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Enantioselective Total Synthesis of Octalactin A Using Asymmetric Aldol Reactions and a Rapid Lactonization To Form a Medium-Sized Ring

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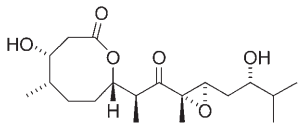
Abstract: Octalactin A, an antitumor agent containing an eight-membered lactone moiety, has been stereoselectively prepared by means of enantioselective aldol reactions of selected silyl enolates with achiral aldehydes, promoted by a chiral Sn^{II} complex. The medium-sized lactone part was effectively constructed by way of a new and rapid mixed-anhydride lactonization using 2-methyl-6-nitrobenzoic anhydride (MNBA) with a catalytic amount of 4-(dimethylamino)pyridine (DMAP) or 4-(dimethylamino)pyridine 1-oxide (DMAPO). The use of only 5 mol% of DMAP or 2 mol% of DMAPO rapidly promoted formation of the medium-sized ring of the octalactin, demonstrating the remarkable efficiency of the new lactonization protocol.

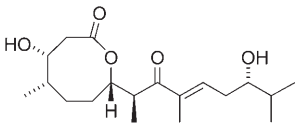
Keywords: aldol reaction · enantioselectivity · octalactin A · rapid lactonization · total synthesis

Introduction

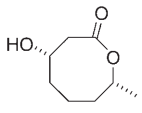
Octalactin A (**1**), a cytotoxic compound, was isolated in 1991 from the marine bacterium *Streptomyces sp.* together with a related eight-membered lactone molecule, octalactin B (**2**).[1] The octalactins consist of highly oxidized medium-sized ring frameworks, and the synthesis of these peculiar and complex structures has become one of the most interesting topics in organic chemistry.[2] The absolute configurations of **1** and **2** were independently determined in 1994 by the total synthesis of the natural octalactins from D- and L-3-hydroxy-2-methylpropionic acids by Buszek et al.[3] and the total synthesis of the *ent*-octalactins (antipodes) from (+)-citronellic acid by McWilliams and Clardy.[4] In 2000, Buszek et al. synthesized octalactins by an alternative approach, which involved the formation of the eight-membered lactone moiety by olefin metathesis.[5] Also, Holmes et al. quite recently accomplished the total synthesis of **1** and **2** utilizing their original rearrangement reaction to form the medium-sized ring of the octalactins.[6] Some formal syntheses and related synthetic studies of octalactins have also been reported.[7]



octalactin A (**1**)



octalactin B (**2**)



cephalosporolide D (**3**)

In 1998, the total synthesis of cephalosporolide D (**3**), an eight-membered lactone similar to the octalactins, was attained by our group.[8] The exact stereochemistry of this molecule was determined by the utilization of a chiral induction technology, which provides optically active compounds (Scheme 1); that is, both asymmetric carbon atoms were constructed by the asymmetric aldol reactions of an enol silyl ether with aldehydes in the presence of a chiral catalyst.[9,10] Furthermore, the desired eight-membered lactone moiety was obtained by the efficient cyclization of the seco acid by a novel mixed anhydride method using (4-trifluoromethyl)benzoic anhydride (TFBA) with $Hf(OTf)_4$.[11,12]

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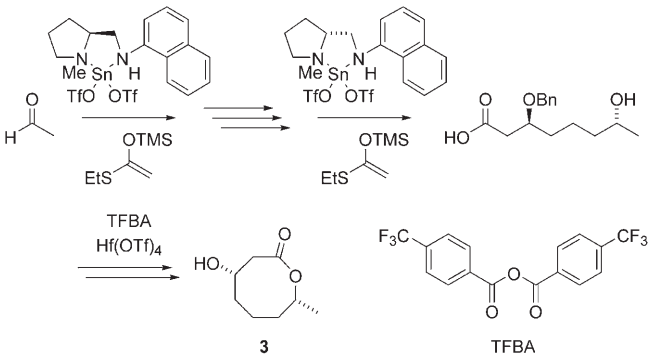


Scheme 1. Stereoselective total synthesis of cephalosporolide D.

