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Published on Web 01/27/2004

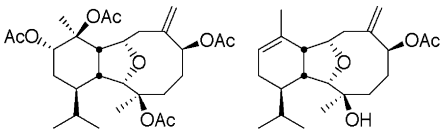
Toward a General Route to the Eunicellin Diterpenes: The Asymmetric Total Synthesis of Deacetoxyalcyonin Acetate

Gary A. Molander,* David J. St. Jean, Jr., and Julia Haas

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

Received November 28, 2003; E-mail: gmolandr@sas.upenn.edu

The eunicellin diterpenes (cladiellins) are a family of marine metabolites isolated from a variety of soft corals and octocorals.[1] Since the isolation of eunicellin (**1**), the first member of this class,[2] over 60 additional members have been reported.[1c,3] As a consequence of their structural complexity and exciting biological activity,[3] the eunicellin diterpenes have received considerable attention from the synthetic community.[4] A challenging structural motif common to all of the eunicellin diterpenes is the hydroisobenzofuran core. We envisioned that this core could be rapidly constructed utilizing a Lewis acid-mediated [4+3] annulation, a method developed in our laboratories.[5,6] Herein, we report the facile construction of this structural motif and its further elaboration to deacetoxyalcyonin acetate **2**.[7,8]

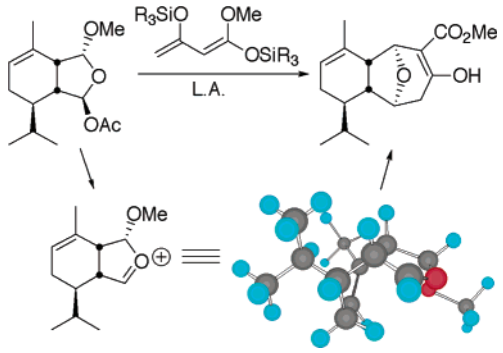


The annulative approach envisioned required a chemically differentiable surrogate for a *cis*-1,2-dialdehyde, such as a bis-acetal, to serve as a dielectrophile. Upon exposure to a Lewis acid, this bis-acetal would ionize selectively to give a single oxocarbenium ion, activating that center toward nucleophilic attack (Scheme 1). A second ionization, followed by cyclization, would assemble the hydroisobenzofuran core present in the eunicellin diterpenes in a single operation. The stereochemistry of the process would be controlled by approach of the nucleophile from the convex face of the bicyclic ionic intermediate. Subsequent alkylation followed by ring expansion would lead to the fully elaborated eunicellin core.

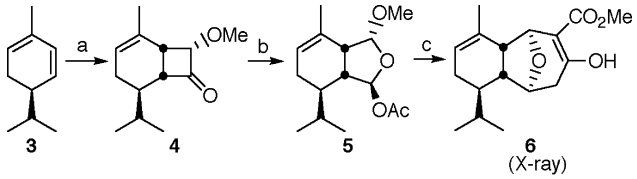
The synthetic sequence initiated to achieve this goal began with the thermally induced [2+2] cycloaddition reaction between methoxy ketene[9,10] and commercially available α-phellandrene **3** (Scheme 2). Photochemical rearrangement of cyclobutanone **4** yielded the desired mixed acetal **5** in high yield with complete retention of the stereocenter adjacent to the carbonyl.[11] Mixed bis-acetal **5** underwent a $TiCl_4$-mediated [4+3] annulation at low temperatures with complete regio- and stereoselectivity, thus realizing a novel approach to differentiate the 1,2-dialdehyde equivalent as required. Notably, in the first three steps of the synthesis, five of the seven stereocenters present in deacetoxyalcyonin acetate have been incorporated, as well as the common hexahydroisobenzofuran core present in the eunicellin diterpenes.

With the desired annulation product **6** in hand, alkylation at the γ-position of the β-keto ester was achieved through a completely diastereoselective methylation of the dianion (Scheme 3).[12] Decarboxylation using Krapcho conditions not only effected the methyl decarboxylation,[13] but also epimerized the newly formed stereocenter to yield a separable mixture of methyl ketones **7** and **8**. For stereoelectronic reasons, only the major diastereomer **8** could be converted to the desired silyl enol ether.[14] Fortunately, the undesired diastereomer **7** could be recycled by epimerization (3.5:1 β-Me/α-Me) under standard conditions. Regioselective silyl enol ether formation[15] followed by reaction with phenylselenenyl chloride and subsequent oxidation produced exocyclic enone **10**.[16] 1,4-Addition using bis-(ethoxyvinyl) cuprate,[17] trapping with Comins' reagent,[18] and acid-mediated cleavage of the ethyl enol ether yielded the desired aldehyde **11** in good overall yield. Further elaboration of enol triflate **11** using an intramolecular Nozaki−Hiyama−Kishi coupling[19] provided desired cyclopentanols **12** and **13** in high overall yield, albeit with low selectivity. This low selectivity, however, was not a serious concern because the undesired alcohol **13** could be recycled via a Mitsunobu inversion.

