# Determination of Relative and Absolute Stereochemistry of Cephalosporolide D and Its Enantioselective Total Synthesis

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An efficient method for the synthesis of (-)-cephalosporolide D was established *via* successive enantioselective aldol reaction and effective construction of 8-membered ring lactone moiety.

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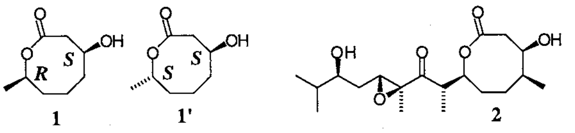
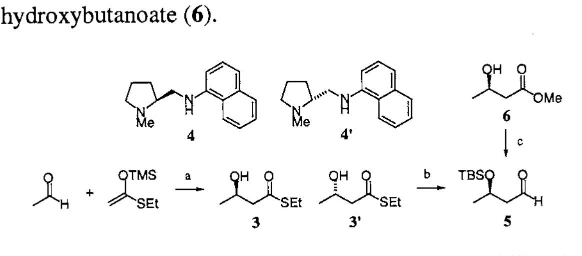
Cephalosporolide D (**1** or **1'**), a metabolite of fungus, was isolated in 1985 from the *C. aphidicola*, ACC 3490 together with the related compounds by Hanson *et al.*[1] The structure containing two chiral centers and an unusual saturated 8-membered ring lactone was determined by mass spectra, IR absorption, $^{13}C$ and $^{1}H$ NMR studies. Though the absolute stereochemistry of the hydroxyl group at C-3 was suggested to be in (*S*) configuration by Horeau's method,[1] the relative stereochemistry and exact absolute stereochemistry have not determined to date. The similarly featured characteristic structure was also found in octalactin A (**2**) which exhibited a potent cytotoxic activity against some tumor cell lines.[2] In this communication, determination of stereochemistry of cephalosporolide D and its asymmetric synthesis by enantioselective aldol reaction and recently developed lactonization method are described.



**Scheme 1.**

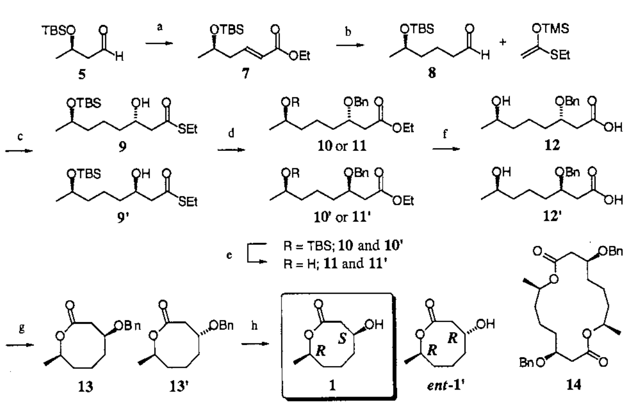
Both optically active *S*-ethyl (*R*)-3-hydroxybutanal (**3**) and its enantiomer **3'** were synthesized with high enantioselectivities by asymmetric aldol reaction between acetaldehyde and enol silyl ether derived from *S*-ethyl propanethioate using chiral Lewis acid consisted of $Sn(OTf)_2$, chiral diamine **4** (or **4'**) and $^{n}Bu_3SnF$.[3] The aldol **3** was converted to optically active 3-(*t*-butyldimethylsiloxy)butanal (**5**) in good yield after protection with a combination of TBSOTf and 2,6-lutidine and subsequent reduction with DIBAL. Absolute configuration of **5** was determined by comparison of its optical rotation with that of the authentic sample derived from commercially available methyl (*R*)-3-hydroxybutanoate (**6**).



a) $Sn(OTf)_2$, $^{n}Bu_3SnF$, chiral diamine **4**, $CH_2Cl_2$, -95 °C (64%, 96% ee for **3**); $Sn(OTf)_2$, $^{n}Bu_3SnF$, chiral diamine **4'**, $CH_2Cl_2$, -95 °C (65%, 96% ee for **3'**); b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C (96%); DIBAL, toluene, -78 °C (84%); c) TBSCl, imidazole, DMF, rt (99%); DIBAL, toluene, -78 °C (100%).

