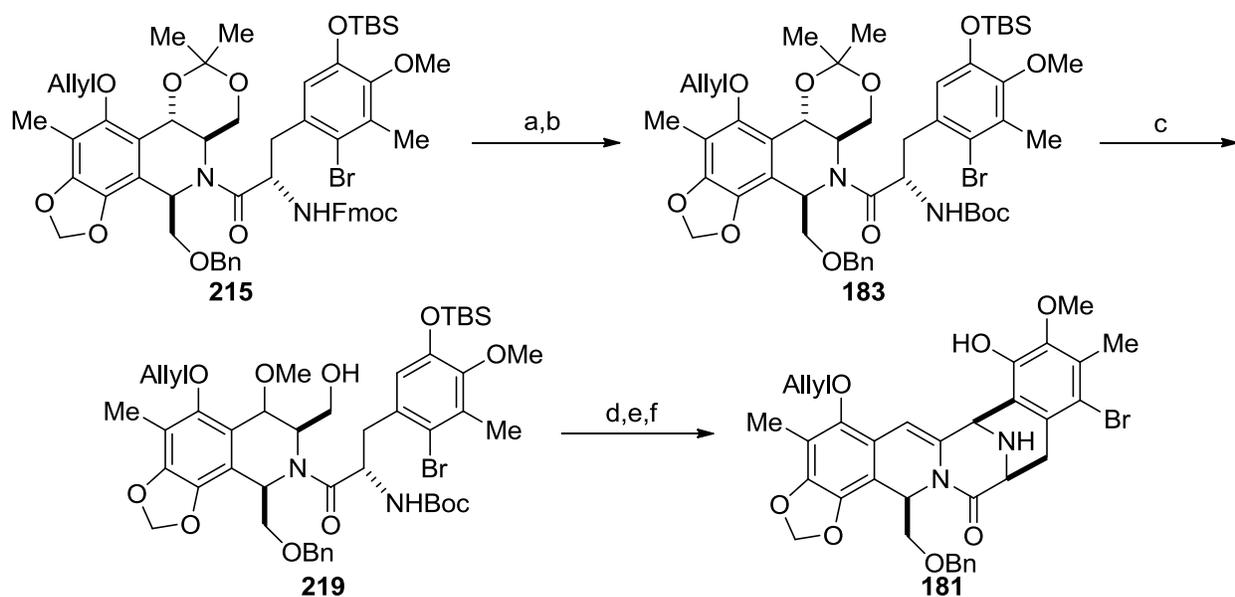
### 2.5.3 Second attempt to the pentacyclic core

We recognized that the issue originated from the Fmoc cleavage by TBAF, we decided to remove this protecting group prior to the treatment with TBAF. As seen in scheme 42, this approach did not give us our expected products. Therefore, we believed that it is necessary to have a protected amine in the silyl deprotection step, and thus the protecting group swap is required in an earlier stage of the synthesis.



**Scheme 42:** *N*-Fmoc deprotection.

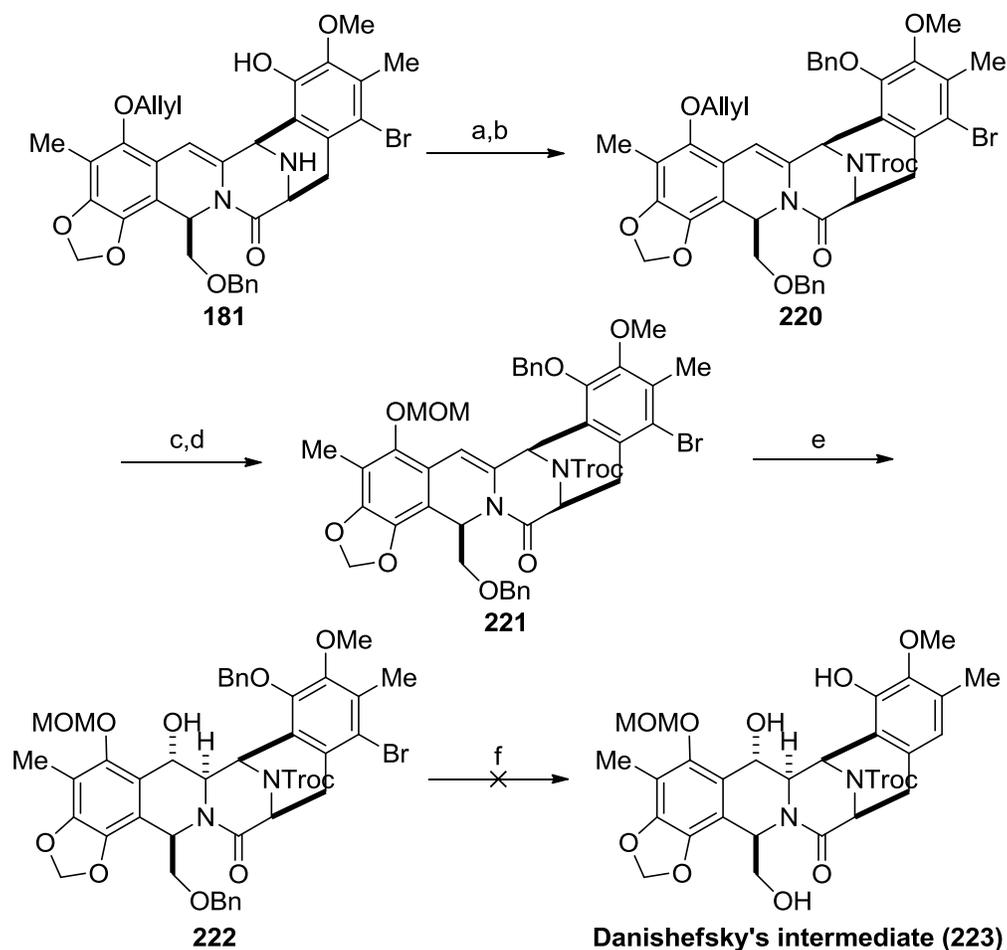
The replacement of the Fmoc of amide **215** by the Boc protecting group was carried out to give **183** in 85% yield over the 2 steps (scheme 43). The acetone was cleaved in the presence of dry Dowex 50W-X8 in dry methanol to generate alcohol **219** in 95% yield. The first attempt to oxidize this alcohol under Swern oxidation condition did not yield target aldehyde efficiently. Purification of the crude aldehyde product did not result in higher quality of the product. The same results were observed under Parikh-Doering oxidation condition and Dess-Martin periodinane. Fortunately, when treating alcohol **219** with Dess-Martin periodinane in a shorter reaction time (17 minutes) and ignoring the sign of remaining starting material on thin layer chromatography, the reaction produced a satisfactory crude product that could be used in the next step without purification. With the aldehyde in hand, we carried out the synthesis of the desired pentacycle by desilylation of the resulting aldehyde followed by acid-catalyzed Boc-deprotection and cyclization.



**Scheme 43:** Synthesis of pentacycle **181**. Reagents and conditions (a)  $\text{Et}_2\text{NH}$ ; (b)  $\text{Boc}_2\text{O}$ , 85% (2 steps); (c) Dowex 50W-X8, dry MeOH, 95%; (d) Dess-Martin periodinane; (e) TBAF; (f) TFA, anisole, 72% (3 steps).

## 2.6 Attempt to intercept Danishefsky's intermediate

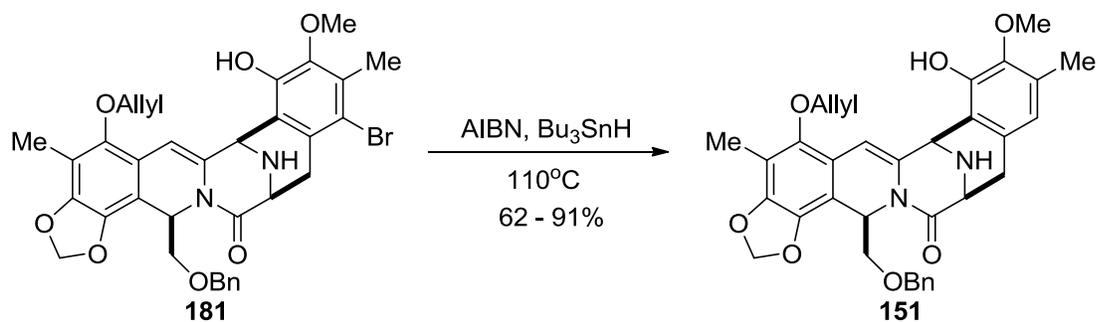
As the bromine auxiliary is not present in the natural product, we thought about possible ways to eliminate this bromine immediately after the synthesis of the pentacyclic core. We foresaw that the bromine would not survive several steps in our planned synthesis of Et-743, such as Pd-catalyzed cleavage of the allyl group or Pd-catalyzed hydrogenation to remove the benzyl protecting group, hence we first carried out the synthesis without adding an extra step to remove the bromine auxiliary. Instead, the amine of pentacycle **181** was Troc-protected and the resulting product was benzylated at the phenol to furnish **220** (scheme 44). Replacement of the allyl group for a MOM group yielded **221**, which was then treated with dimethyl dioxirane and sodium cyanoborohydride to generate alcohol **222**. Pd-catalyzed hydrogenation of **222** under the reported condition by Danishefsky and coworkers to cleave the benzyl protecting groups and at the same time deoxygenation of the benzylic alcohol proved to be not sufficient to cleave the bromine.



**Scheme 44:** Attempt to intercept Danishefski's formal synthesis of Et-743. Reagents and conditions (a) TrocCl, DMAP; (b) BnBr, TBAI, Cs<sub>2</sub>CO<sub>3</sub>, 73% (2 steps); (c) Pd(PPh<sub>3</sub>)<sub>4</sub>, Bu<sub>3</sub>SnH, AcOH; (d) MOMCl, Cs<sub>2</sub>CO<sub>3</sub>, 82% (2 steps); (e) oxone, then NaBH<sub>3</sub>CN, 54%; (f) 10% Pd/C, H<sub>2</sub> (1 atm).

## 2.7 Improved formal synthesis of Et-743

Realizing that any bromide cleavage condition would also affect the *N*-Troc protecting group, we revised our strategy to remove this auxiliary immediately after the synthesis of pentacyclic core **181** by refluxing it with tributyltin hydride and 2,2'-azobisisobutyronitrile in toluene to furnish intermediate **151**. This result completed our synthetic studies of Et-743 as we achieved the synthesis of an intermediate in our formal synthesis of Et-743.



**Scheme 45:** Removal of the auxiliary bromine.

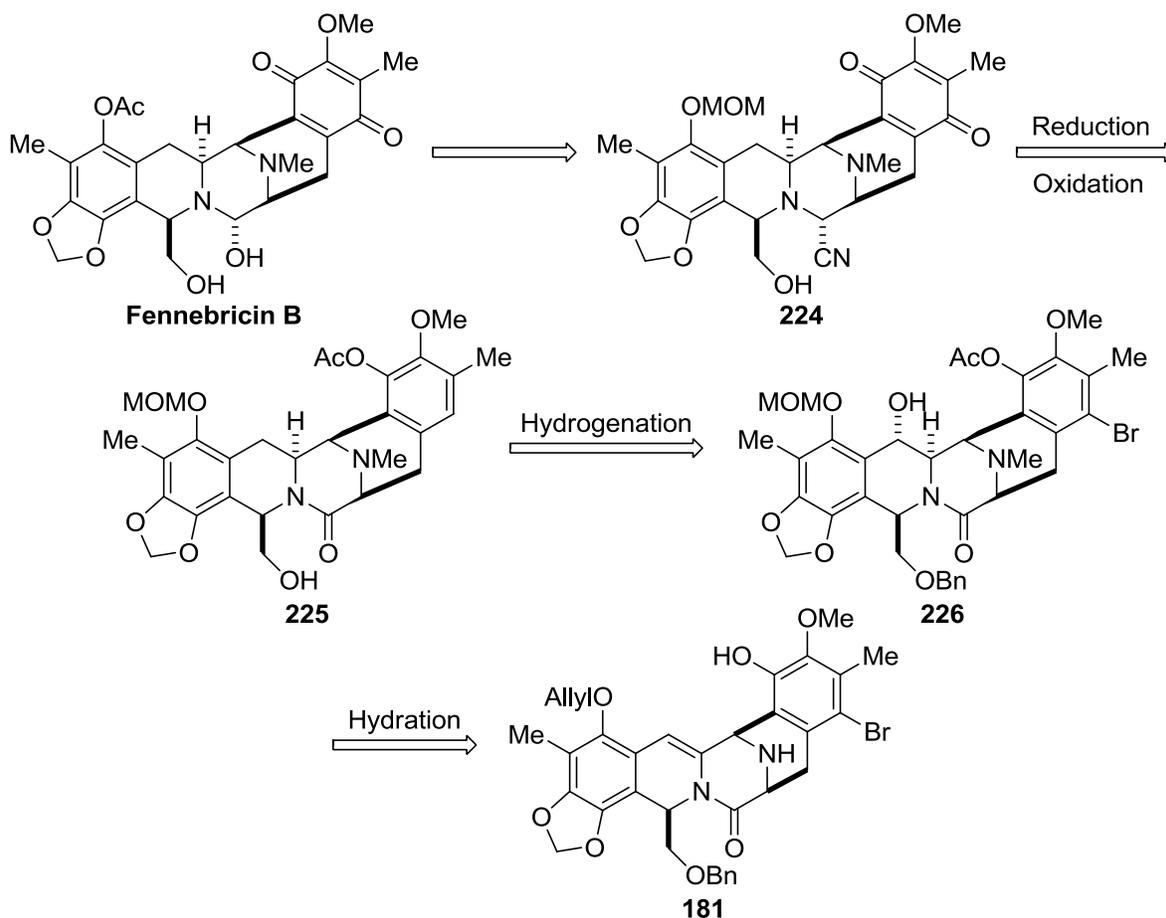
## 2.8 Conclusions

In summary, we successfully developed an efficient and scalable route toward the synthesis of the eastern acid chloride fragment and using this to generate the desired pentacyclic core of Et-743. The synthesis of intermediate **181** did not only improve our previous synthesis of Et-743 but also can be applied in the synthesis of other tetrahydroisoquinoline natural products as we successfully employed this strategy in the total synthesis of renieramycin T.<sup>103</sup> Intermediate **181** was also a starting point of our synthetic studies of fennebricin B, which will be discussed in the next chapter.

## Chapter 3: Synthetic studies of Fennebricin B

### 3.1 First retrosynthesis

We envisioned the synthesis of fennebricin B can be accomplished from pentacyclic core **224** (scheme 46), which is a product of partial reduction and quinone formation of intermediate **225**. **225** can be produced from hydrogenation of pentacycle **226**, an intermediate arising from protecting group manipulations and hydration of the C3-alkene of pentacycle **181**, previously made in the synthesis of Et-743.

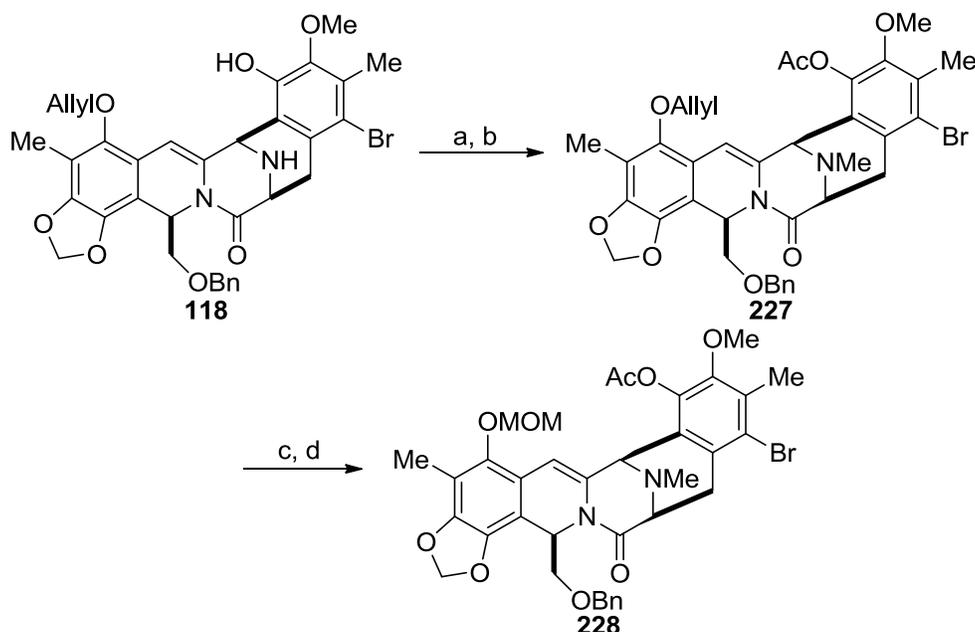


**Scheme 46:** First retrosynthesis of fennebricin B.

## 3.2 Methylated pentacycle 228

### 3.2.1 Synthesis of methylated pentacycle 228

Methylation of pentacycle **118** was done followed by acylation of the phenol provided **227** (scheme 47). Since we had to eliminate the alkene on C3, we anticipated that the allyl group would not survive any condition that would have an effect on this functional group. Thus, allyl-protecting group was replaced by a MOM-protecting group furnishing intermediate **228**.



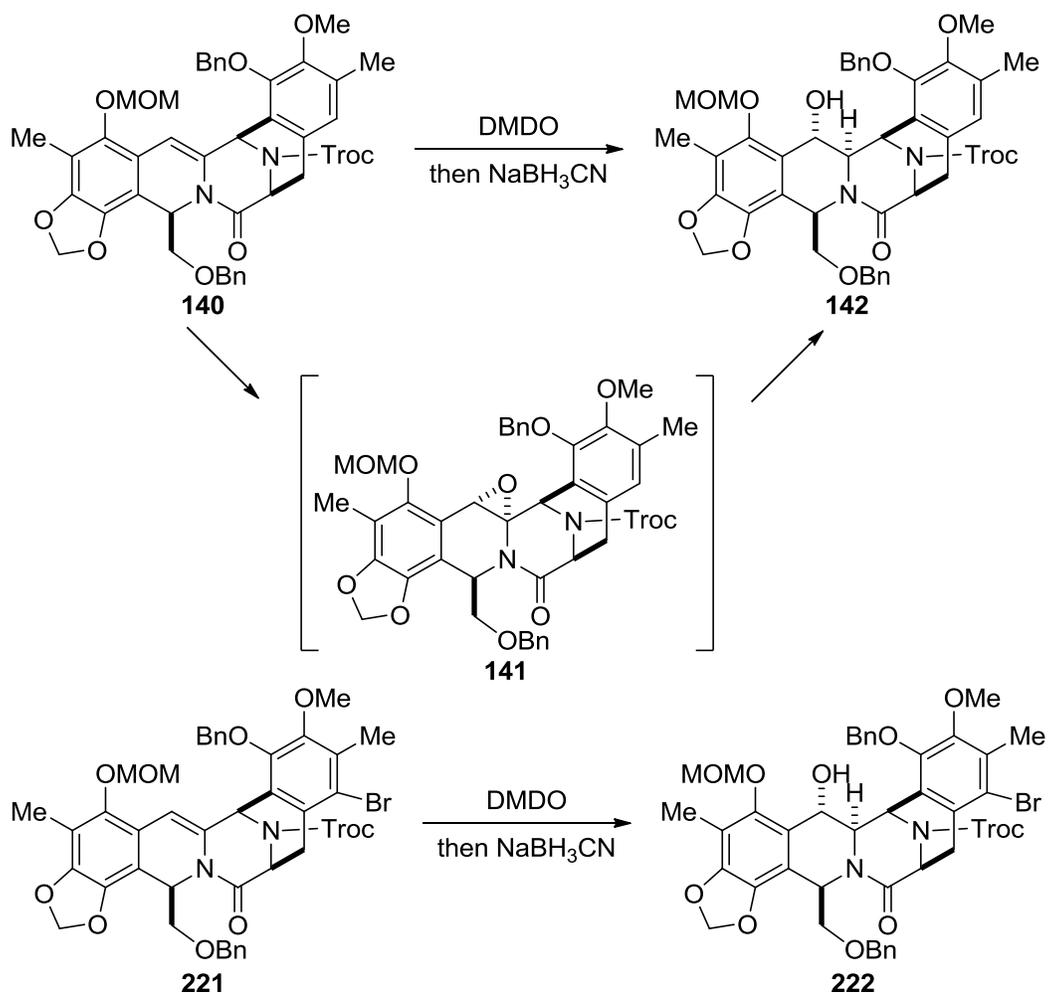
**Scheme 47:** Synthesis of methylated pentacycle **228**. Reagents and conditions (a) HCHO, NaBH<sub>3</sub>CN, 96%; (b) Ac<sub>2</sub>O, DMAP, *i*-Pr<sub>2</sub>NEt, 94%; (c) Pd(PPh<sub>3</sub>)<sub>4</sub>, Bu<sub>3</sub>SnH, AcOH; (d) MOMBr, *i*-Pr<sub>2</sub>NEt, 75-86% (2 steps).

### 3.2.2 Attempts to hydration of pentacycle 228

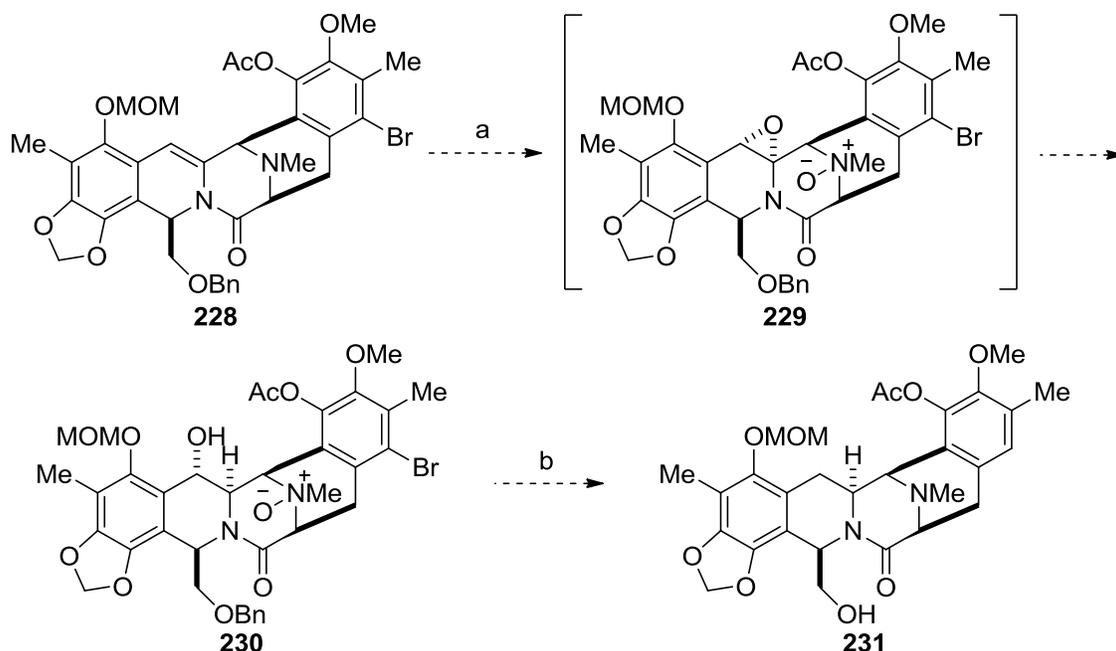
#### 3.2.2.1 Precedences

Danishefsky and coworkers developed a method to produce C4-hydroxyl from alkene **140** via epoxidation of the alkene by dimethyl dioxirane, followed by reductive opening of the epoxide (scheme 48).<sup>81</sup> We also have successfully employed this method in our synthetic studies of Et-743. Therefore, we projected the hydration of C3-alkene of pentacycle **228** using a similar condition, and the resulting benzylic hydroxyl would be cleaved under palladium-catalyzed

hydrogenation simultaneously with the removal of the benzyl protecting group. We expected the oxidation of the N12-amine under this condition as well; however, it would be reduced back to an amine as shown in scheme 49.



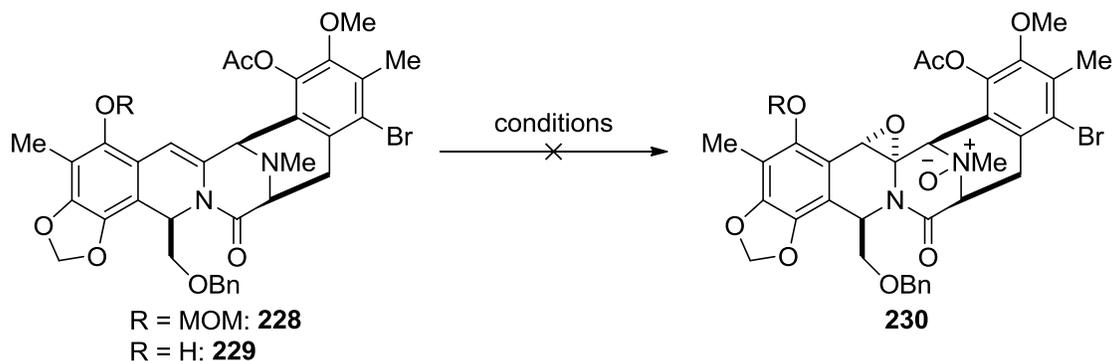
**Scheme 48:** Precedences of hydration of C3-alkene.



**Scheme 49:** Planned synthesis of pentacycle **231**. Reagents and conditions (a) DMDO, then  $\text{NaBH}_3\text{CN}$ ; (b)  $\text{H}_2$ , Pd/C.

### 3.2.2.2 Epoxidation attempts

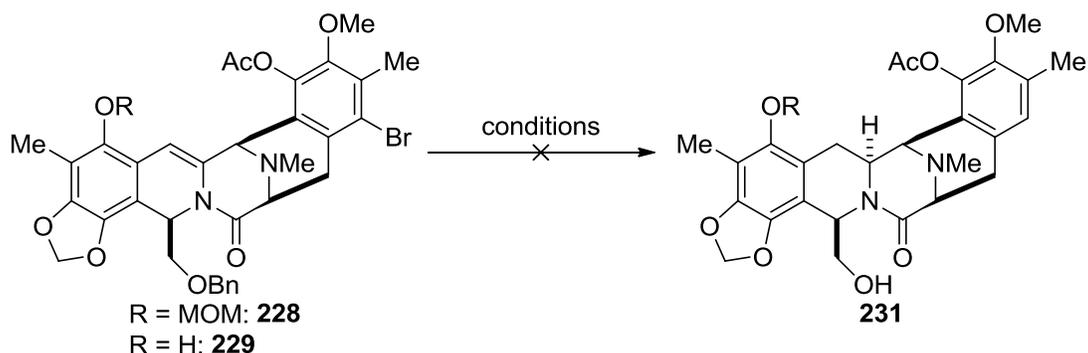
The first attempt of epoxidation of both **228** and **229** did not happen as expected (scheme 50). We then searched for different epoxidation conditions to overcome the issue. Unfortunately, none of the conditions we tried worked and therefore, this approach was not employed in our synthesis of fennebricin B.



**Scheme 50:** Epoxidation attempts on intermediate **228** and **229**. Reagent and conditions: DMDO,  $\text{NaBH}_3\text{CN}$ , with or without TsOH,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  to  $0^\circ\text{C}$ ; *m*-CPBA,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ;  $\text{H}_2\text{O}_2$ ,  $\text{NaHCO}_3$ , THF,  $0^\circ\text{C}$ ;  $\text{H}_2\text{O}_2$ , NaOH, THF;  $\text{BH}_3\cdot\text{SMe}_2$ , THF then  $\text{H}_2\text{O}_2$ , NaOH; 1,1,1-trifluoromethyl methyl dioxirane,  $\text{H}_2\text{O}$ , THF,  $0^\circ\text{C}$ .

### 3.2.3 Hydrogenation attempts

Hydrogenation of C3-alkene of the THIQ family has been proven to be challenging. However, there are reports of successful hydrogenation of this alkene under various conditions.<sup>103,104</sup> Therefore, we also looked into direct reduction of the C3-alkene by metal-catalyzed hydrogenation. Unfortunately, we only either observed debromination product or debenzylation product or both, but never saw the disappearance of this alkene (scheme 51).

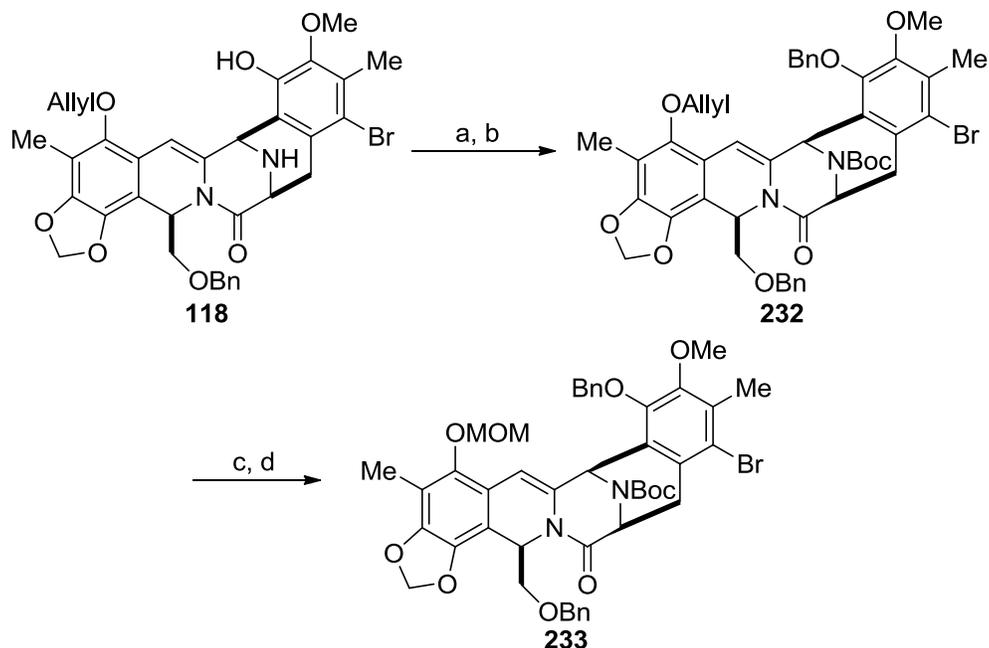


**Scheme 51:** Hydrogenation attempts on intermediate **228** and **229**. Reagents and conditions: 10% Pd/C, H<sub>2</sub> (100 psi), MeOH; Raney-Ni, H<sub>2</sub> (150 psi), MeOH; 10%Pd/C, H<sub>2</sub> (100 psi), THF; 10%Pd/C, H<sub>2</sub> (100 psi), Et<sub>2</sub>O, sonicated; Raney-Ni, H<sub>2</sub> (150 psi), MeOH, sonicated; 5% Rh/C, H<sub>2</sub> (130 psi), MeOH.

## 3.3 N-Boc pentacycle 233

### 3.3.1 Synthesis of N-Boc pentacycle 233

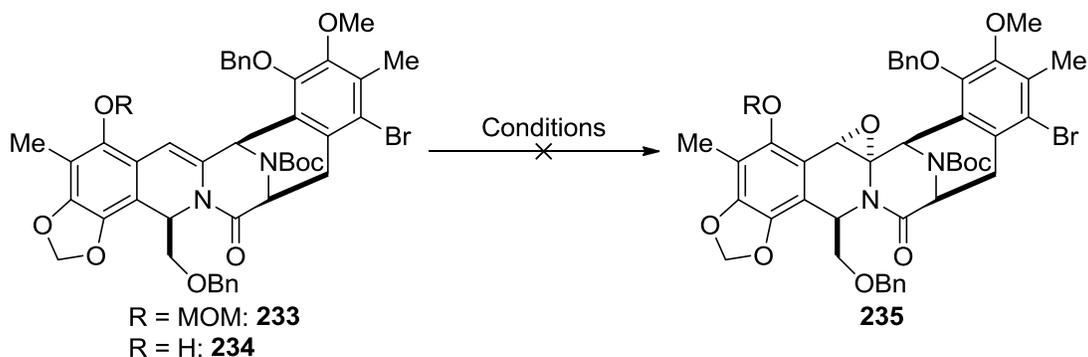
Since epoxidation of the N12-methyl amine **228** did not give any sign of desired product, we looked back into protecting this amine as a *tert*-butyl carbamate. We believed the replacement of an *N*-Troc- to an *N*-Boc-protecting group would not change the chemistry of the pentacyclic core, thus the epoxidation could happen as seen with intermediate **221** (scheme 48). *N*-Boc protection of **118** followed by benzylation of the phenol provided **232** (scheme 52). The allyl protecting group was then switched to MOM-protecting group to give **233**.



**Scheme 51:** Synthesis of *N*-Boc pentacycle **233**. (a) (Boc)<sub>2</sub>O, 92%; (b) BnBr, Cs<sub>2</sub>CO<sub>3</sub>, TBAI, 79%; (c) Pd(PPh<sub>3</sub>)<sub>4</sub>, Bu<sub>3</sub>SnH, AcOH; (d) MOMBr, *i*-Pr<sub>2</sub>NEt, 75-86% (2 steps).

### 3.3.2 Attempts to epoxidation of pentacycles **233** and **234**

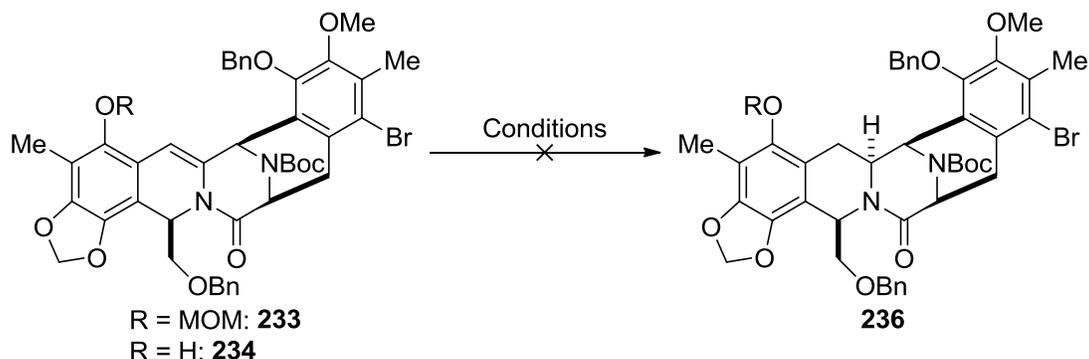
With pentacycle **233** and **234** in hand, we tried out epoxidation and hydration reactions on this substrate. The result, however, was disappointing as we did not observe any desired product (scheme 52).



**Scheme 52:** Epoxidation attempts on intermediate **233** and **234**. Reagents and conditions: DMDO, NaBH<sub>3</sub>CN, with or without TsOH, CH<sub>2</sub>Cl<sub>2</sub>, -78°C to 0°C; *m*-CPBA, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C; H<sub>2</sub>O<sub>2</sub>, NaHCO<sub>3</sub>, THF, 0°C; H<sub>2</sub>O<sub>2</sub>, NaOH, THF; BH<sub>3</sub>•SMe<sub>2</sub>, THF then H<sub>2</sub>O<sub>2</sub>, NaOH; 1,1,1-trifluoromethyl methyl dioxirane, H<sub>2</sub>O, THF, 0°C.

### 3.3.3 Hydrogenation attempts

The hydrogenation of intermediate **233** and **234** also gave the same results as seen with compound **228** and **229** (scheme 53).



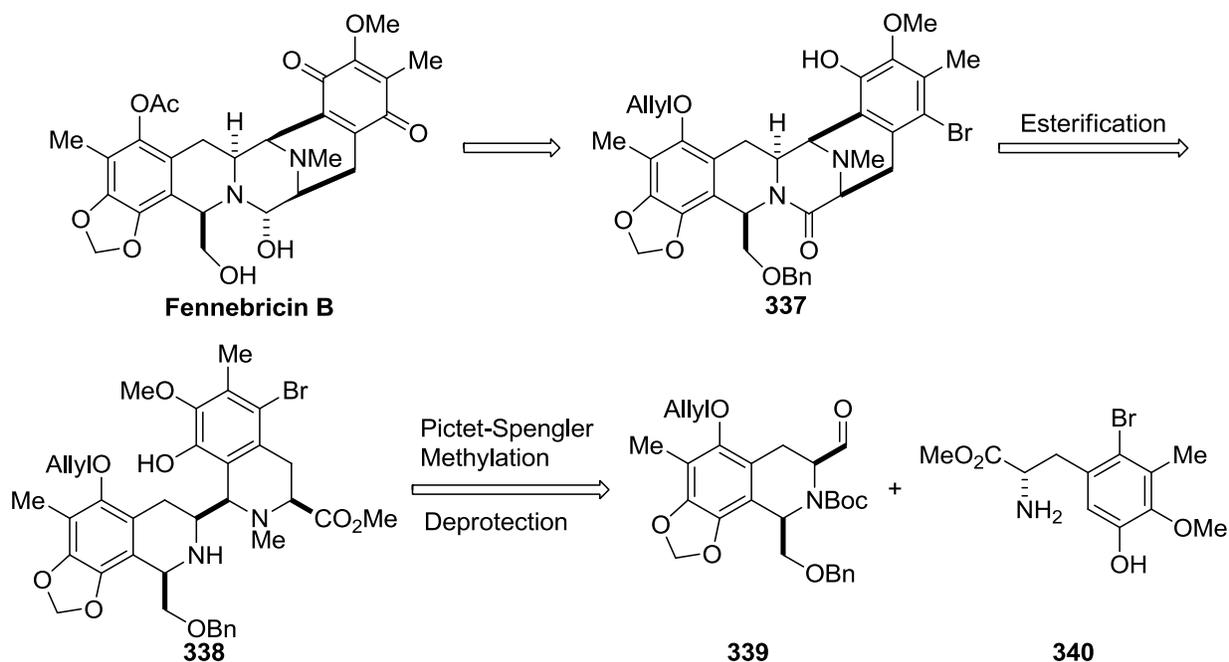
**Scheme 53:** Hydrogenation attempts of pentacycle **233** and **234**. Reagents and conditions: 10% Pd/C, H<sub>2</sub> (100 psi), MeOH; Raney-Ni, H<sub>2</sub> (150 psi), MeOH; 10%Pd/C, H<sub>2</sub> (100 psi), THF; 10%Pd/C, H<sub>2</sub> (100 psi), Et<sub>2</sub>O, sonicated; Raney-Ni, H<sub>2</sub> (150 psi), MeOH, sonicated; 5% Rh/C, H<sub>2</sub> (130 psi), MeOH.

