Enantioselective Total Synthesis of (−)-7-Deacetoxyalcyonin Acetate. First Synthesis of a Eunicellin Diterpene

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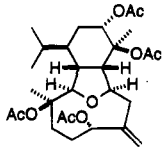
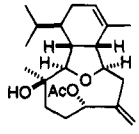
Received July 14, 1995

Eunicellin diterpenes are a family of marine metabolites obtained from gorgonian and soft corals. Eunicellin (**1**), the first member of this family to be described,[1] was isolated in 1968 by Djerassi, Kennard, and co-workers from the coral *Eunicella stricta*. Over 50 other related structures have been reported including (−)-7-deacetoxyalcyonin acetate (**2**), which was obtained from a *Cladiella* species of soft coral.[2] Biological activity in this series has not been extensively studied,[3] although evidence suggests that the natural role of some of these metabolites is to deter mollusk predation.[4] The eunicellin diterpenes are characterized by a unique tricyclic ring system containing hydroisobenzofuran and oxonane subunits. Herein we disclose the first total synthesis of a member of the eunicellin diterpene family.[5] This enantioselective total synthesis confirms the relative and absolute stereochemistry of (−)-7-deacetoxyalcyonin acetate (**2**) proposed by Uchio and co-workers[2] and outlines a practical method for access to substantial quantities of **2** and related eunicellin diterpenes.



eunicellin (**1**)



(−)-7-deacetoxyalcyonin acetate (**2**)

The defining reaction of our total synthesis strategy is the stereoselective Prins-pinacol condensation−rearrangement[6] of a dienyl diol **3** with an aldehyde to assemble the 2-oxabicyclo-[4.3.0]non-4-ene **4** (Figure 1). This reaction comprehensively deals with all the stereochemical and structural issues posed by the bicyclic core of the eunicellin diterpenes. The stereochemical outcome of this condensation−rearrangement can be anticipated from the analysis depicted in Figure 1. Prins cyclization of the more stable (*E*)-oxocarbenium ion intermediate[7] should occur preferentially in a chair topography from the diene face opposite the isopropyl substituent; this transition structure moreover places the R^1 substituent in a favored equatorial orientation.[6]

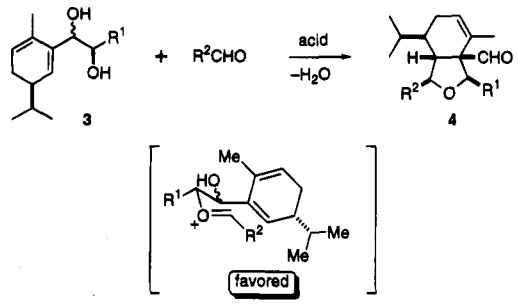
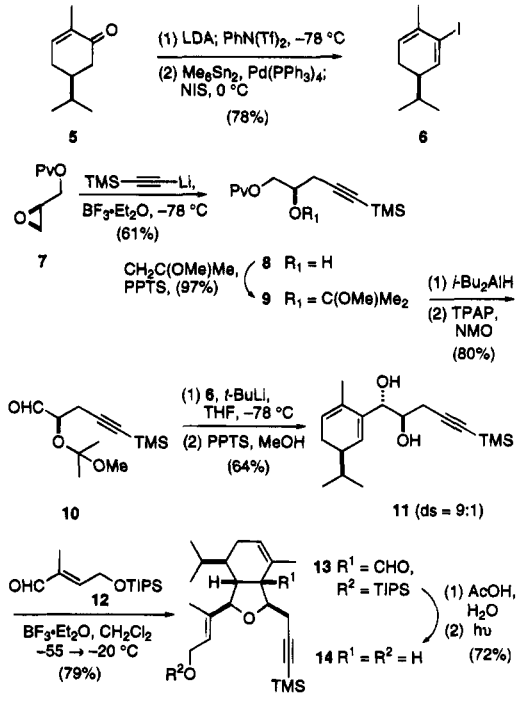


Figure 1. Stereochemical analysis of the Prins-pinacol reaction.

Scheme 1



Synthesis of the bicyclic core of **2** is summarized in Scheme 1. The (*R*)-dienyl iodide **6**[8] was first accessed in 78% overall yield by conversion of (*S*)-dihydrocarvone **5** (available in one step from (*S*)-carvone)[9] to the kinetic enol triflate derivative,[10] followed by palladium-catalyzed coupling with hexamethylditin,[11] and subsequent *in situ* iodination with *N*-iodosuccinimide (NIS).[12] Regioselective opening[13] of (*S*)-glycidyl pivalate (**7**)[14] with lithium (trimethylsilyl)acetylide in the presence of BF_3•Et_2O furnished alcohol **8**, which upon exposure to 2-methoxypropene and PPTS provided the 2-methoxypropyl (MOP) ether **9**. Removal of the pivalate moiety of **9** with excess *i*-Bu_2AlH, followed by oxidation with tetra-*n*-propylammonium perruthenate−*N*-methylmorpholine *N*-oxide (TPAP-NMO)[15] afforded aldehyde **10** in 47% overall yield from **7**.[8b] Treatment

(1) Kennard, O.; Watson, D. G.; Riva di Sanseverino, L.; Tursch, B.; Bosmans, R.; Djerassi, C. *Tetrahedron Lett.* **1968**, 2879.

