ORGANIC LETTERS

2003
Vol. 5, No. 9
1495−1498

An Oxidative Entry into the Amido Trioxadecalin Ring System

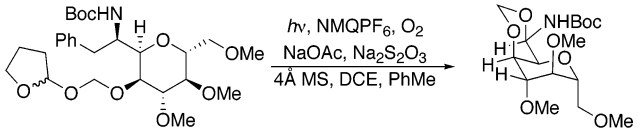
Jason C. Rech and Paul E. Floreancig*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

florean@pitt.edu

Received February 17, 2003

ABSTRACT



The amido trioxadecalin ring system is a key structural component of the architecturally interesting anticancer and immunosuppressive agents of the mycalamide, theopederin, and onnamide families of natural products. We report a new entry into this structure in which a mixed acetal serves as a surrogate for a formaldehyde hemiacetal in an addition to an oxidatively generated acyliminium ion. The stereochemical outcome of this process can be explained by the conformational preferences of the product ring system.

Single-electron oxidation processes provide access to electrophilic intermediates under essentially neutral reaction conditions,[1] thereby creating opportunities for designing unique transformations that would be difficult or impossible to execute in acidic media. In conjunction with our program directed toward exploiting single-electron oxidation reactions in organic chemistry,[2] we have initiated synthetic studies of the mycalamide family of natural products in which an electron transfer initiated cyclization (ETIC) reaction serves as the key operation. Mycalamides A (**1a**) and B (**1b**) are structurally intriguing natural products from the New Zealand sponge *Mycale* sp.[3] that are related to the onnamides, the theopederins, and pederin. This family of compounds displays an impressive array of biological activities, with mycalamide B exhibiting cytotoxicity toward P388 leukemia cells at an IC_{50} value of 1.3 nM[3b] and suppressing T-cell proliferation more effectively than the immunosuppressant FK506.[4] In addition to their biological activity, their unique framework and scarcity from natural sources make these molecules attractive synthetic targets.[5] The most notable structural feature in the mycalamides is the sensitive amido trioxadecalin ring system. Two general synthetic approaches to this subunit have been developed. Kishi described[5a] the preparation of an amino trioxadecalin system and its subsequent acylation. Roush[5c] approached the system through a Curtius reaction of a trioxadecalin carboxylic acid. Although these approaches are impressive in their ability to access the unusual ring system, both create subsequent problems in chemical reactivity and/or stereocontrol. Acylations of amino trioxadecalins proceed efficiently, but anomeric stereocontrol is limited. The Curtius approach solves the stereochemical problem, but the resulting carbamates are difficult to acylate, thereby complicating the completion of the synthesis. In consideration of the essential role of the C10 amido acetal in the biological activity of the mycalamides,[6] we have developed a new approach to this ring system as the basis for synthetic efforts toward these

(1) (a) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550. (b) Baciocchi, E.; Bietti, M.; Lanzalunga, O. *Acc. Chem. Res.* **2000**, *33*, 243.

(2) (a) Seiders, J. R., II; Wang, L.; Floreancig, P. E. *J. Am. Chem. Soc.* **2003**, *125*, 2406. (b) Kumar, V. S.; Floreancig, P. E. *J. Am. Chem. Soc.* **2001**, *123*, 3842. (c) Kumar, V. S.; Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2001**, *3*, 4123.

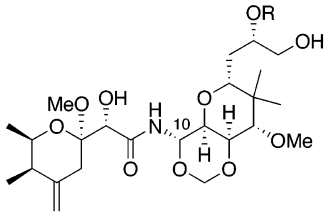
(3) (a) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Am. Chem. Soc.* **1988**, *110*, 4850. (b) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223.

(4) Galvin, F.; Freeman, G. J.; Razi-Wolf, Z.; Benacerraf, S.; Nadler, L.; Reiser, H. *Eur. J. Immunol.* **1993**, *23*, 283.

