Total Synthesis of Amaminol A: Establishment of the Absolute Stereochemistry
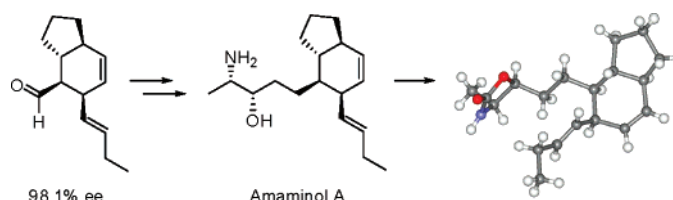
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ABSTRACT

98.1% ee   Amaminol A

The first synthetic route to amaminol A with use of an organocatalytic intramolecular Diels–Alder reaction is reported. The absolute stereochemistry is proven with a crystallographic image of a cyclic carbamate of amaminol A.

Amaminols A (**1**) and B (**2**) are cytotoxic bicyclic aminoalcohols isolated in 1999 from an unidentified tunicate of the family *Polyclinidae* (Figure 1),[1] with an IC$_{50}$ value of 2.1
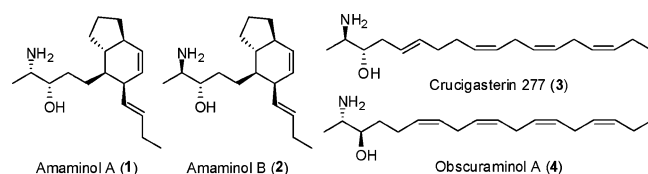

Figure 1. Structures of amaminols A (**1**) and B (**2**), crucigasterin 277 (**3**), and obscuraminol A (**4**).

μg/mL against P$_{388}$ murine leukaemia cells. Their mode of action is unknown, but they are structurally closely related to aliphatic cytotoxic aminoalcohols such as sphingosines,[2] xestoaminols,[3] halaminols,[4] leucettamols,[5] crucigasterins,[6]

and obscuraminols.[7] The interesting trans-fused hexahydro-indene substructure of amaminols has most likely been formed in nature by an intramolecular Diels−Alder reaction of a triene or tetraene, such as found from crucigasterin 277 (**3**) and obscuraminol A (**4**).[8] No synthetic efforts toward amaminols have been reported so far.

Our previous work[9] on the total synthesis of amaminol A (**1**) involved organocatalytic intramolecular Diels−Alder reaction.[10] A concurrent study on organocatalytic IMDA by

(2) (a) Thudichum, J. L. W. A *Treatise on the Chemical Constitution of the Brain*, *Bailliere*, *London*, *1884*, new ed.; Archon Books, Hamden, CT, 1962. (b) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075−1091.

(3) (a) Gulavita, N.; Scheuer, P. *J. Org. Chem.* **1989**, *54*, 366−369. (b) Jiménez, C.; Crews, C. *J. Nat. Prod.* **1990**, *53*, 978−982. (c) Ichihashi, M.; Mori, K. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 329−333. (d) Mori, K.; Matsuda, H. *Liebigs Ann. Chem.* **1992**, 131−137.

(4) Clark, R. J.; Garson, M. J.; Hooper, J. N. A. *J. Nat. Prod.* **2001**, *64*, 1568−1571.

(5) Kong, F.; Faulkner, J. *J. Org. Chem.* **1993**, *58*, 970−971.

(6) Jares-Erijman, E.; Bapat, C.; Lithgow-Bertelloni, A.; Rinehart, K.; Sakai, R. *J. Org. Chem.* **1993**, *58*, 5732−5737.

(7) Garrido, L.; Zubía, E.; Ortega, M. J.; Naranjo, S.; Salvá, J. *Tetrahedron* **2001**, *57*, 4579−4588.

(8) For biosynthetic Diels−Alder reactions see: Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078−3115.

(9) For the synthesis of a diastereomer of amaminol A see: Selkälä, S. Ph.D. Thesis, Helsinki University of Technology, Espoo, Finland, 2003.

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(1) Sata, N. U.; Fusetani, N. *Tetrahedron Lett.* **2000**, *41*, 489−492.

