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Stereocontrolled Synthesis of Onchidins

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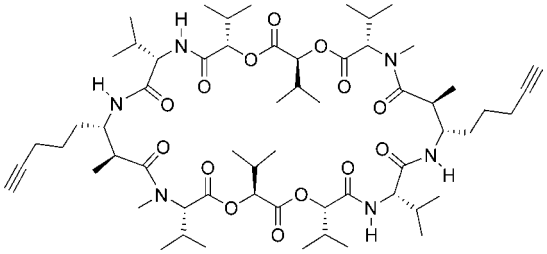
ABSTRACT



The first total synthesis of a molecule possessing the stereochemistry proposed for onchidin is described. The structure synthesized appears to be different from that of the marine natural product.

Marine cyanobacteria have produced a wide variety of natural products, many of which have shown striking biological activity.[1−3] Consequently, they are key synthetic targets in the quest for new leads in the pharmaceutical industry.[4] To date, the compounds extracted have shown anticancer, antifungal, antiviral, and cytotoxic activity, and the diversity of structure exhibited by these secondary metabolites also makes them appealing to synthetic chemists. We have been interested for some time in the metabolites of these bacteria, and view their syntheses as a key route to structural modification and subsequent activity control. In an earlier paper, we were able to amend the stereochemistry of yanucamide A,[5] and here we report on our studies toward the synthesis of onchidin.

Onchidin (**1**) was isolated and structurally assigned in 1994 by Riguera,[6] and it is known to show cytotoxic activity (P-388 cells, $IC_{50} = 8\ \mu g/mL$).[7] Although it was extracted from the marine mollusc *Onchidium* sp., it is firmly believed to be of cyanobacterial biosynthesis, due to structural similarities between it and other metabolites of this species, and because it is a known constituent of the mollusc's diet.[8] Its structure was determined by a combination of chemical degradation, chiral chromatography and spectroscopic analysis. The relative stereochemistry at positions 7 and 9 on the novel α-methyl-β-amino octynoic acid portion was assigned through NOE observations. This was also the case for assigning the absolute stereochemistry of the alkyne-containing chain; an enhancement was observed between the

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(1) Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, J. G.; Wright, P. C. *Tetrahedron* **2001**, *57*, 9347−9377.
(2) Gerwick, W. H.; Tan, L. T.; Sitachitta, N. *Alkaloids (Academic Press)* **2001**, *57*, 75−184.
(3) Luesch, H.; Harrigan, G. G.; Goetz, G.; Horgen, F. D. *Curr. Med. Chem.* **2002**, *9*, 1791−1806.
(4) Proksch, P.; Edrada, R. A.; Ebel, R. *Appl. Microbiol. Biotechnol.* **2002**, *59*, 125−134. Frenz, J. L.; Kohl, A. C.; Kerr, R. G. *Expert Opin. Ther. Pat.* **2004**, *14*, 17−33.
(5) Xu, Z. S.; Peng, Y. G.; Ye, T. *Org. Lett.* **2003**, *5*, 2821−2824.
(6) Rodriguez, J.; Fernandez, R.; Quinoa, E.; Riguera, R.; Debitus, C.; Bouchet, P. *Tetrahedron Lett.* **1994**, *35*, 9239−9242.
(7) Fernandez, R.; Rodriguez, J.; Quinoa, E.; Quinoa, E.; Riguera, R.; Munoz, L.; Fernandez-Suarez, M.; Debitus, C. *J. Am. Chem. Soc.* **1996**, *118*, 11635−11643.
(8) Nakao, Y.; Yoshida, W. Y.; Szabo, C. M.; Baker, B. J.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3272−3280. Reese, M. T.; Gulavita, N. K.; Nakao, Y.; Hamann, M. T.; Yoshida, W. Y.; Coval, S. J.; Scheuer, P. J. *J. Am. Chem. Soc.* **1996**, *118*, 11081−11084. Kimura, J.; Takada, Y.; Inayoshi, T.; Nakao, Y.; Goetz, G.; Yoshida, W. Y.; Scheuer, P. J. *J. Org. Chem.* **2002**, *67*, 1760−1767. Tan, L. T.; Sitachitta, N.; Gerwick, W. H. *J. Nat. Prod.* **2003**, *66*, 764−771. Williams, P. G.; Yoshida, W. Y.; Quon, M. K.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2003**, *66*, 651−654. Luesch, H.; Harrigan, G. G.; Goetz, G.; Horgen, F. D. *Curr. Med. Chem.* **2002**, *9*, 1791−1806. Wan, F.; Erickson, K. L. *J. Nat. Prod.* **2001**, *64*, 143−146.