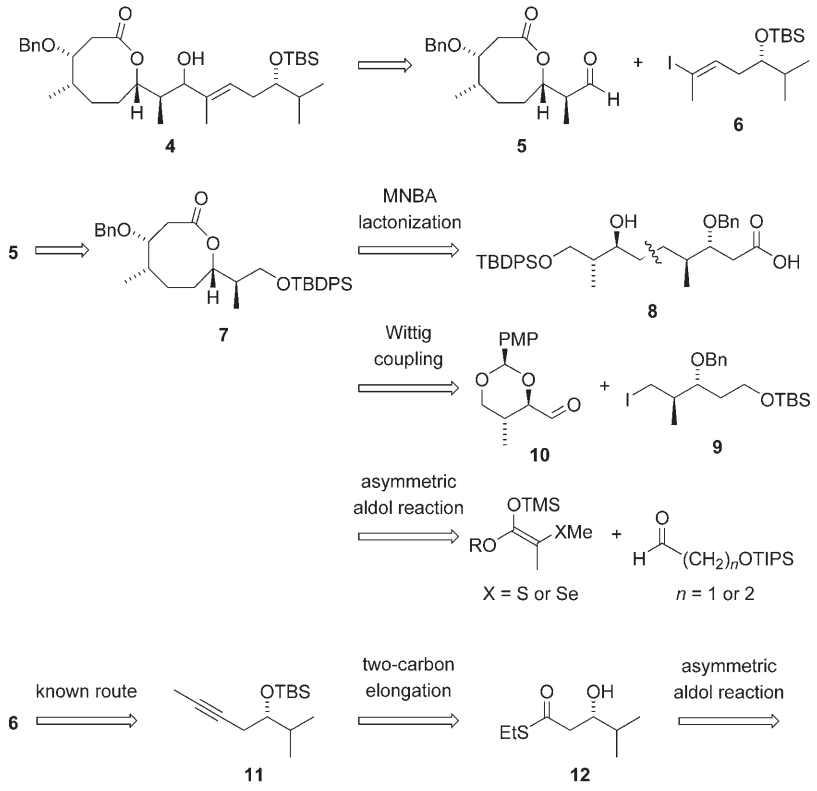
In our continuous efforts directed towards the synthesis of natural compounds containing eight-membered rings,[8,13] the total synthesis of **1** and **2** was planned using a similar strategy.[14] First, we postulated that an optically active seco acid of the eight-membered lactone could be constructed through the enantioselective aldol reactions of a ketene silyl acetal (KSA) with aldehydes promoted by $Sn(OTf)_2$ coordinated to a chiral diamine ligand. Second, effective lactonization using 2-methyl-6-nitrobenzoic anhydride (MNBA) with basic catalysts might then be applicable for producing the eight-membered lactone part of the octalactins.[15]

Because synthetic intermediates similar to **4** have already been prepared, and the transformations of these compounds to **1** and/or **2** have also been described in previous papers,[3,4] allylic alcohol **4** was determined to be our target precursor for the synthesis of **1** and **2** (Scheme 2). It is also assumed that **4** could be prepared by the nucleophilic addition of a metallic species, generated from **6**, to aldehyde **5** according to literature methods.[3,4] Synthesis of the eight-membered lactone part **7** was planned by starting from the linear compound **8**, which could be obtained from the two segments **9** and **10**. Preparation of both of the optically active *anti*-β-hydroxy-α-methyl units **9** and **10** was to be achieved by the enantioselective aldol addition of a tetrasubstituted KSA to an aldehyde, followed by successive stereoselective defunctionalization. Aldol **12** was chosen as a precursor to the siloxyalkyne **11**, which could be converted to the side chain **6**.[3]

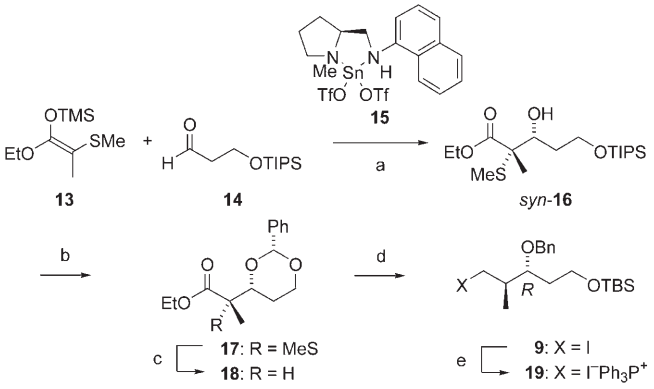
Results and Discussion

Synthesis of aldol-type fragments by desulfurization: The optically active aldol *syn*-**16** was synthesized with high stereoselectivity by the asymmetric aldol reaction of tetrasubstituted KSA **13**, derived from ethyl 2-methylthiopropanoate, with β-siloxyaldehyde **14**. The catalyst for the reaction was a chiral Lewis acid consisting of $Sn(OTf)_2$, chiral diamine, and nBu$_3$SnF (Scheme 3). The enantiomeric excess (*ee*) of *syn*-**16** was determined by HPLC analysis of the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether generated from *syn*-**16**, as shown in the Supporting Information. Direct acetalization of *syn*-**16** with benzaldehyde diethyl acetal in the presence of *p*-toluenesulfonic acid afforded a cyclic compound **17**. Desulfurization of **17** with nBu$_3$SnH was carried out according to a protocol, similar to that developed by Guindon et al., giving the desired *anti*-β-hydroxy-α-methyl unit **18** with high diastereoselectivity.[16,17] The ester group was reduced by $LiAlH_4$ and halogenation of the resulting primary alcohol afforded the corresponding iodoalkane. Successive reductive cleavage of the benzylidene acetal part and protection of the primary alcohol produced the desired right-hand segment **9**, which was further converted to the phosphonium salt **19** by a conventional method.

