Total Synthesis of (+)-Octalactins A and B: Unusual Metabolites from a Marine Microbe

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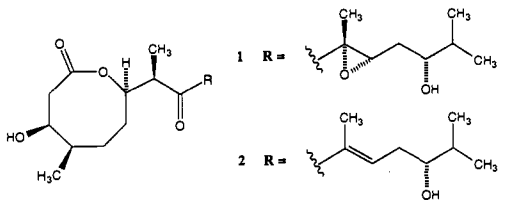
Octalactins A and B, marine metabolites isolated from a *Streptomyces* sp. found living on the surface of a gorgonian coral,[1] both contain an unusual eight-membered lactone and differ as the epoxide (**1**) and alkene (**2**).[1] Octalactin A (**1**) displays potent

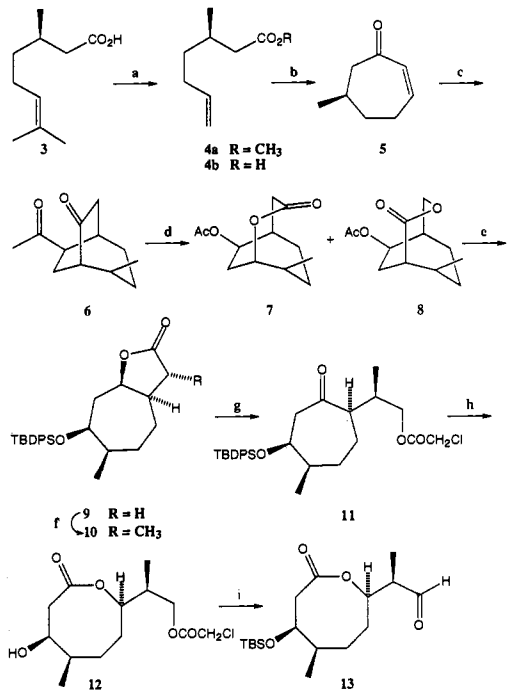


cytotoxicity against tumor cell lines (2×10^{-8} M vs B-16-F10; 1.4×10^{-6} M vs HCT-116); octalactin B (**2**) shows no activity in the same assays. The relative but not the absolute configurations of **1** and **2** are known through an X-ray analysis of **1**,[1] and a recently completed synthesis defines the absolute stereochemistry.[2] This report describes a very different total synthesis that, *inter alia*, also establishes the absolute configurations. The octalactins are constructed by joining two fragments as suggested in structural drawings **1** and **2**.

Synthesis of the left-hand fragment begins with (+)-citronellic acid **3**, which is protected as its methyl ester and oxidized to an aldehyde (Scheme 1). While standard methylene Wittig conditions give low yields of the desired terminal alkene **4a**, the method of Oshima[3] produces the alkene in significantly better yield. Saponification of the ester yields alkenoic acid **4b**. Cyclization to methylcycloheptenone **5** uses a three-step sequence: formation of the acid chloride, $SnCl_4$-induced cyclization to a mixture of β-chlorocycloheptanones, and treatment with DBU to afford **5**.

Kinetic deprotonation of **5** followed by quenching with chlorotrimethylsilane produces the cross-conjugated enol ether. In a key reaction, bicyclic compound **6** is formed (61%) stereoselectively via a Mukaiyama double-Michael reaction with methyl vinyl ketone.[4] A double Baeyer–Villiger oxidation of **6** produces an 85:15 ratio of the regioisomeric lactones **7** and **8**.[5] This lactone mixture is difficult to separate, so it is treated with potassium hydroxide followed by hydrochloric acid to produce a mixture of acyl-migrated hydroxylactones. After the secondary alcohol is protected as the *tert*-butlydiphenylsilyl ether, the desired bicyclic lactone **9** (derived from **7**) can be isolated easily. The sequence from **6** to **9** has an overall yield of 33%. Alkylation on the convex face proceeds with >95% selectivity and furnishes **10**.[6] Lithium borohydride[7,8] reduction to the diol followed by selective protection of the primary alcohol as the chloroacetate

Scheme 1[a]