(5) For total syntheses of the mycalamides, see: (a) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242. (b) Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9693. (c) Roush, W. R.; Pfeifer, L. A. *Org. Lett.* **2000**, *2*, 859. (d) Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T. *Synlett* **1998**, 869. (e) Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357. For formal syntheses, see: (f) Nakata, T.; Matsukura, H.; Jian, D.; Nagashima, H. *Tetrahedron Lett.* **1994**, *35*, 8229. (g) Nakata, T.; Fukui, H.; Nakagawa, T.; Matsukura, H. *Heterocycles* **1996**, *42*, 159. (h) Toyota, M.; Hirota, M.; Hirano, H.; Ihara, M. *Org. Lett.* **2000**, *2*, 2031.

10.1021/ol034273l CCC: $25.00
Published on Web 04/05/2003

compounds and their analogues. In this Letter we report that our ETIC method provides an excellent approach to model cyclic amido acetals. We also report a new functional equivalent of formaldehyde hemiacetals and an unusual conformational dynamic that merits consideration in further synthetic studies of these compounds.



1a: R = H
1b: R = Me

Figure 1. Mycalamides A and B.

We envisioned the amido trioxadecalin ring system as arising from the addition of a formaldehyde hemiacetal or its functional equivalent[7] into an acyliminium ion, as shown in Figure 2. The sensitivity of both the nucleophile and the

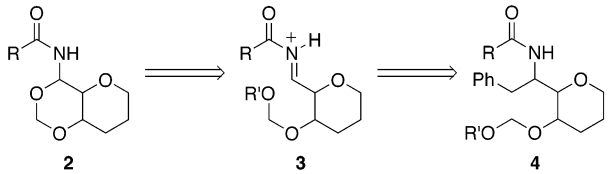


Figure 2. ETIC approach to the amido trioxadecalin ring system.

product mandates that mild reaction conditions be employed for the generation of the acyliminium ion. Recently we reported[8] that radical cations of homobenzylic amides and carbamates undergo mesolytic cleavage of their benzylic carbon−carbon bonds to form acyliminium ions under essentially neutral conditions. Thus, we view acyliminium ion **3** as coming from homobenzylic amide **4**. This approach allows the left portion of the mycalamides to be introduced by acylation of an amine and utilizes the chirality in the tetrahydropyran ring to control the stereochemistry of the nascent acylaminal.

The evolution of our formaldehyde hemiacetal surrogate is shown in Figure 3. Attempts to use an in situ generated formaldehyde hemiacetal of **5** directly were not successful. Our previous successful uses of acetals as functional

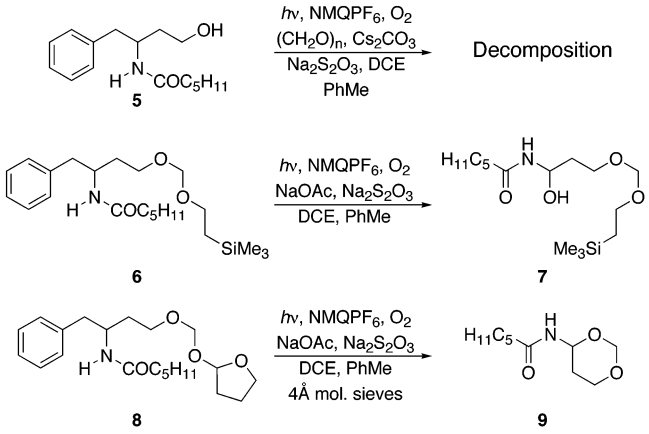


Figure 3. Development of a hemiacetal surrogate.

equivalents of alcohols in these reactions led us to postulate that mixed acetals could serve as hemiacetal surrogates, as shown in Figure 4. Exposing SEM-ether **6** to our standard

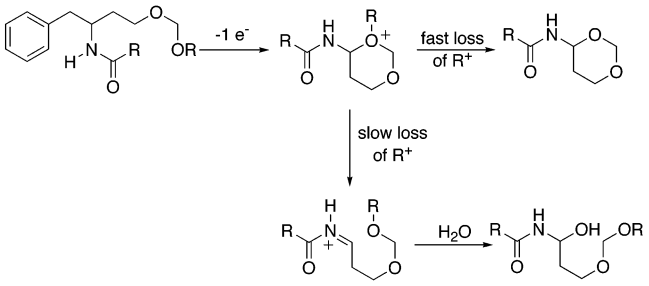


Figure 4. Fates of the intermediate oxonium ion.