**Scheme 2.**

Horner-Wadswarth-Emmons reaction of aldehyde **5** with $(EtO)_2POCH_2COOEt$ produced *trans*-unsaturated ester **7** in high yield and it was in turn transformed to the corresponding saturated siloxyaldehyde **8** by successive hydrogenation under hydrogen atmosphere in the presence of palladium on carbon and reduction with DIBAL. The reaction of the chiral aldehyde **8** with lithium enolate derived from *S*-ethyl propanethioate gave the corresponding aldols **9** and **9'** with poor diastereoselectivity (**9** / **9'** = 47 / 53). However, the asymmetric aldol reaction between aldehyde **8** and the above enol silyl ether in the presence of the chiral Lewis acid consisted of $Sn(OTf)_2$, chiral diamine **4'** and $^{n}Bu_3SnF$ under standard reaction conditions produced the corresponding aldol **9** in good yield with high stereoselectivity (**9** / **9'** = 97 / 3). Further, diastereoisomeric aldol **9'** was also prepared by the same asymmetric aldol reaction using chiral diamine **4** with high stereoselectivity (**9** / **9'** = 3 / 97). The stereochemistry at C-3 had not yet been clear at this stage; however, the empirical rule of our asymmetric aldol reaction made us assume that aldol **9** and **9'** would have (3*S*,7*R*) and (3*R*,7*R*) configurations, respectively.[3] When the aldol reaction of aldehyde **8** with the enol silyl ether was tried in the presence of a catalytic amount of $SnCl_4$, a diastereomeric mixture of the aldols was obtained in good yield with moderate stereoselectivity (**9** / **9'** = 41 / 59, mixture **A**). Further, the cyclization was tried to prepare 8-membered ring lactones from thus obtained diastereomeric mixture. After several examinations on the formation of a diastereomeric mixture of 8-membered ring compounds, the method was finally applied to the single stereoisomeric intermediate, aldol **9** or **9'**. Protection of hydroxyl groups of **9** and **9'** using trichloromethyl benzylimidate gave a mixture of the desired benzyl ethers in poor yield probably because of preferential interaction of the imidate to their thiol ester functions. Therefore, thiol esters **9** and **9'** were converted to the corresponding esters by transesterification in the presence of $Ag(OCOCF_3)$ and $^{i}Pr_2NEt$ in EtOH. Benzylation of the esters using trichloromethyl benzylimidate proceeded rapidly to afford a mixture of the desired dialkoxyesters **10** and **10'** in high yield as expected. TBS groups of **10** and **10'** were removed on treatment with acetic acid in THF and water, then saponification of a mixture of thus formed esters **11** and **11'** with aqueous KOH afforded a mixture of the desired hydroxycarboxylic acids **12** and **12'** in good yield. Then, lactonization of the mixture of **12** and **12'** was tried by previously reported mixed anhydride method using a catalytic amount of Lewis acids and a stoichiometric amount of *p*-trifluoromethylbenzoic anhydride.[4a-d] When the reaction was carried out in the presence of a catalytic amount of $TiCl_2(OTf)_2$, a mixture of 8-membered ring lactones **13** and **13'** was obtained in only 2% yield. On the other hand the cyclization reaction catalyzed by $Sc(OTf)_3$ gave a mixture of 8-membered ring lactones **13** and **13'** in 44% yield along with the recovered mixture of hydroxycarboxylic acids **12** and **12'** in 31% yield.[4e,f] After screening several catalysts in this reaction it was found that $Hf(OTf)_4$ promoted the cyclization effectively to produce a mixture of desired 8-membered ring lactones **13** and **13'** in 67% yield, and 17% of the mixture of **12** and **12'** was recovered.[5] It is noted that this cyclization gave monomeric lactones exclusively and the corresponding diolides were not formed at all though the reason for this phenomenon was not clear.[6] Further studies on the cyclization reaction showed that Yamaguchi's mixed anhydride method promoted by DMAP also gave good result and a mixture of the desired lactones **13** and **13'** was obtained in 74% yield although the hydroxycarboxylic acids **12** and **12'** were not recovered.[7] Lactonization of the precursors by activation using 2-chloro-1-methylpyridinium iodide with triethylamine[8] or di-2-pyridyldisulfide with triphenylphosphine[9] also afforded a mixture of desired lactones in 64% or 34% yield, respectively. Debenzylation of lactones **13** and **13'** took place smoothly to yield a mixture of lactones **1** and ***ent*-1'** in the ratio of 41 to 59.



a) $(EtO)_2POCH_2COOEt$, NaH, THF, 0 °C (83%); b) $H_2$, Pd/C, EtOH, rt (92%); DIBAL, toluene, -78 °C (97%); c) $SnCl_4$, toluene, -78 °C (79% of mixture **A**, **9** / **9'** = 41 / 59); $Sn(OTf)_2$, $^nBu_3SnF$, chiral diamine **4'**, $CH_2Cl_2$, -78 °C (89% of mixture **B**, **9** / **9'** = 97 / 3); $Sn(OTf)_2$, $^nBu_3SnF$, chiral diamine **4**, $CH_2Cl_2$, -78 °C (62%, **9** / **9'** = 3 / 97); d) $Ag(OCOCF_3)$, $^iPr_2NEt$, EtOH, rt (**A**; 100%, **B**; 93%); $BnOC(CCl_3)=NH$, TfOH, $CH_2Cl_2$, rt (**A**; 98% of **10** / **10'**, 1% of **11** / **11'**, **B**; 85% of **10** / **10'**, 9% of **11** / **11'**); e) AcOH, $H_2O$, THF, rt (**A**; 100%, **B**; 95%); f) KOH, $H_2O$, MeOH, rt (**A**; 61%, **B**; 67%); g) $Hf(OTf)_4$, $(p\text{-}CF_3C_6H_4CO)_2O$, $CH_3CN$, THF, reflux (**A**; 2.34 mM, slow addition over a 15 h period, 81% based on 83% conversion, **B**; 1.66 mM, slow addition over a 8 h period, 77% based on 61% conversion); h) $H_2$, Pd/C, EtOH, rt (**A**; 98%, **B**; 73% based on 90% conversion).