## 3.4 Attempts to synthesize novel pentacycle **337**

A new strategy was developed to synthesize a derivative of pentacycle **118** without the problematic alkene. This would fulfill the synthesis of fennebricin B because the natural product does not have this C3-alkene.

### 3.4.1 Second retrosynthesis

We envisioned that fennebricin B could be made from pentacycle **337**, which was an amide product of **338** (scheme 54). **338** could be produced from the coupling of THIQ **339** and amino ester **340** via Pictet-Spengler reaction, followed by methylation and Boc-deprotection of the resulting coupling product.

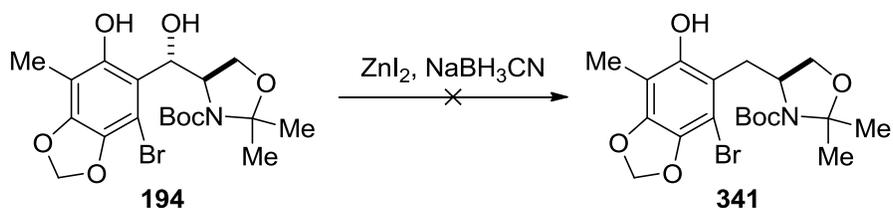


**Scheme 54:** Second retrosynthesis of fennebricin B.

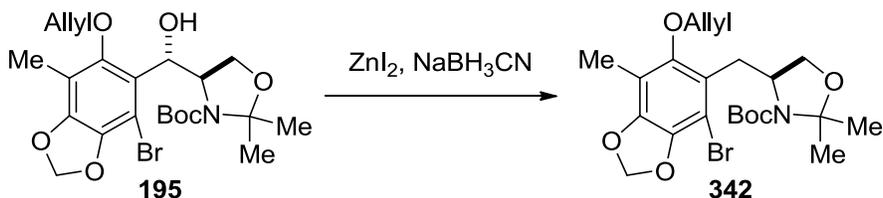
### 3.4.2 Synthesis of the novel THIQ fragment

#### 3.4.2.1 Reduction of the C4-alcohol on intermediate 194 and 195

Diol **194** is the first intermediate in the synthesis of the pentacyclic core containing the C4-alcohol, which would be eliminated later on in the synthesis to form the alkene. Hence, it was the first intermediate we targeted. No desired product was found when treating **194** with zinc iodide in the presence of sodium cyanoborohydride (scheme 55).<sup>105</sup> The reduction of allylated phenol **195** to intermediate **342** was observed under the same condition in small scale (scheme 56); however, this result was not reproducible, especially in slightly larger scale. We believed that the heterogenous reaction condition was the major problem of this reaction because zinc iodide is not soluble in dichloromethane. Switching from dichloromethane to tetrahydrofuran in order to achieve a homogenous reaction condition did not yield any desired product. Therefore, we looked into a different condition to remove this hydroxyl group.



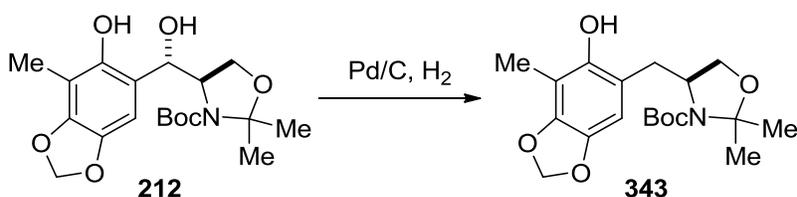
**Scheme 55:** Reduction of diol **194**.



**Scheme 56:** Reduction of alcohol **195**.

### 3.4.2.2 Hydrogenation reaction to reduce the C4-alcohol

Since C4-alcohol is a benzylic alcohol, it was thought that hydrogenation under catalysis of palladium on carbon would effectively remove this alcohol. Intermediate **212** was chosen instead of **194** because we envisioned the bromide would also be removed under this condition (scheme 57). The first attempt of hydrogenation reaction showed signs of desired product. However, when we tried to repeat and scale up this reaction, the results were not optimistic as only starting materials were observed.

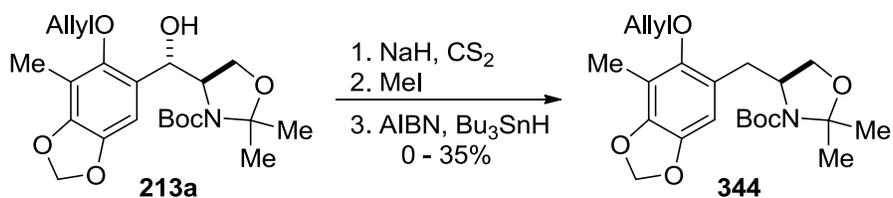


**Scheme 57:** Hydrogenation of diol **212**.

### 3.4.2.3 Barton-McCombie deoxygenation of alcohol 344

Barton-McCombie deoxygenation was performed on intermediate **213a** as the bromide on **195** would not survive this condition. The first few attempts of this reaction gave rise to intermediate **344** (scheme 58), albeit low yield. Unfortunately, the reaction yielded no product at

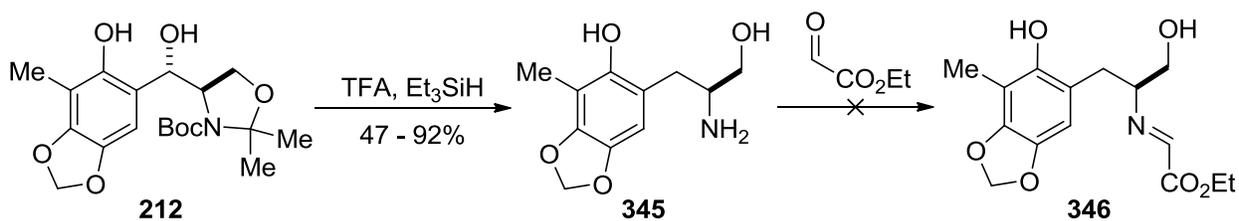
100 mg scale, hence we could not move on with this reaction in the synthesis of the natural product.



**Scheme 58:** Barton-McCombie deoxygenation of alcohol **213a**.

#### 3.4.2.4 Deoxygenation of intermediate **212**

We found success when treating diol **212** with trifluoroacetic acid and triethylsilane in small and large scale furnishing amine **345** (scheme 59). This intermediate, however, had a solubility problem as it turned into a gel in organic solvents when added to a solution of ethyl glyoxalate in toluene. During this time, another approach to remove the C4-alcohol was successfully developed; therefore, this transformation was not pursued further as we foresaw the cyclization of imine **346** could also pose another serious problem to overcome.

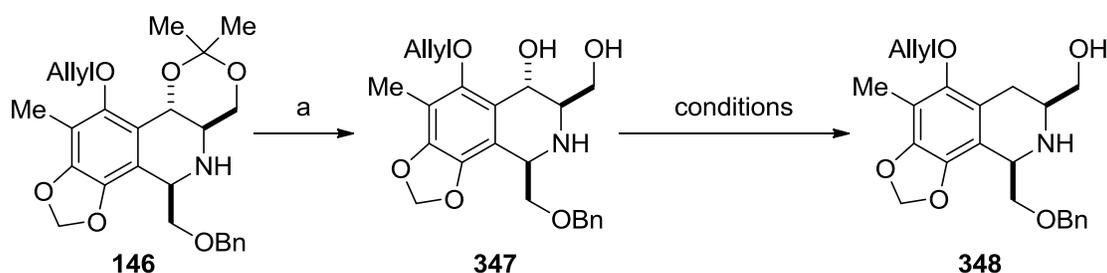


**Scheme 59:** Deoxygenation of **212**.

#### 3.4.2.5 Deoxygenation of intermediate **347**

We then focused on the more advance intermediate (**146**) as this intermediate already possesses the required tetrahydroisoquinoline structure. Treatment of THIQ **146** with tosic acid in methanol gave diol **347** in quantitative yield (scheme 60). The reaction of **347** with zinc iodide and sodium cyanoborohydride in dichloromethane gave **348** in small scale. This reaction never went to completion in larger scale due to solubility problem. Switching the solvent from dichloromethane to tetrahydrofuran to achieve a homogenous solution did not produce any

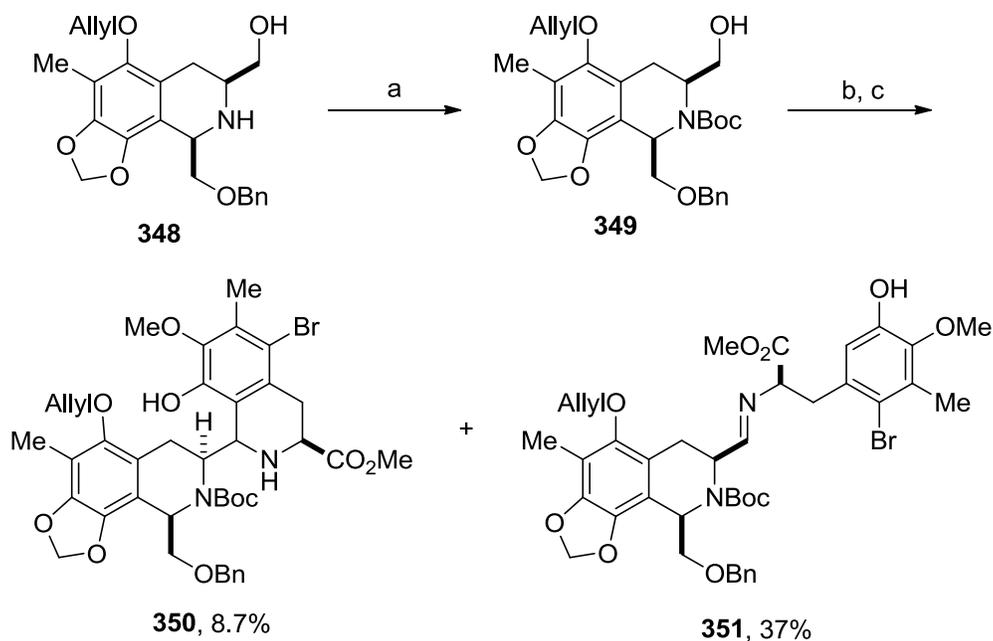
targeted product. Initially, treatment of **347** with 10 equivalent of trifluoroacetic acid and 10 equivalent of triethylsilane furnished **348** in 28% yield. Varying the ratio of reagents and starting material resulted in the best combination of 5 equivalent of trifluoroacetic acid and 5 equivalent of triethylsilane. This result, however, was not consistent when scaling up the reaction. Therefore, we searched for different conditions to synthesize **348** more efficiently. Acetic acid and sodium borohydride was tried and did not give any product.<sup>106</sup> Fortunately, the combination of 5 equivalent of trifluoroborane etherate and 5 equivalent of triethylsilane gave a moderate yield (69%) of **348** at high purity and the crude product can be used in the next step without purification.



**Scheme 60:** Synthesis of the novel THIQ fragment (**348**). Reagents and conditions (a) TsOH, MeOH, quant. (b) ZnI<sub>2</sub>, NaBH<sub>3</sub>CN; TFA, Et<sub>3</sub>SiH; AcOH, NaBH<sub>4</sub>; BF<sub>3</sub>•OEt<sub>2</sub>, Et<sub>3</sub>SiH.

### 3.4.3 Synthetic studies toward the novel pentacycle **339**

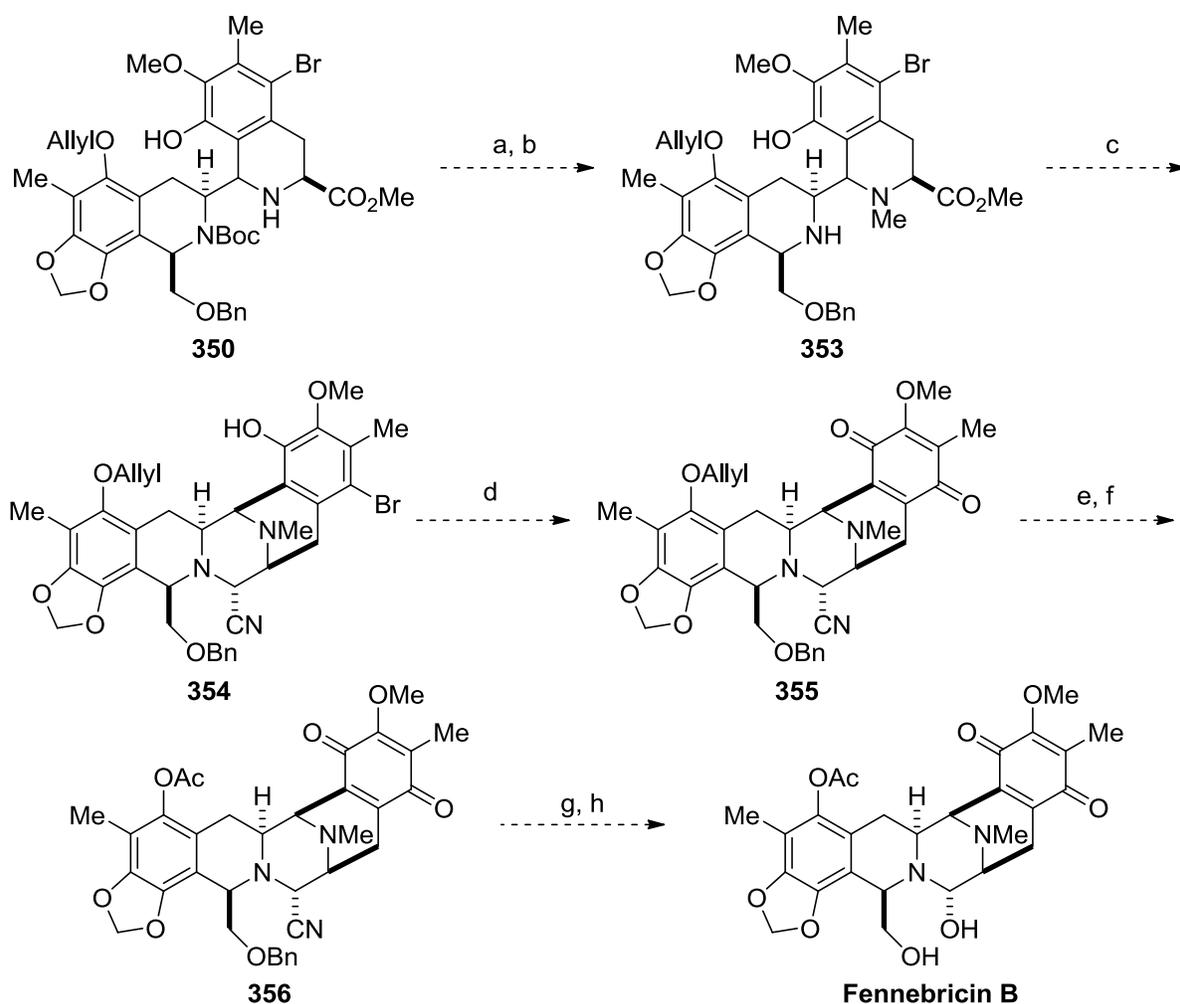
The crude product **348** was treated with di-*tert*-butyl dicarbonate in the presence of Hünig's base to provide alcohol **349** in 75% yield over the two steps (scheme 61). The alcohol was oxidized under Swern oxidation or Dess-Martin periodinane to furnish an aldehyde, which was then coupled with amine **340** in the presence of acetic acid to give tetracycle **350** in 8.7% yield and imine **351** in 35% yield. Replacement of acetic acid with other stronger acid did not improve the yield of the reaction and attempts to convert imine **351** into the tetracycle product were also not successful.



**Scheme 61:** Synthesis of intermediate **350**. Reagents and conditions (a)  $\text{Boc}_2\text{O}$ ,  $i\text{-Pr}_2\text{NEt}$ , THF, 75% yield (2 steps); (b) Dess-Martin periodinane,  $\text{CH}_2\text{Cl}_2$ , quant.; (c) **340**, MS 4Å,  $\text{CH}_2\text{Cl}_2$ , then AcOH.

### 3.5 Future works

We are in search for a new acid or a combination of acid to improve the conversion of imine **351** to tetracycle **350**. The synthesis of fennebricin B from **350** is proposed as shown in scheme 61. **350** can be methylated followed by cleavage of the Boc protecting group to give amine **353**. Our preliminary works revealed that the deprotection reaction can be challenging. However, there are more conditions to try and we can replace Boc for a different protecting group in the earlier step of the synthesis if it is necessary. Boc-deprotection of the tetracyclic core was observed when the methyl ester is reduced to an alcohol; therefore, we are confident that we can achieve the free amine from **350**. Ester **353** can be reduced to an aldehyde and the resulting product will undergo Strecker reaction to produce nitrile **354**. **354** will be oxidized to furnish quinone **355**, which will be submitted to protecting group swap to yield quinone **356**. Removal of the benzyl group, followed by treatment of the resulting alcohol with silver nitrate will generate fennebricin B.



**Scheme 62:** Synthetic plan to fennebricin B. Reagents and conditions (a) HCHO, NaBH<sub>3</sub>CN; (b) HCl, MeOH, reflux; (c) DIBAL, toluene, -78°C, then KCN; (d) DDQ; (e) Pd(PPh<sub>3</sub>)<sub>4</sub>, Bu<sub>3</sub>SnH, AcOH; (f) Ac<sub>2</sub>O, DMAP, *i*-Pr<sub>2</sub>NEt; (g) BCl<sub>3</sub>, pentamethylbenzene; (h) AgNO<sub>3</sub>.

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## APPENDIX

## Experimental Section

### 1. Compound list

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Compound 232	155
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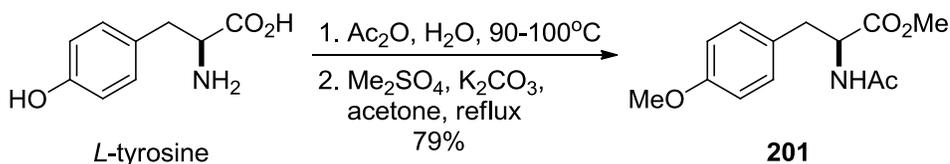
Compound 347	162
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## 2. General considerations

Unless otherwise noted, all reactions were performed under positive pressure of argon in flame-dried glassware. Commercially available materials were used without further purification. Organic solvents were passed through J.C. Meyer of Glass Contour purifying solvent system under positive pressure of argon. The reactions were monitored by thin layer chromatography (TLC) on S-2 0.25 mm E. Merck silica gel plates (60F-254), visualized under UV light and a solution of *para*-anisaldehyde in ethanol. Standard silica gel for flash column chromatography was obtained from Sorbent Technologies. NMR spectra were recorded on Varian 400MHz spectrometer. <sup>1</sup>H- and <sup>13</sup>C-NMR were reported relative to CDCl<sub>3</sub> ( $\delta = 7.26$  for <sup>1</sup>H-NMR spectra and  $\delta = 77.16$  for <sup>13</sup>C-NMR spectra). Infrared spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. Mass spectra were obtained on a Fison VG Autospec. Optical rotations were obtained on a Rudolph Research Autopol III polarimeter.

## 3. Experimental procedures and data

**Compound 201:** (*S*)-methyl 2-acetamido-3-(4-methoxyphenyl)propanoate

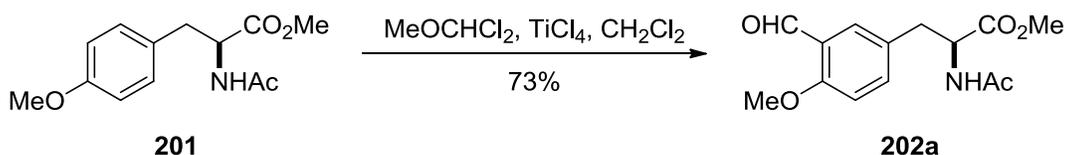


Acetic anhydride (188 ml, 2.00 mol) was added slowly to a suspension of *L*-tyrosine (45.36 g, 0.25 mol) in water (250 ml) at 90°C. The reaction was heated at 90°C to 100°C for 2 hours, and

then concentrated under a reduced pressure to provide yellow oil. Acetone (200 ml) was added to this yellow oil and the solution was stirred at room temperature for 16 hours when white solids were formed. The solids were removed and the solution was concentrated under a reduced pressure to provide *N*-acyl *L*-tyrosine as a white solid. The crude product was used in the next step without further purification.

*N*-acyl *L*-tyrosine was dissolved in acetone (400 ml) and water (600ml), followed by the addition of potassium carbonate (173 g, 1.25 mol) and dimethyl sulfate (71 ml, 0.75 mol). The suspension was stirred and heated to reflux for 4 hours, then allowed to cool to room temperature and concentrated under a reduced pressure. The residue was resuspended in water and stirred vigorously. The solids were filtered and washed with several small portions of water and dried under vacuum to give **201** (50.00 g, 79% over the 2 steps) as an off-white solid. All experimental data matched those reported in the literature.<sup>107</sup>

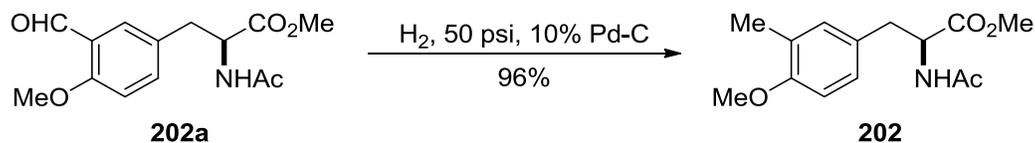
**Compound 202a:** (*S*)-methyl 2-acetamido-3-(3-formyl-4-methoxyphenyl)propanoate



MeOCHCl<sub>2</sub> (39 ml, 0.44 mol) and TiCl<sub>4</sub> (100 ml, 0.87 mol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added dropwise over 4 hours to the solution of **201** (36.47 g, 0.15 mol) in CH<sub>2</sub>Cl<sub>2</sub> (400 ml) at 0°C. The solution was allowed to warm to room temperature and stirred for 1.5 hours, then cooled to 0°C again. Ice-water (600 ml) was added slowly and the resulting suspension was stirred vigorously for 1 hour. The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 300 ml). The combined organic layers were washed with the aqueous saturated NaHCO<sub>3</sub> (2 x 300 ml), brine (300 ml), then dried over MgSO<sub>4</sub> and concentrated. The residue was passed through a silica plug, eluted with EtOAc. The solvent was reduced to half full and an equal amount of

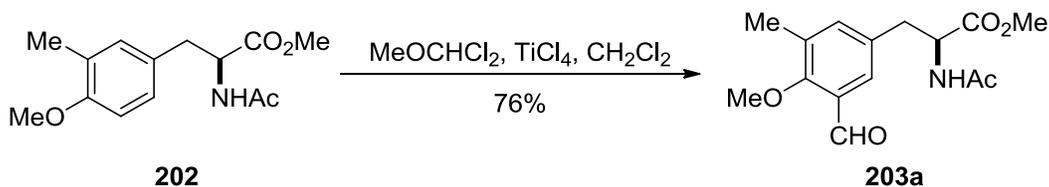
hexanes was added. The solids that crashed out were decanted and washed with hexanes. The filtrate was reduced to half full and more hexane was added to promote precipitation of the product. This process was repeated five times to provide **202a** (29.44 g, 73%) as an off-white solid. All experimental data matched those reported in the literature.<sup>93</sup>

**Compound 202:** (*S*)-methyl 2-acetamido-3-(4-methoxy-3-methylphenyl)propanoate



The wet 10% Pd/C (18.21 g) was added to a solution of **202a** (28.90 g, 0.10 mol) in methanol (500 ml). The flask was placed in a Parr-shaker and filled with H<sub>2</sub> to 50 psi for 4 hours. The suspension was filtered through a pad of celite. The solvent was removed to give a clear oil (26.45 g, 96%), which was used in the next step without purification. All experimental data matched those reported in the literature.<sup>93</sup>

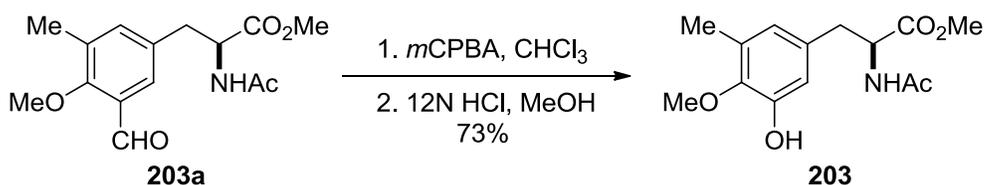
**Compound 203a:** (*S*)-methyl 2-acetamido-3-(3-formyl-4-methoxy-5-methylphenyl)propanoate



TiCl<sub>4</sub> (34 ml, 0.30 mol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added dropwise to a solution of **202** (26.20 g, 0.10 mol) and MeOCHCl<sub>2</sub> (11.6 ml, 0.13 mol) in CH<sub>2</sub>Cl<sub>2</sub> at 0°C. The solution was allowed to warm to room temperature and stirred for 3.5 hours, then cooled to 0°C again. Ice-water (250 ml) was added slowly and the resulting suspension was stirred vigorously for 1 hour. The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 100 ml). The combined organic layers were washed with the aqueous saturated NaHCO<sub>3</sub> (2 x 150 ml), the brine (100 ml), then dried with MgSO<sub>4</sub> and concentrated. The residue was passed through a silica plug,

eluted with EtOAc. The solvent was reduced to half full and an equal amount of hexanes was added. The solids that precipitated out were decanted and washed with hexanes. The filtrate was reduced to half full and more hexane was added to promote precipitation of the product. This process was repeated five times to provide **203a** (21.88 g, 76%) as an off-white solid. All experimental data matched those reported in the literature.<sup>93</sup>

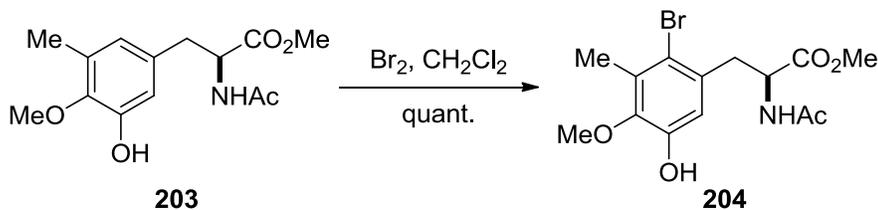
**Compound 203:** (*S*)-methyl 2-acetamido-3-(3-hydroxy-4-methoxy-5-methylphenyl)propanoate



*m*-CPBA (38.62 g, 0.22 mol) was added to a solution of compound **203a** (21.88 g, 74.59 mmol) in CHCl<sub>3</sub> (500 ml). The reaction was heated to reflux for 1 hour, and then allowed to cool to room temperature. The solution was washed with the aqueous saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2 x 200 ml), the 20% aqueous CH<sub>3</sub>CO<sub>2</sub>Na (3 x 200 ml), the brine (200 ml), dried over MgSO<sub>4</sub> and concentrated to provide a yellow oil.

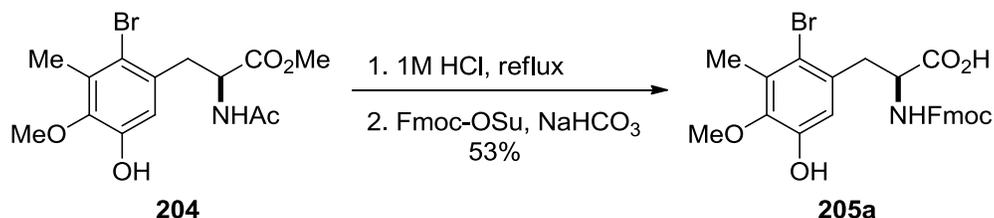
The yellow oil was dissolved in MeOH (250 ml) and cooled to 0°C. 12 N HCl (10 ml) was added dropwise to the solution of the resulting yellow oil in MeOH (250 ml) at 0°C. The reaction was stirred at room temperature for 1.5 hours, and then the solvent was reduced to half full. The remaining solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 ml) and washed with the 20% aqueous CH<sub>3</sub>CO<sub>2</sub>Na until the aqueous layer was colorless. The organic layer was washed with the brine (100 ml), dried over MgSO<sub>4</sub> and concentrated. The residue was purified by column chromatography (75% EtOAc/hexanes) to give phenol **203** as a yellow gel (15.60 g, 73%). All experimental data matched those reported in the literature.<sup>93</sup>

**Compound 204:** (S)-methyl 2-acetamido-3-(2-bromo-5-hydroxy-4-methoxy-3-methylphenyl)propanoate



Br<sub>2</sub> (2.89 ml, 55.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (69 ml) was added dropwise to a vigorously stirred solution of phenol **203** (15.6 g, 55.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (275 ml) until the solution started to change color and NMR of a small aliquot from the reaction showed no trace of the starting material. The solution was washed with water (100 ml), the aqueous saturated NaHCO<sub>3</sub> (3 x 100 ml), the brine (100 ml), then dried over MgSO<sub>4</sub> and concentrated to provide bromophenol **204** as a white solid (19.94 g, quant.). The crude product was used in the next reaction without further purification. All experimental data matched those reported in the literature.<sup>93</sup>

**Compound 205a:** (S)-2-acetamido-3-(2-bromo-5-hydroxy-4-methoxy-3-methylphenyl)propanoic acid

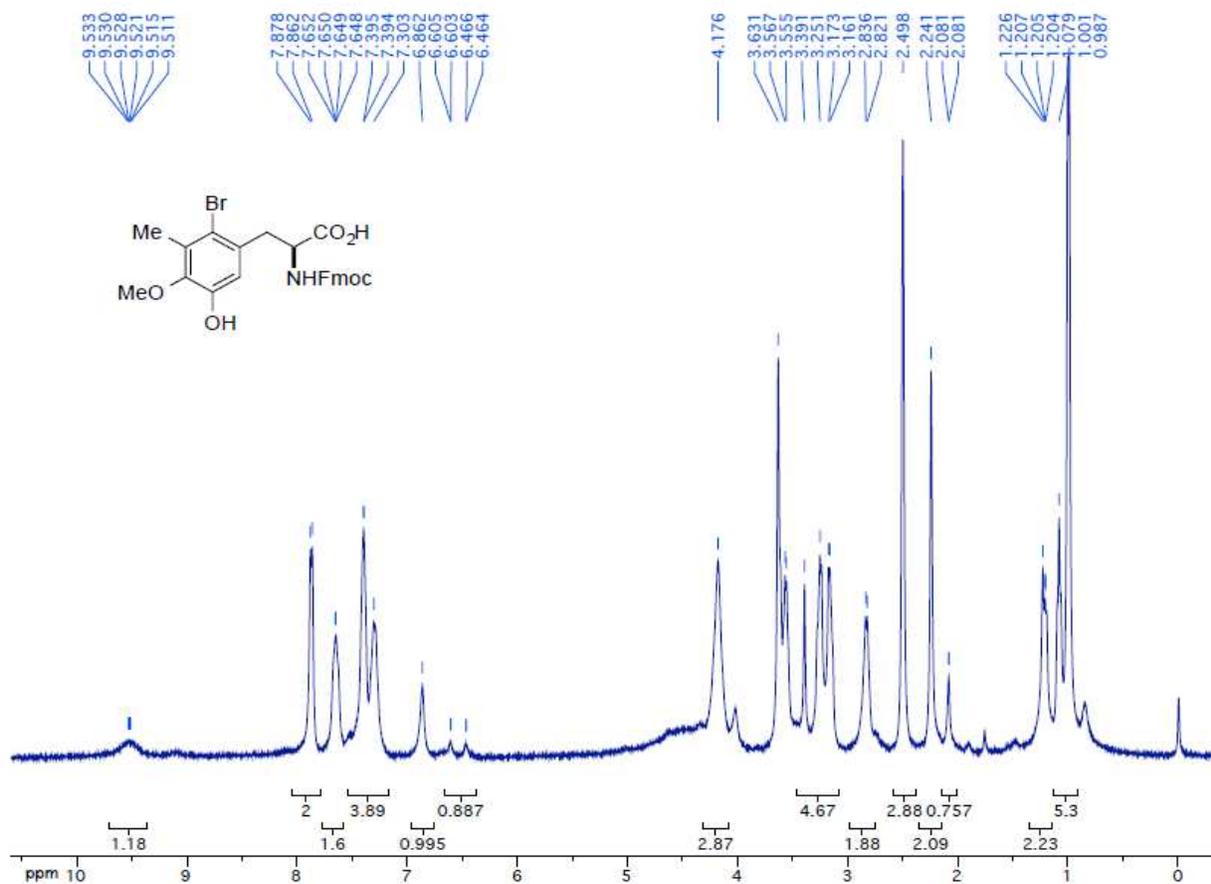


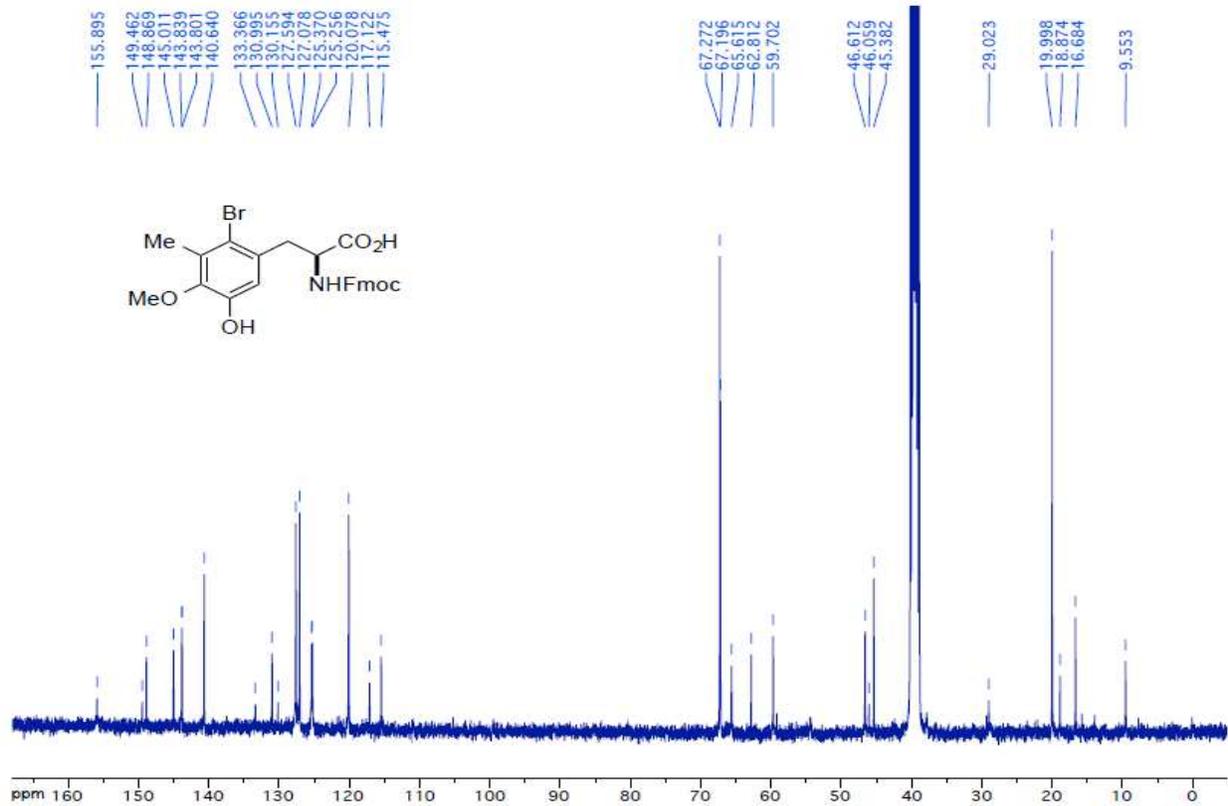
Bromophenol **204** (19.74 g, 54.8 mmol) was dissolved in 1M HCl (300 ml) and the reaction was heated to reflux for 2.5 hours. Water was removed under reduced pressure to provide an amino acid as a white to light brown solid.

