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Asymmetric total synthesis of octalactin B using a new and rapid lactonization

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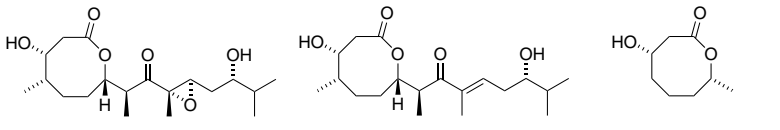
Abstract—A method for the synthesis of octalactin B is established via a new and quite effective mixed-anhydride lactonization for the synthesis of an eight-membered ring moiety using 2-methyl-6-nitrobenzoic anhydride with DMAP. Both an optically active linear precursor of the lactone and a side chain of octalactins are prepared by the enantioselective aldol reaction of ketene silyl acetals with aldehydes.

Octalactin B (**2**) was isolated from the marine bacterium *Streptomyces* sp. together with a related cytotoxic active compound octalactin A (**1**).[1] Synthesis of this unique complex structure has been one of the more interesting topics in organic chemistry (Scheme 1). There are currently three total syntheses of octalactins accomplished by two groups;[2] besides, some formal syntheses and related synthetic studies of octalactins have also been reported[3].

In 1998, the total synthesis of cephalosporolide D (**3**), an eight-membered ring lactone similar to the octalactins was attained by our group,[4] and the exact stereochemistry of this compound was determined through a chiral induction technology for producing optically active compounds;[5] that is, both asymmetric carbons were constructed by the asymmetric aldol reaction of 1-ethylthio-1-(trimethylsiloxy)ethene with aldehydes in the presence of a chiral catalyst. Furthermore, the desired eight-membered ring lactone moiety was obtained by the efficient cyclization of the *seco* acid via a novel mixed-anhydride method using (4-trifluoromethyl)benzoic anhydride (TFBA) with $Hf(OTf)_4$.[4,6]

As our continuous effort for the synthesis of medium-sized natural compounds,[7] the total synthesis of the octalactins was planned using a very effective and convenient lactonization for producing the eight-membered ring part of the octalactins using 2-methyl-6-nitrobenzoic anhydride (MNBA) with DMAP.[8] An optically active *seco* acid of the eight-membered ring lactone might also be constructed according to the enantioselective aldol reaction of a ketene silyl acetal with aldehydes promoted by $Sn(OTf)_2$ coordinated with a chiral diamine.

Because the synthetic intermediates similar to **4** have already been prepared and the transformations of these



Octalactin A (1) **Octalactin B (2)** **Cephalosporolide D (3)**

Scheme 1. Structure of octalactins A and B, and a similar lactone, cephalosporolide D.

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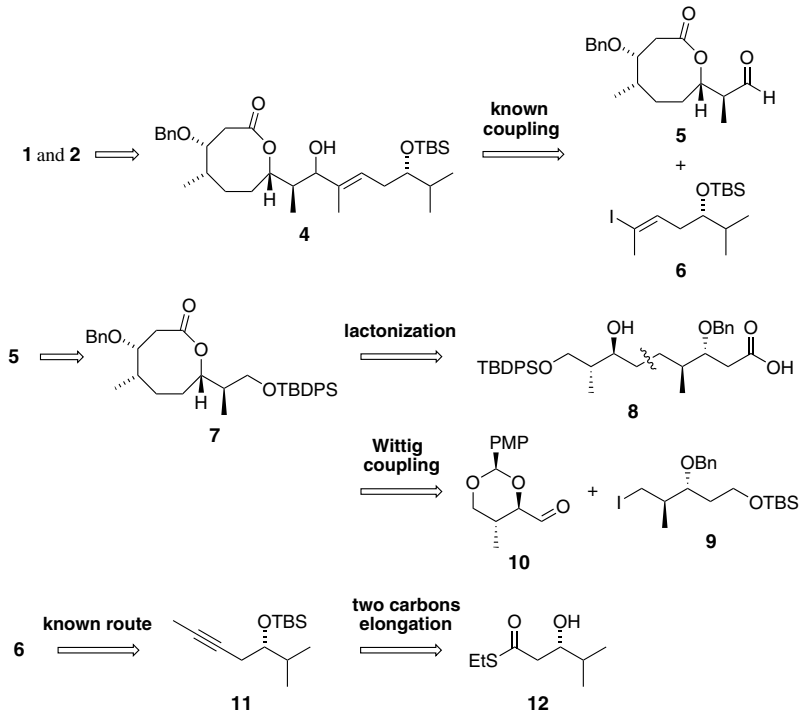
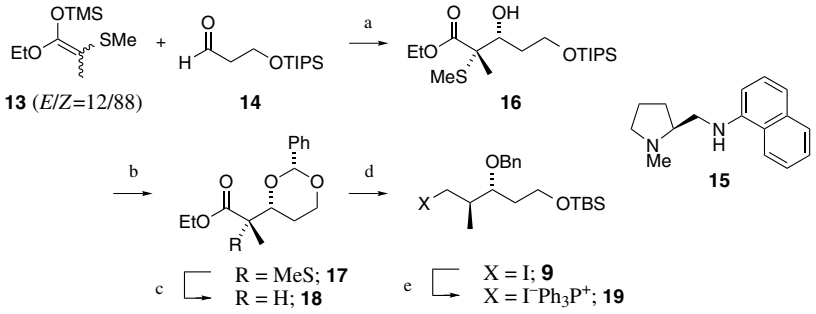


