Natural Products Synthesis

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Total Synthesis of the Marine Natural Product (−)-Cribrostatin 4 (Renieramycin H)**

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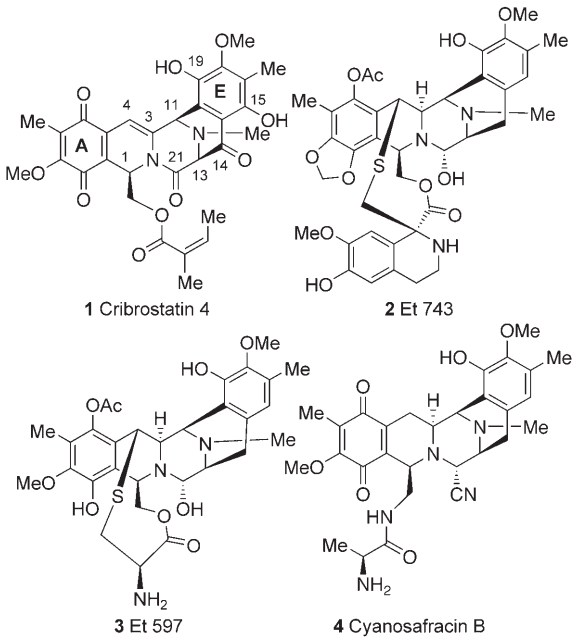
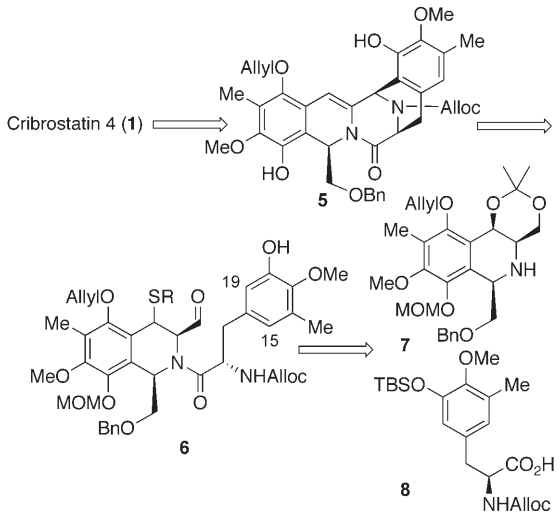
Cribrostatin 4 (**1**), whose structure was determined by X-ray analysis, was isolated by Pettit et al. in 2000 from the blue sponge *Cribrochalina* collected in reef passages in the Republic of Maldives.[1] Shortly thereafter, Kubo and co-workers[2] reassigned the structure of reneiramycin H, isolated by Parameswaran et al. from *Haliclona cribicutis*,[3] to be identical to that of cribrostatin 4. Cribrostatin 4 (**1**) belongs to a large family of complex tetrahydroisoquinoline natural products, which includes ecteinascidin 743 (Et 743, **2**), Et 597 (**3**), and cyanosafracin (**4**; Scheme 1).[4] However, the presence of a C3–C4 double bond in **1** distinguishes it from the other members of this class of alkaloids. Most of these polyheterocycles show potent antitumor activities, and Et 743 is currently undergoing phase II/III clinic trials as an anticancer drug.[5] Although it lacks the hemiaminal (or aminonitrile) function of the other members at C21, cribrostatin 4 (**1**) displays cytotoxic and antimicrobial activities at low micromolar concentrations.[6] Not surprisingly, the fascinating molecular architecture and important biological profile of **1** have attracted interest from the organic-synthesis community. Danishefsky and co-workers described the first total synthesis of cribrostatin 4 (**1**) in 2005,[7] and a second total synthesis was completed very recently by Vincent and Williams.[8]

We have been interested in this family of alkaloids for some time and have developed two different strategies for the total syntheses of Et 743[9,10] and Et 597.[11] As a continuation of this research, we report herein a convergent total synthesis of cribrostatin 4 (**1**). Our strategy, which features a key domino sequence[12] for the construction of pentacyclic core structure **5** from **6**, is highlighted in Scheme 2. The domino sequence involving acyliminium-ion formation, loss of a proton to form the enamide, β elimination, and a phenolic Mannich cyclization led to a dead end in one of our unsuccessful approaches to Et 743,[13] but would be a very efficient way to access the present target. A similar reaction sequence was developed independently by Williams and co-workers.[8,14] Besides the complexity and thus the unpredictability of the sequence, the key issue that needed to be addressed to validate this approach was the regioselectivity of the cyclization (at C19 versus C15 of **6**). We planned to assemble the key intermediate **6** by acylation of the tetrahydroisoquinoline **7** with the known amino acid **8**.[15] The benzylic hydroxy group (at C4) was positioned strategically in compound **7** to allow the concurrent introduction of the C3–



Scheme 1. Structures of cribrostatin 4 (**1**) and related alkaloids.