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acetylenic proton and a distant (through-bonds) methyl group. Our structured synthetic approach appears to disprove this assignment.

There is no obvious choice of position to close the macrocycle of onchidin, although the choice of amide or ester linkage was apparent. An interesting aspect of onchidin is its symmetry, and this was an important factor when considering appropriate disconnections (Figure 1). It can be split

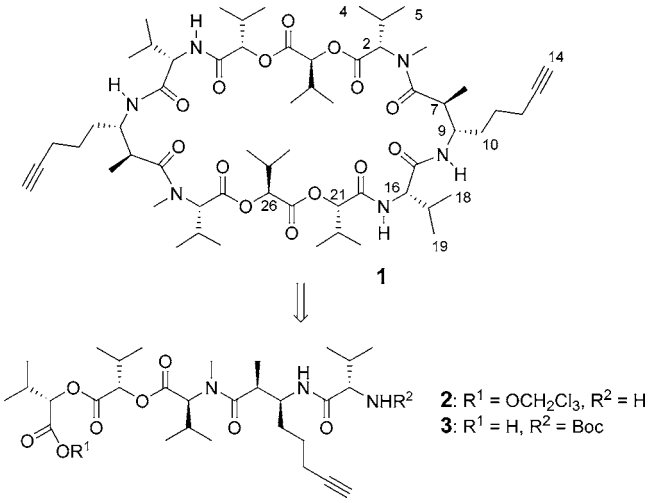
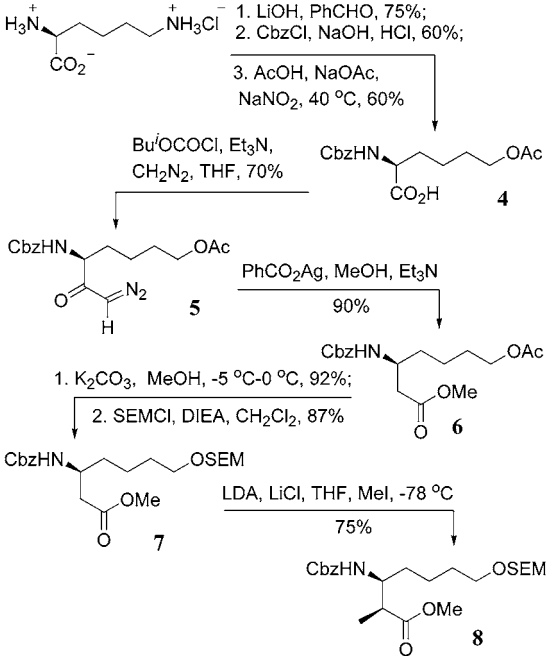


Figure 1. Retrosynthetic analysis of onchidin.

into two fragments **2** and **3**, which differ only in terms of protecting groups and can be made by a common route prior to deprotection. The route toward both fragments **2** and **3** was developed from (*S*)-lysine (Scheme 1). This was converted into the acetoxy derivative **4** by the published route,[9] and a Wolff rearrangement gave the homologated ester **6**, via diazoketone **5**, in 63% overall yield.[10] Deacetylation and reprotection as the SEM ether gave **7** in 92% yield. Methylation α to the ester was performed using LDA and methyl iodide under the conditions of Seebach,[11] to afford **8** in 75% yield with 98% de.

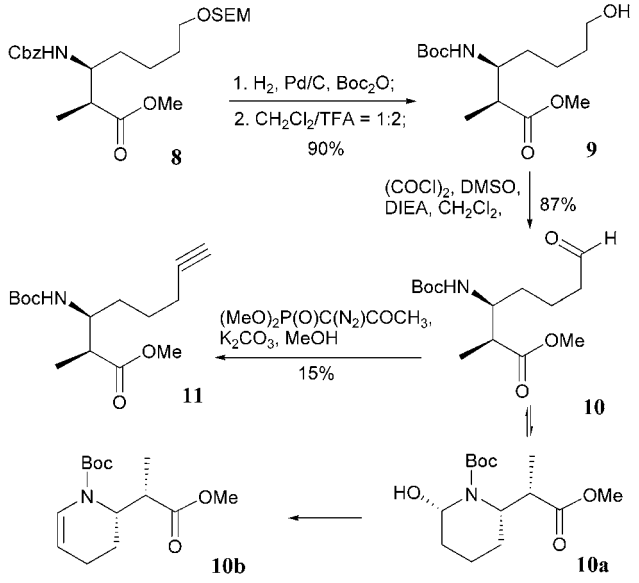
Due to the reaction conditions that would be employed at a later stage, it was necessary to change the protection on nitrogen from Cbz to Boc. This was performed by treatment of **8** with TFA to remove the SEM group, followed by hydrogenolysis of the Cbz group in the presence of Boc

