Total Synthesis of Octalactin A and B

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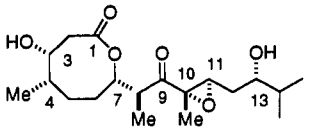
Natural products containing the saturated eight-membered lactone moiety are rare. Fenical and Clardy recently reported the isolation and relative configuration of two closely related, novel, marine-derived natural products, namely, octalactin A (**1**) and B (**2**).[1] Octalactin A showed strong cytotoxicity toward



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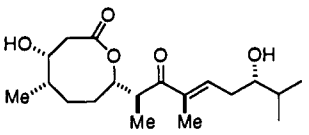

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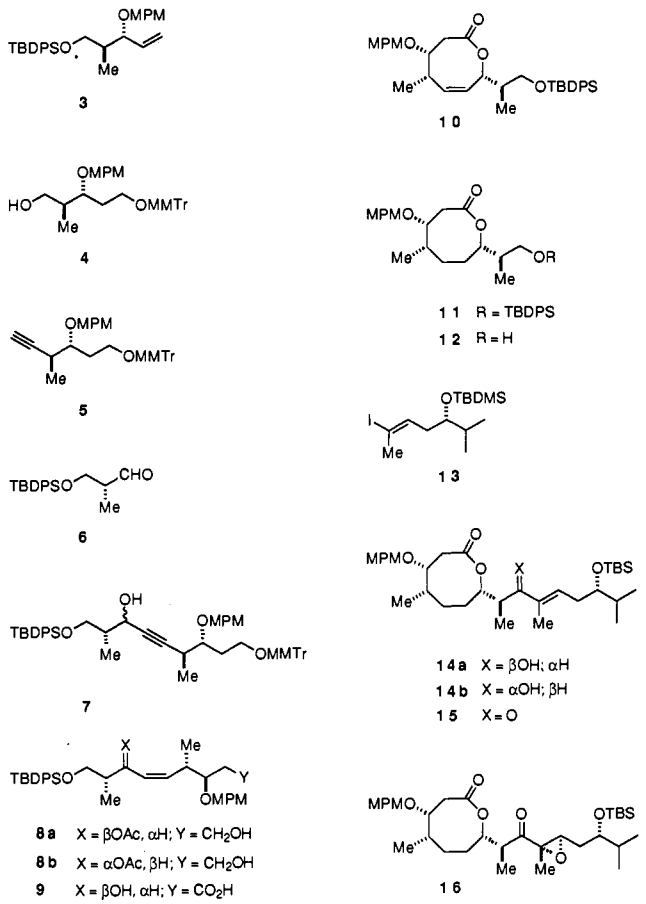
B-16-F10 murine melanoma and HCT-116 human colon tumor cell lines; octalactin B, however, was completely inactive in these assays. The combination of their unusual structural features, the challenges associated with the construction of such systems, and their therapeutic potential makes the octalactins an attractive target for total synthesis. The key step in our approach is based on an unprecedented intramolecular esterification of a saturated hydroxy carboxylic acid precursor using the Corey double activation method to form the eight-membered lactone. We report that this goal has been realized in excellent yield, and now we present the first total synthesis of octalactin A and B.

Our original synthetic strategy for the construction of the saturated eight-membered lactone envisioned the facile lactonization of the unsaturated hydroxy carboxylic **9** followed by hydrogenation of the cis olefin.[2] We started the synthesis with the methoxyphenylmethyl (MPM) ether **3**[3] (Chart 1). The olefin was regioselectively hydroborated and oxidized (9-BBN/THF/65 °C; 15% NaOH/30% H_2O_2) and the resulting primary alcohol protected ($MMTrCl/Et_3N/CH_2Cl_2$/room temperature) as its (*p*-methoxyphenyl)diphenylmethyl ether. Desilylation (*n*-Bu_4NF/THF/65 °C/3 h) gave the corresponding alcohol **4** in 75% overall yield.[4] One-carbon homologation of **4** *via* the acetylene was accomplished in two steps.[5] Oxidation of the primary alcohol with Dess–Martin periodinane[6] to the aldehyde, followed by condensation with Seyferth's reagent[7] ($N_2CHP(=O)(OMe)_2$/*t*-BuOK/THF/–78 °C), afforded the acetylene in 80% yield.