[a] Reagents and conditions: (a) *p*-TsOH, MeOH, reflux, 2.5 h, 88%; O_3, CH_2Cl_2, −78 °C, 3.5 h, then Me_2S, −78 °C → room temperature, overnight, 71%; Zn, CH_2I_2, $AlMe_3$, THF, 0 °C → room temperature, 7.5 h, 63%; LiOH, THF/H_2O, room temperature, 48 h, 86%; (b) $(COCl)_2$, CH_2Cl_2, 0 °C → room temperature, 3 h, then $SnCl_4$, 0 °C, 1 h; DBU, CH_2Cl_2, 0 °C → room temperature, 1.5 h, 67% (3 steps); (c) LDA, THF, then TMSCl, −78 °C → room temperature, overnight, 75%; $SnCl_4$, MVK, CH_2Cl_2, −78 °C (4 h) → −20 °C (overnight) → room temperature (2h), 61%; (d) CH_3CO_3H, CH_3CO_2H/CH_3CO_2Na, 70 °C, 72 h; (e) KOH, MeOH, room temperature, 1.5 h, then HCl (pH < 1), 5 min; TBDPSCl, imidazole, DMF, room temperature, 8 h, 33% overall from **6**; (f) LDA, THF, −78 °C, then CH_3I/HMPA, −78 °C → −40 °C, 20 min, 86%; (g) $LiBH_4$, THF, reflux, 4 h, 96%; chloroacetic anhydride, Et_3N, CH_2Cl_2, −78 °C, 3h, 86%; $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, 30 min, then Et_3N, −60 °C → room temperature, 1 h, 94%; (h) HF, CH_3CN, room temperature, 15 h, 71%; 3 M CF_3CO_3H, CH_2Cl_2, −10 °C, 91 h, 83%; (i) 4-((*tert*-butyldimethylsilyl)oxy)-3-penten-2-one, DMF, *p*-TsOH (catalyst), room temperature, 26 h, 79%; 4:1 NH_3/THF, −50 °C → −40 °C, 2.5 h, 85%; periodinane, CH_2Cl_2, room temperature, 50 min, 95%.

(chloroacetic anhydride and triethylamine[9]) and oxidation under Swern conditions[10] produces ketone **11**.

We had hoped to transform the cycloheptanone into the eight-membered lactone with a Baeyer–Villiger expansion. However, even forcing conditions (buffered trifluoroperoxyacetic acid in refluxing methylene chloride or *m*-chloroperbenzoic acid with radical inhibitors at 70 °C) result in low conversions and substantial decomposition of substrate. This reluctance to undergo the Baeyer–Villiger expansion can be eliminated by removing the silyl protecting group. The hydroxy ketone can be smoothly converted to lactone **12** using unbuffered trifluoroperoxyacetic acid while keeping the reaction temperature below −10 °C to prevent formation of unwanted products.[11] The hydroxy group is reprotected as the silyl ether under acidic conditions since the usual basic conditions give low yields.[12] Deprotection of the chloroacetate using hydrazine dithiocarbonate results in decom-

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(5) More reactive peracids, such as mCPBA and trifluoroperacetic acid, gave no better than 2:1 ratios of **7** and **8**, respectively.
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(7) We noted cleavage of the TBDPS ether with $LiAlH_4$, as has been observed in a related system, in which a β-hydroxyl group was generated upon reduction: Rajaskekhar, B.; Kaiser, E. T. *J. Org. Chem.* **1985**, *50*, 5480–5484.
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(11) Higher temperatures resulted in the formation of the bis-lactone.

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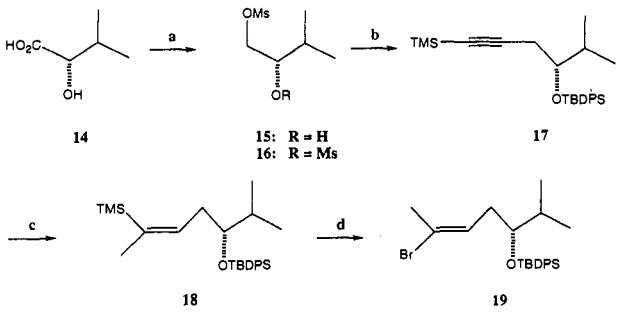
Scheme 2[a]