Scheme 2. Retrosynthetic analysis of **1**. Alloc = allyloxycarbonyl, Bn = benzyl, MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

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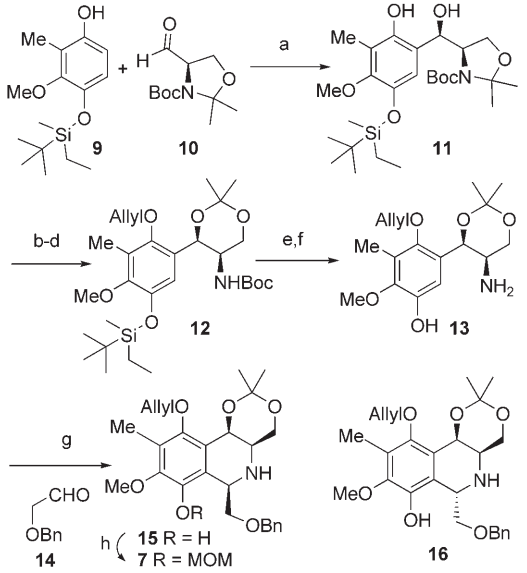
Supporting information for this article, including experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra of synthetic (−)-cribrostatin 4 (**1**), is available on the WWW under http://www.angewandte.org or from the author.

C4 double bond with the formation of the pentacyclic core of the target molecule at a late stage in the synthesis.

The synthesis of the fully substituted tetrahydroisoquinoline **7** is summarized in Scheme 3. A phenolic aldol condensation between phenol **9**[11] and the Garner aldehyde (**10**)[16] afforded the adduct **11** in 90% yield.[17] Standard

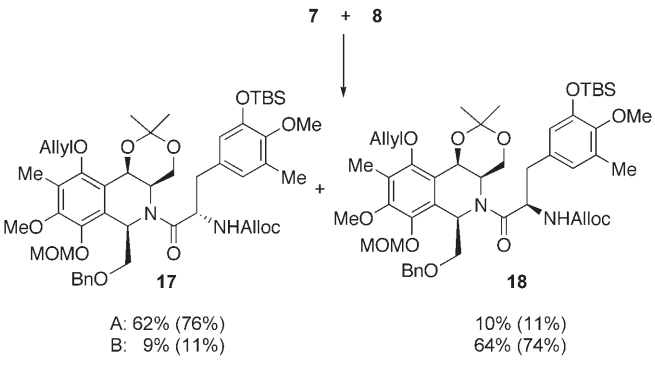


Scheme 3. Synthesis of the fully substituted tetrahydroisoquinoline **7**: a) MeMgCl, Et_2O; evaporation of the ether, then Garner aldehyde, CH_2Cl_2, 90%; b) allyl bromide, Cs_2CO_3, DMF; c) TsOH, MeOH, 0°C; d) 2,2-dimethoxypropane, TsOH, DMF, 67% (for 3 steps); e) TMSOTf, 2,6-lutidine, CH_2Cl_2, −40°C→RT; f) TBAF (1.0 M in THF), AcOH, THF, 84% (for 2 steps); g) AcOH (0.2 equiv), CH_2Cl_2, RT, 91%; h) MOMCl, DIPEA, CH_2Cl_2, 85%. Boc = *tert*-butoxycarbonyl, DIPEA = *N*,*N*-diisopropylethylamine, DMF = *N*,*N*-dimethylformamide, TBAF = tetrabutylammonium fluoride, TMSOTf = trimethylsilyl trifluoromethanesulfonate, Ts = *para*-toluenesulfonyl.