The saturated NaHCO<sub>3</sub> (500 ml) and solid NaHCO<sub>3</sub> (~ 2 g) were added to the amino acid. Acetone (250 ml) and FmocOSu (20.33 g, 60.3 mmol) were added, and the reaction was stirred

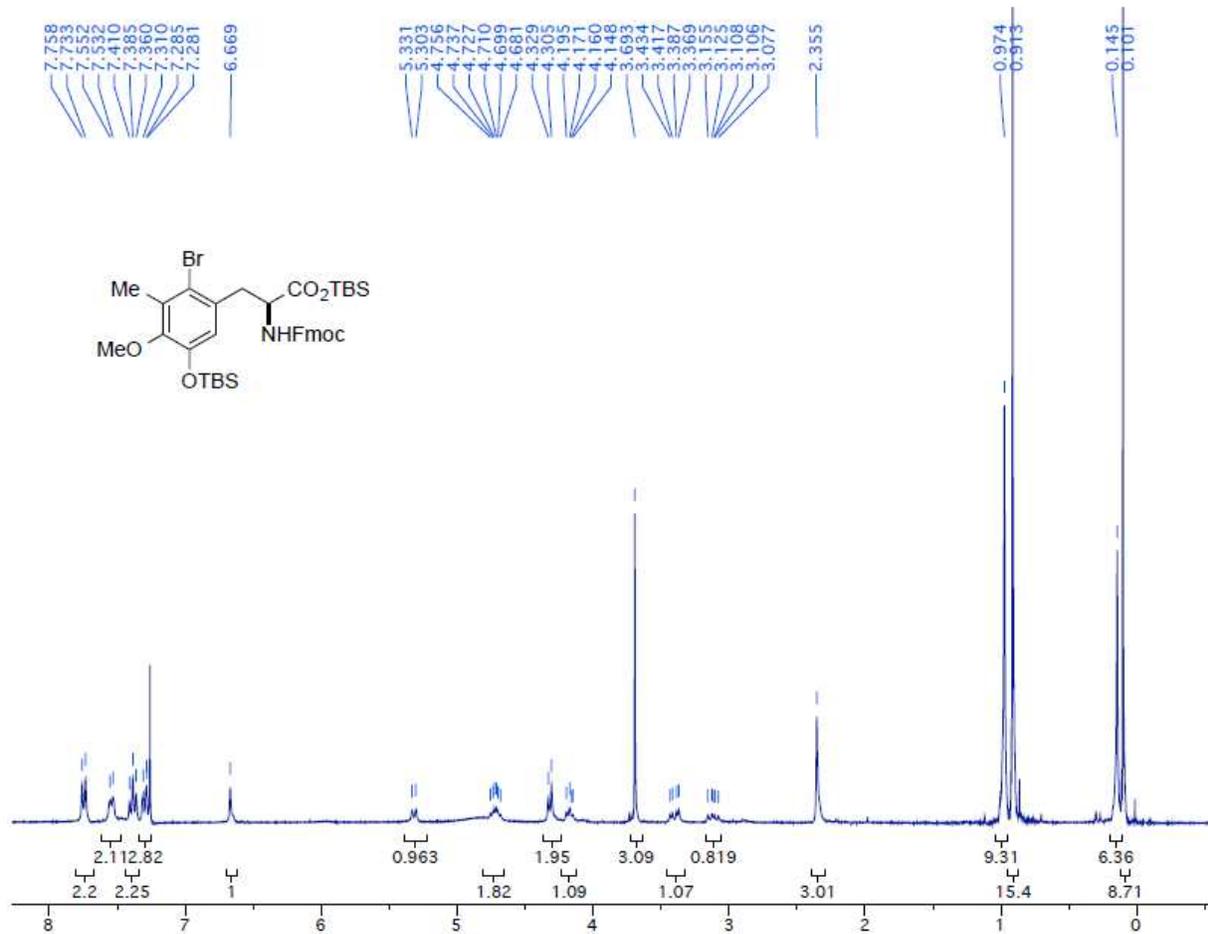
at room temperature for 13 hours. The reaction was acidified with 1 M HCl to pH ~ 1. The suspension was extracted with EtOAc (3 x 500 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (2% MeOH/CHCl<sub>3</sub>) to give **205a** (15.31 g, 53% over the 2 steps) as an off-white solid.

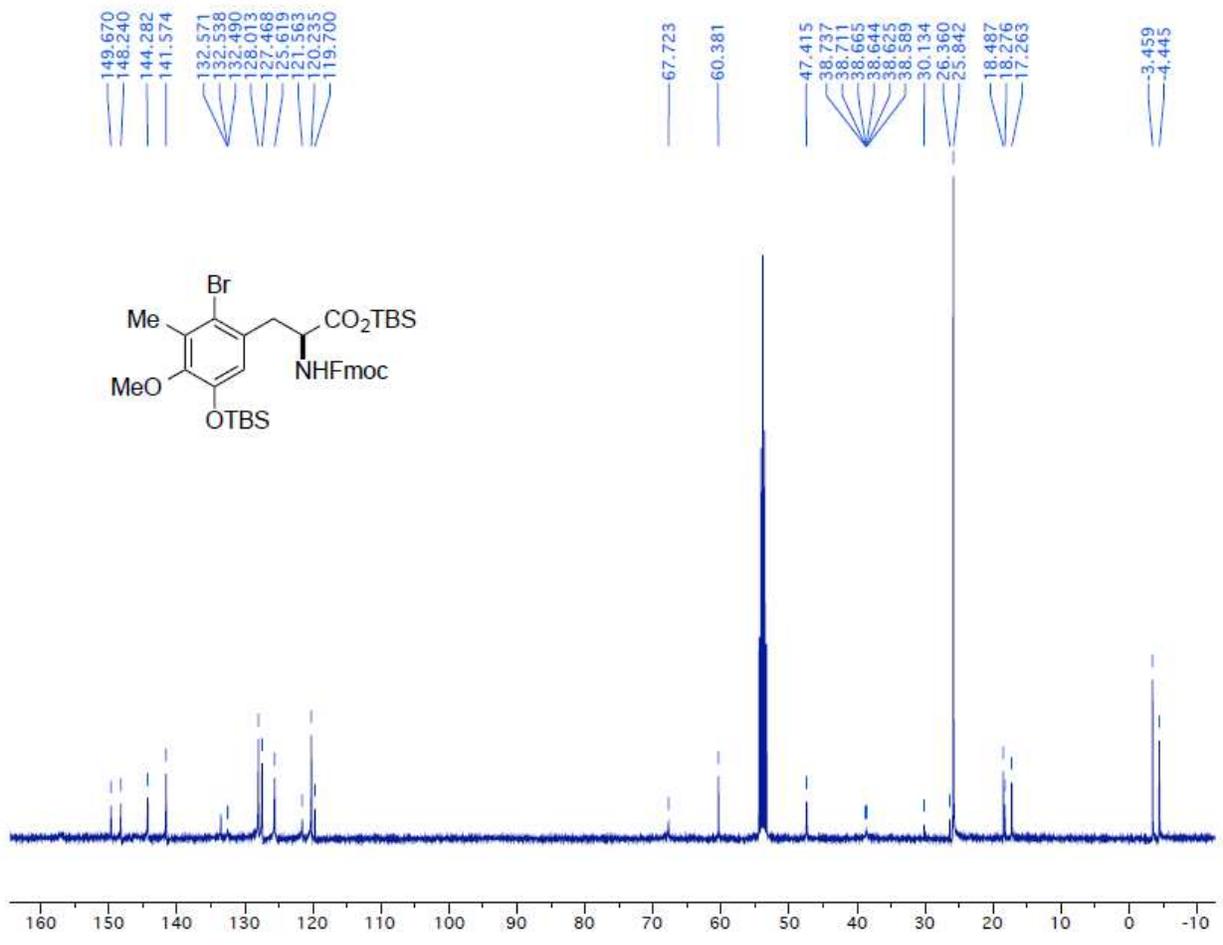
$R_f = 0.2$  (MeOH:CH<sub>2</sub>Cl<sub>2</sub> 1:9, UV, PMA).  $[\alpha]_D -10.5$  ( $c$  0.25, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.63 (br s, 1H), 7.99 (d,  $J = 5.9$  Hz, 2H), 7.77 (br m, 2H), 7.51 (br s, 2H), 7.41 (br m, 2H), 6.98 (s, 1H), 6.72 and 6.58 (br s, 1H), 4.29 (br s, 5 H), 4.14 (br s, 1H), 3.67-3.75 (m, 5H), 3.51 (s, 1H), 3.26-3.39 (m, 6H), 2.36 (s, 3H), 1.35 (m, 3H), 1.20 (t,  $J = 6.3$  Hz, 3H), 1.11 (d,  $J = 5.5$  Hz, 6H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  157.1, 150.6, 150.1, 146.2, 145.0, 141.8, 134.2, 132.2, 131.3, 128.8, 128.3, 126.6, 126.5, 121.3, 118.3, 116.7, 68.5, 68.4, 66.8, 64.0, 60.9, 47.8, 47.3, 46.6, 21.2, 20.1, 17.9, 10.2. IR (thin film) 3334, 2926, 1712, 1521, 1474, 1450, 1412, 1336, 1247. HRMS calcd. for C<sub>24</sub>H<sub>26</sub>BrNNaO<sub>6</sub> (M+H)<sup>+</sup> 526.0865;  $m/z$  found 526.0845.



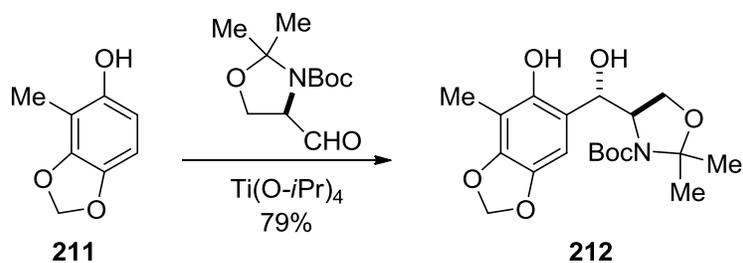






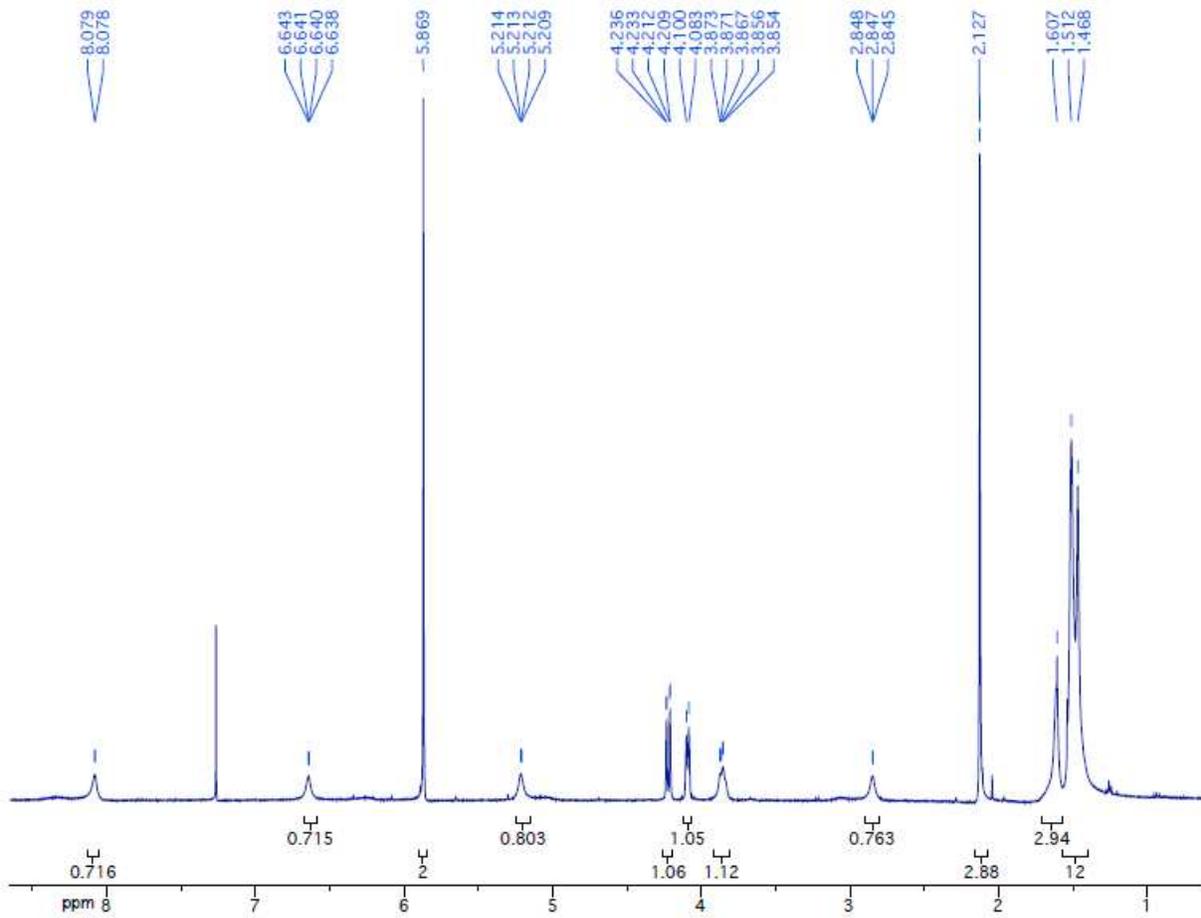


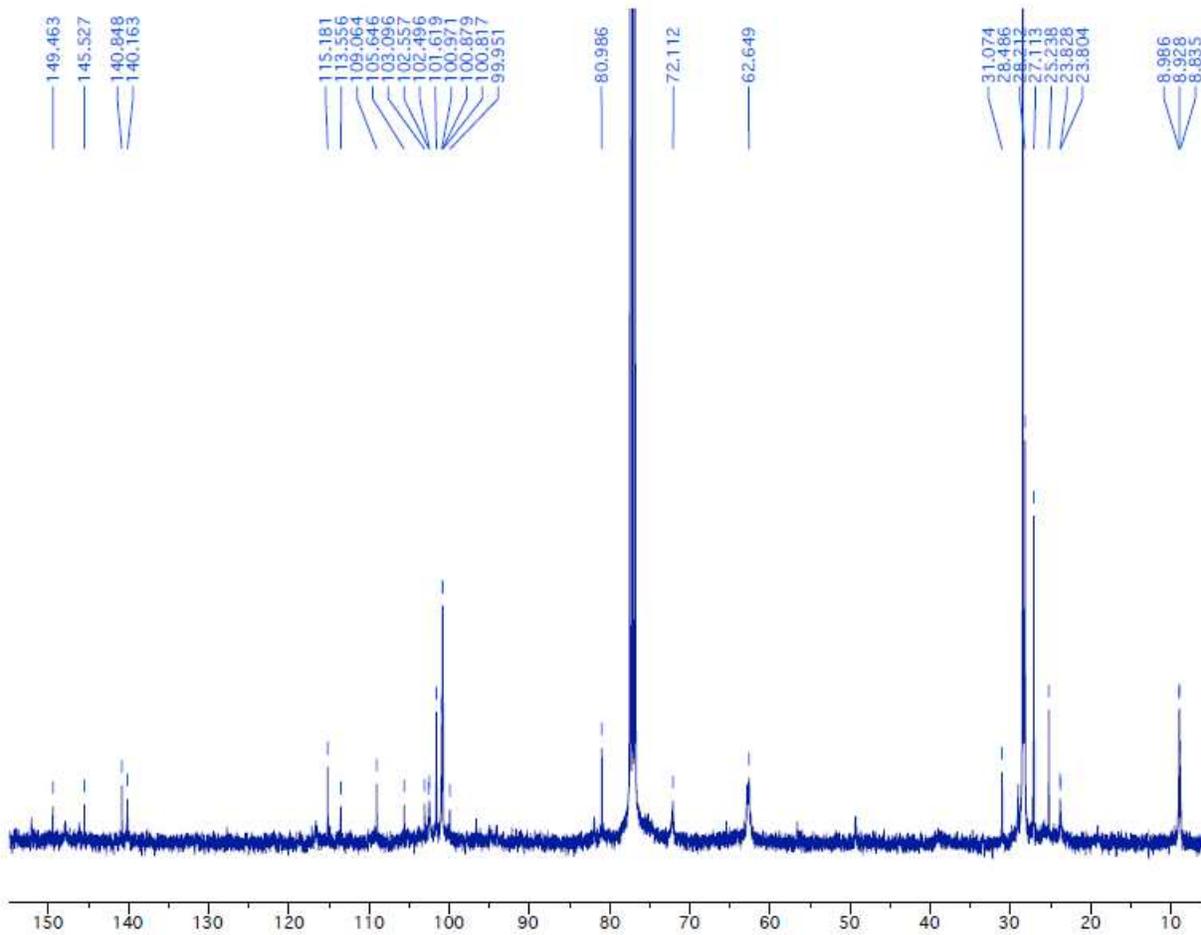
**Compound 212:** (*R*)-*tert*-butyl 4-((*S*)-hydroxy(6-hydroxy-7-methylbenzo[*d*][1,3]dioxol-5-yl)methyl)-2,2-dimethylloxazolidine-3-carboxylate



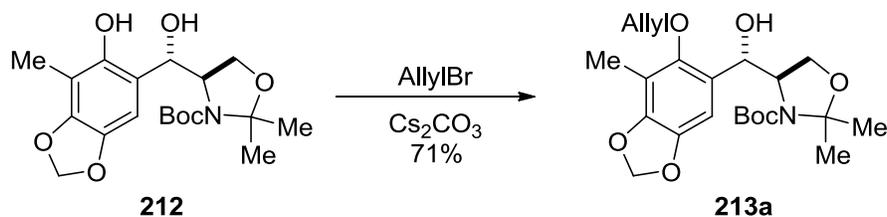
Ti(O-*i*Pr)<sub>4</sub> (1.45 ml, 4.76 mmol) was added to a solution of phenol **211** (1.00 g, 4.33 mmol) in toluene (40 ml). The resulting red solution was distilled to half full 3 times with every time refilled with fresh toluene. The solution was allowed to cool to room temperature, and *D*-Garner's aldehyde (1.29 g, 5.63 mmol) in toluene (6 ml) was added dropwise. The reaction was stirred at room temperature for 18 hours. The red solution was poured into the aqueous solution (50 ml) of *D,L*-tartaric acid (7.50 g) and stirred vigorously for 1 hour. Layers were separated and the aqueous layer was extracted with Et<sub>2</sub>O (3x50 ml). The combined organic layers were washed with the brine (50 ml), dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (5:1 hexanes:EtOAc) to give diol **212** (1.57 g, 79%) as a white foam.

$R_f = 0.2$  (EtOAc:hexanes 25:75, UV, PAA). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers) δ 8.09 (br s, 1H), 6.65 (br s, 1H), 5.87 (s, 2H), 4.27 (dd,  $J = 9.4, 1.3$  Hz, 1H), 4.09 (m, 1H), 3.89 (m, 1H), 2.78 (br s, 1H), 2.13 (s, 3H), 1.62 (br s, 3H), 1.54, 1.51 and 1.47 (s, 12H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers) δ 149.5, 145.5, 140.8, 140.2, 115.2, 113.6, 109.1, 105.6, 103.1, 102.5, 101.6, 100.9, 100.0, 81.0, 72.1, 62.6, 31.1, 28.5, 28.2, 27.1, 25.2, 23.8, 9.0, 8.9, 8.8. HRMS calcd. for C<sub>19</sub>H<sub>27</sub>NNaO<sub>7</sub> (M+Na)<sup>+</sup> 404.1685; m/z found 404.1638.



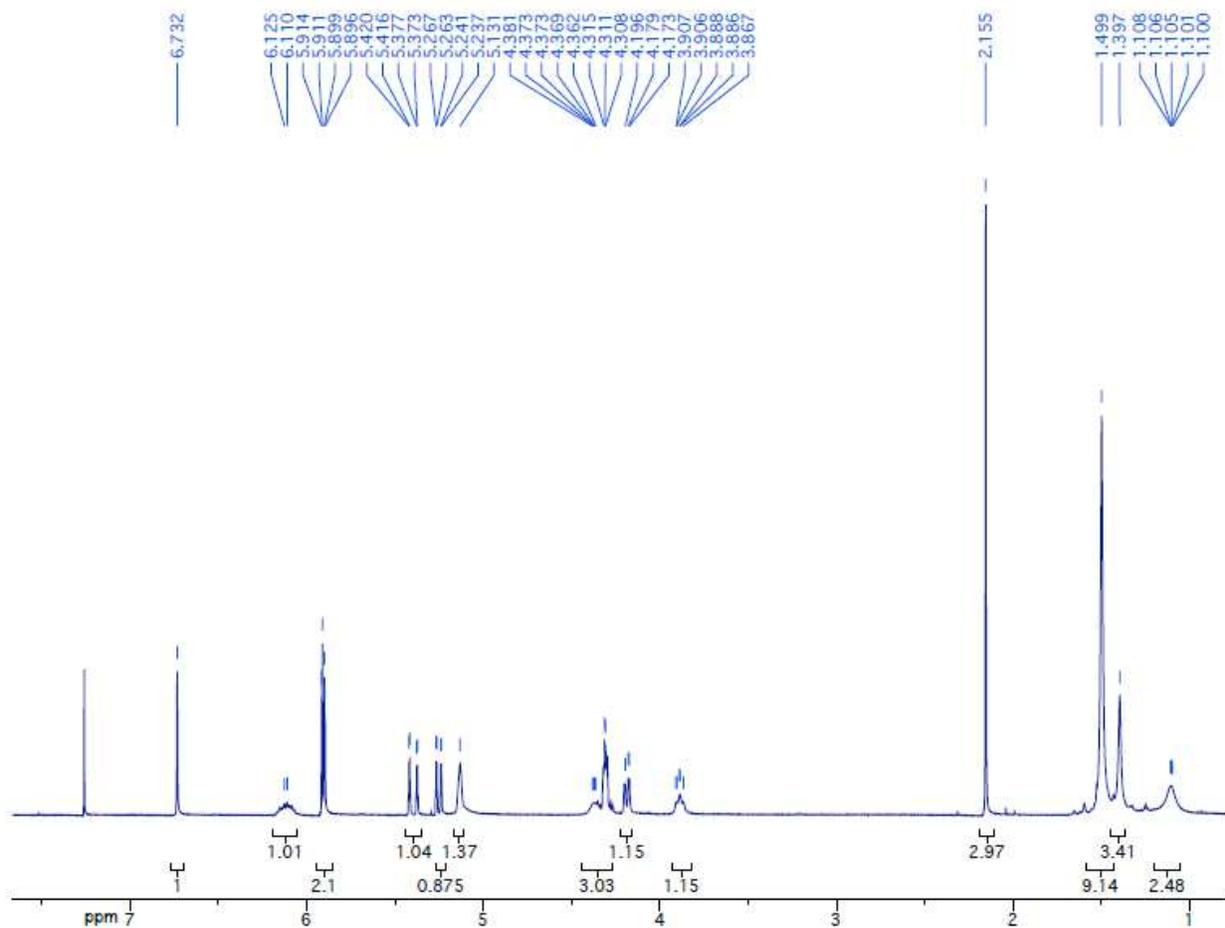


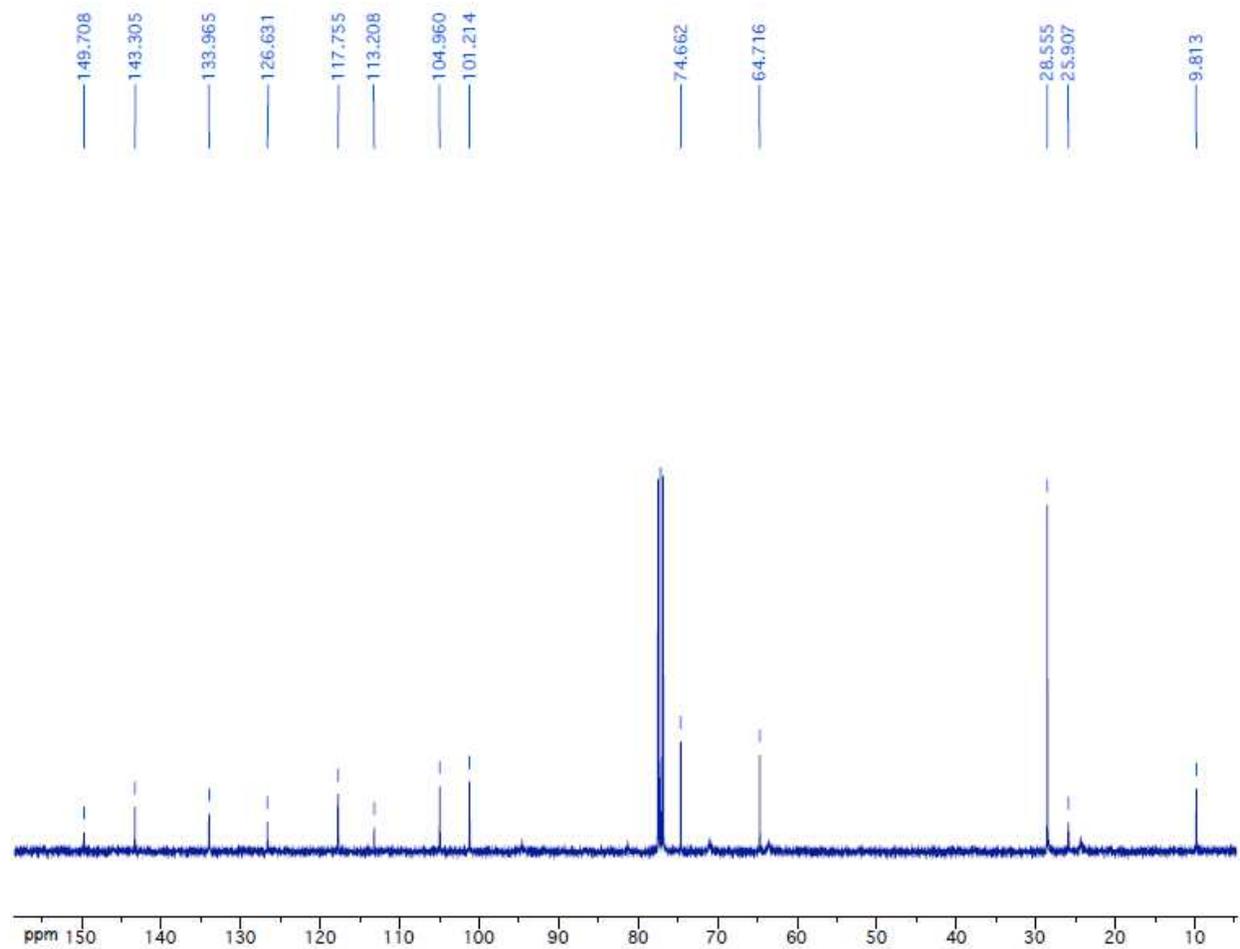
**Compound 213a:** (*R*)-*tert*-butyl 4-((*S*)-(6-(allyloxy)-7-methylbenzo[*d*][1,3]dioxol-5-yl)(hydroxy)methyl)-2,2-dimethylloxazolidine-3-carboxylate



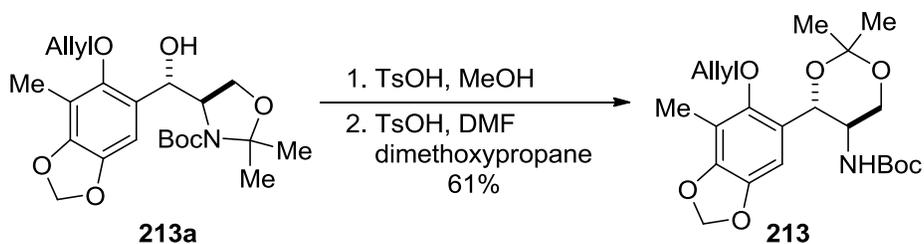
Cs<sub>2</sub>CO<sub>3</sub> (0.99 g, 1.52 mmol) was added to a solution of diol **212** (0.58 g, 1.52 mmol) in DMF (11.5 ml), followed by addition of allyl bromide (0.39 mL, 4.55 mmol). The suspension was stirred at room temperature for 8 hours then diluted with the brine (50 ml). The suspension was extracted with Et<sub>2</sub>O (3x50 ml), dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (6:1 hexanes: EtOAc) to give alcohol **213a** (540 mg, 71%) as a clear oil.

$R_f = 0.3$  (EtOAc:hexanes 25:75, UV, PAA).  $[\alpha]_D^{20} +0.037$  ( $c$  0.84, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  6.73 (s, 1H), 6.11 (ddd,  $J = 16.9, 10.5, 5.3$  Hz, 1H), 5.91 (dd,  $J = 6.0, 1.4$  Hz, 2H), 5.42 (dd,  $J = 3.2, 1.6$  Hz, 0.5H), 5.37 (dd,  $J = 3.2, 1.6$  Hz, 0.5H), 5.27 (dd,  $J = 2.7, 1.2$  Hz, 0.5H), 5.23 (dd,  $J = 2.7, 1.2$  Hz, 0.5H), 5.13 (s, 1H), 4.26-4.42 (m, 3H), 4.19 (dd,  $J = 9.3, 2.5$  Hz, 1H), 3.89 (t,  $J = 7.8$  Hz, 1H), 2.16 (s, 3H), 1.50 (s, 9H), 1.40 (s, 3H), 1.11 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  149.7, 143.3, 133.9, 126.6, 117.7, 113.2, 104.9, 101.2, 74.6, 64.7, 28.5, 25.9, 9.8. IR (thin film) 3448, 2979, 2932, 1693, 1475, 1390, 1366, 1253, 1206, 1175, 1090. HRMS calcd. for C<sub>22</sub>H<sub>31</sub>NNaO<sub>7</sub> (M+Na)<sup>+</sup> 444.1998;  $m/z$  found 444.1993.





**Compound 213:** *tert*-butyl ((4*S*,5*R*)-4-(6-(allyloxy)-7-methylbenzo[*d*][1,3]dioxol-5-yl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate

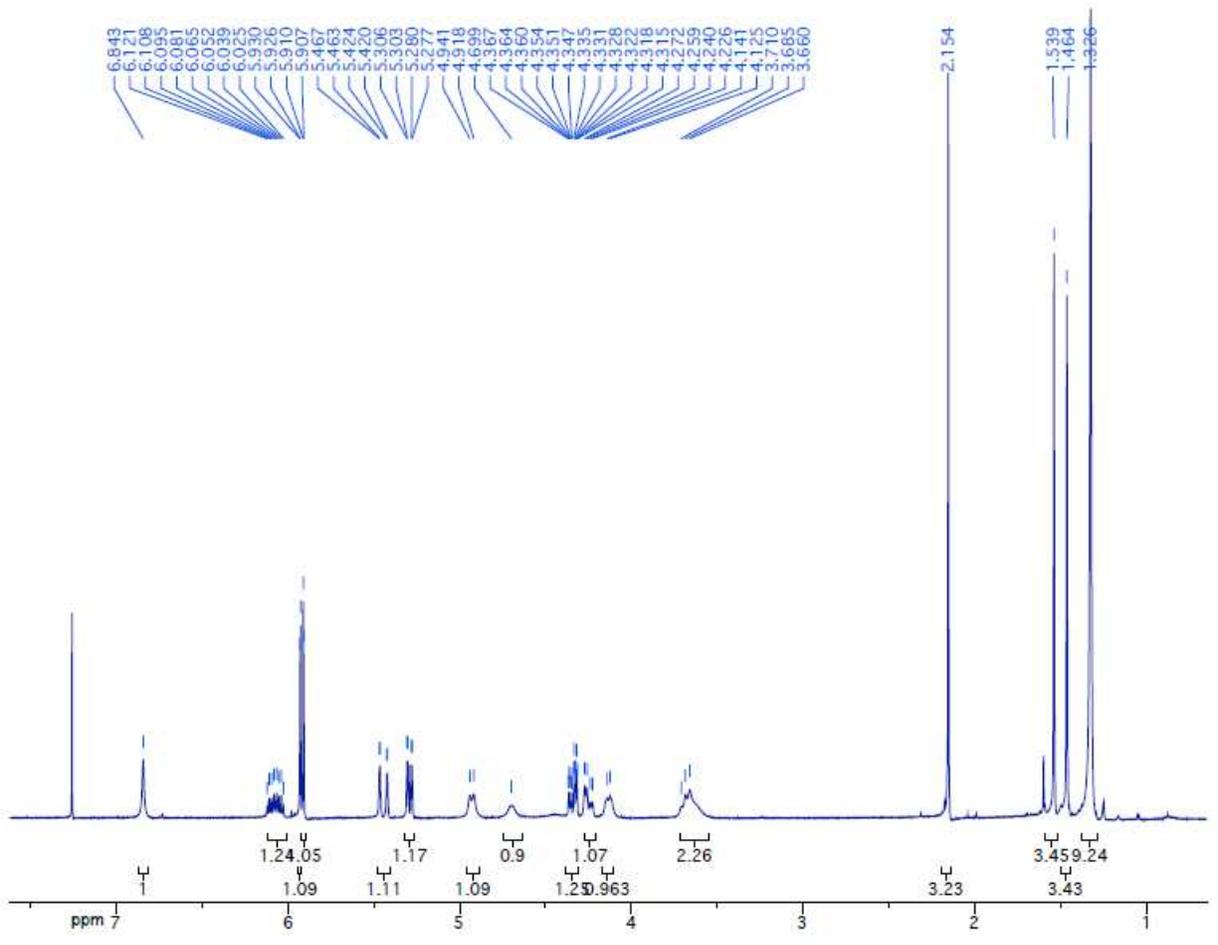


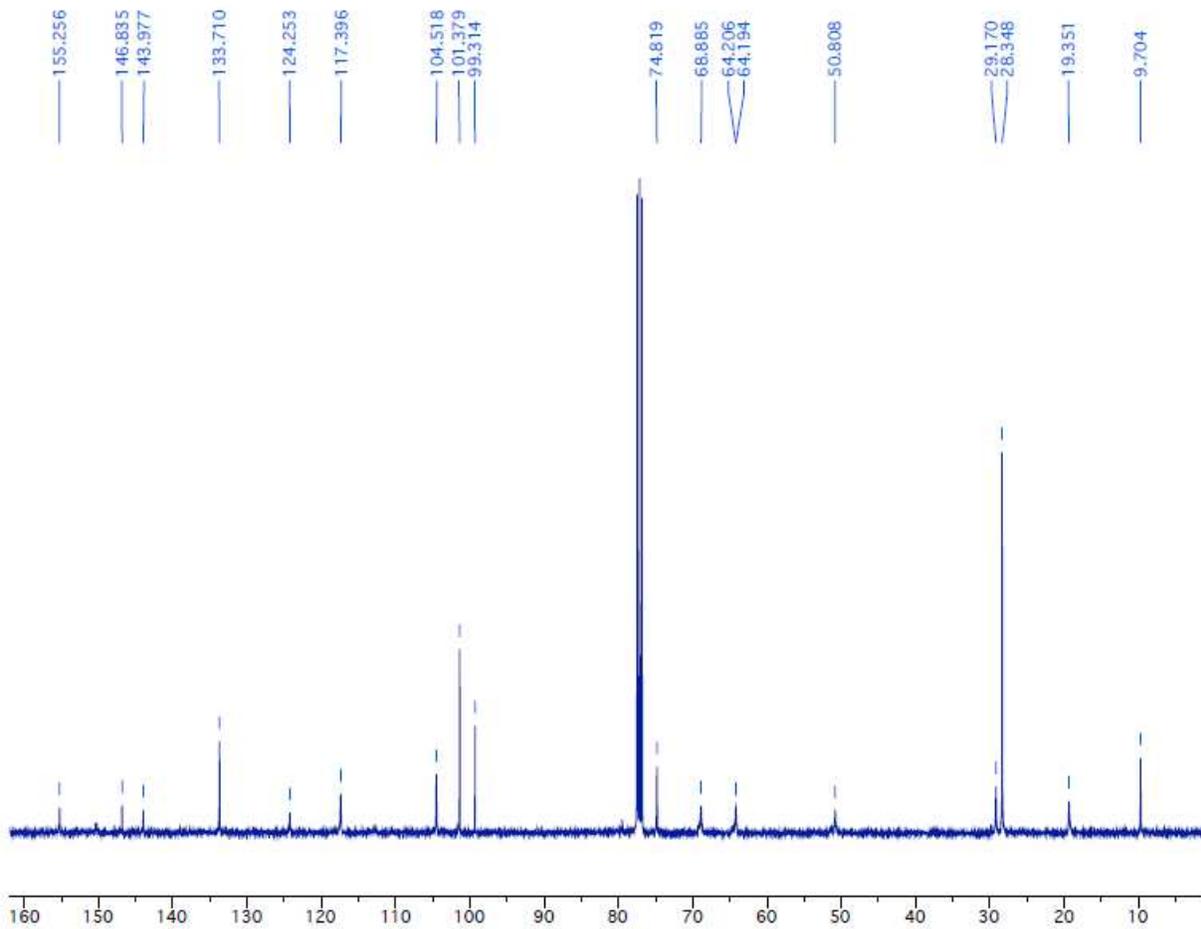
Alcohol **213a** (276 mg, 0.65 mmol) was dissolved in MeOH (3 ml) and TsOH·H<sub>2</sub>O (12.4 mg, 0.065 mmol) was added. The reaction was stirred at room temperature for 4 hours and the solvent was evaporated under reduced pressure. The residue was partitioned between the brine (10 ml) and CH<sub>2</sub>Cl<sub>2</sub> (3x10 ml). The combined organic layers were washed with the brine (10 ml), dried with MgSO<sub>4</sub> and concentrated to give a diol as white foam. The crude product was used in the next step without purification.

The crude diol was dissolved in DMF (1 ml), followed by the addition of TsOH·H<sub>2</sub>O (6.2 mg, 0.037 mmol) and 2,2-dimethoxypropane (0.8 ml, 6.54 mmol). The reaction was stirred at room temperature for 13 hours then quenched with the saturated aqueous solution of NaHCO<sub>3</sub> (10 ml), extracted with Et<sub>2</sub>O (3x10 ml), dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (5:1 hexanes:EtOAc) to give compound **213** (166 mg, 61%) as white foam.

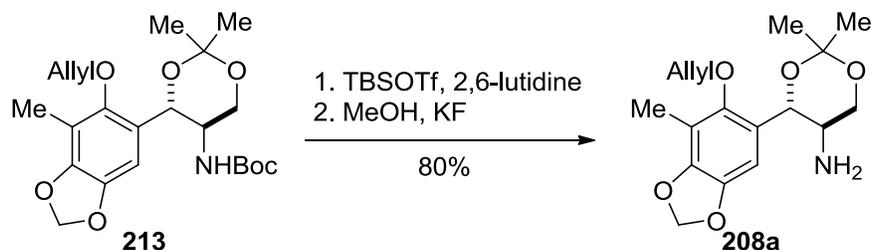
$R_f = 0.4$  (EtOAc:hexanes 25:75, UV, PAA).  $[\alpha]_D -0.19$  (c 0.45, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.84 (s, 1H), 6.07 (ddd,  $J = 17.1, 10.5, 5.3$  Hz, 1H), 5.93 (d,  $J = 1.4$  Hz, 1H), 5.91 (d,  $J = 1.4$  Hz, 1H), 5.44 (dd,  $J = 17.2, 1.6$  Hz, 1H), 5.29 (dd,  $J = 10.5, 1.4$  Hz, 1H), 4.93 (d,  $J = 9.0$  Hz, 1H), 4.70 (br s, 1H), 4.34 (m, 1H), 4.25 (dd,  $J = 12.9, 5.2$  Hz, 1H), 4.14 (d,  $J = 6.3$  Hz, 1H), 3.56-3.72 (m, 2H), 2.15 (s, 3H), 1.54 (s, 3H), 1.46 (s, 3H), 1.33 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  155.3, 146.8, 144.0, 133.7, 124.3, 117.4, 104.5, 101.4, 99.3, 74.8, 68.9, 64.2, 50.8,

29.2, 28.3, 19.4, 9.7. IR (thin film) 3367, 2981, 1708, 1502, 1478, 1420, 1391, 1295. HRMS  
calcd. for  $C_{22}H_{31}NNaO_7$  ( $M+Na$ )<sup>+</sup> 444.1998; m/z found 444.1994.