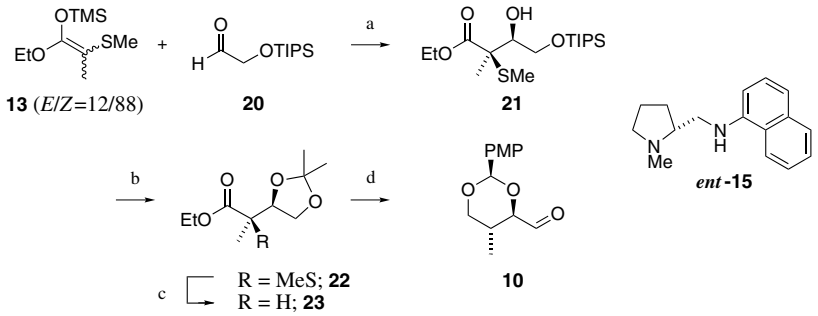
Scheme 2. Retrosynthesis of octalactins from optically active linear compounds.

compounds to **1** and/or **2** were also described in previous papers,[2a,b] **4** was determined to be our target precursor for the synthesis of the octalactins as shown in Scheme 2. It is assumed that the allyl alcohol **4** could be prepared by the nucleophilic addition of a metallic species generated from **6** to aldehyde **5** according to literature methods.[2a,b] The synthesis of the eight-membered ring lactone part **7** was planned by starting from a linear compound **8**, which could be obtained from two segments **9** and **10**. Preparation of both optically active *anti*-β-hydroxy-α-methyl units **9** and **10** might be attained according to the enantioselective aldol addition of the tetra-substituted ketene silyl acetal derived from ethyl 2-methylthiopropanoate to aldehydes and successive stereoselective desulfurization. On the other hand, aldol **12** was chosen as an intermediate of the siloxyalkyne **11**, which could be converted to the side chain **6**.[2a]

First, an optically active aldol **16** was synthesized with high stereoselectivity by the asymmetric aldol reaction of tetra-substituted ketene silyl acetal **13** with β-siloxyaldehyde **14** using a chiral Lewis acid consisting of $Sn(OTf)_2$, chiral diamine **15** and *n*-Bu_3SnF (Scheme 3). The ee was determined by the HPLC analysis of **16** referenced to the corresponding racemic sample. Direct acetalyzation of **16** with benzaldehyde dimethyl acetal in the presence of *p*-toluenesulfonic acid afforded a cyclic compound **17**. Desulfurization of **17** using *n*-Bu_3SnH was carried out according to the similar reactions reported by Guindon et al. and Kiyooka and Shahid to give the desired *anti*-β-hydroxy-α-methyl unit **18** with high diastereoselectivity.[9,10] Successive reductive cleavage of the benzylidene acetal and protection of the primary alcohol gave the corresponding silyl ether. The ester group was reduced by $LiAlH_4$ and halogenation of the formed primary alcohol afforded the desired right



Scheme 3. Reagents and conditions: (a) $Sn(OTf)_2$, *n*-Bu_3SnF, chiral diamine **15**, CH_2Cl_2, −78 °C (56%, *syn*/*anti* = 96/4, 87% ee for *syn*); (b) $PhCH(OMe)_2$, TsOH, CH_2Cl_2, 0 °C (64% from *syn*-**16**); (c) *n*-Bu_3SnH, AIBN, benzene reflux (quant, *anti*/*syn* = 95/5); (d) 1. $LiAlH_4$, THF, 0 °C (47% from *anti*-**18**); 2. TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C (96%); 3. NaI, acetone, reflux (97%); 4. DIBAL, CH_2Cl_2, 0 °C (94%); 5. TBSCl, imidazole, DMF, 0 °C (96%); (e) PPh_3, $^iPr_2NEt$, CH_3CN, reflux (84%).



