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SYNTHETIC STUDIES TOWARD CRIBROSTATIN IV: AN INTRIGUING EPIMERIZATION

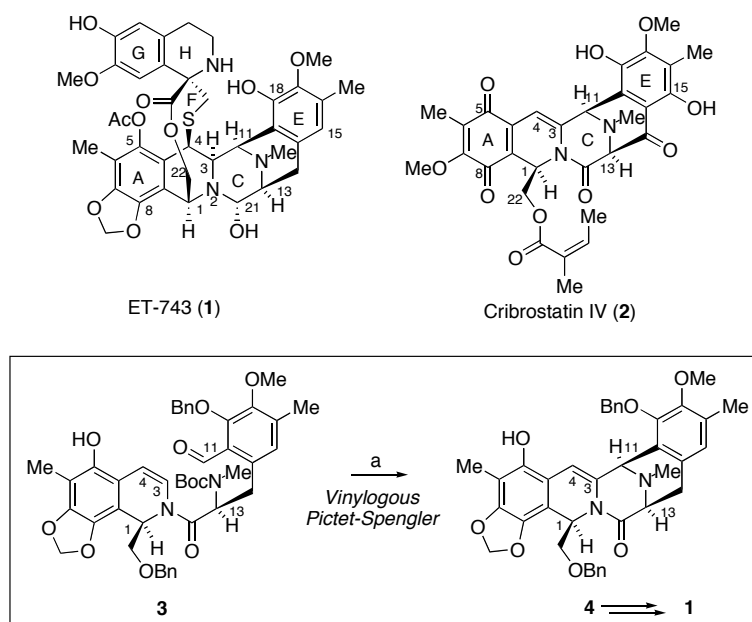
Collin Chan¹ and Samuel J. Danishefsky^{1,2,*}

¹Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027 and ²Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Ave., New York, NY 10021 (USA)

We dedicate this paper to the many accomplishments of Professor Steven Weinreb, including his artistic use of the imino-Diels-Alder Reaction and his discovery of a new reagent for a broad spectrum of acylations (Weinreb amide).

Abstract – Surprising effects of remote substituents on the relative rates of vinylogous Pictet-Spengler reaction versus epimerization through a Grigg like progression have been encountered (contrast cyclizations of **3** and **7**). Deuterium labeling experiments have been used to clarify mechanisms of epimerization, thereby allowing for the assignment of absolute configuration.

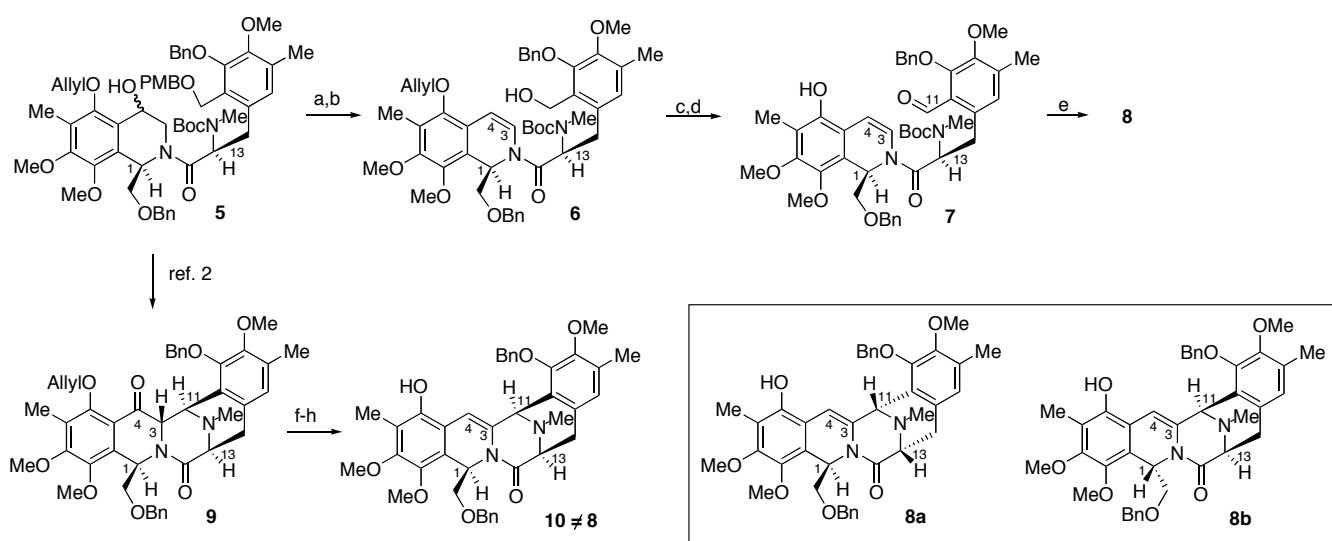
The cytotoxic tetrahydroisoquinoline alkaloids, most notably exemplified by ecteinascidin 743 (**1**), ET-743, are a family of well-studied natural products.¹ Our group has had a longstanding interest within this family of alkaloids, and has reported on the total synthesis of cribrostatin IV (**2**)² and a formal total synthesis of ET-743 (**1**).³ In the context of the ET-743 synthesis, we had developed a highly useful though not high yielding, vinylogous Pictet-Spengler reaction, depicted in Scheme 1. This reaction provided access to a key pentacyclic intermediate (**4**), from **3**. As shown, the reaction accomplishes facile installation of the C₃-C₄ double bond (*vide infra*). We had fully expected to extend this newly developed technology to the cribrostatin IV synthesis. Our efforts toward this end, and a surprising finding are described herein.