**Compound 208a:** (4*S*,5*R*)-4-(6-(allyloxy)-7-methylbenzo[*d*][1,3]dioxol-5-yl)-2,2-dimethyl-1,3-dioxan-5-amine

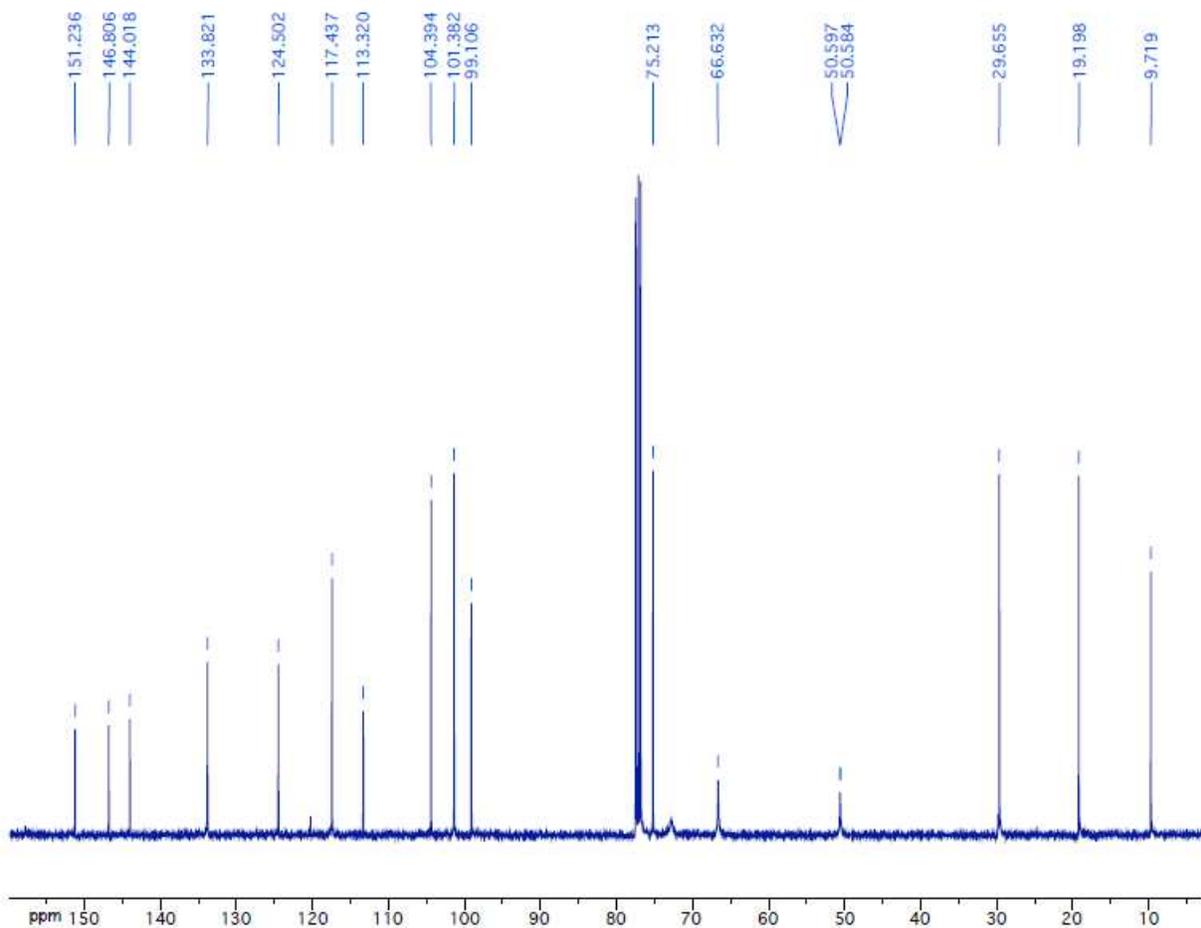


2,6-lutidine (93  $\mu$ l, 0.80 mmol) was added to a solution of **213** (166 mg, 0.40 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 ml). The solution was cooled to  $-78^\circ\text{C}$  and TBSOTf (0.13 ml) was added dropwise. The reaction was warmed to room temperature and stirred for 1.5 hours. MeOH (0.24 ml) was added and stirred at room temperature for 15 minutes. The solvent was evaporated under reduced pressure to give clear oil.

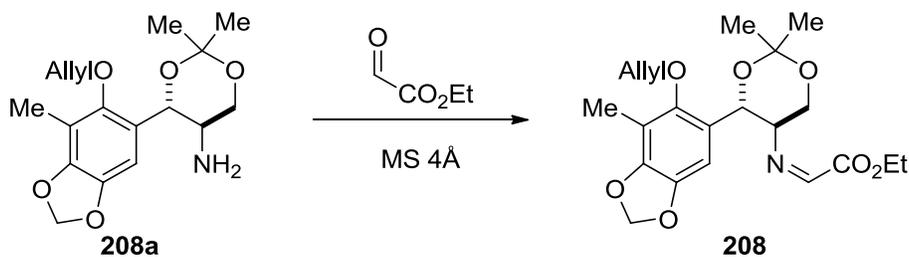
The resulting oil was dissolved in MeOH (3 ml) and  $\text{KF}\cdot 2\text{H}_2\text{O}$  (76 mg, 0.80 mmol) was added. The reaction was stirred at room temperature for 1 hour then diluted with the brine (10 ml). The resulting suspension was extracted with  $\text{CH}_2\text{Cl}_2$  (3x15 ml). The combined organic layers were dried with  $\text{MgSO}_4$  and concentrated. The crude product was purified by column chromatography (2% MeOH/ $\text{CHCl}_3$ ) to give amine **208a** (103 mg, 80%) as an off-white solid.

$R_f = 0.1$  (MeOH: $\text{CHCl}_3$  2:98, UV, PAA).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.80 (s, 1H), 6.09 (ddd,  $J = 17.2, 10.7, 5.4$  Hz, 1 H), 5.94 (d,  $J = 1.4$  Hz, 1H), 5.91 (d,  $J = 1.4$  Hz, 1H), 5.42 (ddd,  $J = 17.2, 3.2, 1.6$  Hz, 1H), 5.28 (ddd,  $J = 10.5, 2.7, 1.3$  Hz, 1H), 4.83 (d,  $J = 9.8$  Hz, 1H), 4.35 (ddt,  $J = 12.6, 5.3, 1.5$  Hz, 1H), 4.25 (ddt,  $J = 12.6, 5.5, 1.4$  Hz, 1H), 3.95 (dd,  $J = 11.4, 5.1$  Hz, 1H), 3.64 (t,  $J = 10.8$  Hz, 1H), 2.94 (br s, 1H), 2.16 (s, 3H), 1.56 (s, 3H), 1.45 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  151.2, 148.6, 144.0, 133.8, 124.5, 117.4, 113.3, 104.4, 101.4, 99.1, 75.2, 66.6, 50.6, 29.7, 19.2, 9.7. HRMS calcd. for  $\text{C}_{17}\text{H}_{24}\text{NO}_5$  ( $\text{M}+\text{H}$ ) $^+$  332.1654;  $m/z$  found 332.1655.



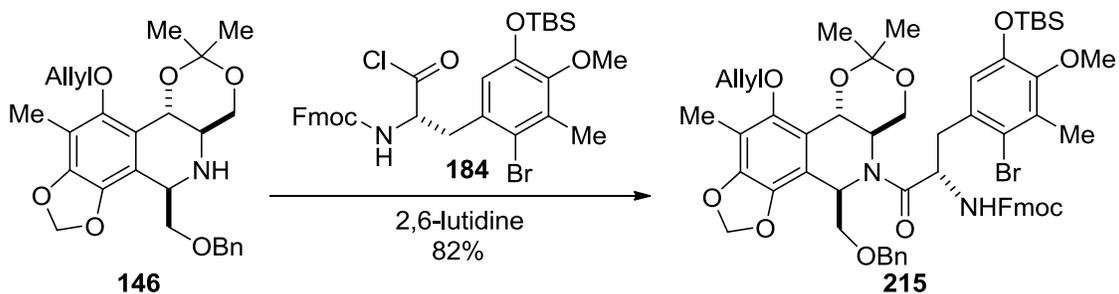


**Compound 208:** (Z)-ethyl 2-(((4*S*,5*R*)-4-(6-(allyloxy)-7-methylbenzo[*d*][1,3]dioxol-5-yl)-2,2-dimethyl-1,3-dioxan-5-yl)imino)acetate



Ethyl glyoxalate (50% in toluene) (78  $\mu$ l, 0.39 mmol) and 4 Å molecular sieves (67 mg) were added to a solution of amine **208a** (90 mg, 0.28 mmol). The reaction was stirred at room temperature for 45 minutes then filtered through a pad of celite and concentrated to give imine **208** as clear oil. The crude product was used in the next step without purification.

**Compound 215:** (9*H*-fluoren-9-yl)methyl ((*S*)-1-((4*R*,5*aR*,9*aS*)-10-(allyloxy)-4-((benzyloxy)methyl)-8,8,11-trimethyl-5*a*,6-dihydro-4*H*-[1,3]dioxino[5,4-*c*][1,3]dioxolo[4,5-*h*]isoquinolin-5(9*aH*)-yl)-3-(2-bromo-5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methylphenyl)-1-oxopropan-2-yl)carbamate

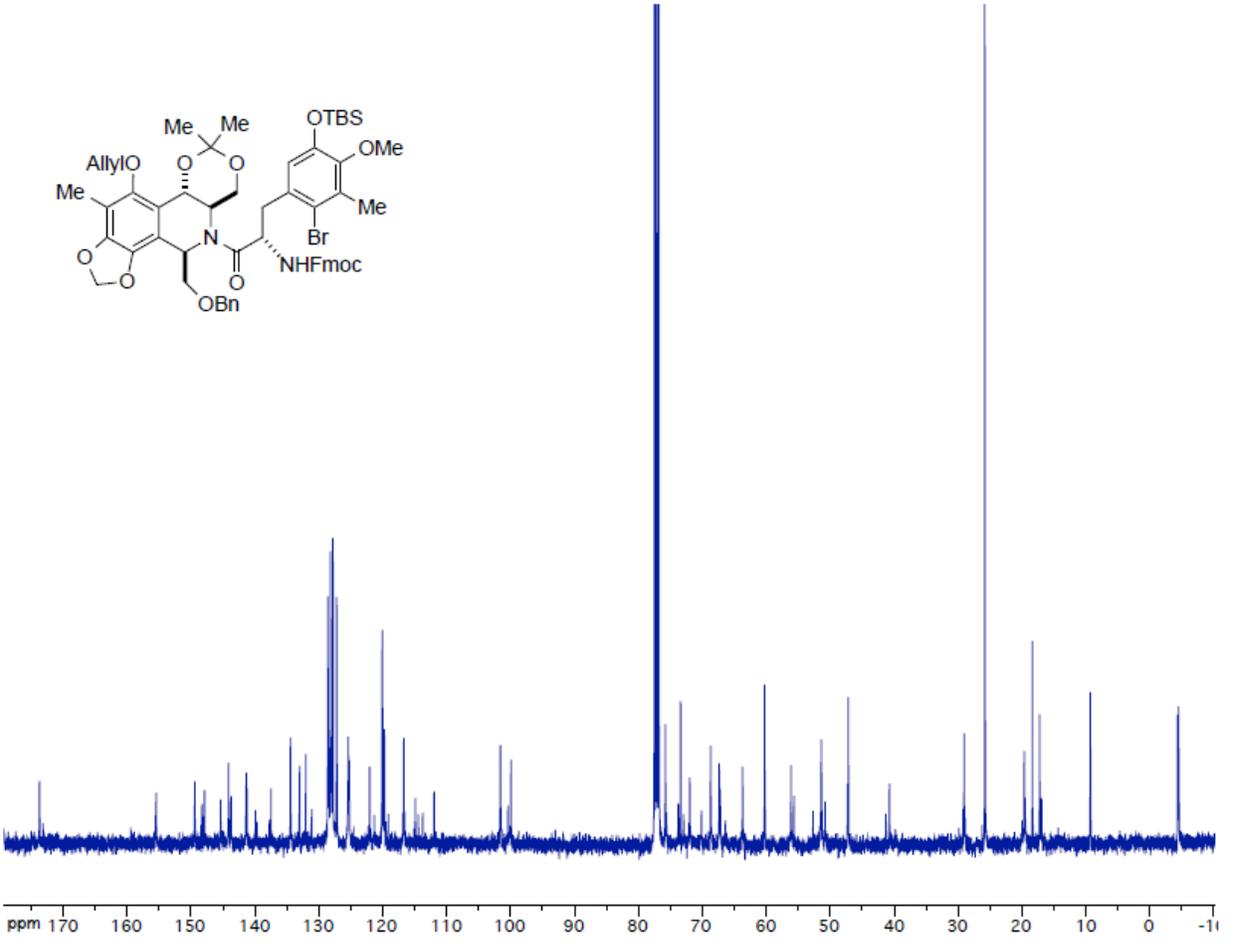


(COCl)<sub>2</sub> (4.7 ml, 53.9 mmol) was added dropwise to a solution of TBS-ester **205** (1.90 g, 2.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (18 ml), followed by the addition of DMF (0.1 ml). The reaction was stirred at room temperature for 30 minutes then concentrated to give the acid chloride **184** as a yellow solid.

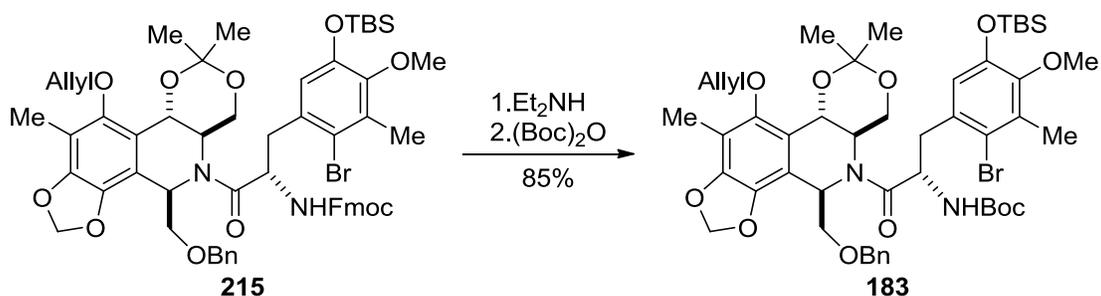
2,6-lutidine was added to a solution of acid chloride in CH<sub>2</sub>Cl<sub>2</sub> (12 ml), and the solution was cooled to 0°C. THIQ **146** (0.81 g, 1.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 ml) was added dropwise, and the reaction was stirred at room temperature for 4 hours. The reaction was quenched with the saturated NaHCO<sub>3</sub> (20 ml). The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 ml). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (6:1 hexanes: EtOAc) to give *N*-Fmoc amide **215** (1.58 g, 82%) as a white solid.

$R_f = 0.3$  (EtOAc:hexanes 1:5, UV, PAA).  $[\alpha]_D -25.8$  ( $c$  1.02, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  7.73-7.77 (m, 2H), 7.48-7.60 (m, 2H), 7.23-7.42 (m, 3H), 7.19-7.27 (m, 5H), 7.13-7.15 (m, 1H), 6.75, 6.64, and 6.61 (s, 1 H), 5.98-6.08 (m, 1H), 5.96 (d,  $J = 2.1$  Hz, 1H), 5.89 and 5.79 (s, 1H), 5.67 (t,  $J = 3.7$  Hz, 0.5 H), 5.73-5.63 (m, 1.5 H), 5.50 and 5.40 (d,  $J = 9.3$ , 1H), 5.18-5.37 (m, 4 H), 4.69 and 4.59 (dd,  $J = 10.7, 4.2$  Hz, 1H), 4.10-4.48 (m, 8H), 3.66-3.86 (m, 3H), 3.62 and 3.58 (s, 3H), 3.00-3.52 (m, 6H), 2.35, 2.31, and 2.13 (s, 3H), 2.16, 2.08, and 2.05 (s, 3H), 1.47 and 1.41 (s, 3H), 1.24-1.28 (m, 3H), 1.00, 0.97, 0.94 (s, 9H), 0.05-0.18 (m, 6H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  173.9, 173.3, 155.7, 148.7, 148.5, 148.3, 148.1, 145.6, 144.3, 144.1, 144.0, 141.6, 141.4, 140.1, 140.0, 138.0, 137.9, 137.7, 134.6, 133.3, 133.2, 132.2, 131.4, 131.3, 128.8, 128.7, 128.6, 128.4, 128.2, 128.2, 128.0, 127.4, 125.6, 125.6, 125.5, 125.4, 122.2, 121.2, 120.3, 120.2, 119.9, 119.7, 119.3, 117.1, 116.9, 116.8, 115.1, 114.6, 114.0, 112.2, 101.8, 100.1, 77.6, 76.0, 75.8, 74.0, 73.7, 73.6, 73.1, 72.3, 72.2, 70.3, 68.9, 67.6, 67.4, 66.6, 63.9, 60.5, 60.4, 56.3, 55.9, 52.9, 51.7, 51.7, 51.6, 51.5, 51.0, 47.5, 47.4, 47.4, 41.5, 41.0, 29.4, 29.2, 29.1, 26.0, 26.0, 19.8, 19.7, 18.6, 18.5, 17.4, 17.4, 17.1, 9.5, 9.5, 9.5. IR (thin film) 3288, 2931, 2859, 2361, 1719, 1638, 1528, 1470, 1420. HRMS calcd. for C<sub>58</sub>H<sub>67</sub>BrN<sub>2</sub>NaO<sub>11</sub>Si (M+Na)<sup>+</sup> 1097.3595; m/z found 1097.3598.





**Compound 183:** *tert*-butyl ((*S*)-1-((4*R*,5*aR*,9*aS*)-10-(allyloxy)-4-((benzyloxy)methyl)-8,8,11-trimethyl-5*a*,6-dihydro-4*H*-[1,3]dioxino[5,4-*c*][1,3]dioxolo[4,5-*h*]isoquinolin-5(9*aH*)-yl)-3-(2-bromo-5-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-3-methylphenyl)-1-oxopropan-2-yl)carbamate



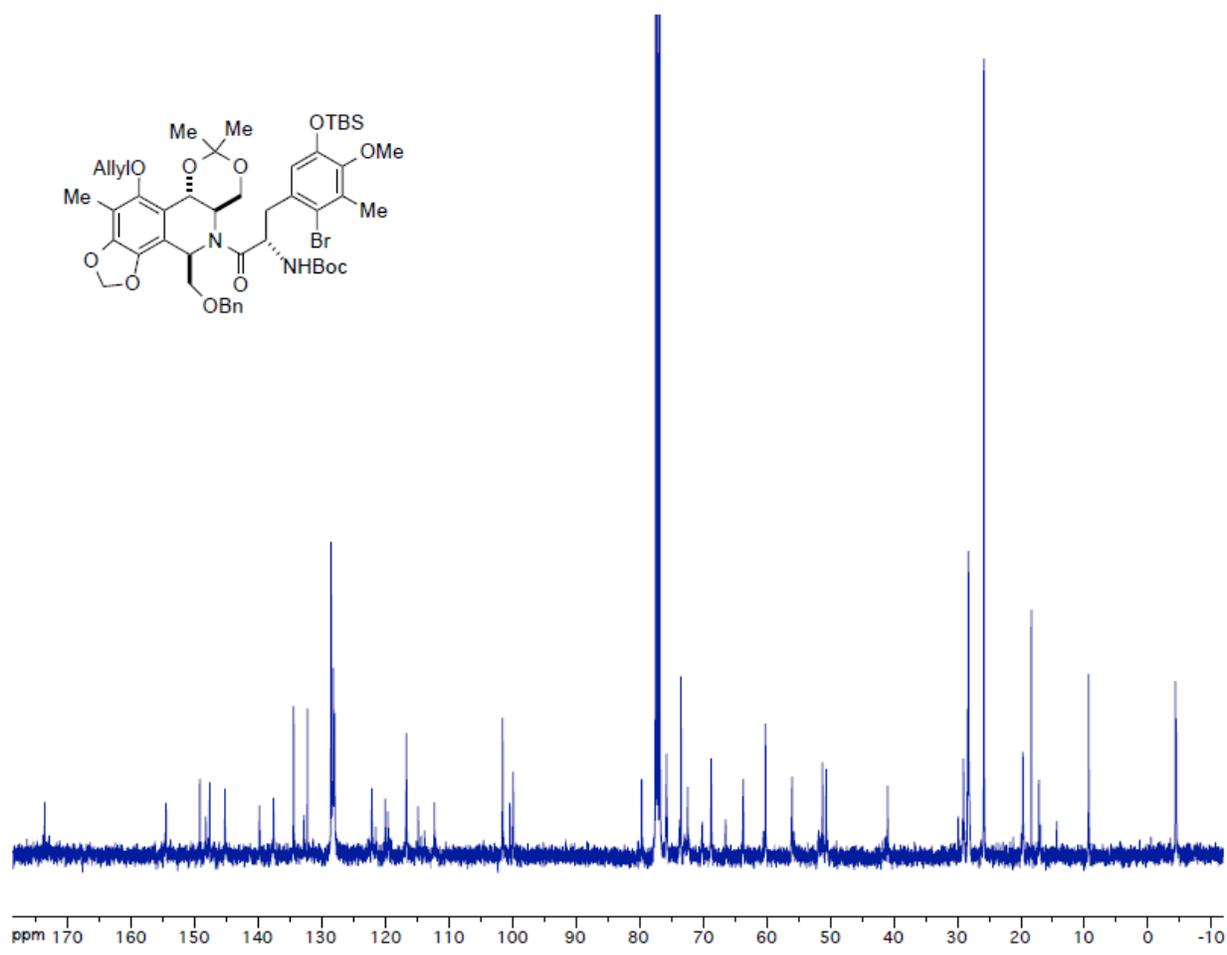
*N*-Fmoc amide **215** (1.58 g, 1.47 mmol) was dissolved in Et<sub>2</sub>NH (4 ml) and CH<sub>2</sub>Cl<sub>2</sub> (15 ml). The solution was stirred at room temperature for 6 hours then concentrated to give the crude amine as a yellow gel.

The crude amine was dissolved in EtOH (15 ml) and CH<sub>2</sub>Cl<sub>2</sub> (4 ml), followed by the addition of Boc<sub>2</sub>O (1.61 g, 7.36 mmol). The reaction was stirred at room temperature for 20 hours then concentrated. The crude product was purified by column chromatography (6:1 hexanes:EtOAc) to give *N*-Boc amide **183** (1.19 g, 85%) as a white solid.

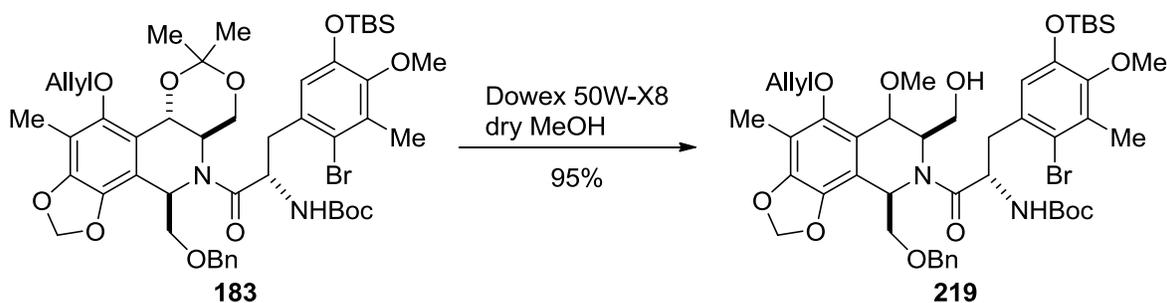
$R_f = 0.5$  (EtOAc:hexanes 25:75, UV, PAA).  $[\alpha]_D -31$  ( $c$  1.08, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  7.15-7.27 (m, 5 H), 6.67, (s, 1 H), 6.03 (m, 1 H), 5.88 (t,  $J = 26.7$  Hz, 2 H), 5.67 and 5.53 (m, 1 H), 5.31-5.359 (m, 1.5 H), 5.13-5.21 (m, 1.5 H), 5.01 and 4.95 (d,  $J = 10.0$  Hz, 1 H), 4.57 (dd,  $J = 10.8, 4.3$  Hz, 1 H), 4.37-4.47 (m, 2 H), 4.28 (m, 1 H), 4.13 (m, 1 H), 3.58-3.83 (m, 5 H), 3.49 (m, 1 H), 3.36 (t,  $J = 10.3$  Hz, 1 H), 3.17 (dd,  $J = 13.4, 6.22$  Hz, 1 H), 3.00 (m, 1 H), 2.35 (s, 1.5 H), 2.17 (s, 0.5 H), 2.11 (d,  $J = 4.3$  Hz, 2.5 H), 2.04 (s, 0.5 H), 1.61 (s, 0.5 H), 1.22-1.46 (m, 12 H), 1.13 (s, 0.5 H), 1.01, 0.99 and 0.98 (s, 7 H), 0.19 and 0.18 (s, 5 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  173.6,

154.5, 149.2, 148.3, 147.7, 145.3, 139.9, 139.8, 139.7, 137.6, 134.5, 132.8, 132.3, 128.6, 128.3, 128.2, 128.0, 122.1, 121.5, 120.1, 119.6, 116.7, 114.9, 112.3, 101.6, 100.4, 100.0, 99.9, 79.7, 77.4, 75.8, 73.7, 73.5, 72.5, 70.1, 68.7, 66.5, 63.7, 60.5, 60.2, 56.0, 55.7, 51.2, 50.6, 41.0, 29.9, 29.2, 29.0, 28.9, 28.4, 28.3, 28.1, 25.8, 19.7, 18.4, 17.2, 16.9, 14.4, 10.1, 9.3, -4.3, -4.5. IR (thin film) 3313, 2931, 2860, 1713, 1648, 1471, 1419, 1366. HRMS calcd. for  $C_{48}H_{65}BrN_2NaO_{11}Si$   $(M+Na)^+$  975.3439; m/z found 975.3392.



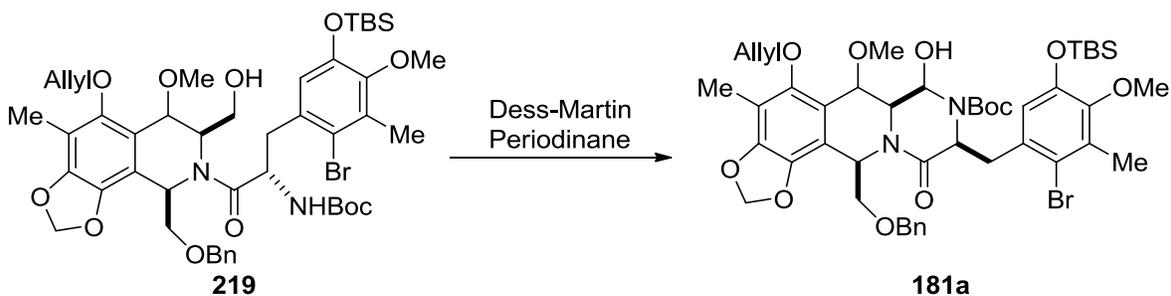


**Compound 219:** *tert*-butyl ((2*S*)-1-((7*R*,9*R*)-5-(allyloxy)-9-((benzyloxy)methyl)-7-(hydroxymethyl)-6-methoxy-4-methyl-6,7-dihydro-[1,3]dioxolo[4,5-*h*]isoquinolin-8(9*H*)-yl)-3-(2-bromo-5-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-3-methylphenyl)-1-oxopropan-2-yl)carbamate



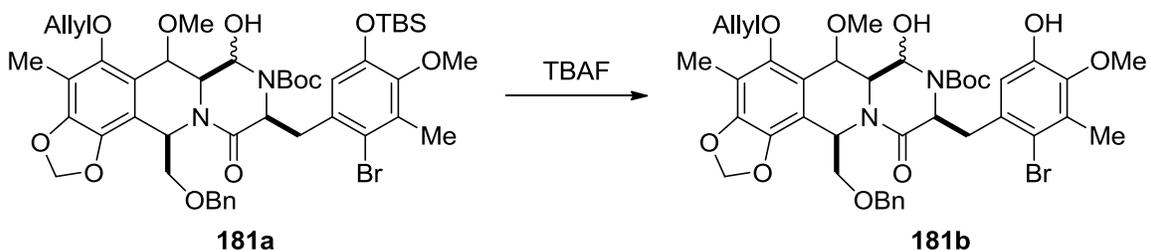
Dowex 50W-X8 (0.6 g) was washed with dry MeOH three times and dried under reduced pressure. *N*-Boc amide **183** (1.19 g, 1.25 mmol) was dissolved in dry MeOH (10 ml) followed by addition of the dry Dowex 50W-X8. The reaction was stirred at room for 5 days then filtered through a pad of celite and concentrated to provide alcohol **219** (1.1 g, 95%) as a white solid. The crude product was used in the next reaction without further purification.

**Compound 181a:** (6*aS*,7*R*,9*S*,12*R*)-*tert*-butyl 5-(allyloxy)-12-((benzyloxy)methyl)-9-(2-bromo-5-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-3-methylbenzyl)-7-hydroxy-6-methoxy-4-methyl-10-oxo-6*a*,7,9,10-tetrahydro-6*H*-[1,3]dioxolo[4,5-*h*]pyrazino[1,2-*b*]isoquinoline-8(12*H*)-carboxylate



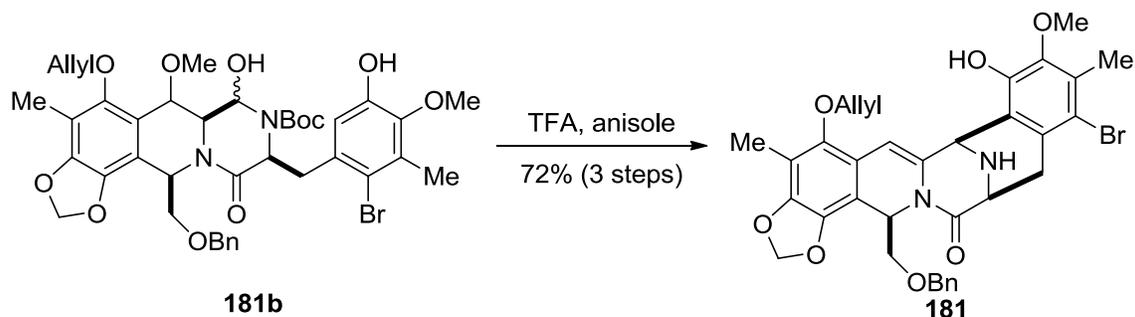
Dess-Martin periodinane (245 mg, 0.58 mmol) was added to a solution of alcohol **219** (268 mg, 0.29 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 ml). The reaction was stirred at room temperature for 20 minutes (an impurity, which cospotted with the major product, is formed when the reaction was allowed to run longer than 20 minutes. This caused problem with purification later on and reduced yield significantly) then quenched with aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>2</sub> (6 ml) and NaHCO<sub>3</sub> (6 ml). Layers were separated and the aqueous layer was extracted with Et<sub>2</sub>O (3x10 ml). Combined organic layers were dried over MgSO<sub>4</sub> and concentrated to give carbinolamine **181a** as an off-white solid (274 mg). The crude product was used in the next reaction without further purification.

**Compound 181b:** (6*aS*,9*S*,12*R*)-*tert*-butyl 5-(allyloxy)-12-((benzyloxy)methyl)-9-(2-bromo-5-hydroxy-4-methoxy-3-methylbenzyl)-7-hydroxy-6-methoxy-4-methyl-10-oxo-6*a*,7,9,10-tetrahydro-6H-[1,3]dioxolo[4,5-*h*]pyrazino[1,2-*b*]isoquinoline-8(12H)-carboxylate



TBAF•3H<sub>2</sub>O (91 mg, 0.29 mmol) was added to a solution of crude hemiaminal **181a** (274 mg) in THF (6 ml). The reaction was stirred at room temperature for 30 minutes then concentrated. The residue was then redissolved in EtOAc and passed through a small plug of silica gel to provide phenol **181b** as brown foam (238 mg). The crude product was used in the next reaction without further purification.

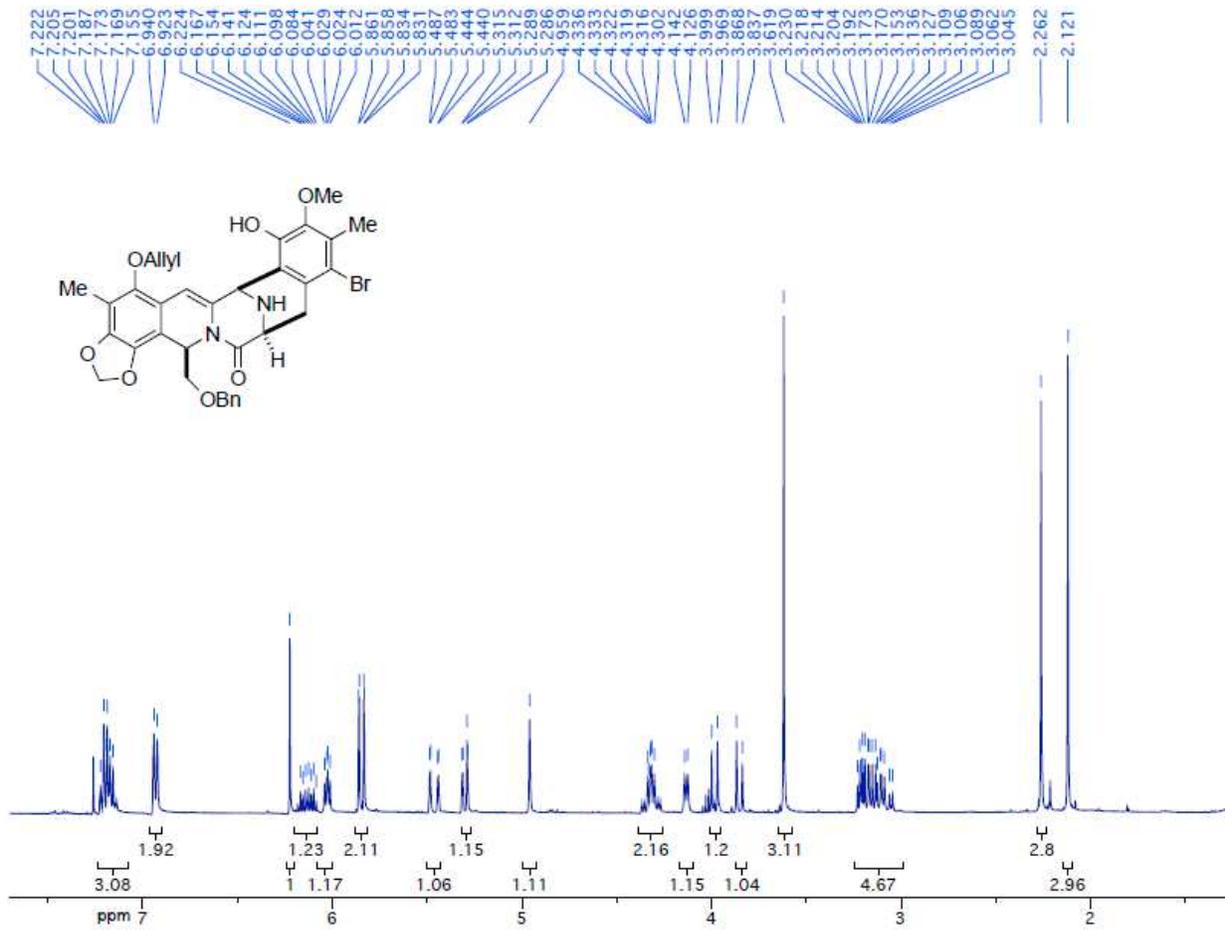
**Compound 181:** (7*R*,13*S*,16*R*)-5-(allyloxy)-16-((benzyloxy)methyl)-11-bromo-8-hydroxy-9-methoxy-4,10-dimethyl-12,13-dihydro-7*H*-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinolin-14(16*H*)-one

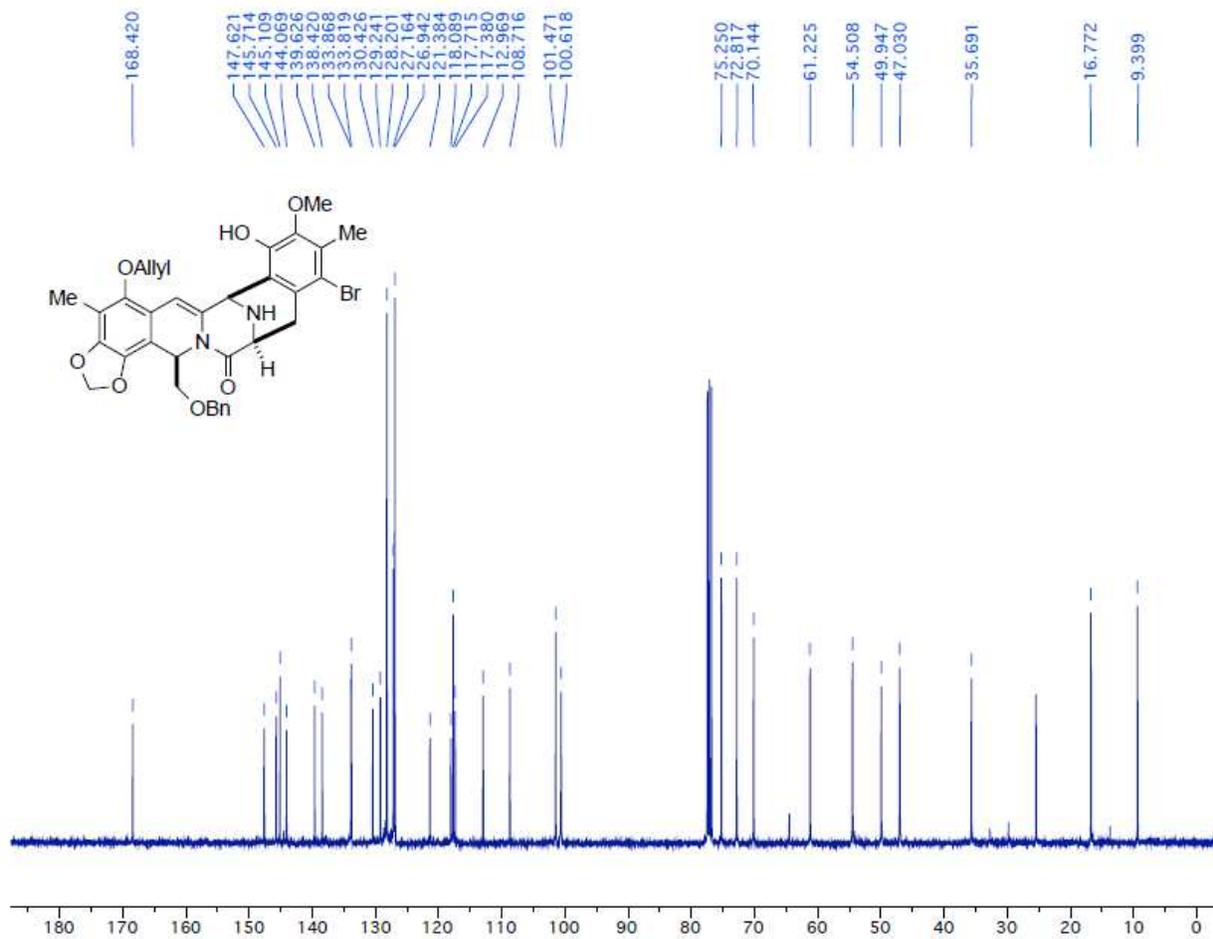


Crude phenol **181b** (238 mg) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 ml), followed by the addition of anisole (0.31 ml, 2.89 mmol) and trifluoroacetic acid (3 ml). The reaction was stirred at room temperature for 14 hours then concentrated. The residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 ml), washed with the saturated NaHCO<sub>3</sub> (30 ml), dried over MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (20% *i*PrOH/hexanes) to give **181** as a brown solid (136 mg, 71% over the 3 steps).

