ORGANIC LETTERS

2002
Vol. 4, No. 6
991−994

Studies Toward the Synthesis of (−)-Zampanolide: Preparation of *N*-Acyl Hemiaminal Model Systems

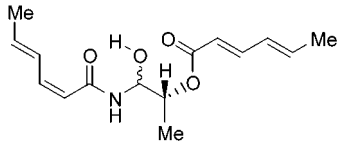
Dawn M. Troast and John A. Porco, Jr.*

Department of Chemistry and Center for Streamlined Synthesis, Metcalf Center for Science and Engineering, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

porco@chem.bu.edu

Received January 15, 2002

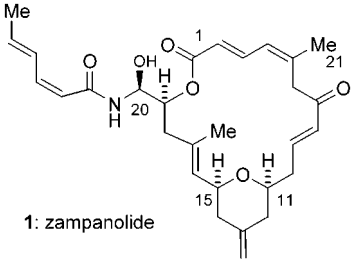
ABSTRACT



N-acyl hemiaminal zampanolide sidechain model

Synthesis of *N*-acyl hemiaminal model systems related to the side chain of the antitumor natural product zampanolide is reported. Key steps involve oxidative decarboxylation of *N*-acyl-α-amino acid intermediates, followed by ytterbium triflate mediated solvolysis. Evidence for stabilization of the *N*-acyl hemiaminal moiety in model compounds by an intramolecular hydrogen-bonding network is described.

The unique 20-membered macrolide (−)-zampanolide (**1**) was isolated in 1996 by Tanaka and Higa from the sponge *Fasciospongia rimosa*, collected near Okinawa, Japan.[1] This structurally interesting molecule has a high degree of unsaturation and an unusual *N*-acyl hemiaminal side chain.[2] In addition to its unique structure, zampanolide displays potent cytotoxic activity (1−5 ng/mL) against a number of tumor cell lines. Recently, Smith et al. reported the total synthesis and tentative stereochemical assignment of the antipode (+)-zampanolide in which the C(20) stereogenic center associated with the *N*-acyl hemiaminal was epimerized in a deprotection step, illustrating the lability of this functionality.[3] We have initiated studies on zampanolide as



1: zampanolide

a synthetic target and have focused our initial efforts on the synthesis of the unusual and unstable *N*-acyl hemiaminal side chain. In this Letter, we report the synthesis of *N*-acyl hemiaminal model compounds related to zampanolide, as

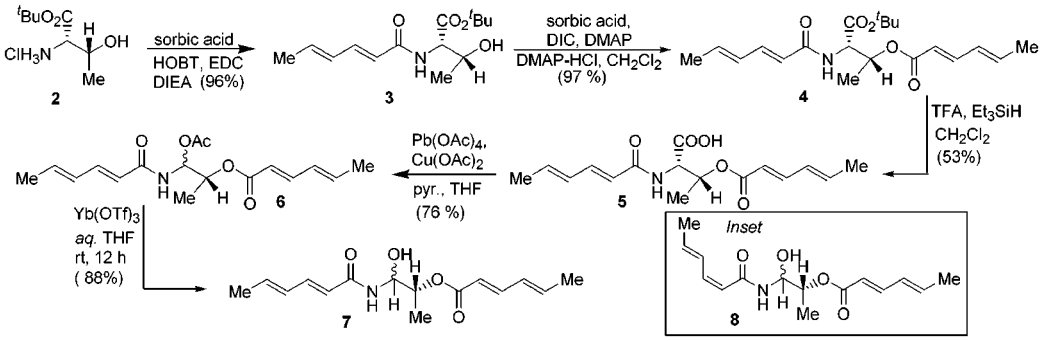
(1) (a) Tanaka, J.-i.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535−5538. (b) Higa, T.; Tanaka, J.-i.; Garcia Gravalos., D. PCT Int. Appl. WO 9710242 A1, 1997. For a related natural product (dactylolide) lacking the *N*-acyl hemiaminal side chain, see: (c) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.* **2001**, 775−778.

