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SYNTHETIC STUDIES TOWARD CRIBROSTATIN IV: AN INTRIGUING EPIMERIZATION

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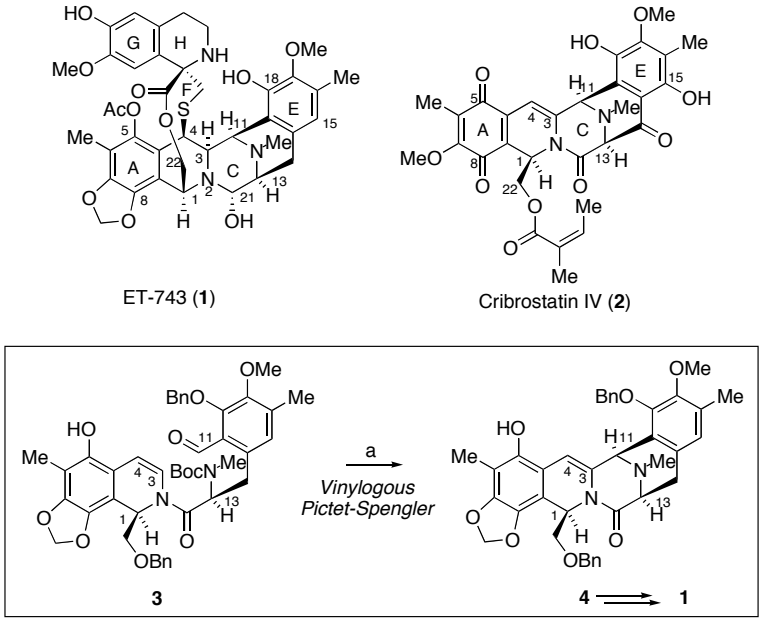
We dedicate this paper to the many accomplishments of Professor Steven Weinreb, including his artistic use of the imino-Diels-Alder Reaction and his discovery of a new reagent for a broad spectrum of acylations (Weinreb amide).

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.

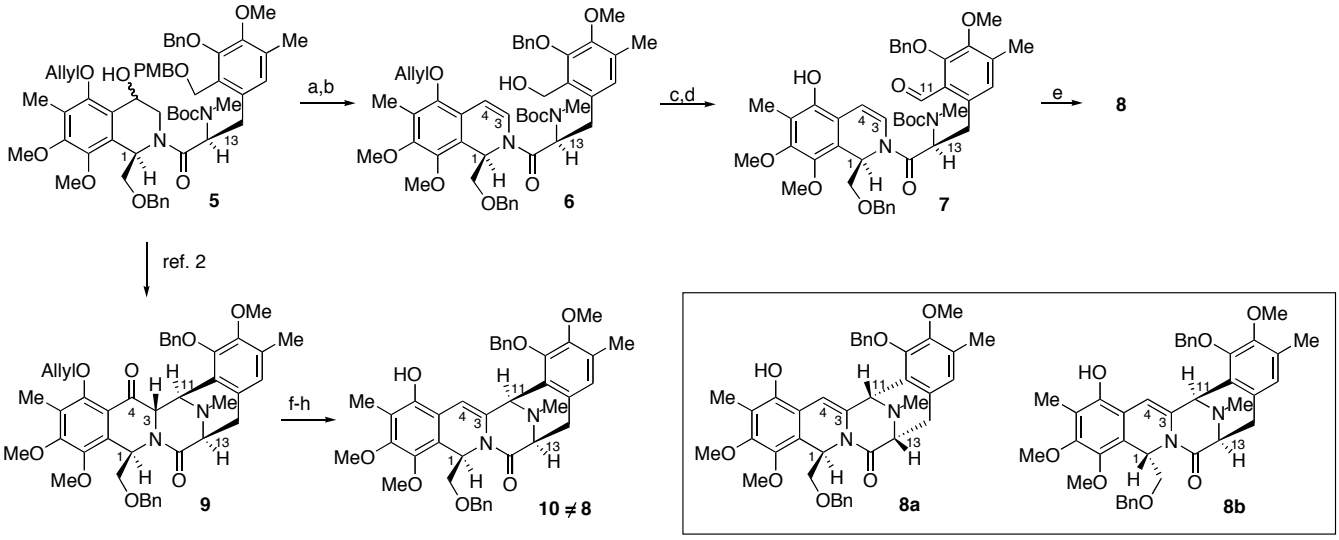
The cytotoxic tetrahydroisoquinoline alkaloids, most notably exemplified by ecteinascidin 743 (**1**), ET-743, are a family of well-studied natural products.[1] Our group has had a longstanding interest within this family of alkaloids, and has reported on the total synthesis of cribrostatin IV (**2**)[2] 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 C_3-C_4 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) CHF_2CO_2H (30 equiv), $MgSO_4$ (4 equiv), benzene, 100 °C, 45 min, 42-58%.