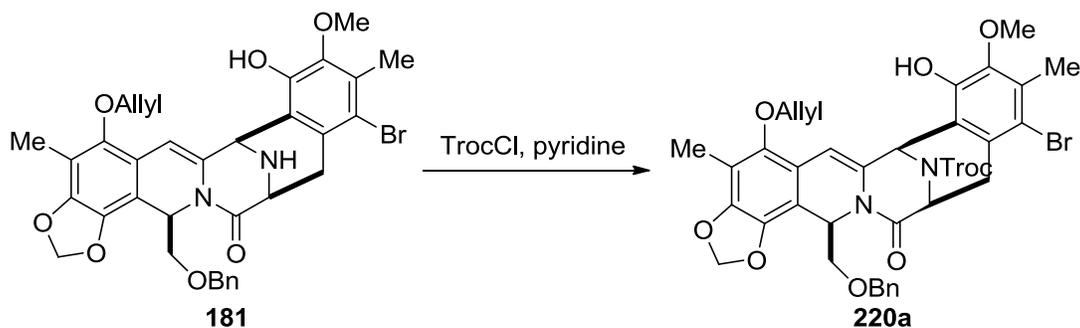
$R_f = 0.3$  (*i*PrOH:hexanes 20:80, UV, PAA).  $[\alpha]_D^{+58}$  ( $c$  0.6, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.14-7.23 (m, 3 H), 6.93 (d,  $J = 6.8$  Hz, 2 H), 6.22 (s, 1 H), 6.13 (ddt,  $J = 16.0, 10.7, 5.6$  Hz, 1 H), 6.03 (dd,  $J = 6.8, 4.8$  Hz, 1 H), 5.85 (dd,  $J = 6.73, 4.84$  Hz, 1 H), 5.46 (dd,  $J = 17.2, 1.6$  Hz, 1 H), 5.30 (dd,  $J = 10.4, 1.3$  Hz, 1 H), 4.96 (s, 1 H), 4.32 (m, 1 H), 4.13 (d,  $J = 6.4$  Hz, 1 H), 3.98 (d,  $J = 12.3$  Hz, 1 H), 3.85 (d,  $J = 12.2$  Hz, 1 H), 3.05-3.23 (m, 4 H), 2.26 (s, 3 H), 2.12 (s, 3 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  168.4, 147.6, 145.7, 145.1, 144.0, 139.6, 138.4, 133.9, 133.8, 130.4, 129.2, 128.2, 127.1, 126.9, 121.4, 118.1, 117.7, 117.4, 112.9, 108.7, 101.4, 100.6, 75.2, 72.8, 70.1, 61.2, 54.5, 49.9, 47.0, 35.7, 16.7, 9.4. IR (thin film) 2923, 2854, 1672, 1633,

1454, 1408, 1374, 1286, 1236. HRMS calcd. for  $C_{34}H_{34}BrN_2O_7$  (M+H)<sup>+</sup> 661.1544; m/z found 661.1560.





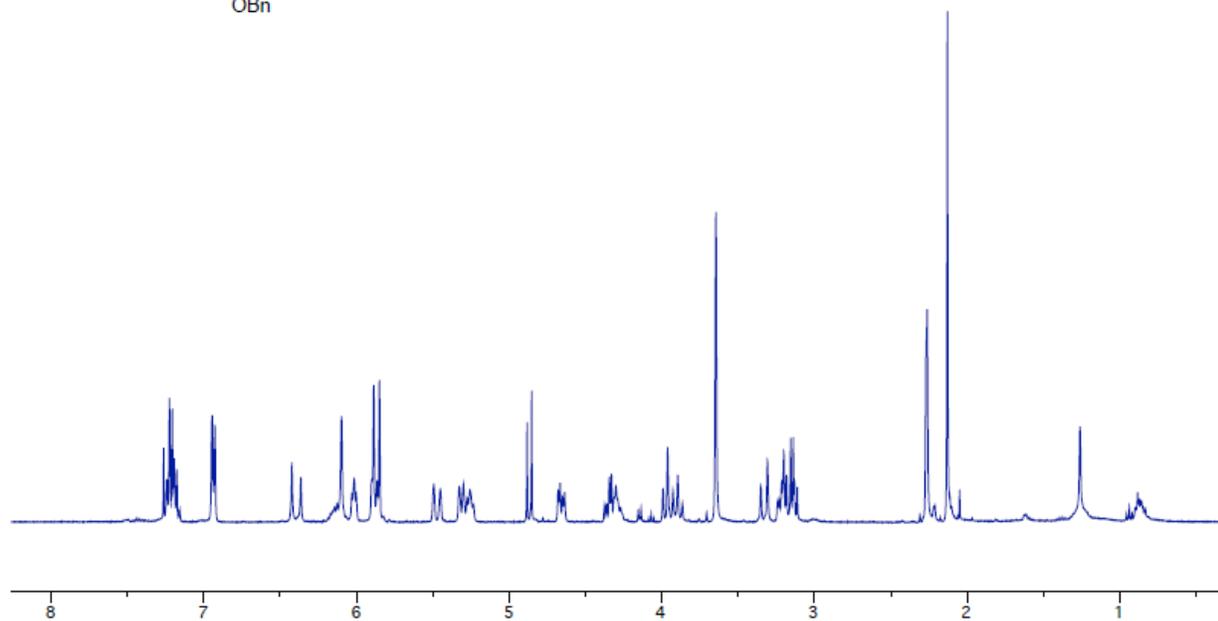
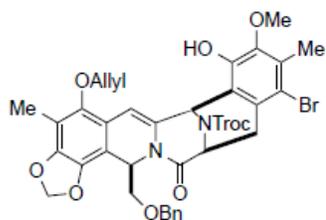
**Compound 220a:** (7*R*,13*S*,16*R*)-2,2,2-trichloroethyl 5-(allyloxy)-16-((benzyloxy)methyl)-11-bromo-8-hydroxy-9-methoxy-4,10-dimethyl-14-oxo-12,13,14,16-tetrahydro-7*H*-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinoline-17-carboxylate

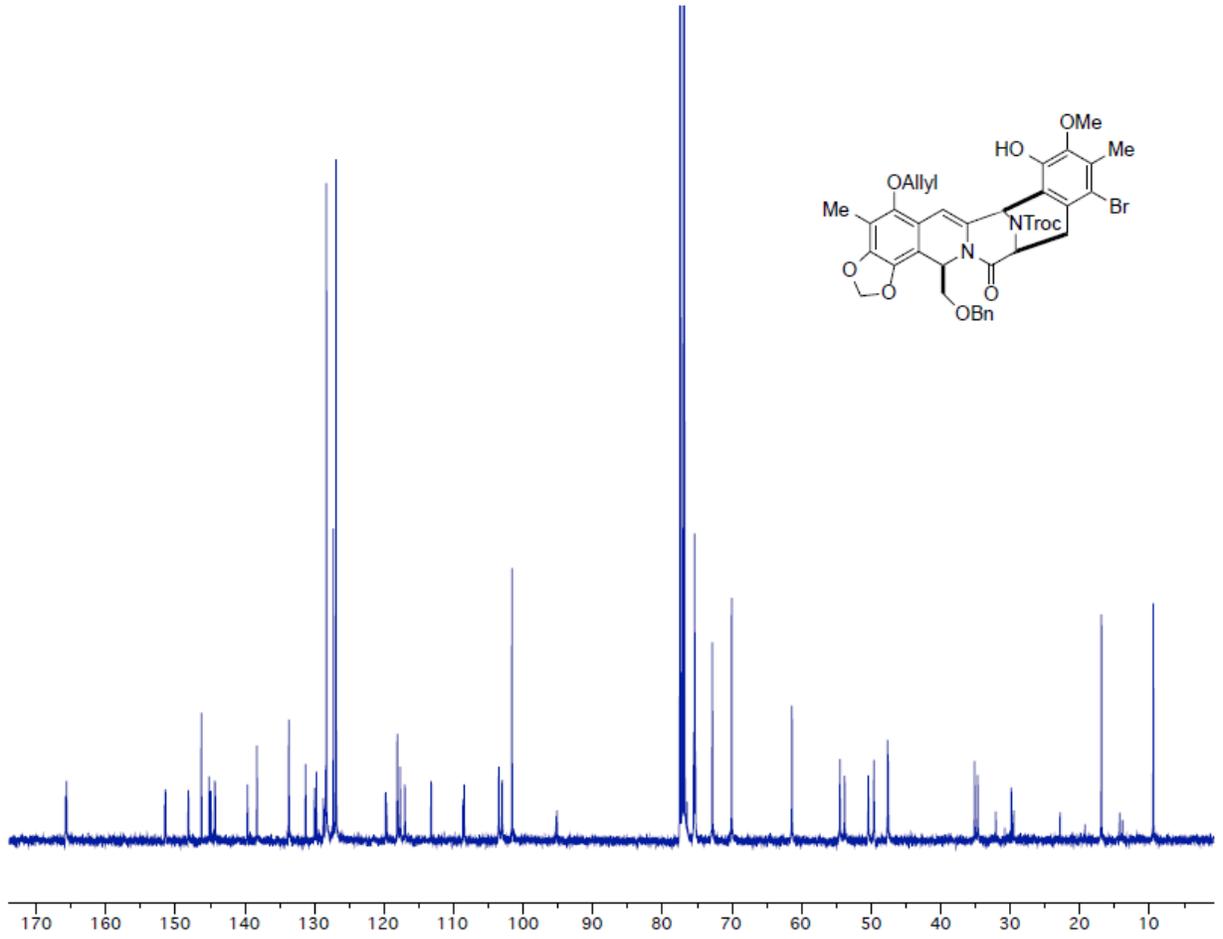


TrocCl (6  $\mu$ l, 0.046 mmol) and pyridine (6  $\mu$ l, 0.069 mmol) was added to a solution of pentacycle **181** (30 mg, 0.046 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 ml). The reaction was stirred at room temperature overnight (15 hours) then concentrated. The crude product was purified by column chromatography (25% EtOAc/ hexanes) to give **220a** as a yellow solid.

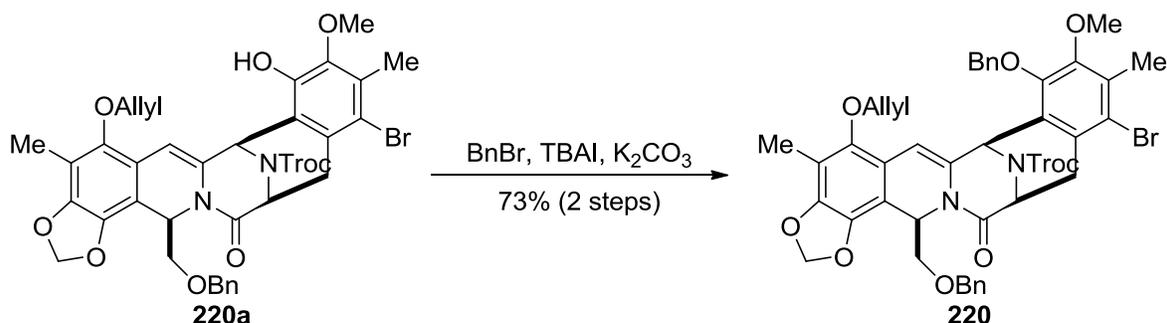
$R_f = 0.3$  (EtOAc:hexanes 25:75, UV, PAA).  $[\alpha]_D +145$  ( $c$  1.75,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , mixture of carbamate rotamers)  $\delta$  7.20 (m, 3 H), 6.93 (d,  $J = 7.0$  Hz, 2 H), 6.42 and 6.36 (s, 1 H), 6.10-6.18 (m, 2 H), 6.01 (t,  $J = 6.0$  Hz, 1 H), 5.87 (dd,  $J = 14.3, 5.5$  Hz, 3 H), 5.47 (d,  $J = 17.2$  Hz, 1 H), 5.31 (d,  $J = 11.1$  Hz, 1 H), 5.25 (t,  $J = 6.7$  Hz, 1 H), 4.88 and 4.85 (s, 1 H), 4.65 (dd,  $J = 12.0, 5.4$  Hz, 1 H), 4.26-4.37 (m, 2 H), 3.86-3.99 (m, 2 H), 3.64 (s, 3 H), 3.35 and 3.31 (s, 1 H), 3.11-3.35 (m, 3 H), 2.26 (s, 3 H), 2.13 (s, 3 H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , mixture of carbamate rotamers)  $\delta$  165.8, 165.6, 151.5, 151.4, 148.2, 148.1, 146.3, 145.1, 144.9, 144.3, 139.6, 138.3, 133.7, 131.3, 130.0, 129.7, 128.7, 128.4, 128.3, 127.3, 126.9, 126.8, 119.8, 119.6, 118.2, 118.1, 117.1, 117.0, 117.0, 113.3, 113.2, 108.7, 108.5, 103.5, 103.0, 101.6, 95.3, 95.1, 75.5, 75.4, 75.3, 72.8, 70.0, 61.4, 54.5, 53.8, 50.4, 49.6, 47.6, 47.5, 35.1, 34.7, 29.8, 16.9, 9.4, . IR (thin

film) 3369, 2926, 1725, 1679, 1640, 1410, 1374, 1287. HRMS calcd. for  $C_{37}H_{35}BrCl_3N_2O_9$   
(M+H)<sup>+</sup> 835.0586; m/z found 835.0584.





**Compound 220:** (7*R*,13*S*,16*R*)-2,2,2-trichloroethyl 5-(allyloxy)-8-(benzyloxy)-16-((benzyloxy)methyl)-11-bromo-9-methoxy-4,10-dimethyl-14-oxo-12,13,14,16-tetrahydro-7*H*-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinoline-17-carboxylate

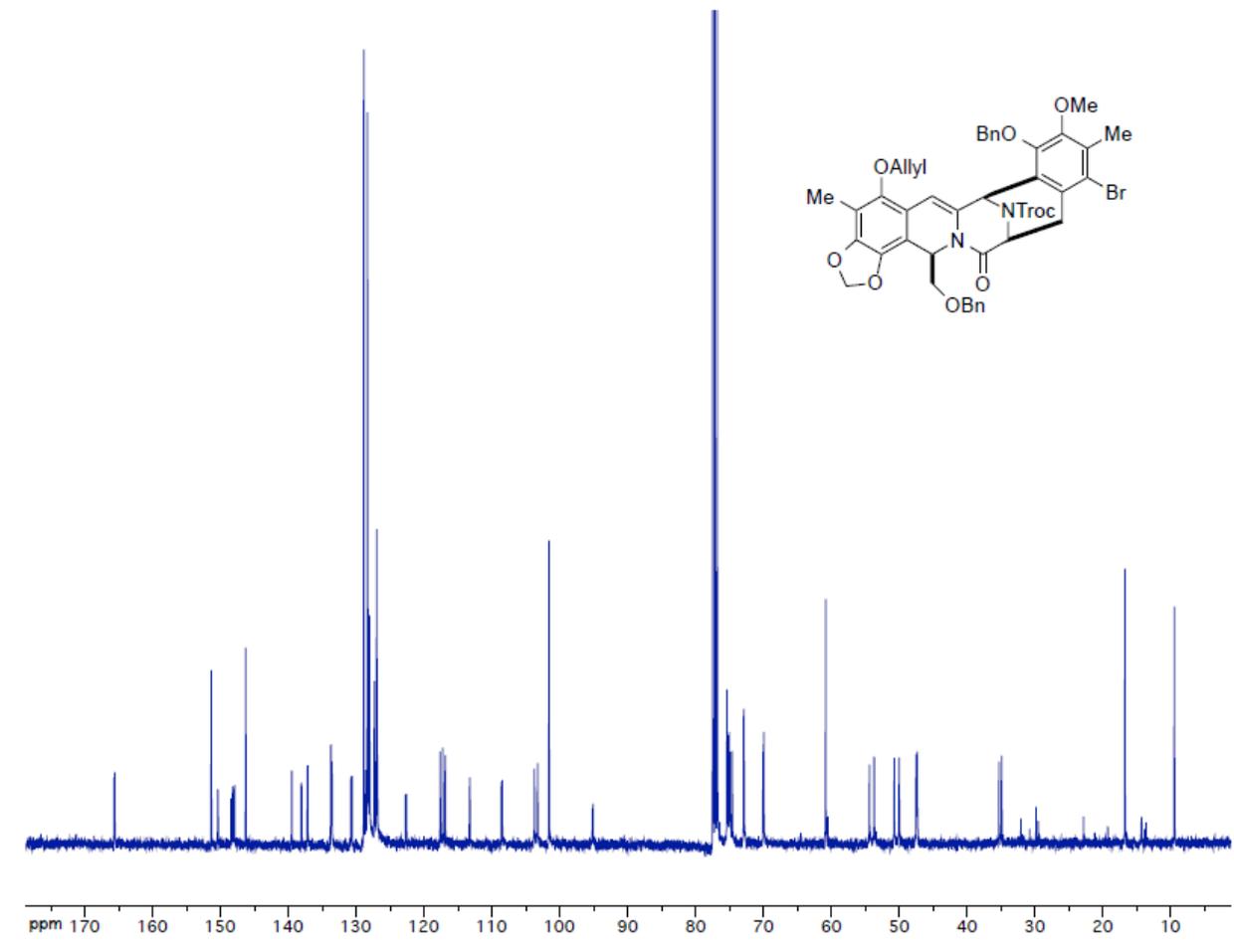


**220a** was dissolved in  $\text{CH}_2\text{Cl}_2$  (0.5 ml) and MeOH (0.2 ml) followed by the addition of  $\text{K}_2\text{CO}_3$  (25 mg, 0.18 mmol), TBAI (1.7 mg, 0.0046 mmol) and BnBr (11  $\mu\text{l}$ , 0.092 mmol). The reaction was stirred at room temperature overnight (17 hours) then filtered through celite. The crude product was purified by column chromatography (5:1 hexanes:EtOAc) to provide **220** as a yellow solid (31 mg, 73% over the 2 steps).

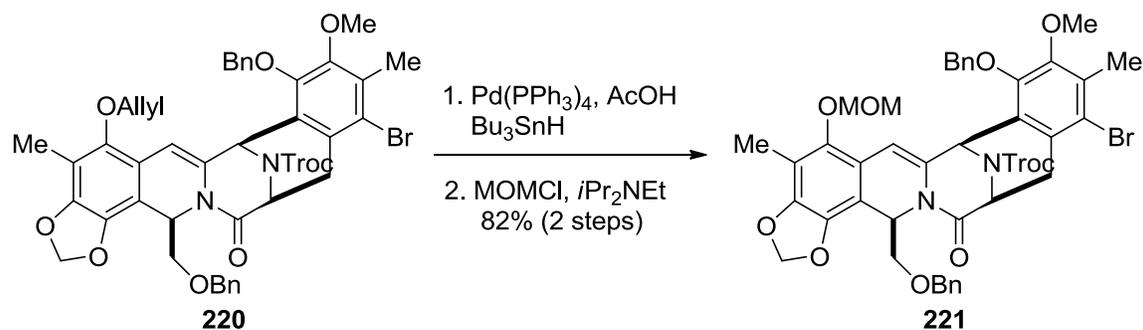
$R_f = 0.2$  (EtOAc:hexanes 1:5, UV, PAA).  $[\alpha]_{\text{D}} +103.4$  ( $c$  0.71,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ , mixture of carbamate rotamers)  $\delta$  7.53 (t,  $J = 6.8$  Hz, 2 H), 7.40 (m, 3 H), 7.16-7.24 (m, 3 H), 6.91 (br s, 2), 6.25 (s, 1 H), 6.15 (d,  $J = 16.7$  Hz, 1 H), 6.02 (dd,  $J = 7.0, 4.5$  Hz, 1 H), 5.86 (m, 3 H), 4.99-5.30 (m, 5 H), 4.85 (dd,  $J = 12.4, 3.5$  Hz, 1H), 4.64 (dd,  $J = 11.9, 2.84$  Hz, 1 H), 3.93-4.15 (m, 4 H), 3.71 (d,  $J = 8.4$  Hz, 3 H), 3.10-3.38 (m, 4 H), 2.32 and 2.26 (s, 3 H), 2.10 and 2.05 (s, 3 H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ , mixture of carbamate rotamers)  $\delta$  165.7, 165.6, 151.4, 150.4, 150.4, 148.5, 148.3, 148.2, 148.0, 146.3, 139.5, 138.1, 138.1, 137.2, 137.2, 133.8, 133.7, 133.6, 133.6, 130.8, 130.6, 128.9, 128.6, 128.4, 128.0, 127.3, 127.2, 127.0, 126.9, 122.8, 122.6, 117.7, 117.3, 116.9, 113.3, 113.3, 108.6, 108.5, 103.8, 103.3, 101.6, 95.2, 95.1, 75.4, 75.3, 75.0, 74.9, 74.6, 72.9, 72.9, 70.1, 70.0, 60.9, 54.4, 53.7, 50.8, 50.0, 47.4, 47.4, 35.334.9, 16.8,

9.5. IR (thin film) 3401, 2929, 1725, 1679, 1640, 1497, 1455, 1433, 1409, 1371. HRMS calcd. for  $C_{44}H_{41}BrCl_3N_2O_9$  ( $M+H$ )<sup>+</sup> 925.1056; m/z found 925.1061.





**Compound 221:** (7*R*,13*S*,16*R*)-2,2,2-trichloroethyl 8-(benzyloxy)-16-((benzyloxy)methyl)-11-bromo-9-methoxy-5-(methoxymethoxy)-4,10-dimethyl-14-oxo-12,13,14,16-tetrahydro-7*H*-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinoline-17-carboxylate

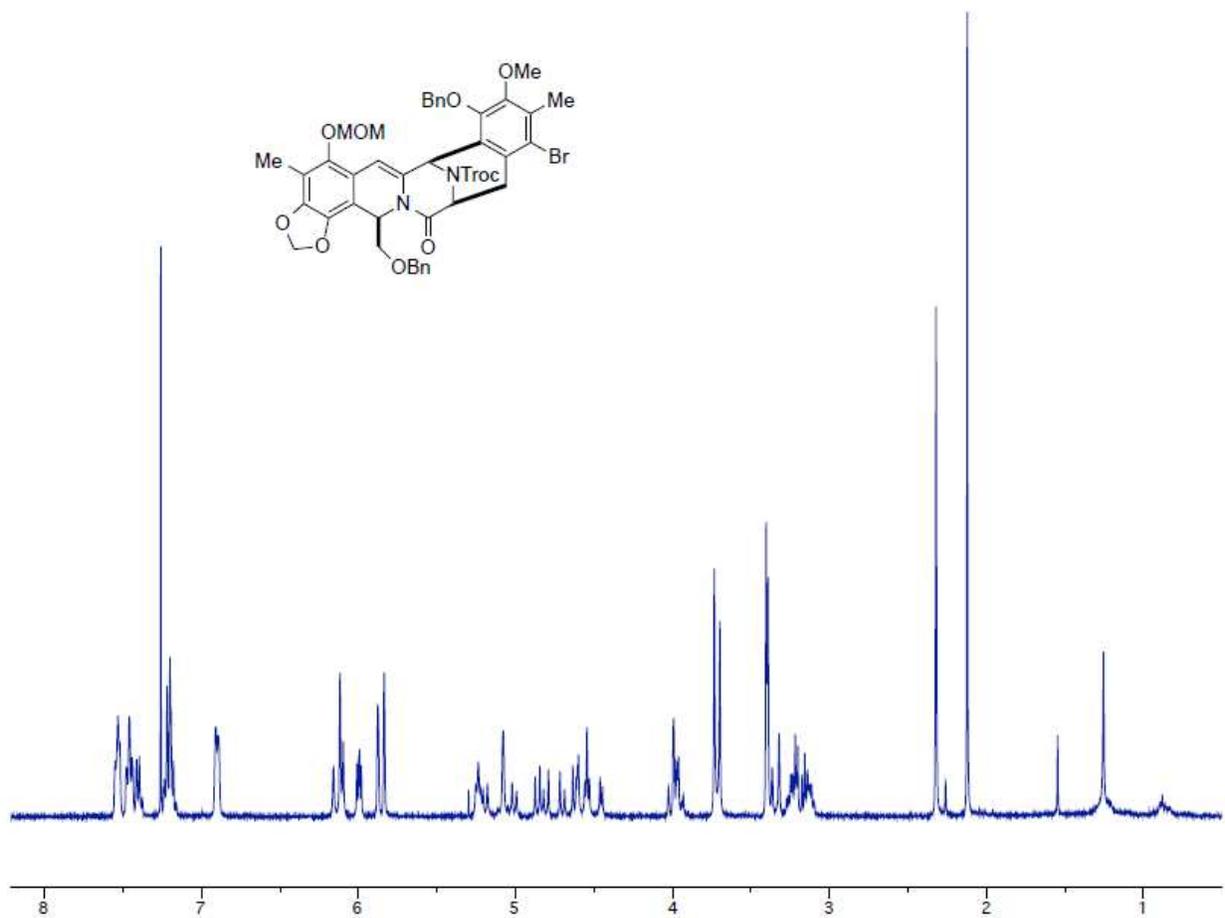
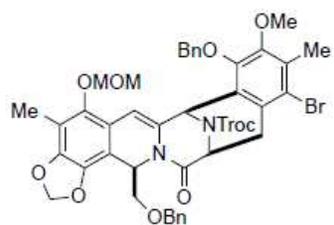


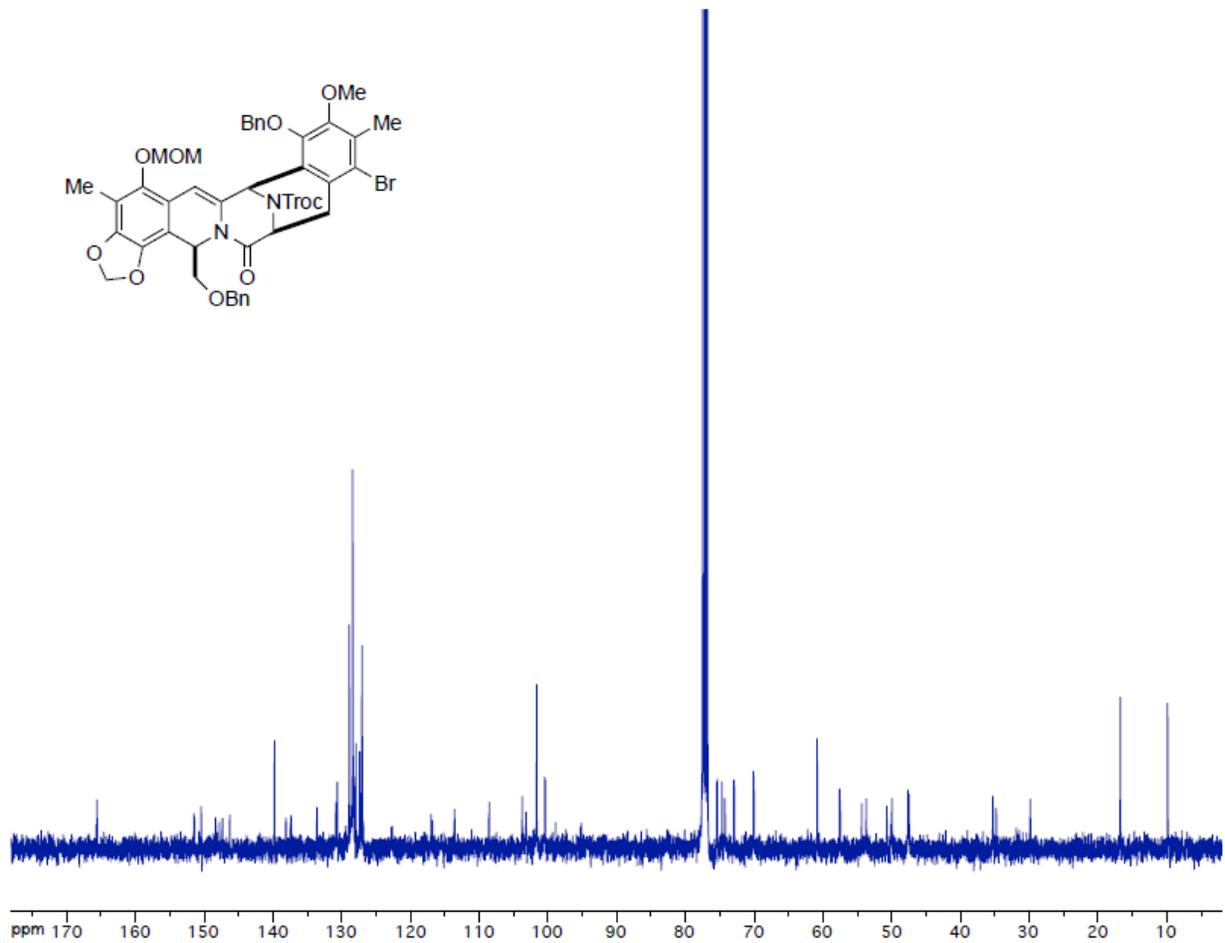
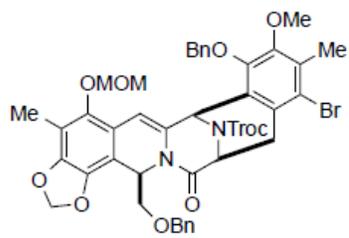
Acetic acid (1  $\mu$ l, 0.016 mmol) and Bu<sub>3</sub>SnH (6  $\mu$ l, 0.022 mmol) was added to a solution of **220** (31 mg, 0.033 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml). The reaction was stirred at room temperature for 1 hour then concentrated. The crude product was purified by column chromatography (20% EtOAc/ hexanes) to give a phenol.

MOMCl (7.5  $\mu$ L, 0.09 mmol) and *i*Pr<sub>2</sub>NEt (9  $\mu$ L, 0.06 mmol) was added to a solution of the phenol in CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml). The reaction was stirred at room temperature overnight (13 hours) then quenched with water (10  $\mu$ l) and concentrated. The crude product (26 mg, 82% over the 2 steps) was clean enough for use in the next step without further purification.

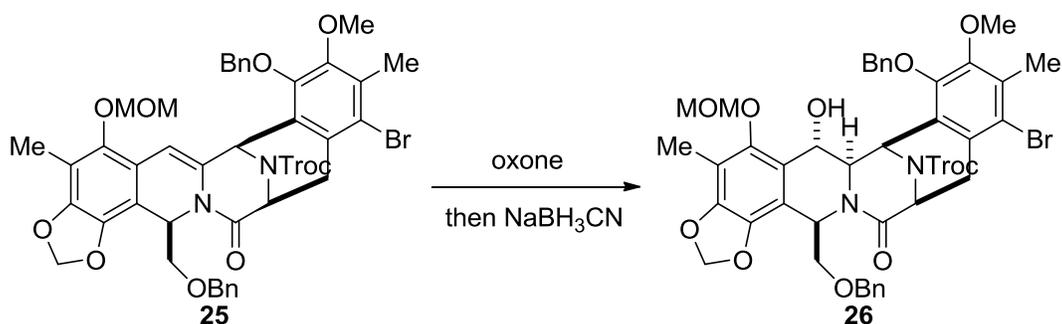
$R_f$  = 0.3 (EtOAc:hexanes 25:75, UV, PAA).  $[\alpha]_D + 97$  ( $c$  0.30, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  7.53 (t,  $J$  = 7.1 Hz, 2H), 7.46 (t,  $J$  = 7.1 Hz, 2H), 7.40 (m, 1 H), 7.20 (m, 3 H), 6.90 (d,  $J$  = 5.3 Hz, 2H), 6.16 and 6.10 (s, 1H), 6.12 (s, 1H), 6.00 (dd,  $J$  = 6.81, 4.6 Hz, 1H), 5.86 (d,  $J$  = 16.1 Hz, 2 H), 4.45-5.25 (m, 10 H), 4.98 (m, 2 H), 3.73 and 3.70 (s, 3H), 3.40 and 3.39 (s, 3H), 3.36 and 3.32 (s, 1H), 3.09-3.27 (m, 4H), 2.32 (s, 3H), 2.12 (s, 3H), 1.55 and 1.25 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  165.9, 165.8, 151.7, 150.6, 148.5, 148.0, 147.6, 147.5, 147.5, 146.5, 140.0, 138.3, 138.3, 137.6,

133.8, 131.1, 130.8, 129.1, 128.6, 128.5, 128.4, 128.1, 127.6, 127.3, 127.2, 127.2, 127.0, 117.2, 117.0, 113.9, 113.8, 113.7, 108.8, 108.8, 108.7, 103.9, 103.4, 101.9, 100.7, 100.6, 75.6, 75.6, 74.9, 74.4, 73.2, 73.1, 70.3, 70.3, 61.0, 57.8, 57.7, 54.6, 50.9, 50.3, 50.2, 47.8, 47.7, 35.5, 35.0, 30.1, 17.0, 10.1. IR (thin film) 3271, 2917, 1724, 1682, 1654, 1456, 1433, 1405. HRMS calcd. for  $C_{43}H_{41}BrCl_3N_2O_{10}$  (M+H)<sup>+</sup> 929.1005; m/z found 929.1018.