Chart 1



Several strategies were investigated to introduce the C7–C9 fragment with good stereocontrol at C7. Of the various methods attempted, the Ni(II)/Cr(II)-mediated coupling protocol offered the most satisfactory solution.[8] Thus, iodination of **5** (I_2/morpholine/PhH/55 °C) was readily accomplished in 90% yield.[9] The desired C6–C7 bond was then formed by the coupling of the iodoacetylene with the aldehyde **6**[10] with 3 equiv of chromium(II) chloride containing 1.0% w/w nickel(II) chloride in THF for 4 h at room temperature to give an inseparable mixture of alcohols **7** (about 1:1) in 75–90% yield.[11] Fortunately, sequential hydrogenation of this product over Lindlar's catalyst [H_2 (1 atm)/Pd($CaCO_3$, Pd)/PhH/room temperature) followed by acetylation (Ac_2O/DMAP/pyridine/room temperature) and deprotection of the MMTr ether [PPTS/CH_2Cl_2–MeOH (2.5:1)/room temperature) now furnished in 85% overall yield a chromatographically separable mixture of diastereomers, of which **8a** was the desired product. The relative stereochemistry at C7 was

(1) Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 4682.

(2) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasas, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263.

(3) This ether and its C3 epimer were prepared on a multigram scale in five steps beginning from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate: (i) DHP/TsOH/Et_2O/room temperature; (ii) DIBAL/CH_2Cl_2/–78 °C, then $BrMgCH{=}CH_2$; (iii) MPMCl/KH/THF/0 °C to room temperature; (iv) PPTS/EtOH/55 °C; (v) TBDPSCl/imidazole/CH_2Cl_2/room temperature. The corresponding 1,3-diols and their acetonides are known, and their ^1H NMR spectra have been reported. See: (a) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825. (b) Nishiyama, H.; Kitajima, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298.

(4) All new compounds reported here gave satisfactory ^1H and ^{13}C NMR, IR, and MS spectroscopic data.

(5) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

(6) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(7) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379.

(8) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

(9) Southwick, P. L.; Kirchner, J. R. *J. Org. Chem.* **1962**, *27*, 3305.

(10) Derived in three steps in 77% yield from methyl (*R*)-(–)-3-hydroxy-2-methylpropionate: (i) TBDPSCl/imidazole/CH_2Cl_2/room temperature; (ii) DIBAL/Et_2O/–78 °C; (iii) Dess–Martin periodinane/CH_2Cl_2/room temperature.

(11) Several attempts were made to improve the stereoselectivity of this reaction without success. However, the undesired isomer **9b** could be recycled in the following manner: (i) Dess–Martin oxidation/CH_2Cl_2/room temperature; (ii) L-Selectride/$CeCl_3$/THF/–78 °C reduction, which gave a separable mixture of diastereomers **9a**–**9b** in a 2:1 ratio in about 50% yield after one cycle.

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tentatively assigned on the basis of the vicinal Karplus correlation of the acetates **8a,b**.[12]

The remaining functional group manipulations prior to cyclization required two steps: first, a two-stage oxidation [Dess–Martin periodinane/CH_2Cl_2/room temperature, then $NaClO_2$ (in a buffered solution adjusted to pH 3.5)/2-methyl-2-butene/*t*-BuOH/room temperature/1 h] gave the carboxylic acid (82%), and then deacetylation (K_2CO_3/MeOH/room temperature) provided the unsaturated hydroxy carboxylic acid **9** (87%). Lactonization was accomplished by using a slight modification of the original Corey "double-activation" protocol[13] [2,2'-pyridine disulfide/PPh_3/CH_2Cl_2/room temperature/8 h, then $AgBF_4$/PhMe/110 °C/20 h] and afforded the desired eight-membered lactone **10** in 63–75% yield. Unfortunately, the seemingly prosaic task of reducing the double bond could not be carried out under the many conditions tried, including both heterogeneous and homogeneous catalytic hydrogenation, diimide reduction, hydroboration, bromination, and oxymercuration.

We finally attempted the formation of a trisubstituted eight-membered ring lactone from the intramolecular esterification of a saturated hydroxy carboxylic acid. Although the literature offered little encouragement for this strategy, it occurred to us that certain stereochemical arrangements and steric factors in the acyclic precursor might contribute to a favorable conformation to bring the two reacting ends into proximity. Hydrogenation of **9** [H_2 (1 atm)/10% Pd–C/EtOAc/room temperature] gave the desired saturated acyclic precursor. The key lactonization was carried out as before and, to our gratification, afforded after 96 h the desired eight-membered lactone **11** in 73% yield. *To our knowledge, this represents the first example of an eight-membered ring lactone synthesis in high yield from a saturated hydroxy carboxylic acid precursor.* Apparently, the stereochemical arrangement in the acyclic precursor in combination with the sterically demanding protecting groups induces in the presumed transition state[14] a preferred conformation that facilitates ring closure.[15] Indeed, the rate of cyclization of the diastereomeric acyclic precursors seems to support this view. Thus, the 3-epi, 7-epi diastereomer of **11** is formed under identical conditions in only 50 h. The 7-epimer was produced at about the same rate as the natural configuration while the 3-epimer required 2 weeks.[16] The rates of lactonization in these examples correlate with the total steric energy of the products as determined by MM2 calculations. Moreover, the calculated bond angles in the ring differ significantly from those found in the unsubstituted eight-membered lactone.[17]