**Scheme 3.**

$^1H$ NMR spectra of thus obtained mixture of lactones **1** and ***ent*-1'** showed that naturally occurring cephalospoloride D is a minor stereoisomer (**1**) and the *epi*-cephalospoloride D is a major stereoisomer (***ent*-1'**). Finally, (-)-cephalosporolide D (**1**) was synthesized from the aldol **9** (the ratio of **9** to **9'** was 97 to 3, mixture **B**) by successive protection, deprotection and lactonization procedures. When the cyclization was applied to carboxylic acid **12** derived from the above synthetic intermediate **9** under relatively concentrated reaction conditions, a very small amount of 16-membered ring diolide **14** was also obtained along with the desired 8-membered ring lactone **13**. The synthetic lactone **1** was recrystallized from hexane to give optically and chemically pure lactone **1**.[10] The spectroscopic properties of synthetic crystalline sample including its optical rotation were identical with those of **1** reported by Hanson *et al.* Furthermore, X-ray crystallography of synthetic lactone **1** showed its exact relative stereochemistry and conformation in crystalline structure.[11] As shown in Figure 1, the lactone **1** has second stable conformation estimated by calculation[12] and it is assumed that there is conformational stabilization effect by hydrogen bonding between neighbor molecules in packing structure.

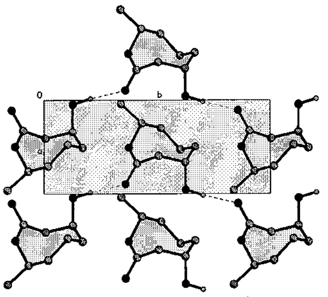


**Figure 1.** X-ray crystallographic structure of cephalosporolide D (**1**).

Thus, an efficient method for the synthesis of (-)-cephalosporolide D (**1**) was established *via* successive enantioselective aldol reaction and effective construction of 8-membered ring lactone moiety. Absolute and relative configuration of the lactone **1** including its conformation was additionally determined by utilizing enantioselective synthesis.

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5 Hafnium tetrakis(trifluoromethanesulfonate) was purchased from Tokyo Kasei Kogyo Co., Ltd. It was effectively employed in Friedel-Crafts reaction, Fries rearrangement and Mannich-type Reaction. See, I. Hachiya, M. Moriwaki, and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, **68**, 2053 (1995); S. Kobayashi, M. Moriwaki, and I. Hachiya, *Bull. Chem. Soc. Jpn.*, **70**, 267 (1997); S. Kobayashi, S. Iwamoto, and S. Nagayama, *Synlett.*, **1997**, 1099. We had observed that $HfCl_2(OTf)_2$, generated *in situ* from 1 mol eq. of $HfCl_4$ and 2 mol eq. of AgOTf was effective catalyst for the synthesis of carboxylic esters in 1992. See, ref. 4a) and 4b).

6 Buszek and Andrus suggested that conformations of the acyclic precursors for high-yielding lactonizations in the syntheses of octalactins are influenced by stereochemical arrangement and location of those protecting groups. See, ref. 2b) and 2e).

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10 **1**; $[\alpha]_D^{28}$ -46.8° (c 2.40, $CHCl_3$). (ref. $[\alpha]_D^{20}$ -46.5° (c 2.23, $CHCl_3$))[1]

11 Crystallographic data are as follows: FW = 158.19, space group, $P2_1$, cell const., $a = 5.036(1)$, $b = 11.793(1)$, $c = 7.173(1)$ Å and $\beta = 108.43(I)°$, $V = 404.1(1)$ Å$^3$, $Z = 2$, R1 ($I > 2\sigma$) = 0.037, and number of unique reflections, 2400 ($I > 2\sigma$). Atomic coodinates, thermal parameters, and bond angles have been deposited at the Cambridge Crystallographic Data Center.

12 Conformational search was performed with the program package SPARTAN 5.0.3 (DEC version) of Wavefunction, Inc.