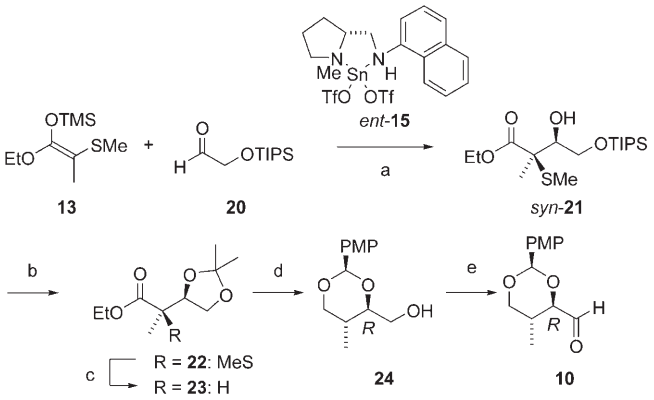
The left-hand segment **10** was also prepared, as illustrated by Scheme 4. The optically active



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



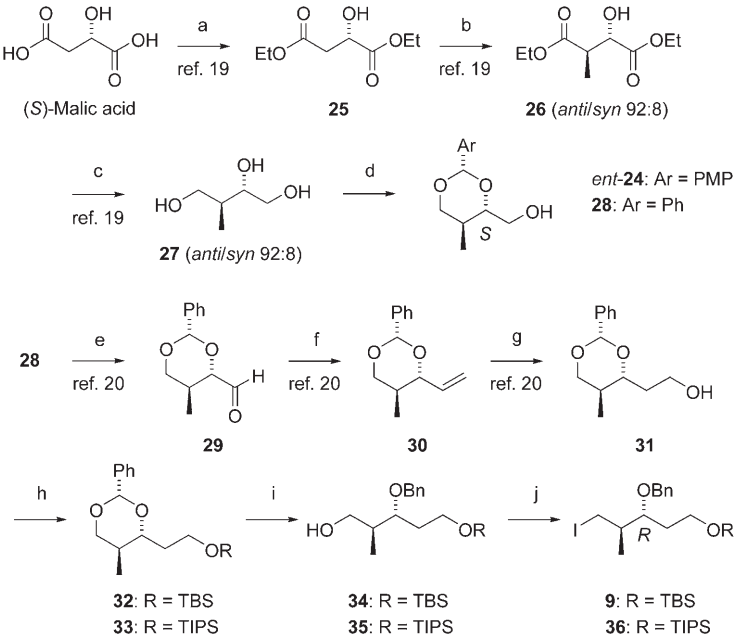
Scheme 3. Reagents and conditions: a) chiral Sn^{II} complex **15**, nBu_3SnF, CH_2Cl_2, −78°C (64%, *syn*/*anti* 93:7, 87% *ee* for *syn*); b) $PhCH(OEt)_2$, TsOH, CH_2Cl_2, RT (77% from *syn*); c) nBu_3SnH, azobisisobutyronitrile (AIBN), benzene, reflux (quant, *anti*/*syn* 89:11); d) i) $LiAlH_4$, THF, 0°C (98% from *anti*); ii) I_2, Ph_3P, imidazole, benzene, RT (94%); iii) diisobutylaluminium hydride (DIBAL), CH_2Cl_2, 0°C (94%); iv) TBSCl, imidazole, DMF, RT (96%); e) Ph_3P, iPr_2NEt, CH_3CN, reflux (84%).



Scheme 4. Reagents and conditions: a) chiral Sn^{II} complex *ent*-**15**, nBu_3SnF, CH_2Cl_2, −78°C (51%, *syn*/*anti* 81:19, 83% *ee* for *syn*); b) i) tetrabutylammonium fluoride (TBAF), AcOH, THF, 0°C (91% from *syn*); ii) $Me_2C(OMe)_2$, MsOH, CH_2Cl_2, RT (85%); c) nBu_3SnH, AIBN, benzene, reflux (93%, *anti*/*syn* 88:12); d) i) $LiAlH_4$, THF, 0°C (82% from *anti*); ii) pyridinium *p*-toluene sulfonate (PPTS), MeOH, reflux; iii) $PMPCH(OMe)_2$ (PMP = 4-methoxyphenyl), PPTS, CH_2Cl_2, RT (86%, two steps); e) PhSNH*t*Bu, NCS, K_2CO_3, MS 4Å, CH_2Cl_2, RT (99%).

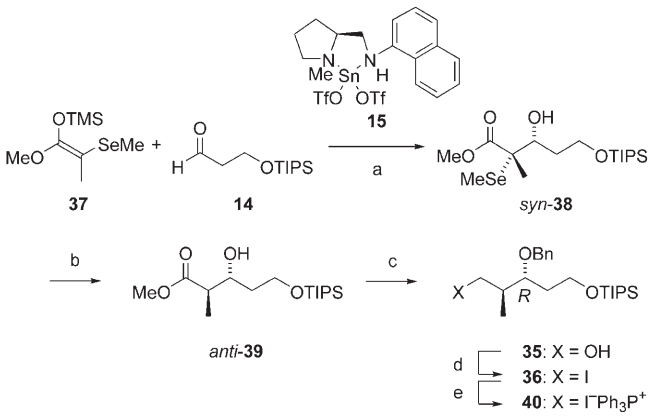
aldol *syn*-**21**, generated from KSA **13** and α-siloxyaldehyde **20**, was transformed to the cyclic acetal **22**, which subsequently underwent smooth diastereoselective desulfurization to preferentially yield the desired *anti*-β-hydroxy-α-methyl unit **23**. Successive reduction of the ester group, formation of *p*-methoxybenzylidene acetal, and oxidation of the intermediary primary alcohol produced the corresponding optically active aldehyde **10**.[18]