Macmillan and co-workers showed improved enantio- and stereoselectivities and therefore we adopted these conditions.[11]

Retrosynthetic analysis reveals a route based on three consecutive olefinations (Scheme 1). The stereogenic center
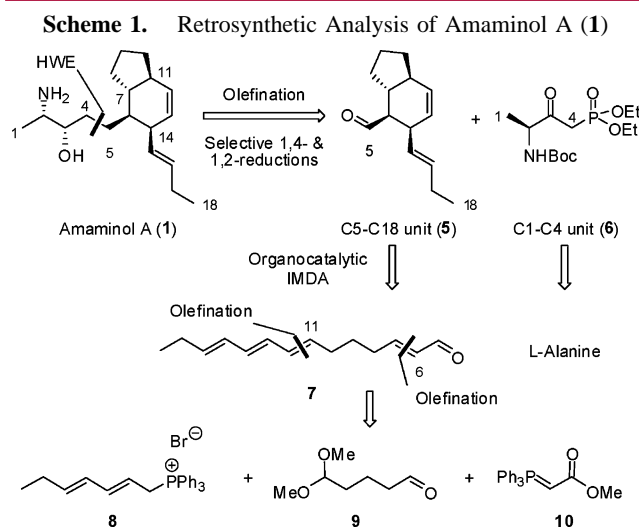
at C2 is derived from L-alanine and the C3 stereocenter was envisaged to be formed through a diastereoselective 1,2-reduction using the chirality derived from L-alanine. The rest of the stereocenters in the C5−C18 unit were to be formed in an enantioselective intramolecular Diels−Alder reaction of the intermediate aldehyde **7**. Obvious disconnections of **7** lead to the known phosphonium salt **8**,[12] protected glutaraldehyde **9**,[13] and commercially available Wittig ylide **10**.
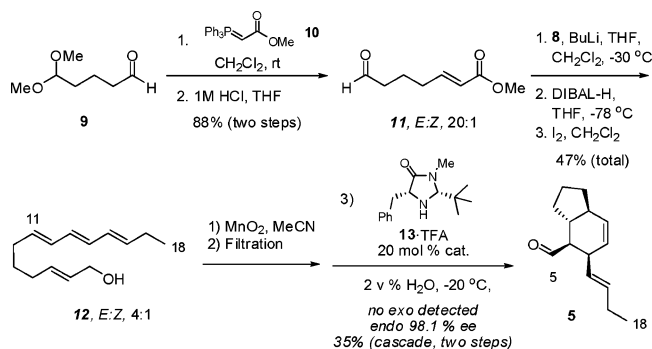
Ozonolysis of cyclopentene in methanol (Scheme 2)[13] gave the partially protected glutaraldehyde **9**, which was converted to the conjugated ester **11** with Wittig ylide **10** followed by hydrolysis in good combined yield (88%) and geometrical selectivity (*E*:*Z*, 20:1). A second Wittig reaction of aldehyde

(10) Selkälä, S. A.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2005**, 1620−1624.

11 with the phosphorane prepared from **8** followed by DIBAL-H reduction gave 14C-aliphatic tetraene alcohol **12** initially in a 2:1 *E*:*Z* ratio, which was improved to 4:1 by treatment with iodine.

Allylic alcohol **12** was initially oxidized with manganese oxide in dichloromethane to the highly volatile and sensitive aldehyde **7**. Isolation of the aldehyde **7** was avoided by conducting the oxidation in acetonitrile, filtering off the mangane oxide, and continuing directly to the organocatalytic intramolecular Diels−Alder step, adding a small amount of water (2 v %), cooling to −20 °C, then adding the catalyst **13** and trifluoroacetic acid. This sequence of operations yielded the desired bicyclo[4.3.0]nonane aldehyde **5** in excellent enantioselectivity (98.1% ee). The organocatalytic IMDA also effected kinetic purification when only (6*E*,11*E*,-13*E*,15*E*)- and (6*E*,11*E*,13*E*,15*Z*)-geometrical isomers were reacted.[11c]

