

Enantioselective Synthesis of Octalactin A

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An efficient enantioselective synthesis of the C1-C9 fragment 2 of octalactin A (**1**) has been achieved starting from (-)-citronellol (**3**).

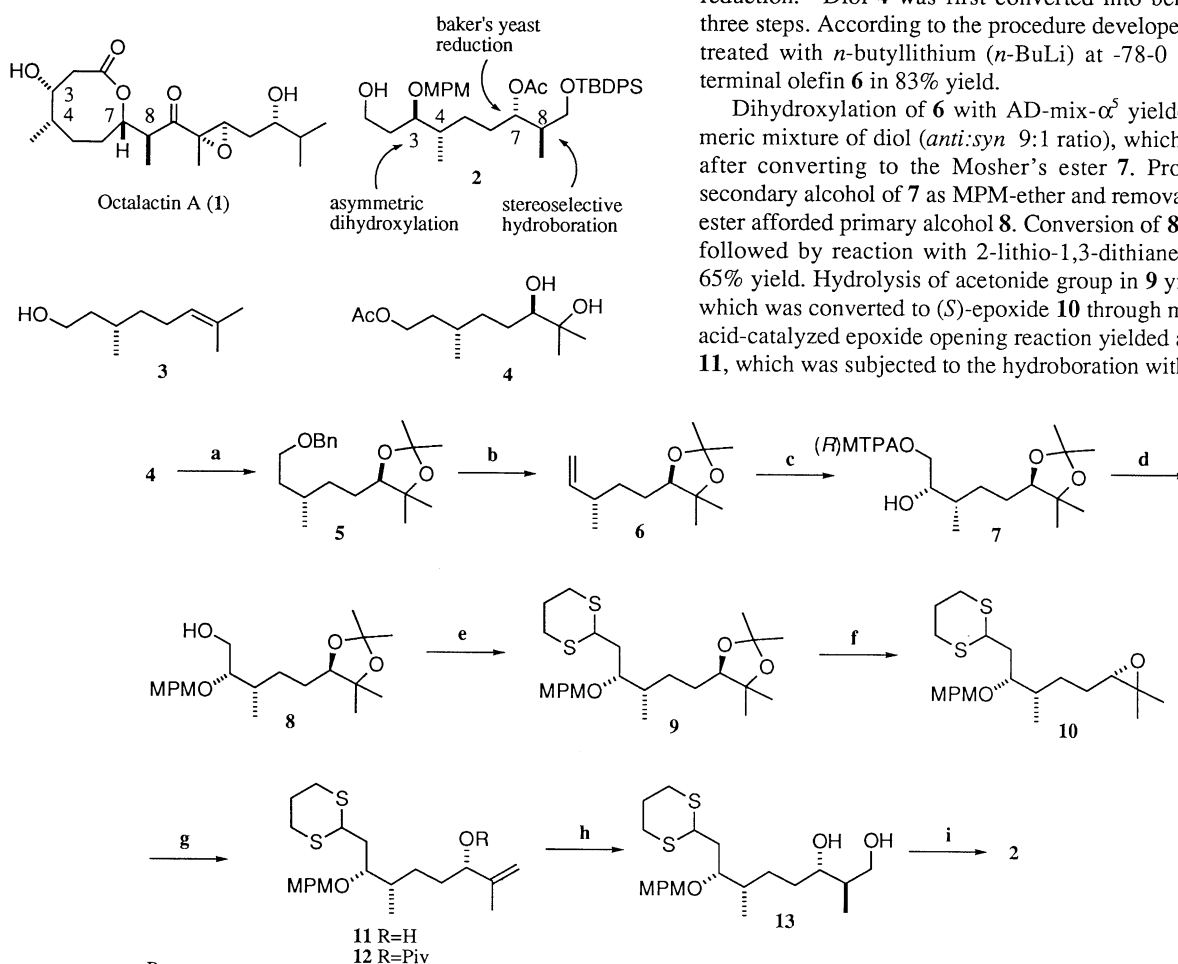
Octalactin A (**1**) was isolated from a marine bacterium *Streptomyces* sp. together with the related compound octalactin B.¹ The novel structure containing seven chiral centers and an unusual eight-membered-ring lactone has been determined by X-ray crystallographic analysis and the absolute stereochemistry has been established by synthesis.² In addition to the characteristic structural feature, **1** exhibits a potent cytotoxic activity against some tumor cell lines.¹ Because of its attractive structure and

potent biological activity, two groups have achieved its total synthesis. As the extension of our natural product synthesis using baker's yeast reduction,³ we would like to report a formal total synthesis of **1** starting from (-)-citronellol (**3**).

