Tetrahydroisoquinoline Alkaloids

DOI: 10.1002/ange.200604126

Asymmetric Total Synthesis of (−)-Cribrostatin 4 (Renieramycin H)**

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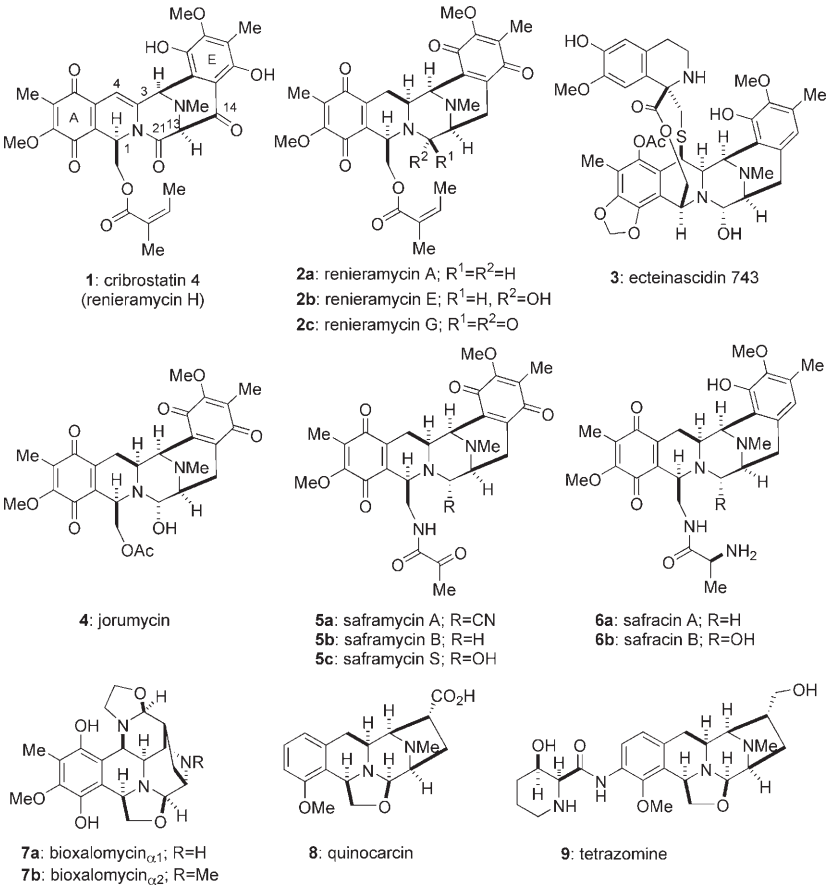
Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

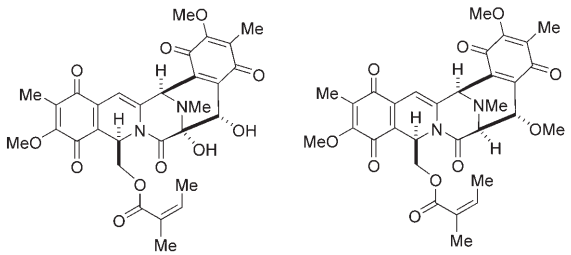
The tetrahydroisoquinoline family of alkaloids that include the renieramycins (**1**, **2a**–**c**), ecteinascidin-743 (Et-743, **3**), jorumycin (**4**), saframycins (**5a**–**c**), safracins (**6a**–**b**), bioxalomycins (**7a**–**b**), quinocarcin (**8**), and tetrazomine (**9**, Scheme 1) has attracted significant attention from the synthetic community over the past 30 years because of the potent antitumor and antimicrobial activities that this family of agents displays.[1] Among them, Et-743 (**3**) is a highly potent antitumor agent which is currently in phase II/III human clinical trials.[2]

Our research group has long been involved in the chemistry and biology of the tetrahydroisoquinoline antitumor antibiotics. Our interest in this field has culminated in the total syntheses of (±)-quinocarcinamide,[3] (−)-tetrazomine (**9**),[4] (−)-renieramycin G (**2c**), and (−)-jorumycin (**4**),[5a] as well as 3-*epi*-renieramycin G, 3-*epi*-jorumycin,[5] and other biologically relevant analogues.[6] In addition, promising synthetic studies toward Et-743 (**3**) are currently being investigated[7] along with studies to further understand the biochemical and cellular modes of action of these agents.[4b,6,8] Herein we report a concise asymmetric total synthesis of (−)-cribrostatin 4 (renieramycin H, **1**) as a part of a broad study into this family of biologically active compounds.