(2) Uchio, Y.; Kodama, M.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1317.

(3) Insect growth inhibition, cell division inhibition, molluscidal activity, and cytotoxicity have been reported: (a) Ochi, M.; Futatsugi, K.; Kume, Y.; Kotsuki, H.; Ishii, M.; Shibata, K. *Chem. Lett.* **1987**, 2207. (b) Ochi, M.; Futatsugi, K.; Kotsuki, H.; Asao, K.; Shibata, K. *Chem. Lett.* **1988**, 1661. (c) Ochi, M.; Yamada, K.; Futatsugi, K.; Kotsuki, H.; Shibata, K. *Chem. Lett.* **1990**, 2183. (d) Ochi, M.; Yamada, K.; Futatsugi, K.; Kotsuki, H.; Shibata, K. *Heterocycles* **1991**, *32*, 29. (e) Fusetani, N.; Nagata, H.; Hirota, H.; Tsuyui, T. *Tetrahedron Lett.* **1989**, *30*, 7079. (f) Sharma, P.; Alam, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2537. (g) Kusumi, T.; Uchida, H.; Ishitsuka, M. O.; Yamamoto, H.; Kakisawa, H. *Chem. Lett.* **1988**, 1077.

(4) Ochi, M.; Yamada, K.; Kataoka, K.; Kotsuki, H.; Shibata, K. *Chem. Lett.* **1992**, 155.

(5) To our knowledge no synthetic endeavors toward these marine metabolites have been reported.

(6) (a) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354. (b) For a brief review, see: Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352.

(7) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435.

(8) (a) Numbered intermediates were fully characterized by ^1H and ^{13}C NMR, IR, and MS analysis. The elemental composition of analytical samples of new compounds was confirmed by combustion analysis or high-resolution mass spectrometry. Yields refer to isolated products purified on silica gel unless noted otherwise. Standard abbreviations employed are defined in *J. Org. Chem.* **1994**, *59*, 7A. (b) Aldehyde **10** was used directly without purification.

(9) Ireland, R. E.; Bey, P. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 459.

(10) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

(11) Wulff, D. W.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277.

(12) Seyferth, D. *J. Am. Chem. Soc.* **1957**, *79*, 2133.

(13) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(14) Molander, G. A.; Bobbitt, K. L. *J. Org. Chem.* **1992**, *57*, 5031.

(15) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

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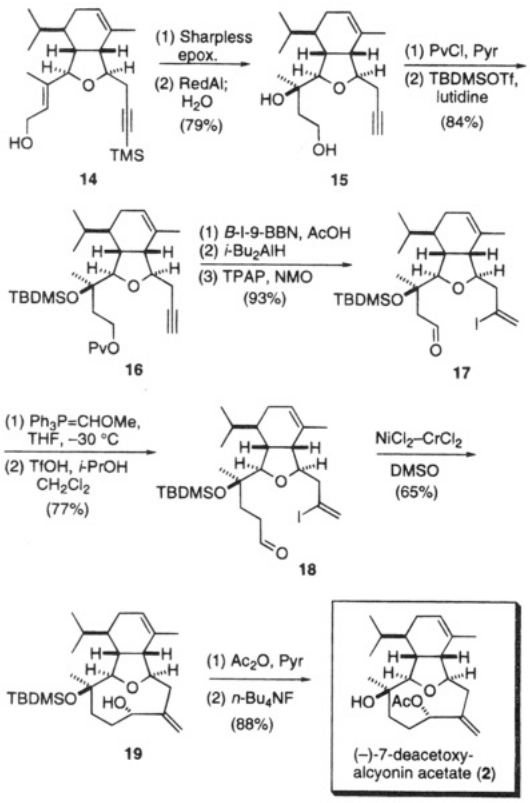
Scheme 2



of **10** with the dienyllithium species generated from **6** (*t*-BuLi, THF, −78 °C), followed by mild acidic cleavage of the MOP group, furnished the Prins-pinacol rearrangement substrate **11** in 64% yield as a 9:1 mixture of anti and syn stereoisomers.[16,17] The key Prins-pinacol reorganization was then triggered by exposure of diol **11** and an excess of enal **12**[18] to BF_3•Et_2O at −55 → −20 °C in CH_2Cl_2 to give hexahydroisobenzofuran **13**, a *single stereoisomer*, in 79% yield. Cleavage of the TIPS ether of **13** under acidic conditions, followed by stereoselective photolytic deformylation,[19] then provided **14** in 72% yield.[20] This intermediate, which is available in seven steps and 28% overall yield from (*S*)-carvone and nine steps and 17% overall yield from epoxide **7**, contains the full bicyclic core of (−)-7-deacetoxyalcyonin acetate (**2**).