Scheme 4. Reagents and conditions: (a) $Sn(OTf)_2$, *n*-Bu_3SnF, chiral diamine ***ent*-15**, CH_2Cl_2, −78 °C (50%, *syn*/*anti* = 87/13, 69% ee for *syn*); (b) 1. TBAF, AcOH, THF, 0 °C (91% from *syn*-**21**); 2. $Me_2C(OMe)_2$, MsOH, CH_2Cl_2, rt (96%); (c) *n*-Bu_3SnH, AIBN, benzene reflux (92%, *anti*/*syn* = 97/3); (d) 1. $LiAlH_4$, THF, 0 °C (82% from *anti*-**23**); 2. PPTS, MeOH; 3. $PMPCH(OMe)_2$, PPTS, CH_2Cl_2, rt (96%, two steps); 4. $PhSNH^tBu$, NCS, K_2CO_3, MS 4 Å, CH_2Cl_2, 0 °C to rt (99%).

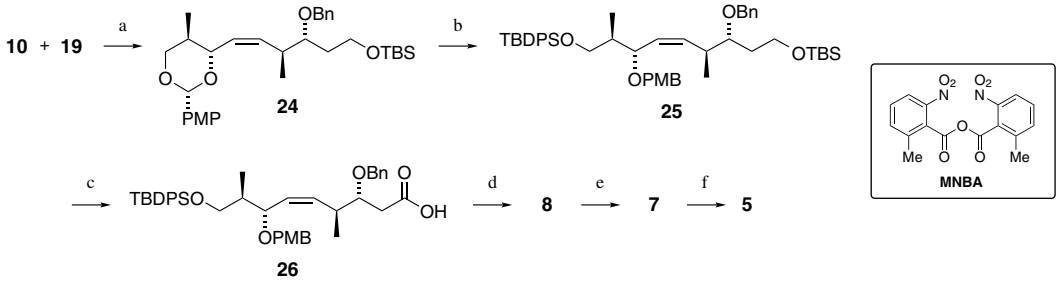
hand **9**, which was further converted to the phosphonium salt **19** by conventional method.

Second, the left-hand segment **10** was also prepared as shown in Scheme 4. The optically active aldol **21** generated from **13** with α-siloxyaldehyde **20** was transformed to the cyclic acetal **22**, and the diastereoselective desulfurization of **22** smoothly took place to preferentially yield the desired *anti*-β-hydroxy-α-methyl unit **23**. Successive reduction of the ester group, formation of *p*-methoxybenzylidene acetal, and oxidation of the intermediary primary alcohol produced the corresponding optically active aldehyde **10**.[11]

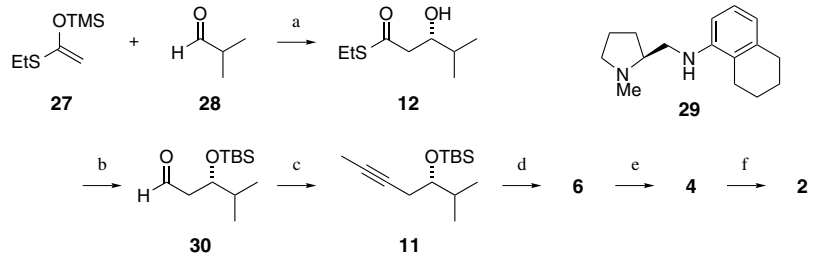
These two segments **10** and **19** were coupled in the presence of NaHMDS to produce a linear polyoxy compound **24** in good yield (Scheme 5). Reductive cleavage of the acetal moiety followed by protection of the resulted primary alcohol afforded the disilyl ether **25**. Deprotection of the TBS group and stepwise oxidation of the formed primary alcohol gave the corresponding carboxylic acid **26**. The desired chiral linear *seco* acid **8** was then obtained by deprotection of the PMB group and hydrogenation of the double bond.

