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Synthesis of (+)- and (−)-Monanchorin

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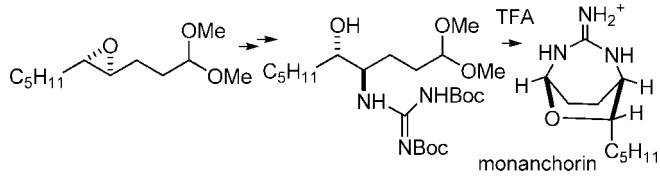
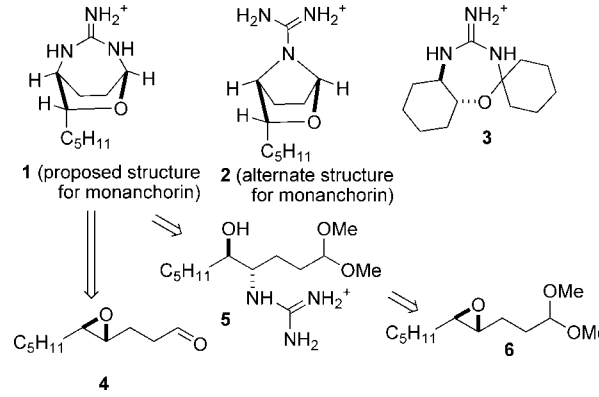
ABSTRACT



The optically pure epoxy acetal was converted to the protected guanidino alcohol by reaction with NaN_3 in DMF, hydrogenation of the azide, and reaction of the amine with MeSC(NBoc)NHBoc, $AgNO_3$, and Et_3N. Treatment of the protected guanidino alcohol with 9:1 $CDCl_3$/TFA afforded monanchorin, whose absolute stereochemistry was assigned as shown.

McKee and co-workers recently isolated the weakly cytotoxic monanchorin (**1**) from the sponge *Monanchora ungiculata* collected in the Maldive islands (see Scheme 1).[1] The carbon skeleton was assigned on the basis of 2D NMR experiments, leading to two possible aminal structures **1** and **2** that differ in the connection of the guanidine to the carbon chain. The ^{13}C NMR shifts fit better with calculated values for **1** suggesting that this is the correct structure. This is consistent with the known reaction of *trans*-2-hydroxycyclohexylguanidine with cyclohexanone to afford aminal **3**, whose structure has been established crystallographically.[2] Crambesidin acid was also isolated from this sponge, and other polycyclic crambescidin, ptilocaulin, and batzelladine guanidine alkaloids have been isolated from *Monanchora* sponges. As part of our continuing interest in the synthesis of these guanidine alkaloids,[3] we decided to investigate the synthesis of monanchorin.

Scheme 1. Retrosynthesis of Monanchorin



Monanchorin is the aminal formed from the intramolecular dehydration of *erythro*-4-guanidino-5-hydroxydecanal. Initially we decided to investigate the reaction of guanidine with epoxy aldehyde **4** hoping that the guanidine would add initially to the aldehyde and then to the proximal end of the epoxide to form a hemiaminal with regiochemical control.[4] Unfortunately, treatment of **4**[5] with guanidine resulted in decomposition. We then turned to

(1) Meragelman, K. M.; McKee, T. C.; McMahon, J. B. *J. Nat. Prod.* **2004**, *67*, 1165–1167.

(2) (a) Takagi, Y.; Kawashima, O.; Tsuchiya, T.; Sano, H.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3108–3112. (b) Nakamura, H.; Iitaka, Y. *Acta Crystallogr.* **1978**, *B34*, 3384–3387.

(3) (a) Snider, B. B.; Faith, W. C. *J. Am. Chem. Soc.* **1984**, *106*, 1443–1445. (b) Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 549–557. (c) Snider, B. B.; Chen, J. *Tetrahedron Lett.* **1998**, *39*, 5697–5700. (d) Yu, M.; Pochapsky, S. S.; Snider, B. B. *J. Org. Chem.* **2008**, *72*, 9065–9074.

(4) For a similar reaction with methoxide, see the conversion of **11** via an epoxy aldehyde to **12** in: Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888–2902.

(5) Prepared from 4*E*-decenal (**7**) by reduction to 4-decen-1-ol with $NaBH_4$, epoxidation with *m*CPBA, and oxidation of the alcohol with Dess-Martin periodinane.