Scheme 1



Scheme 2 [a]



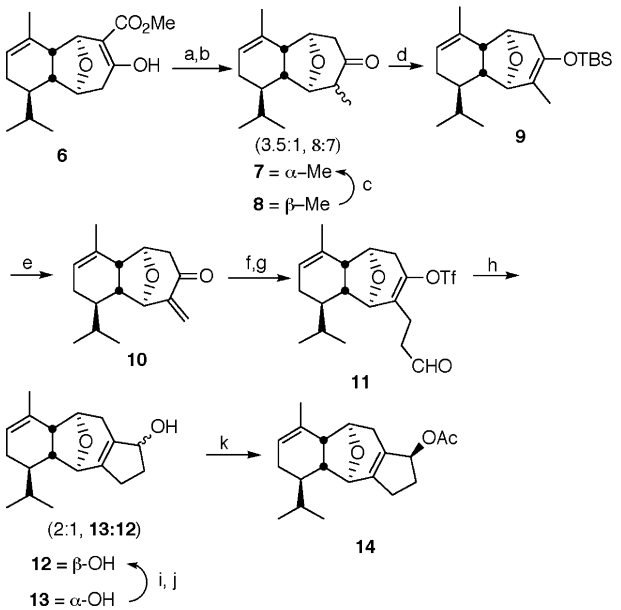
[a] (a) Methoxyacetyl chloride, NEt_3 (25%); (b) AcOH, *hν* (86%); (c) 1-methoxy-1,3-bis(triethylsilanyloxy)buta-1,3-diene, $TiCl_4$, −80 °C (43−80%).

Unfortunately, selective oxidative cleavage of allylic alcohol **13** (ozonolysis, dihydroxylation, etc.) could not be achieved under a variety of conditions. However, after conversion of the allylic alcohol **13** to its acetate **14**, chemoselective epoxidation of the trisubstituted alkene could be accomplished (Scheme 4). Oxidative cleavage of allylic acetate with ozone yielded epoxy dione **15** in 42% yield over two steps.[20] Reduction of epoxide **15** using Sharpless' reagent provided the desired olefin **16**.[21]

To complete the synthesis, chemoselective silyl enol ether formation followed by olefination and hydrolysis of the TBS enol ether with 1 M HCl provided **17** in high yield. Finally, a chemo- and diastereoselective methylation of ketone **17** provided deacetoxyalcyonin acetate **2**.[22] The spectroscopic data were indistinguishable from those of the natural product.[8]

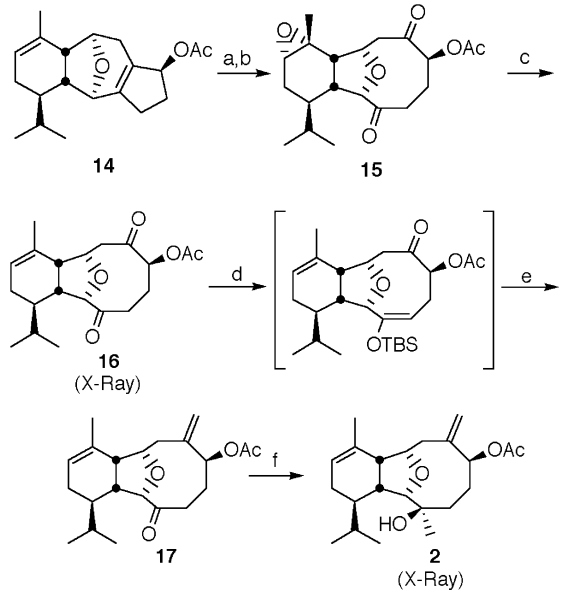
10.1021/ja0398464 CCC: $27.50

Scheme 3 [a]



[a] (a) 2.15 equiv *n*-BuLi, LiCl, −78 °C, then MeI; (b) LiCl, H_2O, DMSO, 130 °C (50% over two steps); (c) NaOMe, MeOH, reflux (100% BRSM, 3.5:1 **8**:**7**; (d) TBSCl, KH, −78 °C to room temperature (95%); (e) PhSeCl −78 to 0 °C, then *m*-CPBA, 0 °C (75%); (f) *cis*-1-bromo-2-ethoxyethylene, *t*-BuLi, 1 h, −78 °C, then CuBr DMS, −78 °C, 1 h, then Comins reagent, −78 °C, 2 h; (g) THF/1 M HCl (2:1) (71% over two steps); (h) $CrCl_2$, $NiCl_2$ (cat.) DMF/THF, room temperature, 12 h (88%); (i) DEAD, BzOH, PPh_3, room temperature, 12 h; (j) MeONa, MeOH, 12 h (71% over two steps); (k) Ac_2O, pyr, DMAP, room temperature, 30 min (100%).

Scheme 4 [a]



[a] (a) *m*-CPBA, 0 °C, 1 h; (b) O_3, −78 °C, then DMS, room temperature, 3 h (43% over two steps); (c) WCl_6, 2.0 equiv of *n*-BuLi (93%); (d) TBSOTf, KHMDS, −78 °C; (e) Ph_3PCH_3Br, *t*-BuOK, THF, 0 °C, then 1 M HCl (61% over two steps); (f) MeLi, $YbOTf_3$, −78 °C (66% BRSM).

In conclusion, the hydroisobenzofuran core present in the eunicellins was constructed in a concise manner utilizing a [4+3] Lewis acid-mediated annulation. A unique strategy to chemodifferentiate 1,2-dialdehyde equivalents was unveiled in this process. The intermediate generated in the annulation was carried on to complete a short synthesis of deacetoxyalcyonin acetate (**2**). Applications of this annulation to the synthesis of other eunicellin diterpenes, as well as further optimization of this route, are currently underway.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (GM35249) for the generous support of this work. We also would like to thank Dr. Pat Carroll for performing the X-ray crystal structure determinations and Dr. Rakesh Kohli for performing the HRMS analyses.

Supporting Information Available: Experimental details and structural data for all new compounds, as well as X-ray structure data for compounds **2**, **6**, **8**, and **16** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0398464