Scheme 1. Synthesis of Protected β-Amino Acid **8**



anhydride to give **9**.[12] Swern oxidation of alcohol **9** yielded the aldehyde **10**, in good yield. However, the proposed conversion of **10** to the corresponding alkyne **11**, by treatment with the Ohira−Bestmann reagent,[13] resulted in a very disappointing yield. This was due to the aldehyde being in equilibrium with its cyclic hemiaminal **10a**. This does not generally pose any problems, but on attempting to form the alkyne, a very low yield was achieved. This may have been due to the formation of byproduct **10b** via elimination of water from **10a**.[14] Some efforts were made to circumvent this side-reaction, but it was impossible to get a workable

Scheme 2. Synthesis of Alkyne **11**

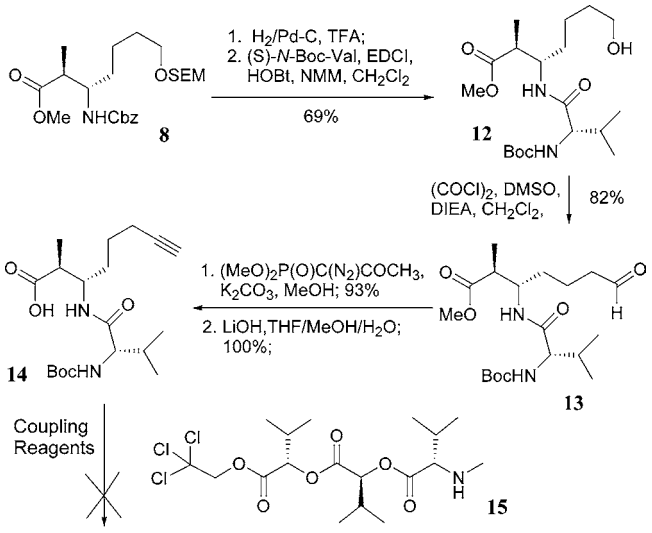


(9) Adger, B.; Dyer, U.; Hutton, G.; Woods, M. *Tetrahedron Lett.* **1996**, *37*, 6399−6402.

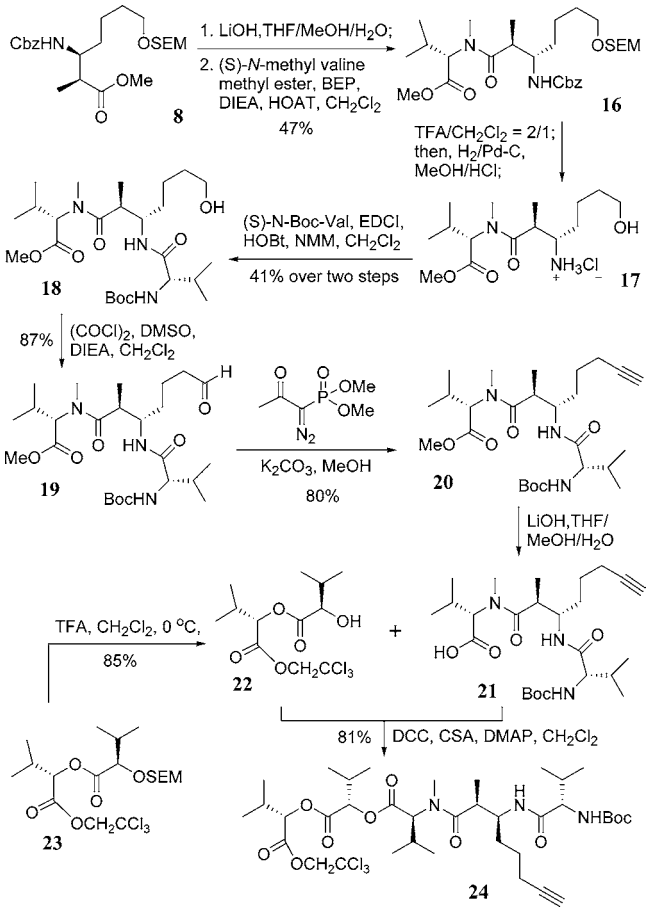
(10) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazocompounds*; Wiley: New York, 1998. Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. Kirmse, W. *Eur. J. Org. Chem.* **2002**, *14*, 2193−2256.