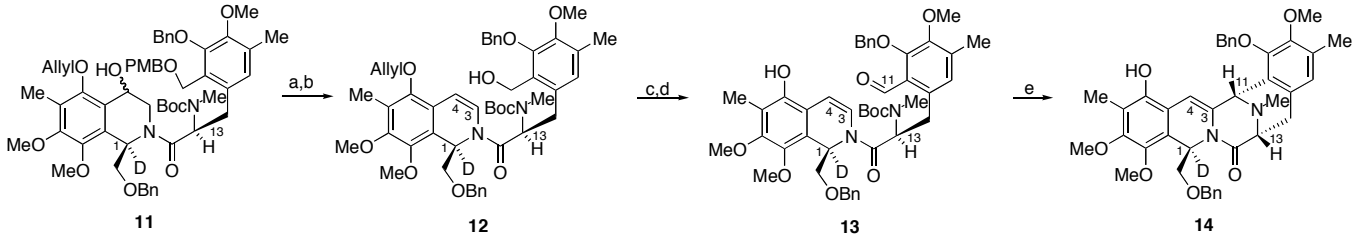
Our studies toward cribrostatin IV (**2**) commenced with the synthesis of **7**, which is analogous to the Pictet-Spengler substrate (**3**) in the ET-743 series. Thus, the previously described amide (**5**),[2] was subjected to oxidative deprotection, followed by dehydration of the secondary alcohol 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) $Cu(OTf)_2$ (0.2 equiv), benzene, 85 °C, 15 min, 61% c) DMP (1.5 equiv), CH_2Cl_2, 25 °C, 5 h, 94% d) $(Ph_3P)_2PdCl_2$ (0.2 equiv), Bu_3SnH (1.2 equiv), AcOH (5 equiv), CH_2Cl_2, 0 °C→25 °C, 1 h, 93% e) CHF_2CO_2H (30 equiv), $MgSO_4$ (4 equiv), benzene, 100 °C, 45 min, 40% f) $NaBH_4$ (10 equiv), THF:H_2O (8:1), 0 °C→25 °C, 1 h, 99% g) $(Ph_3P)_2PdCl_2$ (0.2 equiv), Bu_3SnH (1.2 equiv), AcOH (5 equiv), CH_2Cl_2, 0 °C→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) $Cu(OTf)_2$ (0.2 equiv), benzene, 85 °C, 15 min, 57%; c) DMP (1.5 equiv), CH_2Cl_2, 25 °C, 5 h, 95%; d) $(Ph_3P)_2PdCl_2$ (0.2 equiv), Bu_3SnH (1.2 equiv), AcOH (5 equiv), 0 °C→25 °C, 1 h, 90%; e) CHF_2CO_2H (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 C_1, C_{11}, and C_{13}. 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 C_{13} would be lost, thus enabling epimerization. A β-protonation pathway may lead to the antipodal iminium species (epimeric at C_{13}), which, upon cyclization would yield **8a**, possessing the undesired stereochemistry at C_{11} and C_{13}.

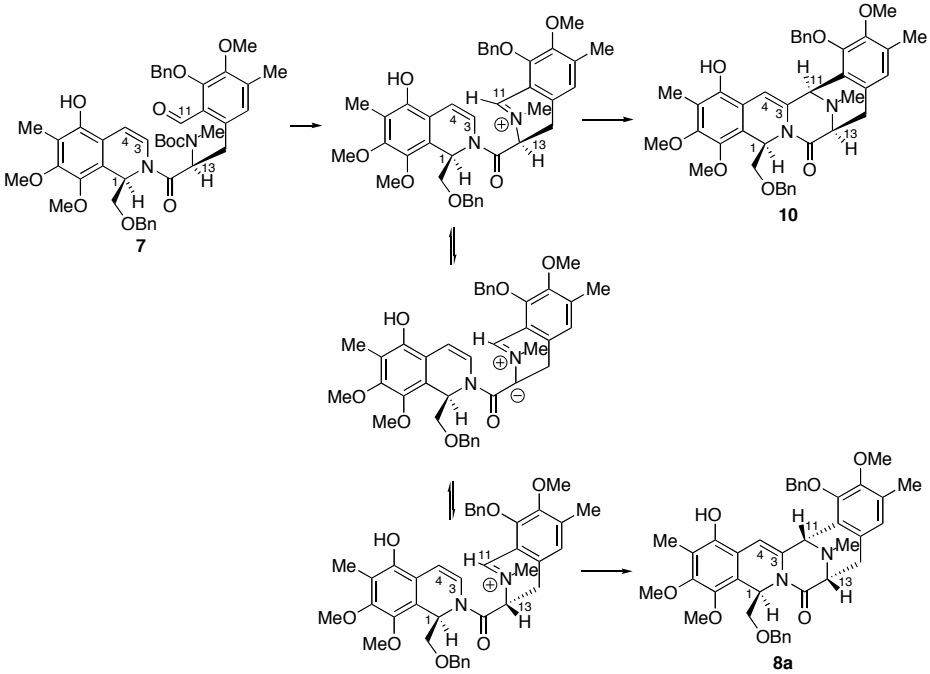
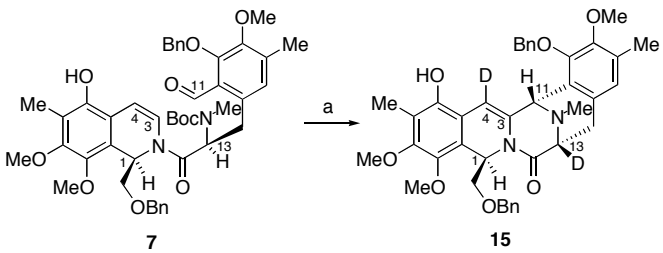


Figure 1. Proposed mechanism of epimerization through an azomethine ylide intermediate.

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 C_4 and C_{13}. The incorporation of deuterium at C_{13} 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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2. C. Chan, R. Heid, S. Zheng, J. Guo, B. Zhou, T. Furuuchi, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2005, **127**, 4596.
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**): ^{1}H NMR ($CDCl_3$, 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**: ^{1}H NMR ($CDCl_3$, 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.
7. R. Grigg and V. Sridharan, "Advances in Cycloaddition," Vol. 3, JAI Press Inc., 1993, pp. 161-204.
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.