The absolute stereochemistry of **10** and **19** was determined as follows (Scheme 5). (*S*)-Malic acid was converted to the corresponding methylated diethyl ester **26** via **25** according Seebach's procedure.[19] Reduction of both ester parts and successive protection of the resulting triol **27** by *p*-methoxybenzylidene acetal afforded *ent*-**24**. By comparison



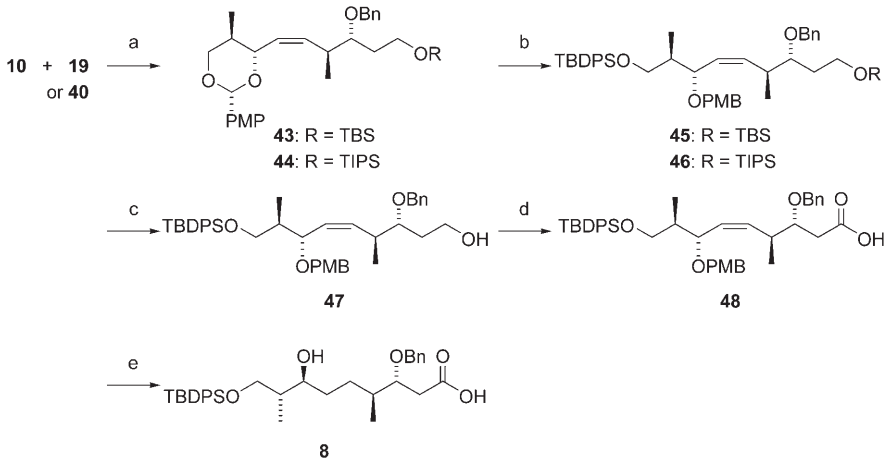
Scheme 5. Reagents and conditions: a) H_2SO_4, EtOH, reflux (67%); b) LDA, MeI, THF, −78°C (74%, *anti*/*syn* 92:8); c) BH_3·THF, reflux (96%); d) $PMPCH(OMe)_2$, CSA, CH_2Cl_2, RT (66% for *ent*-**24**); $PhCH(OMe)_2$, TsOH, CH_2Cl_2, RT (82% for **28**); e) $(COCl)_2$, dimethylsulfoxide (DMSO), Et_3N, CH_2Cl_2, −50°C to RT (98%); f) $Br^-Ph_3P^+CH_3$, KHMDS, THF, toluene, −78 to 0°C (96%); g) 9-BBN, THF, 0°C; then H_2O, 3M NaOH, 35% H_2O_2, RT (99%); h) TBSCl, imidazole, DMF, RT (87% for **32**); TIPSCl, imidazole, DMF, RT (97% for **33**); i) BH_3·SMe_2, $ZnEt_2$·OEt_2, THF, 50°C (86% for **34**); DIBAL, CH_2Cl_2, 0°C (90% for **35**); j) I_2, Ph_3P, imidazole, benzene, RT (90% for **9**; 95% for **36**).

of the sense of optical rotation of **24** (Scheme 4) and *ent*-**24** (Scheme 5), it was revealed that the absolute stereochemistry of C-2 in **24** and **10** was *R*. In addition, **27** was treated with benzaldehyde dimethyl acetal to produce the cyclic compound **28**, and a conventional one-carbon elongation via



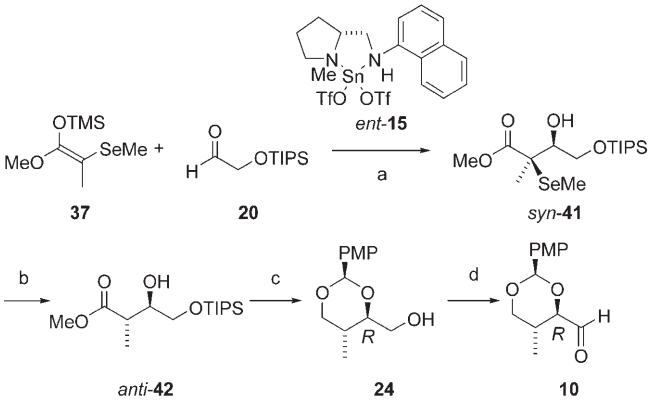
Scheme 6. Reagents and conditions: a) chiral Sn^{II} complex **15**, nBu_3SnF, CH_2Cl_2, −78°C (57%, *syn*/*anti* 75:25, 95% *ee* for *syn*); b) nBu_2BOTf, iPr_2NEt, CH_2Cl_2, 0°C; then nBu_3SnH, Et_3B, −78°C (84%, *anti*/*syn* 90:10); c) i) $BnOC(CCl_3)$=NH, TfOH, Et_2O, 0°C (85%); ii) $LiAlH_4$, THF, 0°C (98% from *anti*); d) I_2, Ph_3P, imidazole, benzene, RT (95%); e) Ph_3P, iPr_2NEt, CH_3CN, reflux (quant).