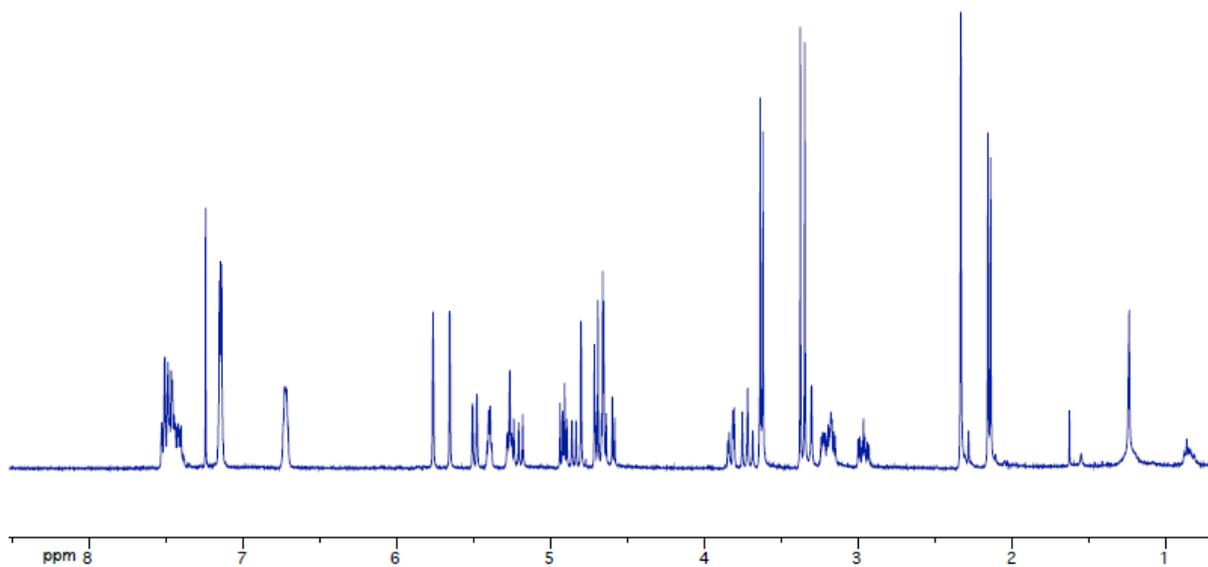
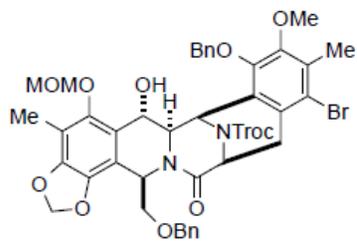
**Compound 222:** (6*S*,6*aR*,7*R*,13*S*,16*R*)-2,2,2-trichloroethyl 8-(benzyloxy)-16-((benzyloxy)methyl)-11-bromo-6-hydroxy-9-methoxy-5-(methoxymethoxy)-4,10-dimethyl-14-oxo-6*a*,7,12,13,14,16-hexahydro-6*H*-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinoline-17-carboxylate

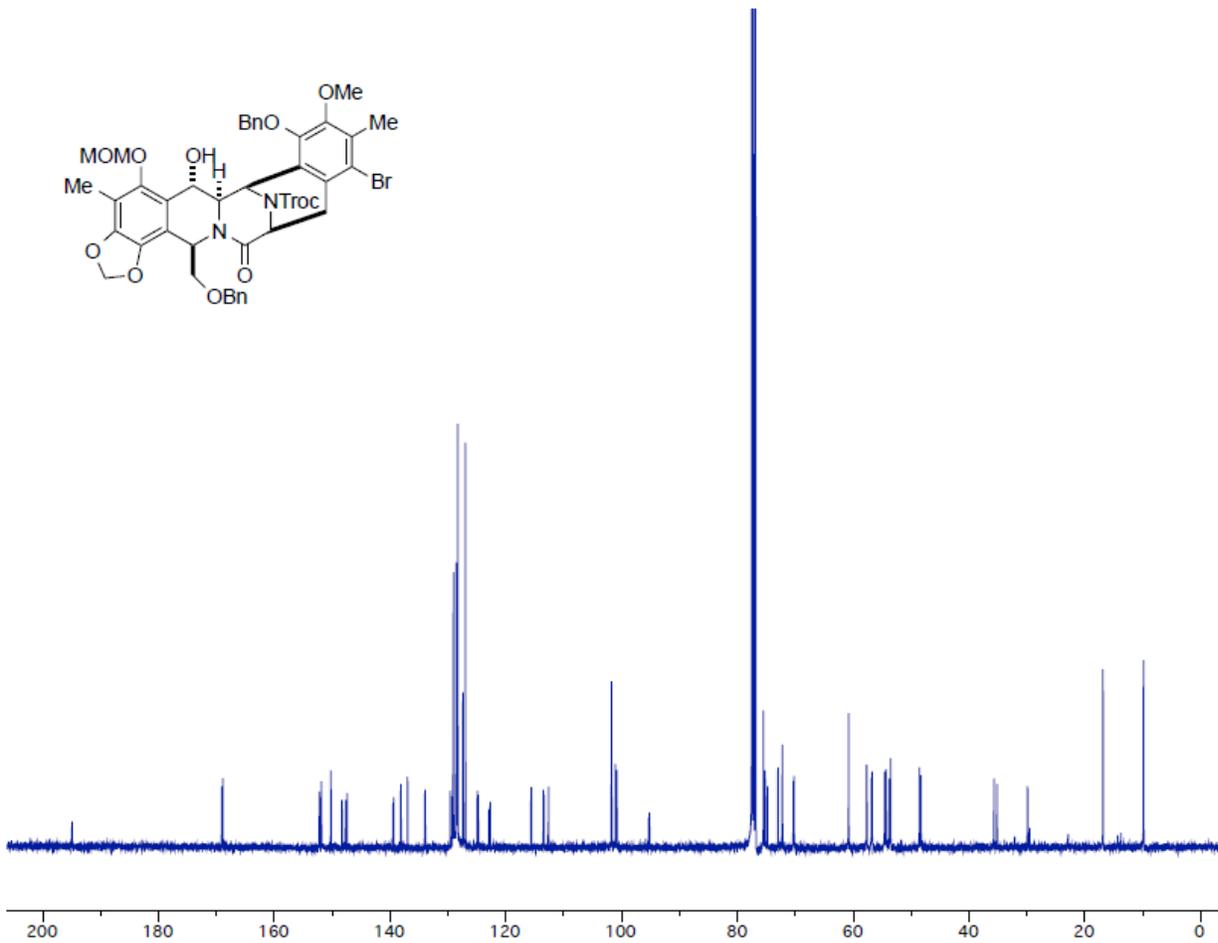


A cold solution (-78°C) of 0.085M of dimethyl dioxirane in acetone (0.65 ml, 0.055mmol) was added to a solution of **25** (26 mg, 0.027 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml) at 0°C. The reaction was stirred at 0°C for 1 hour then NaBH<sub>3</sub>CN (86 mg, 1.37 mmol) was added in one portion. The reaction was stirred at low temperature for 10 minutes then at room temperature for 10 minutes. The reaction was quenched with water (3 ml). The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x5 ml). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (5:1 hexanes:EtOAc) to give a pink gel (14 mg, 54%).

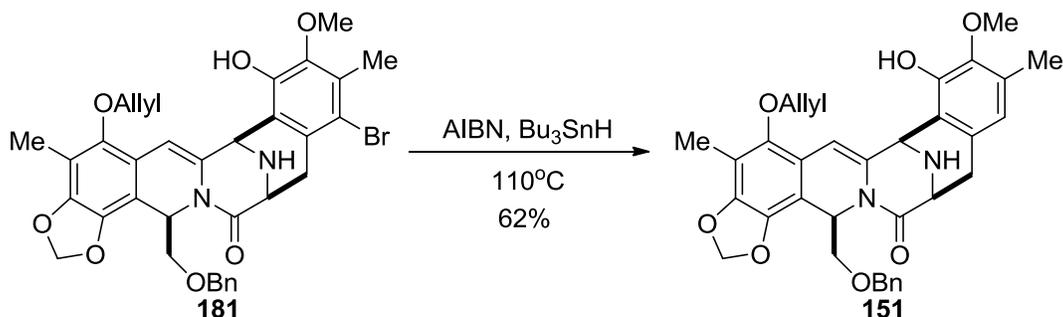
$R_f = 0.3$  (EtOAc:hexanes 25:75, UV, PAA). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers) δ 7.40-7.55 (m, 5H), 7.16 (t,  $J = 3.2$  Hz, 3H), 6.74 (m, 2H), 5.78 (s, 1H), 5.67 (d,  $J = 1.2$ , 1H), 5.51 (d,  $J = 10.9$  Hz, 1H), 5.42 (q,  $J = 4.2$  Hz, 1H), 5.28 (t,  $J = 6.5$  Hz, 1H), 5.22 (t,  $J = 12.2$  Hz, 1H), 4.60-4.95 (m, 7H), 3.84 (dd,  $J = 13.1, 3.5$  Hz, 1H), 3.74 (t,  $J = 13.8$  Hz, 1H), 3.65 and 3.64 (s, 3H), 3.39 and 3.36 (s, 3H), 3.32 (s, 1H), 3.17-3.26 (m, 2H), 3.00 (m, 1H), 2.35 and 2.30 (s, 3H), 2.17 and 2.16 (s, 3H), 1.26 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, mixture of

carbamate rotamers)  $\delta$  195.1, 169.2, 169.0, 152.4, 152.3, 152.0, 152.0, 150.4, 148.5, 147.9, 147.6, 139.6, 139.5, 138.3, 138.3, 137.1, 134.2, 134.1, 129.7, 129.3, 129.2, 128.7, 128.5, 128.4, 127.6, 127.2, 125.1, 124.9, 123.1, 122.9, 115.8, 115.7, 113.7, 113.6, 112.8, 112.8, 101.9, 101.2, 101.0, 95.5, 95.3, 77.7, 77.6, 75.7, 75.4, 75.0, 73.2, 73.1, 72.4, 72.4, 70.5, 70.4, 61.0, 57.9, 57.8, 57.0, 56.9, 54.7, 54.5, 53.9, 53.7, 48.7, 48.5, 35.9, 35.3, 30.1, 17.0, 10.0. HRMS calcd. for  $C_{43}H_{41}BrCl_3N_2O_{10} (M+H)^+$  947.1116; m/z found 947.1118.





**Compound 151:** (7*R*,13*S*,16*R*)-5-(allyloxy)-16-((benzyloxy)methyl)-8-hydroxy-9-methoxy-4,10-dimethyl-12,13-dihydro-7*H*-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinolin-14(16*H*)-one

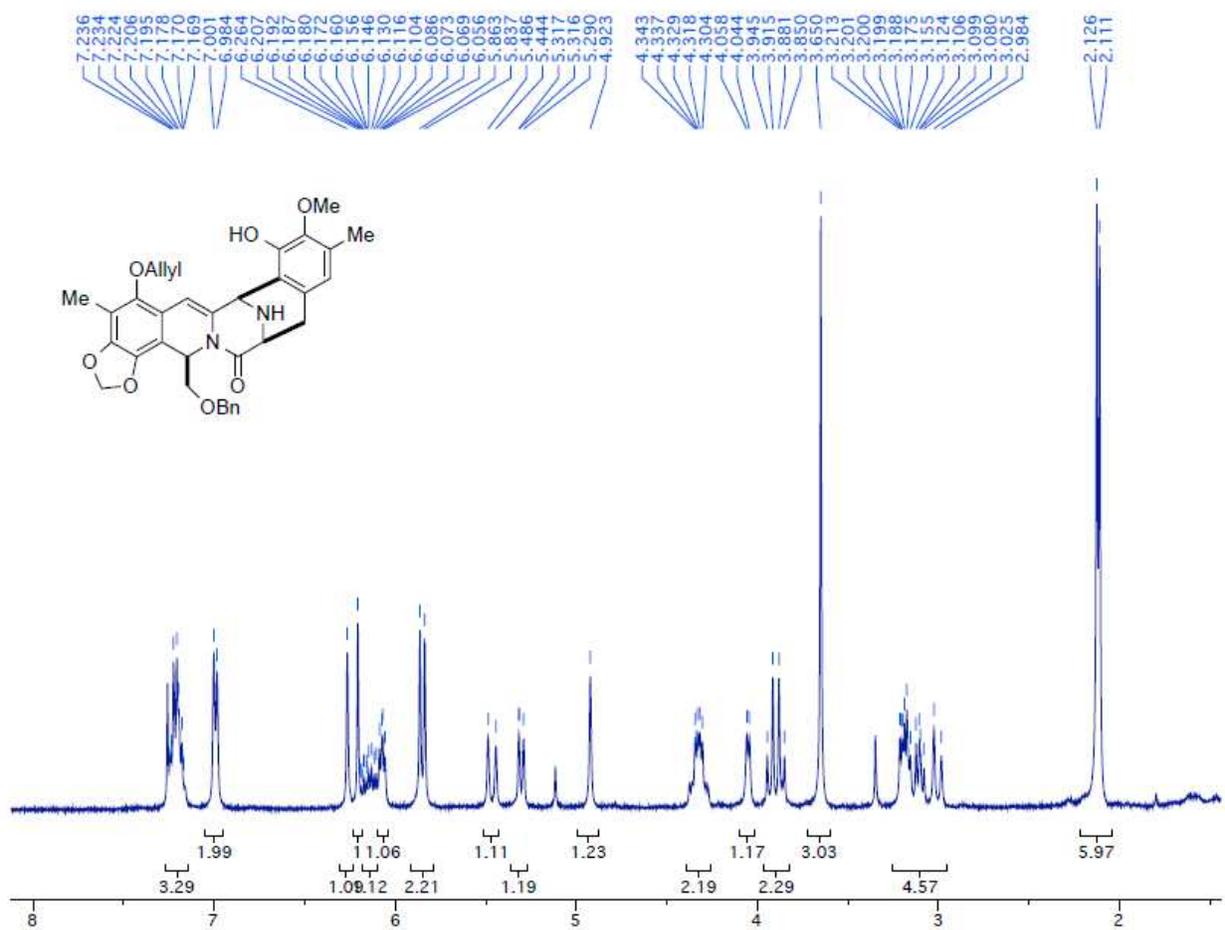


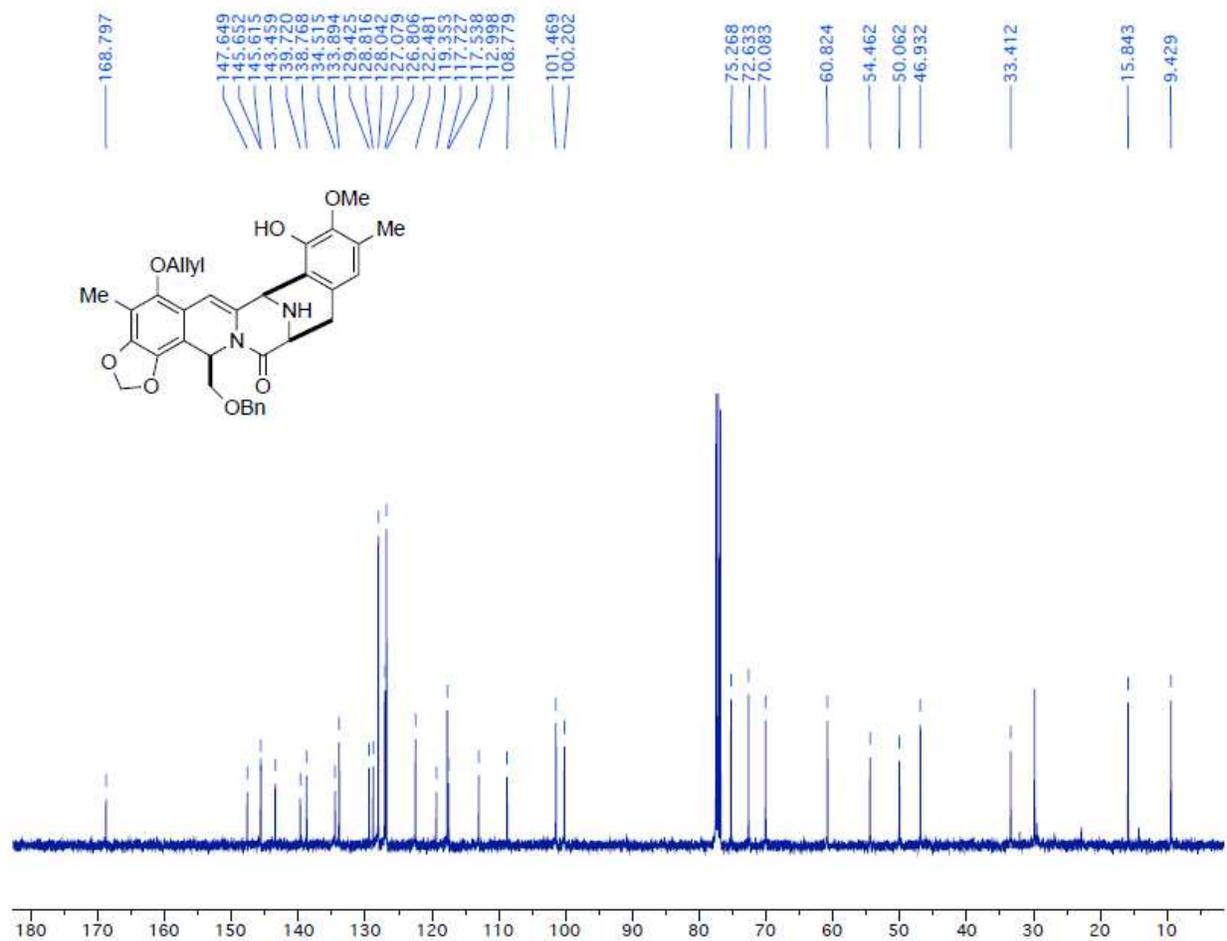
**9** (16 mg, 0.024 mmol) was dissolved in 2 ml of toluene, followed by addition of AIBN (2 mg, 0.012 mmol) and  $\text{Bu}_3\text{SnH}$  (16  $\mu\text{L}$ , 0.061 mmol). The resulting solution was degassed (freeze/pump/thaw x 3), and then heated to 100°C for 30 minutes. The solution was allowed to cool to room temperature and poured into 1 ml of saturated aqueous solution of  $\text{NaHCO}_3$ . The layers were separated and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 1 mL). The combined organic layers were dried over  $\text{CaCl}_2$  and concentrated. The crude product was purified by column chromatography (KF:silica gel 10:90, 50%  $\text{EtOAc}$ /hexanes) to give **3** (9.1 mg, 64%).

All experimental data match those reported in the literature.<sup>86</sup>

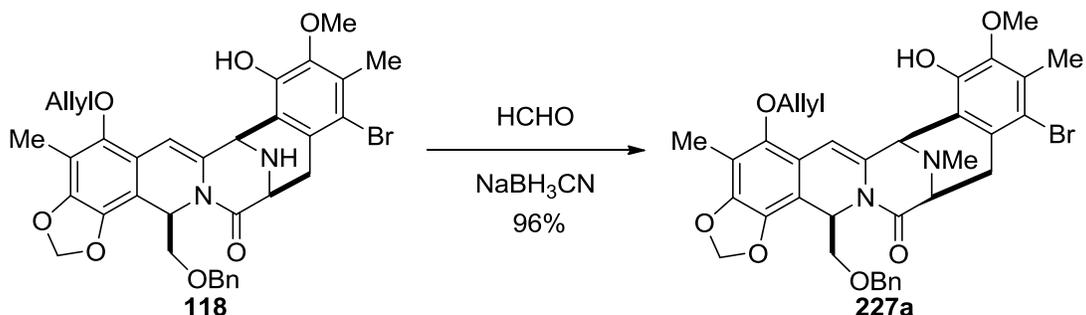
$R_f = 0.1$  ( $\text{EtOAc}$ :hexanes 50:50, UV, PAA).  $[\alpha]_{\text{D}} - 22$  ( $c$  0.40,  $\text{CH}_2\text{Cl}_2$ ) [Literature  $-18$ , ( $c$  0.10,  $\text{CH}_2\text{Cl}_2$ )].  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.16-7.21 (m, 3H), 6.99 (d,  $J = 7.1$  Hz, 2H), 6.21 (s, 1H), 6.21 (s, 1H), 6.14 (dddd,  $J = 16.4, 10.7, 5.7, 5.4$  Hz, 1H), 6.07 (dd,  $J = 6.9, 5.2$  Hz, 1H), 5.84 (s, 1H), 5.84 (s, 1H), 5.46 (d,  $J = 17.1$  Hz, 1H), 5.30 (d,  $J = 10.4$  Hz, 1H), 4.9 (s, 1H), 4.32 (m, 2H), 4.05 (d,  $J = 5.6$  Hz, 1H), 3.90 (q,  $J = 25.7, 12.1$  Hz, 2H), 3.65 (s, 3H), 2.98-3.21 (m, 5H), 2.13 (s, 3H), 2.11 (s, 3H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.0, 147.9, 145.9, 145.8, 143.7, 139.9, 139.0, 134.7, 134.1, 129.6, 129.0, 128.3, 127.3, 127.0, 122.7, 119.6, 117.9, 117.7, 113.2, 109.0, 101.7, 100.4, 75.5, 72.9, 70.3, 61.0, 54.7, 50.3, 47.2, 33.6, 16.1, 9.7. IR (thin film) 3308,

2854, 1672, 1648, 1632, 1497, 1454, 1428, 1410. HRMS calcd. for C<sub>43</sub>H<sub>41</sub>BrCl<sub>3</sub>N<sub>2</sub>O<sub>10</sub> (M+H)<sup>+</sup>  
583.2444; m/z found 583.2433.



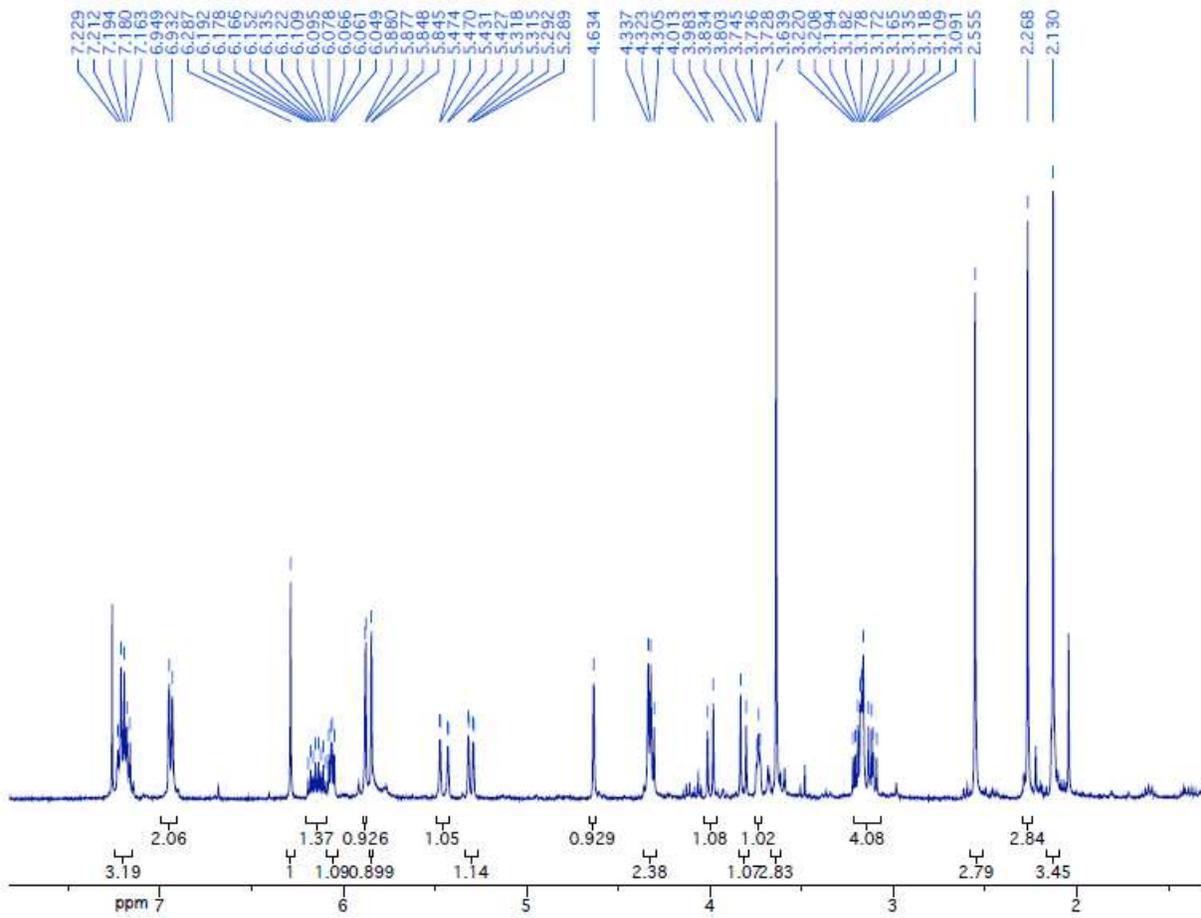


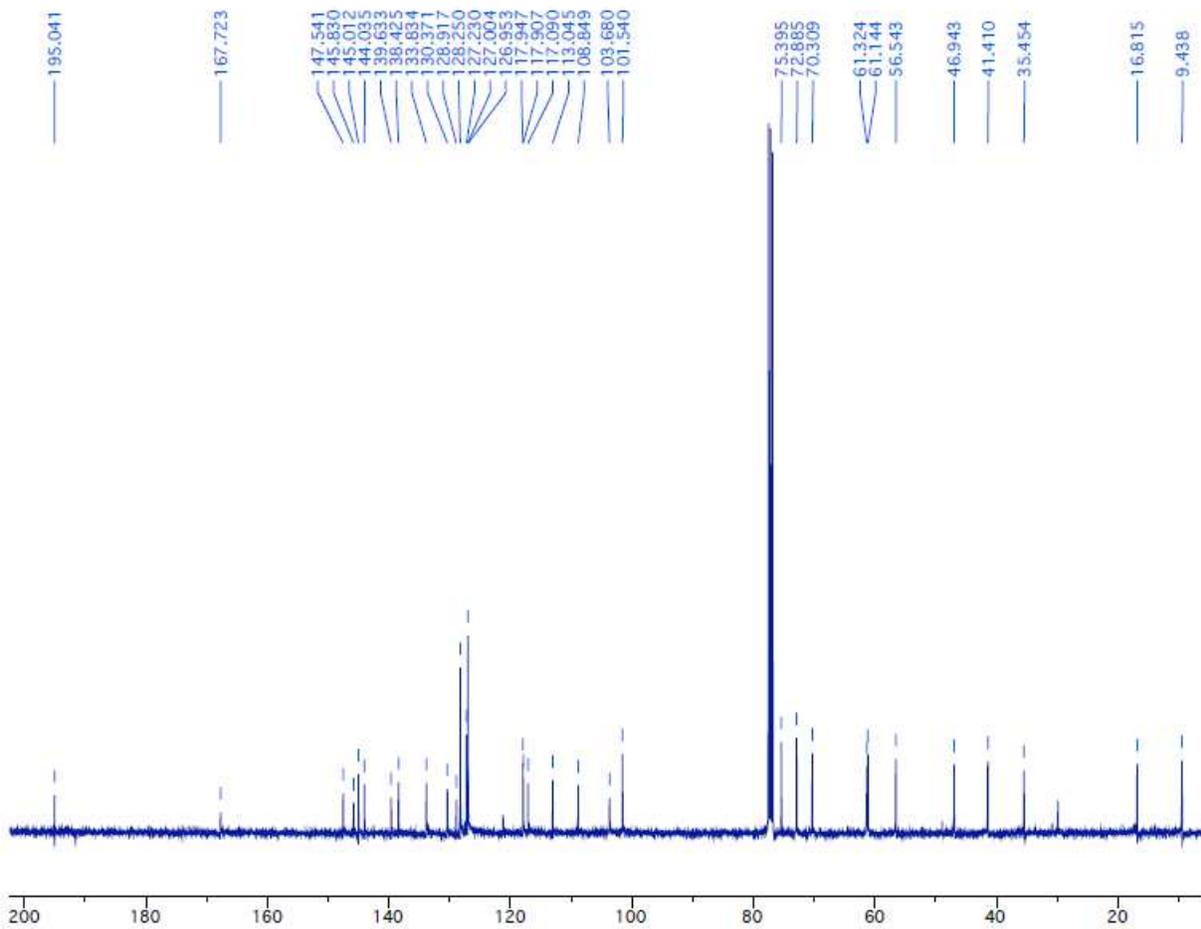
**Compound 227a:** (7*R*,13*S*,16*R*)-5-(allyloxy)-16-((benzyloxy)methyl)-11-bromo-8-hydroxy-9-methoxy-4,10,17-trimethyl-12,13-dihydro-7*H*-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinolin-14(16*H*)-one



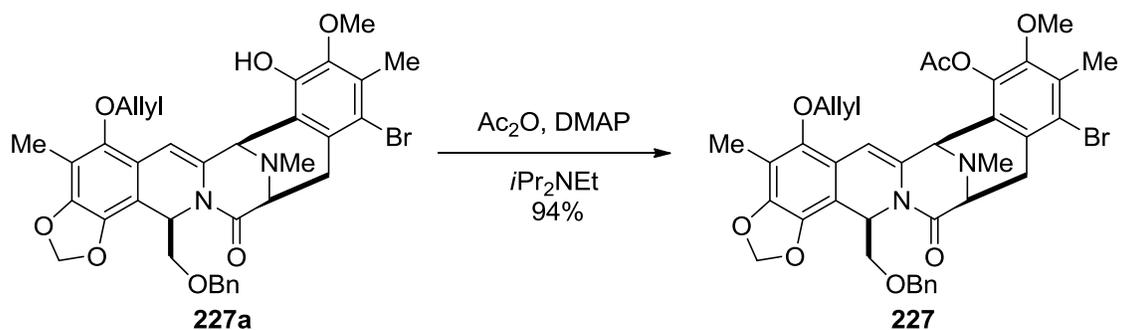
Formaldehyde (37% in water) (73 ml, 9.03 mmol) was added to a solution of pentacycle **118** (298 mg, 0.45 mmol) and the reaction was stirred at room temperature for 15 minutes.  $\text{NaBH}_3\text{CN}$  (284 mg, 4.51 mmol) was added and stirred at for 15 minutes, followed by addition of acetic acid (0.45 ml), stirred for 5 minutes and 2N HCl (9 ml). The reaction was heated to 60°C for 6 hours then washed with a saturated solution of  $\text{NaHCO}_3$ . The layers were separated and the aqueous layer was extracted 3 times with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with the brine, dried with  $\text{MgSO}_4$  and concentrated to give **227a** (294 mg, 96%) as a brown foam. The crude product was used in the next step without purification.

$R_f = 0.3$  (EtOAc:hexanes 50:50, UV, PAA).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 (m, 3H), 6.94 (d,  $J = 6.7$ , 1H), 6.29 (s, 1H), 6.14 (ddd,  $J = 17.09, 10.6, 5.6$  Hz, 1H), 6.06 (dd,  $J = 6.9, 4.7$  Hz, 1H), 5.88 (d,  $J = 1.2$  Hz, 1H), 5.85 (d,  $J = 1.2$  Hz, 1H), 4.63 (s, 1H), 4.32 (m, 3H), 4.00 (d,  $J = 12.2$  Hz, 1H), 3.82 (d,  $J = 12.2$  Hz, 1H), 3.74 (t,  $J = 3.6$  Hz, 1H), 3.64 (s, 3H), 3.09-3.22 (m, 4H), 2.56 (s, 3H), 2.27 (s, 3H), 2.13 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.0, 167.7, 147.5, 145.8, 145.0, 144.0, 139.6, 138.4, 133.8, 130.4, 128.9, 128.3, 127.2, 127.0, 127.0, 117.9, 117.1, 113.0, 108.8, 103.7, 101.5, 75.4, 72.9, 70.3, 61.3, 61.1, 56.5, 46.9, 41.4, 35.5, 16.8, 9.4. HRMS calcd. for  $\text{C}_{35}\text{H}_{36}\text{BrN}_2\text{O}_7$  ( $\text{M}+\text{H}$ ) $^+$  675.1706;  $m/z$  found 675.1695.



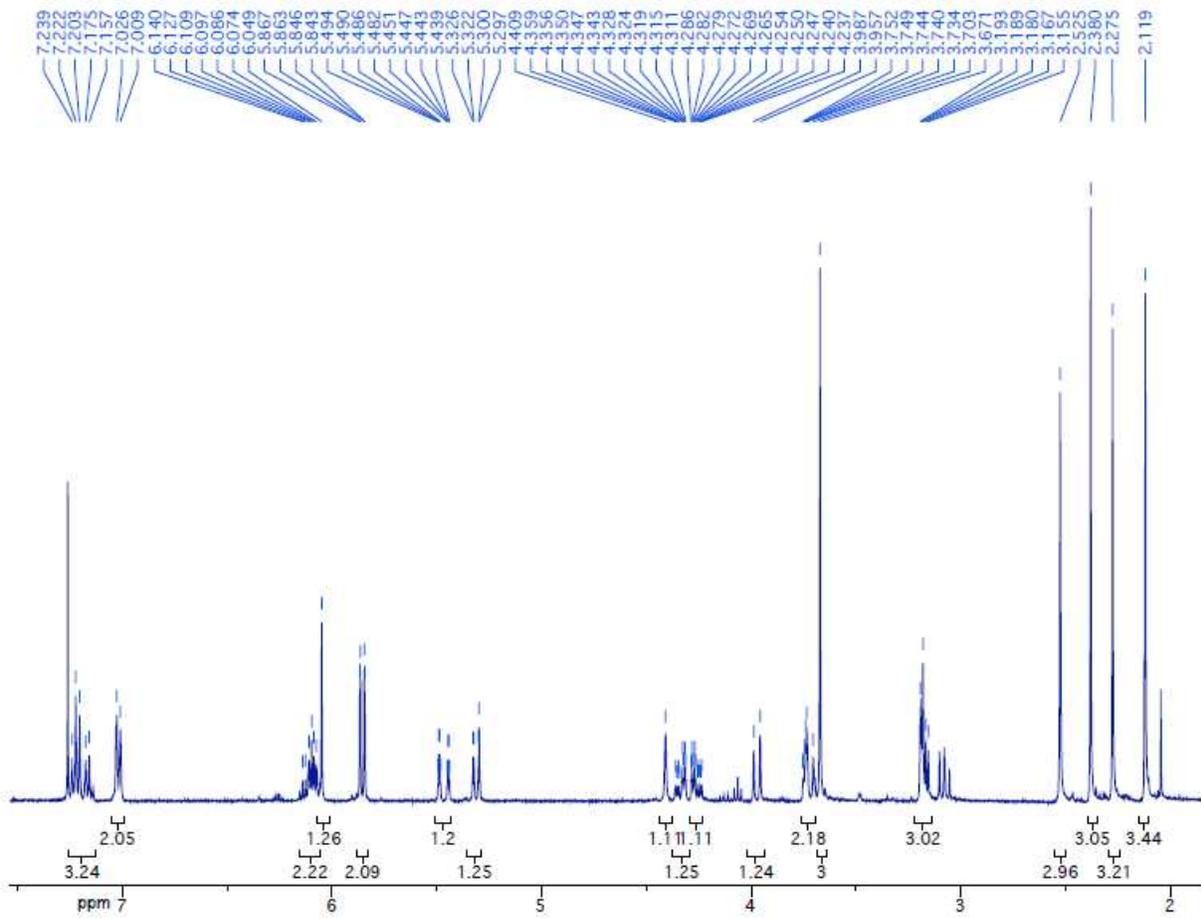


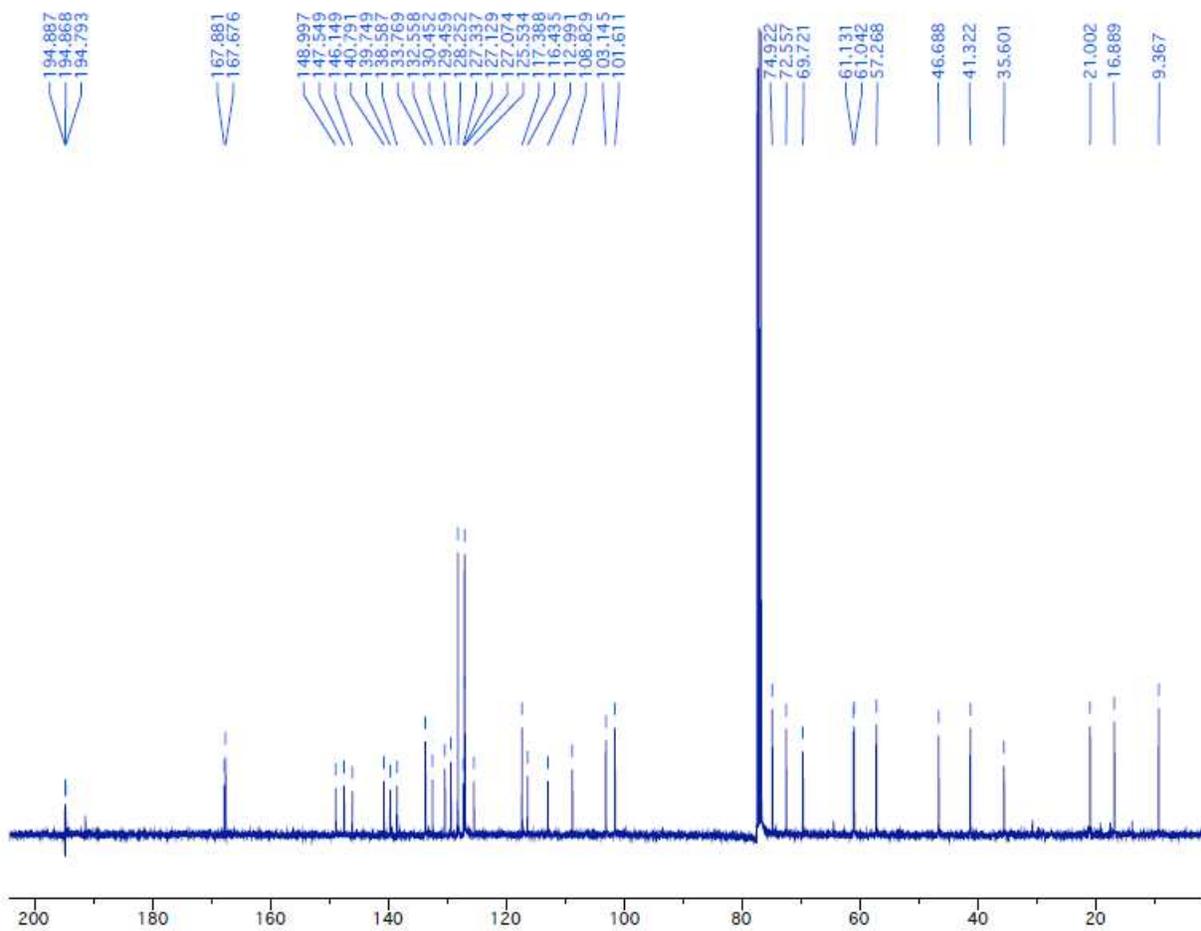
**Compound 227:** (7*R*,13*S*,16*R*)-5-(allyloxy)-16-((benzyloxy)methyl)-11-bromo-9-methoxy-4,10,17-trimethyl-14-oxo-12,13,14,16-tetrahydro-7*H*-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinolin-8-yl acetate



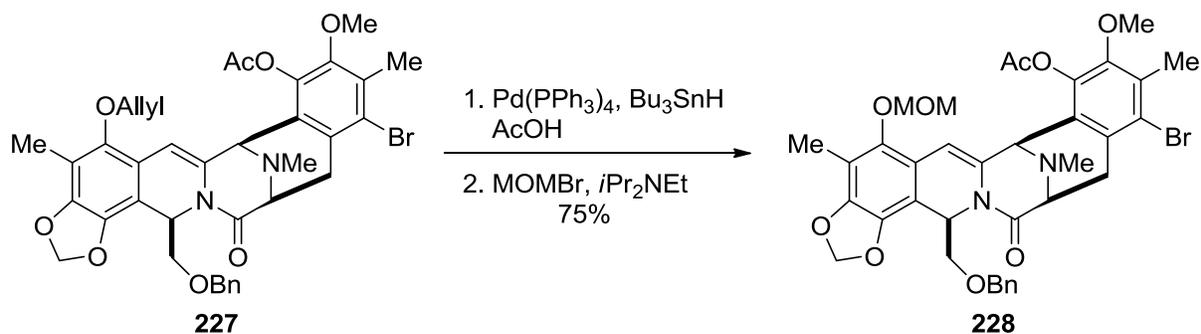
*iPr*<sub>2</sub>NEt (0.36 ml, 2.08 mmol) and DMAP (10.2 mg, 0.08 mmol) were added to a solution of **227a** (294 mg, 0.43 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 ml). The reaction was stirred at room temperature for 3 hours and washed with the saturated solution of NaHCO<sub>3</sub>. The layers were separated and the aqueous layer was extracted 3 times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with the brine, dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (30% EtOAc/hexanes) to give **227** (408 mg, 94%) as an off-white foam.