ETIC conditions (*hν*, medium-pressure mercury lamp, Pyrex filtration, *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$), O_2, NaOAc, $Na_2S_2O_3$, 1,2-dichloroethane, toluene), however, provided the surprisingly stable[9] *N*-acyl hemiaminal **7** in 69% yield. The rapid conversion of **6** to **7** contrasts with the slow reactions we have observed between trace amounts of water and the radical/ion pairs that act as the relevant electrophiles in these processes. Therefore we posit that **7** arises from cyclization to form the expected oxonium ion, which instead of losing the trimethylsilylethyl group reopens to form the more stable acyliminium ion (Figure 4). The acyliminium ion, in the absence of an associated benzyl radical, then reacts with adventitious water to produce **7**. On the basis of this analysis, we realized that the rate of oxonium ion decomposition through alkyl group loss must be enhanced to provide the amido acetal. In confirmation of this hypothesis, subjecting tetrahydrofuranyloxymethyl ether **8** to our standard reaction conditions in

(6) (a) Thompson, A. M.; Blunt, J. W.; Munro, M. H. G.; Clark, B. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1025. (b) Richter, A.; Kocienski, P.; Raubo, P.; Davies, D. E. *Anti-Cancer Drug Dev.* **1997**, *12*, 217.

(7) Synthetic applications of hemiacetals: (a) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 403. (b) Overman, L. E.; Campbell, C. B. *J. Org. Chem.* **1974**, *39*, 1474.

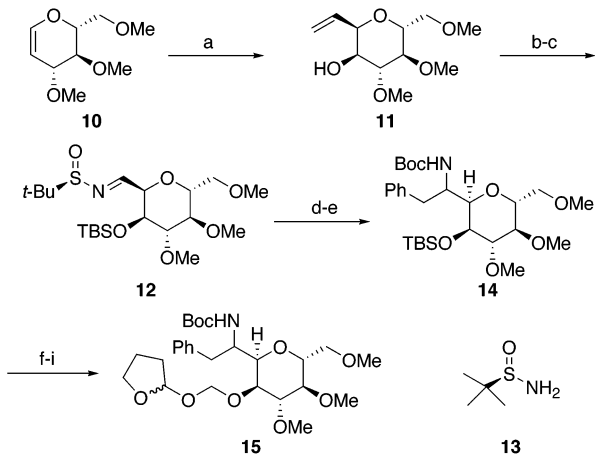
(8) Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2002**, *4*, 3443.

(9) For an interesting discussion of hydrogen bonding as a structural stabilizing feature in *N*-acyl hemiaminals, see: Troast, D. M.; Porco, J. A., Jr. *Org. Lett.* **2002**, *4*, 991.

the presence of 4 Å molecular sieves produced acylaminal **9** in 79% yield.

The trimethyl ether of glucal (**10**) served as the starting material for our extension of this work to a system that is more relevant to the synthesis of the mycalamides (Scheme 1). Epoxidation of **10** with dimethyl dioxirane[10] followed

Scheme 1[a]



[a] Reagents and conditions: (a) i. dimethyldioxirane, CH_2Cl_2, 0 °C; ii. trivinylalane, THF, −60 °C to rt, 62%. (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 77%. (c) i. O_3, CH_2Cl_2, −78 °C, then Ph_3P; ii. **13**, Ti(O-*i*Pr)$_4$, CH_2Cl_2, 71%. (d) BnMgCl, CH_2Cl_2, −78 °C, then MeOH, HCl. (e) Boc_2O, Et_3N, CH_2Cl_2, reflux, 68% for 2 steps. (f) Bu_4NF, THF, 76%. (g) butenyl chloromethyl ether, *i*-Pr_2NEt, CH_2Cl_2, reflux, 97%. (h) BH_3·THF, THF, 0 °C, then NaOOH, 93%. (i) $PhI(OAc)_2$, I_2, *hν*, DCE, 64%.