29 and **30** afforded primary alcohol **31** as preliminarily reported by the Yamamura group.[20] Protection of the hydroxyl group with *tert*-butyldimethylsilyl (TBS) or triisopropylsilyl (TIPS) ether, followed by reductive cleavage of the benzylidene acetal, yielded the five-carbon units **34** and **35**, respectively. Iodoalkanes **9** and **36** were prepared from **34** and **35** by treatment with I_2 and Ph_3P, and the product **9** (Scheme 5) was identified by comparison with the former compound **9** derived from aldol *syn*-**16** (Scheme 3); therefore, it can be deduced that C-3 in compounds **9** and **19** also has an *R* configuration.



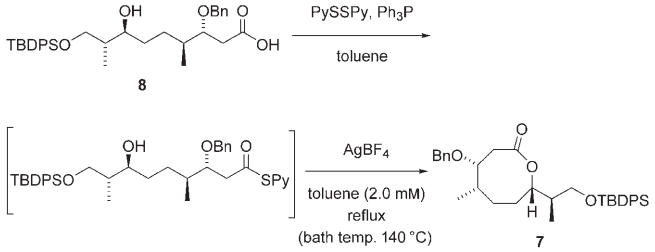
Scheme 8. Reagents and conditions: a) NaHMDS, toluene, −78°C to RT (83% for **43**; 88% for **44**); b) i) DIBAL, CH_2Cl_2, −5 or −10°C (79% from **43**; 86% from **44**); ii) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, RT (91% for **45**; 82% for **46**); c) 1M HCl, THF, RT (99% from **45**; 95% from **46**); d) i) DMP, CH_2Cl_2, RT; ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O, RT (94%, two steps) or TEMPO, $NaClO_2$, NaClO, buffer, H_2O, CH_3CN, 35°C (96%); e) i) CAN, H_2O, CH_3CN, 0°C (94%); ii) H_2, 10% Pd/C, Et_3N, MeOH, RT (87%).

Synthesis of aldol-type fragments by deselenization: Recently, Guindon et al. reported direct deselenization of C-2 selenylated aldols to afford the corresponding *anti*-aldol units.[21] These successful results prompted us to create an alternative pathway for the generation of the optically active right and left-hand segments **40** and **10** utilizing asymmetric aldol reactions and sequential stereoselective deselenization (Schemes 6 and 7). KSA **37** was easily generated from methyl 2-methylselenopropanoate by the general procedure (see Supporting Information). In the presence of chiral Sn^{II} complex **15**, the asymmetric aldol reaction between KSA **37** and aldehyde **14** proceeded smoothly to afford the desired aldol *syn*-**38** in good yield and with high enantioselectivity. The conversion of *syn*-**38** to the corresponding aldol *anti*-**39** was successfully carried out



Scheme 7. Reagents and conditions: a) chiral Sn^{II} complex *ent*-**15**, nBu_3SnF, CH_2Cl_2, −78°C (54%, *syn*/*anti* 79:21, 88% *ee* for *syn*); b) nBu_2BOTf, iPr_2NEt, CH_2Cl_2, RT; then nBu_3SnH, Et_3B, −78°C (77%, *anti*/*syn* 94:6); c) i) DIBAL, CH_2Cl_2, 0°C (80%); ii) $PMPCH(OMe)_2$, CSA, CH_2Cl_2, RT (84% from *anti*); iii) TBAF, THF, 0°C (95%); d) $PhSNHtBu$, NCS, K_2CO_3, MS 4 Å, CH_2Cl_2, RT (99%).

Table 1. Synthesis of the eight-membered lactone **7**: Application of the *S*-pyridyl ester method.



Entry	Time [h]	Yield [%][a]
1	96	63
2	48	51
3	13	5
4[b]	96	0

[a] Isolated yield. [b] The reaction was carried out at room temperature.

by the literature method,[21c] and transformation of **39** to the phosphonium salt **40** via **35** and **36** was also achieved without difficulty (Scheme 6). As compound **40** was prepared via compound **36** (stereochemistry previously determined, Scheme 5), the absolute stereochemistry of C-3 in **40** was deduced to be *R*.

Furthermore, the aldol reaction of aldehyde **20** with KSA **37**, promoted by the chiral Sn^{II} complex *ent*-**15**, produced the four-carbon unit *syn*-**41** with high enantioselectivity (Scheme 7).[22] Treatment of *syn*-**41** with nBu_2BOTf, iPr_2NEt, and nBu_3SnH, effected diastereoselective deselenization producing aldol *anti*-**42** in good yield. Reduction of the ester group and protection of the intermediary diol with a *p*-methoxybenzylidene group provided alcohol **24**, which was identified by comparison with the former compound **24** synthesized by the route shown in Scheme 4. Thus, an im-

proved method for the synthesis of the optically active right- and left-hand segments of the octalactins has been developed according to our chiral induction technology, which employs Sn^{II}-promoted asymmetric aldol reactions and successive diastereoselective deselenization.