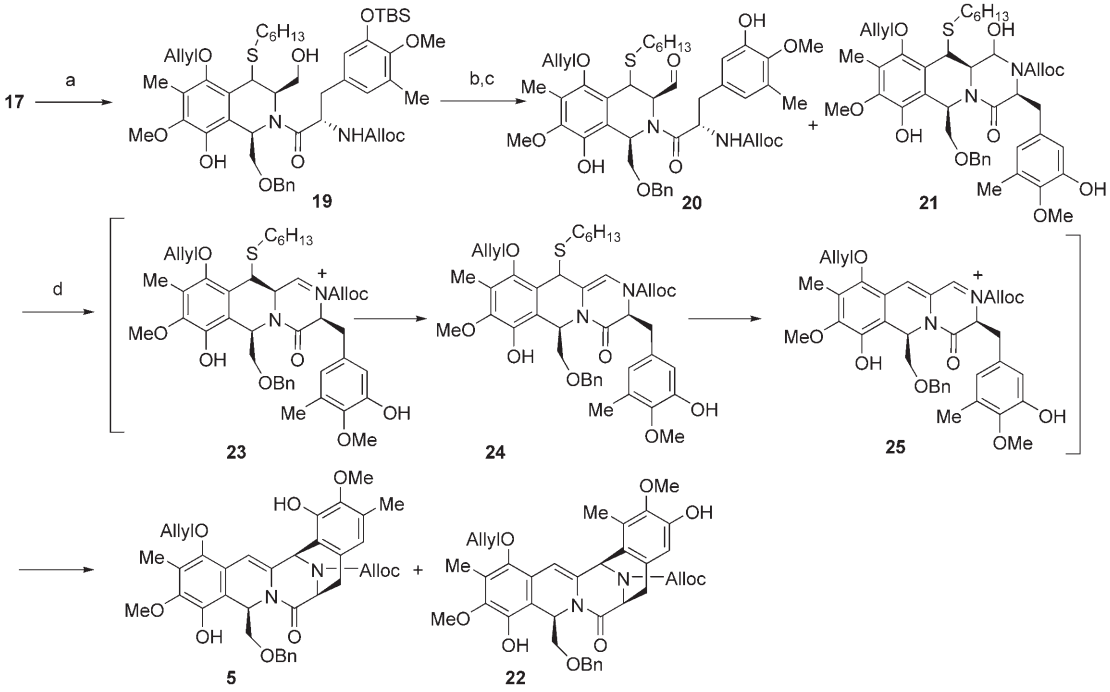
protecting-group manipulations converted **11** into the protected aminodiol **12** in excellent overall yield. Removal of the *N*-Boc functionality from the acid-sensitive compound **12** according to the procedure described by Sakaitani and Ohfune[18a] followed by cleavage of the silyl ether furnished the free aminophenol **13** in 84% overall yield. After much experimentation, the Pictet–Spengler reaction between **13** and benzyloxyacetaldehyde (**14**) provided the 1,3-*cis* tetrahydroisoquinoline **15** in 91% yield as a single diastereomer (d.r. > 30:1).[19] When the same reaction was performed in toluene/hexafluoroisopropyl alcohol (HFIP) in the presence of lithium chloride, the 1,3-*trans* isomer **16** was isolated in 20% yield together with the *cis* isomer **15** (69% yield). The isolation of both diastereomers **15** and **16** allowed us to determine their relative configuration with confidence by detailed NOE studies. Interestingly, and in accord with our previous observation for a related system, the treatment of **13** with ethyl glyoxylate gave the 1,3-*trans* isomer as the major product in 61% yield.[13] We noticed that the *trans* and *cis* isomers are interconvertible even as a solution in $CDCl_3$, and that the *trans* isomer always predominates after the mixture has reached equilibrium. This observation implies that the *trans* selectivity observed with ethyl glyoxylate is probably driven thermodynamically. Finally, the chemoselective protection of phenol **15** as the MOM ether afforded **7** in 85% yield.