Scheme 1. Some examples of tetrahydroisoquinolines alkaloids.

In 1998, two renieramycin derivatives were isolated by Parameswaran et al. from the bright-blue sponge *Haliclona cribicutis*.[9] The structures **10** and **11** (Scheme 2) that were originally assigned were given the names renieramycin H and I, respectively. Kubo and co-workers subsequently revised the structure of renieramycin H to that of **1** (Scheme 1) from



Scheme 2. The structures of cribrostatin 4 (renieramycin H) and renieramycin I.

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[**] We gratefully acknowledge financial support from the National Institutes of Health (Grant CA85419). Mass spectra were obtained on instruments supported by the National Institutes of Health Shared Instrumentation Grant No. GM49631.

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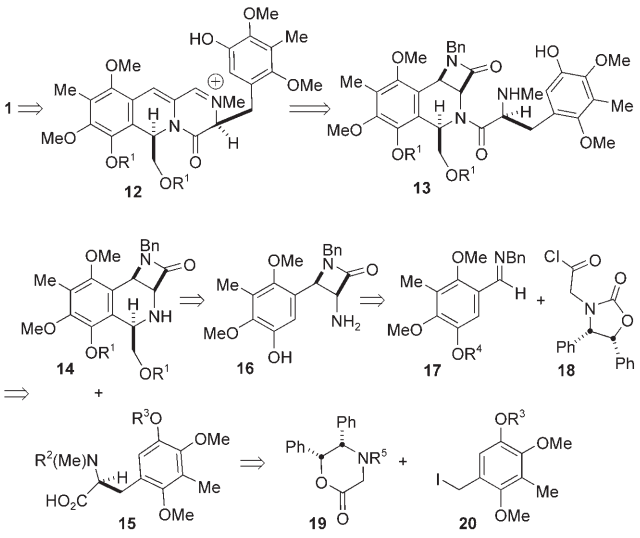
^{13}C NMR studies.[10] Independently, Pettit et al. reported the isolation of cribrostatin 4 from the blue sponge *Cribrochalina* collected from reef passages in the Republic of Maldives.[11] The structure of cribrostatin 4 was determined by X-ray analysis, which revealed that this substance is identical to renieramycin H (**1**).

The C3=C4 benzylic olefin present in compounds **1** and **11** is not present in any other naturally occurring member of the tetrahydroisoquinoline family of antitumor compounds. Cribrostatin 4 (renieramycin H, **1**) displays low-micromolar cytotoxic and antimicrobial activities. In 2005, Danishefsky and co-workers reported the first total synthesis of cribrostatin 4 (**1**) by using a lynchpin Mannich cyclization to establish the pentacyclic core.[12]

Our strategy was an elaboration of the methodology we developed to form pentacyclic tetrahydroisoquinolines bearing the C3=C4 alkene that is present in cribrostatin 4 and renieramycin I (Scheme 3).[13] The key step was thus envisioned to be the reductive opening/elimination of the C3–C4 β-lactam in **13**, immediately followed by spontaneous formation of the iminium ion **12** and Pictet–Spengler cyclization, to afford the pentacyclic skeleton of **1**. The tetrahydroisoquinoline core **14** was targeted by using an asymmetric Staudinger reaction[14] between imine **17** and a ketene derived from **18** to generate the *cis*-fused β-lactam **16**; Pictet–Spengler cyclization would then ultimately furnish the tetrahydroisoquinoline **14**.[15] The highly functionalized tyrosine derivative **15** was to originate from the coupling of aryl iodide **20** and an enolate derived from the chiral glycine template **19**.[16]