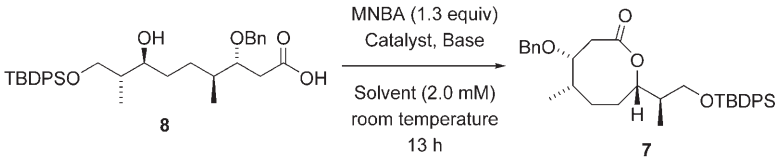
Synthesis of the seco acid of the eight-membered lactone moiety: The two segments **10** and **19** were coupled in the presence of sodium hexamethyldisilazide (NaHMDS) to produce the linear polyoxy compound **43** in good yield (Scheme 8). Reductive cleavage of the acetal moiety followed by protection of the resulting primary alcohol afforded the disilyl ether **45**. Deprotection of the TBS group followed by either conventional stepwise oxidation of the primary alcohol **47** or single-step oxidation with 2,2,6,6-tetramethylpiperdinyloxy free radical (TEMPO)[23] produced the corresponding carboxylic acid **48**. The desired chiral linear seco acid **8** was then obtained by deprotection of the *p*-methoxybenzyl (PMB) group and hydrogenation of the double bond without removal of the benzyl group.[24] In addition, the coupling reaction of the left-hand segment **10** with the alternative right-hand segment **40** produced the nine-carbon unit **44** in high yield. Disilyl ether **44** was converted to the synthetic intermediate **47** by using similar methods to those applied to the synthesis of compounds **43** and **45**.

Formation of the eight-membered lactone moiety by a substituted benzoic anhydride method: Buszek et al. reported the successful lactonization of a similar seco acid, in which the PMB group replaces the Bn group in **8**, by the application of the *S*-pyridyl ester method.[3,25,26] However, it was reported that the cyclization required a high reaction temperature and a long reaction time (96 h); nevertheless, the reaction was accelerated by $AgBF_4$. In actual fact, our group has found that the reaction of the *S*-pyridyl ester of **8** proceeds sluggishly even under very severe conditions (96 h in refluxing toluene with $AgBF_4$) producing the desired eight-membered lactone **7** in 63% yield (Table 1, entry 1). From entries 2 and 3, it can be seen that the yield of **7** decreases when the reaction time is decreased. For example, only 5% of the desired lactone **7** was obtained under the intensive conditions when the reaction was quenched after 13 h. Furthermore, it was revealed that the cyclization of the *S*-pyridyl ester of **8** did not take place at room temperature (entry 4). Therefore, we decided to develop a new and rapid lactonization reaction to produce the medium-sized lactone backbone **7**.

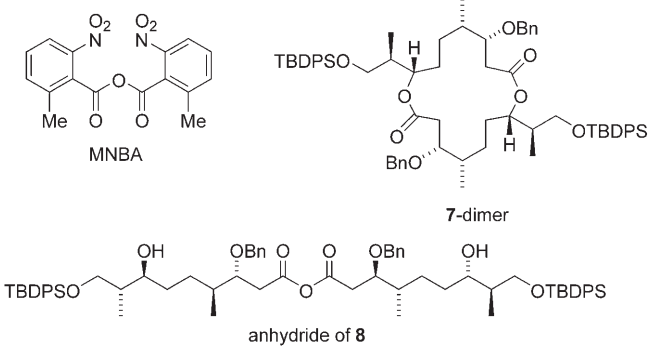
Recently, we reported the effective use of substituted benzoic anhydrides for the preparation of carboxylic esters, thioesters, and carboxamides under acidic or basic conditions.[12,15] As it has already been shown that MNBA is the best dehydrating reagent to produce carboxylic esters and macrocyclic lactones by the promotion of basic catalysts, the MNBA method was applied to seco acid **8** to afford the desired compound **7** (Table 2).

First, excess DMAP (6.0 equiv) was employed as a promoter for the cyclization of **8** in the presence of MNBA (1.3 equiv) in dichloromethane or toluene at room tempera-

Table 2. Synthesis of the eight-membered lactone **7**: Application of the benzoic anhydride method.



Entry	Catalyst (equiv)	Base (equiv)	Solvent	Yield [%][a]
1	DMAP (6.0)	-	CH_2Cl_2	85
2	DMAP (6.0)	-	toluene	84
3	DMAP (0.2)	Et_3N (6.0)	CH_2Cl_2	80
4	DMAP (0.1)	Et_3N (6.0)	CH_2Cl_2	89
5	DMAP (0.05)	Et_3N (6.0)	CH_2Cl_2	81
6	DMAP (0.02)	Et_3N (6.0)	CH_2Cl_2	47
7	DMAP (0.01)	Et_3N (6.0)	CH_2Cl_2	24
8	DMAPO (0.2)	Et_3N (6.0)	CH_2Cl_2	82
9	DMAPO (0.1)	Et_3N (6.0)	CH_2Cl_2	90
10	DMAPO (0.05)	Et_3N (6.0)	CH_2Cl_2	84
11	DMAPO (0.02)	Et_3N (6.0)	CH_2Cl_2	78
12	DMAPO (0.01)	Et_3N (6.0)	CH_2Cl_2	50
13[b]	DMAP (6.0)	-	CH_2Cl_2	50[c]
14[d]	DMAP (3.5)	-	CH_2Cl_2	84
15[d]	DMAP (0.1)	Et_3N (6.0)	CH_2Cl_2	46[e]
16[d]	DMAPO (0.1)	Et_3N (6.0)	CH_2Cl_2	28[f]