We chose a protected tetraol **2** as the target molecule, since **2** has been converted into octalactin A by Buszek et al.^{2d} (-)-Citronellol (**3**) was an ideal starting material because it has a carbon chain less one carbon than **2** and methyl group with desired configuration. Other chiral centers in **2** would be adjusted by baker's yeast reduction (C7), asymmetric dihydroxylation (C3), and stereoselective hydroboration (C8).

Synthesis was started with (*R*)-diol **4** which has already been synthesized in high enantiomeric purity from **3** by yeast reduction.^{3a} Diol **4** was first converted into benzyl ether **5** in three steps. According to the procedure developed by us,⁴ **5** was treated with *n*-butyllithium (*n*-BuLi) at -78-0 °C to give the terminal olefin **6** in 83% yield.

Dihydroxylation of **6** with AD-mix- α^5 yielded a diastereomeric mixture of diol (*anti:syn* 9:1 ratio), which was separated after converting to the Mosher's ester **7**. Protection of the secondary alcohol of **7** as MPM-ether and removal of the MTPA ester afforded primary alcohol **8**. Conversion of **8** to the bromide followed by reaction with 2-lithio-1,3-dithiane afforded **9** in 65% yield. Hydrolysis of acetonide group in **9** yielded (*R*)-diol, which was converted to (*S*)-epoxide **10** through mesylate. Lewis acid-catalyzed epoxide opening reaction yielded an allyl alcohol **11**, which was subjected to the hydroboration with thexyl borane



a: 1) 2,2-dimethoxypropane, PPTS, CH₂Cl₂, 2) K₂CO₃, MeOH, 3) BnBr, NaH, Bu₄NI, THF, 73%; b: *n*-BuLi, THF, -78~0 °C 83%; c: 1) AD-mix- α , H₂O, *t*-BuOH, 0 °C 2) (*R*)-MTPA, DCC, 4-DMAP, CH₂Cl₂, 91%; d: 1) MPM-trichloro-acetimidate, CF₃SO₃H, THF, 2) 2 mol dm⁻¹ NaOH, EtOH, 71%; e: 1) CBr₄, Ph₃P, CH₂Cl₂, 2) 1,3-dithiane, *n*-BuLi, THF, -30 °C, 65%; f: 1) PPTS, MeOH, 2) MsCl, 4-DMAP, pyridine, 3) K₂CO₃, MeOH, 62%; g: 1) (*i*-PrO)₃Al, toluene, 120 °C, 2) PivCl, Et₃N, 4-DMAP, CH₂Cl₂, 79%; h: 1) 9-BBN, THF, -78~50 °C, 2) H₂O₂, 2 mol dm⁻¹ NaOH, 3) LiAlH₄, THF, 36%; i: 1) TBDPSCl, Et₃N, 4-DMAP, CH₂Cl₂, 2) Ac₂O, Et₃N, 4-DMAP, CH₂Cl₂, 3) MeI, CH₃CN, 4) NaBH₄, MeOH, 30%.

to yield 1,3-diol **13** in 79% yield, though, the selectivity was only 3:1. The selectivity was improved to 9:1 when the *O*-pivaloyl derivative **12** was treated with 9-BBN.^{2c,6,7} Protection of 1,3-diol part in **13**, hydrolysis of dithiane group and reduction of the resulting aldehyde gave the target primary alcohol **2**. The spectroscopic properties of **2** including its optical rotation were identical with those of **2** synthesized by Buszek's group.^{2d,8}

In conclusion, we achieved a formal synthesis of octalactin A, using diol **4** as a versatile chiral synthon.

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- 7 The stereochemistry at C8 of the major product was determined unambiguously to be *R* using 600 MHz ¹H-NMR after transformed it into the corresponding acetone.
- 8 $[\alpha]_D^{22} +29.6^\circ$ (*c* 0.05, CHCl₃) (authentic: $+31.5^\circ$ (*c* 1.35, CHCl₃); IR ν max (neat) cm⁻¹: 3429, 2928, 2856, 1736; ¹H-NMR(200 MHz, CDCl₃) δ : 7.68-7.63(4H, m), 7.41-7.23(8H, m), 6.89-6.84(2H, m), 5.14-4.88(1H, m), 4.53(1H, d, *J*=10.5 Hz), 4.35(1H, d, *J*=10.5 Hz), 3.79(3H, s), 3.70-3.48(5H, m), 1.95-1.05(8H, m), 1.95(3H, m), 1.05(9H, s), 0.95(3H, d, *J*=6.8 Hz), 0.88(3H, d, *J*=6.8 Hz); HR-FABMS Calcd. for C₃₇H₅₂O₆SiNa: 643.3431, Found 643.3438.