(2) For examples of *N*-acyl hemiaminal-containing natural products, see: (a) Echinocandin B: Benz, F.; Knuesel, F.; Nuesch, J.; Treichler, H.; Voser, W.; Nyfeler, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 2459−2477. (b) Spergualin: Umezawa, H.; Kondo, S.; Iinuma, H.; Kunimoto, S.; Ikeda, Y.; Iwasawa, H.; Ikeda, D.; Takeuchi, T. *J. Antibiot.* **1981**, *34*, 1622−1624. For *N*-acyl aminal natural products, see: (c) Mycalamides: Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Am. Chem. Soc.* **1988**, *110*, 4850−4851. (d) Pederin: Matsumoto, T.; Yanagiya, M.; Maeno, S.; Yasuda, S. *Tetrahedron Lett.* **1968**, 6297−6300. (e) Tallysomycins (glycosylcarbinolamide): Konishi, M.; Saito, K.; Numata, K.; Tsuno, T.; Asama, K.; Tsukiura, H. Naito, T.; Kawaguchi, H. *J. Antibiot.* **1977**, *30*, 789−805.

(3) Smith, A. B., III; Safanov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426−12427.

10.1021/ol025558l CCC: $22.00
Published on Web 03/01/2002

Scheme 1. Synthesis of Model *N*-Acyl Hemiaminals



well as spectroscopic evidence for their stabilization by intramolecular hydrogen bonding.

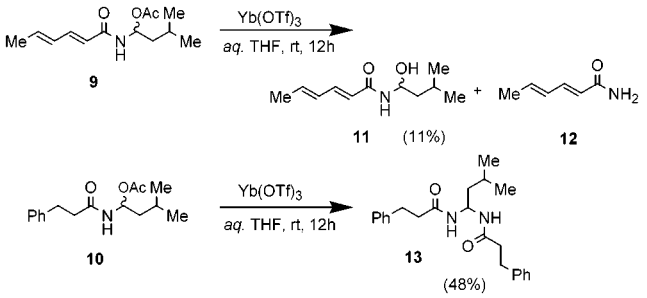
There are relatively few synthetic methods available for the preparation of *N*-acyl hemiaminals. Smith et al. constructed the *N*-acyl hemiaminal of (+)-zampanolide using a stereospecific Curtius rearrangement as a key step.[3] Direct condensation of amides and aldehydes has been reported but is generally limited to very electron-poor aldehydes[4,5] or unsubstituted amides[6] and typically affords *N*,*N*′-alkylidene bisamides via acyl iminium intermediates.[7] *N*-Acyl hemiaminals derived from acrylamide and protected amino aldehydes were obtained as undesired products in an attempted DABCO-mediated Baylis−Hillman reaction.[8] Recently, reduction of an *N*-acyl imidate[9] was used to prepare an *N*-acyl hemiaminal en route to a glycosylcarbinolamide.[10] We were encouraged by reports in which *N*-acyl hemiaminals were obtained as side products in oxidative decarboxylation of *N*-acyl-α-amino acids.[11] In line with our recent synthesis of enamides via elimination of *O*-acetyl-*N*-acyl-*N*,*O*-acetals,[12] we reasoned that these intermediates could be alternatively hydrolyzed under acidic conditions to afford *N*-acyl hemiaminals. Such a route should be amenable to late-stage installation of this labile functionality after construction of the macrolactone ring and would also permit synthesis of chemically stable precursors to zampanolide for biological evaluation.