(11) Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824−1839. Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103−3106. Baldwin, J. E.; Moloney, M. G.; North, M. Tetrahedron **1989**, *45*, 6309−6318. Podlech, J.; Seebach, D. *Liebigs Ann.* **1995**, 1217−1228. Abell, A. D.; Gardiner, J. *Org. Lett.* **2002**, *4*, 3663−3666. Ma, Z. H.; Liu, C.; Zhao, Y. H.; Li, W.; Wang, J. B. *Chin. Chem. Lett.* **2002**, *13*, 721−724. Moran, W. J.; Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2003**, *5*, 3427−3429. Fleck, T. J.; McWhorter, W. W.; DeKam, R. N.; Pearlman, B. A. *J. Org. Chem.* **2003**, *68*, 9612−9617. Gardiner, J.; Anderson, K. H.; Downard, A.; Abell, A. D. *J. Org. Chem.* **2004**, *69*, 3375−3382.

Scheme 3. Synthesis of Alkyne **14**



Scheme 4. Synthesis of Precursor **23**

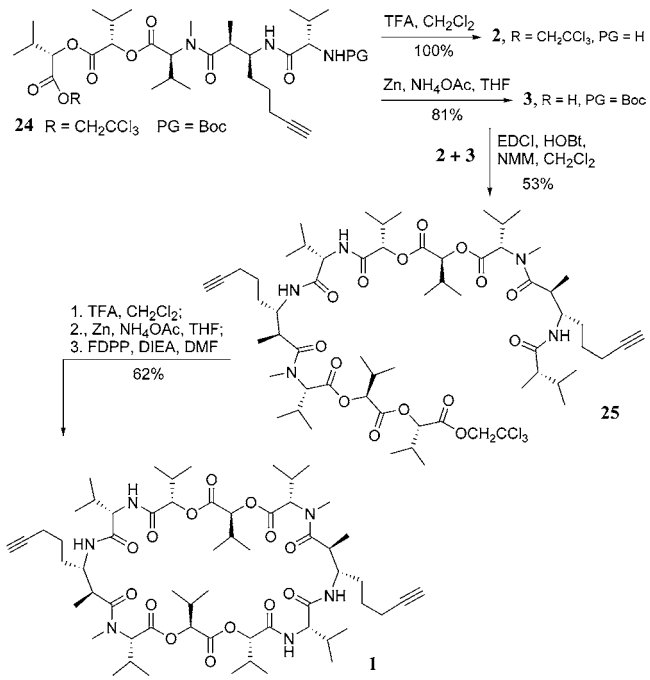


yield of **11**. This side reaction was assumed to be caused by the nucleophilicity of the nitrogen in the carbamate, so it was envisaged that this problem could be avoided if the nitrogen was present as a less nucleophilic amide instead. This would be possible if this fragment had already been coupled.

Starting from **8**, hydrogenolysis of the Cbz group and concomitant SEM removal (with TFA) left the deprotected amine, which was coupled with (*S*)-Boc-valine under standard conditions to produce **12**. Swern oxidation of the alcohol provided aldehyde **13**, which was converted into the alkyne using the Ohira−Bestmann reagent,[12] with a 76% yield for the two steps. There was no competition with hemiaminal formation detected during this process. Saponification of the ester with lithium hydroxide released acid **14**, and the coupling of **14** with fragment **15**[15] was then attempted. However, despite employing a wide variety of coupling agents, it proved to be impossible to accomplish this reaction, probably due to steric limitations, and a new approach was sought.