Scheme 1. a) $\text{CHF}_2\text{CO}_2\text{H}$ (30 equiv), MgSO_4 (4 equiv), benzene, 100 °C, 45 min, 42-58%.

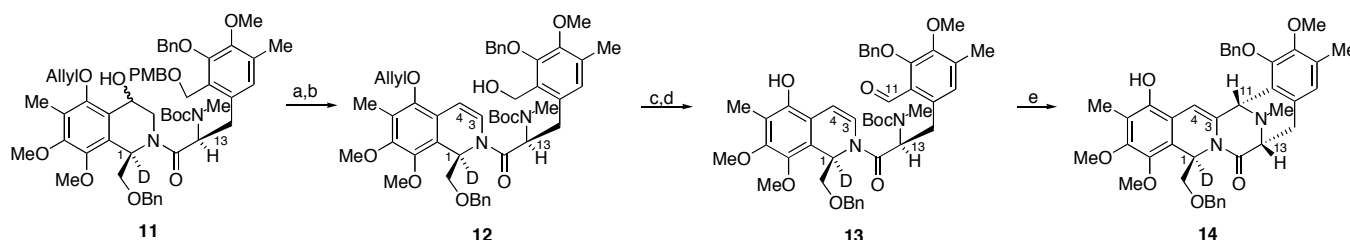
Our studies toward cribrostatin IV (2) commenced with the synthesis of 7, which is analogous to the Pictet-Spengler substrate (3) in the ET-743 series. Thus, the previously described amide (5),² was subjected to oxidative deprotection, followed by dehydration of the secondary alcohol to ene-alcohol (6) (Scheme 2). Oxidation of 6 followed by deprotection of the allyl ether, as shown, gave rise to key aldehyde substrate (7).

In the event, upon exposure to our previously employed acidic conditions,³ 7 indeed underwent loss of the *N*-Boc group and dehydrative cyclization to afford a pentacyclic product, albeit in a disappointingly low yield (40%). To determine the stereochemistry of this product, we compared its spectroscopic properties with those of 10, of established stereochemistry, synthesized from ketone (9), whose structure assignment was corroborated by its intermediacy in the completion of the total synthesis of 2.² Remarkably, the high field NMR spectrum of the cyclization product derived from 7 was *very similar but clearly different* from that of authentic 10.⁴ Given the similarity of the spectra, the presence of a single vinylic hydrogen at C_4 as well as the loss of the aldehyde and *N*-Boc functions, we concluded that the cyclization product derived from 7 was indeed arising from a vinylogous Pictet-Spengler reaction. However, whereas the stereochemical loci (C_1 , C_{11} , and C_{13}) in 10 are "matched" and correspond to those found in the natural products (1 and 2), in 8 there had occurred an epimerization to generate a "mismatched" relationship.⁵ Of course, the *cis* relationship between the tertiary hydrogens at C_{11} and C_{13} in 8 is fixed. Hence, the possibilities for mismatching in 8 are reduced to two antipodes, shown as 8a and 8b (*i.e.* *ent*-8a). In the former, the unanticipated epimerization had occurred at C_{13} . By contrast, in antipode (8b), the epimerization would have taken place at C_1 . There remained the need to distinguish between these possibilities.



Scheme 2. a) DDQ (1.6 equiv), CH_2Cl_2 :pH 7.00 buffer solution (18:1), 25 °C, 30 min, 90% b) $\text{Cu}(\text{OTf})_2$ (0.2 equiv), benzene, 85 °C, 15 min, 61% c) DMP (1.5 equiv), CH_2Cl_2 , 25 °C, 5 h, 94% d) $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (0.2 equiv), Bu_3SnH (1.2 equiv), AcOH (5 equiv), CH_2Cl_2 , 0 °C \rightarrow 25 °C, 1 h, 93% e) $\text{CHF}_2\text{CO}_2\text{H}$ (30 equiv), MgSO_4 (4 equiv), benzene, 100 °C, 45 min, 40% f) NaBH_4 (10 equiv), THF:H₂O (8:1), 0 °C \rightarrow 25 °C, 1 h, 99% g) $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (0.2 equiv), Bu_3SnH (1.2 equiv), AcOH (5 equiv), CH_2Cl_2 , 0 °C \rightarrow 25 °C, 1 h, 98% h) CSA (3 equiv), benzene, 80 °C, 3 h, 90%.