Horner−Wadsworth−Emmons olefination between phosphonate **6**[14] and an aldehyde similar to **5** with potassium carbonate in ethanol led to extensive epimerization (Scheme 3).[9] We evaded this drawback by using conditions reported
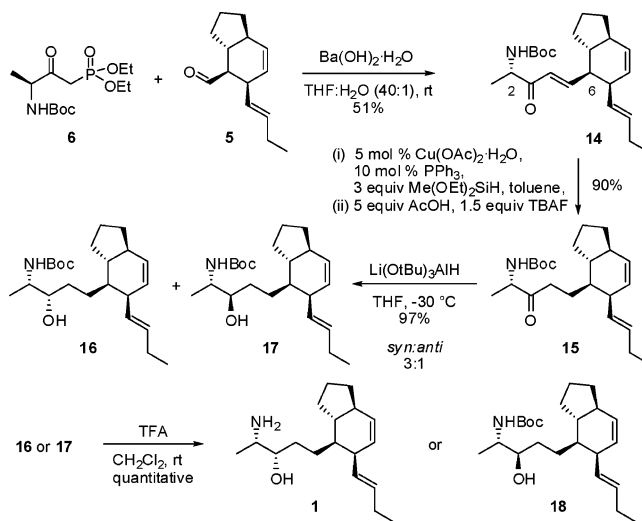
by D'Auria and co-workers.[15] Phosphonate **6** and aldehyde **5** reacted with barium hydroxide[16] to give **14** in moderate yield (51%) without any epimerization.

(11) (a) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616−11617. (b) Jen, W. S. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 2004. (c) Comparable yields have been reported for similar sequences: see ref 11a for similar substrates of Dess−Martin peridionane oxidation, 53%, IMDA, 39% (based on 47% yield and 85% conversion), giving a total yield of 21% (over two steps).

(12) Gunatilaka, A. A. L.; Hirai, N.; Kingston, D. G. I. *Tetrahedron Lett.* **1983**, *24*, 5457−5460.

(13) (a) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867−3870. (b) Aurrecoechea, J. M.; Gil, J. H.; López, B. *Tetrahedron* **2003**, *59*, 7111−7121.

(14) Chakravarty, P. K.; Greenlee, W. J.; Parsons, W. H.; Patchett, A. A.; Combs, P.; Roth, A.; Busch, R. D.; Mellin, T. N. *J. Med. Chem.* **1989**, *32*, 1886−1890.

Chemoselective 1,4-reduction of enones in the presence of acidic NH-protons is a major challenge. Recent reports on using in situ prepared copper hydride catalyst and stoichiometric amounts of silanes as hydride source led us to try such an approach.[17] Most methods are based on catalytic amounts of commercial Stryker's reagent,[17b,c] preformed catalytic complex,[17d–f] basic copper alkoxides,[17a] or copper fluoride systems.[17g,h] Although many practical methods have been introduced for asymmetric copper catalysis, nonasymmetric methods have gained practically no attention. Enone **14** has a high tendency for epimerization and therefore we had to uncover a practical catalytic system avoiding highly basic counterions (Scheme 3). We adopted the Lee and Yun method for the preparation of Stryker's reagent[18] employing the procedure in situ and using Me-(OEt)$_2$SiH as the hydride source.[19] Ketone **15** was obtained in excellent (90%) yield after workup.[20]

Reduction of ketone **15** with Li(OtBu)$_3$AlH gave a separable mixture of alcohols **16** and **17** in a 3:1 (*syn:anti*) selectivity.[21] Final removal of Boc-protection with trifluoroacetic acid gave either natural amaminol A (**1**) or *epi*-amaminol A (**18**).