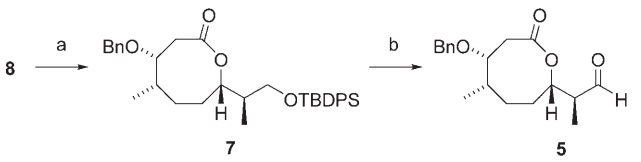
[a] Isolated yield. [b] The reaction was carried out in dichloromethane (100 mM). [c] 16-membered diolide (**7**-dimer) was obtained in 32% yield. [d] Benzoic anhydride was used as a coupling reagent instead of MNBA. [e] The symmetric carboxylic anhydride of **8** and its dibenzoate were obtained in 24% and 13% yield, respectively. [f] The symmetric carboxylic anhydride of **8** was obtained in 22% yield.

ture, producing the eight-membered lactone **7** in 85 and 84% yield, respectively (entries 1 and 2). Next, the amount of the catalyst was gradually decreased as shown in entries 3–7, and it was determined that the use of 5 mol% of DMAP with excess triethylamine (6.0 equiv) was sufficient to produce **7** in over 80% yield at room temperature (entry 5). When the reaction was carried out with less than 5 mol% of DMAP, the yield was considerably lowered (entries 6 and 7).

Alternatively, it has been observed that DMAPO, an oxide of DMAP, is quite an effective basic promoter for our lactonization; therefore, we examined the use of DMAPO as a catalyst in the cyclization reaction (entries 8–12). In every case, the desired lactone **7** was obtained in a relatively greater yield when DMAPO was used as opposed to DMAP. Furthermore, as shown in entry 11, the use of only 2 mol% of DMAPO afforded the targeted lactone in 78% yield under very mild reaction conditions (room temperature) and within a short period of time (13 h).

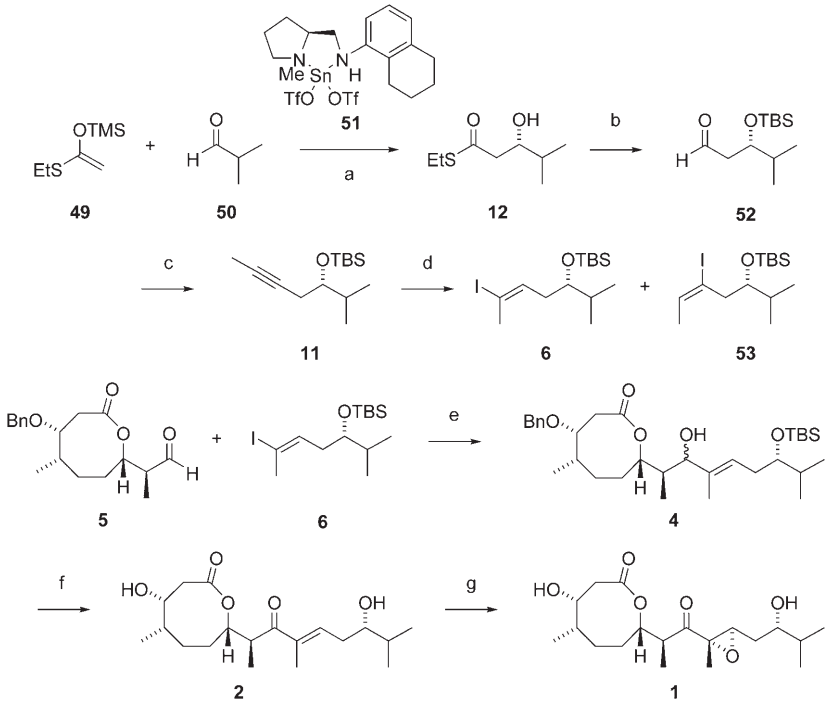
A 16-membered diolide (**7**-dimer) was formed as a by-product (32%) when the lactonization of **8** was carried out under the concentrated reaction conditions (100 mM, entry 13). Interestingly, a simple benzoic anhydride could also be used for the preparation of **7** from **8** by promotion with excess DMAP (entry 14); however, the catalytic reactions of **8** with 10 mol% of DMAP or DMAPO with benzoic anhydride produced the corresponding lactone **7** in low yield (46%, entry 15 and 28%, entry 16, respectively).

Once formed, **7** was then converted to the eight-membered lactone aldehyde **5** by deprotection of the TBDPS group, followed by successive oxidation (Scheme 9).



Scheme 9. Reagents and conditions: a) MNBA, DMAP (10 mol%) or DMAPO (10 mol%), Et_3N, CH_2Cl_2, RT (89% or 90%); b) i) TBAF, AcOH, THF, RT (99%); ii) TPAP, NMO, MS 4Å, CH_2Cl_2, 0°C (91%).