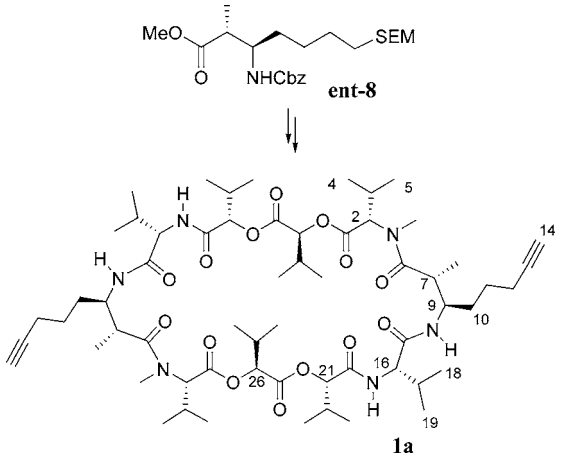
This approach avoided the need to couple two large fragments at the previously attempted position. Instead, compound **8** was saponified and coupled with *N*-methyl valine methyl ester to afford **16**. Double deprotection using TFA (SEM) and hydrogenation (Cbz) gave **17**, which was then coupled with N-Boc valine to give **18**. Swern oxidation gave **19**, and conversion to the alkyne via the previously described method afforded **20** in a good yield. Hydrolysis of the ester in **20** gave free acid **21**, which was readily coupled with **22**, mediated by DCC, CSA, and DMAP, to give the key intermediate **24**. This moiety is readily convertible into compounds **2** and **3**, which were identified in the retrosynthetic analysis. Compound **2** was obtained quanti-

Scheme 5. Completion of Synthesis



(12) Bajwa, J. S. *Tetrahedron Lett.* **1992**, *33*, 2955−2956.
(13) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564. (b) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521−522.
(14) Ojima, I.; Tzamarioudaki, M.; Eguchi, M. *J. Org. Chem.* **1995**, *60*, 7078−7079. Grabowski, S.; Prinzbach, H. *Tetrahedron Lett.* **1996**, *37*, 7951−7954.

Scheme 6. Synthesis of **1a**



tatively by treatment of **24** with TFA, whereas compound **3** was produced by treating **24** with zinc and ammonium acetate. The coupling of the two fragments was promoted by EDCI and HOBt and gave a 53% yield of cyclization precursor **25**. Deprotection as previously described, followed by cyclization (FDPP, DMF), yielded the target molecule **1** in 62% yield.

The analytical data we obtained for **1** were inconsistent with that published for natural onchidin, with significant differences in both the ^{1}H and ^{13}C NMR spectra. We were confident that our synthesis produced the proposed structure of onchidin; we therefore turned our thoughts to the source of stereochemical assignment and looked for potential weaknesses in the interpretation of the data. The most obvious one to us was the observed NOE between protons on C-5 and C-14. Without sophisticated modeling to determine the conformation of the molecule in solution, we felt it would be very difficult to assign, with any confidence, the configuration at C-9 on the basis of this observation. We proposed that the relative stereochemistry at positions C-9 and C-7 was correct but that the enantiomer of this subunit was in fact the one present in the natural product. To this end, we synthesized *ent*-**8** following the same synthesis as for **8**, but starting with (*R*)-lysine. This was readily achieved, and *ent*-**8** was incorporated into the synthesis as previously performed to afford **1a** with no adverse consequences (Scheme 6). To our disappointment, the characterization data were still not consistent with that of the natural product. It would appear that the error in the original assignment of the stereochemistry of onchidin lies somewhere other than in the configuration of the subunit **8**. Further work is still required to give the true structure of natural onchidin.

(15) For the preparation of compound **15**, please see Supporting Information.

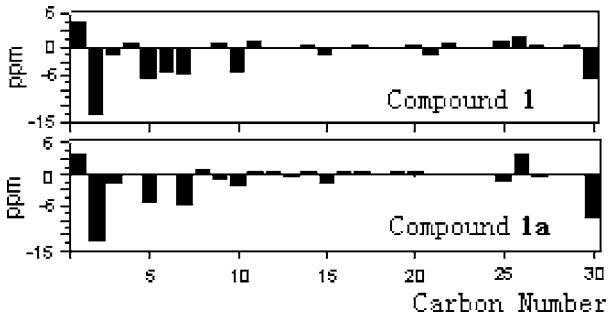


Figure 2. Differences in ^{13}C NMR shifts between natural onchidin and two synthetic stereoisomers.

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Supporting Information Available: Full details for experimental procedures for compounds **1**, **5**−**8**, **12**−**16**, and **18**−**25** and ^{1}H and ^{13}C NMR spectra for compounds **1**, **1a**, **4**, **5**, **7**, **8**, **16**, **16a**, **18**, **18a**, **20**, **20a**, **23**, **24**, **24a**, **25**, and **25a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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