by opening with trivinylalane,[11] in accord with Rainier's studies,[12] proceeded to form **11** as a single diastereomer. Sulfinyl imine **12** was accessed from **11** through hydroxyl group protection, oxidative olefin cleavage, and condensation with Ellman's sulfinamide **13**.[13] The instability of the aldehyde intermediate in this sequence dictated that it be carried into the condensation step without purification. Addition of benzylmagnesium chloride to **12** followed by auxiliary cleavage and carbamate formation provided homobenzylic carbamate **14**. Although this addition proceeded with complete diastereoselectivity, the stereochemistry of the resulting inconsequential stereocenter was not determined. The hemiacetal surrogate was installed through a sequence of silyl deprotection, conversion of the resulting hydroxyl group to a butenoxymethyl ether,[14] hydroboration/oxidation of the terminal olefin, and oxidative etherification under Suarez' conditions.[15]

Oxidative cyclization of **15** proceeded with excellent efficiency to provide a 94% yield of **16** and **17** as a 10:1 mixture (Figure 5). In contrast to our expectations, $^1H-^1H$

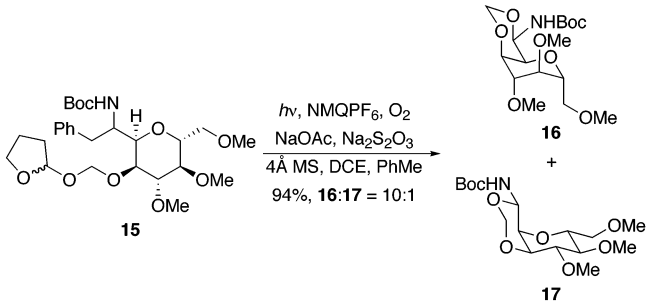


Figure 5. Oxidative entry into the amido trioxadecalin ring system.

NMR coupling constants revealed that **16** adapts a conformation that places the majority of the substituents on the tetrahydropyran ring in axial orientations. This result, as well as the stereochemistry of the newly formed acylaminal center, was confirmed by a NOESY experiment. The tetrahydropyran ring in **17** showed the expected conformation as determined by NOESY and $^1H-^1H$ coupling constants.

The unexpected stereochemical outcome[16] of the cyclization reaction warrants further discussion. Our previous observation that the intermediate oxonium ion in these transformations is unstable relative to the acyliminium ion implies a late transition state for the cyclization that reflects the conformational biases of the product (Figure 6). The preferential formation of **16**, therefore, indicates that **19** is more stable than **18**. The source of this energetic difference can be attributed to the conformational energetics of the *cis*-trioxadecalin ring system. Fuchs and co-workers calculated[17] that conformation **20** (Figure 7) of the parent ring system (the conformation reported for the mycalamides) is 4.3 kcal/mol higher in energy than conformation **21** (observed in **16**). This preference was ascribed to the presence of strongly disfavored *gauche*-CCOC interactions in **20** in contrast to the *anti*-relationships found in **21**. The energetic penalty conferred by the axial substituents in **19** is partially offset by the equatorial orientation of the sterically demanding branched carbon that bears the carbamate group. This balance is supported by our observation of ∼4 Hz $^1H-^1H$ coupling constants around the tetrahydropyran ring of **15**, indicative of a nearly 1:1 mixture of conformers.[18] Although the stabilities of the intermediate oxonium ions need not reflect

(10) (a) Murray, R. W.; Jeyaraman, T. *J. Org. Chem.* **1985**, *50*, 2847. (b) Adam, W.; Bialas, J.; Hadjcarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377. (c) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

(11) Saulnier, M. G.; Kadow, J. F.; Tun, M. M.; Langley, D. R.; Vyas, D. M. *J. Am. Chem. Soc.* **1989**, *111*, 8320.

(12) (a) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997. (b) Rainier, J. D.; Cox, J. M. *Org. Lett.* **2000**, *2*, 2707.

(13) (a) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011. (b) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (c) Tang, T. P.; Volkman, S. K.; Ellman, J. E. *J. Org. Chem.* **2001**, *66*, 3707.

(14) Bedford, C. D.; Harris, R. N., III.; Howd, R. A.; Goff, D. A.; Koolpe, G. A.; Petesch, M.; Koplovitz, I.; Sultan, W. E.; Musallam, H. A. *J. Med. Chem.* **1989**, *32*, 504.