In order to explain the formation of antipode (**8b**), it would have to be assumed that an epimerization had occurred at C_1 during the acid-induced cyclization step. In an effort to determine if epimerization had actually taken place at C_1 , **11**⁶ was synthesized with a deuterium label at C_1 . The thought was that if a hidden epimerization was taking place at C_1 , some or all of the deuterium label should be “washed out.” In the event, the pentacycle (**14**), arising from the acid-induced cyclization of **13**, showed no detectable signs of deuterium label loss. Given that epimerization was apparently not occurring at C_1 , we inferred that epimerization must have been occurring at C_{13} . Accordingly, we tentatively assigned the absolute stereochemistry at C_1 , C_{11} , and C_{13} as shown in **14** (cf. **8a**).



Scheme 3. a) DDQ (1.6 equiv), CH_2Cl_2 :pH 7.00 buffer solution (18:1), 25 °C, 30 min, 93%; b) $\text{Cu}(\text{OTf})_2$ (0.2 equiv), benzene, 85 °C, 15 min, 57%; c) DMP (1.5 equiv), CH_2Cl_2 , 25 °C, 5 h, 95%; d) $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (0.2 equiv), Bu_3SnH (1.2 equiv), AcOH (5 equiv), 0 °C \rightarrow 25 °C, 1 h, 90%; e) $\text{CHF}_2\text{CO}_2\text{H}$ (30 equiv), MgSO_4 (4 equiv), benzene, 100 °C, 45 min, 35%.

In an attempt to understand the basis for epimerization at C_{13} , we considered the intermediate species that may arise during the course of the cyclization. As suggested in Figure 1, exposure of compound (**7**) to

acidic cyclization conditions first leads to the removal of the *N*-Boc group, allowing for formation of an intermediate iminium species. This species, if intercepted directly by the styrenic double bond, will lead to the pentacyclic compound (**10**), possessing the desired stereochemistry at C₁, C₁₁, and C₁₃. However, a pathway competitive with direct cyclization might intercede, leading to formation of an azomethine ylide intermediate.⁷ Upon formation of the ylide, the stereochemical constraint at C₁₃ would be lost, thus enabling epimerization. A β-protonation pathway may lead to the antipodal iminium species (epimeric at C₁₃), which, upon cyclization would yield **8a**, possessing the undesired stereochemistry at C₁₁ and C₁₃.

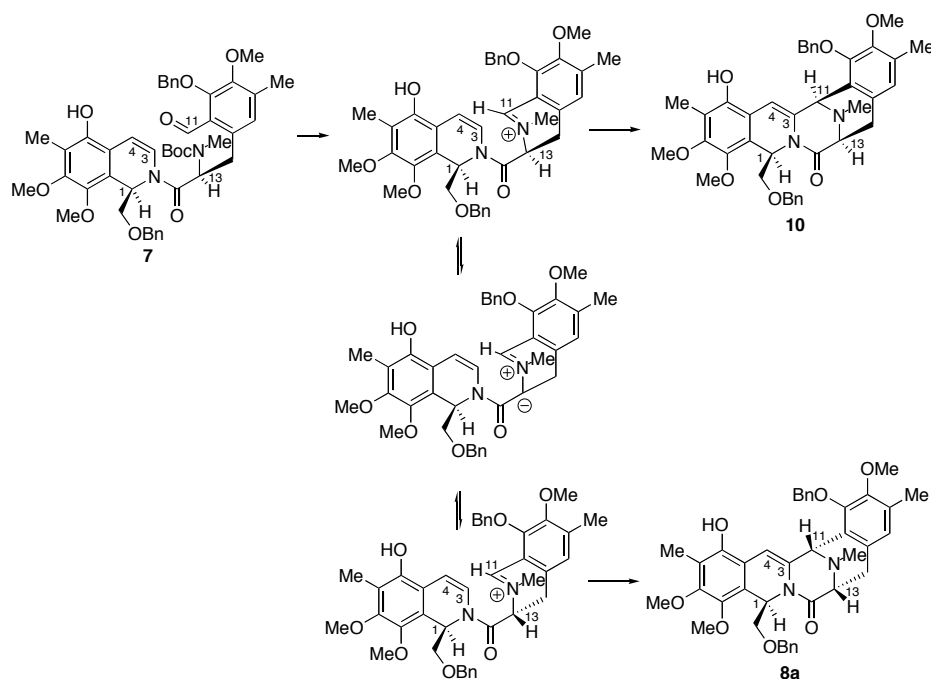
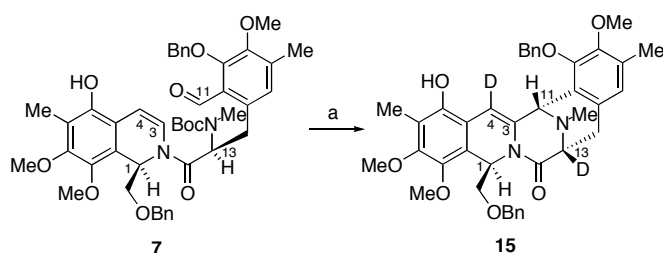