*R<sub>f</sub>* = 0.3 (EtOAc:hexanes 50:50, UV, PAA). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.20 (m, 3H), 7.02 (d, *J* = 5.9 Hz, 1H), 6.07-6.14 (m, 2H), 6.05 (s, 1H), 5.86 (d, *J* = 1.3 Hz, 1H), 5.84 (d, *J* = 1.3 Hz, 1H), 5.47 (m, 1H), 5.31 (m, 1H), 4.41 (br s, 1H), 4.34 (m, 1H), 4.26 (m, 1H), 3.97 (d, *J* = 12.3, 1H), 3.74(m, 2H), 3.67 (s, 3H), 3.17 (m, 3H), 2.53 (s, 3H), 2.38 (s, 3H), 2.28 (s, 3H), 2.12 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 194.9, 194.8, 167.9, 167.7, 149.0, 147.5, 146.1, 140.8, 139.7, 138.6, 133.8, 132.6, 130.5, 129.5, 128.3, 127.3, 127.1, 127.0, 125.5, 117.4, 116.4, 113.0, 108.8, 103.1, 101.6, 74.9, 72.6, 69.7, 61.1, 61.0, 57.3, 46.7, 41.3, 35.6, 21.0, 16.9, 9.4. HRMS calcd. for C<sub>37</sub>H<sub>38</sub>BrN<sub>2</sub>O<sub>8</sub> (M+H)<sup>+</sup> 717.1812; *m/z* found 717.1805.





**Compound 228:** (7*R*,13*S*,16*R*)-16-((benzyloxy)methyl)-11-bromo-9-methoxy-5-(methoxymethoxy)-4,10,17-trimethyl-14-oxo-12,13,14,16-tetrahydro-7*H*-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinolin-8-yl acetate

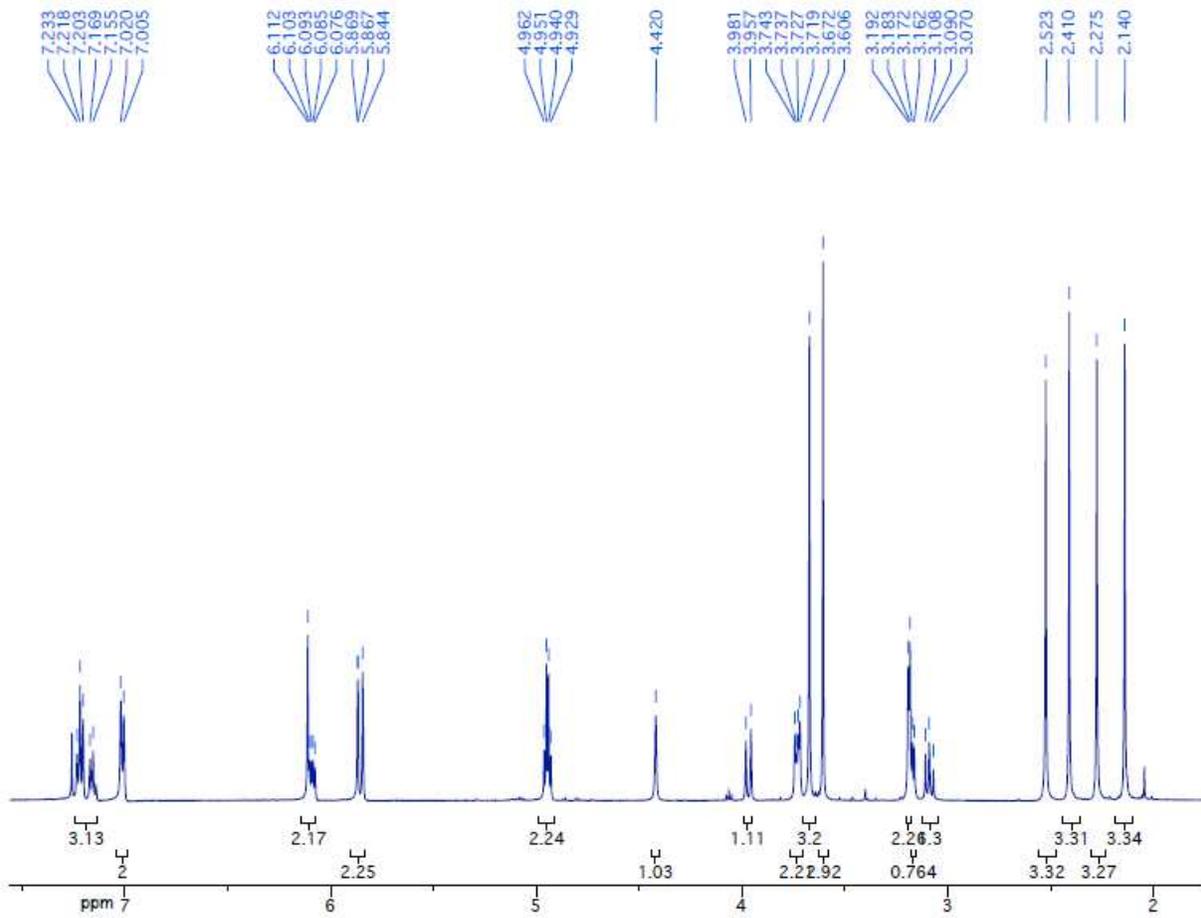


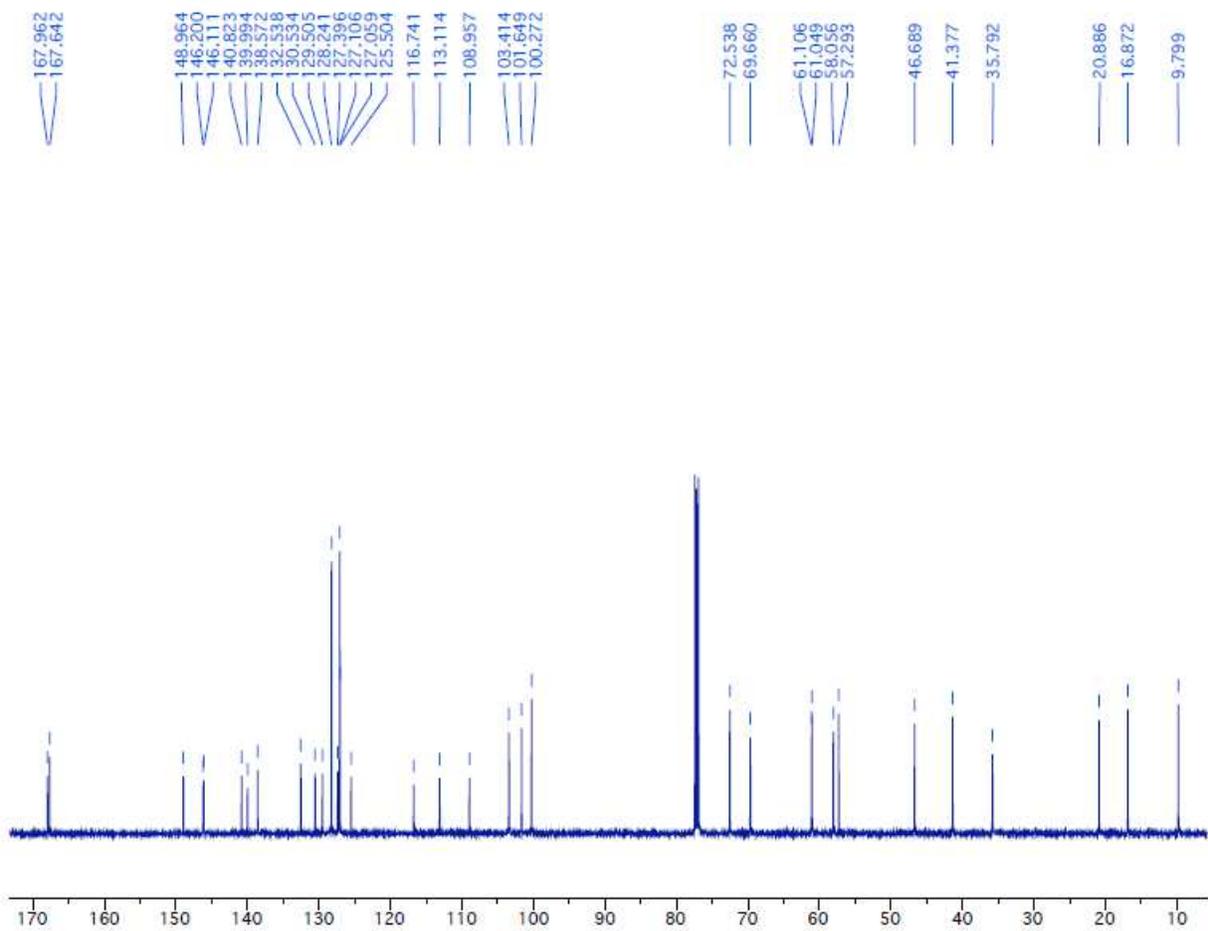
Pd(PPh<sub>3</sub>)<sub>4</sub> (33 mg, 0.029 mmol) was added to a solution of **227** (207 mg, 0.29 mmol) in EtOAc (6 ml), followed by the addition of Bu<sub>3</sub>SnH (0.12 ml, 0.58 mmol) and AcOH (0.05 ml, 0.87 mmol). The reaction was stirred at room temperature for 30 minutes. The reaction was washed with a saturated solution of NaHCO<sub>3</sub>. The layers were separated and the aqueous solution was extracted 3 times with EtOAc. The combined organic layers were dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (20 g of 10% KF/silica gel, 50% EtOAc/hexanes) to give the phenol (188 mg, 96%) as a brown foam.

The phenol (268 mg, 0.40 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, followed by addition of MOMBr (65 μl, 0.79 mmol) and *i*Pr<sub>2</sub>NEt (0.21 ml, 1.19 mmol). The reaction was stirred at room temperature for 1 hour then quenched with a saturated solution of NaHCO<sub>3</sub>. The layers were separated and the aqueous solution was extracted 3 times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (50% EtOAc/hexanes) to give **228** (224 mg, 78%) as an off-white solid.

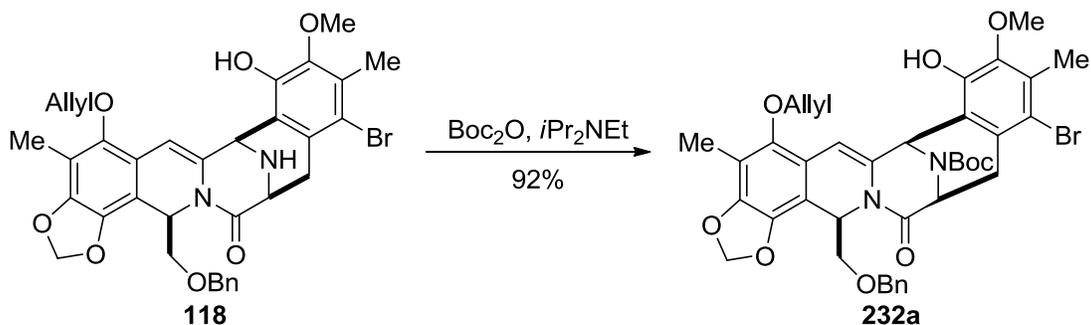
*R*<sub>f</sub> = 0.4 (EtOAc:hexanes 75:25, UV, PAA). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.19 (m, 3H), 7.01 (d, *J* = 7.3 Hz, 2H), 6.09 (m, 3H), 5.87 (d, *J* = 0.9 Hz, 1H), 5.84 (s, 1H), 4.95 (dd, *J* = 34.9, 5.6

Hz, 2H), 4.42 (s, 1H), 3.97 (d, J = 12.3 Hz, 1H), 3.74 (m, 2H), 3.67 (s, 3H), 3.61 (s, 3H), 3.19 (d, J = 4.4 Hz, 2H), 3.17 (d, J = 4.7 Hz, 1H), 3.09 (t, J = 9.1 Hz, 1H), 2.52, (s, 3H), 2.41 (s, 3H), 2.28 (s, 3H), 2.14 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 168.0, 167.6, 149.0, 146.2, 146.1, 140.8, 140.0, 138.6, 132.5, 130.5, 129.5, 128.2, 127.4, 127.1, 127.0, 125.5, 116.7, 113.1, 109.0, 103.4, 101.6, 100.3, 72.5, 69.7, 61.1, 61.0, 58.1, 57.3, 46.7, 41.4, 35.8, 20.9, 16.9, 9.8. HRMS calcd. for C<sub>36</sub>H<sub>38</sub>BrN<sub>2</sub>O<sub>9</sub> (M+H)<sup>+</sup> 721.1761; m/z found 721.1766.



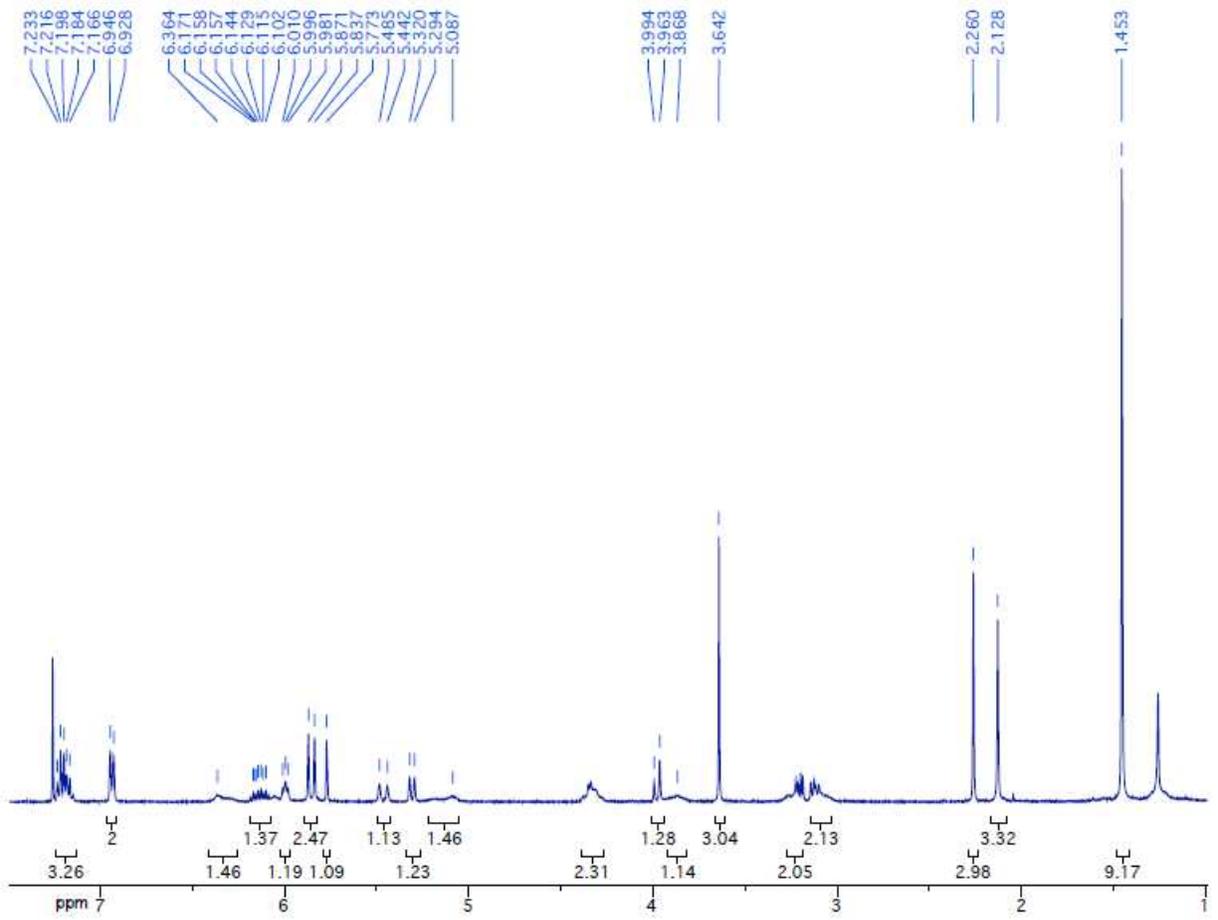


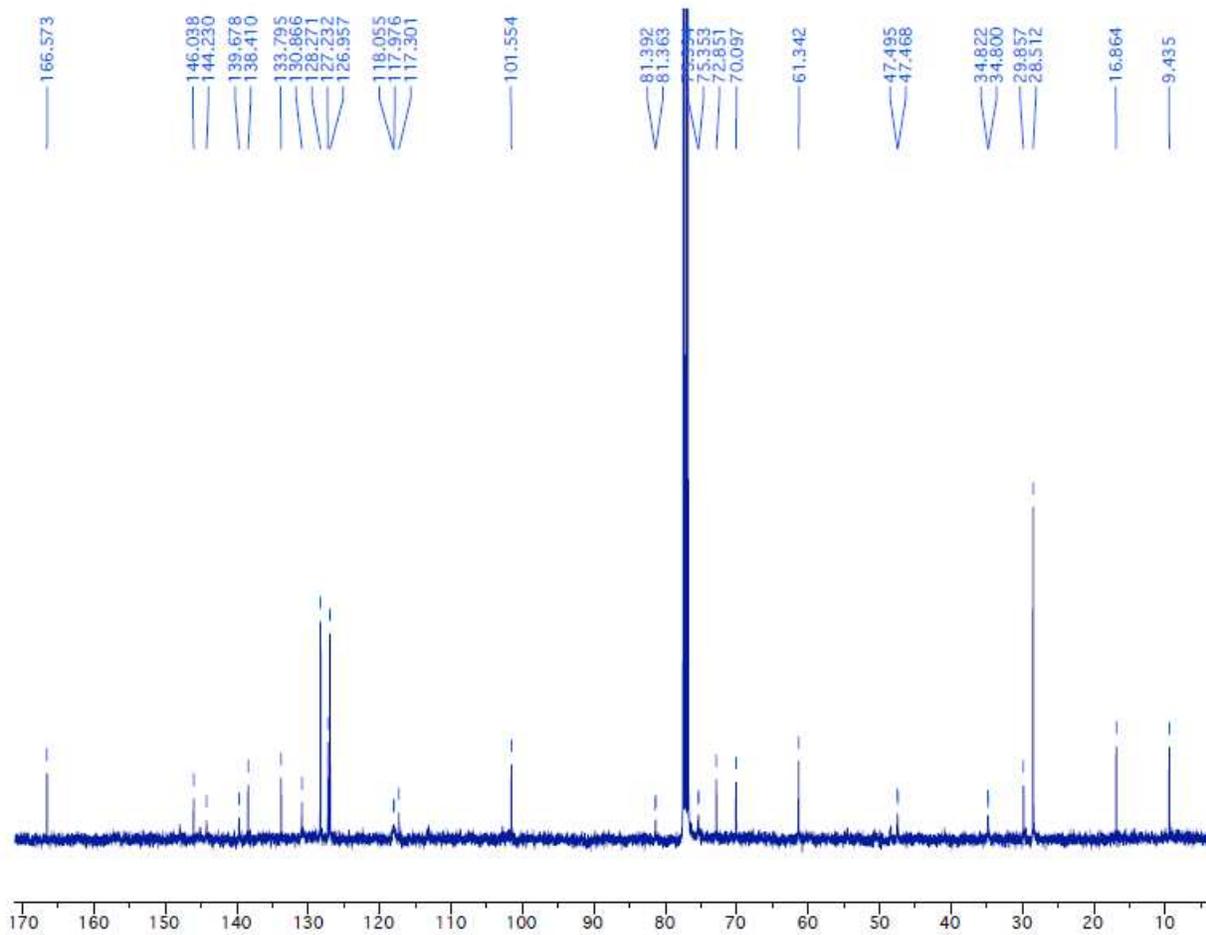
**Compound 232a:** (7*R*,13*S*,16*R*)-*tert*-butyl 5-(allyloxy)-16-((benzyloxy)methyl)-11-bromo-8-hydroxy-9-methoxy-4,10-dimethyl-14-oxo-12,13,14,16-tetrahydro-7*H*-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinoline-17-carboxylate



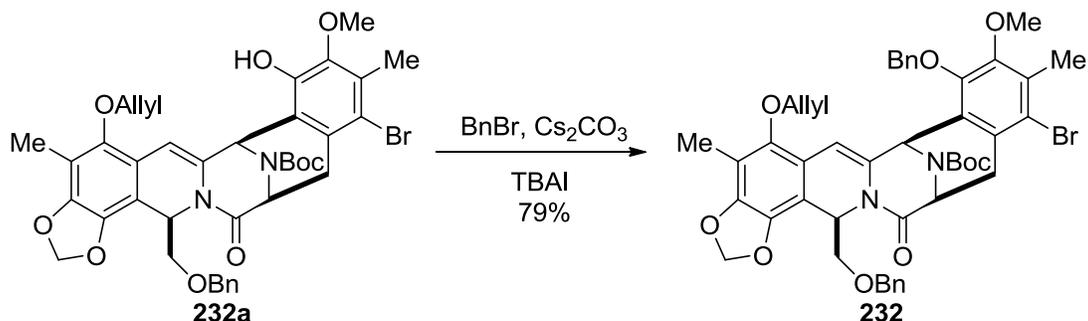
Boc<sub>2</sub>O (39 mg, 0.18 mmol) and *i*Pr<sub>2</sub>NEt (0.09 ml, 0.52 mmol) was added to a solution of **118** (106 mg, 0.16 mmol) in THF (3 ml). The reaction was stirred at room temperature for 19 hours then concentrated. The residue was purified by column chromatography (25% EtOAc/hexanes) to give **232a** (120 mg, 92%) as an off-white solid.

$R_f$  = 0.3 (EtOAc:hexanes 25:75, UV, PAA). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers) δ 7.19 (m, 3H), 7.94 (d, *J* = 7.1 Hz, 2H), 6.33 (br s, 1.5H), 6.14 (m, 1H), 6.00 (t, *J* = 5.8 Hz, 1H), 5.85 (d, *J* = 13.6 Hz, 2H), 5.77 (s, 1H), 5.46 (d, *J* = 17.3 Hz, 1H), 5.31 (d, *J* = 10.5 Hz, 1H), 5.14 (br s, 1.5H), 4.26-4.40 (m, 2H), 3.98 (d, *J* = 12.2 Hz, 1H), 3.87 (br s, 1H), 3.64 (s, 3H), 3.23 (m, 2H), 3.11 (m, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.45 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers) δ 166.6, 146.0, 144.2, 139.7, 138.4, 133.8, 130.9, 128.3, 127.2, 127.0, 118.1, 118.0, 117.3, 101.6, 81.4, 75.4, 72.9, 70.1, 61.3, 47.5, 34.8, 29.9, 28.5, 16.9, 9.4. HRMS calcd. for C<sub>39</sub>H<sub>42</sub>BrN<sub>2</sub>O<sub>9</sub> (M+H)<sup>+</sup> 761. 2074; *m/z* found 761.209.



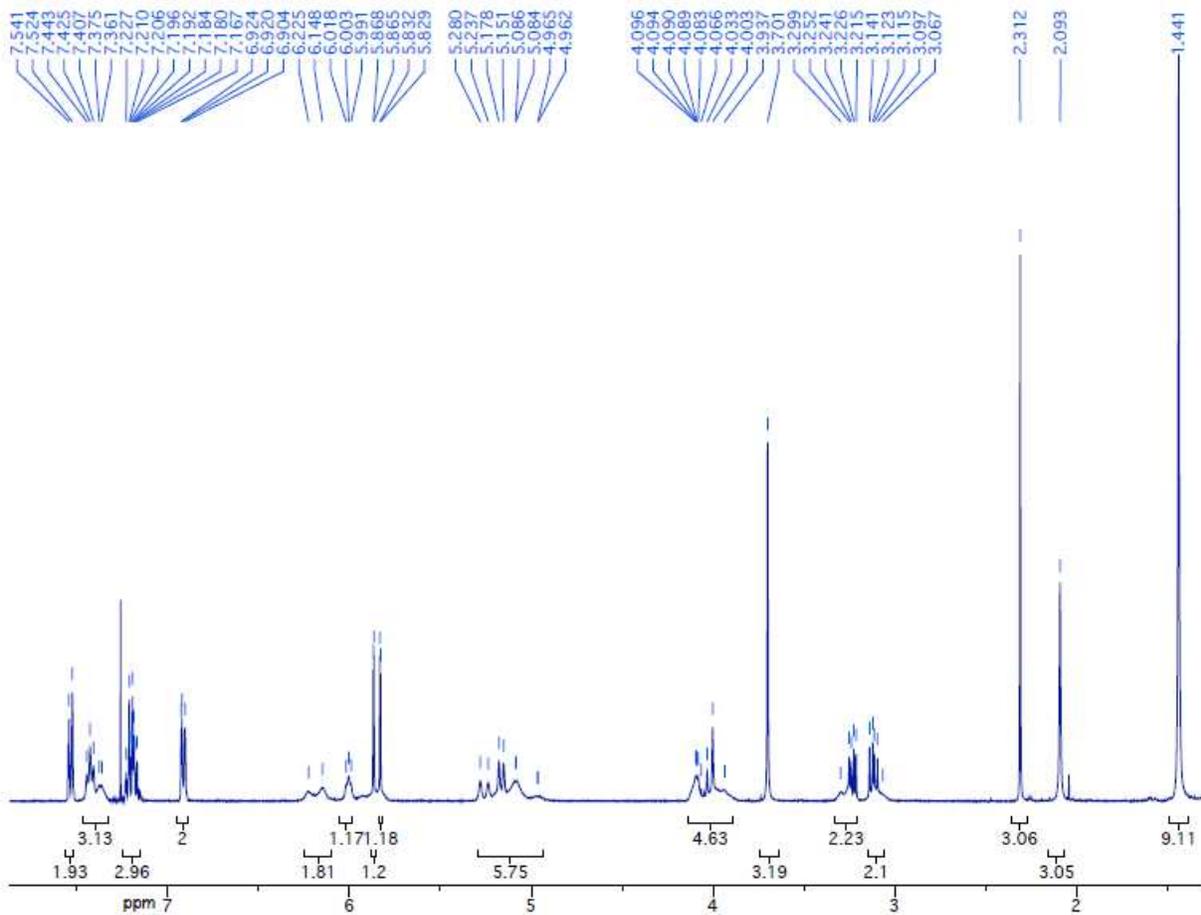


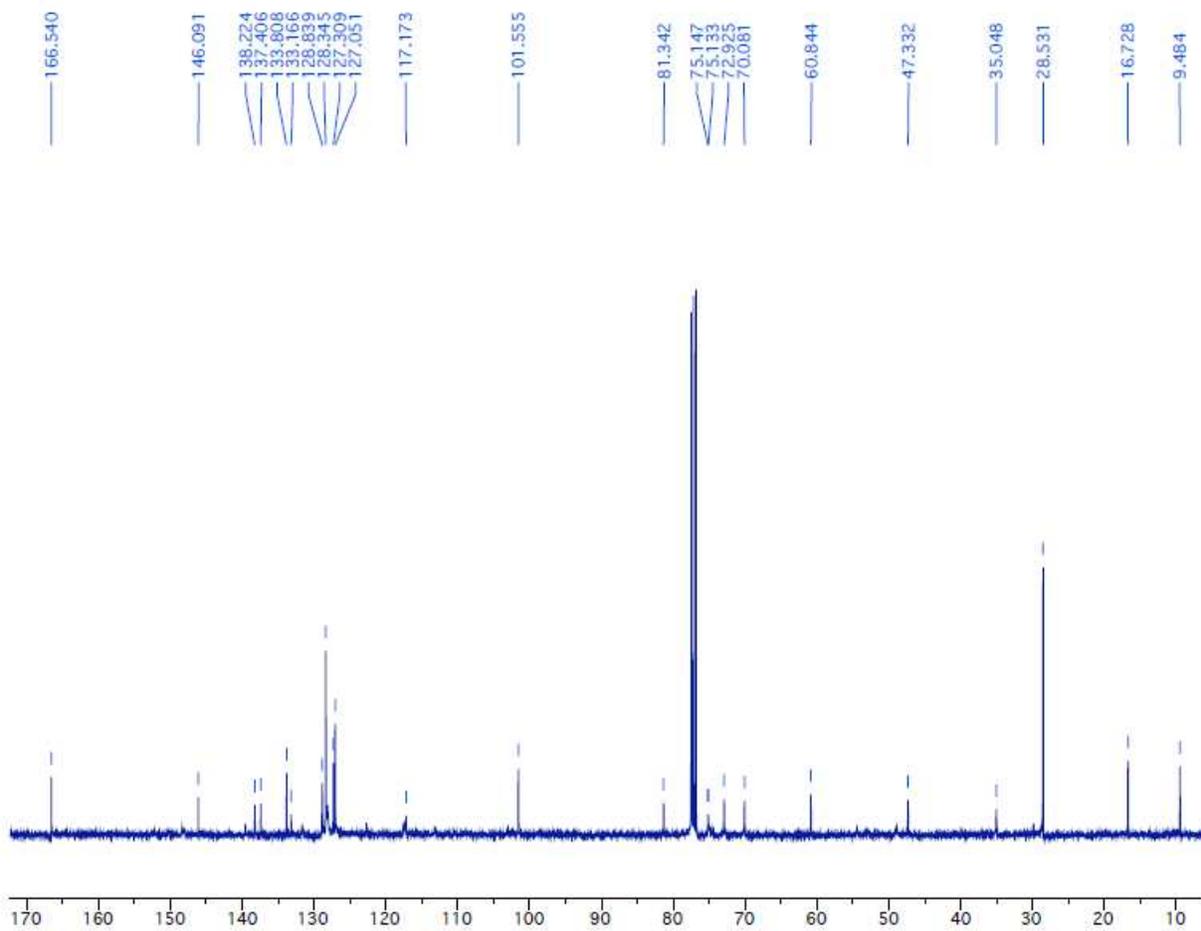
**Compound 232:** (7R,13S,16R)-tert-butyl 5-(allyloxy)-8-(benzyloxy)-16-((benzyloxy)methyl)-11-bromo-9-methoxy-4,10-dimethyl-14-oxo-12,13,14,16-tetrahydro-7H-7,13-epiminobenzo[4,5]azocino[1,2-b][1,3]dioxolo[4,5-h]isoquinoline-17-carboxylate



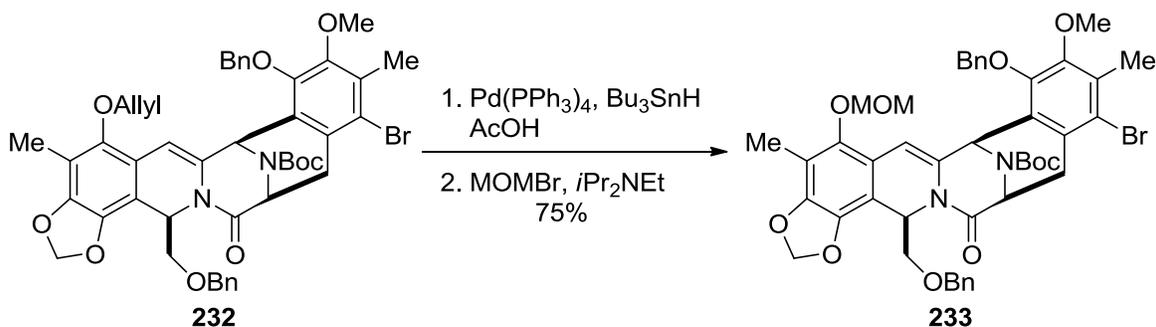
$\text{Cs}_2\text{CO}_3$  (22.5 mg, 0.68 mmol) was added to a solution of **232a** (120 mg, 0.16 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) and MeOH (1 ml), followed by the addition of TBAI (6.4 mg, 0.017 mmol) and BnBr (0.06 ml, 0.52 mmol). The reaction was stirred at room temperature for 24 hours then concentrated. The residue was purified by column chromatography (15% EtOAc/hexanes) to give **232** (107 mg, 79%).

$R_f = 0.4$  (EtOAc:hexanes 25:75, UV, PAA).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , mixture of carbamate rotamers)  $\delta$  7.53 (d,  $J = 6.9$  Hz, 2H), 7.40 (m, 3H), 7.20 (m, 3H), 6.91 (d,  $J = 6.5$  Hz, 2H), 6.19 (d,  $J = 30.7$  Hz, 2H), 6.00 (t,  $J = 5.0$  Hz, 1H), 5.87 (d,  $J = 1.3$  Hz, 1H), 5.83 (d,  $J = 1.3$  Hz, 1H), 4.96-5.28 (m, 6H), 3.90-4.14 (m, 5H), 3.70 (s, 3H), 3.05-3.32 (m, 4H), 2.31 (s, 3H), 2.09 (s, 3H), 1.44 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , mixture of carbamate rotamers)  $\delta$  166.5, 146.1, 138.2, 137.4, 133.8, 133.2, 128.8, 128.3, 127.3, 127.1, 117.2, 101.6, 81.3, 75.1, 72.9, 70.1, 60.8, 47.3, 35.0, 28.5, 16.7, 9.5. HRMS calcd. for  $\text{C}_{46}\text{H}_{48}\text{BrN}_2\text{O}_9$  ( $\text{M}+\text{H}$ ) $^+$  851.2543;  $m/z$  found 851.2540.





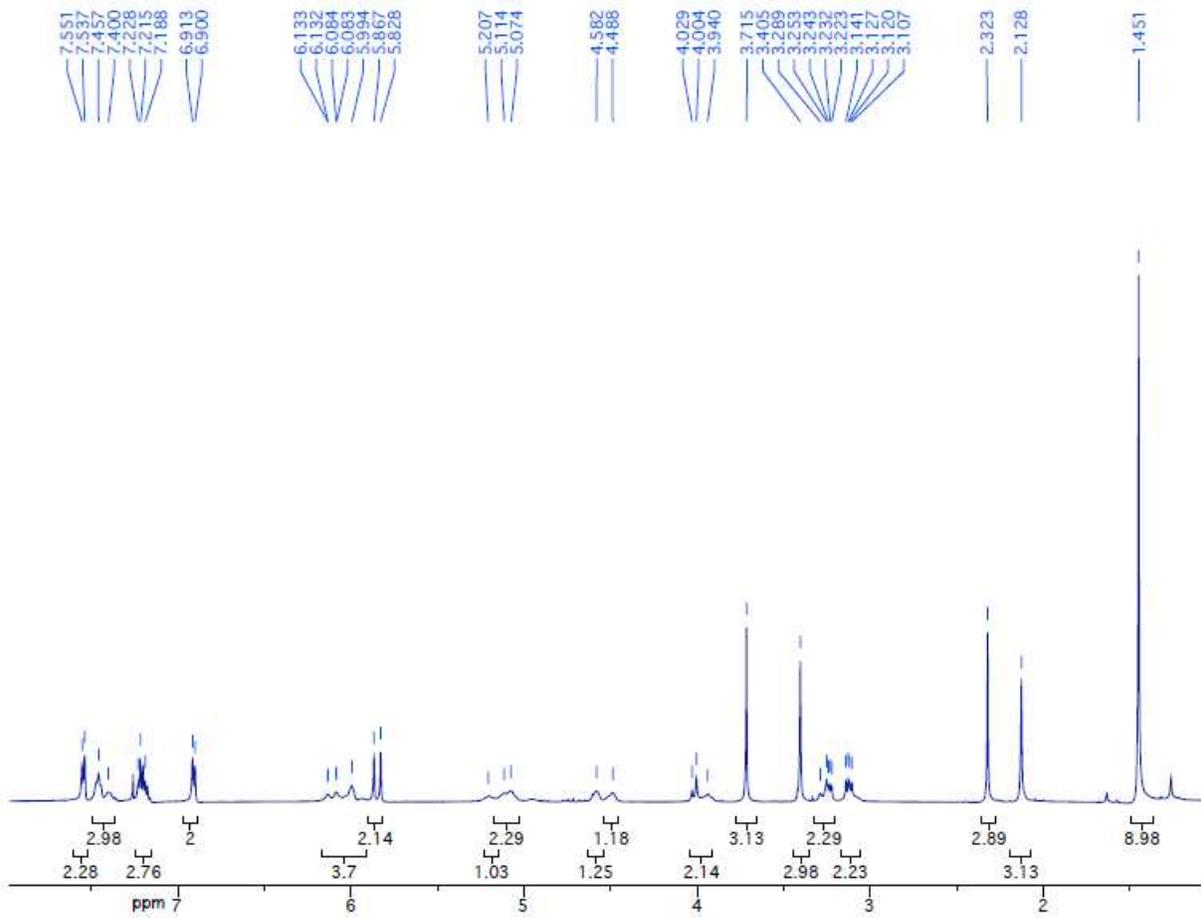
**Compound 233:** (7*R*,13*S*,16*R*)-tert-butyl 8-(benzyloxy)-16-((benzyloxy)methyl)-11-bromo-9-methoxy-5-(methoxymethoxy)-4,10-dimethyl-14-oxo-12,13,14,16-tetrahydro-7*H*-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinoline-17-carboxylate

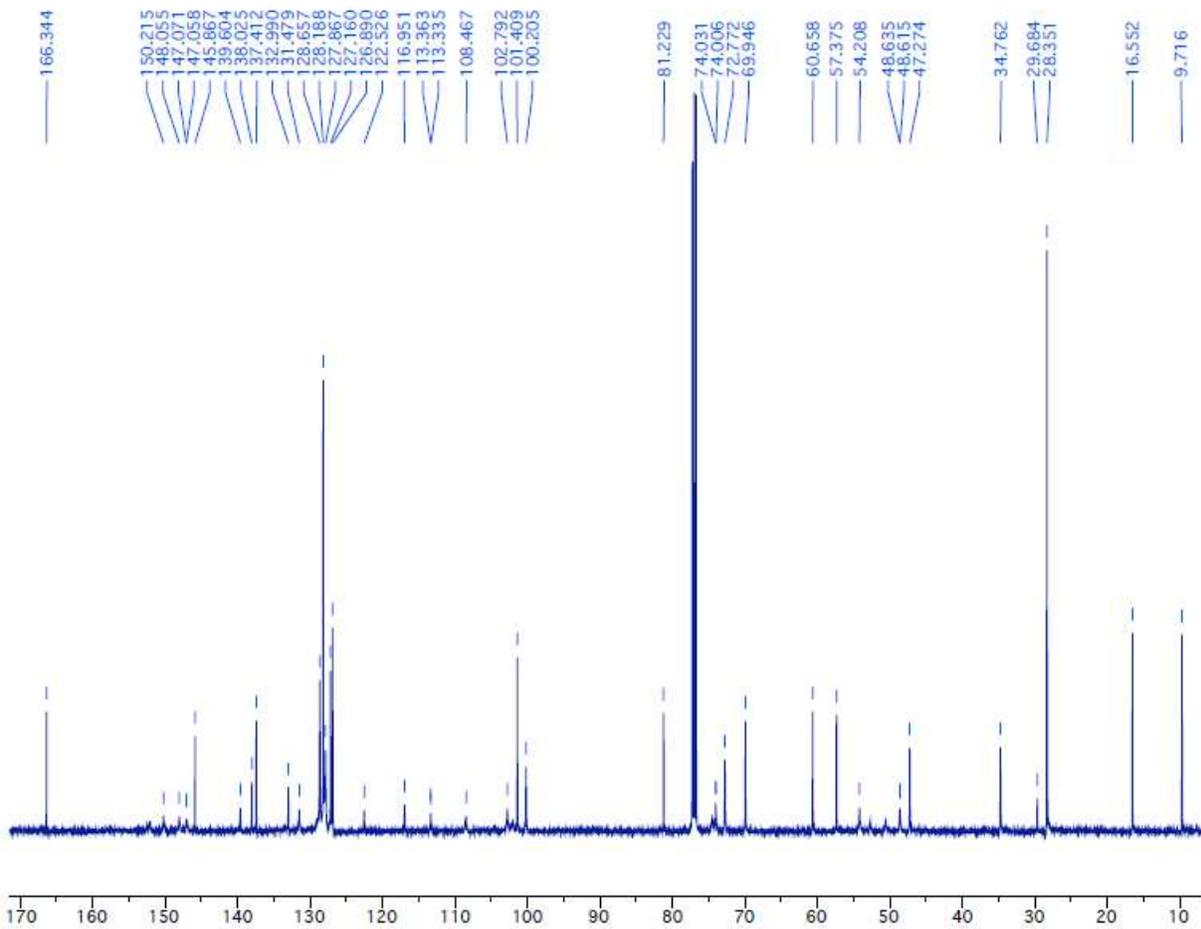


Pd(PPh<sub>3</sub>)<sub>4</sub> (14.5 mg, 0.013 mmol) was added to a solution of **232** (107 mg, 0.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 ml), followed by the addition of Bu<sub>3</sub>SnH (68 μl, 0.25 mmol) and AcOH (18 μl, 0.31 mmol). The reaction was stirred at room temperature for 1.5 hours then concentrated. The residue was dissolved in Et<sub>2</sub>O and washed with 5% aqueous solution of NH<sub>4</sub>OH. The layers were separated and the aqueous solution was extracted 3 times with Et<sub>2</sub>O. The combined organic layers were dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (10 g of 10% KF/silica gel, 50% EtOAc/hexanes) to give the phenol as a yellow solid.