The coupling of the secondary amine **7** with amino acid **8** turned out to be more difficult than it might appear. Owing to the low reactivity of **7**, the reaction proceeded slowly regardless of the coupling conditions, and a significant amount of racemization occurred. We screened a variety of reaction conditions; we varied the coupling reagent, the solvent, and the base, and under optimized conditions (HATU, HOAt, DIPEA, CH_2Cl_2, room temperature; conditions A in Scheme 4) the amidation occurred to afford the desired amide **17** in 62% yield (76% based on conversion), along with a small amount of the epimerized compound **18**. Interestingly, when the reaction was mediated by EDCI in the presence of 4-dimethylaminopyridine (DMAP, 0.5 equiv; conditions B in Scheme 4), the epimerized product **18** was produced as the major isomer (74% based on conversion) together with the desired stereoisomer **17** (11%). The assignment of the configuration of **17** (and **18**) by standard spectroscopic methods is nontrivial; the configuration was determined only after completion of the total synthesis.

The regioselective dioxane ring opening at C4 by hexane-1-thiol provided sulfide **19** in 93% yield (Scheme 5).[20,21] The MOM protecting group was also removed under these conditions. This transformation differentiated efficiently the two hydroxy groups of the protected 1,3-diol in **17** and set the stage for the next operations. Swern oxidation of compound **19** followed by TBAF-mediated deprotection of the TBS ether furnished a mixture of the aldehyde **20** and the cyclic hemiaminal **21**. When the mixture of **20** and **21** was stirred as a solution in dichloromethane in the presence of methylsulfonic acid, an efficient domino process occurred with formation of the pentacyclic core and concurrent generation of the C3–C4 double bond to give **5** in 51% overall yield from **19**. The regioisomer **22** was also isolated in 15% yield. The regioisomeric nature of **5** and **22** was deduced by detailed NMR spectroscopic studies, including NOE, HMBC, and HMQC experiments, and was confirmed by the conversion of **5** into the natural product.



Scheme 4. Peptide coupling of **7** and **8** (the yield of the isolated product is given, followed in parentheses by the yield based on the conversion of the starting materials). Conditions: A) HATU, HOAt, DIPEA, CH_2Cl_2, RT; B) DMAP, EDCI, CH_2Cl_2, RT. EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole.



Scheme 5. Domino cyclization to construct the pentacyclic core of cribrostatin 4 (**1**): a) *n*-$C_6H_{13}SH$, TFA/TFE 1:100, 93%; b) Swern oxidation; c) TBAF, AcOH, THF; d) $MeSO_3H$ (0.01% by volume, $c = 0.01$ M), CH_2Cl_2, 51% (for 3 steps). TFA = trifluoroacetic acid, TFE = trifluoroethanol.

We suspect that the domino reaction is initiated by the formation of the acyliminium ion **23**, which is converted subsequently into the conjugated iminium ion **25** via the enamide intermediate **24**. Nucleophilic addition of the tethered aromatic ring onto the *N*-acyliminium group in **25** then provides the observed pentacycle. The regioselectivity of this reaction is highly dependent on the concentration of methylsulfonic acid, as well as on the reaction medium. When the same reaction was performed with 0.1% methylsulfonic acid in CH_2Cl_2, compound **22** was formed in preference to the desired isomer **5** (**22**/**5** 3:2). Furthermore, if the reaction was carried out in MeCN, the undesired regioisomer **22** was produced predominantly (**22**/**5** 10:1), in accord with our previous observations.[13]

The total synthesis of cribrostatin 4 (**1**) was completed as shown in Scheme 6. Although compound **5** is structurally very similar to one of the advanced intermediates in the synthesis by Danishefsky and co-workers,[7] we developed an alternative and more straightforward reaction sequence for the conversion of **5** into the natural product. The simultaneous removal of the *N*-Alloc and *O*-Allyl groups in **5** under the conditions described by Guibé and co-workers,[22] followed by N methylation, O debenzylation by hydrogenolysis, and oxidation of the A ring with air, afforded the quinone **26** in 76% overall yield. The acylation of **26** with angeloyl chloride (**27**) in toluene afforded the desired angelate ester **28** in 84% yield. The use of neutral conditions for this reaction is important, as the presence of a base led to the degradation of starting materials and product. The oxidation of the E ring of **28** with air and the Fremy salt proceeded slowly in this case,[23] and low conversion was observed even after a prolonged reaction time. Fortunately, the desired oxidation occurred smoothly with air in the presence of a catalytic amount of salcomine[24] to afford the quinone **29** in 88% yield. The oxidation of **29** with selenium dioxide occurred regioselectively at C14 to afford **30** in 62% yield with 22% recovery of **29**.[25] The benzylic alcohol was then oxidized with Dess–Martin periodinane[26] to the corresponding ketone. Finally, the selective reduction of the E-ring quinone to the hydroquinone provided (−)-cribrostatin 4 (**1**) in 87% yield. Synthetic **1** exhibited physical, spectroscopic, and spectrometric characteristics (^{1}H NMR, ^{13}C NMR, IR, and HRMS) identical to those reported for the natural product. The downfield shift of the C15−OH signal ($\delta = 11.34$ ppm) in the ^{1}H NMR spectrum relative to that of C19−OH ($\delta = 5.65$ ppm) is indicative of a hydrogen bond formed between C15−OH and C14=O. This H bond might stabilize the hydroquinone form of the E ring of cribrostatin 4 (**1**).