Figure 1. Proposed mechanism of epimerization through an azomethine ylide intermediate.

We were able to corroborate our findings by conducting an additional labeling experiment. Thus, in the presence of a perdeuterated acetic acid, **7** underwent cyclization to yield the pentacyclic compound (**15**), exhibiting deuterium incorporation at both C₄ and C₁₃. The incorporation of deuterium at C₁₃ is readily rationalized in terms of an azomethine ylide intermediate. While we are confident in assigning the absolute stereochemistry of the vinylogous Pictet-Spengler product as shown in **8a**,⁸ we have not successfully trapped the Grigg type structure.



Scheme 4. a) Acetic-*d*₃-Acid-*d*, 100 °C, 48 h.

The striking difference between the vinylogous cyclization behavior in the pre ET-743 series (see cyclization of **3**) and the cribrostatin IV series (see cyclization of **7**) given the minimal differences in the substitution patterns of the seemingly remote A ring is quite interesting. Apparently in the ET-743 series, the methylene dioxyaromatic ring imparts a degree of nucleophilic enhancement of cyclization in **3** relative to the dimethoxy pattern in **7**. The results of further studies pursuant to this series of alkaloids will be described in due course.

ACKNOWLEDGEMENTS

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3. S. Zheng, C. Chan, T. Furuuchi, B. J. D. Wright, B. Zhou, J. Guo, and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2006, **45**, 1754.
4. Cyclization product (*cf.* **8a**): ¹H NMR (CDCl₃, 400 MHz, relative to TMS) δ 7.61- 7.36 (5H, m), 7.30-7.18 (5H, m), 6.68 (1H, s), 6.36 (1H, m), 6.18 (1H, s), 5.40 (1H, d, *J* = 11.45 Hz), 5.02 (1H, d, *J* = 11.41 Hz), 4.81 (1H, s), 4.65 (1H, d, *J* = 12.00 Hz), 4.40 (1H, d, *J* = 12.00 Hz), 4.34 (1H, bs), 3.79 (1H, m), 3.76 (6H, s), 3.71 (3H, s), 3.63 (1H, m), 3.49 (1H, dd, *J* = 3.87 Hz, 10.86 Hz), 3.21 (1H, dd, *J* = 7.24 Hz, 16.81 Hz), 2.93 (1H, d, *J* = 17.13 Hz), 2.51 (3H, s), 2.20 (3H, s), 2.18 (3H, s) ppm. **10**: ¹H NMR (CDCl₃, 400 MHz, relative to TMS) δ 7.45 (5H, m), 7.25 (3H, m), 6.95 (2H, m), 6.42 (1H, s), 6.25 (1H, dd, *J* = 3.42 Hz, 8.21 Hz), 5.97 (1H, s), 5.21 (1H, d, *J* = 11.06 Hz), 4.98 (1H,

d, $J = 11.09$ Hz), 4.58 (1H, s), 3.95 (1H, d, $J = 12.32$ Hz), 3.82 (3H, s), 3.77 (3H, s), 3.75 (3H, s), 3.74 (2H, m), 3.63 (1H, m), 3.24 (2H, m), 3.09 (1H, dd, $J = 8.85$ Hz, 9.80 Hz), 3.00 (1H, d, $J = 16.70$ Hz), 2.48 (3H, s), 2.12 (6H, s) ppm.

5. In an attempt to determine if the pentacyclic products were susceptible to epimerization, pentacycles (**8** and **10**) were subjected to the acidic reaction conditions. However, in both cases the starting pentacycles were recovered unchanged.
6. Compound (**11**) was synthesized under the usual protocol, with the substitution of formic acid with formic acid- d_2 , used in the Noyori transfer hydrogenation reaction; see ref. 2.
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8. An X-Ray crystal structure of an advanced compound in this series also confirmed the stereochemical assignment of **8a**. Although there is no question about the structure, the margin of uncertainty in the R-value is such that the data should not be deposited in the CCDC at this time. However, even in the absence of any X-Ray corroboration, this structure would be certain.