The resulting phenol was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 ml), followed by addition of MOMBr (30 μl, 0.038 mmol) and *i*Pr<sub>2</sub>NEt (65 μl, 0.37 mmol). The reaction was stirred at room temperature for 1 hour then quenched with a saturated solution of NaHCO<sub>3</sub>. The layers were separated and the aqueous solution was extracted 3 times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (50% EtOAc/hexanes) to give **233** (92.4 mg, 86%) as a purplish solid.

$R_f = 0.3$  (EtOAc:hexanes 1:5, UV, PAA).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , mixture of carbamate rotamers)  $\delta$  7.54 (d,  $J = 7.2$  Hz, 1H), 7.43 (m, 3H), 7.21 (m, 3H), 6.91 (d,  $J = 6.9$  Hz, 1H), 5.91-6.16 (m, 4H), 5.85 (d,  $J = 19.3$  Hz, 1H), 5.03-5.23 (m, 3H), 4.58 (s, 1H), 4.49 (s, 1H), 3.90-4.04 (m, 3H), 3.72 (s, 3H), 3.41 (s, 3H), 3.25 (m, 2H), 3.12 (m, 2H), 2.32 (s, 3H), 2.13 (s, 3H), 1.45 (s, 9H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , mixture of carbamate rotamers)  $\delta$  166.3, 150.2, 148.1, 147.1, 145.9, 139.6, 138.0, 137.4, 133.0, 131.5, 128.7, 128.2, 127.9, 127.2, 126.9, 122.5, 117.0, 113.4, 108.5, 102.8, 101.4, 100.2, 81.2, 74.0, 72.8, 69.9, 60.7, 57.4, 54.2, 48.6, 47.3, 34.8, 29.7, 28.4, 16.6, 9.7. HRMS calcd. for  $\text{C}_{45}\text{H}_{48}\text{BrN}_2\text{O}_{10}$  ( $\text{M}+\text{H}$ ) $^+$  855.2492;  $m/z$  found 855.2478.



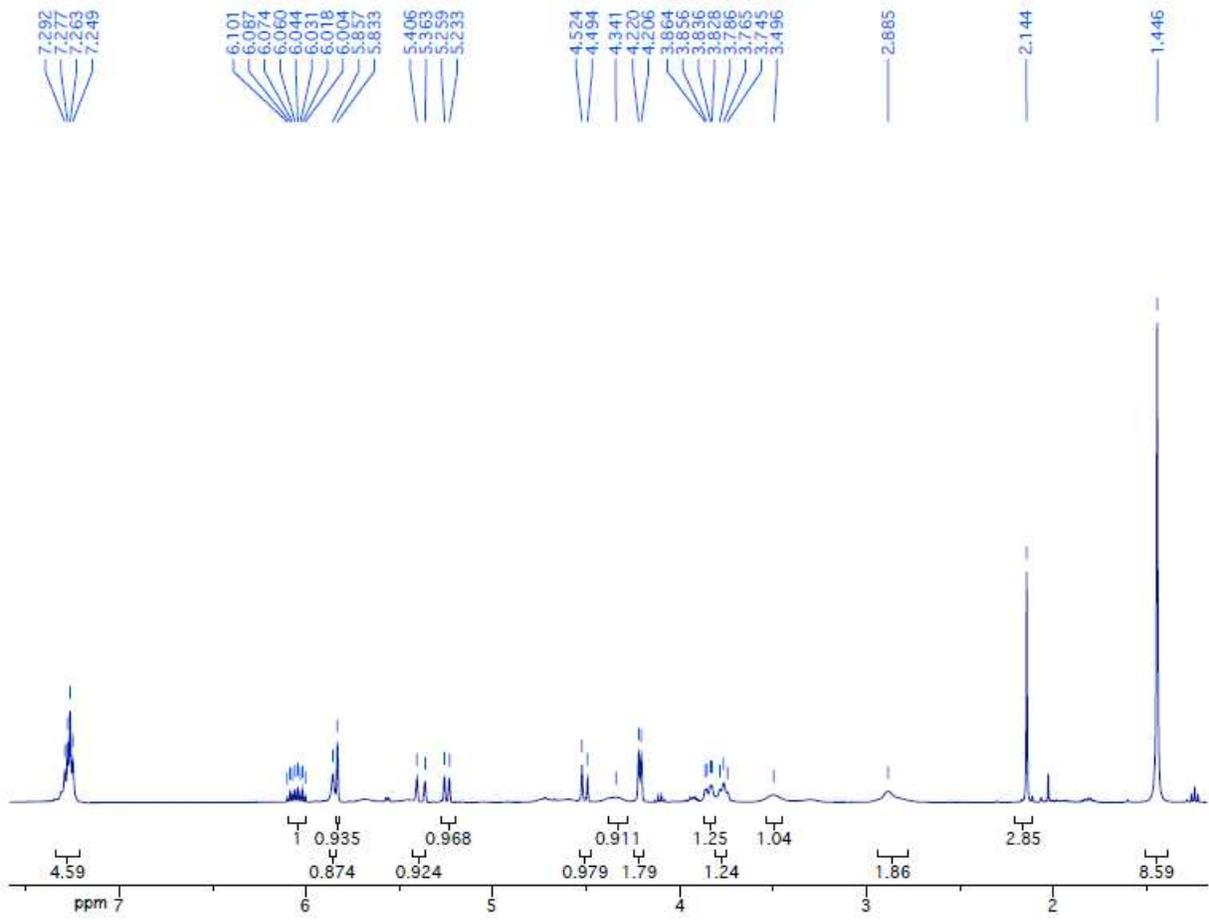


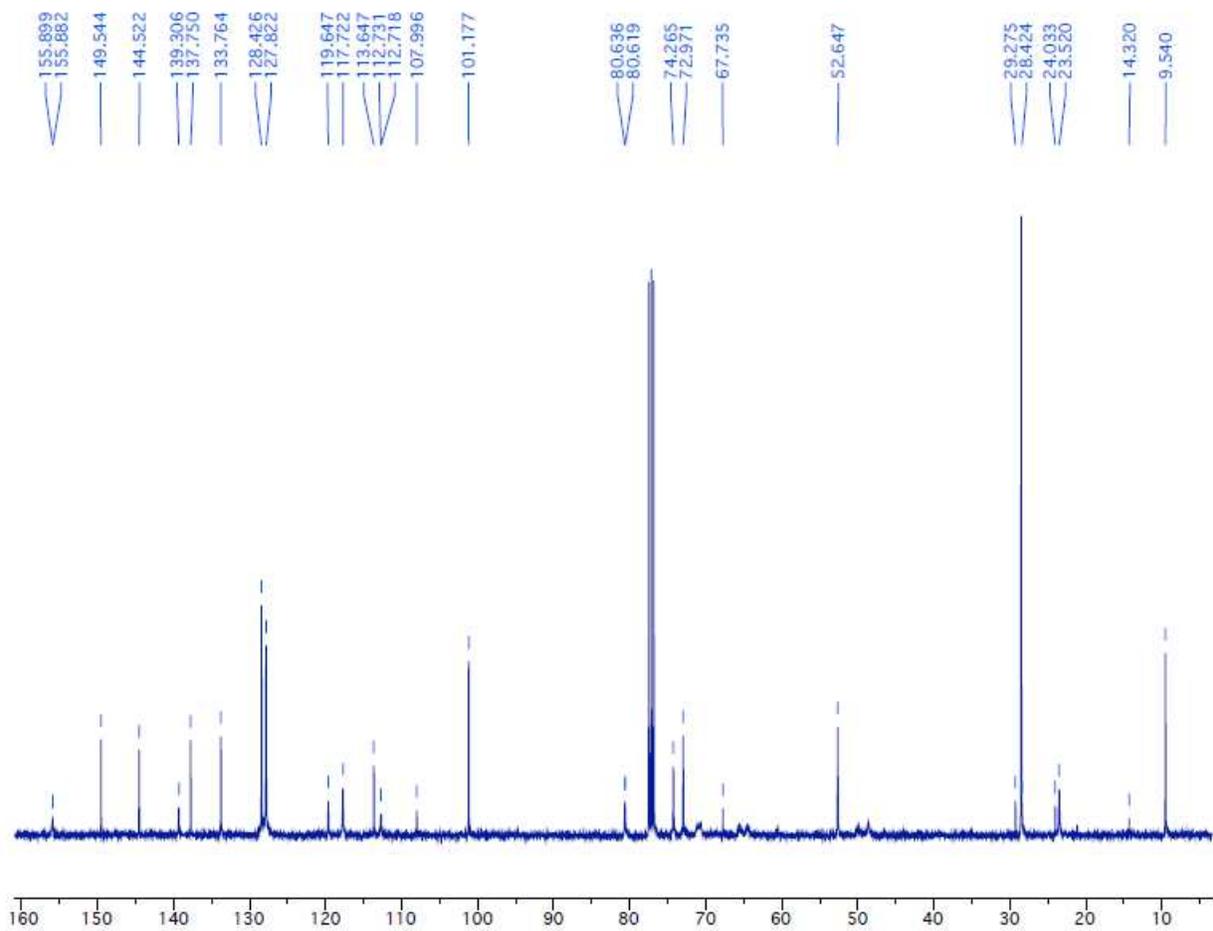


dried with MgSO<sub>4</sub> and concentrated to give a crude product as a bright yellow solid. The crude product was used in the next step without purification.

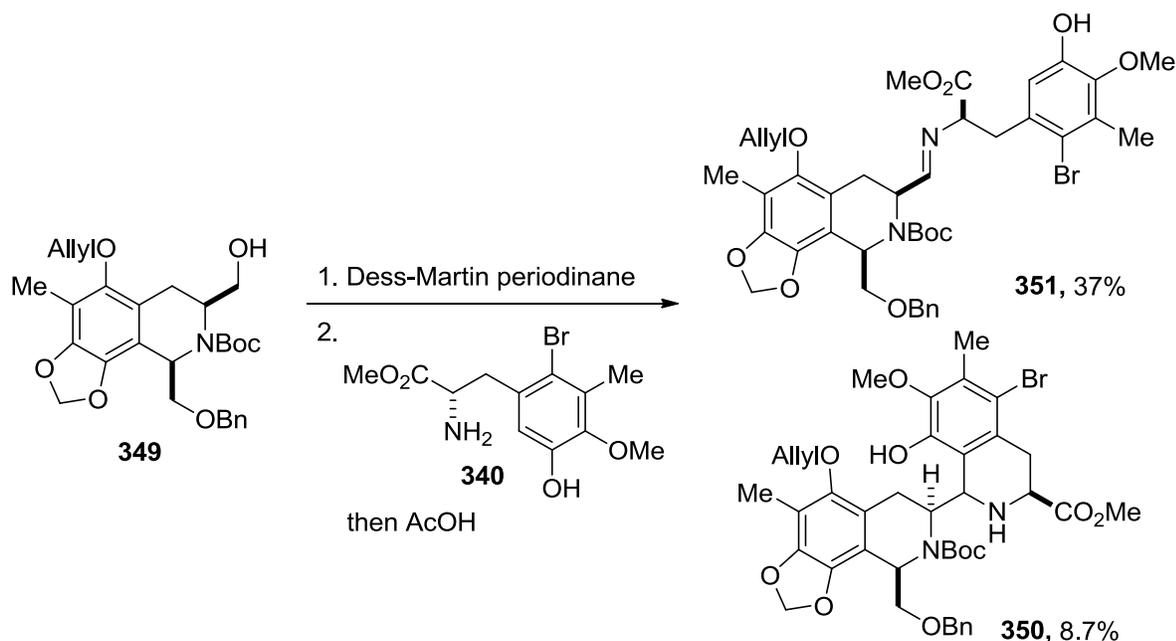
The crude alcohol was dissolved in THF (4 ml), followed by the addition of Boc<sub>2</sub>O and iPr<sub>2</sub>NEt. The reaction was stirred at room temperature for 18 hours then concentrated. The residue was purified by column chromatography (25% EtOAc/Hexanes) to give **348** (135 mg, 66%) as clear oil.

$R_f = 0.2$  (EtOAc:hexanes 25:75, UV, PAA). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  7.28 (m, 5H), 6.05 (ddd,  $J = 17.0, 11.0, 5.6$  Hz, 1H), 5.86 (s, 1H), 5.83 (s, 1H), 5.38 (d,  $J = 17.1$  Hz, 1H), 5.25 (d,  $J = 10.4$  Hz, 1H), 4.51 (d,  $J = 11.8$  Hz, 1H), 4.34 (br s, 1H), 4.21 (d,  $J = 5.5$  Hz, 2H), 3.85 (dd,  $J = 11.4, 3.3$  Hz, 1H), 3.77 (t,  $J = 8.4$  Hz, 1H), 3.50 (br s, 1H), 2.89 (br s, 2H), 2.14 (s, 3H), 1.45 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  155.9, 149.5, 144.5, 139.3, 137.8, 133.8, 128.4, 127.8, 119.6, 117.7, 113.6, 112.7, 108.0, 101.2, 80.6, 74.3, 73.0, 67.7, 52.6, 29.3, 28.4, 24.0, 23.5, 14.3, 9.5. HRMS calcd. for C<sub>45</sub>H<sub>48</sub>BrN<sub>2</sub>O<sub>10</sub> (M+H)<sup>+</sup> 855.2492; m/z found 855.2478.





**Compound 350:** (7S,9R)-tert-butyl 5-(allyloxy)-9-((benzyloxy)methyl)-7-((3S)-5-bromo-8-hydroxy-7-methoxy-3-(methoxycarbonyl)-6-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-4-methyl-6,7-dihydro-[1,3]dioxolo[4,5-h]isoquinoline-8(9H)-carboxylate, and **compound 351:** (7S,9R)-tert-butyl 5-(allyloxy)-9-((benzyloxy)methyl)-7-((E)-(((R)-3-(2-bromo-5-hydroxy-4-methoxy-3-methylphenyl)-1-methoxy-1-oxopropan-2-yl)imino)methyl)-4-methyl-6,7-dihydro-[1,3]dioxolo[4,5-h]isoquinoline-8(9H)-carboxylate

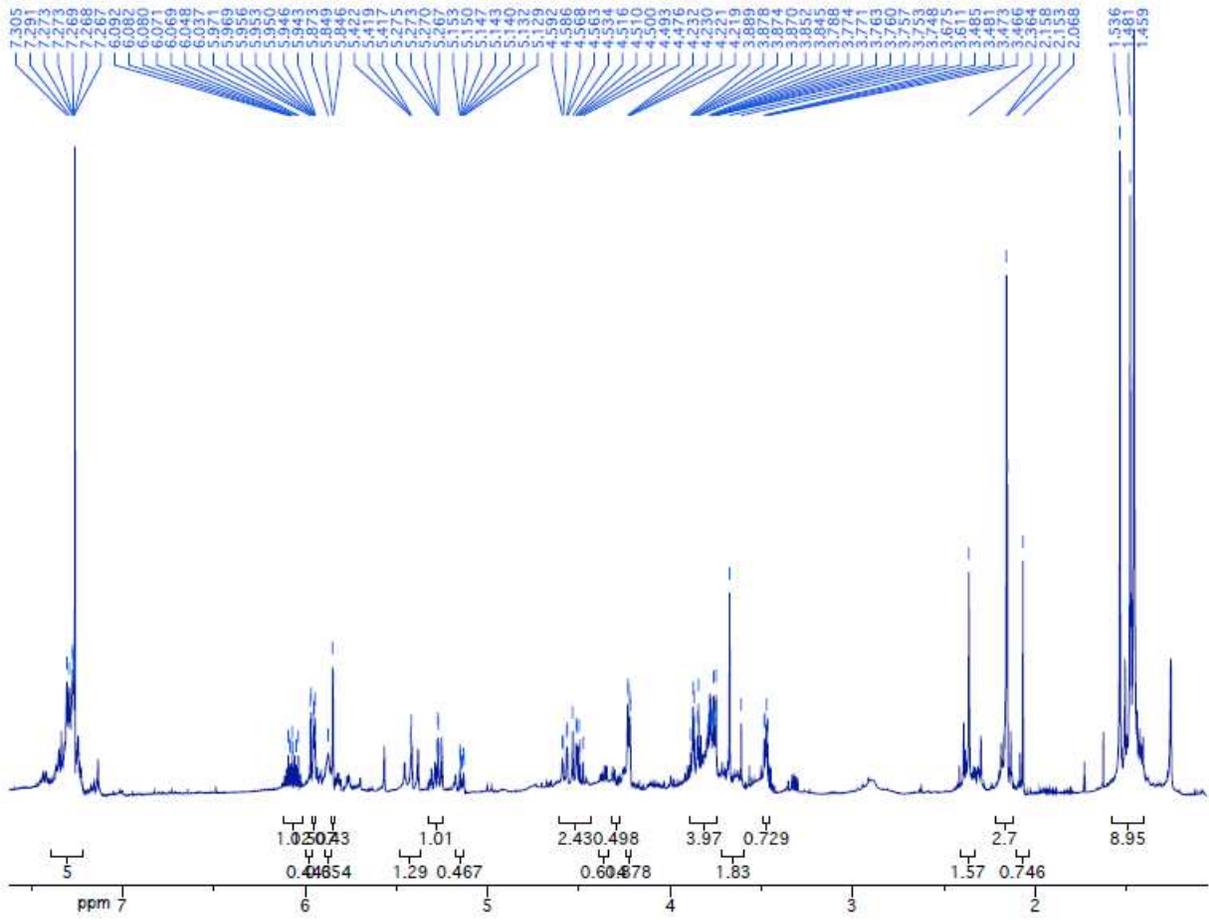


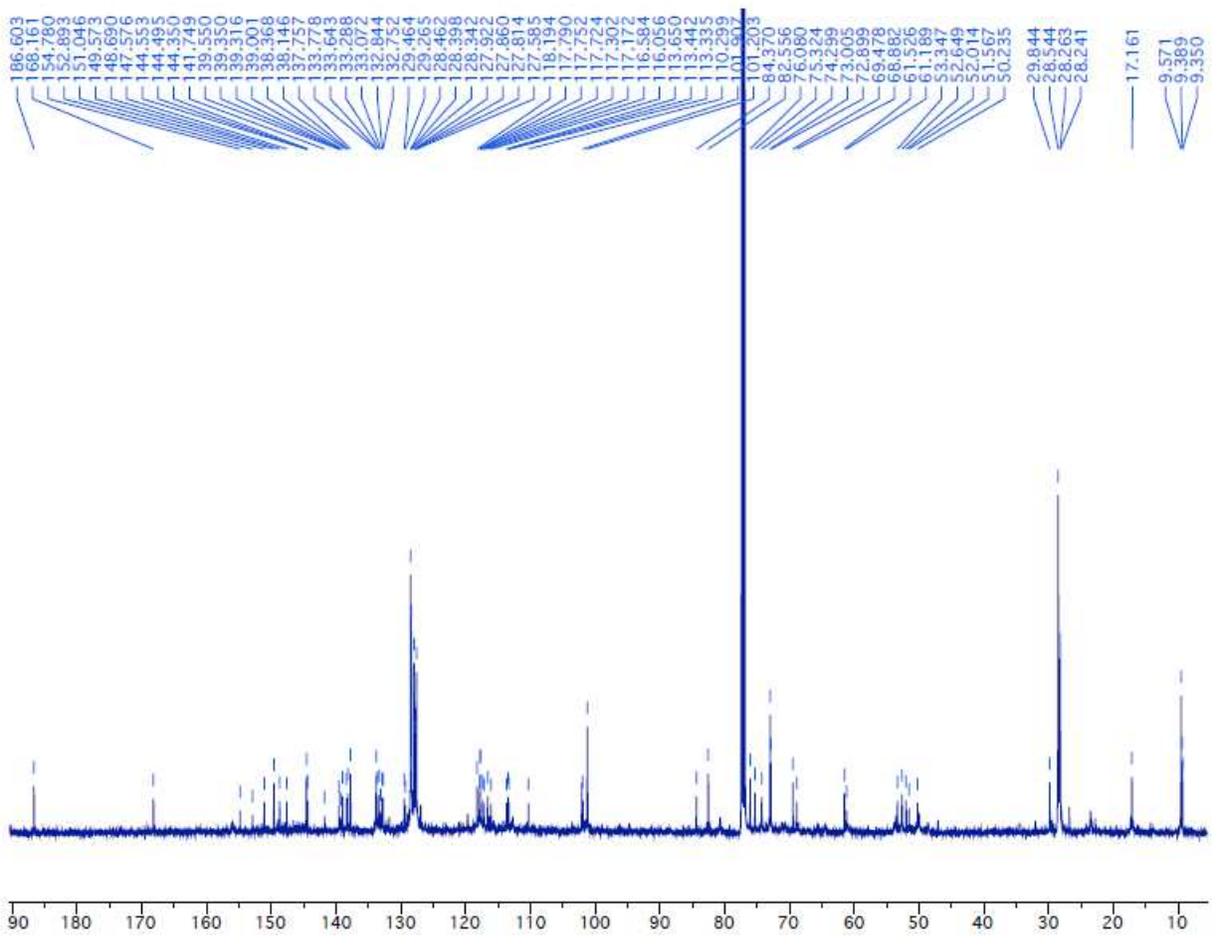
Dess-Martin periodinane (167 mg, 0.39 mmol) was added to a solution of alcohol **348** (98 mg, 0.20 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 ml). The reaction was stirred at room temperature for 2 hours then concentrated. The residue was partitioned between  $\text{Et}_2\text{O}$  and a saturated aqueous solution of  $\text{NaHCO}_3$ . The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 times). The combined organic layers were dried with  $\text{MgSO}_4$  and concentrated to give an aldehyde as an off-white solid. The crude product was used without purification.

The crude aldehyde was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 ml), followed by addition of 4Å molecular sieves and **340** (88 mg, 0.28 mmol). The reaction was stirred at room temperature for 7 hours

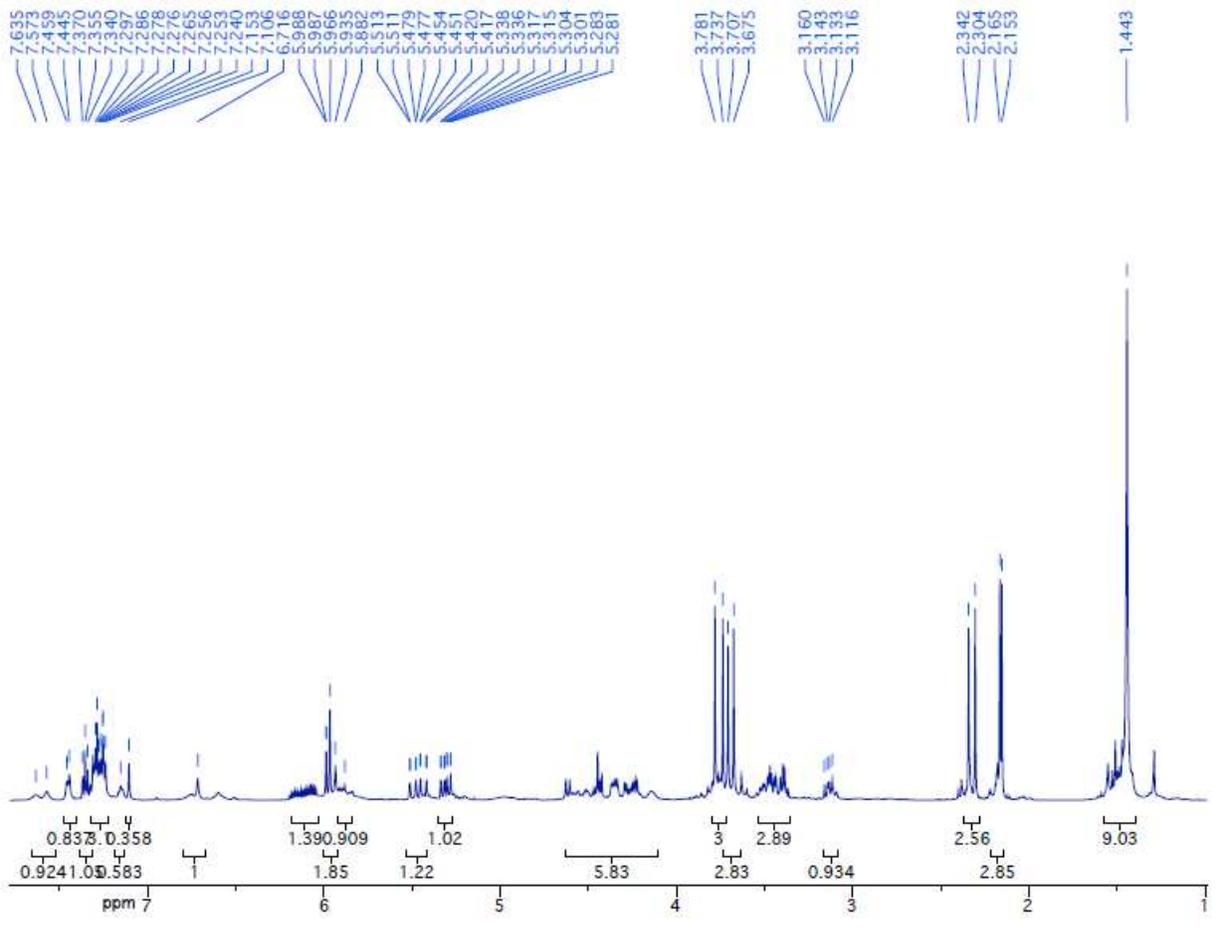
then AcOH (0.02 ml) was added. The reaction was stirred at room temperature for 20 hours then filtered through a pad of silica gel, washed with a saturated aqueous solution of NaHCO<sub>3</sub>, dried with MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (25% EtOAc/Hexanes) to give imine **351** (57 mg, 36%) as a brown solid and **350** (14 mg, 8.7%) as an off-white solid.

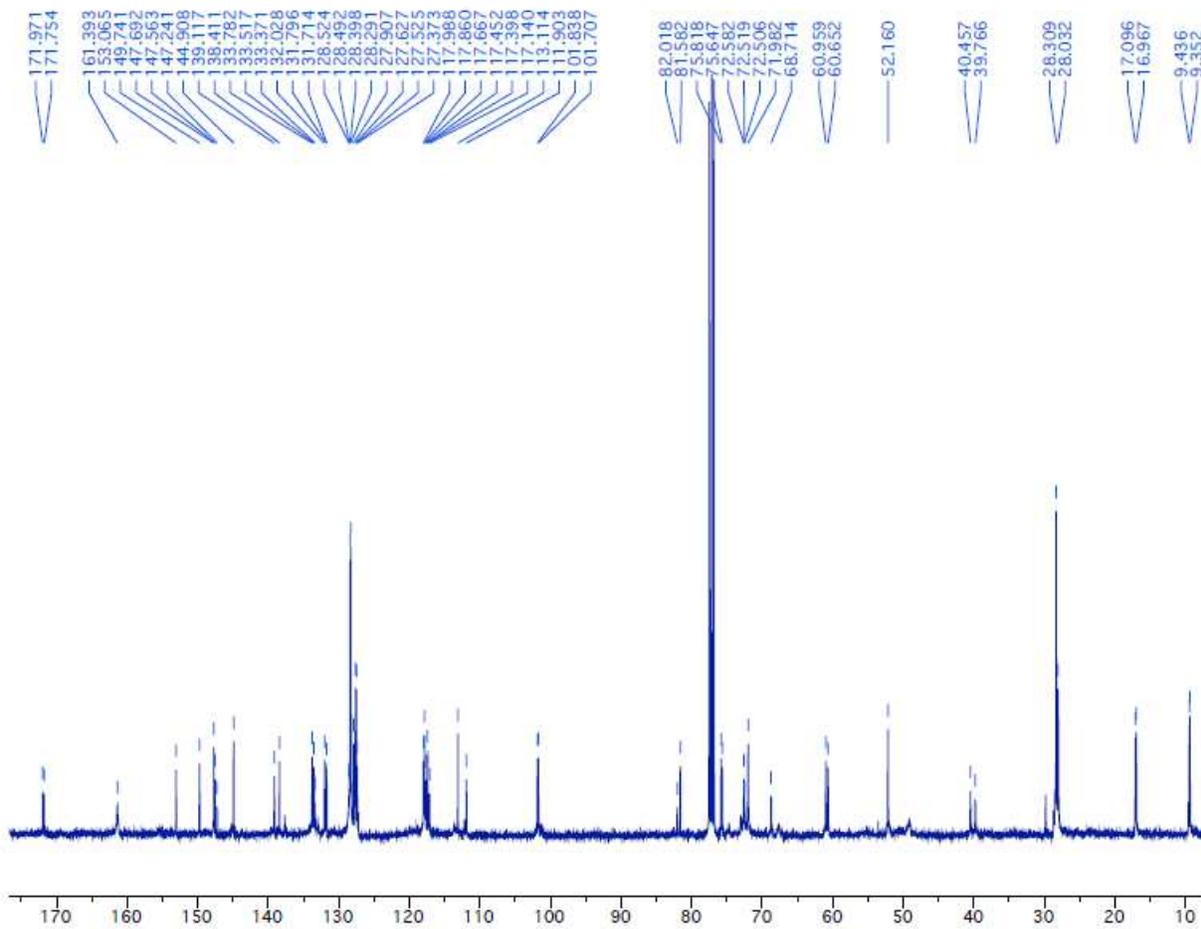
Compound **350**:  $R_f = 0.16$  (EtOAc:hexanes 25:75, UV, PAA). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  7.27 (m, 5H), 6.07 (m, 1H), 5.97 (d,  $J = 1.4$  Hz, 0.5H), 5.95 (m, 0.5H), 5.87 (br s, 0.5H), 5.85 (d,  $J = 1.4$  Hz, 0.5H), 5.42 (m, 1H), 5.27 (m, 1H), 5.14 (m, 0.5H), 4.47-4.59 (m, 2.5H), 4.27-4.39 (m, 1H), 4.23 (dd,  $J = 5.6, 1.1$  Hz, 1H), 3.74-3.89 (m, 4H), 3.68 and 3.61 (s, 2H), 3.48 (m, 1H), 2.36 (s, 2H), 2.16 and 2.15 (s, 3H), 2.07 (s, 1H), 1.54, 1.48 and 1.49 (9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, mixture of carbamate rotamers)  $\delta$  186.6, 168.2, 154.8, 152.9, 151.0, 149.6, 148.7, 147.6, 144.6, 144.4, 141.7, 139.6, 139.3, 139.0, 138.4, 138.1, 137.8, 133.8, 133.6, 133.3, 132.8, 129.5, 129.3, 128.5, 128.4, 128.3, 127.9, 127.8, 127.6, 118.2, 117.8, 117.7, 117.3, 117.2, 116.6, 116.1, 113.7, 113.4, 113.3, 110.3, 101.9, 101.2, 84.4, 82.6, 76.1, 75.3, 74.3, 73.0, 72.9, 69.5, 68.9, 61.5, 61.2, 53.3, 52.6, 52.0, 51.6, 50.2, 29.8, 28.5, 28.3, 17.2, 9.6, 9.4.





**Compound 351:**  $R_f = 0.1$  (EtOAc:hexanes 25:75, UV, PAA).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , mixture of carbamate rotamers)  $\delta$  7.64 and 7.57 (br s, 1H), 7.45 (d,  $J = 7.2$  Hz, 1H), 7.36 (t,  $J = 7.2$  Hz, 1H), 7.27 (m, 3H), 7.15 (m, 0.5H), 7.11 (s, 0.5H), 6.72 (s, 1H), 6.11 (m, 1H), 5.99, 5.97 and 5.94 (s, 2H), 5.88 (m, 1H), 5.47 (ddd,  $J = 28.4, 17.0, 1.2$  Hz, 1H), 5.31 (ddd,  $J = 16.0, 10.5, 0.8$  Hz, 1H), 4.11-4.64 (m, 6H), 3.78 and 3.74 (s, 3H), 3.71 and 3.68 (s, 3H), 3.36-3.55 (m, 3H), 3.14 (dd,  $J = 13.5, 8.7$  Hz, 1H), 2.34 and 2.30 (s, 3H), 2.17 and 2.15 (s, 3H), 1.44 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , mixture of carbamate rotamers)  $\delta$  172.0, 171.8, 161.4, 153.1, 149.7, 147.7, 147.6, 147.2, 144.9, 139.1, 138.4, 133.8, 133.5, 133.4, 132.0, 131.8, 131.7, 128.5, 128.5, 128.4, 128.3, 127.9, 127.6, 127.5, 127.4, 118.0, 117.9, 117.7, 117.5, 117.4, 117.1, 113.1, 111.9, 101.8, 101.7, 82.0, 81.6, 75.8, 75.6, 72.6, 72.5, 72.0, 68.7, 61.0, 60.6, 52.2, 40.5, 39.8, 28.3, 28.0, 17.1, 17.0, 9.4, 9.4. HRMS calcd. for  $\text{C}_{40}\text{H}_{48}\text{BrN}_2\text{O}_{10}$  ( $\text{M}+\text{H}$ ) $^+$  795.2492;  $m/z$  found 795.2471.





## List of abbreviations

2,6-lutidine	2,6-dimethylpyridine
Ac	Acetyl
AcOH	Acetic acid
AIBN	2,2'-azobisisobutyronitrile
Alloc	trichloroethyl carbonyl
aq.	aqueous
BHT	2,6- <i>di-tert</i> -butyl- <i>para</i> -cresol
Bn	Benzyl
Boc	<i>tert</i> -Butyl carbonyl
Boc <sub>2</sub> O	Di- <i>tert</i> -butyl dicarbonate
Bu	Butyl
BuLi	Butyllithium
<i>t</i> -BuLi	<i>tert</i> -Butyllithium
cat.	catalytic
Cbz	benzyloxycarbonyl
CIP	2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate
COD	1,5-cyclooctadiene
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.1]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL	diisobutylaluminum hydride
DiPAMP	1,2- <i>bis</i> ( <i>o</i> -anisylphenylphosphino)ethane
DKP	diketopiperazine
DMAP	<i>N,N</i> -4-dimethylaminopyridine
DMDO	dimethyl dioxirane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
DPEN	diphenylethylenediamine
DPPA	diphenylphosphoryl azide
<i>dr</i>	diastereomeric ratio
DuPHOS	bis-[2,5-dialkylphospholano]benzene
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
<i>ee</i>	enantiomeric excess
eq.	equivalent
Et	ethyl
Fl	9-fluorenyl
Fmoc	fluorenylmethoxycarbonyl
Fmoc-Osu	fluorenylmethoxycarbonyl succinimide
HOAT	1-hydroxy-7-azabenzotriazole
imid.	imidazole
LAH	lithium aluminum hydride
Me	methyl
MOM	methoxy methyl

Ms	methanesulfonyl
MS	molecular sieves
NVOC	6-Nitroveratryloxycarbonyl
Pd	palladium
Pd/C	palladium in carbon
Ph	phenyl
PMP	<i>para</i> -methoxyphenyl
<i>i</i> -Pr	<i>iso</i> -propyl
py.	pyridine
quant.	quantitative
Red-Al	sodium bis(2-methoxyethoxy) aluminium hydride
rt	room temperature
sat.	saturated
Su	Succinimidyl
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
Teoc	2-(trimethylsilyloxy)carbonyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline

TMEAD	tetramethylethylene diamine
TMG	<i>N,N,N',N'</i> -tetramethylguanidine
TMS	trimethylsilyl
<i>o</i> -tol	<i>ortho</i> -tolyl
Troc	2,2,2-trichloroethoxycarbonyl
Ts	<i>para</i> -toluenesulfonyl