In conclusion, a convergent total synthesis of (−)-cribrostatin 4 (**1**) has been completed in a longest linear sequence of 21 steps from the known phenol **9** in 4.3% overall yield (or in 26 steps from vanillin in 2.8% overall yield). A key feature of the synthesis is the domino β elimination/cyclization reaction of the aminoaldehyde **20**. This domino sequence, initiated by acyliminium-ion formation followed by the loss of a proton to generate an enamide, allowed the construction of the pentacyclic core with concurrent introduction of the C3−C4 double bond of **1**. The chemistry developed in the course of these studies should be amenable to the synthesis of a large array of (−)-cribrostatin 4 analogues, including the C11 and C13 epimers, and to further structure–activity-relationship studies of this intriguing natural product.[27]

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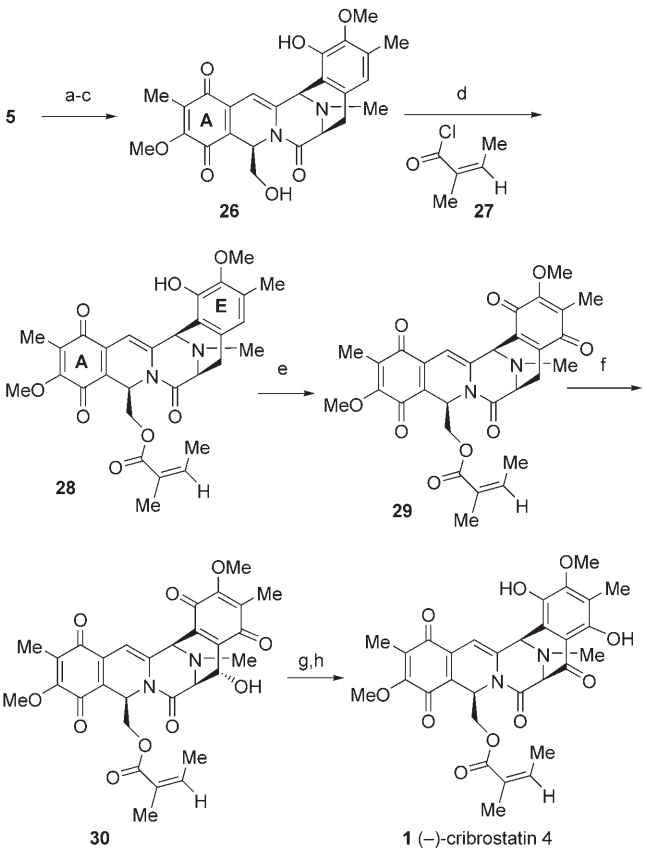

Scheme 6. Completion of the total synthesis of (−)-cribrostatin 4 (**1**): a) $[Pd(PPh_3)_2Cl_2]$, Bu_3SnH, AcOH, CH_2Cl_2; b) HCHO, $NaBH_3CN$, AcOH, MeOH; c) 10% Pd/C, HCO_2H, MeOH; then air, MeOH, 76% (for 3 steps); d) angeloyl chloride (**27**), toluene, 80°C, 84%; e) salcomine, air, MeCN, 88%; f) SeO_2, 1,4-dioxane, 90°C, 62%, with 22% recovered starting material; g) Dess–Martin periodinane, CH_2Cl_2; h) Zn, MeOH, 87% (for 2 steps). Salcomine = *N*,*N*′-bis(salicylidene) ethylenediaminecobalt(II) hydrate.

Keywords: alkaloids · antitumor agents · asymmetric synthesis · domino reactions · marine natural products

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