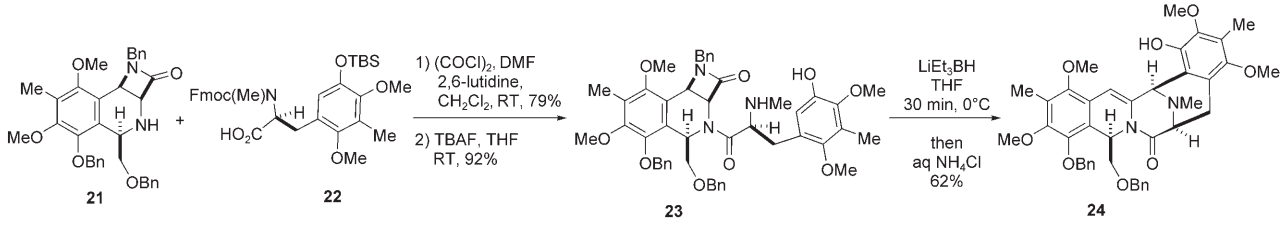
Scheme 3. Retrosynthetic analysis of **1**. Bn = benzyl.

We have previously described asymmetric syntheses of the tetrahydroisoquinoline **21** and the amino acid derivative **22** in two separate reports following the retrosynthesis outlined in Scheme 3.[5a,13] After completion of the syntheses of the two fragments, the next step was their assembly (Scheme 4). Amino acid **22** was converted into the corresponding acid chloride, which was coupled with tetrahydroisoquinoline **21** in 79% yield without noticeable epimerization at the C13 stereogenic center. Removal of both the TBS and Fmoc protecting groups was effected with TBAF to afford the peptide **23** in 92% yield, which set the stage for the key formation of the pentacycle. Reduction of the β-lactam with $LiEt_3BH$, followed by workup with aqueous ammonium chloride, delivered the pentacycle **24** bearing the required C3–C4 alkene in 62% yield.

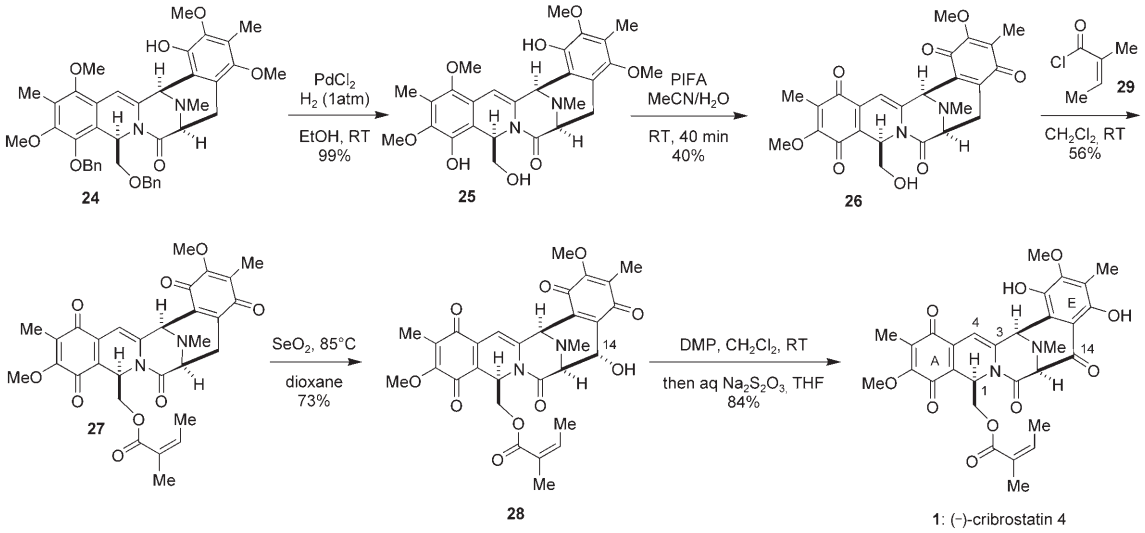
Two pathways could be envisioned to explain the origin of the benzylic alkene. In the first, β-elimination of the benzylamine residue at the C4 position via the incipient aldehyde is plausible prior to the formation of the pentacycle. The Pictet–Spengler cyclization would thus be realized on an intermediate α,β-unsaturated iminium ion. An alternative pathway would involve the elimination of the C4 benzylamine after formation of the pentacycle through a mechanism involving an *ortho*-quinone methide intermediate. Some preliminary evidence suggests that this second pathway may be operating, and current studies might provide more information and will be reported in due course.