The synthesis of *N*-acyl hemiaminal model systems related to zampanolide is illustrated in Scheme 1. L-Threonine was chosen as a model *β*-hydroxy-α-amino acid and 2,4-hexadienoic (sorbic) acid as a surrogate for the unsaturated lactone segment of the natural product. Commercially available L-threonine derivative **2** was acylated with sorbic acid to afford hydroxyamide **3**, which was further esterified with sorbic acid using Keck conditions[13] to furnish **4**. *tert*-Butyl ester removal was accomplished using TFA/Et_3SiH to afford acid **5**. Since we were unable to achieve direct conversion of the carboxylic acid to the *N*-acyl hemiaminal,[14] we focused on development of conditions to produce the acetate cleanly for solvolysis experiments. *N*-Acyl-α-amino acid **5** was subjected to oxidative decarboxylation to afford pure *N*,*O*-acetal **6** after extractive workup, with no evidence of *N*-acyl hemiaminal formation. A number of Lewis acid catalysts were then screened for the solvolysis **6** → **7**. After considerable experimentation, we found that $Yb(OTf)_3$ (20 mol %, aq. THF), followed by purification through a neutral alumina cartridge,[15] gave optimal results to afford *N*-acyl hemiaminal **7** (88%). Other acid catalysts either led to no reaction ($LiClO_4$), intolerably slow reactions ($Mg(ClO_4)_2$), or destruction of the compound (TMSOTf/CH_2Cl_2 or $BF_3{\cdot}Et_2O$/aq. CH_3CN[16]), the latter conditions affording considerable amounts of an aldehyde product by ^{1}H NMR spectroscopy. A series of analogous transformations was employed for the synthesis of the *Z*,*E* sorbamide-based *N*-acyl hemiaminal related to the zampanolide side chain. Acylation of **2** with (2*Z*,4*E*)-sorbic acid[17] afforded an amide product, which was converted in four steps to **8** (inset, Scheme 1). In the latter transformations, isomerization of the (*Z*,*E*)-diene was a significant concern, but fortunately the (*Z*)-olefin configuration was maintained throughout the synthesis without difficulty.

The generality of the $Yb(OTf)_3$-mediated solvolysis and the ability to cleanly prepare *N*-acyl hemiaminal products was further explored by examination of other *N*,*O*-acetals as shown in Scheme 2. Substrates lacking either one or both

(4) Glyoxylic acid: Schouteeten, A.; Christidis, Y.; Mattioda, G. *Bull. Soc. Chim. Fr*. **1978**, (5−6, Pt. 2), 248−254.
(5) Perhaloaldehydes: Ingrassia, L.; Mulliez, M. *Synthesis* **1999**, 1731−1738.
(6) Johnson, A. P.; Luke, R. W.; Steele, R. W.; Boa, A. N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 883−893.
(7) (a) Fernandez, A. H.; Alvarez, R. M.; Abajo, T. M. *Synthesis* **1996**, 1299−1301. (b) For a recent example, see: Labrecque, D.; Charron, S.; Rej, R.; Blais, C.; Lamothe, S. *Tetrahedron Lett*. **2001**, *42*, 2645−2648.
(8) Bussolari, J. C.; Beers, K.; Lalan, P.; Murray, W. V.; Gauthier, K.; McDonnell, P. *Chem. Lett*. **1998**, 787−788.
(9) Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1988**, *44*, 7063−7080.
(10) Sznaidman, M. L.; Hecht, S. M. *Org. Lett*. **2001**, *3*, 2811−2814.
(11) Corcoran, R. C.; Green, J. M. *Tetrahedron Lett.* **1990**, *31*, 6827−6830.
(12) Wang, X.; Porco, J. A., Jr. *J. Org. Chem*. **2001**, *66*, 8215−8221.
(13) Boden, E. P.; Keck, G. E. *J. Org. Chem*. **1985**, *50*, 2394−2395.
(14) Oxidative decarboxylation with $Pb(OAc)_4$, $Cu(OAc)_2$ with $^iPr_2EtN$ in THF afforded a mixture of *N*-acyl hemiaminal and acetate products, in low (10−20%) yields.
(15) A Waters Sep-Pak neutral alumina cartidge (12 cc, 2 g) was utilized. Attempted purification of *N*-acyl hemiaminal products such as **7** using silica gel chromatography led to low recoveries of product.
(16) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem*. **1987**, *52*, 62−35.
(17) Prepared by Stille coupling of tributyl-(1*E*)-1-propenyl-stannane with (*Z*)-3-iodoacrylic acid; cf. Abarbri, M.; Parrain, J.-L.; Cintrat, J.-C.; Duchene, A. *Synthesis* **1996**, 82−86.

Scheme 2. $Yb(OTf)_3$-Mediated Solvolysis of Other Substrates



of the sorbic side chains (e.g., **9** or **10**) were also evaluated in the hydrolysis protocol and did not give favorable results, presumably because of lack of stability of the *N*-acyl hemiaminal product. For example, hydrolysis of **9** led to a low yield of the desired *N*-acyl hemiaminal (**11**) and a significant amount of sorbamide (**12**). Similarly, hydrolysis of **10** led to none of the desired product but afforded the bisamide (**13**) as a major product.