Allylic alcohol **14** was next elaborated by Sharpless epoxidation[21] [(+)-diethyl tartrate, Ti(O-*i*-Pr)$_4$, *tert*-butyl hydroperoxide, CH_2Cl_2, −20 °C], reduction[22] of the derived epoxy alcohol with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in THF at −15 °C, and concomitant cleavage of the trimethylsilyl group with aqueous NaOH (generated *in situ* by adding H_2O) to provide 1,3-diol **15** in 79% yield (Scheme 2). Preparation for closure of the final nine-membered ring began with sequential protection of **15** with pivaloyl chloride (PvCl) and *tert*-butyldimethylsilyl triflate to furnish bis-protected diol **16**. Selective iodoboration of the alkyne moiety of **16** with

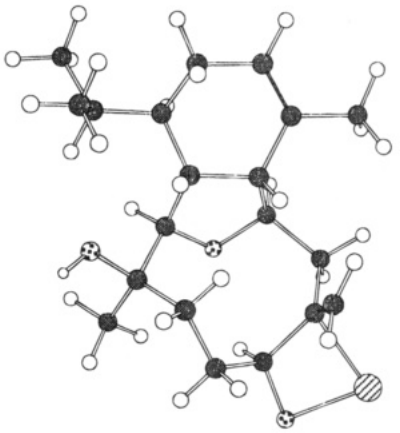


Figure 2. Possible transition structure for forming **19**. Carbonyl addition is modeled as a four-centered transition state, and the chromium ligands and the TBDMS group are excluded for clarity.

B-iodo-9-borabicyclo[3.3.1]nonane (*B*-I-9-BBN),[23] followed by cleavage of the pivaloyl group with *i*-Bu_2AlH, and TPAP−NMO oxidation[15] of the resulting primary alcohol provided aldehyde **17**. This intermediate was then homologated by sequential treatment with (methoxymethylene)triphenylphosphorane and triflic acid (*i*-PrOH−CH_2Cl_2) to afford **18** in 48% overall yield from **14**. The oxonane ring was then fashioned by treating **18** with $NiCl_2$−$CrCl_2$ in DMSO, following procedures pioneered by Nozaki and Kishi,[24] to provide tricyclic ether **19** in 65% yield. Stereoselection in this cyclization was notably high (>20:1) and in accord with the cyclization topography shown in Figure 2.[25] Acetylation of **19** followed by cleavage of the silyl ether with *n*-Bu_4NF then gave (−)-7-deacetoxyalcyonin acetate (**2**) in 88% yield: mp 140−142 °C, $[\alpha]_D$ −35.6° (*c* 1.0, $CHCl_3$). Synthetic **2** showed ^1H and ^{13}C NMR and IR spectra that were indistinguishable from those of the coral extract.[26]

In summary, the first total synthesis of (−)-7-deacetoxyalcyonin acetate (**2**) was accomplished in a concise fashion from (*S*)-glycidyl pivalate and (*S*)-carvone. This synthesis establishes a general approach to eunicellin diterpenes and further highlights the power of pinacol-terminated cationic cyclizations for constructing complex tetrahydrofurans.

Acknowledgment. This research was supported by Grant NS-12389 from the NINDS. NMR and mass spectra were determined at Irvine using instruments acquired with the assistance of the NSF Shared Instrumentation Program. We thank Professor Uchio for providing comparison spectra of natural **2** and the SERC for fellowship support to D.W.C.M. We are also grateful to Drs. Joseph Ziller and John Greaves for their advice and assistance with X-ray and mass spectrometric analyses.

Supporting Information Available: Listings of spectroscopic, analytical, and optical data for new compounds reported in Schemes 1 and 2 and copies of ^1H and ^{13}C NMR spectra for synthetic **2** (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA9523193

(16) That addition to **10** proceeded predominantly in the Felkin−Ahn sense[17] is consistent with preferential formation of anti diol **11** also from the reaction of the *tert*-butyldimethylsilyl analog of **10** with the lithium derivative of **6** followed by cleavage of the silyl protecting group.

(17) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(18) Enal **12** was prepared in two steps from commercially available 3-methyl-2-buten-1-ol by the following sequence: (a) TIPSCl, imidazole; (b) SeO_2, TBHP, salicylic acid.

(19) Baggiolini, E.; Hamlow, H. P.; Schaffner, K. *J. Am. Chem. Soc.* **1970**, *92*, 4906.

(20) Approximately 10% of the $\Delta^{1,12a}$ tetrasubstituted alkene regioisomer was removed at this point by chromatography.

(21) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(22) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719. (b) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (c) Viti, S. M. *Tetrahedron Lett.* **1982**, *23*, 4541.

(23) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.

(24) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281.

(25) The related transition structure leading to the alcohol epimer of **19** is destabilized by torsional and transannular interactions in the forming nine-membered ring.

(26) A rotation of −132° (*c* 0.13, $CHCl_3$) was reported for natural **2**, which was described as an oil.[2] Unfortunately a sample of the natural isolate is no longer available for direct comparison.[27] The structure of our crystalline synthetic product was verified by single-crystal X-ray analysis.

(27) Personal communication to L.E.O. from Professor Y. Uchio (June 28, 1994).