To verify the relative stereochemistries, the aminoalcohols **1** and **18** were converted to the cyclic carbamate analogues **19** and **20** with carbonyl diimidazole (Im$_2$CO) (Scheme 4).[22]

Scheme 4. Formation of Cyclic Carbamates **19** and **20**
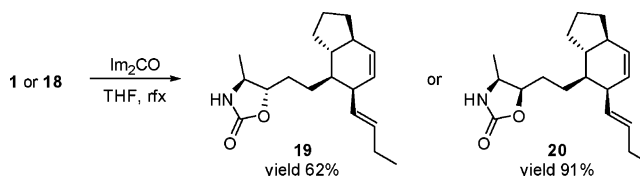
Most convincingly, we succeeded in crystallizing the cyclic carbamate **19** and obtaining its crystal structure.[22] For additional proof we compared the original NMR spectra of Boc-protected amaminol A (**16**) and cyclic carbamate **19** to those we obtained and found them to be indistinguishable.

Initially, we could not match the spectra of our synthetic amaminol A (**1**) to the originally reported spectra. Careful examination of the original isolation procedure revealed that the reported data are most likely for the corresponding trifluoroacetic acid salts of natural amaminols. Accordingly, after conversion of synthetic **1** to its corresponding TFA salt, the NMR spectra of the synthetic and the natural product matched.[1]

In summary, we have accomplished the first total synthesis of amaminol A (**1**) in 10 steps and 6.5% overall yield using a route based on organocatalytic intramolecular Diels−Alder reaction. We also developed an efficient practical method for selective conjugate reduction of enones. Crystallographic analysis of a derivate of amaminol A and synthetic correlation of the stereochemistry derived from L-alanine proves the relative and absolute stereochemistry of amaminols beyond question. The synthesis of amaminol analogues is currently in progress in our laboratory.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) Zampella, A.; Sepe, V.; D'Orsi, R.; Bifulco, G.; Bassarello, C.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2003**, *14*, 1787−1798. (b) Shin, Y.; Fournier, J.-H.; Balachandran, R.; Madiraju, C.; Raccor, B. S.; Zhu, G.; Edler, M. C.; Harnel, E.; Day, B. W.; Curran, D. P. *Org. Lett.* **2005**, 7, 2873−2876. (c) Alvarez-Ibarra, C.; Aras, S.; Bānón, G.; Fernández, M. J.; Rodrígues, M.; Sinisterra, V. *J. Chem. Soc.*, *Chem. Commun.* **1987**, 1509−1511.

(16) Abdel-Magid, A. F.; Koskinen, A. M. P. *Barium Hydroxide*, Electronic Encyclopedia of Reagents for Organic Synthesis; Paquette, L. A., Fuchs, P. L., Wipf, P., Crich, D., Eds.; John Wiley & Sons: Chichester, UK, 2007.

(17) (a) Minireview, on chiral copper hydrides: Rendler, S.; Oestreich, M. *Angew. Chem.*, *Int. Ed.* **2007**, *46*, 498−504. (b) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627−4630. (c) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J A.; Vivian, E. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779−2788. (d) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417−2420. (e) Yun, J.; Kim, D.; Yun, H. *Chem. Commun.* **2005**, 5181−5183. (f) Welle, A.; Díez-González, S.; Tinant, B.; Nolan, S. P.; Riant, O. *Org. Lett.* **2006**, *8*, 6059−6062. (g) Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* **1999**, *55*, 4573−4582. (h) Courmarcel, J.; Mostefaï, N.; Sirol, S.; Choppin, S.; Riant, O. *Isr. J. Chem.* **2001**, *41*, 231−240.

(18) Lee, D.-W.; Yun, J. *Tetrahedron Lett.* **2005**, *46*, 2037−2039.

(19) When PMHS was used, overreduction to **16** and **17** was observed.

(20) Without acetic acid, extensive C2 epimerization was observed.

(21) (a) Koskinen, A. M. P.; Koskinen, P. M. *Tetrahedron Lett.* **1993**, *34*, 6765−6768. (b) Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045−1056. (c) Lindsay, K. B.; Skrydstrup, T. *J. Org. Chem.* **2006**, *71*, 4766−4777. (d) Våbenø, J.; Brisander, M.; Lejon, T.; Luthman, K. *J. Org. Chem,* **2002**, *67*, 9186−9191. (e) Other reductants (DIBAL-H, L-Selectride) were *anti*-selective except (*S*)-Alpine hydride, which showed *syn*-selectivity but major contamination of the product.

(22) See the Supporting Information.