The surprising stability of model compounds such as **7** and **8** in comparison to other *N*-acyl hemiaminals such as **11** may be due to stabilization resulting from a hydrogen-bonding network as well as electron-withdrawing effects of the unsaturated ester in **7** and **8**, which may discourage formation of transient iminium ion species. To evaluate potential hydrogen bond effects in these compounds, we obtained ^{1}H NMR spectra of the model systems **7** and **8** in acid-free $CDCl_3$. Figure 1 shows an expansion plot of the

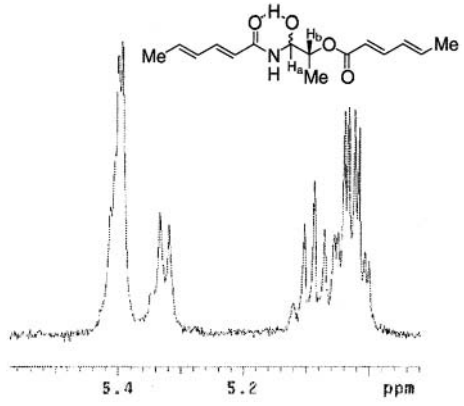


Figure 1. ^{1}H NMR spectrum of **7** in $CDCl_3$.

^{1}H NMR spectrum of *N*-acyl hemiaminal **7** in $CDCl_3$ after exhaustive D_2O exchange.[18] The epimeric H_a protons for the 1*R* and the 1*S* diastereomers occur at δ 5.3 and 5.4 ppm with J_{ab} = 7.0 and 2.0 Hz, respectively. MM2 calculations[19] were performed to determine if the observed vicinal ^{1}H NMR coupling constants were consistent with those predicted on the basis of a Karplus-type relationship.[20] The calculations are summarized in Figure 2 and show that for model system

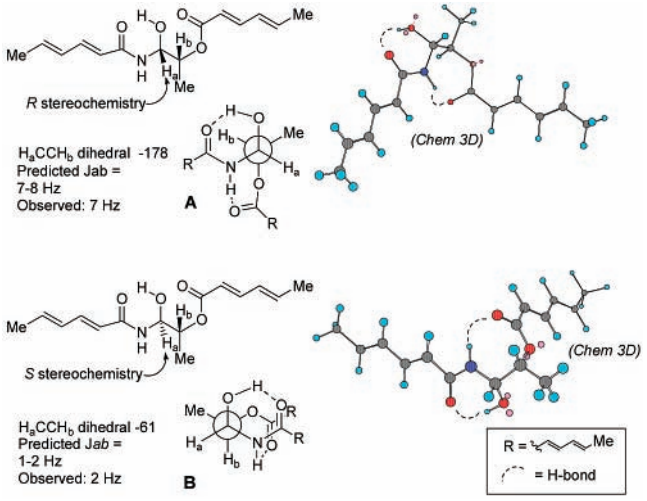


Figure 2. MM2 calculations for *N*-acyl hemiaminal model **7**.

7, each diastereomer has minimum energy conformers **A** and **B,** which are approximately equal in steric energy. However, in conformer **A** the H_aCCH_b dihedral angle (−178°) predicts a J_{ab} of 7−8 Hz by use of the Haasnoot−Altona equation, which includes a correction for electronegative substituents. In conformer **B**, the H_aCCH_b dihedral angle is −61°, which predicts a J_{ab} of 1−2 Hz. Analysis of both minimized conformations indicates that each contains a hydrogen bond between the amide carbonyl and the OH, and the ester carbonyl and amide NH. Support for this intramolecular hydrogen-bonding network was found by comparison of both the chemical shift and the D_2O exchange rate of amide protons. It has been reported that a hydrogen-bonded amide proton exhibits a downfield shift relative to a non-hydrogen-bonded NH.[21] The NH of **7** is shifted downfield 0.6−0.8 ppm relative to **11**,[22] which suggests that the amide proton of **7** is involved in an intramolecular hydrogen bond. H−D exchange experiments were performed at 8.0 mM[23] to compare the rate of exchange of the amide proton for **7** and **11**.[24] In these experiments, **11** showed complete H−D exchange within 5 min, whereas **7** was only half exchanged

(18) Related NMR experiments were performed with (*Z*,*E*) isomer **8**. However, in this compound the epimeric H_a protons (cf. Figure 1) overlapped in the ^{1}H NMR spectra, which led us to focus efforts on **7**.