At this point, only a few transformations were required to reach cribrostatin 4 (**1**, Scheme 5). Simultaneous hydrogenolytic removal of both of the benzyl groups on the phenol and primary alcohol with palladium chloride (H_2, 1 atm) led to **25** (99% yield), leaving the C3=C4 alkene intact.[17] Both phenols were then oxidized with bis(trifluoroacetoxy)iodobenzene (PIFA) to form the bisquinone **26** in 40% yield.[18] Other oxidants, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and ceric ammonium nitrate (CAN) also provided the desired product **26**, but in lower yields. Treatment with angeloyl chloride **29** subsequently furnished product **27** in 56% yield.[19] Attempts to realize this esterification using modified Yamaguchi conditions, as reported by Greene and co-workers,[20] were disappointing (10% yield) because of the formation of undetermined by-products.

In contrast to the route reported by Danishefsky and co-workers,[12] our substrate **26** was more stable than their β-dicarbonyl (C14–C21) substrate, and the esterification to



Scheme 4. Construction of the pentacyclic framework. DMF = *N*,*N*-dimethylformamide, Fmoc = 9-fluorenylmethyloxycarbonyl, TBS = *tert*-butyldimethylsilyl, TBAF = tetrabutylammonium fluoride.



Scheme 5. Completion of the synthesis of (−)-cribrostatin 4 (**1**).

form the angelate ester **27** proceeded in synthetically useful yield without the need to fine-tune the A ring. Oxidation of **27** with selenium dioxide proved to be chemo-, regio-, and diastereoselective at the C14 position, and delivered **28** in 73% yield. The stereochemistry of the hydroxy group at C14 was assigned on the basis that no coupling constant was observed between H14 and H13. This oxidation method was first introduced by Kubo, Saito, and co-workers in their conversion of saframycin B into saframycin D,[21] and was subsequently used by Danishefsky and co-workers in their synthesis of **1**.[12]

Finally, (−)-cribrostatin 4 (**1**) was obtained in 84% yield by treating **28** with Dess–Martin periodinane (DMP) to oxidize the alcohol group at C14 into a ketone,[22] followed by the addition of an aqueous solution of sodium thiosulfate to reduce the quinone of the E ring into the desired hydroquinone. The high stability of the hydroquinone E ring is attributable to the presence of the keto group at C14, while related hydroquinones at the A ring have been shown to rapidly oxidize in air to the corresponding quinone.[23] The spectroscopic data of the synthetic (−)-cribrostatin 4 (**1**) are consistent with those reported for the natural product.

The asymmetric total synthesis of (−)-cribrostatin 4 (**1**) has been realized in 17 steps in the longest linear sequence from the known 2,4-dimethoxy-3-methyl-5-benzyloxybenzaldeyde in 1.4% overall yield (or 25 steps from the commercially available 2,6-dimethoxytoluene in 1% overall yield). This concise synthesis compares very favorably to the synthesis reported by Danishefsky and co-workers of thirty-two steps in the longest linear sequence and 1.7% overall yield from the commercially available 2,3-dimethoxytoluene. This study features sequential asymmetric Staudinger and Pictet–Spengler reactions to form the tetrahydroisoquinoline and a reductive opening/elimination of a β-lactam immediately followed by a Pictet-Spengler cyclization to access the unsaturated pentacyclic framework. Efforts to extend the chemistry described herein to the preparation of analogues of the natural product are currently underway in our research group. We have previously reported the synthesis of 3-*epi*-renieramycin G and 3-*epi*-jorumycin.[5] To complete this study, the synthesis of analogues of renieramycin G (**2c**) and jorumycin (**4**) which bear a C3=C4 alkene would be valuable to understand more fully the influence of the stereochemistry at the C3 position on the cytotoxicity and biochemical reactivity. Moreover, it is speculated that the antitumor activity of cribrostatin 4 (**1**) could be substantially increased by introducing a carbinolamine or cyano function at the C21 position in place of the amide carbonyl residue present in the natural product. This modification would allow the formation of a potent electrophilic iminium ion species, implicated in the formation of covalent bonds with DNA, as observed in other members of the tetrahydroisoquinoline family.[1] These and other mechanistically-inspired studies into analogues are underway.

Received: October 7, 2006
Published online: January 19, 2007

Keywords: antitumor agents · heterocycles · natural products · Pictet–Spengler reaction · total synthesis

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