(15) de Armas, P.; Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Chem. Soc., Perkin Trans. 1* **1989**, 405.

(16) For other reports of the inverted conformer in mycalamide studies, see: (a) Roush, W. R.; Marron, T. G. *Tetrahedron Lett.* **1993**, *34*, 5421. (b) Hoffman, R. W.; Schlapbach, A. *Tetrahedron Lett.* **1993**, *34*, 7903.

(17) Golender, L.; Senderowitz, H.; Fuchs, B. *THEOCHEM* **1996**, *370*, 221.

(18) For example, see: Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825.

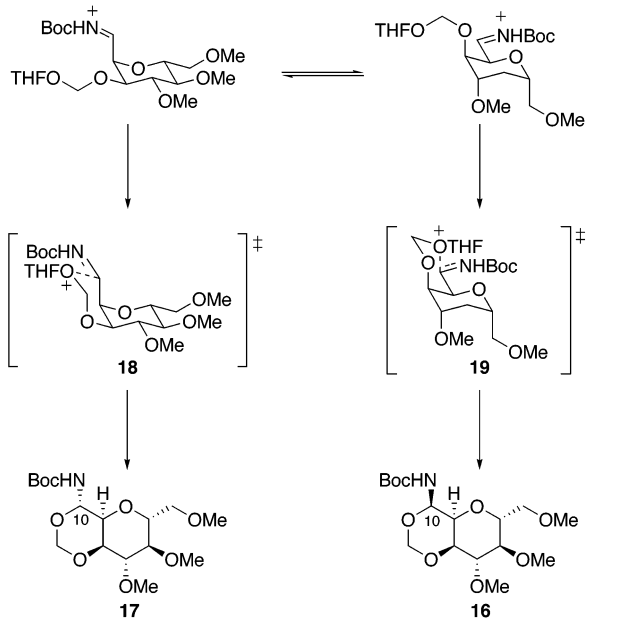


Figure 6. Competing cyclization pathways. An axial methoxy group in the right series was deleted for clarity.

those of the neutral products, calculations (MM3) show **16** to be 4.4 kcal/mol lower in energy than **17**, suggesting that analyses of product stabilities could prove to be useful in designing substrates that cyclize to provide the requisite stereochemical outcome for mycalamide synthesis. Of note,

Figure 7. *Gauche*-(red) and *anti*-(blue) CCOC interactions in the trioxadecalin ring system.

calculations show the mycalamides to be 3 kcal/mol lower in energy than the 10-*epi*-mycalamides.

In summary, we have developed a new oxidative entry into the amido trioxadecalin ring system in which a mixed acetal serves as a functional equivalent of a formaldehyde hemiacetal and adds into an oxidatively generated acyliminium ion. We have shown that the electrofugacity of the tetrahydrofuranyl cation makes the tetrahydrofuranyloxymethyl ether an excellent hemiacetal surrogate. The *cis*-stereochemical relationship required for the synthesis of our mycalamide model was formed with high selectivity through a sequence of glycal epoxidation followed by trivinylalane-mediated addition, and the homobenzylic carbamate was generated through a diastereoselective addition to a sulfinyl imine. The stereochemical outcome of the oxidative cyclization was controlled by the preference for the "inverted" conformation of the ring system in the late transition state that results from a minimization of energetically unfavorable CCOC *gauche*-interactions. We are currently developing strategies for inverting the conformational preference in our substrates in order to reverse the stereochemical outcome of the process.[19] Results of these studies will be reported in due course.

Acknowledgment. This work was supported by generous funding from the National Science Foundation, the National Institutes of Health (GM-62924), the Petroleum Research Fund, and the Research Corporation (Research Innovation Award). We thank Prof. Jon Rainier (University of Utah) for a helpful discussion and Prof. Chris Schafmeister for assistance with NMR experiments.

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

OL034273L

(19) Preliminary studies have shown that the inclusion of geminal methyl groups, as required for mycalamide synthesis, significantly reduces the conformational dynamics of the tetrahydropyranyl ring. Rech, J. C., unpublished results.