Desilylation (*n*-Bu_4NF made acidic with AcOH (1 equiv)/THF/0 °C) afforded the hydroxy lactone **12** in 96% yield. The use of Ni(II)/Cr(II) chemistry again proved most satisfactory for appending the C10–C15 side chain. Oxidation of the alcohol (Dess–Martin periodinane/CH_2Cl_2/room temperature) followed by coupling of the resulting aldehyde with the vinyl iodide **13**[18] [0.1% w/w $NiCl_2/CrCl_2$ (excess)/DMSO/room temperature) gave an approximately 1.5:1 separable mixture of diastereomers in 74% yield for the two steps. Again, the relative stereochemistry at C9 was assigned on the basis of the vicinal Karplus correlation. Oxidation with the Dess–Martin reagent afforded the enone **15** in nearly 78% yield. Desilylation (HF/CH_3CN/room temperature) and oxidative removal of the MPM ether [DDQ/CH_2Cl_2–H_2O (9:1)/room temperature][19] gave in 88% yield synthetic octalactin B. The major *syn* allylic alcohol **14a** was subjected to epoxidation (*t*-BuOOH/$VO(acac)_2$/PhH/room temperature)[20] to afford a single diastereomer. Oxidation with the Dess–Martin reagent gave the protected octalactin A **16** in 95% yield for the two steps. We attempted to convert the *anti* allylic alcohol to **16** in a similar manner. Epoxidation of **14b** with *m*-chloroperbenzoic acid (MCPBA buffered with sodium bicarbonate/CH_2Cl_2/0 °C) proceeded in 90% yield and also occurred with nearly complete but *opposite* stereoselectivity; however, reaction with a molybdenum–hydroperoxide reagent [*t*-BuOOH/$Mo(CO)_6$/PhH/55 °C][20] delivered a 1:1 separable mixture of epoxy alcohols. Oxidation of the more polar product gave **16**. Finally, deprotection as before furnished in 77% overall yield from **14a** synthetic octalactin A. Both octalactin A and B exhibited the same physical and spectroscopic data as that reported for the authentic samples.[21] The foregoing total synthesis establishes that the absolute configurations of the octalactins are as shown.

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Supplementary Material Available: Experimental procedures for the preparation of compounds **1–16** and ^1H and ^{13}C NMR spectra for key intermediates (54 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) This assignment was confirmed by the successful conversion of **8a** into octalactin A.

(13) (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. (b) Reference 2. (c) Gerlach, H.; Thalman, A. *Helv. Chim. Acta* **1974**, *57*, 2661.

(14) Corey, E. J.; Brunelle, D. J.; Stork, P. J. *Tetrahedron Lett.* **1976**, 3405.

(15) Since the olefin is not required for lactonization, a shorter route to the saturated precursor to **11** has been identified and is in progress. The results of these efforts will be disclosed in due course.

(16) A detailed investigation of this phenomenon is under investigation.

(17) Allinger, N. L. *Pure Appl. Chem.* **1982**, *54*, 2512.

(18) Jeong, Y. M.S. Thesis, Kansas State University, 1993. The vinyl iodide **12** was prepared as follows: (*R*)-Isopropyloxirane (Koppenhoefer, B.; Schurig, V. *Org. Synth.* **1988**, *66*, 160) was coupled with lithium trimethylsilylacetylide under Yamaguchi conditions (Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391). The alcohol was silylated (TBDMSCl, imidazole, CH_2Cl_2, room temperature), C-desilylated [1 N NaOH, THF–MeOH (1:1), room temperature], methylated (*n*-BuLi, THF, –78 °C, then MeI), and regioselectively hydrozirconated and iodinated (Cp_2ZrClH, PhH, room temperature, then I_2) according to a known procedure (Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679).

(19) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(20) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(21) We are grateful to Professor William Fenical, Scripps Institution of Oceanography, University of California, San Diego, for providing us with copies of the ^1H NMR spectra for authentic octalactin A and B. The specific rotations for synthetic **1**, $[\alpha]_D = -152°$, and **2**, $[\alpha]_D = -126°$, are each nearly 10 times higher than those reported for the natural compounds.