(19) Molecular models were constructed using the MM2 energy minimization algorithm in CS Chem 3D Pro (Version 5.0).

(20) Haasnoot, C. A. G.; DeLeeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792. For a calculation program, see: http://www.kemi.slu.se/~stenutz/jhh.html.

(21) (a) Langenhan, J. M.; Fisk, J. D.; Gellman, S. H. *Org. Lett.* **2001**, *3*, 2559−2562. (b) Gardner, R.; Liang, G.-B.; Gellman, S. *J. Am. Chem. Soc.* **1999**, *121*, 1806−1816.

(22) **11**: δ NH = 5.91 ppm. **7**: δ NH = 6.74, 6.55 ppm.

(23) A study of δ NH versus concentration revealed that no intermolecular hydrogen boding occurs at ≤16.0 mM. See Supporting Information for further details.

(24) For a pertinent study, see: Tonan, K,; Adachi, K.; Ikawa, S.-i. *Spectrochim. Acta, Part A* **1998**, *54*, 989−997.

after 2 h, which provides further evidence for an intramolecular hydrogen-bond network in zampanolide model compounds.

Interestingly, there is literature precedent for stabilization of an *N*-acyl hemiaminals such as **7** and **8** by hydrogen-bonded networks (Figure 3).[8] Compounds such as **14** were

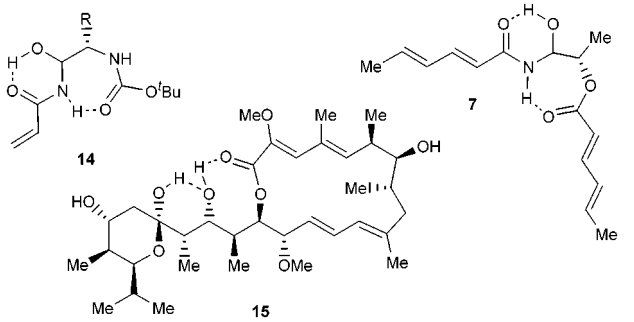


Figure 3. Hydrogen bonding networks.

found to be stable to chromatography conditions and to have good shelf lives, likely as a result of stabilization provided by intramolecular hydrogen bonding. Moreover, it is conceivable that the hydrogen bonding observed in model systems **7** and **8** may indicate that structural rigidity of the *N*-acyl hemiaminal side chain is important for the cytotoxicity of zampanolide. In support of this notion, the potent vacuolar H^+-ATPase inhibitor, bafilomycin A_1 (Figure 3, **15**) has been shown to form a unique H-bonding network that causes a particular topology in the molecule, which has been proven irreplaceable for its biological activity.[25]

In summary, we have synthesized *N*-acyl hemiaminal model compounds related to the side chain of the unique antitumor natural product zampanolide. Key steps involve oxidative decarboxylation of suitably functionalized *N*-acyl-α-amino acids to afford *O*-acetyl-*N*-acyl-*N*,*O*-acetal intermediates and solvolysis using aqueous ytterbium triflate. We have also found spectroscopic evidence in nonpolar solvents for the stabilization of model compounds through a hydrogen-bonding network that may have implications for the biological activity of zampanolide itself. Further studies related to the total synthesis of zampanolide and related analogues are in progress and will be reported in due course.

Acknowledgment. We thank Professor John Snyder (Boston University) and Dr. William V. Murray (The R.W. Johnson Pharmaceutical Research Institute) for helpful discussions and Waters, Inc. for providing extraction columns.

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

OL025558L

(25) (a) Everett, J. R.; Baker, G. H.; Dorgan, R. J. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 717−724. (b) Sundquist, K.; Lakkakorpi, P.; Wallmar, B.; Vaananen, K. *Biochem. Biophys. Res. Commun.* **1990**, *168*, 309−313.