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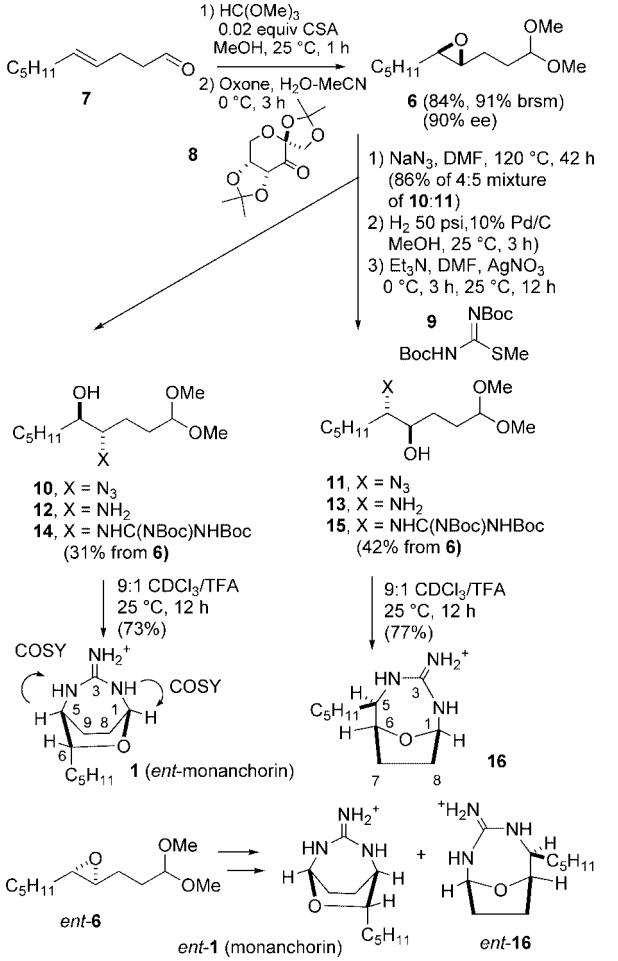
the nonregioselective preparation of guanidino hydroxy acetal **5** from epoxy acetal **6**.

Protection of 4*E*-decenal (**7**) with $HC(OMe)_3$ and camphorsulfonic acid (CSA) in MeOH afforded the acetal quantitatively, which was treated with Shi's D-fructose derived ketone (**8**)[6] and Oxone in H_2O/MeCN to give epoxy acetal **6** in 84% yield (91% brsm) and 90% ee[7] (see Scheme 2). Guanidine reacts as a nucleophile with terminal epoxides[8] and cyclohexene oxides[9] but failed to react with the more hindered *trans*-epoxide of **6**.

Scheme 2. Synthesis of (−)- and (+)-Monanchorin



We therefore treated **6** with NaN_3 in DMF at 120 °C for 42 h to provide an inseparable 4:5 mixture of **10** and **11** in 86% yield. Reaction of **6** with NaN_3 and NH_4Cl in 8:1 MeOH/H_2O at 80 °C for 24 h proceeded in slightly lower yield and gave a 3:5 mixture of **10** and **11**. Hydrogenation of the mixture of **10** and **11** at 50 psi over 10% Pd/C gave an inseparable mixture of **12** and **13**, which was treated with **9**, Et_3N, and $AgNO_3$[10] in DMF at 0 °C for 3 h and at 25 °C overnight to give a readily separable mixture of **14** (31% from **6**) and **15** (42% from **6**).[11]

Stirring **14** in 9:1 $CDCl_3$/TFA at 25 °C for 12 h cleaved both Boc groups and the methyl acetal forming the aminal monanchorin (**1**) as the only nonvolatile product. Flash chromatography (20:1 CH_2Cl_2/MeOH) gave pure **1** in 73% yield. Cross peaks in the COSY spectrum between H-1 at δ 4.81 and H-2 at δ 8.47 and between H-5 at δ 3.22 and H-4 at δ 8.66 confirmed that we had prepared **1**, not **2**. The ^1H and ^{13}C NMR spectral data of synthetic **1** are identical to those of monanchorin unambiguously establishing the structure of the natural product. The optical rotation of synthetic **1**, $[\alpha]_D^{22}$ −42.3 (*c* 0.74, MeOH), is similar in magnitude but opposite in sign to that of the natural product, [α] +39 (*c* 3.90, MeOH), establishing that **1** is the enantiomer of monanchorin.

Stirring **15** in 9:1 $CDCl_3$/TFA at 25 °C for 12 h gave **16** in 77% yield. A COSY cross peak between H-1 at δ 5.23 and H-2 at δ 8.73 established that different guanidine nitrogens are bound to C-1 and C-5 in **16**. A cross peak between H-5 at δ 3.46 and H-4 at δ 7.18 is not seen because the torsion angle is close to 90°.

The natural enantiomer of monanchorin (*ent*-**1**), $[\alpha]_D^{22}$ +33.7 (*c* 0.67, MeOH), was prepared analogously from *ent*-**6**, which was prepared from **7** using Shi's L-fructose derived ketone.[12]

In conclusion, we have developed an enantiospecific six-step route from 4*E*-decenal to monanchorin (*ent*-**1**) (21% overall yield) that establishes the absolute stereochemistry of the natural product and the connection of the guanidine to the carbon chain.

Acknowledgment. We are grateful to the National Institutes of Health (GM-50151) for support of this work. We thank Dr. Tanya C. McKee, NCI-Frederick, for a copy of the 1D and 2D NMR spectra of monanchorin.

Supporting Information Available: Complete experimental procedures and copies of ^1H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The ee was determined by analysis of the ^{13}C NMR spectrum in the presence of europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate].

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(10) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett.* **2001**, *3*, 2189–2191.

(11) The regiochemistry of **14** and **15** was established by COSY correlations from H-1 through H-4.

(12) Zhao, M.-X.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 5377–5379.