Preparation of the side chain and completion of the total synthesis: 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 (**49**) with 2-methylpropionaldehyde (**50**) (Scheme 10).[9,10] Protection of **12** and successive reduction using Et_3SiH with Pd/C afforded the chiral aldehyde **52**.[27] According to Buszek's synthesis of the side chain, **52** was transformed into the desired vinyl iodide **6** via the siloxyalkyne **11**.[3] The side chain **6** was finally introduced to the aldehyde **5** by using the method reported by McWilliams and Clardy[4] to give the multioxygenated eight-membered lactone **4**, a precursor of the octalactins. A mixture of diastereomers was oxidized to generate the corresponding enone, and successive deprotection of the TBS and Bn groups afforded octalactin B (**2**; $[\alpha]_D^{23} = -124°$ ($c = 0.42$ in $CHCl_3$)).[28] The final conversion of octalactin B to octalactin A was achieved by using *tert*-butyl hydroperoxide (TBHP), according to the literature method.[4] All spectral data including the optical rotations of synthetic **1** corresponded to those of natural octalactin A ($[\alpha]_D^{26} = -148°$ ($c = 0.20$ in $CHCl_3$)).[29]



Scheme 10. Reagents and conditions: a) chiral Sn^{II} complex **15**, nBu_3SnF, CH_2Cl_2, −78°C (65%, 94% *ee*) or chiral Sn^{II} complex **51** (20 mol%), CH_2Cl_2, −78°C (48%, 90% *ee*); b) i) TBSCl, imidazole, DMF, RT (95%); ii) Et_3SiH, 10% Pd/C, acetone, RT (88%); c) i) CBr_4, PPh_3, CH_2Cl_2, −78 to 0°C (86%); ii) *n*BuLi, THF, −78°C; then MeI, RT (91%); d) Cp_2ZrHCl, benzene, sunlamp, 35°C; then I_2, 7°C (72%, **6**/**53** 70:30); e) **6**, *t*BuLi, Et_2O, −78°C; then **5** (49%, α/β = 57/43); f) i) tetra-*n*-propylammonium perruthenate (TPAP), NMO, MS 4Å, CH_2Cl_2, 0°C (75%); ii) 46% HF, CH_3CN, 0°C (91%); iii) BBr_3, CH_2Cl_2, −95 to −45°C (76%); g) TBHP, $VO(acac)_2$, CH_2Cl_2, 5–10°C (40% based on 70% conversion).

Conclusion

An efficient method for the synthesis of octalactin A and its intermediates, which include octalactin B, has been established by enantioselective aldol reactions and a very effective lactonization using a substituted benzoic anhydride. Through our chiral induction technology, a systematic method for providing chiral compounds, from both achiral silylenolates and aldehydes by enantioselective aldol reactions, has successfully been applied to the preparation of an optically active linear precursor to the eight-membered lactone and side chain of the octalactins. Furthermore, a new method for constructing the eight-membered lactone moiety of the octalactins has been established, that utilizes a rapid cyclization reaction, promoted by MNBA under the influence of a catalytic amount of DMAP or DMAPO. This synthetic method would be widely applicable to the creation of various derivatives of octalactin-type antitumor agents.

Experimental Section

General methods, detailed experimental procedures, and the spectroscopic data of all compounds have been provided in the Supporting Information.

Typical experimental procedure for the lactonization reaction: 2-Methyl-6-nitrobenzoic anhydride (MNBA) was purchased from Tokyo Kasei Kogyo (TCI, M1439).

An experimental procedure is described for the preparation of lactone 7 using MNBA with a catalytic amount of DMAP (Table 2, entry 4): A solution of **8** (53.2 mg, 94.5 μmol) in dichloromethane (1 mL) was added to a solution of MNBA (42.8 mg, 0.124 mmol), DMAP (1.2 mg, 9.6 μmol), and triethylamine (58.0 mg, 0.574 mmol) in dichloromethane (46.8 mL) at room temperature. After the reaction mixture had been stirred for 13 h at room temperature, saturated aqueous sodium hydrogencarbonate was added at 0°C. The mixture was then extracted with dichloromethane, and the organic layer was washed with water and brine, and dried over sodium sulfate. Filtration of the resulting mixture and evaporation of the solvent provided the crude product, which was purified by thin-layer chromatography to afford lactone **7** (45.8 mg, 89%) as a colorless oil.

An experimental procedure for the preparation of both 7 and 7-dimer (Table 2, entry 13): A solution of **8** (36.1 mg, 64.1 μmol) in dichloromethane (0.64 mL) was added to a mixture of MNBA (28.7 mg, 83.4 μmol) and DMAP (47.0 mg, 0.385 mmol) at room temperature. After the reaction mixture had been stirred for 13 h at room temperature, saturated aqueous sodium hydrogencarbonate was added at 0°C. The mixture was then extracted with dichloromethane, and the organic layer was washed with water and brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography to afford both the lactone **7** (17.6 mg, 50%) and its dimer (11.1 mg, 32%) as colorless oils.

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[28] Compare lit:[1,4] $[\alpha]=-123°$ (revised); lit:[3] $[\alpha]=-126°$; lit:[6] $[\alpha]=-123°$; lit:[4] $[\alpha]=+132°$ (enantiomorph).
[29] Compare lit:[1,4] $[\alpha]=-140°$ (revised); lit:[3] $[\alpha]=-152°$; lit:[6] $[\alpha]=-153°$; lit:[4] $[\alpha]=+141°$ (enantiomorph).

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