This *seco* acid **8** was eventually cyclized to form the eight-membered ring lactone using a new effective mixed-anhydride method involving MNBA with DMAP as shown in Scheme 5. Actually, the reaction proceeded quite smoothly at *room temperature* and the desired saturated eight-membered ring lactone **7** was obtained in 84% yield within 13 h.[12] Buszek et al. reported the successful lactonization of a similar *seco* acid, which has the PMB group instead of the Bn group in **8** using the *S*-Py ester method.[2a,13,14] It is reported that the cyclization requires a high reaction temperature and longer reaction time (96 h); nevertheless, the reaction is accelerated by $AgBF_4$. Although our desired lactone **7** could also be obtained from **8** by the *S*-Py ester method, the reaction sluggishly proceeded even under very severe conditions (96 h in refluxing toluene with $AgBF_4$). Furthermore, it was revealed that this reaction did not take place at all at room temperature. The conversion of the formed **7** to the eight-membered ring lactone aldehyde **5** was then carried out through deprotection of the TBDPS group and successive oxidation.

Next, the side chain **6** was prepared from an optically active aldol **12**, which was generated by the asymmetric aldol reaction of 1-ethylthio-1-(trimethylsiloxy)ethene (**27**) with 2-methylpropionaldehyde (**28**) as shown in Scheme 6.[5c] The protection of **12** and the successive reduction using Et_3SiH with Pd/C afforded the chiral aldehyde **30**.[15] According to Buszek's synthesis of the side chain,[2a] **30** was transformed into the desired vinyl iodide **6** through the siloxyalkyne **11**. The side chain **6** was finally introduced to the aldehyde **5** using the method reported by McWilliams and Clardy[2b] to give the multi-oxygenated eight-membered ring lactone **4**, a precursor of the octalactins. Both diastereomers were



Scheme 5. Reagents and conditions: (a) NaHMDS, toluene, −78 °C to rt (80%, >97% ee); (b) 1. DIBAL, CH_2Cl_2, 0 °C (79%); 2. TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt (84%); (c) 1. 1 M HCl, THF, rt (95%); 2. DMP, CH_2Cl_2, rt; 3. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH, H_2O, rt (94%, two steps); (d) 1. DDQ, H_2O, CH_2Cl_2, rt (81%); 2. H_2, Pd/C, AcOEt, rt (83%); (e) MNBA, DMAP, toluene, rt (84%); (f) 1. TBAF, AcOH, THF, rt (86%); 2. TPAP, NMO, MS 4 Å, CH_2Cl_2, 0 °C (quant).



Scheme 6. Reagents and conditions: (a) $Sn(OTf)_2$, chiral diamine **29**, CH_2Cl_2, −78 °C (48%, 90% ee); (b) 1. TBSCl, imidazole, DMF, rt (93%); 2. Et_3SiH, Pd/C, acetone, rt (85%); (c) 1. CBr_4, PPh_3, CH_2Cl_2, −78 to 0 °C (81%); 2. *n*-BuLi, MeI, THF, −78 °C to rt (88%); (d) Cp_2ZrHCl, benzene, sun-lamp, 35 °C, then I_2, 7 °C (86%, *E*/*Z* = 51/49); (e) ***E*-6**, ^{t}BuLi, **5**, Et_2O, −78 °C (27%, α/β = 48/52); (f) 1. TPAP, NMO, MS 4 Å, CH_2Cl_2, 0 °C (75%); 2. 46% HF, CH_3CN, 0 °C (93%); 3. BBr_3, CH_2Cl_2, −45 °C (68%).

oxidized to generate the corresponding enone, and successive deprotections of the TBS and Bn groups furnished the targeted compound **2**.[16]

Thus, an efficient method for the synthesis of octalactin B (**2**) was established via the enantioselective aldol reaction and a new and quite effective lactonization using MNBA. It is already known that ***ent*-2** could be converted to ***ent*-1** by nonselective epoxidation,[2b] therefore, the present report showed the related formal synthesis of octalactin A (**1**). An advanced investigation of the alternative highly stereoselective synthesis of **1** is now in progress in this laboratory.

Acknowledgements

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References and Notes

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12. Experimental procedure for the synthesis of the eight-membered ring lactone moiety of octalactins: To a

solution of MNBA (6.9 mg, 0.020 mmol) and DMAP (11.3 mg, 0.092 mmol) in toluene (5.3 mL) at room temperature was added **8** (8.7 mg, 0.015 mmol) in toluene (2.4 mL). After the reaction mixture had been stirred for 13 h at room temperature, saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with ethyl acetate and the organic layer was washed with brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography (AcOEt/hexane = 1/5) to afford **7** (7.1 mg, 84%) as a colorless oil.

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16. $[\alpha]_D^{23}$ −124° (*c* 0.42, $CHCl_3$) (>99% ee), cf. −123° (revised),[1,2b] −126°,[2a] $[\alpha]_D^{24}$ +132° (*c* 1.00, $CHCl_3$) (enantiomorph).[2b]