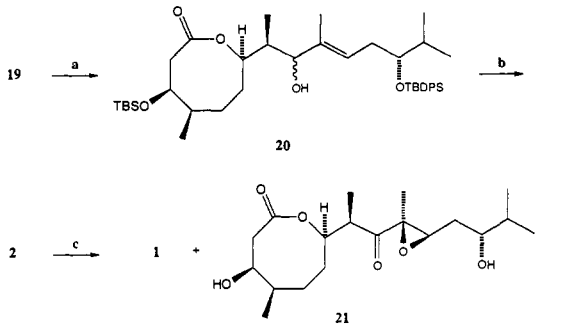


[a] Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 7 h, 97%; MsCl, Et_3N, Et_2O, −20 °C, 12 h; (b) K_2CO_3, MeOH, room temperature, 1 h, extract with pentane, then add to lithium (trimethylsilyl)acetylide, BF_3·Et_2O, THF, −78 °C, 2 h, 43% from diol; TBDPSCl, imidazole, DMF, room temperature, overnight, 83%; (c) Cy_2BH (2 equiv), THF, 0 °C → room temperature, overnight, then MeLi (3.5 equiv), 0 °C, 30 min, then MeI (50 equiv), 0 °C → room temperature, 50 h, 73%; (d) Br_2, CH_2Cl_2, −78 °C, ≤ 5 min; MeONa, CH_2Cl_2/MeOH, 0 °C (1 h) → room temperature (2 h), 75% (two steps).

position,[13] but clean and selective cleavage is achieved by ammonolysis at low temperature. Oxidation with the Dess–Martin protocol[14] proceeds smoothly to complete the synthesis of the left-hand fragment aldehyde **13**.

The synthesis of the right-hand fragment starts with the readily available (*S*)-2-hydroxy-3-methylbutanoic acid (**14**) (Scheme 2). Reduction to the diol with lithium aluminum hydride followed by mesylation at low temperature gives **15** and **16** in an 85:15 ratio, respectively. A slight excess of methanesulfonyl chloride ensures that any secondary mesylate formed is mesylated at the primary position as well since any remaining regioisomeric hydroxymesylate results in an inversion of stereochemistry in the subsequent cyclization. Cyclization to the volatile epoxide is effected with potassium carbonate in methanol. After extraction with pentane from the aqueous diluted solution, the mixture containing the epoxide is added to a cold solution of lithium (trimethylsilyl)acetylide and boron trifluoride etherate.[15] The propargylic alcohol is isolated in 43% overall yield from the diol and protected as the *tert*-butyldiphenylsilyl ether **17**. Regioselective addition of methane across the triple bond is effected by the method of Nozaki.[16] Interestingly, using diisobutylaluminum hydride in place of dicyclohexylborane results in incomplete addition and the formation of the *cis*-alkene, not the methylated product. Conversion to the vinyl halide[17] **19** finishes the right-hand fragment.

Scheme 3[a]



[a] Reagents and conditions: (a) *t*BuLi (2 eq), THF/Et_2O, ≤ −100 °C, then 13 in precooled (−78 °C) THF, 10 min, then NH_4Cl; (b) periodinane, CH_2Cl_2, room temperature, 40 min, 56% from 13; HF, 4:1 CH_3CN/THF, 13 °C, 120 h, 49%; (c) $VO(acac)_2$, CH_2Cl_2, room temperature, 30 min, then 3 M *t*BuOOH in 2,2,4-trimethylpentane, 0 °C → 10 °C, 42 h, 2:1 1:21 (31% isolated 1).

Coupling the right- and left-hand pieces generates the octalactin system (Scheme 3). Metalation of **19** using *tert*-butyl lithium is done at very low temperature (≤−100 °C) due to competition in the elimination reaction with *tert*-butyl bromide. Addition of **13** to the vinyllithium solution results in nonselective addition to the aldehyde, yielding a mixture of epimers **20**. The mixture is oxidized to bis(silyl)octalactin B with the Dess–Martin reagent,[14] and deprotection yields **2**. Treating **2** with vanadyl acetylacetonate and *tert*-butylhydroperoxide[18] gives a 2:1 mixture of epoxides **1** and **21**. Comparing synthetic and natural[1] **1** and **2** showed that the ^1H and ^{13}C NMR, IR, and mass spectral data are identical. However, the optical rotations differ by roughly a factor of 10 (−12.3° for natural **2** and +132° for synthetic **2**; −14° for natural **1** and +141° for synthetic **1**), a result initially noted by Buszek and co-workers.[2] To check that nothing had gone awry in the synthesis, we carried out a single crystal X-ray structure determination on synthetic **1**, and it agrees in all details with that originally reported for the natural product. We conclude that a simple calculational error occurred in the original optical rotation data. The synthesis shows that the absolute configurations of naturally occurring octalactins correspond to (−)-**1** and (−)-**2**, the enantiomers of those synthesized.

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Supplementary Material Available: Detailed experimental procedures and spectral data for the synthesis of **1** and **2** (22 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.

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(18) A greater degree of selectivity had been expected on the basis of results obtained with the model compound, (*S*)-10-hydroxy-7,11-dimethyl-6-dodecanone, which gave a single epoxide under similar conditions.